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# SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS—II†

## STEREOSELECTIVE AND ENANTIOSELECTIVE SYNTHESIS OF (+)-VINCAMINE

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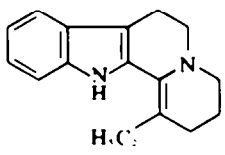
**Abstract**—Addition of α-acetoxy acrilic acid ( )-menthyl ester to enamine 1 produces about 40% asymmetric induction. The compound obtained, **9b**, can be converted into (+)-vincamine with ease and in good yield. The catalytic effect of metal ions on the epimerisation of the vincamine–epivincamine system was investigated.

The recognition of the valuable therapeutic effect[1] of (+)-vincamine alkaloid **11a** greatly stimulated work on a rational synthesis.[2] We reported in a preliminary communication such a synthesis;[3] meanwhile this has been developed into an enantioselective method.

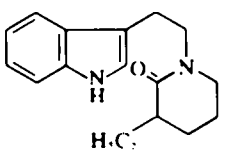
### RESULTS AND DISCUSSION

*Preparation of enamine* **1**

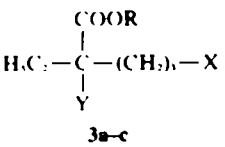
One of the key intermediates in the vincamine synthesis is the enamine **1**, which has already been described by Wenkert.[4] ω-Chloropropylethylmalonic acid diethyl ester was used as the starting material, because it can be obtained more readily and in better yield than the corresponding bromo derivative,[4] and the amount of bis-alkylation is considerably lower.



**1**



**2**



**3a–c**

| | R | X | Y |
|---|---|---|---|
| **3a** | $C_2H_5$ | Cl | $COOC_2H_5$ |
| **b** | $CH_3$ | Cl | H |
| **c** | H | OH | COOH |

The product was obtained by one of two routes: (a) The ester was partially hydrolysed with an equivalent quantity of alkali and decarboxylated with acid, or hydrolysed and decarboxylated by heating with acid and converted into its methyl ester. The reaction of the ω-chloro valeric acid ester obtained with tryptamine gave a good yield of the desired amide **2**, which was then cyclised with phosphorus oxychloride followed by basification to give the enamine **1**.[4]

(b) The ester was hydrolysed with alkali, and after acidifying gave the crystalline carboxylic acid **3c**,[5] which on heating with acid or melting yielded the lactone **4**.

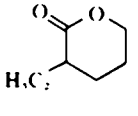
It should be mentioned that when ω-chloropropylethylmalonic acid diethyl ester was hydrolysed with 70% (or more concentrated) sulfuric acid instead of alkali, or when lactone **4** was subjected to similar treatment, a 5-membered lactone **5** was obtained, in the latter case by ring contraction. Lactone **5** is presumably formed by the 1,2-sigmatropic rearrangement of the intermediate carbonium ion **6**, leading to a thermodynamically more stable ion. Lactone **5** is an approximately 1:1 mixture of diastereomers, as has been established by Ollis and others.[6]

The reaction of lactone **4** with tryptamine in chlorobenzene yields almost quantitatively the amide **7**.

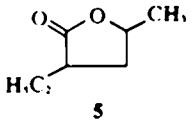
Instead of tryptamine the cheaper tryptophan may be used. Tryptophan is decarboxylated according to the method of Kametani[7] by heating in diphenylmethane, and the tryptamine formed is acylated without isolation, in the same medium, with lactone **4**. In this way, based on tryptophan, a yield of 85% may be obtained.

On fusion, the hydroxy acid amide **7** is converted into the amide **2**. The same amide **2** can be obtained by reacting tryptamine at a temperature of about 230°C with lactone **4** in the presence of tryptamine hydrochloride salt as catalyst.

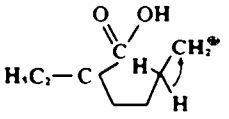
However, the reaction of amide **7** with $POCl_3$ proved to be the best method; this leads to ring closure and substitution of hydroxyl by chlorine, and gives after basifying the enamine **1**.



**4**



**5**



**6**

*Preparation of the hydroxy acid ester* **9b**

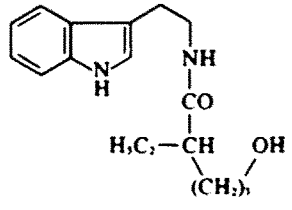
In methylene chloride, α-acetoxyacrylic acid methyl ester,[8] readily obtained from pyruvic acid methyl ester with acetic anhydride, is added to the enamine **1** in the presence of a small amount of methanol as proton

†Ref. 3 is considered as the first communication of the series.

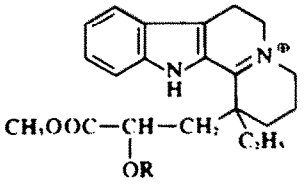
source. The acetoxy derivative, isolated as the perchlorate **8a**, is formed in good yield, and can easily be converted with sodium methoxide/methanol or with HCl/methanol into the hydroxy acid **8b**. However, the carbon–nitrogen double bond in **8a** can be conveniently reduced directly, catalytically or with sodium borohydride. This gives a mixture of **9a**, containing a *cis* C/D ring linkage, and its *trans*-epimer **10a**. Catalytic hydrogenation is highly stereoselective, and yields predominantly the *cis* product **9a**.

The selectivity proved to be temperature-dependent, when the reduction was carried out with sodium borohydride in methanol. At temperatures below 0°C, a ratio of 3:7 was observed, while at room temperature the ratio of trans **10a** to **9a** increased to 2:3.

Catalytic hydrogenation is less selective, if the reaction is carried out on the deacetylated compound **8b**. This confirms our general experience that the higher the spatial requirement of the substituents in position 1, the higher is the ratio of the *cis* product in the reduction product, when reduction is carried out with Pd/C catalyst or with sodium borohydride.

