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STEREOSELECTIVE PREPARATION OF INDOLOQUINOLIZIDINE N-OXIDES: PREDOMINANT CONFORMATIONS.

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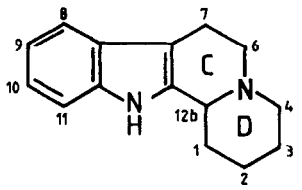
Abstract - Stereoselective preparation of indoloquinolizidine N-oxides possessing the N_b-oxygen - C(12b)-hydrogen relationship, trans or cis at will, is described. Contribution of the different conformations to the conformational equilibrium is studied by ^{13}C NMR spectroscopy, and significance of the N_b-oxygen - C(12b)-hydrogen relationship for the regioselective transformation of indoloquinolizidine N-oxides to the corresponding iminium ions is discussed.

Indoloquinolizidine N-oxides are important intermediates in indole alkaloid syntheses, because they can be used as precursors for iminium ions.[1-7] The relationship between the N_b-oxygen and the neighbouring hydrogens [C(4)H, C(6)H and C(12b)H] is known to direct the initial iminium ion formation.[8] The ease with which these iminium ions are isomerized[9] makes it difficult, however, to study the regioselectivity of the iminium ion formation by trapping methods.[10]



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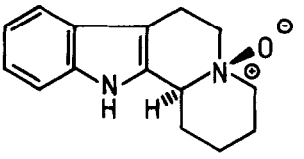
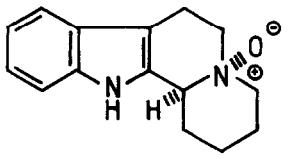


1a



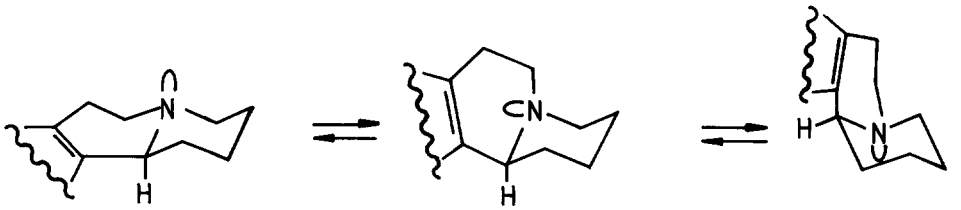
1b

Indoloquinolizidine 1, and similar compounds, can form two N-oxides differing in the relationship between the N_b-oxygen and the C(12b)-hydrogen (compound 1a, trans; compound 1b, cis). Simultaneously, the ring juncture between the C and D rings (C/D ring juncture) becomes determined (compound 1a, C/D trans juncture; compound 1b, C/D cis juncture).

To be able to draw more accurate conclusions concerning the regioselectivity in iminium ion formation we considered it important to know more about the stereoselective preparation and predominant conformations of indoloquinolizidine N_b-oxides. This is the subject of the present paper.

The N_b-oxides of the present study were prepared from the corresponding indoloquinolizidines by combining mCPBA-oxidation, BOC-protection, BOC-deprotection, and catalytic hydrogenation procedures (vide infra). ^{13}C NMR spectroscopy was used to determine the structures and predominant conformations of the N_b-oxides, mainly taking advantage of the N-O γ-effects on C(1), C(3) and C(7).[8]

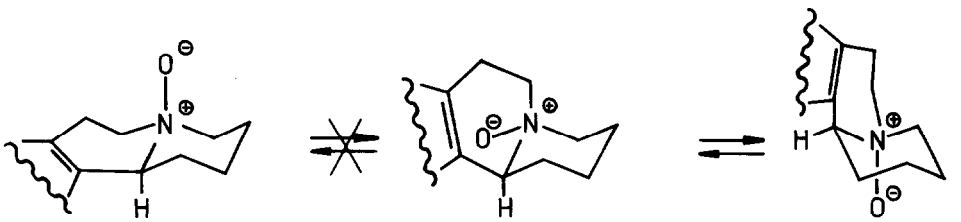
An indoloquinolizidine system of the present type can exist in three conformations with equilibration by nitrogen inversion and cis-decalin type ring interconversion (Scheme 1).[11-14] Normally, conformations a and c are assumed to predominate in the conformational equilibrium and conformation b is considered to be just a "transition state" between a and c.[13] The relative contributions of conformations a and c are strongly influenced by the substitution pattern.



a b c

Scheme 1

In the corresponding indoloquinolizidine N-oxides the C/D ring juncture (trans or cis) (vide supra) is fixed. Thus, there is no equilibrium between conformations a and b/c. Transition between conformations b and c is possible, however (Scheme 2).

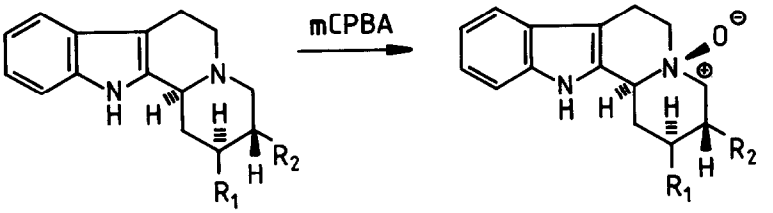


a b c

Scheme 2

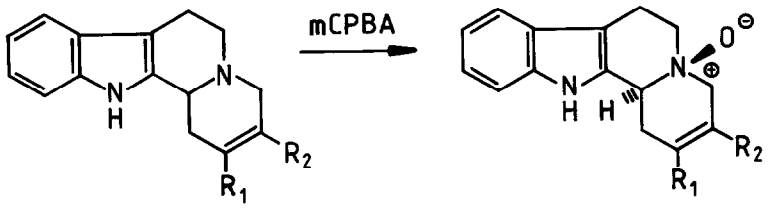
RESULTS AND DISCUSSION

Compounds 1, 2, 3, 4 and 5 normally exist predominantly in conformation a (vide supra). Oxidation of these compounds with mCPBA yields N-oxides 1a, 2a, 3a, 4a and 5a, respectively (C/D trans juncture) (Schemes 3 and 4), which, as expected, show negative γ-effects in ^{13}C NMR spectra (Fig. 1) in all three γ-positions. However, the upfield shifts in C(1) (-6.6 to -7.9 ppm) and C(3) (-5.2 to -7.1 ppm) are exceptionally large. Szántay[8] has found in the eburnamonine-vincamine series, on average, -3 ppm shifts in all directions. In a similar way, the open-chain derivative 18a [prepared from compound 18 (Scheme 5)] shows γ-effects -2.7 ppm [C(1)], -4.1 ppm [C(3)] and -4.6 ppm [C(7)], differing thereby considerably from compound 2a.



