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INDOLOQUINOLIZIDINE IMINIUM SPECIES FORMED UNDER THE MODIFIED POLONOVSKI REACTION CONDITIONS

TARJA TAMMINEN, REIJA JOKELA, BIRGIT TIRKKONEN AND MAURI LOUNASMAA*

Laboratory for Organic and Bioorganic Chemistry,
Technical University of Helsinki, SF-02150 Espoo, Finland

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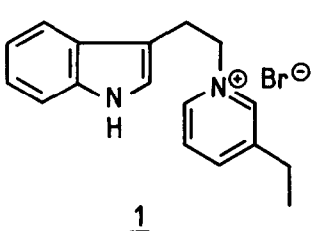
Abstract - The regioselectivity in the formation of different iminium species, generated from four indoloquinolizidines under the modified Polonovski reaction conditions, was studied using $NaBD_4$-reduction and cyanide trapping of the intermediate iminium ions.

In connection with our studies on compounds of vincamine-eburnamine type[1-4] and sarpagine-ajmaline type[1,5] we became interested in studying the formation of iminium salts from indoloquinolizidine N-oxides under modified Polonovski reaction conditions in more detail. Previous reports[6,7] indicate that the thermodynamically most stable iminium salt is formed as the main product when stereoelectronic requirements for E2-type trans-axial elimination are fulfilled. In most cases this means elimination of the C(12b) proton.

$NaBD_4$-reduction and cyanide trapping of the iminium intermediates were chosen as a means of determining the orientation of the reaction of four different starting compounds 3, 5, 8 and 11 (vide infra).[8]

RESULTS AND DISCUSSION

Compound 3, prepared from compound 1 via compound 2,[9] bears a $\Delta^{2,3}$ double bond, known to have a strong orientating effect on iminium ion formation.[10] Competition between C(12b)- and C(4)-elimination could thus



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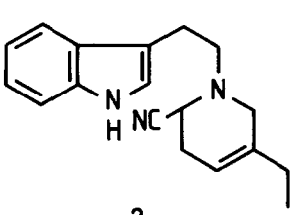

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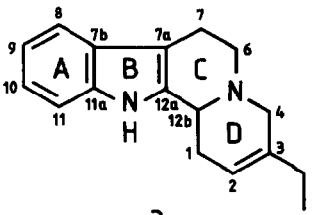
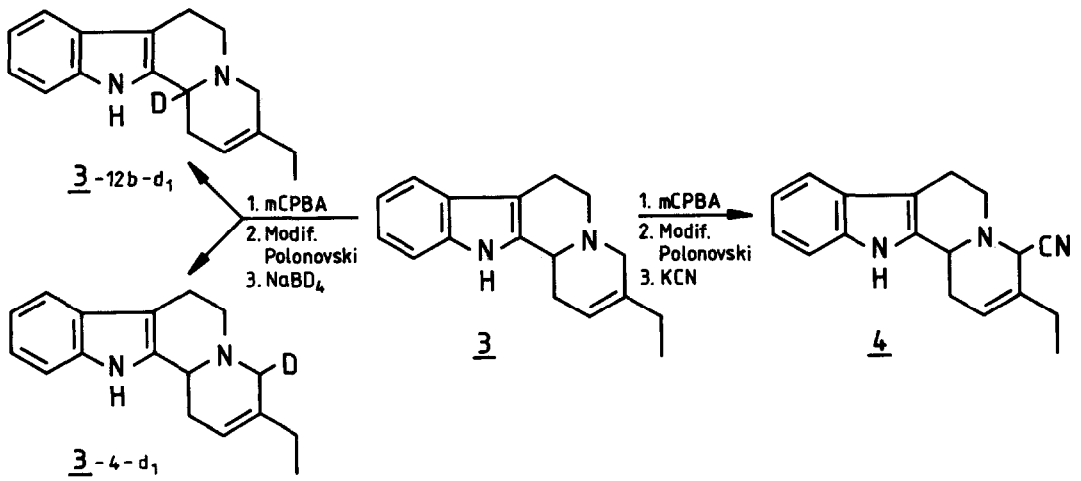


