178. A New Enantioselective Total Synthesis of Natural Vincamine *via* an Intramolecular *Mannich* Reaction of an Silyl Enol Ether[1])

by **Wolfgang Oppolzer**[2]), **Hartmut Hauth, Paul Pfäffli** and **Roland Wenger**

SANDOZ Ltd., Pharmaceutical Division, Chemical Research, CH-4002 Basel

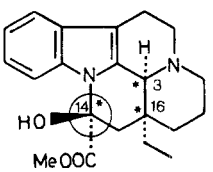
(18.III.77)

Summary

Natural Vincamine (**1**) has been synthesized in an enantioselective manner starting from the ethylpentenal **7**. In the key step a mixture of the diastereoisomeric racemates, **14** and **15**, was directly obtained from the silyl enol ether **11** and the dihydro-β-carboline **12** by way of an intramolecular *Mannich* reaction of the intermediate **13** *(Scheme 4)*. The undesired stereoisomers, **14** and **15b**, were recycled to **15a** using the related reversible *Mannich* reaction **18** $\rightleftarrows$ **14** + **15**, followed by crystallization of the salt from **15a** and (+)malic acid. **15a** was converted to natural vincamine (**1**) in several steps including the known transformation **20** $\rightarrow$ **1**.

1. Introduction. – Vincamine, the major alkaloid constituent of *Vinca minor* L. *(Apocyanaceae)*, was first isolated in 1953 [2]. Its structure, as depicted in **1**, follows from chemical, spectral [3] and X-ray evidence [4]. Over the past few years this

Scheme 1



1

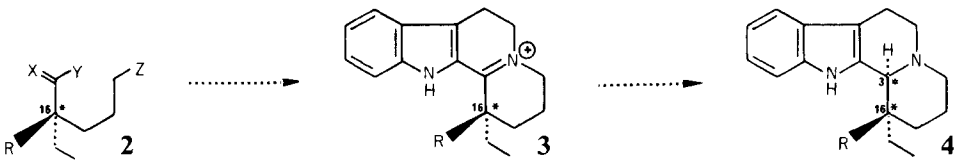
compound has been found to be potentially useful in the medical treatment of cerebral insufficiency in man [5]. Consequently several sterically nonselective [6] as well as stereocontrolled [7] syntheses of racemic **1** have been developed. Recently we reported the first total synthesis of optically pure natural vincamine [7c][3]) which

[1]) Presented by one of us (W.O.) at the University of Rochester, Harvard University and Columbia University in August 1975; see also [1].

[2]) Present address: Département de Chimie Organique, Université de Genève, CH-1211 Genève 4, where part of this work has been carried out.

[3]) For a partial synthesis of natural **1** from tabersonine see [8].

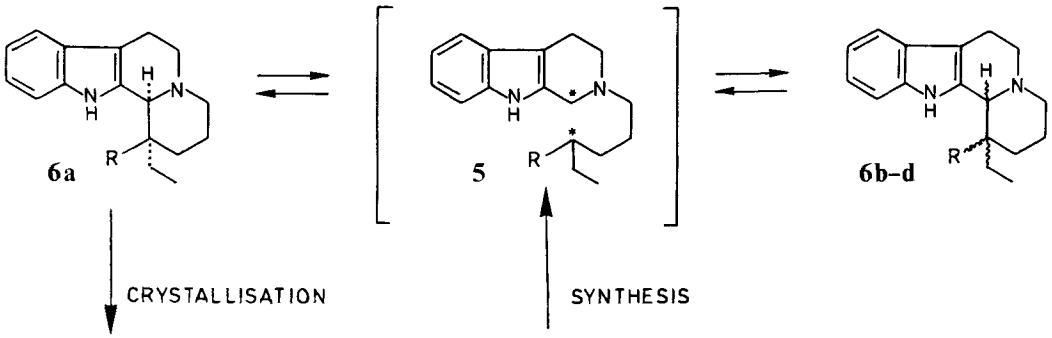
Scheme 2



involves an early key intermediate **2** containing the quaternary center C(16)[4]) with the natural chirality. During the reduction **3**→**4** center C(16) induces selectively the formation of center C(3) which, at a later stage, together with center C(16), controls the epimerizable center C(14)[5]) *(Scheme 2)*.

We now have accomplished a different enantioselective approach to natural vincamine *(Scheme 3)* in which the tetracyclic skeleton **6** is obtained *via* racemic

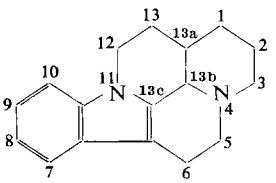
Scheme 3



intermediates; conversion of the undesired stereoisomers (**6b–d**) to the desired one (**6a**) was envisaged by a reversible cleavage of the C(3)–C(16)-bond, followed by selective crystallization of a suitable salt of **6a**.

