SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS XCI.[1] SYNTHESIS OF ISOLARUTENSINE

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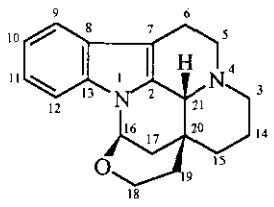
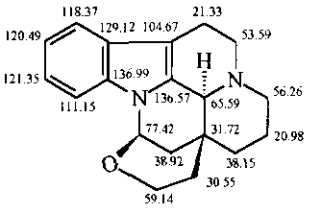
Abstract - The synthesis of isolarutensine was elaborated from the mixture of enamines (**3a**) and (**3b**).

In the course of our previous studies[2] we have found an easy access to the nitrile derivative (**1**). This compound seemed to be an appropriate precursor for the synthesis of alkaloid larutensine (**11a**) or its 21-epimer (**11b**). Larutensine itself was isolated from *Kopsia larutensis* in 1991[3] (Scheme 1).



11a

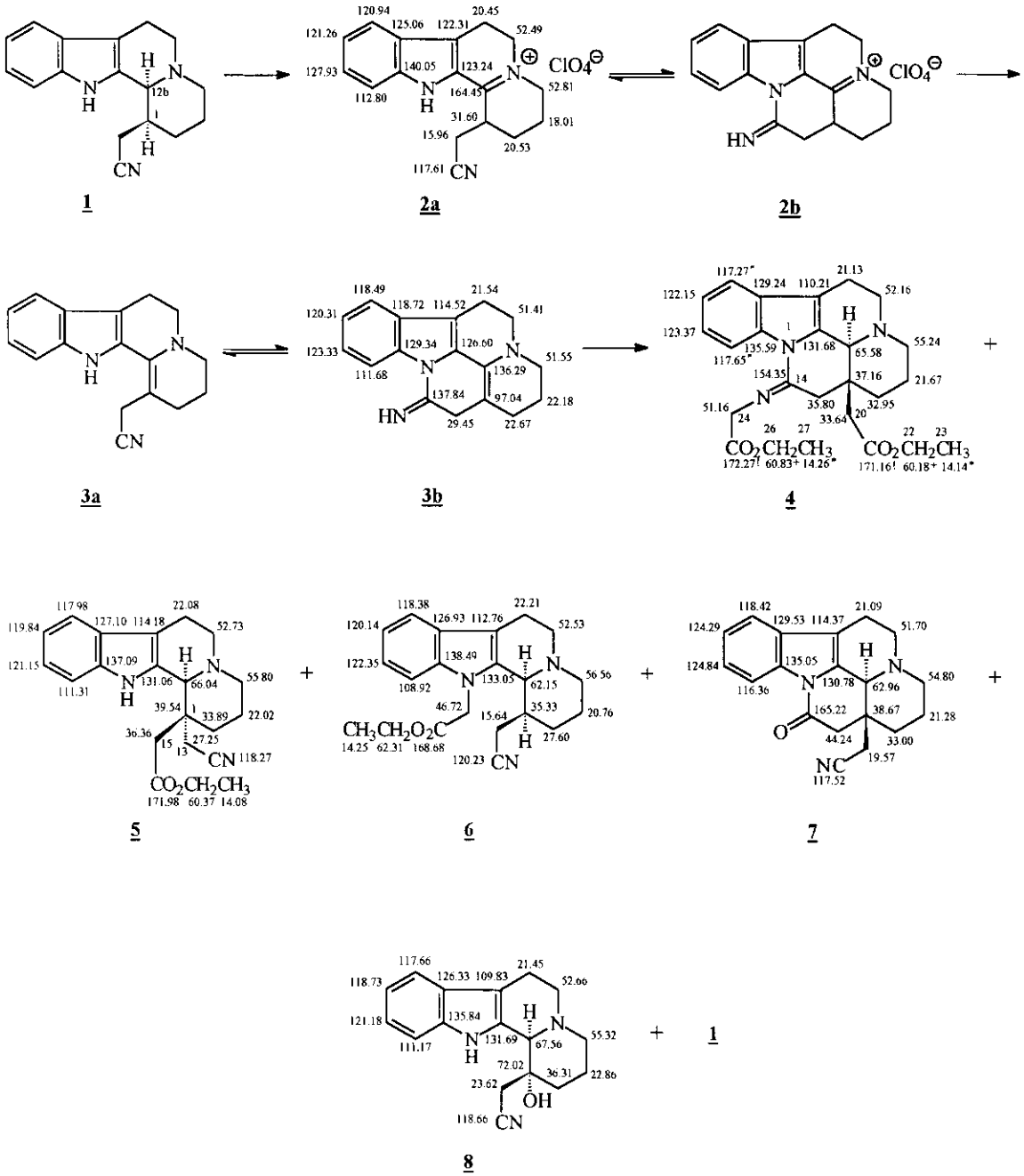


11b

Scheme 1.