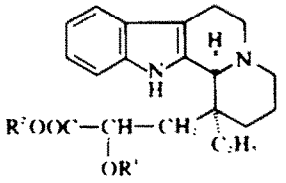


7



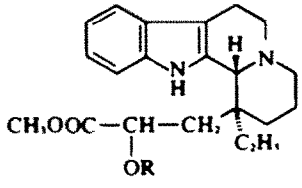
**8a,b**

| | R |
|---|---|
| **8a** | $COCH_3$ |
| **b** | H |



| | R' | R² |
|---|---|---|
| **9a** | $COCH_3$ | $CH_3$ |
| **b** | H | $CH_3$ |
| **c** | $COCH_3$ | (−)-menthyl |

**9a–c**



| | R |
|---|---|
| **10a** | $COCH_3$ |
| **b** | H |

**10a–b**

The separation of the *cis* and *trans* isomers is expediently undertaken in the deacetylated form. Compound **9b** is a readily crystallizable substance, easily identified, and has been prepared earlier by another route.[9]

The PMR spectra of compounds **9a, b** and **10a, b** are characteristic. The C-2' proton exhibits a one-proton quartet due to the diastereotopic protons at the neighbouring C-3'. In the spectra of the *cis*-type compounds **9a, b** the signals of $N_{ind}$–H and $COOCH_3$ are seen at lower $\delta$ values than in the *trans* derivatives (**10a, b**, while the $-CH_2-CH_3$ protons show the opposite trend (see Table 1).

Table 1. The $^1H$ chemical shifts ($\delta$) of compounds **9** and **10** in $CDCl_3$

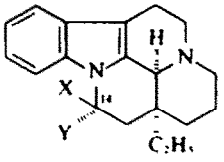
| Compound | indole NH | $-CO_2CH_3$ | $-CH_2-CH_3$ |
|---|---|---|---|
| **9a** | 7.82 | 3.60 | 1.22 |
| **9b** | 7.85 | 3.60 | 1.10 |
| **10a** | 8.60 | 3.80 | 0.73 |
| **10b** | 9.46 | 3.87 | 0.66 |

The IR spectra show the Bohlmann bands characteristic of the trans-axial arrangement of the 12bH and the lone pair of the neighbouring nitrogen. In the most likely conformation of **9a, b** the ester, of **10a, b** the ethyl group is close to the indol nucleus. This results in shielding of the appropriate protons. The $N_{ind}$–H is deshielded by the carbonyl group in **10a, b**.

The alcohol **9b** can be easily resolved with dibenzoyl tartaric acid.[10] Optical purity can be readily checked by NMR in the presence of an optishift reagent. Attempts at the racemisation of the undesired enantiomer were unsuccessful. We therefore attempted to improve the optical yield with the aid of asymmetric induction.

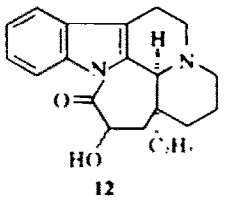
Pyruvic acid was esterified with (−)-menthol.[11] When the product was boiled with acetic anhydride, α-acetoxyacrylic acid (−)-menthyl ester was obtained. Addition to the enamine **1** proved successful, and after catalytic reduction, afforded about 41% of the desired enantiomer **9c**. The latter substance can be converted without isolation by boiling in a sodium methoxide/methanol system into the methyl ester **9b**. When processed appropriately, (−)-menthol can be recovered almost quantitatively. The product **9b** of about 40% optical purity can be converted by means of dibenzoyl tartaric acid into a completely optically pure product.

The addition reaction has also been carried out with α-acetoxyacrylic acid (−)bornyl ester, but in this case the optical yield was somewhat lower with maintenance of the desired direction of rotation.

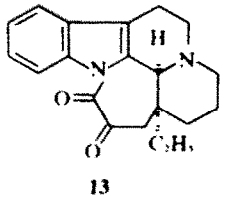


| | X | Y |
|---|---|---|
| **11a** | OH | $COOCH_3$ |
| **b** | $COOCH_3$ | OH |

**11a,b**



**12**



**13**

*Preparation of (+)-vincamine*

The ester **9b** can be converted in two ways into vincamine. Its direct oxidation can be performed in a pyridine—$SO_3$ + DMSO system,[9] but Fétizon's reagent[12] (silver carbonate/celite) has been found most convenient. In boiling toluene, it converts **9b** in good yield into a mixture of vincamine **11a** and epivincamine **11b**, while the oxidising agent is easily separated and can be recovered almost quantitatively.

Vincamine and epivincamine form an equilibrium mixture in toluene at about 100°C of about 80% vincamine and 20% epivincamine. According to our observations, the rate at which the equilibrium is established is catalysed by certain metal ions, while inhibited by other metal ions. $Ag^{I}$, $Hg^{I}$ and $Hg^{II}$ ions proved to be the best catalysts. In the presence of their salts, e.g. acetates, and preferably in a solvent, e.g. acetonitrile at the boiling point equilibrium is established in a few hours, whereas the presence of $Fe^{II}$ and particularly of $Zn^{II}$ ions inhibits epimerisation. One of the explanations of this phenomenon may be the following: According to Pearson's classification,[13] Ag and Hg ions belong to the group of soft acids, while $Fe^{II}$ and $Zn^{II}$ fall in the borderline region. The indole-nitrogen of vincamine is a soft base, reacting primarily with soft acids, which thus weakens the $N_{ind}$–$C_{14}$ bond, decreases the activation energy of the bond opening, and thereby catalyses the epimerisation. On the other hand, $Fe^{II}$ and $Zn^{II}$ ions are preferentially bound to the carbonyl oxygen or to the oxygen of the hydroxyl group, both of which are considered as hard bases; ring opening is thereby inhibited.