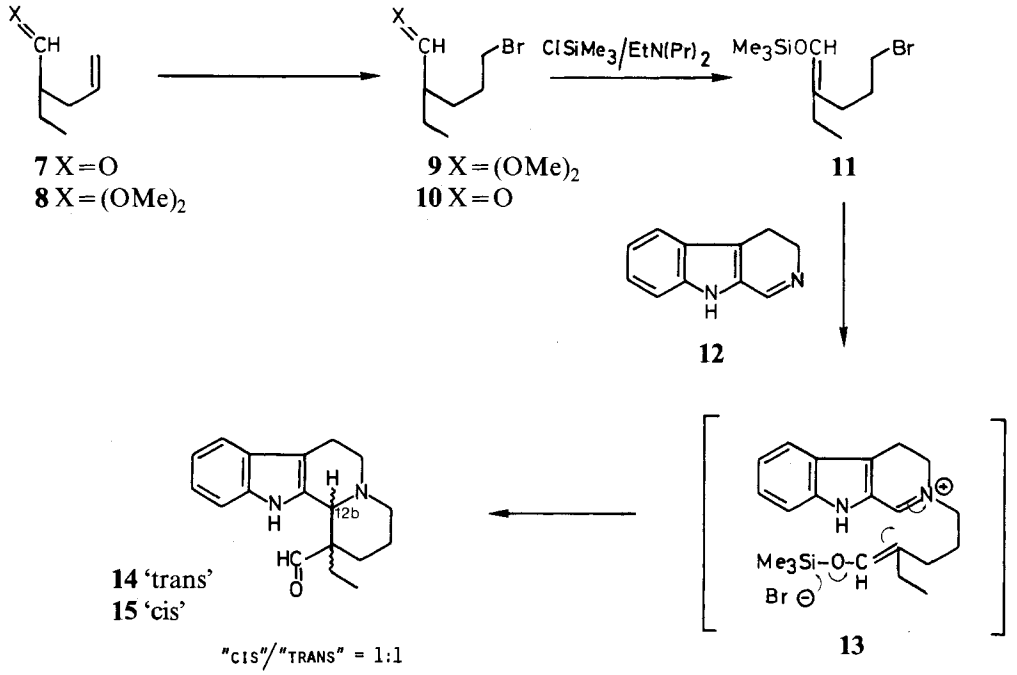
2. Preparation of the Tetracyclic Aldehydes *14* and *15* by an *Intramolecular Mannich* Reaction of the Silyl Enol Ether *13* *(Scheme 4)*. – Starting from the easily accessible ethylpentenal **7** [9] protection of the carbonyl group, hydroboration of the olefinic bond in **8**, bromination of the intermediate organoborane [10] and

[4]) The numbering of centers in the formulas **1**, **2**, **3**, and **4** corresponds to that proposed for vincamine (**1**) by *Trojanek et al.* [3] and actually used by Chemical Abstracts.
The IUPAC-numbering for the ring system of vincamine is as follows: (Ed.B.).



[5]) Epimerization of 14-epivincamine to vincamine via the α-ketoester **23** is easily achieved with sodium methoxide in methanol [7a]. Accordingly in any synthesis of **1** the stereochemical problem is confined to the assembly of the centers C(3) and C(16).

Scheme 4



hydrolysis of the acetal **9** furnished the bromoaldehyde **10** in 55% overall yield. After conversion of **10** to its silyl enol ether **11** [11] (85% yield) the latter was reacted with the dihydro-β-carboline **12** [12] in the presence of ethyldiisopropylamine in dimethylformamide at 70° for 64 h to obtain directly a (1:1)-mixture of the tetracyclic aldehydes **14** and **15** in 74% yield. The reaction apparently proceeds *via* initial alkylation of **12** by the bromide **11** to give the intermediate iminium salt **13**, which then undergoes an intramolecular *Mannich* reaction involving cleavage of the Si,O-bond and closure of the crucial C,C-bond. This first observation[1]) that silyl enol ethers may efficiently participate as enol equivalents in the *Mannich* reaction may be of general utility[6]). In this particular case the advantage of this modification over the classical one is clearly obvious: reaction of the free bromoaldehyde **10** with **12** leads to the cyclized aldehydes **14** and **15**[7]) in only 10% yield, compared to a yield of 74% from the silyl ether **11**.

However, both modifications furnished under kinetic control[8]) a (1:1)-mixture of the '*trans*'-racemate **14** (C_2H_5 and H–C(12b) *trans*) and the diastereoisomeric '*cis*'-racemate **15**.

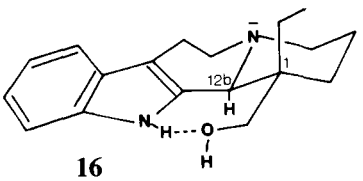
[6]) For the bimolecular addition of silyl enol ethers to dimethyl(methylene) ammonium iodide see [13]. *Mannich* reactions of enol borinates have been described earlier [14]. For electrophilic substitutions of silyl enol ethers see [15].

[7]) For the preparation of octahydroindolo[2,3-*a*]quinolizinones from **12** and conjugated enones *via* an intramolecular *Mannich* reaction see [16].

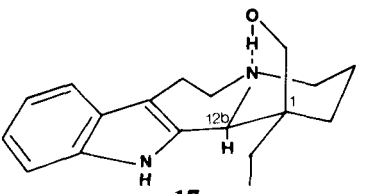
[8]) The isolated isomers **14** and **15** were not interconverted under the conditions of their formation.

3. Configurational Assignment of the Aldehydes *14* and *15*. – Both isomers **14** and **15** exhibit well-defined *Bohlmann* bands at 2750 and 2800 cm^{-1} in the IR.- as well as NMR.-signals of H–C(12b) at $\delta = 3.70$ and 3.57 ppm, indicating their *trans*-