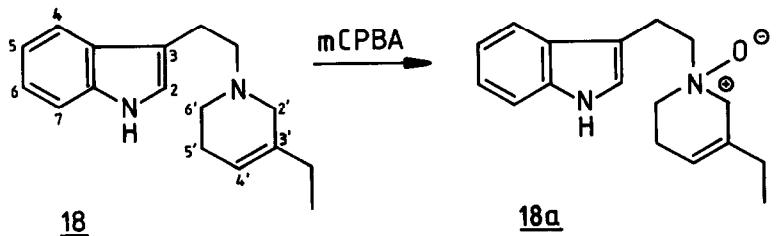
1	$R_1 = R_2 = H$	1a
3	$R_1 = H$; $R_2 = CH_2CH_3$	3a
4	$R_1 = C(CH_3)_3$; $R_2 = H$	4a

Scheme 3



2	$R_1 = H$; $R_2 = CH_2CH_3$	2a
5	$R_1 = C(CH_3)_3$; $R_2 = H$	5a

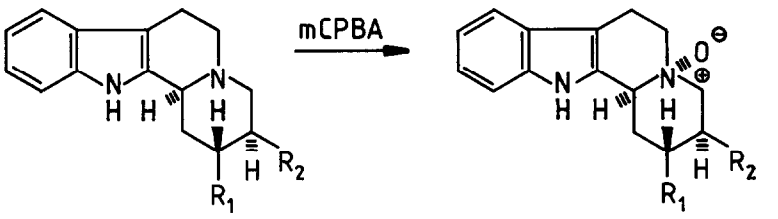
Scheme 4



18 18a

Scheme 5.

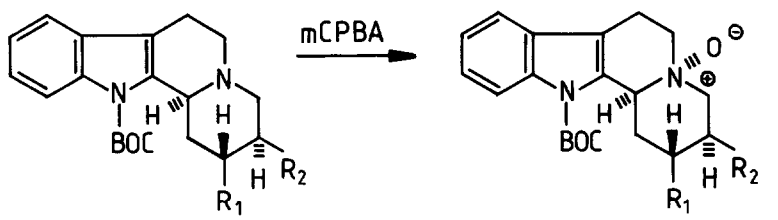
Oxidation of compounds 6, 7, 8 and 9 yields N-oxides 6b, 7b, 8b and 9b (C/D cis juncture) (Schemes 6 and 7) existing mainly in conformation c (vide supra). Only in the case of 2-tert-butyl derivatives 8b and 9b is the estimation of γ-effects straightforward, since the starting compounds (8 and 9) and the products 8b and 9b are predominantly in the same conformation. The observed shifts are in good agreement with theory, C(7) showing positive γ-trans effects. The predominant conformation of the ethyl derivative 7 is most probably a where the D-ring adopts a boat form (cf. Refs. 15-18). In the case of compound 6 a strong contribution of conformation c to the conformational equilibrium is evident.



6 $R_1 = H$; $R_2 = CH_2CH_3$ 6b

8 $R_1 = C(CH_3)_3$; $R_2 = H$ 8b

Scheme 6



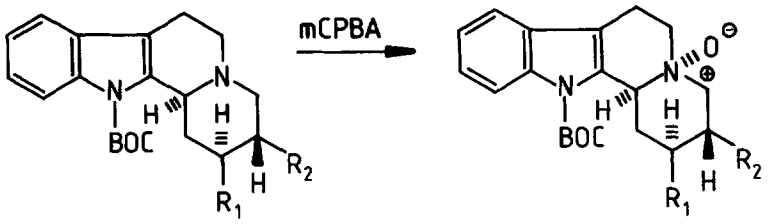
7 $R_1 = H$; $R_2 = CH_2CH_3$ 7b

9 $R_1 = C(CH_3)_3$; $R_2 = H$ 9b

Scheme 7

An exceptional result was obtained when BOC-protected compounds 10, 11, and 12 (vide infra) were oxidized (Scheme 8). The ^{13}C NMR spectra of the products (10b, 11b, and 12b) were totally different from the spectra of the products (1a, 3a, and 4a) of the corresponding unprotected compounds 1, 3 and 4 even though the spectra of the starting compounds (1, 3 and 4 versus 10, 11 and 12) differed only slightly from each other except for the upfield shift (~ 5 ppm) of C(6) in the BOC-protected compounds. A plausible explanation is a drastic difference in conformation between the protected and unprotected

compounds, with much greater effects on the ^{13}C NMR spectra of the N-oxides than their unoxidized counterparts.



10	$R_1 = R_2 = H$	10b
11	$R_1 = H$; $R_2 = CH_2CH_3$	11b
12	$R_1 = C(CH_3)_3$; $R_2 = H$	12b

Scheme 8

The ^{13}C NMR values of compounds 10b, 11b and 12b (Fig. 1) seem to be perfectly suited to the structures proposed for them (C/D ring juncture cis) conformation b predominating. In conformation b, one would expect the γ-effects to be negative towards C(7) and positive towards C(1) and C(3). And this is in fact the case, except for C(3) which shows practically no γ-effect. Consideration of the β-effects provides still more evidence for conformation b. In the conformation b the N-O group is axial with respect to ring C and equatorial with respect to ring D, reversely to the situation in conformation c. The β-effects should therefore be high for C(1) and C(4) and low for C(6).[8] In agreement with this, the observed effects for compounds 10b, 11b and 12b range from 13.5 to 15.9 ppm for C(1) and C(4) and from 6.2. to 7.2 ppm for C(6). If it is accepted that conformation b is the predominating conformation in compounds 10, 11 and 12, this would also explain the upfield shift of C(6) and slight upfield shift of C(3) [C(3) approaches C(6) in conformation b]. Conformation b thus seems to be favoured over conformation a in the BOC-protected series.

The double bond compound 13 yielded a mixture of two N-oxides (~ 2:1) (Scheme 9). The main product was the cis-isomer 13b existing mainly in conformation b and the minor product the trans-isomer 13a. Similarly, compound 14 yielded two N-oxides (~ 1:1) 14a, and 14b, the latter existing mainly in conformation b.

The oxidation of compound 15 (apparently existing mainly in conformation b), prepared from compound 16 by $(BOC)_2O$ treatment (vide infra), yielded only one product, the cis-isomer 15b, mainly existing in conformation b. The unprotected counterpart 16b was formed as the only product in the oxidation of compound 16, which in its turn was prepared from compound 17 by mCPBA oxidation and modified Polonovski reaction. Compound 16b could equally well be formed from compound 15b by HCOOH treatment (Scheme 10). The predominant conformation of compound 16b is somewhat problematic. Its ^{13}C NMR values, especially those of C(4), C(6) and C(7) (see Fig. 1), differ from those of compound 15b, pointing to a distorted conformation b.