The epimerisation-accelerating action of Ag ions is also exerted during oxidation with Fétizon's reagent. When the toluene or xylene solution is further boiled after the termination of the reaction, the quantity of **11a** increases at the expense of **11b**. A rise in temperature shifts the equilibrium in the direction of vincamine. However, epimerisation can be carried out most readily in the sodium methoxide/methanol system, from which the less soluble vincamine crystals separate, so that the equilibrium gradually shifts.

The preparation of $MnO_2$/celite is described in the experimental part. This reagent, which is easier to filter off after the reaction than the usual activated $MnO_2$-reagents, was also found advantageous for the oxidation of **9b** in boiling toluene. The procedure yielded a mixture of **11a** and **11b** containing chiefly epi-vincamine. The subsequent epimerization with $NaOCH_3$/methanol gave vincamine in 64% yield. The yields by this method were not as consistent as those using the Fétizon-reagent.

In the other method of conversion of the ester alcohol **9b** into vincamine, **9b** was first cyclised with potassium *t*-butoxide. The hydroxylactame **12** formed is, similar to the substance prepared by Saxton, a mixture of the two diastereomers, in spite of the fact that **9a** is a stereochemically homogeneous compound. Thus, it is evident that the epimerisation of the carbon atom next to the carbonyl group is catalysed by the base. The configuration of the carbon atom adjacent to the hydroxyl group has not been investigated, as it is eliminated in the later course of the reaction. Oxidation of **12** with activated manganese dioxide gives **13**, the conversion of which into vincamine in the sodium methoxide/methanol system is already known.[14]

The above reactions can be realized with both the racemic and the optically active **9b**. Racemic vincamine can be resolved with dibenzoyltartaric acid, but naturally, the previous resolution of **9b** is preferred. The oxidation of vincamine with potassium dichromate and its subsequent reduction gave "*trans*-vincamine",[15] which also occurs naturally.

The C-3 epimer of **11b** was obtained in a similar way. The mass spectra of the four vincamine isomers differ markedly. This will be reported in detail in another communication.

Compound **9b** proved to be a versatile intermediate. Its use in the synthesis of other alkaloids will be discussed in our next communication.

## EXPERIMENTAL

IR spectra were recorded with a Spectromom spectrophotometer. The $^1$H-NMR spectra were obtained using a Perkin Elmer R12 (60 Mc) instrument; chemical shifts are reported in ppm ($\delta$) downfield from TMS. Mass spectra (MS) were recorded with an AEI MS 902 instrument (70 eV, ion source temperature 150°, direct insertion). M.ps are uncorrected.

*γ-Chloropropyl ethyl malonic acid diethylester* **3a**

To a solution of sodium (26.8 g; 1.16 mole) in abs. ethanol (500 ml) ethyl-malonic acid diethyl ester (219.6 g; 1.16 mole) was added. After stirring for a few minutes a solution of 1-bromo-3-chloropropane (186 g; 1.18 mole) in ethanol (100 ml) was added and the mixture stirred at room temp. for 0.5 h and thereafter boiled for 2 h under reflux. After removing half the ethanol the residue was diluted with water (500 ml) and extracted with benzene. Having evaporated the solvent the residue was fractionally distilled *in vacuo* to yield 180.1 g (58.8%) **3a**.[16] B.p. 104–108°/2 mmHg; $n_D^{25}$: 1.4421 (Found: C, 54.28; H, 8.02; Cl, 13.11. Calc. for $C_{12}H_{21}ClO_4$ (264.74): C, 54.43; H, 7.99; Cl, 13.39%) IR (neat): 1728 cm$^{-1}$ (C=O). $^1$H-NMR ($CCl_4$): 4.15 (4H, q, $-COOCH_2-$); 3.60 (2H, t, $-CH_2-Cl$); 1.25 (6H, t, $-COOCH_2-CH_3$); 0.82 (3H, t, $-CH_2-CH_3$).

*2-Ethyl-5-chloro-valeric acid methyl ester* **3b**

(A) **3a** (90.0 g; 0.342 mole) was boiled in aq. HBr (48%, 360 ml) under nitrogen for 30 h. After cooling the solution was extracted with benzene. Having removed the solvent the "crude acid" (62.2 g) was obtained. The "crude acid" (15.2 g) was boiled in a mixture of $CH_2Cl_2$ (60 ml), abs. methanol (10 ml) and *p*-toluenesulfonic acid monohydrate (1.0 g) for 31 h. After cooling the organic phase was separated, washed with aq. $Na_2CO_3$ (5%), water and dried. The solvent was removed and the residue distilled *in vacuo* to yield **3b** (11.5 g; 77.8%) as a colourless oil. Bp. 104–108°/11 mmHg. $n_D^{25}$: 1.4538. (Found: C, 53.43; H, 8.19; Cl, 19.57. Calc. for $C_8H_{15}ClO_2$ (178.65) C, 53.78; H, 8.46; Cl, 19.84). IR (neat): 1732 cm$^{-1}$ (CO). $^1$H NMR ($CCl_4$): 3.64 (3H, s, $-OCH_3$); 3.42 (2H, t, $-CH_2-Cl$); 2.44–2.13 (1H, m, $-CH$); 0.88 (3H, t, $-CH_3$).

(B) To a soln of **3a** (53.2 g; 0.2 mole) in abs. ethanol (140 ml) the soln of KOH (12.8 g; 0.23 mole) in the same solvent (140 ml) was added over a period of 1 h. After stirring for 2 h at room temp. the ethanol was removed *in vacuo* and the residue dissolved in water (50 ml), extracted with benzene (3 × 50 ml) to recover the unchanged starting material (35%). The water phase was acidified with 50% $H_2SO_4$ with cooling. The precipitated oil was separated and heated in a bath at 170–180° for 1.5 h. Distillation *in vacuo* gave **3b** (8.95 g, 23%) identical with the ester prepared according procedure A.