Scheme 5



16

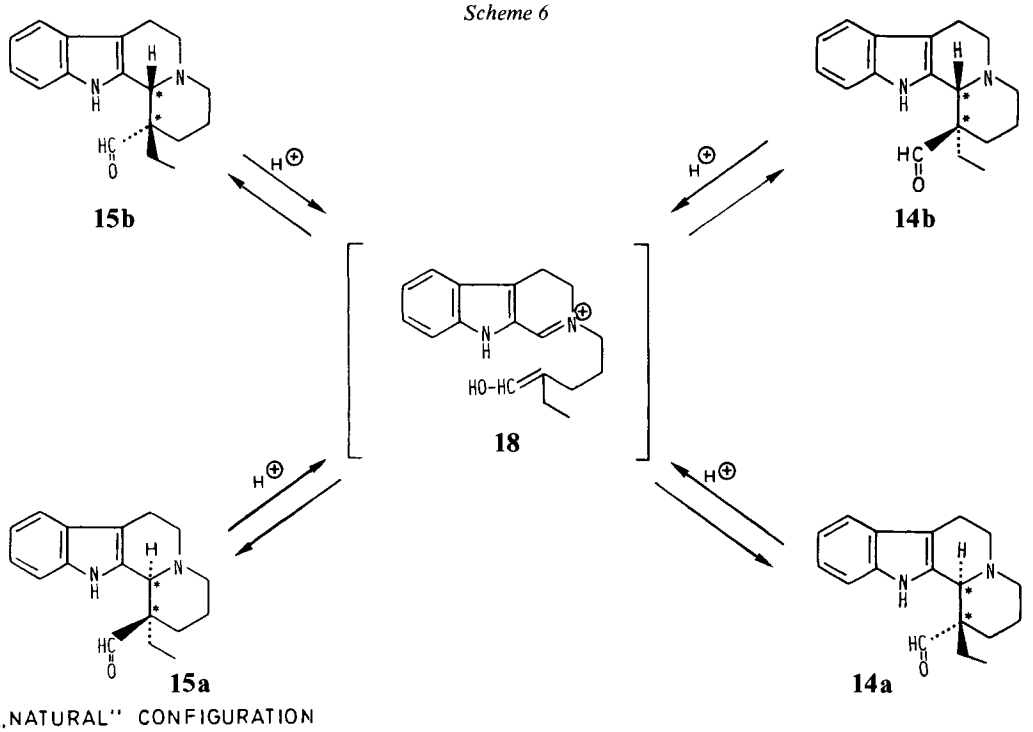


17

quinolizidine structures [17] [18]. In the ^{1}H-NMR. spectra the H_3C–C-signals of **14** and **15** appear at $\delta = 0.78$ and 1.02 ppm, respectively, showing for **15** an axial ethyl group and thus the desired *'cis'*-configuration [7c]. Similar ^{1}H-NMR.-derived arguments apply to the alcohols **16** and **17**, obtained by reduction of **14** and **15** with sodium borohydride. Further unambiguous stereochemical evidence is provided by the IR. spectra of **16** and **17**. Both alcohols show similar *Bohlmann* bands but significantly different OH- and NH-absorptions. Thus, **16** exhibits a sharp OH-band at 3600 cm^{-1}, whereas the slightly broadened NH-band is shifted to 3330 cm^{-1}; this agrees with an intramolecular hydrogen bonding of the NH-group indicating the *'trans'*-configuration of **16**. In contrast the *'cis'*-isomer **17** exhibits a sharp NH-band at 3500 cm^{-1}, but now the OH-hydrogen atom is subject to a strong intramolecular hydrogen bond as follows from a broad, concentration-independent band at 3300 cm^{-1}.

4. Separation and Interconversion of the Stereoisomeric Aldehydes *14* and *15* (*Scheme 6*). – Having arrived at an equimolar mixture of the four stereoisomers **14a**, **14b**, **15a**, and **15b** it now seemed appropriate to channel the synthetic pathway towards the single enantiomer **15a**. The racemates **14** and **15** were easily separated since the toluenesulfonic acid salt of the *'trans'*-racemate **14** crystallized selectively from dioxane, whereas the free base **15** is less soluble in ether than its isomer **14**. After heating the crystalline salt of the *'trans'*-racemate **14** in boiling dioxane for 30 min on cooling only half of the starting **14**-toluenesulfonate crystallized, the other half of the material was recovered from the mother liquor as the pure *'cis'*-racemate **15**. Hence it appears that the reversible *Mannich* reaction **14** + **15** ⇄ **18** leads to a (1:1)-equilibrium mixture of the isomers **14** and **15**. Accordingly conversion of the undesired *'trans'*-racemate **14** to the *'cis'*-racemate **15** required merely heating of the less soluble **14**-toluenesulfonate in dioxane, cooling and reheating of the separated crystals. The collected and evaporated mother liquors furnished, after crystallization of the free base, the pure 'cis'-racemate **15** (74% yield from the mixture obtained by way of **11**). Separation of the enantiomers **15a** and **15b** was accomplished by selective crystallization of the salt formed from (+)-malic acid with **15a**, whose absolute configuration follows from its conversion to natural vincamine as described below. The 'unnatural' enantiomer **15b** could be recycled by heating with 1 mol.-equiv. of toluene sulfonic acid in dioxane to give again a (1:1)-mixture of the racemates **14** and **15**. By this procedure the racemic mixture **14** + **15** was

Scheme 6



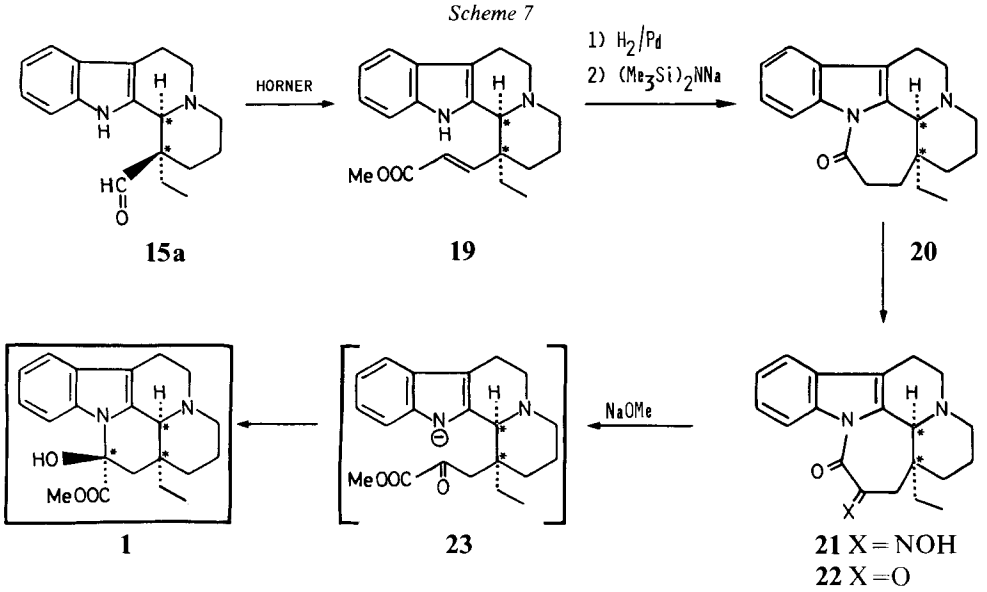
transformed to the desired enantiomer **15a** in 40% yield. Although it is conceivable, in analogy to an enantioselective synthesis of natural emetine[9]), to crystallize a suitable salt of **15a**, effecting a simultaneous equilibration with its isomers[10]), it appears to be preferable to proceed, as described above, by way of the pure racemate **15**.