Except for compound 16b, deprotection of those BOC-protected N-oxides, which exist in conformation b, yielded compounds (Schemes 11 and 12) different

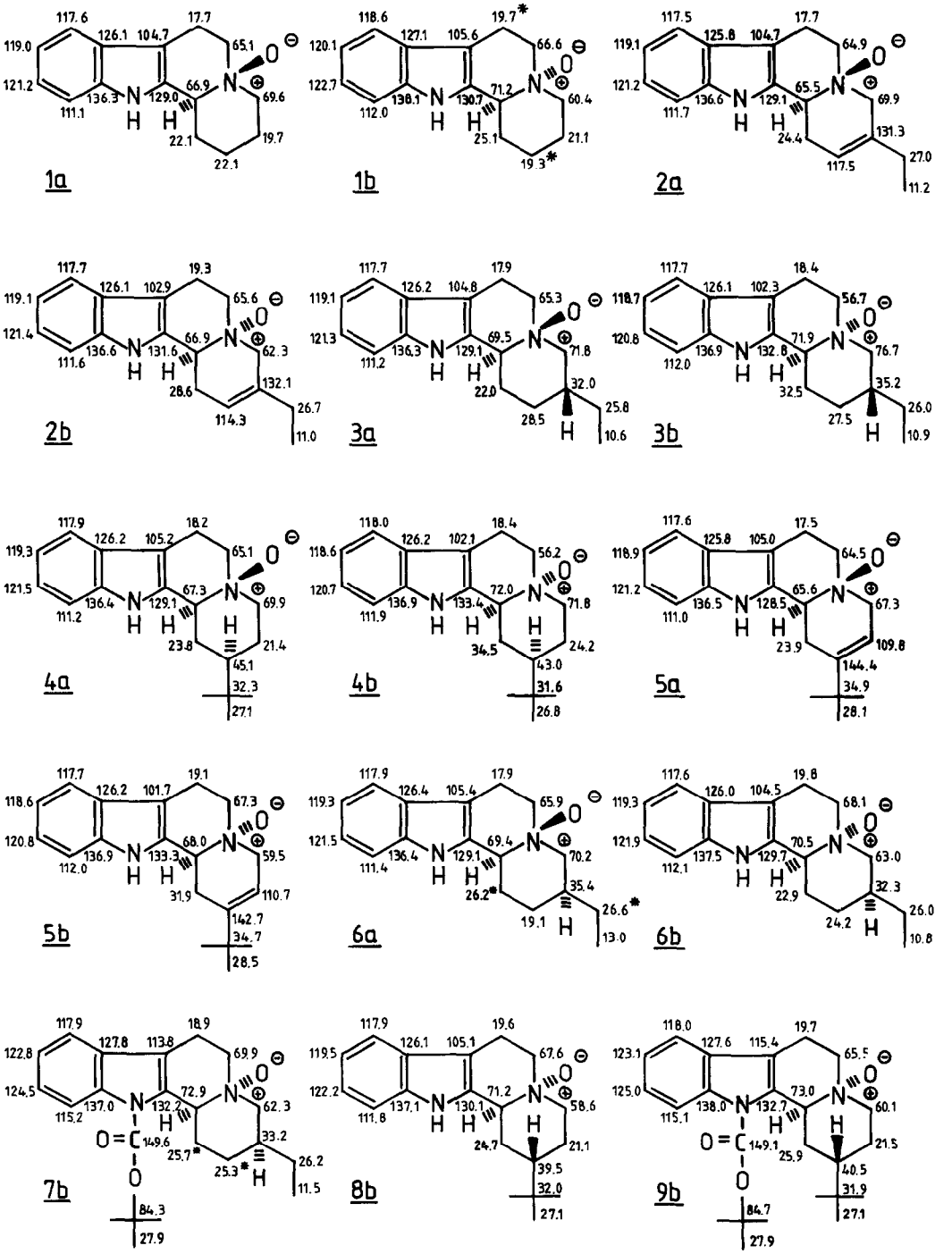


Fig. 1

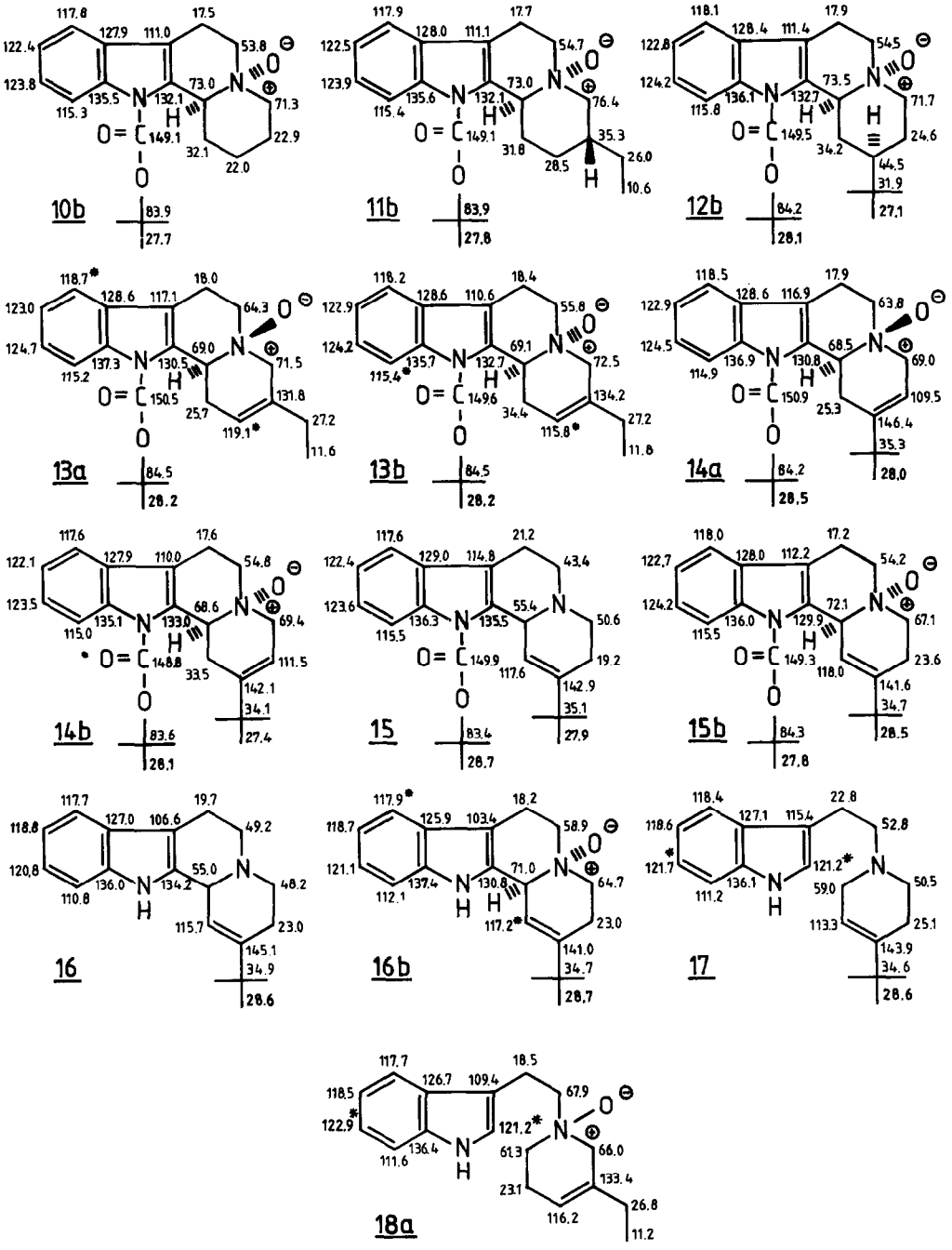
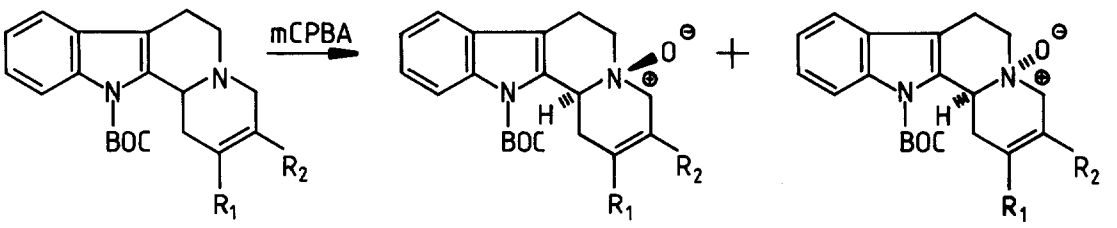


