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Acid-Catalysed Epimerization of Indolo[2,3-*a*]quinolizidines. 1-, 2- and 3-Monosubstituted Alkyl Derivatives

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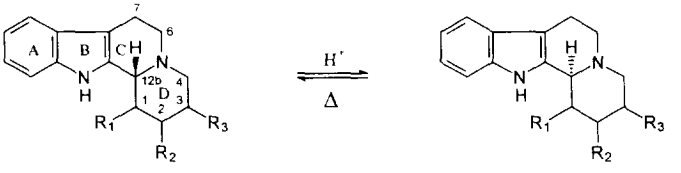
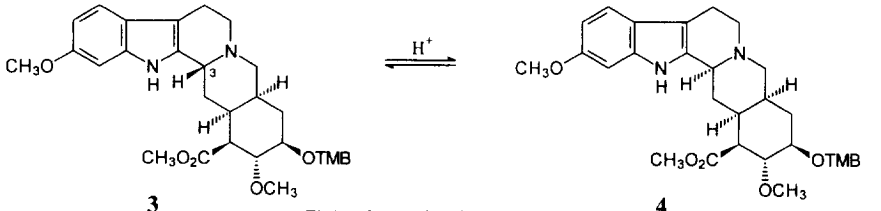
Abstract: Acid-catalysed epimerization of 1-, 2- and 3-monosubstituted 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine alkyl derivatives in refluxing trifluoroacetic acid (TFA) leads to an equilibrium mixture of C-12b diastereomers. The thermodynamically more stable epimer predominates over the kinetically favoured epimer in a ratio of about 85:15 unless the substituent is at C-1, in which case the ratio is 55:45. The proton at C-12b is exchanged when the epimerization is performed in refluxing TFA-*d*. New stereoselective synthesis of the missing 2-ethylindolo[2,3-*a*]quinolizidines is described. © 1997 Elsevier Science Ltd.

The indolo[2,3-*a*]quinolizidine system **1** ($R_1 = R_2 = R_3 = H$, Scheme 1) is a part of the carbon skeleton of corynantheines, yohimbines, heteroyohimbines and many other indole alkaloids.[1] Because of their pharmacologically valuable properties, indole alkaloids and indole alkaloid derivatives possessing this system have over the years been the subject of extensive chemical and synthetic investigations. It is well known that the bridgehead hydrogen at C-12b (C-3 in the biogenetic numbering[2]) can be epimerized with bases[3] and acids[4] (for example, equilibration of diastereomers **1** and **2**, Scheme 1). The epimerization of H-12b occurs with respect to the substituent at a chiral C-1, C-2 or C-3. The earliest and one of the most studied acid-catalysed epimerizations of this kind is the conversion of the clinically important natural product reserpine **3** into isoreserpine **4**[5] (Scheme 2). First proposals for the mechanism were introduced in the 1950's and the discussion of the reaction pathway has continued until the present.[6]



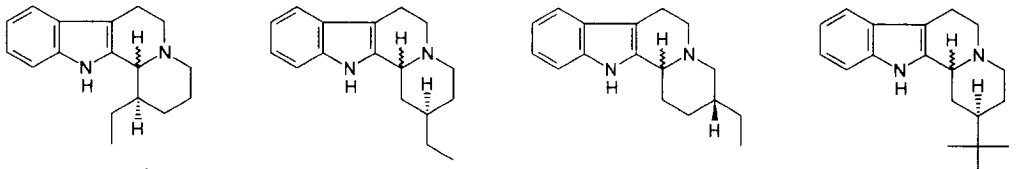
1 **2**

Scheme 1



Scheme 2

The highly stereoselective Pictet-Spengler cyclization is widely used for the synthesis of compounds containing an indolo[2,3-*a*]quinolizidine system.[6-8] Usually it gives the kinetically more favoured C-12b epimer as the major or only product. Acid-catalysed epimerization of the kinetic product leads generally to an equilibrium mixture, consisting of both the thermodynamic and the kinetic isomer.