5. Conversion of the Enantiomerically Pure Aldehyde *15a* into Vincamine *(1)* *(Scheme 7).* – After having solved the stereochemical problem, there remained the task to transform the aldehyde **15a** into natural vincamine. As one of the possible routes we envisaged as a key intermediate the lactam **20** since its conversion to vincamine is already known [6c]. Accordingly the aldehyde **15a** was subjected to a *Horner* reaction with ethylphosphonoacetate to obtain the acrylic ester **19** (86% yield). After catalytic hydrogenation of **19** treatment of the resulting saturated ester with sodium hexamethyldisilazane gave the seven-membered lactam **20** which was identical with a sample provided by *Roussel Uclaf*, Paris. Following the previously described procedure [6c], α-isonitrosation of **20** with amyl nitrite furnished the oxime **21**, which was cleaved to the α-ketolactam **22** with aqu. formal-

[9]) This approach to (–)-emetine involves stereoselective equilibration of a hexahydro-benzo[*a*]-quinolizone intermediate by way of a reversible *Mannich* reaction, accomplished in the presence of 1 mol.-equiv. of (+)-camphor-10-sulfonic acid [19].

[10]) In fact, the salt of **15a** with (+)-malic acid crystallized selectively (20% yield) from acetone in presence of equimolar quantities of **14a**, **14b** and **15b**.

Scheme 7



dehyde/HCl. However, it seemed to be more appropriate to effect the deoximation **21** → **22** with ceric ammonium nitrate [20] in methanol[11]). Methanolysis of the lactam **22** with sodium methoxide in methanol finally afforded natural vincamine **1**. Using the same route d,l-vincamine was obtained from the racemic *'cis'*-aldehyde **15**.

We are indebted to Dr. *J. Weill-Raynal, Roussel Uclaf* for kindly providing a sample of the enantiomerically pure lactam **20**. We also wish to thank *K. Baettig* and *G. Würtele* for their able experimental assistance and Mrs. *F. Klöti* for carrying out the mass spectroscopic measurements. Financial support by the *Fonds National Suisse de la recherche scientifique* and by the *Sandoz Ltd*, Basel, concerning the work carried out in Geneva is gratefully acknowledged.

Experimental Part

General remarks. – Preparative chromatography was carried out on silica gel (*Merck*, 0.05–0.20 mm). Melting points (m.p.) are not corrected. UV. spectra: λ_{max} in nm. log ε in parentheses. IR. spectra: in CH_2Cl_2 unless specified otherwise: $\tilde{\nu}_{max}$ in cm^{-1}. ^{1}H-NMR. spectra: in $CDCl_3$ unless specified otherwise, internal standard tetramethylsilane ($\delta = 0$ ppm); abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, *J* = spin-spin coupling constant (Hz). Mass spectra (MS.): *m/e*, relative peak intensity in % in parentheses. Satisfactory elemental analytical (C, H, N) or MS.-data were obtained for all compounds reported herein.

Preparation of the Tetracyclic Aldehydes *14* and *15* (*Scheme 4*). *2-Ethyl-4-pentenal dimethylacetal* (8). A mixture of 2-ethyl-4-pentenal (7) (44.8 g), *p*-toluenesulfonic acid (11.2 g), trimethyl orthoformate (55.0 g) and methanol (50 ml) was stirred at 25° for 60 h and then shaken with pentane/aqu. saturated $NaHCO_3$ solution. The organic layer was dried and evaporated to give a viscous residue which, after filtration through SiO_2 (120 g, ether), furnished the 2-ethyl-4-pentenal dimethylacetal (**8**) (51.3 g, 81%) as a colourless oil. – IR. (film): no OH, no C=O, 1145, 1115, 1080, 1065, 1000, 970, 816. – ^{1}H-NMR. (60 MHz): 0.70 (*t*, *J* = 6.0, 3H); 0.9–1.7 (*m*, 2H); 1.93 (*m*, 2H); 3.13 (*s*, 6H); 3.94 (*d*, *J* = 5.5, 2H); 4.5–5.0 (2H); 5.2–6.0 (1H). – MS.: no $C_9H_{18}O_2^+$-peak, 127 (9), 97 (16), 95 (13), 75 (100).

[11]) Partial formation of vincamine (**1**) was observed under these conditions.

5-Bromo-2-ethyl-pentenal (**10**). A 1N solution of diborane in tetrahydrofurane (196 ml) was added dropwise under an argon atmosphere to a stirred solution of 2-ethyl-4-pentenal dimethylacetal (**8**) (85 g) in tetrahydrofurane (65 ml) at 0°. After stirring the reaction mixture at 0° for 30 min and at 25° for a further 30 min methanol (1.7 ml) was added. To the cooled (ice-bath) and stirred mixture bromine (92 g in 90 ml CCl_4) and a 5N solution of sodium methoxide in methanol (122 ml) were added simultaneously at a rate such that the reaction mixture was always slightly yellow and that its temperature never rose above 5°. Then the solution was shaken with pentane/2N aqu. K_2CO_3. The organic layer was dried and evaporated to afford an oily residue which after filtration through SiO_2 (200 g, benzene) furnished the 5-bromo-2-ethylpentanal dimethylacetal (**9**) as a colourless unstable oil (119 g, 92%) containing variable amounts of the free aldehyde **10**. A mixture of the so obtained crude **9** (237 g), tetrahydrofurane (700 ml) and 3N aqu. $HClO_4$-solution (1.1 l) was stirred at 25° for 45 min, saturated with solid $NaHCO_3$ and then extracted with CH_2Cl_2. Evaporation of the dried extracts and distillation of the residue furnished the bromoaldehyde **10** as a colourless oil (140 g, 68% from **8**), b.p. 60°/0.2 Torr. – IR. (film): 2710, 1730. – ^{1}H-NMR. (60 MHz): 0.93 (*t*, *J*=7, 3H); 1.3–2.4 (7H); 3.42 (*m*, 2H); 9.6 (*d*, *J*=2.5, 1H). – MS.: no $C_7H_{13}BrO^+$-peak, 166 (9), 164 (9), 113 (44), 83 (38), 72 (32), 57 (100), 55 (85), 43 (53), 41 (50).