Fig. 1 (continued)

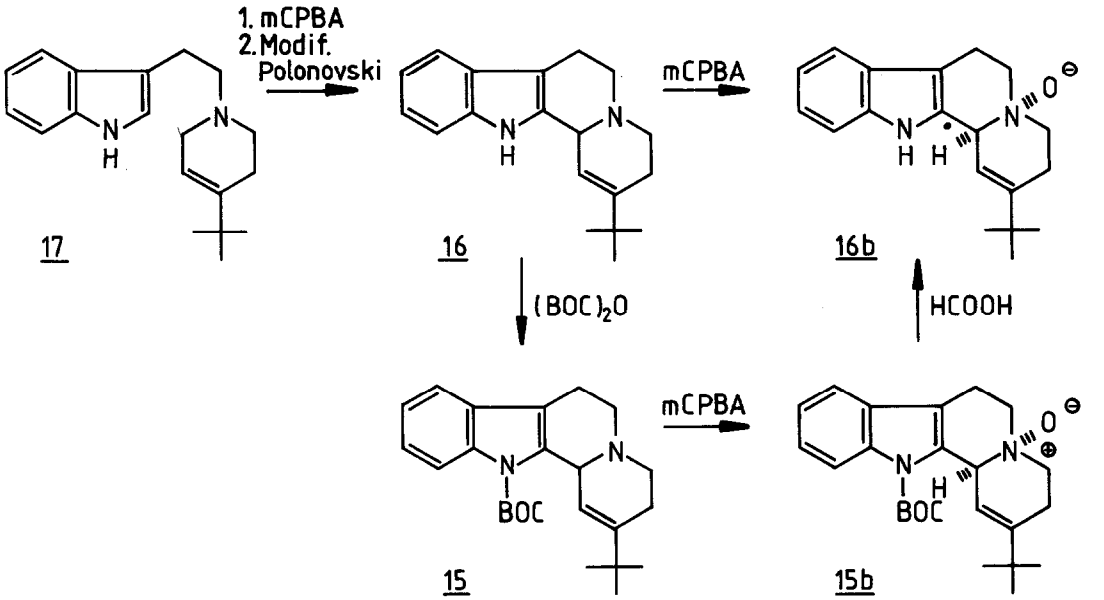


13 $R_1 = H; R_2 = CH_2CH_3$ 13a 13b

14 $R_1 = C(CH_3)_3; R_2 = H$ 14a 14b

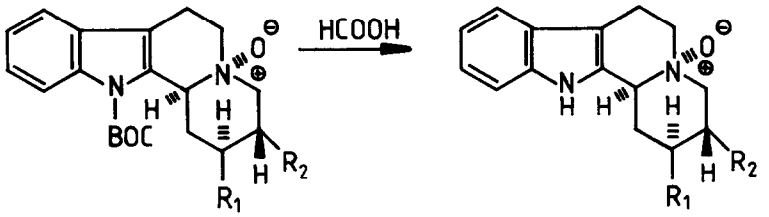
Scheme 9

from those formed by direct oxidation (cf. Schemes 3 and 4). This is because the C/D ring juncture (cis or trans) is not affected in deprotection. Which conformation, b or c, predominates in compounds possessing the cis C/D ring juncture depends on the substitution pattern.



Scheme 10

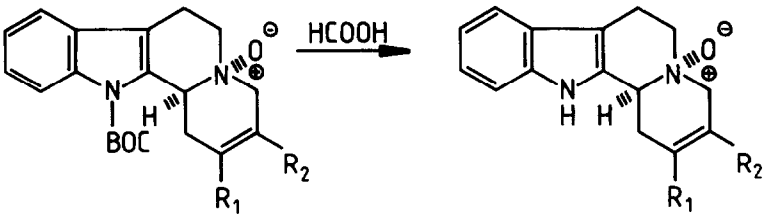
Cleavage of compound 11b yielded compound 3b (Scheme 11). These two compounds give very similar ^{13}C NMR spectra (Fig. 1), and we conclude that both exist predominantly in conformation b (C/D cis juncture) with equatorial ethyl groups. The same is true even more pronouncedly for compounds 12b and 4b with equatorial tert butyl groups in conformation b.



10b	$R_1 = R_2 = H$	1b
11b	$R_1 = H; R_2 = CH_2CH_3$	3b
12b	$R_1 = C(CH_3)_3; R_2 = H$	4b

Scheme 11

The two double bond N-oxides 13b and 14b yielded, after HCOOH treatment, compounds 2b and 5b, respectively (Scheme 12). Their predominant conformation is c, which seems to be the preferred one for unprotected compounds (C/D cis juncture) unless it causes extra strain. Compound 1b, formed from compound 10b by HCOOH cleavage (Scheme 11), gives a ^{13}C NMR spectrum (Fig. 1) with several aliphatic carbons poorly resolved, probably due to the slowness of the transition at room temperature between conformations b and c (predominant).

