Pergamon

Tetrahedron 54 (1998) 10205–10216

TETRAHEDRON

Acid-Catalysed Epimerization of Indolo[2,3-*a*]quinolizidine Derivatives: Role of the Nitrogen Lone Pairs in the Mechanism

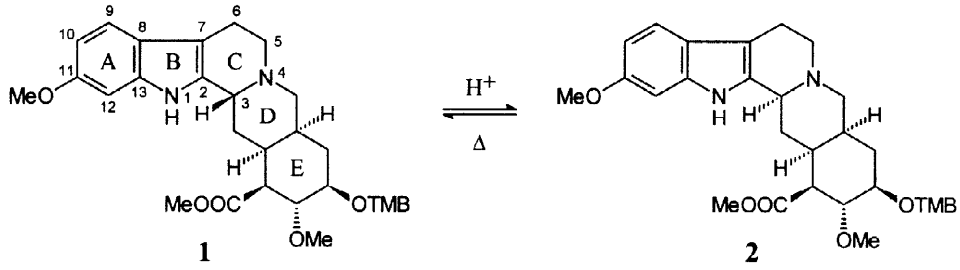
Mauri Lounasmaa*, Mathias Berner, Martin Brunner[#], Harri Suomalainen, and Arto Tolvanen

Laboratory for Organic and Bioorganic Chemistry
Technical University of Helsinki, P. O. Box 6100, HUT-02015 Espoo, Finland
E-mail: mauri.lounasmaa@hut.fi

Received 14 May 1998; revised 8 June 1998; accepted 18 June 1998

Abstract: The role of the nitrogen lone pairs in the mechanism of the acid-catalysed epimerization of indolo[2,3-*a*]quinolizidines is investigated using lactams as model compounds. Deethyleburnamonine (**3**) did not epimerize with trifluoroacetic acid (TFA), whereas deethyldihydroeburnamenine (**7**) underwent epimerization smoothly. Under treatment with TFA, lactams **12** and **13** both epimerized with ease to a mixture of lactams **12** and **13**. An analogous equilibrium was achieved when the experiment was repeated with lactams **18** and **19**. Intermediate **20** was trapped (Zn reduction) in the acid-catalysed epimerization of lactam **12**, allowing conclusions about the mechanism.

The mechanism of the acid-catalysed epimerization of indolo[2,3-*a*]quinolizidine derivatives has long been a matter of discussion. Already in the 1950's, when the phenomenon was first detected, proposals were made for the possible reaction pathways. Under acid (or base) catalysis the pharmacologically important indole alkaloid reserpine (**1**) was found to equilibrate to a mixture of **1** and its 3-epimer, isoreserpine (**2**).[1,2]



1 **2**

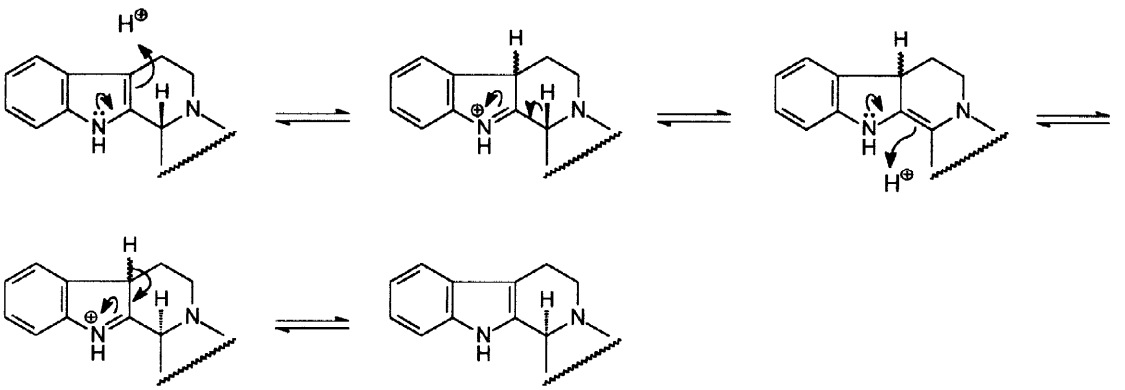
TMB = 3,4,5-trimethoxybenzoyl

We have recently published a detailed review dealing with different aspects of the acid-catalysed epimerization reaction.[3] A short summary of the proposed mechanisms is presented below. Gaskell and Joule[4] did the pioneer experimental work towards elucidating the mechanism of the acid-catalysed epimerization of reserpine. The three alternative reaction pathways they investigated had earlier been

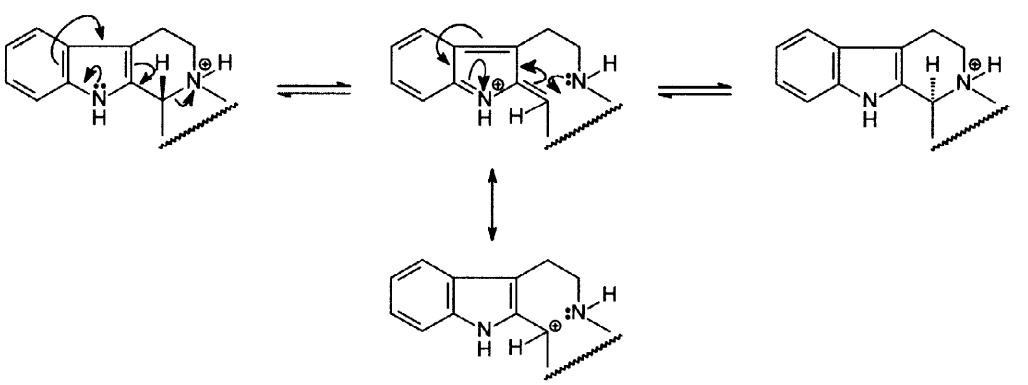
[#] On leave from Eidgenössische Technische Hochschule, CH-8092 Zürich, Switzerland