*Ethyl γ-hydroxy-propyl malonic acid* **3c**

γ-Chloropropyl ethyl malonic acid diethyl ester (200 g; 0.76 mole) and NaOH (100 g; 2.5 mole) were boiled in water–ethanol mixture (600 ml; 50%) for 0.5 h whilst stirring. After evaporating 300 ml of solvent the residue was boiled for further 0.5 h, cooled to 20° and acidified with conc hydrochloric acid to pH 1. The separated crystals were washed with water and dried, to yield **3c** (130 g; 84%), m.p. 129–130° [Found: C, 50.53; H, 7.37. Calc. for $C_8H_{14}O_5$ (190.19) C, 50.35; H, 7.30%.] IR (KBr): 1700, 1725 cm$^{-1}$ (C=O).

*2-Ethyl-5-pentanolid* **4**

The acid **3e** (19.0 g; 0.1 mole) was heated cautiously under stirring to 150–160° and after the evolution of gas ceases it was kept at that temp. for a further 0.5 h. Fractionation *in vacuo* gave 11.6 g (91%) **4**. B.p.: 128–132/16 mmHg. $n_D^{20}$: 1.4507. (Found: C, 65.74; H, 9.49. Calc. for $C_7H_{12}O_2$ (128.17): C, 65.59; H, 9.44%). IR (neat): 1740 cm$^{-1}$ (C=O). $^1$H NMR ($CCl_4$): 4.22 (2H, t, CO–O–$CH_2$–); 2.60–1.30 (7H, $-CH_2$–, CH–); 0.94 ppm (3H, t, $-CH_2$–$CH_3$).

*2-Ethyl-4-pentanolid* **5**

(A) A solution of **3a** (68.0 g; 0.257 mole) in a mixture of conc $H_2SO_4$ (175 ml) and water (120 ml) was boiled under nitrogen for 17 h. After cooling the dark solution was diluted with water (200 ml), and extracted with benzene. The organic phase was washed with aq. $NaHCO_3$ (5%), water and dried. After removal of the solvent the residue was fractionally distilled to yield **5** (23.8 g; 72.8%) as a colourless oil, b.p. 101–102°/14 mmHg. $n_D^{25}$: 1.4312. (Found: C, 65.62; H, 9.36. Calc. for $C_7H_{12}O_2$ (128.17): C, 65.59; H, 9.44.) IR (neat): 1765 cm$^{-1}$ (C=O).

**5** is a 1:1 mixture of diastereomers. For the GC separation and NMR assignments see ref. 6.

(B) The lacton **4** was treated with sulfuric acid as described above (A). **5** was obtained in 75.9% yield.

*N-α-Ethyl-δ-hydroxy-valeroyl-tryptamine* **7**

(A) A suspension of L-tryptophan (1.0 g; 4.91 mmole) in diphenyl-methane (40 ml) was heated under nitrogen in an oil-bath at 260–270°. After the $CO_2$ evolution had ceased (10–15 min) lactone **4** (0.95 g; 7.42 mmole) was added and the mixture boiled under reflux for 30 min. After cooling the red solution was diluted with benzene (250 ml). The precipitated crystals were filtered off after standing several hours and washed with $CH_2Cl_2$ to yield **7** (1.24 g; 88.2%), m.p. 72–74°. (Found: C, 70.52; H, 8.43; N, 9.55 Calc. for $C_{17}H_{24}N_2O_2$ (288.38): C, 70.80; H, 8.39; N, 9.71%). IR (KBr): 3260 (ind-NH); 1620 ($CONH_2$) cm$^{-1}$.

(B) A soln of tryptamine (16.0 g; 100 mmole) and **4** (12.8 g; 100 mmole) in xylene (100 ml) was boiled for 4 h. The mixture was kept in a refrigerator overnight as the precipitate filtered off (27.8 g) and recrystallized from dichloroethane (90 ml) to yield **7** (26.2 g; 90.8%). The white crystalline powder melted at 72–74°.

*1 - Ethyl - 1,2,3,4,6,7 - hexahydro - indolo[2,3 - a] - quinolizinium perchlorate*

(A) **7** (14.4 g; 50 mmole) was dissolved in $POCl_3$ (135 ml; 1.47 mole) and boiled for 8 h. After removal of the $POCl_3$ *in vacuo* the residue was dissolved in 1,2-dichloroethane. Under cooling and stirring water (60 ml) and aq. NaOH (40%) was added until the pH reached 11. The water was separated, washed with dichloroethane (20 ml) and the combined organic phase was dried and evaporated. The remaining red oil was dissolved in methanol (15 ml) and acidified with 70% perchloric acid until pH 5 was reached. After cooling overnight the crystals were separated yielding the desired salt (14.2 g; 80.8%) with m.p. 175–177° (lit.[4] 175–177.5°).

(B) Tryptamine (3.20 g; 20 mmole) and **3b** (1.80 g; 10.1 mmole) were dissolved in xylene (32 ml). $K_2CO_3$ (5.50 g; 39.8 mmole) powder was added to the soln and boiled for 72 h while after 16, 40 and 48 h 1.80 g. of **3b** were added. After cooling and filtering off and solid phase the xylene was removed *in vacuo*, the residue dissolved in benzene (50 ml) was washed with diluted acetic acid (1:1; 2 × 30 ml), water and dried. The benzene was distilled off until crystals began to separate at the bottom of the flask. After diluting with hexane and cooling overnight the while crystals of **2** (4.25 g; 78.8%) were filtered off, m.p. 123–125° (lit.[4] 124–126°).