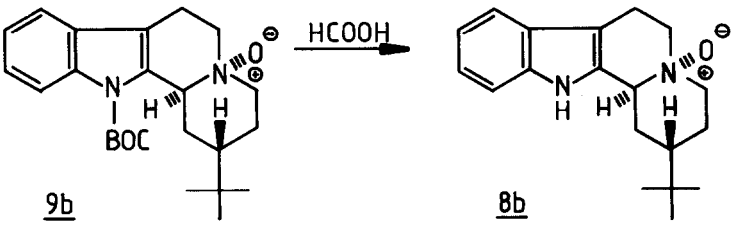


13b	$R_1 = H; R_2 = CH_2CH_3$	2b
14b	$R_1 = C(CH_3)_3; R_2 = H$	5b

Scheme 12

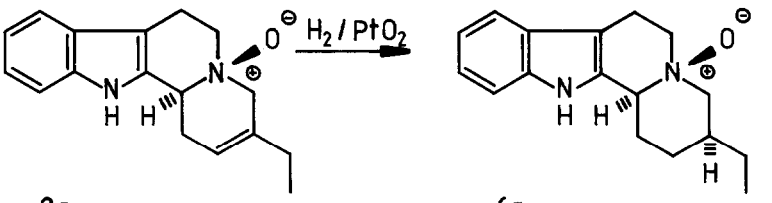
Two pairs of compounds, 6b and 7b, and 8b and 9b, exist in conformation c (vide supra), which thus turns out to be predominant for the BOC-protected compounds 7b and 9b (the substitution pattern disfavours conformation b). Deprotection of compound 9b yielded 8b as expected (Scheme 13), proving that no extra reactions took place during the HCOOH treatments.

To obtain as many isomers in the unprotected ethyl and tert butyl series as possible, we took advantage of the known stereoselectivity[7,19,20] of catalytic hydrogenation of compounds of type 2 and 14. Hydrogenation of compound 2a did, indeed, yield 6a, having the C/D trans juncture, which could not be achieved by direct oxidation (Scheme 14). It is interesting, that ^{13}C NMR



9b 8b

Scheme 13



2a 6a

Scheme 14

provides strong evidence that compound 6a exists in a form where the D-ring adopts a slightly twisted boat conformation (Fig. 2) (cf. Refs. 15-18). Thus, its ^{13}C NMR spectrum is very similar to that of compound 3a (Fig. 1), both compounds having equatorial ethyl groups. The only notable differences are that the C(2) signal is shifted upfield in compound 6a due to the proximity of the C(2)βH to the N-O group (Fig. 2) and the γ-effects on C(1) and C(3) are smaller in compound 6a than in compound 3a.

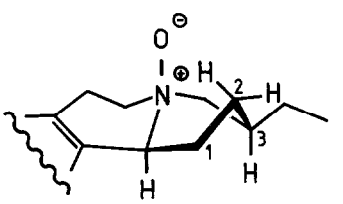
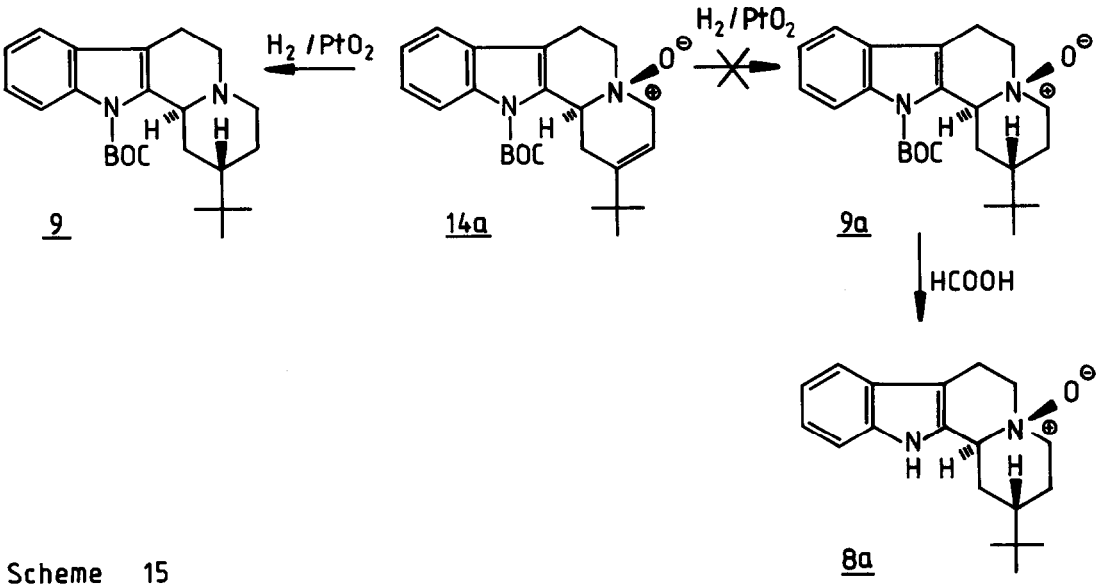


Fig. 2

Because of the simultaneous reduction of the N-oxide and the $\Delta^{2(3)}$ double bond, hydrogenation of the BOC-protected compound 14a led to compound 9. As a result, we were unable to prepare either compound 9a, the expected $\Delta^{2(3)}$ double bond hydrogenation product of compound 14a, or compound 8a, the expected deprotection product of compound 9a (Scheme 15).



9 14a 9a 8a

Scheme 15

CONCLUSIONS

It has been shown, that conformation b, rather than conformation a is preferred for BOC-protected indoloquinolizidines. If the substitution pattern is unfavourable for these conformations, the molecules adopt conformation c, or, in some cases, conformation a, where the ring D is in a boat form.

N-oxides possessing the C/D ring juncture cis or trans could be formed from indoloquinolizidines with good stereoselectivity. In many cases the desired stereochemistry was obtained by combining mCPBA-oxidation, BOC-protection, BOC-deprotection, and catalytic hydrogenation procedures (vide supra).

Knowing the exact conformation of the indoloquinolizidine N-oxides might help to predict their behaviour in iminium ion formation (preference for trans diaxial elimination). This is important in the use of iminium ions as intermediates in alkaloid syntheses. In theory, conformation a (C/D trans juncture) should lead to iminium ion formation towards C(4), C(6) and C(12b), conformation b (C/D cis juncture) towards C(6) and conformation c (C/D cis juncture) towards C(4)[21]. Studies on the applicability of this principle to the preparation of different indole alkaloid structures are in progress.

EXPERIMENTAL

IR spectra were recorded with a Perkin-Elmer 700 spectrophotometer using liquid film between NaCl crystals. IR absorption bands are expressed in reciprocal centimetres (cm^{-1}). ^{1}H and ^{13}C NMR spectra were measured with a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^{1}H NMR) and 15.04 MHz (^{13}C NMR). Chemical shift data are given in ppm downfield from TMS. Abbreviations s, d, t, m, br and def are used to designate singlet, doublet, triplet, multiplet, broad and deformed, respectively. For the ^{13}C NMR data, see Fig. 1. Mass spectrometry was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compound 17
1.10 g (3.06 mmol) of the pyridinium salt prepared from tryptophyl bromide and 4-tert-butyl pyridine was reduced with 0.30 g (2.6 equiv.) of $NaBH_4$ in a

mixture of 8 ml of MEOH and 2 ml H_2O. After 3 h, 20 ml of H_2O was added and stirring was continued for 0.5 h. Extraction with CH_2Cl_2 yielded almost pure compound 17, which was used for the preparation of compound 16 without further purification.
Y. 96%. Mp. 118°C (Lit.[22] Mp. 120°C).
^1H NMR ($CDCl_3$): 1.00 [9H, s, $-C(CH_3)_3$], 5.43 (1H, br s, H-3'), 6.79 (1H, s, H-2), 7.00 - 7.64 (4H, m, H-4, 5, 6, 7), 9.11 (1H, br s, NH). MS: 282 (M^+), 152 (100%), 144, 130; exact mass: 282.2104 (calc. for $C_{19}H_{26}N_2$: 282.2096).