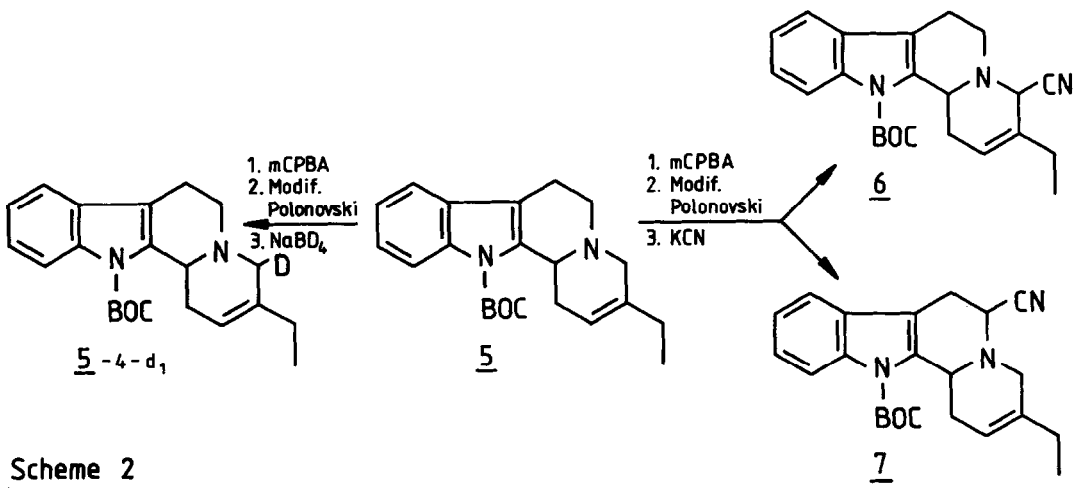
3

be anticipated. Cyanide trapping of the iminium ion(s) formed from the corresponding N-oxide under the modified Polonovski reaction conditions yielded 4 as the only isolable product, pointing to elimination of C(4)H (thermodynamic end product). However, when the same iminium "intermediate" was reduced with $NaBD_4$, deuterium was found at C(12b) (compound 3-12b-d_1) and at C(4) (compound 3-4-d_1) (kinetic end products), indicating the presence of both of the expected iminium isomers in the mixture. The ^{13}C NMR spectrum of the product mixture showed an approximately 1:1 proportion of compounds 3-12b-d_1 and 3-4-d_1 (Scheme 1).



Scheme 1

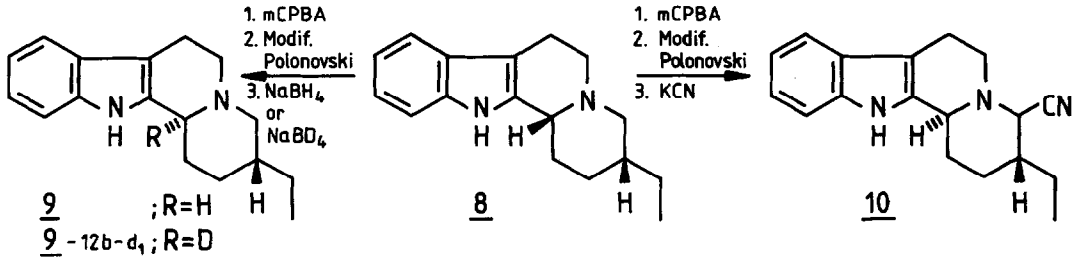
Compound 5 with the protective t-butyloxycarbonyl (BOC) group at the indole nitrogen also confirmed the orientating effect of the $\Delta^{2,3}$ double bond. Both deuterium and the cyanide group were found only at C(4) (compounds 5-4-d_1 and 6) (Scheme 2).



Scheme 2

An interesting result was obtained with compound 5 when the modified Polonovski reaction conditions were slightly altered. When the temperature of the reaction mixture was allowed to rise from -17°C to 0°C instead of to room temperature before cyanide addition (for details, see Experimental), compound 7 was formed in addition to 6 indicating the elimination of C(6)H (Scheme 2). Useful applications for this reaction might be found in the synthesis of the sarpagine-ajmaline group alkaloids.[4]

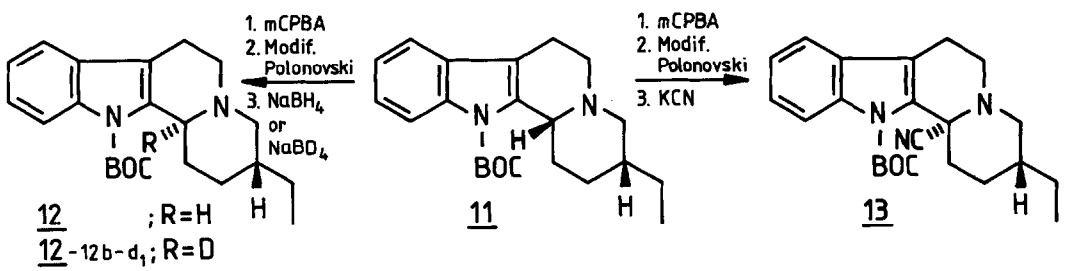
When the iminium ion derived from compound 8 was $NaBH_4$- and $NaBD_4$-reduced, hydride and deuteride incorporation at C(12b) (as expected) and epimerization were observed (compounds 9 and 9-12b-d_1, respectively). When the iminium ion was trapped with cyanide ion, however, only compound 10 whose formation must be preceded by the elimination of C(4)H (Scheme 3) was found. The structure of 10 was unambiguously deduced from its ^{13}C NMR spectra using the corresponding non-cyanated compound 9 as a reference[11] and the observed substituent increments for the cyano group in a corresponding piperidine derived compound.[12] The observed epimerizations may be due either to equilibration between two iminium ions or between C(4)-iminium ion and the corresponding enamine form.