The amide **4** was converted to the desired perchlorate according to Wenkert's method.[4]

(C) To the solution of tryptamine (4.80 g; 30 mmole) in **4** (7.80 g; 61 mmole) tryptamine·HCl (0.60 g; 3 mmole) was added. The mixture was slowly heated under nitrogen to 230–240° and kept at that temp. for 15 h while the water formed was continuously removed. Unchanged **4** was distilled off (3.45 g; 26.8 mmole) *in vacuo*. The residue was dissolved in benzene, extracted with 2N HCl (2 × 50 ml), washed with water, dried and evaporated. The work-up followed procedure B to yield **2** (4.35 g; 49.1%).

*1 - (2' - Acetoxy - 2' - methoxycarbonyl - ethyl) - 1 - ethyl - 1,2,3,4,6,7 - hexahydro - 12H - indolo[2,3a]aquinolizine - 5 - ium perchlorate* **8a**

To a soln of enamine **1** (7.09 g, 28.1 mmole) in $CH_2Cl_2$ (100 ml) α-acetoxy-methyl-acrylate (10.00 g, 69.4 mmole) and MeOH (1 ml) were added, and the reaction mixture was allowed to stand at room temp. for 2 days. The soln was evaporated *in vacuo* and the resulting oil was triturated with petroleum ether (3 × 50 ml). The residue was dissolved in MeOH (10 ml), and acidified with 70% $HClO_4$ aq. to pH 5 under ice-cooling. The separated salt was filtered off, washed with cold MeOH and ether to yield **8a** (8.40 g, 60%), m.p. 152–154° (Found: C, 55.40; H, 5.60; N, 5.90. Calc. for $C_{21}H_{29}ClN_2O_8$ (496.93): C, 55.58; H, 5.88; N, 5.63%). IR (KBr): 3480 (indole NH); 1740, 1736 ($OCOCH_3$, $CO_2CH_3$); 1630, 1525 cm$^{-1}$ (C=N).

*1 - (2' - Hydroxy - 2' - methoxycarbonyl - ethyl) - 1 - ethyl - 1,2,3,4,6,7 - hexahydro - 12H - indolo[2,3 - a]quinolizine - 5 - ium perchlorate* **8b**

A soln of **8a** (0.30 g, 0.6 mmole) in HCl–MeOH (10 ml; 0.16 g HCl per ml) was heated under reflux for 2 h, thereafter it was evaporated to dryness. The residue was dissolved in water (15 ml) treated with 5% $Na_2CO_3$ aq. to pH 8 and extracted with $CH_2Cl_2$ (3 × 15 ml). The organic layer was dried ($MgSO_4$), and concentrated *in vacuo*. The residual dark oil was dissolved in MeOH (5 ml), and acidified with 70% $HClO_4$ aq. to pH 6. The product was filtered off and recrystallised from MeOH to yield **8b** (0.20 g, 73%); m.p. 180–181° (Found: C, 55.49; H, 5.98; N, 6.08. Calc. for $C_{21}H_{27}ClN_2O_7$ (454.90): C, 55.44; H, 5.98; N, 6.15%). IR (KBr): 3450, 3360 (OH, indole NH); 1718 ($CO_2CH_3$); 1620, 1535 cm$^{-1}$ (C=N).

*1β - (2' - Acetoxy - 2' - methoxycarbonyl - ethyl) - 1α - ethyl - 1,2,3,4,6,7,12,12bα - hexahydro - and 12bβ - octahydro - indolo[2,3-a]quinolizine* **10a**

(A) To a stirred suspension of **8a** (2.00 g, 4.0 mmole) in MeOH (200 ml) $NaBH_4$ (0.40 g) was added portionwise at room temp. After the addition was complete, stirring was continued for 15 min. The mixture was acidified with AcOH to pH 6, and evaporated to dryness *in vacuo*. The residue was treated with 5% aq. $Na_2CO_3$ and extracted with ether. The organic layer was evaporated and the resulting oil (1.5 g) was separated by preparative TLC [silica gel, benzene–MeOH (14:3), $R_f$ **10a** > **9a**, elution with ether].

*Compound* **9a**. 0.55 g (34%); m.p. 144° (from MeOH). (Found: C, 69.58; H, 7.77; N, 7.06. Calc. for $C_{21}H_{30}N_2O_4$ (398.49): C, 69.32; H, 7.58; N, 7.03%). IR (KBr): 3410 (indole NH); 2780, 2740 (Bohlmann bands); 1750 ($OCOCH_3$); 1720 cm$^{-1}$ ($CO_2CH_3$). MS (*m/e*; %): 398 ($M^+$; 38); 397 (20.8); 268 (25); 267 (100); 197 (21.6); 170 (31); 169 (36). $^1$H NMR (δ; $CDCl_3$): 7.82 (1H, s, indole NH); 7.30 (4H, m, aromatic); 4.98 (1H, q, J 10, 2.4 cps, 2'-H); 3.60 (3H, s, $CO_2CH_3$); 3.48 (1H, s, 12bH); 2.05 ppm (3H, s, $OCOCH_3$), 1.22 (3H, t, J 7.0 cps, $-CH_2CH_3$).

*Compound* **10a**. 0.45 g (28%) (Found: C, 69.20; H, 7.35; N, 7.22. Calc. for $C_{21}H_{30}N_2O_4$ (398.49): C, 69.32; H, 7.58; N, 7.03%). IR (KBr): 3420 (indole NH); 2780, 2740 (Bohlmann bands); 1740 cm$^{-1}$ ($OCOCH_3$, $CO_2CH_3$). MS (*m/e*; %): 398 ($M^+$, 34.6); 396 (23.5); 268 (22.5); 267 (100); 170 (13.6); 169 (14). $^1$H NMR (δ, $CDCl_3$): 8.60 (1H, s, indole NH); 7.22 (4H, m, aromatic); 5.27 (1H, q, J 9.3, 2.6 cps, 2'-H); 3.80 (3H, s, $CO_2CH_3$); 3.29 (1H, s, 12bH); 2.00 (3H, s, $OCOCH_3$); 0.73 ppm (3H, t, J 7.0 cps, $-CH_2CH_3$). **10a** hydrochloride: m.p. 174° (MeOH-ether).