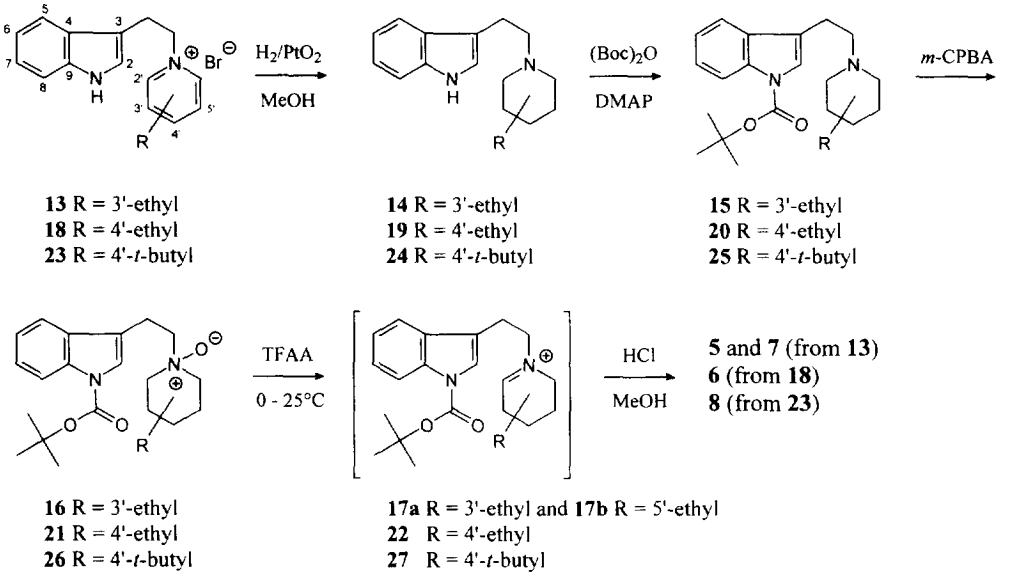


5 (H-12bβ) **6** (H-12bβ) **7** (H-12bβ) **8** (H-12bβ)
9 (H-12bα) **10** (H-12bα) **11** (H-12bα) **12** (H-12bα)

In addition to compounds related to reserpine there are several examples of acid-catalysed epimerization of indolo[2,3-*a*]quinolizidines, including 1-substituted,[9] 1,1-disubstituted,[10] 1,3-disubstituted[11] and 2-substituted[12] derivatives and some related compounds containing a vinylogous urethane moiety.[13,14] Although the epimerization behaviour of indolo[2,3-*a*]quinolizidines has long been a subject of investigation, we have not found any systematic studies on the epimerization of differently substituted derivatives. Because there are several indole alkaloids containing an ethyl side chain in ring D, the 1-, 2- and 3-ethyl substituted compounds **5**,[15] **6**[16] and **7**[15] were chosen as model compounds, and trifluoroacetic acid (TFA) was chosen as epimerization reagent. The epimerization was also performed with the 2-*t*-butyl-substituted compound **8**[17,18a] to investigate how a bulky side chain affects the reaction. Finally, an epimerization was performed with TFA-*d* to obtain information about a possible proton exchange at C-12b.

Results and Discussion

Model compounds for the epimerization experiments were prepared from corresponding pyridinium salts according to literature procedures[15,17] with slight modifications (see Experimental). Alkylation of alkylpyridines with tryptophyl bromide[19] yielded the corresponding pyridinium salts **13**, **18** and **23**. Catalytic hydrogenation of the salts furnished ethylpiperidines **14**, **19** and **24**, whose indole nitrogen was protected by the acid labile *t*-butyloxycarbonyl (Boc) group. The Boc-protected compounds **15**, **20** and **25** were converted to the corresponding *N*-oxides **16**, **21** and **26**, which were subjected to the Polonovski-Potier reaction[20-22] to give intermediate iminium salts **17**, **22** and **27**. These salts were cyclized by treatment with HCl/MeOH, which yielded the thermodynamically less stable C-12b epimers **5**, **6**, **7** and **8** (Scheme 3).