While our work has already been in progress we learnt about the successful synthesis of larutensine and isolarutensine disclosed by Lounasmaa.[4,5]

The nitrile (**1**) was oxidized by sodium dichromate in almost quantitative yield to the imino compound (**2b**), which is in equilibrium with its nitrile tautomeric form (**2a**). In deuterodimethyl sulfoxide solution the equilibrium between **2a** and **2b** has been shifted towards the form (**2a**), as attested by the presence of the cyano group in the ^{13}C NMR spectrum (117.61 ppm). The mixture of **2a** and **2b** was transformed with

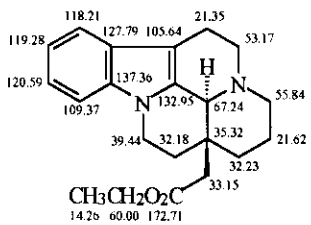


Scheme 2.

base into its tautomer enamine forms (**3a**) and (**3b**). The reaction of tautomer enamines (**3a**) and (**3b**) with ethyl iodoacetate followed by reduction with sodium borohydride provided the suitable intermediate (**4**) in 22.2% yield in addition to five other compounds (**1, 5-8**), which were also isolated and their structure

elucidated (Scheme 2). The *trans* C/D ring junction of compounds (**5**), (**6**), and (**8**) followed from the chemical shift of the 12b-H protons (3.34-3.67 ppm) and 7-C carbons (21.45-22.21 ppm). The spin-spin couplings of compound (**6**) reveals equatorial orientation for 1-H proton ($J_{1,2ax}$=3 Hz, $J_{1,2eq}$=2.5 Hz). The stereochemistry of the substituents at 1-C carbon in compound (**5**) was identified by NOE experiments; irradiation of the 12b-H multiplet gave NOE enhancement on the 13-H resonance. Similarly, the NOE connection between the OH and 12b-H protons gave the steric arrangement of the substituents in compound (**8**) as depicted in Scheme 2. *Trans* C/D and D/E ring junctions were proposed for compounds (**4**) and (**7**) on the basis of the chemical shifts of proton 3-H and carbons 6-C and 18-C.

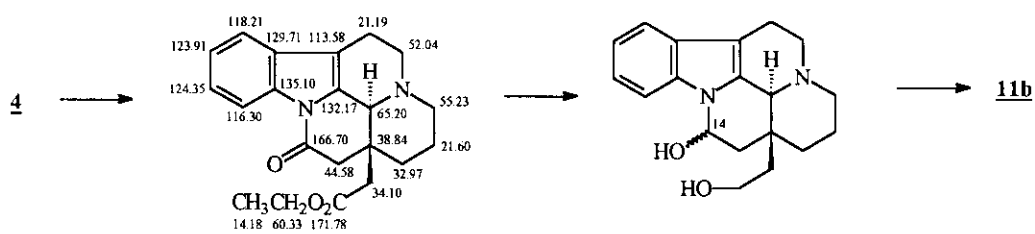
If instead of sodium borohydride Zn activated with $FeCl_3$-$HgCl_2$ in conc. HCl was used as reducing agent, overreduced product (**14**) was isolated. (Spectral data of **14** see in ref.[6] and Chart 1).