(B) to a prehydrogenated suspension of 10% Pd/C in MeOH (50 ml) a soln of **8a** (7.5 g; 15.1 mmole) in MeOH (350 ml) was added, and the suspension was stirred for 2 h under $H_2$. The catalyst was then removed by filtration, and the filtrate was evaporated to dryness. The resulting perchlorate, which could have been used for the next step without purification (7.00 g), was dissolved in 80% aq. acetone (35 ml) and the soln was treated with 15% aq. $NH_4OH$ to pH 8. The crystalline product was separated by filtration and recrystallised from MeOH to yield **9a** (4.70 g, 78%).

Preparative TLC of the mother-liquor (see above) yielded the isomer **10a** (0.40 g, 6.6%).

(±) - 1β - (2' - *Hydroxy* - 2' - *methoxycarbonyl* - *ethyl*) - 1α - *ethyl* - 1,2,3,4,6,7,12,12bα - **9b** *and* 12bβ - *octahydro* - *indolo*[2,3 - a]*quinolizine* **10b**

(A) Compound **8b** (2.00 g, 4.4 mmole) was hydrogenated over 10% Pd/C (1.0 g) in MeOH (100 ml). When the $H_2$ consumption had ceased, the catalyst was removed by filtration, the filtrate was evaporated. The residue was treated with 5% aq. $Na_2CO_3$ (50 ml), and extracted with $CH_2Cl_2$. The organic layer was dried ($MgSO_4$) and evaporated. The crude product was recrystallised from MeOH (50 ml) to yield **9b** (0.95 g, 61%); m.p. 234° (Found: C, 70.47; H, 7.92; N, 8.04. Calc. for $C_{21}H_{28}N_2O_3$ (356.45): C, 70.75; H, 7.91; N, 7.86%). IR (KBr): 3420 (OH, indole NH); 2820, 2720 (Bohlmann bands); 1742 cm$^{-1}$ ($CO_2CH_3$). MS (*m/e*; %): 356 ($M^+$; 23); 355 (12); 268 (24); 267 (100); 170 (10.5); 169 (12.8). $^1$H NMR (δ, $CDCl_3$): 7.85 (1H, s, indole NH); 7.26 (4H, m, aromatic); 4.38 (1H, 2, J 8.6, 4.4 cps, 2'-H), 3.60 (3H, s, $CO_2CH_3$); 3.36 (1H, s, 12bH); 1.10 ppm (3H, t, J 7.1 cps, $-CH_2-CH_3$).

The mother-liquor, which consisted of a mixture of **9a** and **10a** was subjected to preparative TLC (silica gel, $CH_2Cl_2$–MeOH (20:1); $R_f$ **9b** > **10b**, elution with acetone). **9b** 10.10 g; total yield: 1.05 g, 67%) and **10b** (0.20 g, 13%) were collected; m.p. 165–167°. (Found: C, 70.52; H, 7.78; N, 7.80. Calc. for $C_{21}H_{28}N_2O_3$ (356.45): C, 70.75; H, 7.91; N, 7.86%). IR (KBr): 3450, 3380 (indole NH, OH); 2800–2730 (Bohlmann bands); 1745 cm$^{-1}$ ($CO_2CH_3$). MS (*m/e*; %): 356 ($M^+$; 28); 355 (12.4); 268 (24); 267 (100); 169 (12.5). $^1$H NMR (δ, $CDCl_3$): 9.46 (1H, s, indole NH); 7.25 (4H, m, aromatic); 4.66 (1H, q, J 6.6, 2.6 cps, 2'-H); 3.87 (3H, s, $CO_2CH_3$); 3.62 (1H, s, 12bH); 0.66 ppm (3H, t, J 7.0 cps, $-CH_2-CH_3$).

(B) Compound **9a** (4.70 g; 11.7 mmole) was dissolved in HCl–MeOH (120 ml; 0.16 g HCl per ml), and the soln was refluxed for 2 h. The solvent was evaporated *in vacuo*, and the residue was dissolved in acetone (50 ml) and water (50 ml), thereafter the soln was treated with 5% aq. $Na_2CO_3$ to pH 8. The separated crystalline product was filtered off and washed with water to yield **9b** (3.57 g; 85%).

(C) Compound **10a** (1.00 g; 2.5 mmole) was refluxed in methanolic $NaOCH_3$ (30 ml; 54 mg Na) for 1 h. The $NaOCH_3$ was decomposed with AcOH, and the soln was evaporated to dryness *in vacuo*. The residue was suspended in 5% aq. $NaHCO_3$ and extracted with $CH_2Cl_2$. The solvent was dried ($MgSO_4$), evaporated under reduced pressure, and recrystallised from MeOH to yield **10b** (0.73 g; 82%).

( ) - 1α - *Ethyl* - 1β - (2' - *hydroxy* - 2' - *methoxycarbonyl* - *ethyl*) - 1,2,3,4,6,7,12,12bα - *octahydro* - *indolo*[2,3-a]*quinolizine* ( ) - **9b**

(+)-**9b** (2.20 g) was dissolved in $CH_2Cl_2$ (32 ml) and *D*-dibenzoyltartaric acid (2.20 g) in MeOH (4 ml) was added to the soln, and allowed to stand at 5° for 2 days. The crystalline product was separated by filtration, washed with cold $CH_2Cl_2$, dissolved in DMF (5 ml) treated with 15% aq. $NH_4OH$. The crystals were filtered off, washed with water, and recrystallised from DMF–water to yield (−)-**9b** (0.88 g, 40%), m.p. 235–237°. $[\alpha]_D^{20}$ −88° (c 1, $CHCl_3$).