Preparation of compound 16
0.695 g (2.46 mmol) of compound 17 was dissolved in CH_2Cl_2 (10 ml) and mCPBA (1.1 equiv.) was added as such. After stirring for 3 h, TFAA (2.5 equiv.) was added dropwise at -17°C. Stirring was continued at r.t. for 2 h. Then 100 ml of 50% HOAc was added. After 2 d, the reaction mixture was evaporated to dryness. The residue was thoroughly shaken with a mixture of 2N Na_2CO_3 and CH_2Cl_2. Extraction yielded compound 16, which was purified by column chromatography (silica, CH_2Cl_2/MeOH, 95/5).
Y. 56%. Amorphous material.
^1H NMR ($CDCl_3$): 1.05 [9H, s, $-C(CH_3)_3$], 4.39 (1H, br s, H-12b), 5.67 (1H, br s, H-1), 6.95 - 7.55 (4H, m, H-8, 9, 10, 11), 8.39 (1H, br s, NH). MS: 280 (M^+), 279 (100%), 265, 223; exact mass: 280.1943 (calc. for $C_{19}H_{24}N_2$: 280.1939).

Preparation of compound 15
0.285 g (1.02 mmol) of compound 16 was stirred with p-dimethylamino pyridine (DMAP) (0.1 equiv.) and di-t-butyl dicarbonate [$(BOC)_2O$] (1.2 equiv.) for 4 h. The reaction mixture was evaporated and purified by column chromatography (silica, CH_2Cl_2/MeOH, 95/5).
Y. 68%. Amorphous material.
IR: 1730 (C=O). ^1H NMR ($CDCl_3$): 1.05 [9H, s, $-C(CH_3)_3$], 1.68 [9H, s, $-OC(CH_3)_3$], 5.14 (1H, br s, H-12b), 5.62 (1H, s, H-1), 7.16 - 7.45 (3H, m, H-8, 9, 10), 8.14 - 8.31 (1H, m, H-11). MS: 380 (M^+), 323 (100%), 267; exact mass: 380.2490 (calc. for $C_{24}H_{32}N_2O_2$: 380.2464).

Preparation of compounds 1a, 2a, 3a, 4a, 5a, 6b, 7b, 8b, 9b, 10b, 11b, 12b, 13a, 13b, 14a, 14b, 15b, 16b and 18

General procedure: 1 Mmol of the corresponding indoloquinolizidine (reference to literature is given in parenthesis for each compound) was dissolved in 5 ml of CH_2Cl_2. mCPBA (1.1 equiv.) was added and the solution was stirred for 4 h. The N-oxide was obtained by passage through a column of alumina according to Craig and Purushothaman[23] (CH_2Cl_2/MeOH, 95/5).

Compound 1a (prepared from compound 1[24])
Y. 30%. Mp. 211 - 212°C (lit.[9] Mp. 210.5 - 211.5°C).
^1H NMR ($CDCl_3$ + 10 drops MeOH-d_4): 4.08 (1H, br s, H-12b), 6.99 - 7.51 (4H, m, H-8, 9, 10, 11), 10.07 (1H, br s, NH). MS: 242 (M^+), 226, 225 (100%), 224, 223, 197, 170, 169; exact mass: 242.1449 (calc. for $C_{15}H_{18}N_2O$: 242.1419).

Compound 2a (prepared from compound 2[7])
Y. 88%. Mp. 216 - 217°C.
^1H NMR ($CDCl_3$ + 5 drops MeOH-d_4): 0.99 (3H, t, J=7.2 Hz, $-CH_3$), 4.99 (1H, br s, H-2), 6.90 - 7.40 (4H, m, H-8, 9, 10, 11), 10.59 (1H, s, NH). MS: 268 (M^+), 252, 249, 247, 170 (100%), 169; exact mass: 268.1588 (calc. for $C_{17}H_{20}N_2O$: 268.1576).

Compound 3a (prepared from compound 3[7])
Y. 78%. Mp. 188 - 189°C.
^1H NMR ($CDCl_3$ + 10 drops MeOH-d_4): 0.93 (3H, def t, $-CH_3$), 6.96 - 7.51 (4H, m, H-8, 9, 10, 11), 10.10 (1H, br s, NH). MS: 270 (M^+, <1%), 254, 253 (100%), 223, 170, 169; exact mass: 270.1711 (calc. for $C_{17}H_{22}N_2O$: 270.1732).

Compound 4a (prepared from compound 4[24])
Y. 57%. Mp. 167 - 168°C.
^{1}H NMR ($CDCl_3$ + 5 drops MeOH-d_4): 0.97 [9H, s, -C(CH_3)$_3$], 4.09 (1H, br s, H-12b), 6.78 - 7.54 (4H, m, H-8, 9, 10, 11), 9.75 (1H, br s, NH). MS: 298 (M^+), 282, 281, 225, 223 (100%); exact mass: 298.2066 (calc. for $C_{19}H_{26}N_2O$: 298.2045).

Compound 5a (prepared from compound 5[24])
Y. 67%. Mp. 198 - 199°C.
^{1}H NMR ($CDCl_3$ + 7 drops MeOH-d_4): 1.14 [9H, s, -C(CH_3)$_3$], 5.32 (1H, s, 3-H), 6.81 - 7.51 (4H, m, H-8, 9, 10, 11), 10.30 (1H, br s, NH). MS: 296 (M^+), 280, 279, 278, 277 (100%), 170, 169; exact mass: 296.1898 (calc. for $C_{19}H_{24}N_2O$: 296.1889).

Compound 6b (prepared from compound 6[7])
Y. 63%. Mp. 183 - 184°C.
^{1}H NMR ($CDCl_3$): 0.83 (3H, def t, -CH_3), 4.59 (1H, br s, H-12b), 7.00 - 7.63 (4H, m, H-8, 9, 10, 11), 12.10 (1H, br s, NH). MS: 270 (M^+), 254, 253 (100%), 223, 170, 169; exact mass: 270.1723 (calc. for $C_{17}H_{22}N_2O$: 270.1732).