14

Chart 1. ^{13}C NMR Data of Compound (**14**)

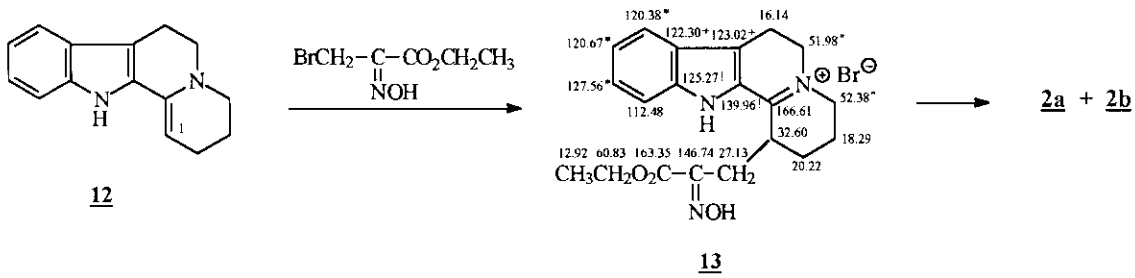
Compound (**4**) was hydrolyzed with aq. HCl in high yield to the eburnane-derivative (**9**) followed by a quantitative reduction by $LiAlH_4$ affording 14-epimer diols (**10**) described by Lounasmaa,[4] which were subjected to the action of acid (5% aq. HCl) and subsequently ammonium hydroxide yielding isolarutensine (**11b**) in 69% yield (Scheme 3).



Scheme 3.

The proton assignment of compound (**11b**) was obtained from ^{1}H-^{1}H decoupling and NOE experiments. The configuration at carbons 20-C and 21-C was assigned by observing the NOE effect between protons 17$_\alpha$-H and 21-H. HETCOR correlations between identified protons and protonated carbons gave the carbon assignment.

The tautomeric mixture of **2a** and **2b** was also prepared from enamine (**12**)[7]. The latter compound was allowed to react with bromopyruvic acid oxime[8] giving the iminium salt (**13**) in 90% yield. Hydrolysis followed by decarboxylation afforded the iminium derivatives which were isolated as their perchlorates (**2a**) and (**2b**) (Scheme 4).



12

13

Scheme 4.

^{13}C NMR data of compounds (**2a**), (**3b**), (**4**)-(**9**), (**11b**) and (**13**) see in Schemes 1-4.

EXPERIMENTAL

Melting points are uncorrected. Thin-layer chromatography separations were carried out on silica gel (Kieselgel 60 F_{254}). IR spectra were recorded on a Specord IR 75 spectrophotometer and Perkin Elmer 2000 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured with a Varian XL-400 spectrometer, chemical shifts (δ values) are relative to the internal standard Me_4Si. Abbreviations s, d, t, m and br s are used to designate singlet, doublet, triplet, multiplet and broad singlet, respectively. EI, FAB and HRMS were taken on a VG-ZAB 2SEQ-Hybride Tandem mass spectrometer.

Oxidation of **1**:

To a solution of **1** (3.39 g, 12.79 mmol) in hot AcOH (20 mL) was added $Na_2Cr_2O_7 2H_2O$ (2.26 g, 7.58 mmol) in AcOH (25 mL). The reaction mixture was stirred at 90°C for 5 min and then allowed to cool to rt (30 min). The dark green solution was treated with 70% aq. $HClO_4$ (2.39 g, 1.3 eq.), during cooling at 0°C for 2 h yellow crystals were precipitated which were collected by filtration and washed twice with

AcOH and twice with ether. The crude product was scrapped at 40°C in MeOH (20 mL), filtered off and washed with ether. The yellow crystals were dried in exsiccator over $CaCl_2$ to give **2b**+**2a**(minor) (4.44 g, 95.5 %), mp: 184-186°C. FTIR (KBr): 3283 (N-H), 3183 (C=NH), 2251 (CN), 1693 ($C=N^+$), 1626 (C=NH), 1573 (N-H), 1545 (C=NH), 1101 (ClO_4^-). ^1H NMR (DMSO-d_6, **2a**): δ 2.00-2.22 (m, 4H, 2-H_2+3-H_2), 2.08 (m, 1H, 1-H), 3.09 (dd, 1H, J=17.2+4.5 Hz, 13-H_A), 3.12 (dd, 1H, J=17.2+10.2 Hz, 13-H_B), 3.25 (m, 2H, 7-H_2), 3.85-4.20 (m, 4H, 4-H_2+6-H_2), 7.26 (ddd, 1H, J=7.8+7.5+1.3 Hz, 9-H), 7.52 (ddd, 1H, J=7.5+7.6+1.2 Hz, 10-H), 7.62 (dd, 1H, J=7.6+1.3 Hz, 11-H), 7.82 (dd, 1H, J=7.8+1.2 Hz, 8-H), 12.35 (br s, 1H, NH). HRMS (FAB): m/z 265, 264 (M^+, 100%), 263, 262, 261, 260, 232, 223, 154, 136; exact MS 264.1481 (calcd for $C_{17}H_{18}N_3$ 264.1501).