13 R = 3'-ethyl
18 R = 4'-ethyl
23 R = 4'-*t*-butyl

14 R = 3'-ethyl
19 R = 4'-ethyl
24 R = 4'-*t*-butyl

15 R = 3'-ethyl
20 R = 4'-ethyl
25 R = 4'-*t*-butyl

16 R = 3'-ethyl
21 R = 4'-ethyl
26 R = 4'-*t*-butyl

17a R = 3'-ethyl and **17b** R = 5'-ethyl
22 R = 4'-ethyl
27 R = 4'-*t*-butyl

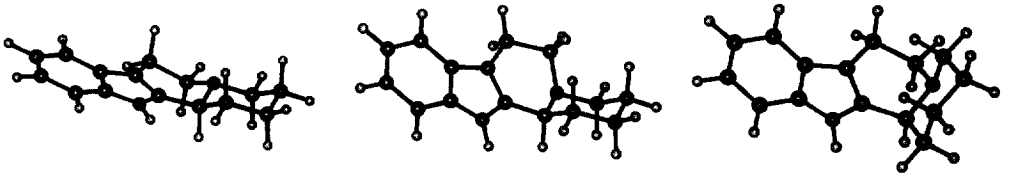
Scheme 3

Compounds **5**, **6**, **7** and **8** were refluxed for 16 h with TFA, which led to mixtures consisting of the starting compound and the thermodynamically more favoured C-12b epimers **9**,[15] **10**,[16] **11**[15] and **12**,[17,18a] respectively. The results are shown as entries 1-4 in Table 1. Epimerization of the epimers **9**, **10**, **11** and **12** under identical conditions (*vide supra*) gave the same ratios for the reaction mixtures (entries 5-8). This confirms that the acid-catalysed epimerization of monosubstituted indolo[2,3-*a*]quinolizidines is a true equilibrium reaction. Furthermore, refluxing of compound **6** with TFA for 2 h, 4 h, 8 h and 16 h (entries 9-11 and 2, respectively) confirmed that the equilibrium point was reached after 16 h reaction time.

Table 1. The Results of Acid-Catalysed Epimerization (ratio A:B determined by ^{1}H NMR).

Entry	Compound (A)	Time (h)	C-12b epimer (B)	Ratio A:B
1	**5**	16	**9**	45:55
2	**6**	16	**10**	15:85
3	**7**	16	**11**	20:80
4	**8**	16	**12**	15:85
5	**9**	16	**5**	55:45
6	**10**	16	**6**	85:15
7	**11**	16	**7**	80:20
8	**12**	16	**8**	85:15
9	**6**	2	**10**	38:64
10	**6**	4	**10**	24:76
11	**6**	8	**10**	18:82

The indolo[2,3-*a*]quinolizidine system can exist in three main conformations - one *trans*-quinolizidine (*a*) and two *cis*-quinolizidine conformations (*b* and *c*), which are in equilibrium by nitrogen inversion and *cis*-decalin type ring interconversion. Ring C is considered to be in a half chair conformation and ring D in a chair conformation.[18]



a *b* *c*

At equilibrium the thermodynamically more stable product in all cases but one predominated over the kinetic product in a ratio of about 85:15. An exception to this pattern occurred when the substituent was at C-1 (Table 1, entries 1 and 5), in which case the corresponding ratio was 55:45. Examination of the ^{13}C NMR chemical shifts of C-7 (Chart 1) reveals that in $CDCl_3$ the thermodynamically more stable epimers **9**, **10**, **11** and **12** exist almost purely as C/D *trans*-fused indoloquinolizidines (conformation *a*), whereas in the less stable epimers **5**, **6** and **7** there is a considerable contribution of conformer *c* (C/D *cis*) to the conformational equilibrium. The thermodynamically less favoured compound **8** exists in pure conformation *c*, however, allowing the bulky *t*-butyl group to lie in the favourable equatorial position.