Compound 7b (prepared from compound 7[7])
Y. 71%. Amorphous material.
IR: 1730 (C=O). ^{1}H NMR ($CDCl_3$): 0.93 (3H, t, J=7.2 Hz, -CH_3), 1.65 [9H, s, -C(CH_3)$_3$], 4.85 (1H, br s, H-12b), 7.18 - 7.42 (3H, m, H-8, 9, 10), 7.99-8.13 (1H, m, H-11). MS: 370 (M^+ <1%), 354, 352, 297 (100%), 267, 253; exact mass (M^+ - 16): 354.2338 (calc. for $C_{22}H_{30}N_2O_2$: 354.2307).

Compound 8b (prepared from compound 8[24])
Y. 82%. Mp. 198 - 199°C.
^{1}H NMR ($CDCl_3$ + 2 drops MeOH-d_4): 0.94 [9H, s, -C(CH_3)$_3$], 4.53 (1H, s, H-12b), 7.06 - 7.45 (4H, m, H-8, 9, 10, 11), 11.27 (1H, s, NH). MS: 298 (M^+), 282, 281, 225, 223 (100%); exact mass: 298.2079 (calc. for $C_{19}H_{26}N_2O$: 298.2045).

Compound 9b (prepared from compound 9[24])
Y. 100%. Amorphous material.
IR: 1730 (C=O). ^{1}H NMR ($CDCl_3$): 0.88 [9H, s, -C(CH_3)$_3$], 1.65 [9H, s, -OC(CH_3)$_3$], 4.40 (1H, br s, H-12b), 7.22 - 7.46 [3H, m, H-8, 9, 10), 7.94-8.20 (1H, m, H-11). MS: 382 (M^+ - 16, <1%), 325, 282, 281 (100%), 225, 223, 197; exact mass (M^+ - 16): 382.2625 (calc. for $C_{24}H_{34}N_2O_2$: 382.2620).

Compound 10b (prepared from compound 10[24])
Y. 98%. Amorphous material.
IR: 1730 (C=O). ^{1}H NMR ($CDCl_3$): 1.65 [9H, s, -C(CH_3)$_3$], 4.88 (1H, br d, J=10.2 Hz, H-12b), 7.15 - 7.51 (3H, m, H-8, 9, 10), 8.00 - 8.16 (1H, m, H-11). MS: 342 (M^+), 326, 324, 269 (100%), 225, 223; exact mass: 342.1962 (calc. for $C_{20}H_{26}N_2O_3$: 342.1944).

Compound 11b (prepared from compound 11[7])
Y. 97%. Amorphous material.
IR: 1730 (C=O). ^{1}H NMR ($CDCl_3$): 0.93 (3H, def t, -CH_3), 1.64 (9H, s, -C(CH_3)$_3$), 4.83 (1H, br d, J=10.2 Hz, H-12b), 7.16 - 7.50 (3H, m, H-8, 9, 10), 8.05 - 8.17 (1H, m, H-11). MS: 354 (M^+ - 16, <1%), 352, 254, 253 (100%), 223, 170, 169; exact mass (M^+ - 16): 354.2304 (calc. for $C_{22}H_{30}N_2O_2$: 354.2307).

Compound 12b (prepared from compound 12[24])
Y. 92%. Amorphous material.
IR: 1730 (C=O). ^{1}H NMR ($CDCl_3$): 0.93 [9H, s, -C(CH_3)$_3$], 1.69 [9H, s, -OC(CH_3)$_3$], 4.96 (1H, d, J=10.8 Hz, H-12b), 7.17 - 7.55 (3H, m, H-8, 9, 10), 8.07 - 8.20 (1H, m, H-11). MS: 382 (M^+ - 16, <1%), 282 (100%), 281 ,

225, 223, 197; exact mass (M^+ - 16): 382.2625 (calc. for $C_{24}H_{34}N_2O_2$: 382.2620).

Compounds 13a and 13b (prepared from compound 13[7])
Y. 75% (a:b; 1:2).
The components (13a and 13b) were separated with PLC (silica, CH_2Cl_2/MeOH, 90/10).
Compound 13a (slightly contaminated with compound 13b).
Amorphous material.
IR: 1730 (C=O). ^1H NMR ($CDCl_3$): 1.08 (3H, t, J=7.2 Hz, $-CH_3$), 4.70 (1H, br s, H-12b), 5.73 (1H, br s, H-2), 7.16 - 7.54 (3H, m, H-8, 9, 10), 7.87 - 8.10 (1H, m, H-11). MS: 368 (M^+, <1%), 352, 350, 295, 293, 249, 247, 214, 170 (100%), 169; exact mass 368.2112 (calc. for $C_{22}H_{28}N_2O_3$: 368.2100).
Compound 13b.
Amorphous material.
IR: 1730 (C=O). ^1H NMR ($CDCl_3$): 1.08 (3H, t, J=7.2 Hz, $-CH_3$), 5.11 (1H, dd, J_1=10.2 Hz, J_2=6.3 Hz, H-12b), 5.47 (1H, br s, H-2), 7.16 -7.45 (3H, m, H-8, 9, 10), 7.94 - 8.11 (1H, m, H-11). MS: 368 (M^+, <1%), 352 (<1%), 268, 252, 247, 186,[25] 170 (100%), 169; exact mass (M^+ - 16): 352.2159 (calc. for $C_{22}H_{28}N_2O_2$: 352.2151).

Compounds 14a and 14b (prepared from compound 14[24]).
Y. 83% (a:b; 1:1).
The components (14a and 14b) were separated by column chromatography (alumina, CH_2Cl_2/MeOH, 95/5)
Compound 14a.
Mp. 161-162°C.
IR: 1730 (C=O). ^1H NMR ($CDCl_3$): 1.13 [9H, s, $-C(CH_3)_3$], 1.68 [9H, s,-$OC(CH_3)_3$], 4.68 (1H, d, J=8.4 Hz, H-12b), 5.37 (1H, br s, H-3), 7.16 - 7.45 (3H, m, H-8, 9, 10), 7.81 - 8.02 (1H, m, H-11). MS: 396 (M^+), 380, 378, 323, 321, 278, 277 (100%), 170, 169; exact mass: 296.2376 (calc. for $C_{24}H_{32}N_2O_3$: 396.2413).
Compound 14b (slightly contaminated with compound 14a).
Amorphous material.
IR: 1730 (C=O). ^1H NMR ($CDCl_3$): 1.07 [9H, s, $-C(CH_3)_3$], 1.68 [9H, s,-$OC(CH_3)_3$], 5.11 (1H, dd, J_1=10.2 Hz, J_2=6.0 Hz, H-12b), 5.42 (1H, br s, H-3), 7.17 - 7.44 (3H, m, H-8, 9, 10), 7.84 - 8.20 (1H, m, H-11). MS: 396 (M^+), 296, 278, 277, 221, 186 (100%),[25] 170, 169; exact mass: 396.2387 (calc. for $C_{24}H_{32}N_2O_3$: 396.2413).