9 ; R=H
9-12b-d_1 ; R=D
8
10

Scheme 3

In the normal $NaBH_4$- and $NaBD_4$-treatment the iminium ion derived from compound 11 (with the protective BOC-group) yielded the corresponding epimerized products 12 and 12-12b-d_1, respectively.[13] But contrary to the situation for compound 8, also the cyanide trapped product was the C(12b)-isomer (compound 13) (Scheme 4). The position of the cyano-group was readily deduced from the two triplets and a singlet (SFORD) in the region from 49 to 61 ppm in the ^{13}C NMR spectra; and it was indicated by the absence of the proton at C(12b) in the ^{1}H NMR spectrum. Compounds of this type may be useful in the preparation of alkaloids of the pseudovincamine series.[14]



12 ; R=H
12-12b-d_1 ; R=D
11
13

Scheme 4

The role of the BOC-group in these reactions was clearly not just protective. The observed orientating effect might be due to the conformational changes (e.g. in the N-oxides) that are caused by this bulky group.

The present investigation shows that the formation of iminium ions varies strongly with the structure of the starting compounds and with slight changes in the reaction conditions that are chosen. Further, it underlines the caution needed in interpreting the results obtained from the use of different intermediates, results which may at first glance appear contradictory.

^{13}C NMR data of all the compounds formed are given in Fig. 1.[15]

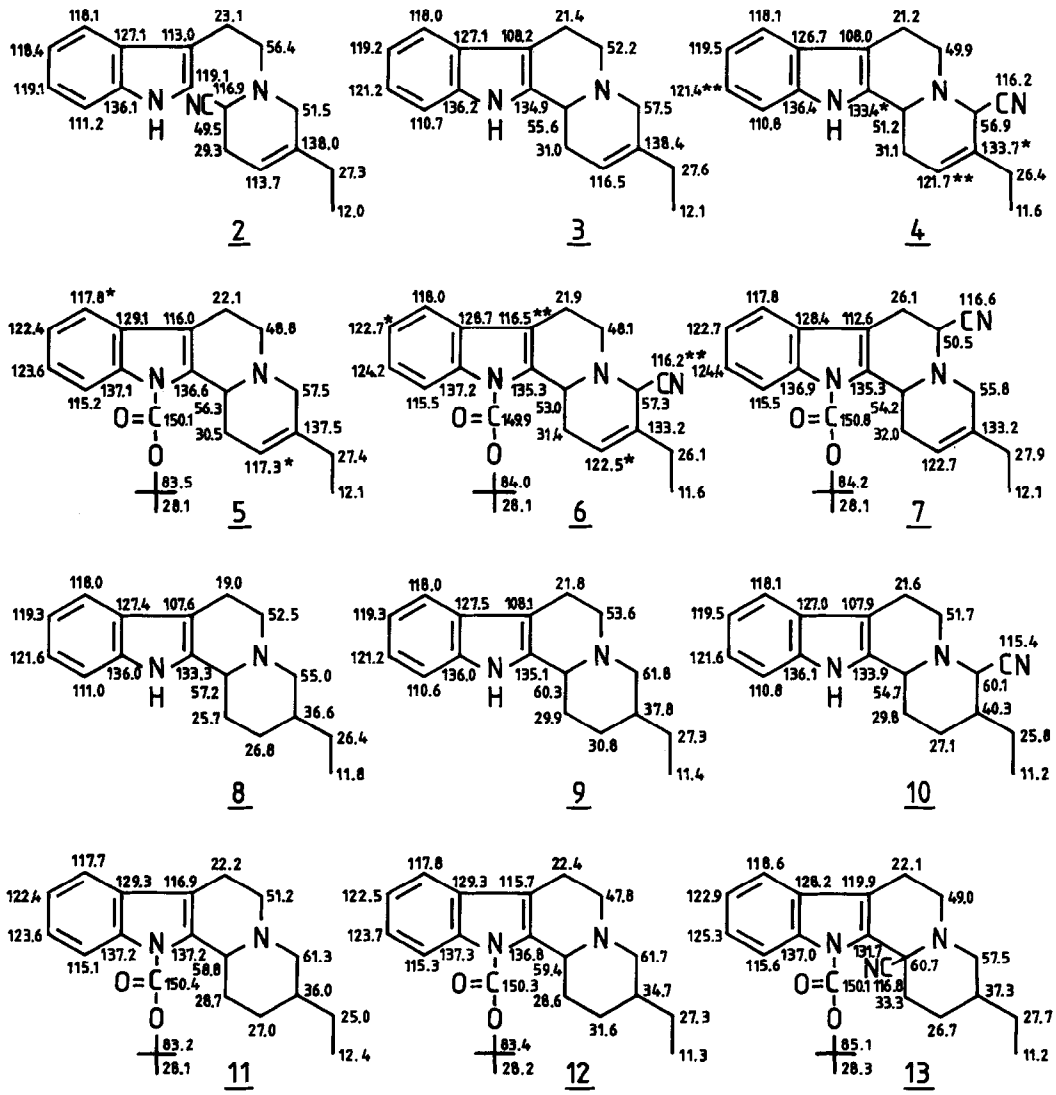
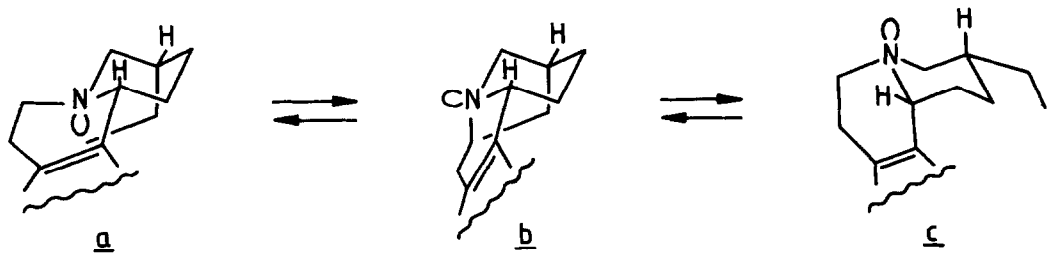