Preparation of **3a**+**3b**:

The perchlorate salt (**2b**) (3.90 g, 10.7 mmol) was suspended in CH_2Cl_2 (120 mL) and treated with 54 mL of 2.5% aqueous NaOH solution for 5 min. The two phases were separated, the organic layer was washed with water (15 mL), dried with K_2CO_3, filtered and evaporated to dryness to give **3b**+**3a**(minor) (2.51 g, 89 %). Amorphous. IR (KBr): 3425 (N-H), 2920, 2820 (Bohlmann bands), 2240 (CN, minor), 1620 (C=NH), 1595 (C=C), 1540 (C=NH). ^1H NMR ($CDCl_3$, **3b**): δ 1.97 (m, 2H, 18-H_2), 2.32 (t, 2H, J=7.4 Hz, 17-H_2), 2.94 (t, 2H, J=6.2 Hz, 6-H_2), 3.10 (t, 2H, J=6.1 Hz, 19-H_2), 3.14 (t, 2H, J=6.2 Hz, 5-H_2), 3.52 (s, 2H, 15-H_2), 7.13 (m, 1H, 10-H), 7.22 (m, 1H, 11-H), 7.41 (m, 1H, 9-H), 7.52 (m, 1H, 12-H), 8.02 (br s, 1H, NH). HRMS (EI): m/z 264, 263 (M, 100%), 262, 234, 167, 131.5; exact MS 263.1424 (calcd for $C_{17}H_{17}N_3$ 263.1422).

Alkylation of Enamines (**3a**)+(**3b**); Formation of **1**, **4**, **5**, **6** ,**7**, and **8**:

The enamines (**3a**)+(**3b**) (2.51 g, 9.54 mmol) were dissolved in ethyl iodoacetate (60.93 g, 284.7 mmol) and the solution was stirred at 125°C under nitrogen for 5.5 h. The excess of iodoacetate was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (90 mL) and dry EtOH (100 mL) was added. The solution was stirred in ice-bath and $NaBH_4$ (1.90 g, 50.3 mmol) was added in portions at 5-7°C. Stirring was continued for 30 min at 0°C and 30 min at rt. AcOH was added to adjust the pH to 4 and the solvents were evaporated. Water (80 mL) was added to the residue and the pH was adjusted to 9 with 10% aq. Na_2CO_3. The aqueous phase was extracted with CH_2Cl_2 (80+2x50+30 mL), the combined organic phase was extracted with water (30 mL). After drying ($MgSO_4$) and evaporation of the solvent the crude product was dissolved in 5.3 mL of MeOH + 4.7 mL of toluene and purified by column chromatography. (silica gel; 14:1, toluene-MeOH) to give the mixture of **4**, **5**, **6**, **7** (1118 mg), the pure nitrile (**1**) (610 mg, 24.1%) and the pure (**8**) (131 mg, 4.9%). R_f: **4**,**5**,**6**,**7** > **1** > **8**.

Repeated column chromatography (silica gel; 3:1, hexane-EtOAc) gave diester (**4**), ester (**5**), ester (**6**) and lactam (**7**). R_f: **5** > **6** > **4** > **7**.

Conversion: 75.9%.