5-Bromo-2-ethyl-1-trimethylsilyloxy-1-pentene (**11**). A solution of the bromoaldehyde **10** (18 g), chlorotrimethylsilane (13.4 g) and ethyldiisopropylamine (32.0 g) in dimethylformamide (46 ml) was heated at 110° under argon for 15 h. The reaction mixture was diluted with pentane, washed rapidly with cold aqu. 1N HCl and then with cold aqu. $NaHCO_3$-solution. Evaporation of the dried solution and distillation of the residue furnished the silyl enol ether **11** (mixture of *(E)*- and *(Z)*-isomers) as a colourless oil (21.0 g, 85%), b.p. 63°/0.6 Torr. – IR. (film): no OH, no C=O, 1670, 1260, 1177, 885, 850. – ^{1}H-NMR. (60 MHz): −0.2 (4.5H); 0.0 (4.5H); 0.77 (*t*, *J*=6.5, 1.5H); 0.81 (*t*, *J*=6.5, 1.5H); 1.2–2.2 (6H); 3.33 (*t*, *J*=6.5, 2H); 5.9 (br. *s*, 1H). – MS.: no $C_{10}H_{21}BrOSi^+$-peak, 220 (10), 157 (72), 148 (15), 147 (94), 83 (13), 75 (31), 73 (100), 72 (19).

3,4-Dihydro-9H-pyrido[3,4-b]indole (**12**)[12]. N-Formyltryptamine [21], m.p. 80–82° (ether, 10 g) was added portionwise to vigorously stirred and cooled $POCl_3$ (50 g) at such a rate that the temperature of the mixture remained between 5 and 10°. Stirring of the ice-cooled mixture for a further 30 min, dilution with ether (30 ml) and filtration furnished the crystalline hydrochloride of **12**, which was washed with ether and then shaken with ice/1N NaOH/CH_2Cl_2. Evaporation of the dried organic layer furnished a solid residue which was dissolved in a small amount of boiling CH_2Cl_2. After addition of boiling ether (250 ml) the solution was filtered and concentrated to a volume of 100 ml to give pure crystalline **12** (4.0 g, 45%), m.p. 99–101°. – IR.: 3200 br., 1560, 1340, 1175, 996. – ^{1}H-NMR. (60 MHz): 2.15–3.1 (3H); 3.3–4.1 (2H); 6.9–7.7 (4H), 8.25 (br. *s*, 1H).

(1RS,12bRS)-1-Ethyl-1,2,3,4,5,6,7,12b-octahydro-indolo[2,3-a]quinolizine-1-carbaldehyde (**14**) *and (1RS,12bSR)-1-Ethyl-1,2,3,4,5,6,7,12b-octahydro-indolo[2,3-a]quinolizine-1-carbaldehyde* (**15**). A mixture of the silyl enol ether **11** (1.59 g, 6 mmol), dihydro-β-carboline **12** (1.53 g, 9 mmol), ethyldiisopropylamine (1.16 g, 9 mmol) and dimethylformamide was heated under an argon atmosphere at 70° for 64 h. The mixture was then shaken with aqu. $NaHCO_3$/CH_2Cl_2 and filtered through *Celite*. The dried and evaporated organic layer was filtered through SiO_2 (10 g, toluene/ethylacetate 9:1). Evaporation of the filtrate and crystallization of the residue (1.5 g) from ether furnished a first crop of the racemic *'cis'*-aldehyde **15** (440 mg, 25%), m.p. 149–153°. – IR.: 3490, 2810, 2755, 1714. – UV. (methanol): 224 (4.55), 282 (3.92), 290 (3.83). – ^{1}H-NMR. (100 MHz): 1.02 (*t*, *J*=7.5, 3H); 1.15–2.10 (5H); 2.1–3.2 (7H); 3.57 (*s*, 1H); 6.7–7.6 (4H); 7.88 (*s*, 1H); 9.38 (*d*, *J*=1.5, 1H). – MS.: 282 ($C_{18}H_{22}N_2O^+$, 40), 281 (31), 267 (28), 253 (15), 197 (56), 170 (100), 169 (74). Crystallization of the mother liquor (ether/pentane) furnished a second crop of colourless crystals (810 mg, 49%, total yield of **14**+**15**=74%), constituting a mixture of the diastereoisomeric racemates **14** and **15**, which was dissolved in dioxane (8 ml); after addition of toluenesulfonic acid (550 mg) crystallization afforded the pure toluenesulfonate of **14** (940 mg); the mother liquor contained mainly **15**. For characterization a sample of the **14**-toluenesulfonate was shaken with aqu. 1N NaOH/CH_2Cl_2. Evaporation of the dried organic layer followed by crystallization (ether/pentane) gave the racemic *'trans'*-aldehyde **14**, m.p. 111–113°. – IR.: 3460, 2810, 2755, 1716. – UV. (methanol): 223.5 (4.53), 282 (3.89), 290 (3.80). – ^{1}H-NMR. (100 MHz): 0,78 (*t*, *J*=7.5, 3H); 1.1–2.1 (6H); 2.1–3.2 (6H); 3.70 (*s*, 1H); 6.8–7.7 (4H); 8.09 (*s*, 1H); 9.73 (*s*, 1H).

[12]) We thank Prof. *E. Winterfeldt* for suggesting to us this modified procedure [12].