Fig. 1

Relative to the corresponding non-protected indoloquinolizidines 3, 4, 8 and 9, drastic changes are seen in the shift values for C(6), C(7a), C(9), C(10), C(11) and C(12a) in the BOC-protected indoloquinolizidines 5, 6, 11 and 12 (Fig. 1). The shift value of ~ 48 ppm, found in the spectra of compounds 5, 6 and 12 for C(6), is probably the most characteristic one. For compound 11, the situation is more complicated. The C(6) signal appears at 51.2 ppm and apparently indicates a conformational change between the C and D rings (vide infra).

We have shown earlier[1,16] that the contribution of conformations a and c to the conformational equilibrium of compound 8 is approximately 44% and 56% (Scheme 5). In the corresponding BOC-protected compound 11, the conformation a predominates owing to the strong interaction in conformation c between the BOC-group and the D-ring. In the conformation a the C(3) ethyl group is in axial position and can reach the proximity of N_b (Scheme 5), which has an effect on the chemical shift of C(6). A more detailed investigation of the phenomenon is in progress.



Scheme 5

EXPERIMENTAL

IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer 700 spectrophotometer, using liquid film between NaCl crystals. ^1H and ^{13}C NMR spectra were measured on a Jeol JNM - FX 60 spectrometer working at 59.80 MHz (^1H NMR) and 15.04 MHz (^{13}C NMR). The spectra were recorded in $CDCl_3$. Chemical shift data are given in ppm downfield from TMS. For ^{13}C NMR data see Fig. 1. Mass spectrometry (EIMS and HRMS) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compound 2
Hydrochloric acid (6 N, 1.50 ml) was added dropwise to a stirred solution of KCN (1.13 g, 17.38 mmol) in H_2O (1.5 ml), layered with Et_2O (9 ml), and kept at 0°C (Ar-atm). Pyridinium salt 1[16] (1.00 g, 3.02 mmol) prepared by alkylation of 3-ethylpyridine with tryptophyl bromide[17] and MeOH (2.4 ml) were added. $NaBH_4$ (0.127 g, 3.32 mmol) was added during 0.5 h and the mixture was stirred at rt for 3.5 h. The Et_2O layer was