Diester (**4**): Yield: 700.6 mg (22.2 %), mp: 150-151°C (EtOH). IR (KBr): 2980, 2920, 2840 (Bohlmann bands), 1740, 1720, (C=O), 1660, 1630 (C=NH). ^{1}H NMR ($CDCl_3$): δ 1.20+1.35 (t, 6H, J=6.8 Hz, 27-H_3+23-H_3), 1.27 (m, 1H, 17-H_A), 1.60 (m, 1H, 18-H_A), 1.71 (dd, 1H, J=15.5+1.5 Hz, 20-H_A), 1.96 (m, 1H, 18-H_B), 1.99 (m, 1H, 17-H_B), 2.09 (dd, 1H, J=16.5+1 Hz, 15-H_A), 2.29 (m, 1H, 19-H_A), 2.52 (m, 1H, 5-H_A), 2.67 (m, 1H, 6-H_A), 2.85 (m, 1H, 6-H_B), 2.89 (dd, 1H, J=15.5+2 Hz, 20-H_B), 2.95 (m, 1H, 3-H_2), 3.05 (m, 2H, 5-H_B+19-H_B), 3.51 (d, 1H, J=16.5 Hz, 15-H_B), 4.05+4.26 (m, 4H, 26-H_2+22-H_2), 4.28 (dd, 1H, J=17.8+1 Hz, 24-H_A), 4.43 (dd, 1H, J=17.8+1.2 Hz, 24-H_B), 7.19 (m, 1H, 10-H), 7.28 (m, 1H, 11-H), 7.40 (dd, 1H, J=7.6+1.2 Hz, 9-H), 8.78 (dd, 1H, J=7.7+1.1 Hz, 12-H). HRMS (EI): m/z 438, 437 (M, 100%), 436, 422 ([M-CH_3^+]), 392 ([M-HCO_2^+]), 364 ([M-CO_2Et^+]), 352, 351, 350 ([M-NCO_2Et^+]), 307, 237; exact MS 437.2312 (calcd for $C_{25}H_{31}N_3O_4$ 437.2315).

Ester (**5**): Yield: 80 mg (2.4 %), viscous oil. IR (KBr): 3300 (indole NH), 3000, 2920, 2820 (Bohlmann bands), 2240 (CN), 1720 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.20 (t, 3H, J=6.7 Hz, 18-H_3), 1.61 (m, 1H, 3-H_A), 1.78 (m, 1H, 2-H_A), 1.91 (m, 1H, 3-H_B), 1.95 (m, 1H, 2-H_B), 1.98 (d, 1H, J=15.5 Hz, 15-H_A), 2.51 (m, 1H, 4-H_A), 2.59 (m, 1H, 6-H_A), 2.61 (m, 1H, 7-H_A), 2.87 (m, 1H, 7-H_B), 2.95 (m, 1H, 6-H_B), 3.00 (m, 1H, 4-H_B), 3.09 (s, 2H, 13-H_2), 3.20 (d, 1H, J=15.5 Hz, 15-H_B), 3.67 (m, 1H, 12b-H), 4.26 (q, 2H, J=6.7 Hz, 17-H_2), 7.11 (m, 1H, 9-H), 7.17 (m, 1H, 10-H), 7.36 (dd, 1H, J=7.5+1.2 Hz, 11-H), 7.46 (dd, 1H, J=7.8+1.3 Hz, 8-H), 7.80 (br s, 1H, NH). HRMS (EI): m/z 352, 351, 350 (M^+, 100%), 278, 197; exact MS 351.1944 (calcd for $C_{21}H_{25}N_3O_2$ 351.1947).

Ester (**6**): Yield: 320 mg (9.6 %), mp: 110-112°C (EtOH). IR (KBr): 2920, 2800 (Bohlmann bands), 2235 (CN), 1740 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.29 (t, 3H, J=6.8 Hz, 18-H_3), 1.61 (m, 1H, 3-H_A), 1.79 (m, 1H, 2-H_A), 1.87 (m, 1H, 3-H_B), 2.12 (ddd, 1H, J=17.5+3.8+1.2 Hz, 13-H_A), 2.17 (m, 1H, 2-H_B), 2.36 (m, 1H, J=11.5+3.8+3+2.5 Hz, 1-H), 2.56 (m, 1H, 6-H_A), 2.60 (m, 1H, 4-H_A), 2.61 (m, 1H, 7-H_A), 2.85 (m, 1H, 7-H_B), 2.87 (m, 1H, 6-H_B), 2.88 (dd, 1H, J=17.5+11.5 Hz, 13-H_B), 3.01 (m, 1H, 4-H_B), 3.62 (m, 1H, J=2.0+2.0+1.5 Hz, 12b-H), 4.25+4.33 (m, 2H, 17-H_2), 4.71 (s, 2H, 15-H_2), 7.14 (dd, 1H, J=7.5+1.2 Hz, 11-H), 7.15 (m, 1H, 9-H), 7.22 (m, 1H, 10-H), 7.46 (dd, 1H, J=7.8+1.3 Hz, 8-H). HRMS (EI): m/z 352, 351 (M, 100%), 322 ([M-$CH_2CH_3^+$], 311 ([M-CH_2CN^+]), 283 ([M-$CH_2CH_2CH_2CN^+$]), 256 ([M-$CH_2CH_2CHCH_2CN^+$]), 237, 209, 183; exact MS 351.1934 (calcd for $C_{21}H_{25}N_3O_2$ 351.1947).