(1RS,12bRS)-1-Ethyl-1-hydroxymethyl-1,2,3,4,5,6,7,12b-octahydro-indolo[2,3-a]quinolizine (**16**) *and (1RS,12bSR)-1-Ethyl-1-hydroxymethyl-1,2,3,4,5,6,7,12b-octahydro-indolo[2,3-a]quinolizine* (**17**) *(Scheme 5).* A mixture of the *'trans'*-aldehyde **14** (50 mg), $NaBH_4$ (10 mg) and ethanol (1 ml) was heated at 50° for 2 h and then evaporated. Shaking the residue with aqu. $NaHCO_3$-solution/CH_2Cl_2, evaporation of the dried organic layer and crystallization of the residue (CH_2Cl_2/pentane) furnished the *'trans'*-alcohol **16** (44 mg, 88%), m.p. 220–222°. – IR.: 3600, 3300, 2800, 2750 (no change in 0.03% solution). – ^{1}H-NMR. (100 MHz, d-DMSO): 0.63 (*t*, *J* = 7, 3H); 0.8–2.0 (6H); 2.0–3.1 (6H); 3.28 (*s*, 1H); 3.50 (*d* × *q*, *J* = 11 and 4.5, 2H); 5.70 (*t*, *J* = 4.5, 1H); 6.7–7.1 (2H); 7.1–7.5 (2H); 10.7 (*s*, 1H). The *'cis'*-aldehyde **15** (10 mg) was reduced with $NaBH_4$ as described above to give the *'cis'*-alcohol **17** (9 mg, 90%), m.p. 224–225°. – IR.: 3500*s*, 3300 br., 2850, 2800, 2750 (no change in 0.2% solution). – ^{1}H-NMR. (100 MHz, d-DMSO): 1.02 (*t*, *J* = 7, 3H); 0.8–2.1 (6H); 2.2–3.0 (6H); 3.1 (*d*, *J* = 10.5, 1H); 3.38 (*s*, 1H); 3.64 (*d*, *J* = 10.5, 1H); 4.72 (*s*, 1H); 6.8–7.2 (2H); 7.2–7.5 (2H); 9.75 (*s*, 1H).

Conversion of the Racemic Aldehydes *14* and *15* to (–)-*15a*. *(Scheme 6). – Conversion of* the *'trans'-Racemate* **14** *to the* 'cis'-*Racemate* **15**. A solution of the crystalline **14**-toluenesulfonate (1.68 g) in boiling dioxane (100 ml) was heated under reflux under argon for 45 min, concentrated to 10 ml and then seeded with crystalline **14**-toluenesulfonate. The separated crystals were again heated in dioxane (45 ml) under reflux and under argon for 45 min and then concentrated to 5 ml to give again a crop of crystalline **14**-toluenesulfonate (44 mg). The combined and evaporated mother liquors were shaken with aqu. 1N NaOH/CH_2Cl_2. Evaporation of the dried organic layer and crystallisation of the residue (ether) gave the pure *'cis'*-racemate **15**, m.p. 149–153° (600 mg, 60%); the mother liquor (m.l. II, 215 mg) was recycled as described below.

Separation of the Optically Pure (1R,12bS)-1-Ethyl-1,2,3,4,5,6,7,12b-octahydro-indolo[2,3-a]-quinolizine-1-carbaldehyde **15a** *and Recyclization of its Stereoisomers.* A solution of (+)-malic acid (804 mg) in acetone (3 ml) was added to a solution of the *'cis'*-racemate **15** (1.69 g) in acetone (8 ml) at 25°. After seeding crystallization afforded, apart from the mother liquor (m.l. III, 670 mg), reddish crystals (1.85 g) which were dissolved in cold methanol (12 ml). The solution was filtered through charcoal, concentrated i.V. at 20°, diluted with acetone (5 ml) and seeded to give, apart from the mother liquor (m.l. IV, 650 mg), the optically pure salt of (+)-malic acid with **15a** (1.0 g, 80%), m.p. 150–152°, $[\alpha]_D^{20°} = -131.8°$ (*c* = 0.5, DMF). These crystals were shaken with an excess of aqu. $NaHCO_3$-solution/CH_2Cl_2. Evaporation of the dried organic layer and crystallization of the residue furnished the enantiomerically pure (–)-**15a** (640 mg), m.p. 140–142°, $[\alpha]_D^{20°} = -178.5°$ (*c* = 0.5, DMF). The combined mother liquors III and IV were converted to the free base (870 mg) which was heated with toluenesulfonic acid (570 mg) in boiling dioxane (40 ml) until the mixture showed no optical rotation (2h). The evaporated solution was shaken with 1N NaOH/CH_2Cl_2. The dried and evaporated organic layer was filtered through SiO_2 (toluene/ethyl acetate 9:1) to give an equimolar mixture of the racemates **14** and **15** (559 mg); this mixture was combined with the mother liquor I and with the equilibrated mother liquor II and recycled to enantiomerically pure **15a** as described above (total yield of **15a** from the racemic (1:1)-mixture of **14** + **15** = 40%).

Transformation of the Enantiomerically Pure Aldehyde (–)-*15a* to Natural Vincamine *(1)* *(Scheme 7). – (1S,12bS)-1-Ethyl-1,2,3,4,5,6,7,12b-octahydro-indolo[2,3-a]quinolizine-1-acrylic acid ethylester* (**19**). Triethyl phosphonoacetate (680 mg) was stirred with sodium hydride (100 mg, washed with pentane) in dimethylformamide (8 ml) under argon at –10° until the gas evolution had stopped. Addition of the (–)-aldehyde **15a** (500 mg), heating the solution at 60° for 4 h and evaporation (0.2 Torr) furnished a viscous residue which was shaken with ether/water. The dried and evaporated organic layer was stirred with SiO_2 (400 mg) in benzene/ethyl acetate 3:1 to give, after filtration and evaporation of the filtrate, the ethyl acrylate **19** as a viscous residue (534 mg, 86%), $[\alpha]_D^{20} = -166°$ (*c* = 0.94, DMF). – IR.: 3500, 2800, 2750, 1710, 1645, 1033. – ^{1}H-NMR. (100 MHz): 0.99 (*t*, *J* = 7.5, 3H); 0.8–3.2 (15H); 3.57 (*s*, 1H); 4.11 (*q*, *J* = 7, 2H); 5.80 (*d*, *J* = 16, 1H); 6.99 (*d*, *J* = 16, 1H); 6.9–7.6 (4H); 7.82 (*s*, 1H). – MS.: 353 (21), 352 ($C_{22}H_{28}N_2O_2^+$, 100), 351 (83), 337 (15), 323 (13), 307 (15), 265 (16), 198 (16), 197 (90). (rac.)-**19**, m.p. 145–157° (ether/pentane).