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00614-0

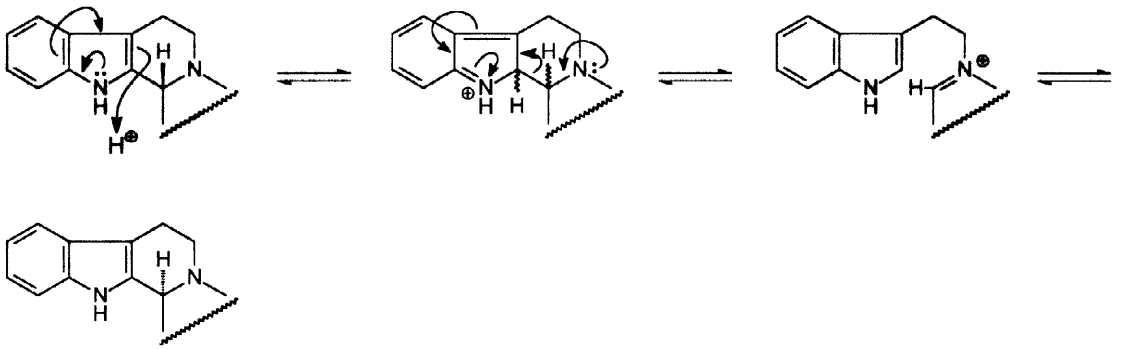
discussed by Woodward in connection with his classic total synthesis of reserpine (**1**).[5] In mechanism 1, protonation of the indole ring at C-7 (C-7a in indolo[2,3-*a*]quinolizidines) results in the cleavage of H-3 (Scheme 1). In mechanism 2, as originally proposed by Wenkert and Liu,[6] the C-3 – N_b bond is broken, giving a carbocation intermediate (Scheme 2). Cook and co-workers[7] recently demonstrated the operation of this mechanism in the acid-catalysed epimerization of tetrahydro-*β*-carboline derivatives. They also have suggested[8] that the same mechanism works for the epimerization of reserpine. The third possible mechanism, which was originally favoured by Gaskell and Joule,[4] begins with protonation at C-2 and results in rupture of the C-2 - C-3 bond (Scheme 3). It should be noted that none of these mechanisms actually requires the presence of the methoxy group in ring A as in reserpine (**1**), but some intermediates are, of course, better stabilized by resonance when the methoxy group is present. This would explain why the methoxy-substituted compounds are epimerized faster.[4] It is also noteworthy that, in the latter two routes (Schemes 2 and 3), H-3 remains unchanged during the epimerization process.



Scheme 1 (mechanism 1)



Scheme 2 (mechanism 2)

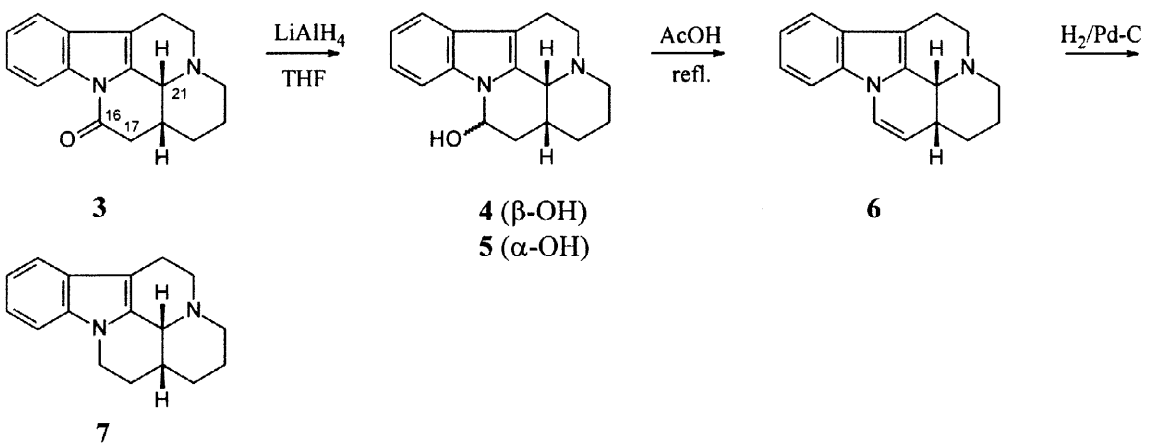


Scheme 3 (mechanism 3)

In all three mechanisms the nitrogen lone pairs play an important role. To diminish the participation of the nitrogen lone pairs in the epimerization process, we chose N_a and N_b lactams as model compounds. Lactams, where the nitrogen lone pair is delocalized over the amide N-C-O system, constitute an intriguing subject for epimerization studies.