Lactam (**7**): Yield: 5 mg (0.2 %), mp: 220-224°C (EtOH). IR (KBr): 3040, 3000, 2930 (Bohlmann bands), 2290 (CN), 1710 (C=O), 1670. ^{1}H NMR ($CDCl_3$): δ 1.46 (m, 1H, 17-H_A), 1.76 (m, 1H, 18-H_A), 1.81 (dd, 1H, J=17.7+1.9 Hz, 20-H_A), 1.90 (m, 1H, 18-H_B), 2.17 (m, 1H, 17-H_B), 2.38 (m, 1H, 19-H_A), 2.62 (dd,

1H, J=17+2.2 Hz, 15-H_A), 2.63 (m, 1H, 5-H_A), 2.66 (m, 1H, 6-H_A), 2.83 (m, 1H, 6-H_B), 3.01 (d, 1H, J=17 Hz, 15-H_B), 3.09 (br s, 1H, 3-H), 3.09 (m, 1H, 19-H_B), 3,10 (m, 1H, 5-H_B), 3.12 (dd, 1H, J=17.7+1.9 Hz, 20-H_B), 7.29-7.34 (m, 2H, 10-H+11-H), 7.42 (dd, 1H, J=7.7+1.2 Hz, 9-H), 8.32 (dd, 1H, J=7.6+1.3 Hz, 12-H). HRMS (EI): m/z 306, 305 (M, 100%), 304, 265, 264, 263, 237, 207, 167; exact MS 305.1519 (calcd for $C_{19}H_{19}N_3O$ 305.1528).

Nitrile (**8**): mp: 243-245°C (EtOH). IR (KBr): 3410 (indole NH, OH), 2960, 2920, 2860, 2820, 2780 (Bohlmann bands), 2285 (CN). ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 1.75 (m, 1H, 2-H_A), 1.70-1.80 (m, 2H, 3-H_2), 2.20 (d, 1H, J=17.1 Hz, 13-H_A), 2.22 (m, 1H, 2-H_B), 2.42 (m, 1H, 6-H_A), 2.65 (m, 2H, 7-H_A+4-H_A), 2.85 (m, 1H, 7-H_B), 2.97 (m, 1H, J=17.1 Hz, 13-H_B), 3.0 (m, 2H, 6-H_B+4-H_B), 3.34 (br s, 1H, 12b-H), 5.51 (br s, 1H, OH), 7.00-7.08 (m, 2H, 9-H+10-H), 7.30 (dd, 1H, J=7.6+1.2 Hz, 11-H), 7.42 (dd, 1H, J=7.7+1.3 Hz, 8-H), 9.15 (s, 1H, NH). HRMS (EI): m/z 282, 281 (M, 100%), 280, 264, 241, 197, 171, 170, 169, 143; exact MS 281.1522 (calcd for $C_{17}H_{19}N_3O$ 281.1528).

Preparation of Lactam (**9**):