D-*Homoeburnamonine* (**20**). A solution of the (–)-ethylacrylate **19** (504 mg) in ethanol (15 ml) was stirred with Pd/C (10%, 80 mg) under hydrogen for 16 h. Filtration of the mixture, evaporation of the filtrate and crystallization of the residue (ether/pentane) furnished the (1*S*, 12b*S*)-1-Ethyl-1,2,3,4,5,6,7-12b-octahydro-indolo[2,3-*a*]quinolizine-1-propionic acid ethyl ester (347 mg, 68%), m.p. 100–101°, $[\alpha]_D^{20} = -136.4°$ (*c* = 1.1, DMF). – IR.: 3500, 2800, 2750, 1726. – ^{1}H-NMR. (100 MHz): 1.0–3.2 (22H);

3.35 (*s*, 1H); 4.01 (*qa*, $J=7$, 2H); 7.0–7.6 (4H); 7.84 (*s*, br., 1H). – MS.: 354 ($C_{22}H_{30}N_2O_2^+$, 5), 353 (5), 341 (15), 340 (83), 339 (81), 325 (9), 309 (10), 268 (23), 267 (100), 197 (35). The (1*RS*,12b*RS*)-1-ethyl-1,2,3,4,5,6,7,12b-octahydro-indolo[2,3-*a*]quinolizine-1-propionic acid ethyl ester, prepared from the (rac.)-ethylacrylate **19** melts at 134–136° (ether/pentane). A 1.9M solution of sodium bistrimethylsilylamide in toluene (6.4 ml) was added under N_2 to a solution of (–)-(1*S*, 12b*S*)-1-ethyl-1,2,3,4,5,6,7-12b-octahydro-indolo[2,3-*a*]quinolizine-1-propionic acid ethyl ester (1.28 g) in dioxane (26 ml) at +5°. Stirring the mixture at 25° for 2 h, shaking with aqu. $NaHCO_3$-solution/ether, evaporation of the dried ether layer and crystallization of the residue furnished the enantiomerically pure (+)-lactam **20** (920 mg, 83%), m.p. 154–155°. $[\alpha]_D^{20} = +20.7°$ ($c=1.0$, DMF). – IR.: 1700. – ^{1}H-NMR. (100 MHz): 0.88 (*t*, $J=7$, 3H); 0.9–3.5 (16H); 4.40 (*s*, 1H); 7.1–7.5 (3H); 8.42 (*m*, 1H). – MS.: 309 (21), 308 ($C_{20}H_{24}N_2O^+$, 100), 307 (61), 280 (11), 279 (12), 252 (21), 251 (20), 237 (10). The thus obtained (+)-lactam **20** was shown to be identical with a sample provided by *Roussel Uclaf* on the basis of a mixed m.p. and the specific rotation. (rac.)-**20**, m.p. 163–166° (ether).

(D)-*15-Hydroximino-homoeburnamonine* (**21**)[13]. *t*-Butylnitrite (1.1 ml) followed by a 2N sodium bistrimethylsilylamide in toluene (0.54 ml) was added to a solution of the (+)-lactam **20** (130 mg) in toluene (0.8 ml). Stirring of the mixture at 50° for 1.5 h, shaking with toluene/10% aqu. NH_4Cl, evaporation of the dried organic layer and chromatography of the residue (0.7 g SiO_2, benzene/ethyl acetate 3:1) furnished the oxime **21** as a non-crystalline foam (96 mg, 68%). $[\alpha]_D^{20} = +30.5°$ ($c=1.0$, DMF). – IR.: 3600, 3300 br., 1700. – ^{1}H-NMR. (100 MHz): 0.8–3.6 (18H); 4.03 (*s*, br., 1H); 7.1–7.5 (3H); 8.37 (*m*, 1H). – MS.: 337 ($C_{20}H_{23}N_3O_2^+$, 59), 336 (34), 320 (29), 308 (30), 307 (100), 293 (24), 292 (63), 251 (23). (rac.)-**21**, m.p. 230–236° (ether).

D-*Homoeburnamonin-15-one* (**22**)[13]. a) A mixture of the (+)-oxime **21** (165 mg), 40% aqu. formaldehyde (850 mg), conc. aqu. hydrochloric acid (0.4 ml) and water (0.5 ml) was heated under N_2 at 70–80° for 30 min and then shaken with an excess of aqu. $NaHCO_3$-solution/CH_2Cl_2. Evaporation of the dried organic layer and chromatography of the residue (3 g SiO_2, toluene/ethyl acetate 3:1) furnished the ketone **22** (44 mg, 28%). m.p. 116–118° (ether). – IR.: 1730, 1700. – ^{1}H-NMR. (100 MHz): 0.95 (*t*, $J=7.3$, 3H); 0.9–2.0 (6H); 2.0–3.8 (8H); 4.1 (*s*, 1H); 7.2–7.4 (3H); 8.5 (*m*, 1H). – MS.: 322 ($C_{20}H_{22}N_2^+$, 13), 321 (9), 294 (38), 293 (32), 266 (23), 265 (23), 237 (54), 235 (38), 197 (22), 180 (18), 170 (19), 169 (28), 167 (22), 156 (32), 155 (38), 141 (18), 130 (16), 129 (100), 128 (64), 127 (16), 115 (35). (rac.)-**22**, m.p. 150–155° (ether). Further elution afforded the unchanged more polar oxime **21** (30 mg, 18%).

b) A solution of the (+)-oxime **21** (50 mg) in methanol (3 ml) was added at –30° to a stirred solution of ceric ammonium nitrate (125 mg) in methanol. Stirring of the mixture at –20° for 10 min, shaking with aqu. $NaHCO_3$-solution/CH_2Cl_2, evaporation of the dried organic layer and chromatography of the residue gave the ketone **22** (14 mg, 29%), $[\alpha]_D^{20} = +40.2°$ ($c=0.6$, DMF) and the more polar natural vincamine (8 mg, 16%), m.p. 225–228° (CH_2Cl_2/ether).