Results and Discussion

To test the necessity of the indole nitrogen lone pair (N_a) we prepared deethyleburnamonine (**3**)[2,9], which was converted in three steps (**3** → **4** and **5** → **6** → **7**) to *cis*-deethyldihydroeburnamenine (**7**) (Scheme 4). Analogous reactions were performed by Bartlett and Taylor in connection with their classic studies on eburnamonine.[10]

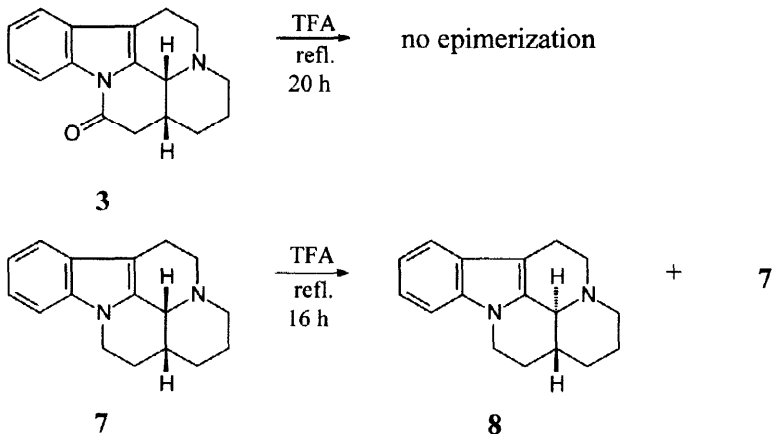


3 **4** (β-OH) **5** (α-OH) **6** **7**

Scheme 4

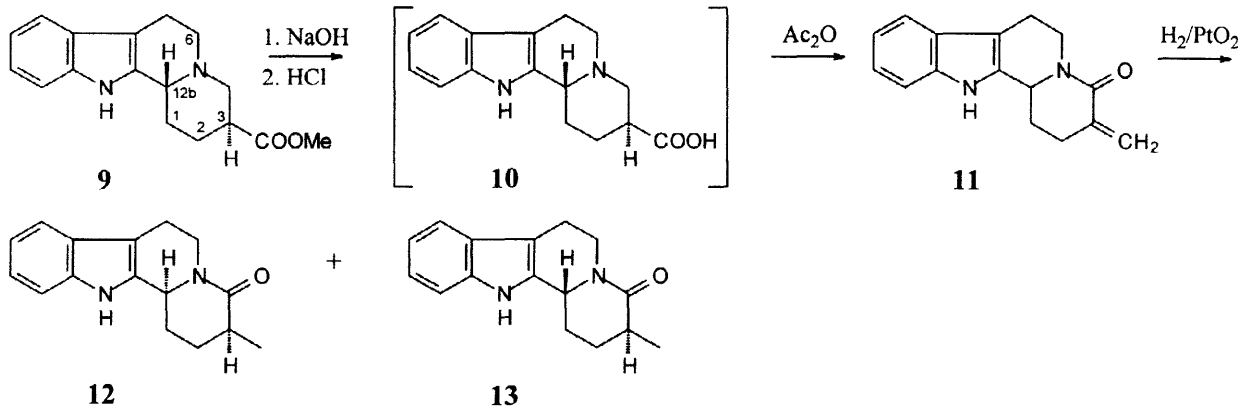
Deethyleburnamonine (**3**) was not expected to epimerize because the indole nitrogen lone pair participates in the amide system. And indeed, the *trans*-epimer was not detected when *cis*-deethyleburnamonine (**3**) was refluxed with trifluoroacetic acid (TFA) for 20 h. In contrast, when *cis*-

deethyldihydroeburnamenine (**7**) was refluxed with TFA, an equilibrium mixture (20:80 by ^{1}H NMR integration) of **7** and its more stable *trans*-isomer **8** was obtained (Scheme 5). Backwards epimerization of compound **8** resulted in the same equilibrium.



Scheme 5

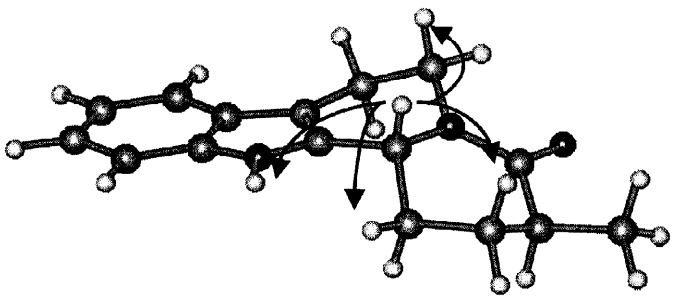
Next we studied the N_b lactams. The easily accessible lactam **11**[11] was prepared from ester **9**[12] *via* acid **10** using methylenelactam rearrangement.[13] Lactam **11** was hydrogenated to give mainly *cis*-3-methyl lactam **12** (IUPAC numbering) in addition to its *trans*-epimer **13** (Scheme 6).



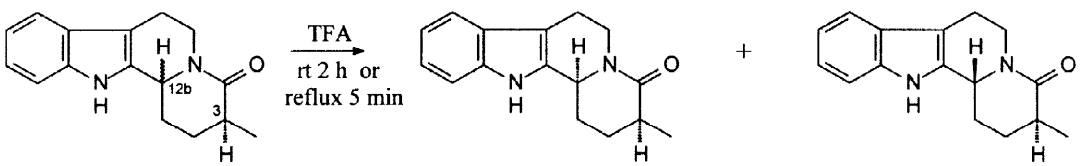
Scheme 6

The stereochemistry of lactam **13** was deduced from ^{1}H NMR data. In addition to other signals, two coupling systems were clearly distinguished in the spectrum: δ 1.80 (dddd, J = 13, 12, 12 and 3 Hz) and 1.65 (dddd, J = 13, 13, 12 and 2.5 Hz). On the basis of the COSY spectrum, these signals were assigned to H-1_{ax} and H-2_{ax}, respectively. Unequivocal proof for the stereochemistry of compound **13** was obtained from the NOE difference experiment. Irradiation at H-12b (δ 4.78) resulted in NOEs at H-1_{eq} (δ 2.47), H-2_{ax} (δ 1.65),

H-6_{ax} (δ 2.84), and NH (δ 7.99). These interactions are shown in the stereoformula of lactam **13** (see figure below).