The ethyl-substituted compounds **9**, **10** and **11** are all 1.5 ± 0.1 kcal/mol[23] more stable than their kinetically favoured epimers **5**, **6** and **7**. The corresponding energy difference between *t*-butyl substituted compounds **8** and **12** is 1.4 kcal/mol. Because the energy calculations did not show any significant deviations for the model compounds, the different epimerization behaviour of 1-ethyl substituted compounds **5** and **9** cannot be explained in terms of the energy difference between the kinetic and thermodynamic products. It is noteworthy that for the 2- and 3-substituted compounds the equilibrium ratio seems not to be principally dependent on the position or size of the alkyl side chain. Some other factors evidently play a major role in directing the outcome of the epimerization, as is suggested by the nearly 1:1 ratio in the equilibrium mixture of 1-substituted compounds **5** and **9**. The thermodynamically more stable compound **9**, which is in conformation *a* to avoid steric interactions between an equatorial ethyl group and the indolic part of the molecule, has the ethyl side chain in an unfavoured axial position.

Interesting results were obtained in an initial experiment with TFA-*d* as the epimerization medium. Epimerization of **6** with TFA-*d* under these conditions (*vide supra*) led to an equilibrium mixture of deuterated **6** and **7**. ^1H NMR analysis of the reaction mixture revealed that the proton at C-12b had been totally exchanged in both epimers. Similar proton exchange was detected in epimerization experiments made by Rosentreter *et al.*[13]

Conclusions

TFA-catalysed epimerization provides an easy route to the thermodynamically more stable C-12b epimers of monosubstituted indolo[2,3-*a*]quinolizidines. When the alkyl substituents is at C-2 or C-3, the yields are

good and at thermodynamical equilibrium the more stable C-12b epimer heavily predominates (80-85%). When the substituent is at C-1 the equilibrium ratio is close to 1:1. The procedure described can probably be used to epimerize H-12b of any monosubstituted indolo[2,3-*a*]quinolizidine with a side chain able to withstand vigorous acid treatment. The observed deuteration at C-12b under the conditions described adds an interesting perspective to the ongoing discussion of the reaction mechanism.[24]