The compound (**4**) (431 mg, 0.986 mmol) was refluxed in a mixture of water (20 mL) and 2N HCl (0.9 mL) for 10 min. After cooling the solution was basified with 15% aq. NaOH to pH 9 and extracted with CH_2Cl_2 (3x30 mL). The organic layer was separated, dried ($MgSO_4$), filtered and evaporated to dryness in vacuo. The residue was recrystallized from acetone:hexane 1:1 to give **9** (321 mg, 92.5%), mp: 159-161°C (lit.,[4] mp: 165°C). IR (KBr): 2910, 2900, 2840 (Bohlmann bands), 1710, 1700 (C=O), 1650. ^{1}H-NMR ($CDCl_3$): δ 1.20 (t, 3H, J=6.8 Hz, 23-H_3), 1.35 (m, 1H, 17-H_A), 1.67 (m, 1H, 18-H_A), 1.78 (dd, 1H, J=15.5+1.8 Hz, 20-H_A), 2.01 (m, 1H, 18-H_B), 2.12 (m, 1H, 17-H_B), 2.35 (m, 1H, 19-H_A), 2.47 (dd, 1H, J=16.9+2.1 Hz, 15-H_A), 2.55 (m, 1H, J=11.5+11+4.5 Hz, 5-H_A), 2.65 (m, 1H, 6-H_A), 2.85 (m, 1H, 6-H_B), 2.94 (dd, 1H, J=15.5+2 Hz, 20-H_B), 3.03 (br s, 1H, 3-H), 3.07 (m, 1H, 19-H_B), 3.09 (m, 1H, 5-H_B), 3.18 (d, 1H, J=16.9 Hz, 15-H_B), 4.06 (q, 2H, J=6.8 Hz, 22-H_2), 7.25-7.35 (m, 2H, 10-H+11-H), 7.41 (dd, 1H, J=7.6+1.2 Hz, 9-H), 8.36 (dd, 1H, J=7.6+1.3 Hz, 12-H). MS spectral data were identical with those described earlier.[4,9]

Preparation of (±) Isolarutensine ((±)-**11b**):

$LiAlH_4$ (169 mg, 4.45 mmol) was suspended in anhydrous THF (25 mL) and the solution of lactam (**9**) (321 mg, 0.912 mmol) in anhydrous THF (8 mL) was added dropwise to the stirred suspension at 0°C. After 1.5 h of stirring at rt water (2 mL) was carefully added and the reaction mixture was stirred for 10 min, then diluted with CH_2Cl_2 (20 mL). The precipitate was filtered off, washed with CH_2Cl_2 (2x20 mL), the filtrate was dried ($MgSO_4$) and evaporated to dryness, yielding 283 mg (100%) of a 2:1 mixture of 14-

epimer diols (**10**). The mixture (280 mg, 0.897 mmol) was dissolved in 5% aq. HCl (50 mL) and stirred overnight at rt. The solution was basified by dropwise addition of concentrated ammonia until the pH reached 9. Extractive work-up (CH_2Cl_2, 3x20 mL), drying ($MgSO_4$) and evaporation gave the crude product (238 mg), which was recrystallized from EtOH (3 mL).

Yield: 183 mg (69.3 %), mp: 174-177°C (lit.,[4] mp: 175-177°C). FTIR (KBr): 3051, 2926, 2879, 2852, 2799, 2751 (Bohlmann bands), 1633, 1460, 1446, 1322, 1303, 1122, 1073, 834, 754. ^{1}H NMR ($CDCl_3$): δ 1.37 (m, 1H, 15-H_A), 1.49 (m, 1H, 19-H_A), 1.52 (m, 1H, 15-H_B), 1.61 (m, 1H, 14-H_A), 1.92 (m, 1H, J=13+2.6+2.2 Hz, 17-H_A), 2.03 (m, 1H, 14-H_B), 2.10 (dd, 1H, J=13+2.8 Hz, 17-H_B), 2.12 (m, 1H, 18-H_A), 2.22 (m, 1H, 19-H_B), 2.25 (m, 1H, 3-H_A), 2.52 (m, 1H, 5-H_A), 2.73 (m, 1H, 6-H_A), 2.93 (m, 1H, 6-H_B), 2.97 (br s, 1H, 21-H), 3.08 (m, 1H, 3-H_B), 3.15 (m, 1H, 5-H_B), 3.32 (m, 1H, 18-H_B), 5.97 (dd, 1H, J=2.8+2.6 Hz, 16-H), 7.10-7.18 (m, 2H, 10-H+11-H), 7.40 (dd, 1H, J=7.7+1.3 Hz, 12-H), 7.46 (dd, 1H, J=7.7+1.2 Hz, 9-H). HRMS (EI): m/z 295, 294, 293 (M, 100%), 266, 265, 251, 249, 237, 221, 197, 169, 124; exact MS 294.1705 (calcd for $C_{19}H_{22}N_2O$ 294.1732).