Epimerization of indoloquinolizidine derivatives with TFA usually requires heating,[14] but lactams, such as **12**, actually epimerize at room temperature.[15] Treatment of **12** with TFA[16] at room temperature for 2 h led to an equilibrium mixture (70:30) of **12** and **13** (Scheme 7). The same equilibrium was reached when **13** was subjected to analogous conditions. The facility of the epimerization was underlined by the achievement of equilibrium within 5 minutes under refluxing.



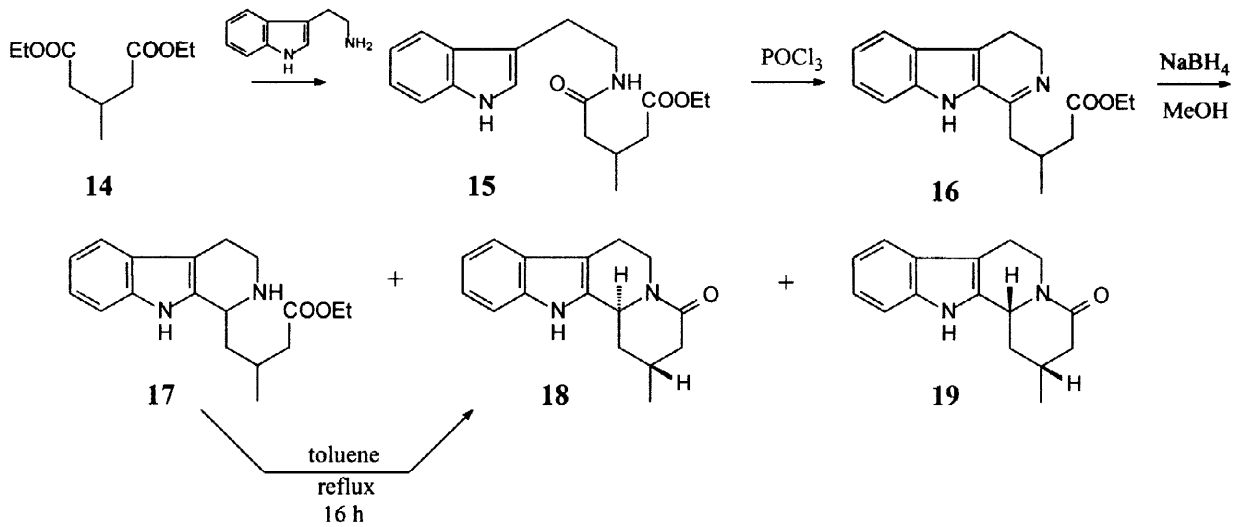
12 (H-12b α)
13 (H-12b β)

12 **13**

Scheme 7

To confirm that the epimerization takes place at H-12b and not at the α-position of lactam (H-3), we prepared the epimeric 2-methyl lactams **18** and **19** according to Gootjes and Nauta (Scheme 8).[17] The separation of **18** and **19** was achieved through multiple recrystallizations from ethanol. On the other hand, the cyclization of tetrahydro-β-carboline **17** resulted only in the pure epimer **18**. The stereochemistry of lactam **19** was confirmed through its spectral similarity with lactam **13** (for example, irradiation of H-12b gives analogous NOE correlations).

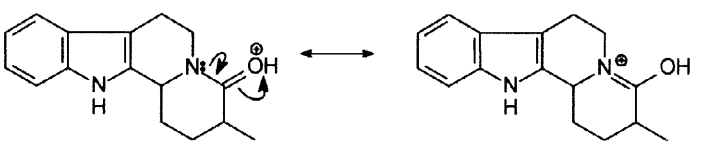
Under epimerization conditions the 2-methyl lactams behaved analogously to the 3-methyl lactams. Thus, the results were also similar: a ratio of 80:20 (**18**:**19**) was obtained confirming that the epimeric centre is H-12b.



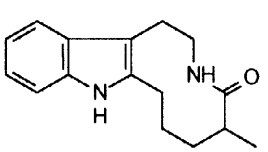
14 15 16 17 18 19

Scheme 8

It is commonly accepted that in strong acid media lactams are protonated at the carbonyl oxygen.[18] The protonated oxygen enables delocalization of the nitrogen lone pair:



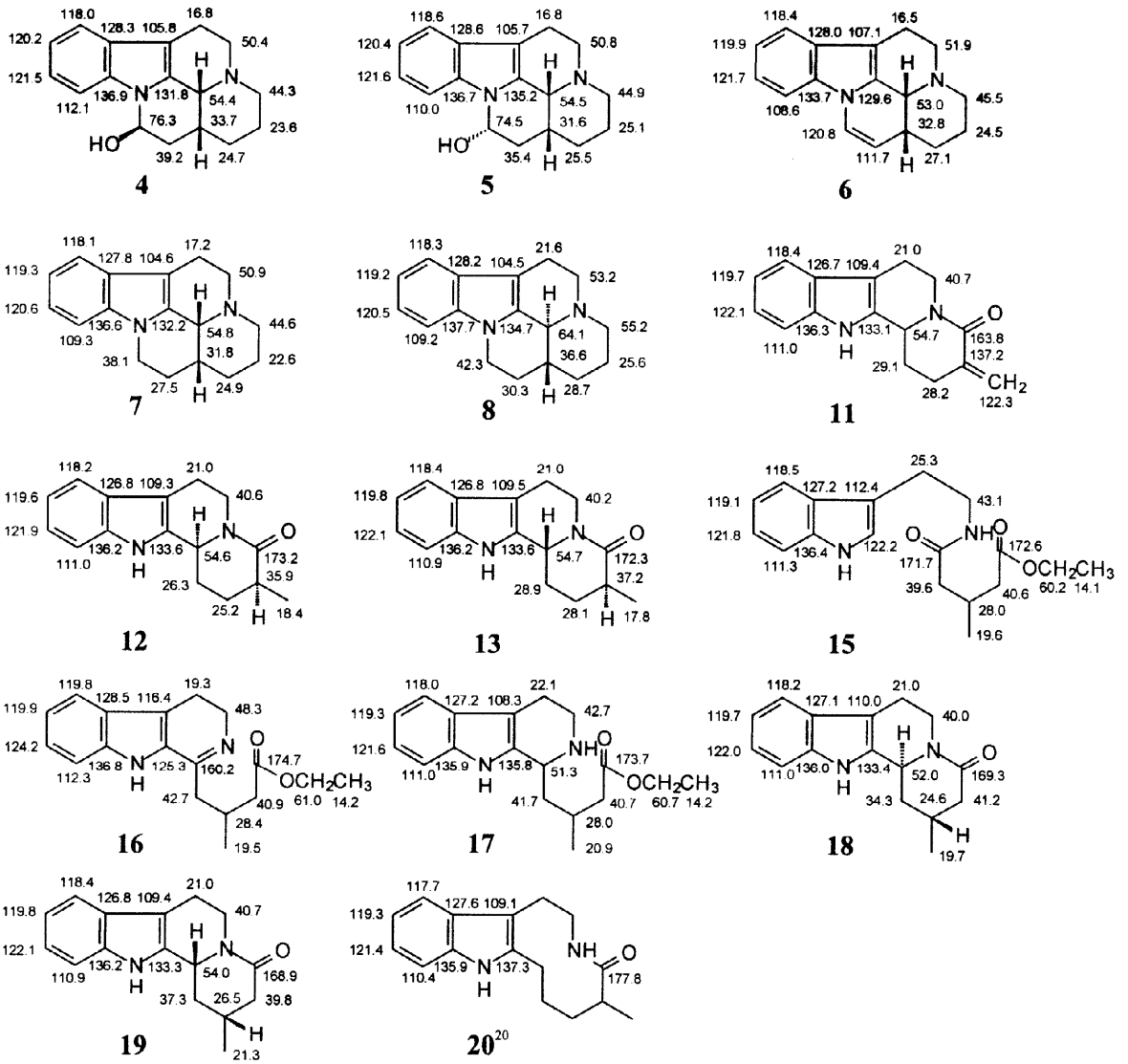
Inspection of the canonical forms of the protonated lactam revealed a certain similarity with mechanism 2. To obtain more support for this we attempted to trap an intermediate. Lactam **12** was refluxed for 3.5 h in TFA with zinc.[19] The experiment yielded 22% of secolactam **20** possessing two broad NH signals in its ^{1}H NMR spectrum. The formation of compound **20** is a strong indication towards mechanism 2.



20

Conclusions

Lactam derivatives were tested for their epimerization behaviour. When the indole nitrogen lone pair participates in the amide N-C-O system, epimerization is prevented. On the other hand, participation of the N_b lone pair in the amide system considerably accelerates the epimerization rate. As shown by trapping of the intermediate **20**, mechanism 2 is active under the employed conditions.



Chart

Experimental

Except where otherwise stated, all reactions were carried out under argon. Alkaline work-up comprised addition of sat. aq $NaHCO_3$, extraction with CH_2Cl_2 (3x), drying of the combined organic layers with Na_2SO_4, and evaporation of the solvent under vacuum. Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. IR spectra (cm^{-1}, in $CHCl_3$) were recorded on a Perkin-Elmer 700 spectrophotometer. ^1H NMR (399.958 MHz, reference: TMS, δ_H = 0.0 ppm) and ^{13}C NMR (100.578 MHz, reference: $CDCl_3$, δ_C = 77.0 ppm) spectra were recorded on a Varian Unity 400 spectrometer with $CDCl_3$ used as solvent. Coupling constants (J) are given in Hz. Signal assignments are based on standard APT, COSY, NOE, and HETCOR experiments. For the ^{13}C NMR data of compounds **4-8**, **11-13**, and **15-20**, see Chart. EI and HR mass spectra (70 eV, m/z) were measured with a Jeol DX 303/DA 5000 mass

spectrometer. Merck Kieselgel 60 (230-400 mesh) was used in column chromatography. In the epimerization experiments the temperature of the oil bath was kept at (90±5)°C.