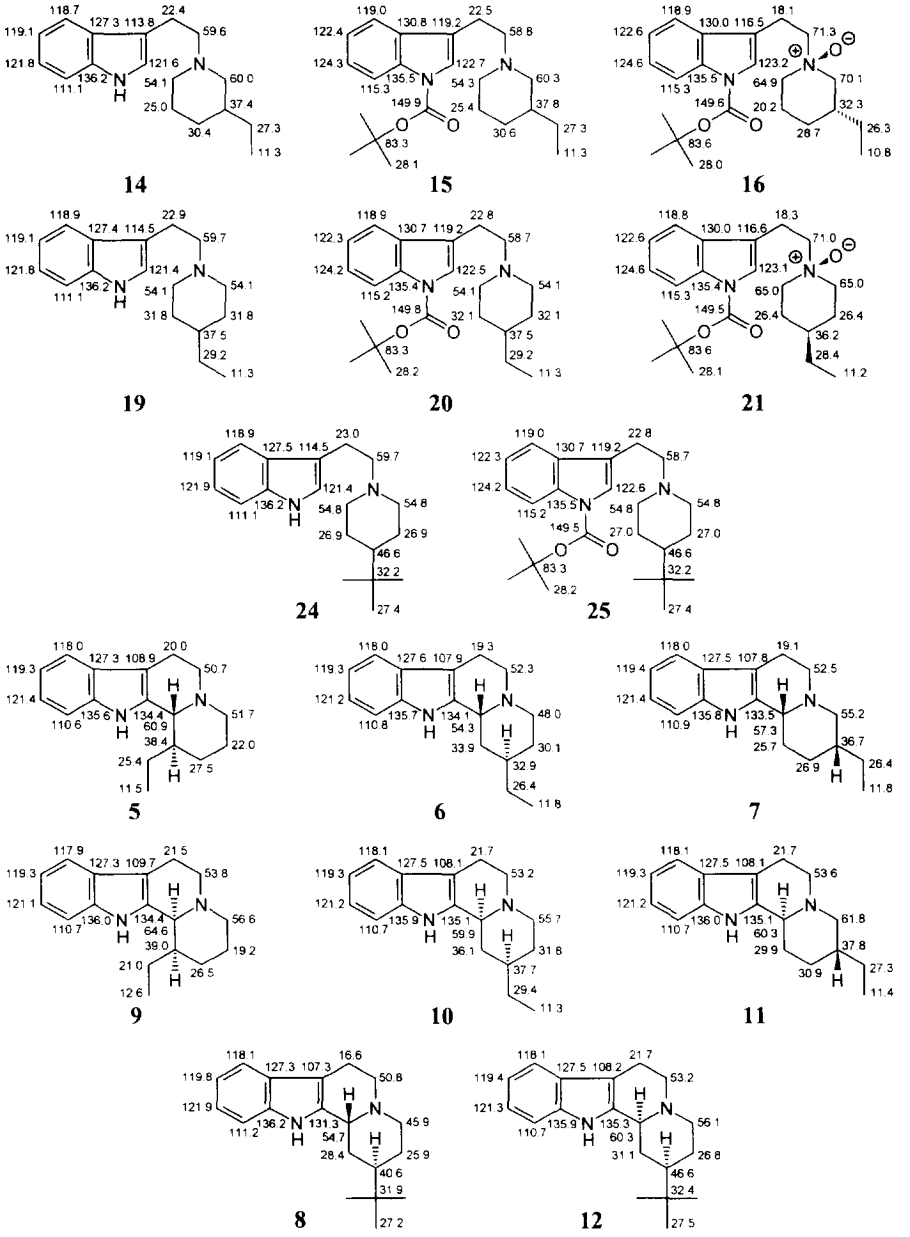


Chart 1

Experimental

All reactions were carried out under argon. Solvents were distilled over appropriate drying materials before use. Alkaline work up: addition of 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 (400 MHz, reference: TMS, δ_H = 0.0 ppm) and ^{13}C NMR (100 MHz, reference: $CDCl_3$, δ_C = 77.0 ppm) spectra were recorded on a Varian Unity 400 spectrometer using $CDCl_3$ as solvent. Coupling constants (J) are given in Hz. Signal assignments are based on standard APT, COSY and HETCOR experiments. For the ^{13}C NMR data of compounds **5-12**, **14-16**, **19-21** and **24-25**, see Chart 1. 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 (unless otherwise noted). Epimerization ratios were determined by ^1H NMR integration.

Preparation of Pyridinium Salt 18. Tryptophyl bromide (3.00 g, 13.4 mmol), prepared according to a literature procedure,[19] and 4-ethylpyridine (1.44 g, 13.4 mmol) were dissolved in a small amount of diethyl ether. After the ether was removed with streaming argon, the temperature of the mixture was raised to 100°C for 2 h. The product was washed several times with Et_2O to give 2.185 g (49%) of pure **18**: mp. 189-191°C (MeOH).

Catalytic Hydrogenation of 18 to Compound 19. Pyridinium salt **18** (1.00 g, 3.02 mmol) in MeOH (20 ml) was hydrogenated (PtO_2, 100 mg) for 16 h. Alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 96:4) afforded 668 mg (86%) of compound **19**: mp. 110-112°C (MeOH); IR: 3470 (NH); ^1H NMR δ: 8.26 (1H, br s, NH), 7.62-7.07 (4H, m, arom.), 6.97 (1H, s, indolyl α-H), 0.89 (3H, t, J = 7.5, $-CH_3$); MS: 256 (M^+, 4), 144 (5), 130 (8), 127 (11), 126 (100); HR-MS: calcd for $C_{17}H_{24}N_2$: 256.1939, found: 256.1953.

Preparation of Boc-protected Compound 20. Compound **19** (624 mg, 2.44 mmol) and $(Boc)_2O$ (801 mg, 1.5 equiv.) were dissolved in CH_2Cl_2 and DMAP (30 mg, 0.1 equiv.) was added. The solution was stirred at rt for 2 h. Alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 98:2) gave 856 mg (99 %) of **20**: viscous oil; IR: 1730 (C=O); ^1H NMR δ: 8.11 (1H, br d, H-8), 7.55-7.20 (4H, m, arom.), 1.66 (9H, s, *t*-butyl), 0.90 (3H, t, J = 7.5, $-CH_3$); MS: 356 (M^+, 1), 127 (10), 126 (100); HR-MS: calcd for $C_{22}H_{32}N_2O_2$: 356.2464, found: 356.2438.