*α-Acetoxyacrylic acid* (−)-*menthylester*

( )-Menthyl-pyruvate (38.00 g; 0.17 mole)[11] and *p*-TsOH (1.40 g) was refluxed in $Ac_2O$ (80 ml) under argone for 20 h. The $Ac_2O$ was removed *in vacuo*, and residue was separated by destillation to yield the titled compound (34.00 g; 79%); b.p. 118–120°/2 Hg mm. $n_D^{20}$ 1.4570. IR (KBr): 2960, 2930, 2880 ($CH_3$); 1760, 1720 (ester CO); 1642 cm$^{-1}$ (C–C). $^1$NMR (δ, $CDCl_3$): 6.08 (1H, d, J 3 cps, olefinic); 5.50 (1H, d, J 3 cps, olefinic); 4.90 (1H, m, 3-H); 2.25 ppm (3H, t, $OCOCH_3$). $[\alpha]_D$ − 78.4° (c 5.0, $CHCl_3$).

*Asymmetric synthesis of* **9b**

α-Acetoxyacrylic acid (−)-menthylester (17.2 g; 64.0 mmole) was added to the soln of enamine 1 (7.16 g; 28.4 mmole) in *t*-BuOH (90 ml). The mixture was allowed to stand at room temp. under argone for 3 days. The solvent was removed *in vacuo*, and the residue was treated with cold petroleum ether (200 ml) to remove excess reagent. The resulting red oil was hydrogenated in MeOH (200 ml) over 10% Pd/C. When the $H_2$ consumption ceased (460 ml), the catalyst was removed by filtration. $NaOCH_3$ (1.64 g) was added to the filtrate and the soln was refluxed under $N_2$ for 6 h. Thereafter the reaction mixture was cooled to 0°, and the crystalline product was collected by filtration, washed with cold MeOH to yield (±)-**9b** (2.60 g). The mother-liquor was acidified with 70% aq. $HClO_4$ to pH 5, and concentrated *in vacuo* to 30 ml. The crystalline ( )-**9b** perchlorate was filtered off, washed with MeOH, dissolved in DMF (5 ml), and treated with 15% aq. $NH_4OH$ to pH 9. The white crystals were separated by filtrated, washed with water to yield (−)-**9b** (1.50 g). $[\alpha]_D$ = −88° (c 1, $CHCl_3$). After the usual resolution of the (+)-**9b** with *D*-dibenzoyl-tartaric acid 1.04 g of (−)-**9b** was obtained. Total yield of (−)-**9b**: 2.54 g (25%). The preparative TLC (see above) of the crude product (200 mg) obtained from the trans-esterification gave a mixture of (+)-**9b** and (−)-**9b** (80 mg); $[\alpha]_D$ − 36° (c 1, $CHCl_3$). Optical yield: 41%.

(−)-*Epivincamine* (−)-**11b**

Compound (−)-**9b** (500 mg; 1.4 mmole) was refluxed with Fétizon-reagent ($Ag_2CO_3$–celite; 4.0 g) in dry benzene (32 ml) under stirring in $N_2$ atmosphere for 14 h. The reagent was removed by filtration, and the solvent was evaporated *in vacuo*. The crude product was separated by preparative TLC (alumina, Typ T; $CH_2Cl_2$/MeOH (100:0.2); elution with $CH_2Cl_2$/MeOH (100:5); $R_f$ **11a** > **11b**) to yield ( )-**11b** (250 mg; 50%); m.p. 187–188° (from ether). (Found: C, 71.30; H, 7.25; N, 7.80. Calc. for $C_{21}H_{26}N_2O_3$ (354.44): C, 71.16; H, 7.39; N, 7.90%). IR (KBr): 1750 cm$^{-1}$ ($CO_2CH_3$). MS (*m/e*; %): 354 ($M^+$; 77.5); 353 (41); 307 (41); 295 (21); 266 (10); 252 (100); 224 (20). $^1$H NMR (δ, $CDCl_3$): 7.22 (4H, m, aromatic); 4.37 (1H, s, OH); 3.66 (3H, s, $CO_2CH_3$), 0.84 (3H, t, J 7.0 cps, $-CH_2-CH_3$). $[\alpha]_D$ − −37.5 (c, 0.88, $CHCl_3$). When the reaction was carried out with (±)-**9b**, (±)-epivincamine was isolated; m.p. 210° (from MeOH).

*Preparation of $MnO_2$/celite reagent*

To a solution of $KMnO_4$ (19.2 g) in water (120 ml) purified celite[12] (18.0 g) was added. To the boiling suspension a solution of $MnSO_4 \cdot 4H_2O$ (22.2 g) in water (30 ml) and sodium hydroxide (40%, 23.4 ml) was added drop wise simultaneously and under vigorous stirring. After stirring for 1 h the solid phase was filtered off, washed with water until it became colourless, and dried in air. The reagent thus obtained (35.0 g) is hydrated, and can be stored without loss of activity. Dehydration was performed in two ways: (a) by azeotropic destillation with benzene, or (b) by drying at 110°. The dehydrated reagent can be stored under benzene.