Preparation of (±)-*cis*-Deethyleburnamines (Epimers 4 and 5). (±)-*cis*-Deethyleburnamonine (**3**) (25.7 mg, 0.097 mmol) in THF (2 ml) was added to a suspension of $LiAlH_4$ (18.6 mg, 0.497 mmol) in THF (2 ml) at 0°C and stirred for 1h at room temperature. After alkaline work-up (aq NaOH) the crude product was purified by column chromatography (EtOAc:MeOH:Et_3N, 95:4:1) to give 21.5 mg (83%) of crystalline **4** and 3.2 mg (12%) of amorphous **5**.

(±)-*cis*-Deethyleburnamine (**4**): mp. 181-182°C ($MeOH/CH_2Cl_2$); IR: 3300 (OH); ^1H NMR: 7.75-7.10 (4H, m, arom.), 5.62 (1H, dd, J = 9 and 5, H-16), 4.27 (1H, br s, H-21); MS: 268 (M^+, 100), 249 (18), 224 (16), 206 (87); HR-MS: calcd for $C_{17}H_{20}N_2O$: 268.1576, found: 268.1563.

(±)-*cis*-Deethylisoeburnamine ((±)-*cis*-Deethyl-16-epieburnamine) (**5**): IR: 3300 (OH); ^1H NMR: 7.55-7.10 (4H, m, arom.), 6.06 (1H, dd, J = 4.5 and 1.5, H-16), 4.39 (1H, br s, H-21); MS: 268 (M^+, 100), 267 (96), 250 (13), 224 (17), 206 (84), 180 (21); HR-MS: calcd for $C_{17}H_{20}N_2O$: 268.1576, found: 268.1570.

Preparation of (±)-*cis*-Deethyleburnamenine (6). The epimeric mixture of (±)-*cis*-deethyleburnamines (**4** and **5**) (27.9 mg, 0.104 mmol) was refluxed with acetic acid (1.5 ml) for 45 min. Alkaline work-up of the cooled reaction mixture gave the crude product, which was purified by column chromatography (CH_2Cl_2:MeOH, 98:2) to yield 19 mg (73%) of amorphous **6**; IR: 1640 (C=C); ^1H NMR: 7.50-7.05 (4H, m, arom.), 6.96 (1H, d, J = 7.5, H-16), 5.32 (1H, dd, J = 7.5 and 6.5, H-17), 4.58 (1H, br d, J = 7, H-21); MS: 250 (M^+, 67), 249 (41), 207 (36), 206 (100), 180 (93); HR-MS: calcd for $C_{17}H_{18}N_2$: 250.1470, found: 250.1459. Further elution (CH_2Cl_2:MeOH, 96:4) gave 4.7 mg of starting compound **5**.

Preparation of (±)-*cis*-Deethyldihydroeburnamenine (7). Compound **6** (12.5 mg, 0.050 mmol) was hydrogenated for 2.5 h in MeOH (4 ml) using Pd/C (10%, 3.8 mg) as catalyst. The catalyst was removed by filtration. After evaporation of the solvent, the crude product was purified by column chromatography (CH_2Cl_2:MeOH, 95:5) to furnish 10.6 mg (84%) of amorphous **7**; IR: no significant absorptions; ^1H NMR: 7.55-7.10 (4H, m, arom.), 4.44 (1H, d, J = 5, H-21), 4.15 (1H, dd, J = 12 and 6.5, H-16_{eq}), 3.79 (1H, ddd, J = 12, 12 and 5, H-16_{ax}); MS: 252 (M^+, 90), 251 (100), 224 (15), 208 (28), 195 (22), 182 (27); HR-MS: calcd for $C_{17}H_{20}N_2$: 252.1626, found: 252.1635.

Epimerization of (±)-*cis*-Deethyleburnamonine (3). (±)-*cis*-Deethyleburnamonine (**3**) (13.1 mg, 0.049 mmol) was dissolved in TFA (2 ml) and the mixture was refluxed for 20 h. After evaporation of the acid, alkaline work-up was performed. The ^1H NMR spectrum of the crude product showed no trace of the corresponding *trans*-epimer.

Epimerization of (±)-*cis*-Deethyldihydroeburnamenine (7). (±)-*cis*-Deethyldihydroeburnamenine (**7**) (8.7 mg, 0.035 mmol) was refluxed in TFA (2 ml) for 16 h. TFA was evaporated and alkaline work-up was performed. The crude product was purified by column chromatography (CH_2Cl_2:MeOH, 93:7) to yield 1.4 mg of **7** (16%) and 5.1 mg (59%) of crystalline **8**; mp. 124-125°C (hexane/CH_2Cl_2); IR: 2820-2750 (Wenkert-Bohlmann bands); ^{1}H NMR: 7.50-7.05 (4H, m, arom.), 4.24 (1H, ddd, J = 12, 5.5 and 1, H-16_{eq}), 3.72 (1H, ddd, J = 12, 12 and 5, H-16_{ax}); MS: 252 (M^+, 74), 251 (100), 224 (12), 208 (12), 195 (8), 182 (10); HR-MS: calcd for $C_{17}H_{20}N_2$: 252.1626, found: 252.1622. Epimerization of compound **8** under the same conditions yielded a 20:80 (^{1}H NMR integration) mixture of **7** and **8**.