Preparation of *N*-Oxide 21. Compound **20** (813 mg, 2.28 mmol) and *m*-CPBA (85%, 509 mg, 1.1 equiv.) were dissolved in CH_2Cl_2 (10 ml) and stirred at rt for 4.5 h. The mixture was evaporated and the residue neutralized and purified by column chromatography (alumina, CH_2Cl_2/MeOH, 99:1) to yield 724 mg (85%) of compound **21**: amorphous; IR: 1730 (C=O); ^1H NMR δ: 8.12 (1H, br d, J = 7, H-8), 7.64-7.23 (3H, m, arom.), 1.66 (9H, s, *t*-butyl), 0.94 (3H, t, J = 7.5, $-CH_3$); MS: 356 ($M-O^+$, 3), 271 (5), 243 (12), 167 (41), 143 (100), 126 (86); HR-MS: calcd for $C_{22}H_{32}N_2O_2$ $(M-O)^+$: 356.2464, found: 356.2441.

Preparation of 2-Ethylindoloquinolizidine 6. The *N*-oxide **21** (442 mg, 1.29 mmol) in CH_2Cl_2 (25 ml) was stirred at 0°C and trifluoroacetic anhydride (TFAA) was added during 15 min. Stirring was continued for 2 h at rt and the mixture, containing iminium intermediate **22**, was evaporated. The residue was dissolved in MeOH (50 ml) saturated with HCl gas and stirred at rt for 16 h. Alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 97:3) gave 173 mg (57%) of compound **6**: amorphous; IR: 3470 (NH); ^1H NMR δ: 7.87 (1H, br s, NH), 7.48-7.06 (4H, m, arom.), 3.92 (1H, br s, H-12b), 0.93 (3H, t, J = 7, $-CH_3$); MS: 254 (M^+, 73), 253 (100), 225 (23), 197 (36), 184 (12), 170 (24), 169 (32), 156 (21); HR-MS: calcd for $C_{17}H_{22}N_2$: 254.1782, found: 254.1776.

Epimerization of 6. Compound **6** (97 mg, 0.38 mmol) was dissolved in trifluoroacetic acid (13 ml) and the solution was refluxed (90°C) for 16 h. After evaporation of acid, alkaline work-up of the residue gave a mixture consisting of compounds **6** and **10**. Column chromatography (CH_2Cl_2/MeOH, 98:2) gave 14 mg (14%) of starting compound **6** and 70.5 mg (73 %) of epimer **10**: amorphous; IR: 3470 (NH), 2750-2830

(Wenkert-Bohlmann bands); ^{1}H NMR δ: 7.77 (1H, br s, NH), 7.48-7.05 (4H, m, arom.), 3.19 (1H, dd, J = 11 and 2, H-12b), 0.95 (3H, t, J = 7.5, -CH_3); MS: 254 (M^+, 75), 253 (100), 225 (16), 197 (22), 184 (7), 170 (10), 169 (13), 156 (9), 144 (5), 143 (6); HR-MS: calcd for $C_{17}H_{22}N_2$: 254.1782, found: 254.1778. The same experiment was repeated with different refluxing times. The ratio of **6** to **10** was at 0 h 100:0, 2 h 38:64, 4 h 24:76, 8 h 18:82, 16 h 15:85.

Epimerization of 10. Compound **10** (35 mg, 0.137 mmol) was dissolved in trifluoroacetic acid (5 ml) and the solution was refluxed overnight for 16 h. After evaporation of acid, alkaline work-up of the residue gave 34 mg (97 %) of a mixture consisting of starting compound **10** and its epimer **6** in ratio 85:15.