Natural Vincamine (**1**). The (+)-ketone **22** (10 mg) was dissolved in a solution of sodium (5 mg) in methanol (1 ml). Stirring of the mixture under argon at 25° for 1 h, acidification to pH=4 with acetic acid, evaporation, shaking of the residue with aqu. $NaHCO_3$-solution/CH_2Cl_2, evaporation of the dried organic layer and crystallization of the residue (CH_2Cl_2/ether) gave the natural vincamine (**1**) (7 mg, 63%), m.p. 227–230°, $[\alpha]_{436\,nm}^{23} = +21.3°$; $[\alpha]_{364\,nm}^{23} = +127°$ ($c=0.5$, $CHCl_3$). – MS.: 355 (29), 354 ($C_{21}H_{26}N_2O_2^+$, 100), 353 (40), 339 (7), 325 (5), 307 (12), 295 (36), 284 (12), 267 (39), 252 (75). The m.p. of the synthetic alkaloid **1** was not depressed on admixture with an authentic sample which exhibited the same IR., ^{1}H-NMR. [7c] and mass-spectra. (rac.)-vincamine (**1**). m.p. 235–239° (CH_2Cl_2/ether).

[13]) For numbering see Footnote [4]).

REFERENCES

[1] *W. Oppolzer,* Deutsche Offenlegungschrift 2318329 (1973); French Patent, application 7620771.

[2] *E. Schlittler & A. Furlenmeier,* Helv. *36,* 2017 (1953).

[3] *J. Trojánek, O. Štrouf, J. Holubek & Z. Čekan,* Tetrahedron Letters *1961,* 702; *J. Mokrý, I. Kompiš & P. Šefčovič,* ibid. *1962,* 433; *O. Clauder, K. Gesztes & K. Szász,* ibid. *1962,* 1147; *J. Mokrý, M. Shamma & H. E. Soyster,* ibid. *1963,* 999; *J. Mokrý & I. Kompiš,* Lloydia *27,* 428 (1964); *J. Trojánek, Z. Koblicová & K. Bláha,* Chemistry & Ind. *1965,* 1261.

[4] *H. P. Weber & T. J. Petcher,* J. chem. Soc. Perkin II *1973,* 2001.

[5] *L. Szporny & K. Szász,* Arch. Exp. pathol. Pharmakol. *236,* 296 (1959); *M. Aurousseau,* Chim. Ther. *1971,* 221; *M. Aurousseau, M. Dupont, C. Rondeaux & J. C. Rondeaux,* ibid. *1972,* 235.

[6] a) *M. E. Kuehne,* J. Amer. chem. Soc. *86,* 2946 (1964); *Lloydia 27,* 435 (1964); b) *K. H. Gibson & E. Saxton,* Chem. Commun. *1969,* 1940; c) *Roussel Uclaf,* Deutsche Offenlegungschrift 2115718 (1971).

[7] a) *C. Szántay, L. Szabo & G. Kalaus,* Tetrahedron Letters *1973,* 191; b) *J. L. Herrmann, R. J. Cregge, J. E. Richman, C. L. Semmelhack & R. H. Schlessinger,* J. Amer. chem. Soc. *96,* 3702 (1974); c) *P. Pfäffli, W. Oppolzer, R. Wenger & H. Hauth,* Helv. *58,* 1131 (1975); Deutsche Offenlegungschrift 2314876 (1973).

[8] *G. Hugel, J. Lévy & J. LeMen,* C.r. hebd. Séances Acad. Sci. C *274,* 1350 (1972).

[9] *G. Opitz & H. Mildenberger,* Liebigs Ann. Chem. *649,* 26 (1961).

[10] *H. C. Brown & C. F. Lane,* J. Amer. chem. Soc. *92,* 6660 (1970).

[11] *H. O. House, L. J. Czuba, M. Gall & H. D. Olmstead,* J. org. Chemistry *34,* 2324 (1969).

[12] *N. Whittaker,* J. chem. Soc. (C) *1969,* 85.

[13] *S. Danishefsky, T. Kitahara, R. Mc Kee & P. F. Schuda,* J. Amer. chem. Soc. *98,* 6715 (1976).

[14] *J. Hooz & J. N. Bridson,* J. Amer. chem. Soc. *95,* 602 (1973).

[15] *P. F. Hudrlik* in 'New Applications of Organometallic Reagents in Organic Synthesis', *Ed. D. Seyfert,* Elsevier 1976, p. 127.

[16] *Cs. Szántay & L. Töke,* Tetrahedron Letters *1963,* 251; *Cs. Szántay, L. Töke, K. Honty & Gy. Kalaus,* J. org. Chemistry *32,* 423 (1967).

[17] *M. Uskoković, H. Bruderer, C. von Planta, T. Williams & A. Brossi,* J. Amer. chem. Soc. *86,* 3364 (1964).

[18] *D. L. Coffen, D. A. Katonak & F. Wong,* J. Amer. chem. Soc. *96,* 3966 (1974).

[19] *H. T. Openshaw & N. Whittaker,* J. chem. Soc. C, *1963,* 1461.

[20] *J. W. Bird & D. G. Diaper,* Canad. J. Chemistry *47,* 145 (1969).

[21] *C. Schöpf & H. Steuer,* Liebigs Ann. Chem. *558,* 124 (1947).