Preparation of Methylenelactam 11. Ester **9** (79 mg, 0.278 mmol) was dissolved in MeOH (3 ml), after which 1% NaOH solution (2 ml) was added. The mixture was stirred at 45°C for 1 h. The solution was acidified (pH=2) with 10% HCl and then extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and evaporated, and the crude acid **10** was dissolved in acetic anhydride (4 ml). The mixture was refluxed for 2.5 h. Saturated $NaHCO_3$ (20 ml) was added and the solution was stirred for 2 h. Extraction with CH_2Cl_2, drying (Na_2SO_4), and evaporation of the solvent gave the crude product, which was purified by column chromatography (CH_2Cl_2:MeOH, 98:2) to give 46 mg (66%) of lactam **11**; mp. 217-218°C (ethyl acetate); IR: 1650 (C=O), 1610 (C=C); ^{1}H NMR: 8.08 (1H, br s, NH), 7.55-7.10 (4H, m, arom.), 6.29 (1H, dd, J = 2 and 2, C=CH_Z), 5.35 (1H, dd, J = 2 and 1, C=CH_E), 5.23 (1H, m, H-6_{eq}), 4.89 (1H, dd, J = 11 and 4.5, H-12b); MS: 252 (M^+, 100), 251 (44), 237 (15), 223 (14), 169 (26), 156 (22); HR-MS: calcd for $C_{16}H_{16}N_2O$: 252.1263, found: 252.1271.

Preparation of 3-Methyl Lactams 12 and 13. Methylenelactam **11** (110.7 mg, 0.44 mmol) was hydrogenated for 16 h in MeOH (20 ml) using PtO_2 (20 mg) as catalyst. The catalyst was removed by filtration. After evaporation of the solvent, the crude product was purified by column chromatography (CH_2Cl_2: MeOH, 99.5:0.5), which yielded 96 mg (86%) of crystalline *cis*-3-methyl lactam **12** and 13 mg (12%) of amorphous *trans*-3-methyl lactam **13**.

cis-3-Methyl lactam **12**: mp. 220-222°C (EtOH); IR: 1640 (C=O); ^{1}H NMR: 8.68 (1H, br s, NH), 7.55-7.05 (4H, m, arom.), 5.13 (1H, m, H-6_{eq}), 4.78 (1H, m, H-12b), 1.24 (3H, d, J = 7, -CH_3); MS: 254 (M^+, 100), 253 (53), 239 (10), 184 (36), 170 (72), 169 (93), 168 (29); HR-MS: calcd for $C_{16}H_{18}N_2O$: 254.1419, found: 254.1430.

trans-3-Methyl lactam **13**: IR: 1640 (C=O); ^{1}H NMR: 7.99 (1H, br s, NH), 7.55-7.05 (4H, m, arom.), 5.17 (1H, m, H-6_{eq}), 4.78 (1H, dd, J = 11 and 5, H-12b), 1.32 (3H, d, J = 7, -CH_3) (see also text); MS: 254 (M^+, 100), 253 (50), 239 (10), 184 (23), 170 (33), 169 (52), 168 (29); HR-MS: calcd for $C_{16}H_{18}N_2O$: 254.1419, found: 254.1411.

Epimerization of *cis*-3-Methyl Lactam 12. *cis*-3-Methyl lactam **12** (1.5 mg, 0.0059 mmol) was stirred in TFA[16] (1.5 ml) for 2 h at room temperature. The acid was removed by bubbling Ar through the solution and the crude product was dried under vacuum. The ^{1}H NMR spectrum showed a ratio of 70:30 (**12**:**13**).

Epimerization of *trans*-3-Methyl Lactam 13. *trans*-3-Methyl lactam **13** (1.7 mg, 0.0067 mmol) was stirred in TFA[16] (1.5 ml) for 2 h at room temperature. The acid was removed by bubbling Ar through the solution and the crude product was dried under vacuum. The ^{1}H NMR spectrum showed a ratio of 30:70 (**13**:**12**).

Epimerization of *trans*-3-Methyl Lactam 13 by Refluxing. *trans*-3-Methyl lactam **13** (2.9 mg, 0.011 mmol) was refluxed in TFA[16] (2 ml) for 5 min. The acid was evaporated and the crude product was dried under vacuum. The ^{1}H NMR spectrum showed the same ratio as above.

Preparation of Amide 15. Diethyl 3-methylglutarate (**14**) (3.32 g, 16.42 mmol) and tryptamine (2.69 g, 16.81 mmol) were stirred for 17 h at 165-168°C. The crude product was purified by column chromatography (CH_2Cl_2:MeOH, 99:1) to give 1.63 g (31%) of amide **15**; mp. 70-73°C (CH_2Cl_2/hexane); IR: 1710 (EtO-*CO*-), 1650 cm^{-1} (-NH-*CO*-); ^{1}H NMR: 8.69 (1H, br s, indole NH), 7.60-7.05 (4H, m, arom.), 6.96 (1H, br s, indolyl α-H), 5.90 (1H, br s, NH), 4.08 (2H, q, J = 7, -O*CH*$_2$-CH$_3$), 1.22 (3H, t, J = 7, -OCH$_2$-*CH*$_3$), 0.96 (3H, d, J = 7, -CH$_3$); MS: 316 (M$^+$, 6), 271 (5), 144 (23), 143 (100), 130 (40); HR-MS: calcd for $C_{18}H_{24}N_2O_3$: 316.1787, found: 316.1793.