Catalytic Hydrogenation of 13 to Compound 14. Prepared from pyridinium salt **13** (1.2 g, 3.62 mmol) as described above for compound **19**. Compound **14**: yield 78%; mp. 115-116°C (MeOH), lit. mp. 113-115°C (aq MeOH).[25] Analytical data were identical with those described earlier.[26]

Preparation of Boc-protected Compound 15. Prepared from **14** as described above (compound **20**). Compound **15**: yield 98%; viscous oil. Analytical data were identical with those described earlier.[26]

Preparation of *N*-Oxide 16. Prepared from **15** as described above for compound **21**. Compound **16**: yield 86%; amorphous; IR: 1730 (C=O); ^{1}H NMR δ: 8.13 (1H, d, J = 8, H-8), 7.66-7.21 (3H, m, arom.), 1.66 (9H, s, *t*-butyl), 0.95 (3H, t, J = 7, -CH_3); MS: 372 (M^+), 143 (100); HR-MS: calcd for $C_{22}H_{32}N_2O_3$: 372.2413, found: 372.2392.

Preparation of 1- and 3-Ethylindoloquinolizidines 5 and 7. Prepared from **16** (273 mg, 0.73 mmol) *via* iminium intermediates **17a** and **17b**, respectively, as described above for compound **6** to yield a mixture of **5** and **7**. Column chromatography (CH_2Cl_2/MeOH, 98:2) gave 32 mg (17%) of pure **5** and 24 mg (13%) of pure **7**. Analytical data for compounds **5** and **7** were identical with those described earlier.[27]

Epimerization of Compounds 5 and 9. Compound **5** (25 mg, 0.098 mmol) was dissolved in trifluoroacetic acid (4 ml) and the solution was refluxed (90°C) for 16 h. After evaporation of acid, alkaline work-up of the residue gave a 45:55 mixture of compounds **5** and **9**. Column chromatography (CH_2Cl_2/MeOH, 99:1) gave 6.4 mg (26%) of compound **9**, analytical data of which were identical with those described earlier.[15] Epimerization of compound **9** under the same conditions yielded a 55:45 mixture of compounds **9** and **5**.

Epimerization of Compounds 7 and 11. Compound **7** (24 mg, 0.094 mmol) was dissolved in trifluoroacetic acid (4 ml) and the solution was refluxed (90°C) for 16 h. After evaporation of acid, alkaline work-up of the residue gave a 20:80 mixture of compounds **7** and **11**. Column chromatography (CH_2Cl_2/MeOH, 99.5:0.5) gave 13 mg (54%) of compound **11**, analytical data of which were identical with those described earlier.[15] Epimerization of compound **11** under the same conditions yielded a 80:20 mixture of compounds **11** and **7**.

Catalytic Hydrogenation of 23 to Compound 24. Prepared from pyridinium salt **23** (2.01 g, 5.61 mmol) as described above for compound **19**. Compound **24**: yield 72 %; mp. 158-159°C (MeOH), lit.[17] mp. 157°C. Analytical data were identical with those described earlier.[17]

Preparation of Boc-protected Compound 25. Prepared from **24** (1.02 g, 3.59 mmol) as described above for compound **20**. Compound **25**: yield 100 %; viscous oil; IR: 1730 (C=O); ^{1}H NMR δ: 8.10-7.23 (4H, m, arom.), 7.39 (1H, s, indolyl α-H), 1.66 (9H, s, Boc, *t*-butyl), 0.88 (9H, s, piperidine, *t*-butyl); MS: 384 (M^+, 1), 154 (100), 144 (8), 130 (8); HR-MS: calcd for $C_{24}H_{36}N_2O_2$: 384.2777, found: 384.2787.

Preparation of 2-*t*-Butylindoloquinolizidine 8. Prepared from compound **25** (30 mg, 0.078 mmol) *via* *N*-oxide **26** (not purified) and iminium intermediate **27** as described above for compound **6**. Compound **8**: yield 40%; amorphous material. Analytical data were identical with those described earlier.[18]

Epimerization of Compounds 8 and 12. Compound **8** (8.9 mg, 0.032 mmol) was dissolved in trifluoroacetic acid (4 ml) and the solution was refluxed (90°C) for 16 h. After evaporation of acid, alkaline work-up of the residue gave a 15:85 (8.9 mg) mixture of compounds **8** and **12**.[18] Epimerization of compound **12** under the same conditions yielded a 85:15 mixture of **12** and **8**.

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