Preparation of **13**:

To an ice-cooled solution of enamine (**12**) (4.76 g, 21.25 mmol) in CH_2Cl_2 (60 mL), dry EtOAc (30 mL) and dry EtOH (5 mL), ethyl bromopyruvate oxime (4.50 g, 21.43 mmol), dissolved in dry EtOAc (90 mL), was added dropwise at 0-7°C with stirring. Thereafter the reaction mixture was stirred at rt for 4 h. The crystalline product was filtered off and recrystallized from EtOH to give 8.30 g (90%) of the adduct (**13**), yellow crystals, mp: 202-204°C, (lit.,[2] mp: 198-199°C). IR spectral data were identical (lit.,[2]). ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 1.28 (t, 3H, J=6.8 Hz, 17-H_3), 1.80-2.30 (m, 4H, 2-H_2+3-H_2), 2.28 (m, 1H, 1-H), 2.81 (m, 1H, J=13.5+4 Hz, 13-H_A), 3.26 (m, 1H, J=13.5+10 Hz, 13-H_B), 3.85-4.30 (m, 6H, 4-H_2+6-H_2+7-H_2), 4.26 (m, 2H, 16-H_2), 7.58+7.60 (m, 2H, 8-H+11-H), 7.18+7.40 (m, 2H, 9-H+10-H), 11.25 (br s, 1H, NH), 12.55 (br s, 1H, OH).

Preparation of **2a**+**2b** from **13**:

A suspension of the oxime ester (**13**) (15.0 g, 34.8 mmol) in EtOH (250 mL) was heated to reflux with a solution of NaOH (5.55 g, 139 mmol, 4 eq.) in water (50 mL) for 2 h. After evaporation of the solvent the residue was treated with saturated HCl (methanol). The precipitated NaCl was filtered off and the solvent was evaporated. The oxime acid was dried in exsiccator over P_2O_5 and K_2CO_3. The crude product was suspended in decaline (125 mL) and heated at 130-140°C for 1 h. After cooling the product was filtered off, washed with ether and dried in exsiccator over paraffin. The residue (13.11 g) was dissolved in MeOH:CH_2Cl_2 9:1 (200 mL), treated with 70% aq. $HClO_4$ (6.3 g) and concentrated to give the crude

iminium perchlorate (15.11 g). The orange crystals were treated with MeOH, the inorganic salt (4.75 g) was filtered off and the solution was concentrated. The yellow crystals were dried in exsiccator over P_2O_5 and $CaCl_2$.

Yield: 10.20 g (80.6%), mp: 184-187°C. For the spectral data of **2a** and **2b**, see above.

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6. Spectral data of **14:**

   IR (KBr): 2980, 2930, 2860 (Bohlmann bands), 1720 (C=O), 1650. ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 3H, J=6.8 Hz, 23-H_3), 1.30 (m, 1H, 17-H_A), 1.65 (m, 1H, 18-H_A), 1.75 (dd, 1H, J=15.5+1.5 Hz, 20-H_A), 1.85 (m, 1H, J=13+12.5+6.6+1.5 Hz, 15-H_A), 2.06 (m, 1H, 17-H_B), 2.12 (m, 1H, 18-H_B), 2.29 (m, 1H, 19-H_A), 2.37 (m, 1H, J=13+5.2+0.8 Hz, 15-H_B), 2.51 (m, 1H, 5-H_A), 2.71 (m, 1H, 6-H_A), 2.86 (dd, 1H, J=15.5+1.5 Hz, 20-H_B), 2.89 (m, 1H, 6-H_B), 2.96 (br s, 1H, 3-H), 3.05 (m, 1H, 5-H_B), 3.06 (m, 1H, 19-H_B), 3.99 (ddd, 1H, J=12.5+12.2+5.2 Hz, 14-H_A), 4.17 (ddd, 1H, J=12.2+6.6+0.8 Hz, 14-H_B), 4.86 (q, 2H, J=6.8 Hz, 22-H_2), 7.11 (ddd, 1H, J=7.7+7.5+1.3 Hz, 10-H), 7.17 (ddd, 1H, J=7.6+7.5+1.2 Hz, 11-H), 7.28 (dd, 1H, J=7.6+1.3 Hz, 12-H), 7.48 (dd, 1H, J=7.7+1.3 Hz, 9-H). HRMS (EI): m/z 339, 338, 337 (M, 100%), 309, 293, 251, 223, 194, 167; exact MS 338.1982 (calcd for $C_{21}H_{26}N_2O_3$ 338.1994).
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