Preparation of Imine 16. Amide **15** (203 mg, 0.64 mmol) was dissolved in Na-dried benzene (1.5 ml). $POCl_3$ (0.4 ml) was added and the solution was refluxed for 2 h.The mixture was cooled to 0°C and 10% NaOH was slowly added until the solution was alkaline. The solution was extracted with CH_2Cl_2 and the extracts were washed with H_2O (10 ml). The organic phase was dried (Na_2SO_4), filtered, and evaporated to give 183 mg (96%) of amorphous imine **16**; IR: 1720 (C=O); ^{1}H NMR: 10.11 (1H, br s, NH), 7.60-7.10 (4H, m, arom.), 4.26 (2H, q, J = 7, -O*CH*$_2$-CH$_3$), 1.32 (3H, t, J = 7, -OCH$_2$-*CH*$_3$), 1.03 (3H, d, J = 6, -CH$_3$); MS: 298 (M$^+$, 20), 253 (10), 225 (22), 184 (100), 155 (25); HR-MS: calcd for $C_{18}H_{22}N_2O_2$: 298.1681, found: 298.1690.

Cyclization of Imine 16. Imine **16** (171 mg, 0.57 mmol) was dissolved in MeOH (2 ml). $NaBH_4$ (65 mg, 1.72 mmol) was added and the mixture was stirred for 1 h at room temperature. Alkaline work-up gave the crude product, which was purified by column chromatography (CH_2Cl_2:MeOH, 99:1-96:4) to give 78.8 mg (54%) of epimers **19** and **18** (ratio 3:1) and 46 mg (27%) of amorphous compound **17**. The separation of epimers was conducted by multiple recrystallizations in ethanol.

Tetrahydro-β-carboline **17**: IR: 1710 (C=O); ^{1}H NMR: 8.64 (1H, br s, NH), 7.50-7.05 (4H, m, arom.), 4.17 (2H, q, J = 7, -O*CH*$_2$-CH$_3$), 1.27 (3H, t, J = 7, -OCH$_2$-*CH*$_3$), 1.10 (3H, d, J =6.5, -CH$_3$); MS: 300 (M$^+$, 17),

171 (100); HR-MS: calcd for $C_{18}H_{24}N_2O_2$: 300.1838, found: 300.1859.

trans-2-Methyl lactam **18**: mp. 235-236°C (EtOH); IR: 1630 (C=O); ^{1}H NMR: **8.38 (1H, br s, NH), 7.50-7.05 (4H, m, arom.)**, 5.10 (1H, m, H-6_{eq}), 4.92 (1H, m, H-12b), 1.10 (3H, d, J = 6.5, -CH_3); MS: 254 (M^+, 100), 253 (55), 239 (23), 184 (36), 170 (55), 169 (64), 168 (30); HR-MS: calcd for $C_{16}H_{18}N_2O$: 254.1419, found: 254.1434.

cis-2-Methyl lactam **19**: mp. 220-222°C (EtOH); IR: 1630 (C=O); ^{1}H NMR: 8.02 (1H, br s, NH), 7.55-7.05 (4H, m, arom.), 5.17 (1H, m, H-6_{eq}), 4.79 (1H, dd, J = 11.5 and 5, H-12b), 1.08 (3H, d, J = 6, -CH_3); MS: 254 (M^+, 100), 253 (52), 239 (18), 184 (17), 170 (30), 169 (41), 168 (17); HR-MS: calcd for $C_{16}H_{18}N_2O$: 254.1419, found: 254.1426.

Cyclization of Tetrahydro-*β*-carboline 17. Compound **17** (80 mg, 0.27 mmol) was refluxed in toluene (3 ml) for 16 h. The solvent was evaporated and the crude product was purified by column chromatography (CH_2Cl_2:MeOH, 98:2) to give 52 mg (77%) of pure epimer **18**.

Epimerization of *trans*-2-Methyl Lactam 18. *trans*-2-Methyl lactam **18** (2.0 mg, 0.0079 mmol) was stirred in TFA[16] (1.5 ml) for 2 h at room temperature. The acid was removed by bubbling Ar through the solution and the crude product was dried under vacuum. The ^{1}H NMR spectrum showed a ratio of 80:20 (**18**:**19**).

Epimerization of *cis*-2-Methyl Lactam 19. *cis*-2-Methyl lactam **19** (5.0 mg, 0.020 mmol) was stirred in TFA[16] (1.5 ml) for 2 h at room temperature. The acid was removed by bubbling Ar through the solution and the crude product was dried under vacuum. The ^{1}H NMR spectrum showed a ratio of 20:80 (**19**:**18**).

Formation of Secolactam 20. *cis*-3-Methyl lactam **12** (68.7 mg, 0.27 mmol) was dissolved in TFA[16] (4 ml). Zn (176 mg, 2.69 mmol) was added to the solution, which was then refluxed for 3.5 h. Zn was removed by filtration and TFA was evaporated. Alkaline work-up gave the crude product, which was purified by column chromatography (CH_2Cl_2:MeOH, 99:1) to yield 15.1 mg (22%) of amorphous secolactam **20**; IR: 1650 (C=O); ^{1}H NMR: 7.92 (1H, br s, indole NH), 7.50-7.05 (4H, m, arom.), 5.32 (1H, br s, NH), 1.11 (3H, d, J = 7, -CH_3); MS: 256 (M^+, 100), 239 (12), 198 (26), 184 (55), 170 (50), 157 (47), 156 (61), 144 (40), 143 (42), 130 (35); HR-MS: calcd for $C_{16}H_{20}N_2O$: 256.1576, found: 256.1552.

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20. Due to the flexibility of the 10-membered ring in compound **20**, several signals are broad. Distinguishable signals not assigned appeared at δ 39.0, 32.8, 26.5, 22.6, and 21.0.