Compound 15b [prepared from compound 15, (vide supra)]
Y. 100%. Amorphous material.
IR: 1740 (C=O). ^1H NMR ($CDCl_3$): 1.07 [9H, s, $-C(CH_3)_3$], 1.67 [9H, s,-$OC(CH_3)_3$], 5.58 (2H, br, H-2, 12b), 7.19 - 7.57 (3H, m, H-8, 9, 10), 8.11-8.28 (1H, m, H-11). MS: 396 (M^+, <1%), 380, 378, 323, 321, 277, 275, 223, 221 (100%); exact mass: 396.2430 (calc. for $C_{24}H_{32}N_2O_3$: 396.2413).

Compound 16b [prepared from compound 16, (vide supra)].
Y. 58%. Mp. 194 - 195°C.
^1H NMR ($CDCl_3$): 0.87 [9H, s, $-C(CH_3)_3$], 4.50 (1H, s, H-12b), 5.49 (1H, s, H-1), 6.93 - 7.39 (4H, m, H-8, 9, 10, 11), 12.29 (1H, s, NH). MS: 296 (M^+, <1%), 280, 278, 277, 275, 263, 223, 221; (100%) exact mass: 296.1902 (calc. for $C_{19}H_{24}N_2O$: 296.1889).

Compound 18a (prepared from compound 18[7])
Y. 95%. Amorphous material.
^1H NMR ($CDCl_3$): 0.97 (3H, t, J=7.2 Hz, $-CH_3$), 5.53 (1H, br s, H-4'), 6.99 (1H, d, J=2.1 Hz, H-2), 7.06 - 7.52 (4H, m, H-4, 5, 6, 7), 11.27 (1H, s, NH). MS: 270 (M^+, <1%), 254 (<1%), 252, 143 (100%), 127, 124, 115; exact mass (M^+ - 16): 254.1792 (calc. for $C_{17}H_{22}N_2$: 254.1783).

Preparation of compounds 1b, 2a, 2b, 3b, 4b, 5a, 5b, 8b, and 16b

General procedure: 1 Mmol of the corresponding BOC-protected N-oxide was stirred with 20 ml of HCOOH for 2 d. After evaporation, the mixture was neutralized with 2N Na_2CO_3, extracted with CH_2Cl_2 and purified by column chromatography.

Compound 1b [prepared from compound 10b (vide supra)]
Y. 71%. Mp. 189°C (lit.[9] Mp. 212 - 213.5°C)
^{1}H NMR (MeOH-d_4): 4.50 (1H, br s, H-12b), 7.08 - 7.54 (4H, m, H-8, 9, 10, 11), 10.73 (1H, br s, -NH). MS: 242 (M^+), 226, 225 (100%), 197, 170, 169; exact mass: 242.1443 (calc. for $C_{15}H_{18}N_2O$: 242.1419).

Compounds 2a and 2b [prepared from the mixture of compounds 13a and 13b]
The components (2a and 2b) were separated by column chromatography (alumina, CH_2Cl_2/MeOH, 95/5).
Compound 2a
Y. 27%. Mp. 216 - 217°C.
Analytical data were identical with those given above.
Compound 2b
Y. 48%. Mp. 179 - 180°C.
^{1}H NMR ($CDCl_3$ + 2 drops MeOH-d_4): 0.93 (3H, t, J=7.2 Hz, $-CH_3$), 5.36 (1H, br s, H-2), 6.95 - 7.36 (4H, m, H-8, 9, 10, 11), 10.97 (1H, s, NH). MS: 268 (M^+), 252, 250, 249, 186 (100%),[25] 170, 169; exact mass: 268.1588 (calc. for $C_{17}H_{20}N_2O$: 268.1576).

Compound 3b [prepared from compound 11b (vide supra)]
Y. 89%. Mp. 207°C.
^{1}H NMR ($CDCl_3$ + 3 drops MeOH-d_4): 0.82 (3H, def t, $-CH_3$), 6.83 - 7.50 (4H, m, H-8, 9, 10, 11), 12.33 (1H, br s, NH). MS: 270 (M^+), 254 (100%), 253, 223, 170, 169; exact mass: 270.1729 (calc. for $C_{17}H_{22}N_2O$ 270.1732).

Compound 4b [prepared from compound 12b (vide supra)]
Y. 85%. Mp. 192 - 193°C.
^{1}H NMR ($CDCl_3$): 0.68 (9H, s, $-C(CH_3)_3$), 6.93 - 7.54 (4H, m, H-8, 9, 10, 11), 12.71 (1H, s, NH). MS: 298 (M^+), 282, 281 (100%), 225, 223, 197; exact mass: 298.2046 (calc. for $C_{19}H_{26}N_2O$: 298.2045).

Compounds 5a and 5b [prepared from the mixture of compounds 14a and 14b (vide supra)]
The components (5a and 5b) were separated by column chromatography (alumina, CH_2Cl_2/MeOH, 95/5).
Compound 5a.
Y. 38%. Mp. 198 - 199°C.
Analytical data were identical with those given above.
Compound 5b
Y. 37%. Mp. 177°C.
^{1}H NMR ($CDCl_3$): 0.91 (9H, s, $-C(CH_3)_3$), 5.16 (1H, s, 3-H), 6.91 - 7.43 (4H, m, H-8, 9, 10, 11), 12.38 (1H, s, NH). MS: 296 (M^+), 280, 279, 278, 277, 186 (100%),[25] 170, 169; exact mass: 296.1857 (calc. for $C_{19}H_{24}N_2O$: 296.1889).

Compound 8b [prepared from compound 9b (vide supra)]
Y.85%. Mp. 198 - 199°C.
Analytical data were identical with those given above.

Compound 16b [prepared from compound 15b (vide supra)]
Y. 57%. Mp. 194 - 195°C.
Analytical data were identical with those given above.

Preparation of compound 6a
Compound 2a (45 mg, 0.17 mmol) was catalytically (PtO_2) hydrogenated to give

6a, which was purified by column chromatography (alumina, CH_2Cl_2/MeOH, 95/5). Y. 72%. Mp. 193 - 194°C.
^1H NMR ($CDCl_3$ + 3 drops MeOH-d_4): 0.96 (3H, t, J=7.2 Hz, $-CH_3$), 4.04 (1H, d, J=12.0 Hz, H-12b), 6.99 - 7.52 (4H, m, H-8, 9, 10, 11), 9.58 (1H, br s, NH). MS: 270 (M^+), 254, 253 (100%), 170, 169; exact mass: 270.1758 (calc. for $C_{17}H_{22}N_2O$: 270.1732).

Attempt to prepare compounds 9a and 8a
Compound 14a (58 mg, 0.15 mmol) was catalytically (PtO_2) hydrogenated. Normal work-up led to the isolation of compound 9.
Y. 88%. Amorphous material.
Analytical data were identical with those described earlier.[24]
The desired compound 9a, indispensable intermediate for the preparation of compound 8a, was not detected in the reaction mixture.

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