(+)-*Vincamine* (±)-**11a**

(A) Compound (±)-**9b** (200 mg, 0.56 mmole) was stirred and heated under reflux in toluene (20 ml) with $MnO_2$–celite (1.3 g) for 25 h, and then the reagent was removed by filtration, washed with hot toluene. The filtrate was evaporated *in vacuo*. The residue was refluxed under $N_2$ in MeOH (5 ml) containing $NaOCH_3$ (20 mg) for 1 h. After cooling at 0° the crystalline product was filtered off, and washed with MeOH to yield (±)-**11a** (128 mg; 64%); m.p. 234–236° (from chlorobenzene). (Found: C, 71.00; H, 7.42; N, 7.75. Calc. for $C_{21}H_{26}N_2O_3$ (354.44): C, 71.16; H, 7.39; N, 7.90%). IR (KBr): 3400–2950 (strong, breit band, OH); 1750 cm$^{-1}$ ($CO_2CH_3$). MS (*m/e*; %): 354 ($M^+$; 100); 325 (14); 307 (31); 295 (45); 267 (51); 252 (87). $^1$H NMR (δ, $CDCl_3$): 7.27 (4H, m, aromatic), 4.60 (1H, s, OH); 3.93 (1H, s, 3-H); 3.80 (3H, s, $CO_2CH_3$); 0.90 ppm (3H, t, J 7.2 cps, $-CH_2-CH_3$).

(B) Compound (±)-**9b** (2.00 g; 5.61 mmole) was dissolved in hot xylene (100 ml), and Fétizon-reagent (8.0 g) was added to the soln, and the reaction mixture was refluxed and stirred under $N_2$ for 5 h. Thereafter the reagent was filtered off hot, washed with hot xylene, and the filtrate was cooled to 15°. The separated crystalline product was filtered off, washed with cold xylene to yield (±)-**11a** (1.50 g; 72%). The mother-liquor was evaporated to one-third of its original volume and cooled to −15°. A further 0.10 of crystalline (±)-**11a** was obtained (total yield: 1.60 g; 80%).

*(+)-Vincamine* (+)-**11a**

To a hot soln of compound (−)-**9b** (10.00 g; 28.0 mmole) in dry toluene (400 ml) Fétizon-reagent (50.0 g) was added. The reaction mixture was refluxed and stirred under $N_2$ for 6 h. Thereafter the reagent was removed by filtration, washed with hot toluene (3 × 50 ml), and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in dry MeOH (50 ml), and refluxed and stirred under $N_2$ with $NaOCH_3$ (1.17 g) for 2 h. After cooling to 0° the crystalline product was separated by filtration, washed with cold MeOH to yield (+)-**11a** (6.50 g; 65%), m.p. 234–235° (from chlorobenzene). $[\alpha]_D^{22} = +44°$ (c 1, pyridine).

*The 15-epimers (isomer "A" and "B") of (±)-cis-14-oxo-15-hydroxy-E-homo-eburnane* (±)-**12**

A soln of (±)-**9b** (5.00 g; 14.0 mmole) in dry toluene (500 ml) and acetophenone (5.0 g) was refluxed with *t*-BuOK (0.68 g) under $N_2$, and stirred for 4 h. The mixture was cooled to 0°, and extracted with cold 2.5% aq. $H_2SO_4$ (3 × 80 ml). The combined acidic layer was treated with conc $NH_4OH$ to pH 9, and extracted with $CH_2Cl_2$ (4 × 50 ml). The organic layer was dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The crude product (3.80 g) was recrystallised from MeOH (15 ml) to yield isomer "A" (3.10 g); m.p. 193–195°. (Found: C, 77.52; H, 7.48; N, 8.50. Calc. for $C_{20}H_{24}N_2O_2$ (324.41): C, 77.74; H, 7.45; N, 8.63%). IR (KBr): 3450 (OH); 1685 cm$^{-1}$ (amide CO). MS (*m/e*; %): 324 ($M^+$; 100); 323 (39); 296 (9); 295 (7.6); 280 (6.5); 267 (55); 265 (10); 252 (12).

The mother-liquor was separated by preparative TLC (silica gel, benzene/MeOH (14:3), $R_f$ isomer "A" > isomer "B", elution with ether) to yield further 0.10 g of isomer "A" (total yield: 3.20 g; 70%), and 0.36 g (7.9%) of isomer "B"; m.p. 164–165° (from MeOH) (Found: C, 77.80; H, 7.35; N, 8.58%). IR (KBr): 3400 (OH); 1670 cm$^{-1}$ (amide CO). MS *m/e*; %): 324 ($M^+$; 100); 323 (39); 296 (7.8); 295 (6.4); 280 (8); 267 (55); 265 (10); 252 (12).

When the reaction was carried out with (−)-**9b** (2.50 g), the isomer "A" of (+)-**12** was isolated as a hydrochloride (1.55 g; 61%); m.p. 250–252° (from MeOH). $[\alpha]_D^{20} = +52°$ (c 1.75, pyridine).

(±)-cis-14,15-*Dioxo*-E-homo-*eburnane* (+)-**13**

A soln of isomer "A" of (±)-**12** in $CH_2Cl_2$ (50 ml) was stirred with active $MnO_2$ (8.0 g) at room temp. for 5 h. The reagent was removed by filtration, washed with $CH_2Cl_2$. The filtrate was evaporated *in vacuo*, and the residue was recrystallised from ether to yield (±)-**13** (0.56 g; 70%); m.p. 156° (lit.[14]: 158°). (Found: C, 74.22; H, 7.02; N, 8.83. Calc. for $C_{20}H_{22}N_2O_2$ (322.40): C, 74.50; H, 6.87; N, 8.69%). IR (KBr): 1730 (CO); 1695 cm$^{-1}$ (amide CO). MS (*m/e*; %): 322 ($M^+$; 100); 294 (86.5); 266 (80); 252 (77); 237 (41); 197 (42); 169 (40); 168 (40.6).

Compound (+)-**12** ("A"-isomer; 0.40 g; 1.2 mmole) was oxidised with $MnO_2$ as described above to (+)-**13**, which was purified by preparative TLC (silica gel; benzene/MeOH (14:3); $R_f$ **13** > **12** > **11a**; elution with ether). Yield: 0.25 g; (63%); m.p. 116° (from ether); lit.[14] 118°. $[\alpha]_D = +80.3°$ (c 0.90, $CHCl_3$).

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