separated and the aqueous layer was extracted several times with Et_2O. The combined ethereal extracts were dried (Na_2SO_4) and evaporated to give compound 2 as a viscous oil. Y. 0.759 g, 90%.
IR: 3440 (NH), 2260 (CN).
^1H NMR: 1.03 (3H, t, J=7.5 Hz, $-CH_2\underline{CH_3}$), 2.02 (2H, q, J=7.5 Hz, $-\underline{CH_2}CH_3$), 3.92 (1H, m, H-2), 5.42 (1H, br s, H-4), 6.94 (1H, d, J=2.4 Hz, H-ind.2), 7.10 - 7.58 (4H, m, arom. H), 8.15 (1H, br s, NH).
MS: 279 (M^+), 252, 149 (100%), 144, 130; exact mass: 279.1755 (calc. for $C_{18}H_{21}N_3$: 279.1735).

Preparation of compound 3
Compound 2 (0.759 g, 2.72 mmol) was dissolved in 80 ml of 50% HOAc and the solution was stirred at rt (N_2-atm) for 3 d. It was then evaporated and shaken with 2N Na_2CO_3. Extraction with CH_2Cl_2 and drying (Na_2SO_4) yielded a raw product of 3, which was purified by column chromatography (silica, CH_2Cl_2-MeOH, 95:5). Y. 0.305 g, 44%. Mp. 146-148°C (EtOH) (lit. 143-145°C[18]; 147-148°C[19]).
IR: 3440 (NH).
^1H NMR: 1.05 (3H, t, J=7.5 Hz, $-CH_2\underline{CH_3}$), 2.02 (2H, q, J=7.5 Hz, $-\underline{CH_2}CH_3$), 5.46 (1H, br s, H-2), 7.04 - 7.55 (4H, m, arom. H), 7.83 (1H, br s, NH).
MS: 252 (M^+), 170 (100%), 169; exact mass: 252.1704 (calc. for $C_{17}H_{20}N_2$: 252.1626).

Preparation of compound 5
To compound 3 (116 mg, 0.46 mmol) in 1 ml of abs. CH_2Cl_2 was added p-dimethylamino pyridine (DMAP) (6 mg, 0.1 equiv.) and di-t-butyl dicarbonate [$(BOC)_2O$] (120 mg, 1.2 equiv.) with stirring at rt (Ar-atm). After 2h the mixture was evaporated and purified by column chromatography (silica, CH_2Cl_2-MeOH-Et_3N, 97.75:2:0.25) to afford compound 5 as a viscous oil. Y. 146 mg, 90%.
IR: 1730 (C=O).
^1H NMR: 1.04 (3H, t, J=7.5 Hz, $-CH_2\underline{CH_3}$), 1.63 (9H, s, $-C(CH_3)_3$), 2.00 (2H, q, J=7.5 Hz, $-\underline{CH_2}CH_3$), 4.04 (1H, dd, J_1=2.2 Hz, J_2=10.3Hz, H-12b), 5.49 (1H, m, H-2), 7.12 - 7.35 (3H, m, H-8,9,10), 8.06 (1H, m, H-11).
MS: 352 (M^+), 296, 295, 214 (100%), 170, 169; exact mass: 352.2158 (calc. for $C_{22}H_{28}N_2O_2$: 352.2151).

Preparation of compound 11
Reaction of compound 8[16] (133 mg, 0.52 mmol) with DMAP (6 mg, 0.1 equiv.) and $(BOC)_2O$ (137 mg, 1.2 equiv.), using the procedure described for compound 5, afforded compound 11 as a viscous oil. Y. 163 mg, 88%.
IR: 1730 (C=O).
^1H NMR: 0.88 (3H, t, J=6.0 Hz, $-CH_2\underline{CH_3}$), 1.62 (9H, s, $-C(CH_3)_3$), 3.63 (1H, br s, H-12b), 7.10 - 7.30 (3H, m, H-8,9,10), 8.06 (1H, m, H-11).
MS: 354 (M^+), 298, 297 (100%), 253; exact mass: 354.2317 (calc. for $C_{22}H_{30}N_2O_2$: 354.2307).

Preparation of compounds 3-4-d_1, 3-12b-d_1 and 5-4-d_1
m-Chloroperbenzoic acid (mCPBA) (1.5 equiv.) in abs. CH_2Cl_2 (5 ml) was added with a syringe during 10 min to a cooled (0°C), stirred solution of compound 3 or 5 (0.5 mmol) in abs. CH_2Cl_2 (5 ml) under argon. Stirring was continued at 0°C for 90 min and the solution was cooled to -17°C. Trifluoroacetic anhydride (TFAA) (2.5 equiv.) was added with a syringe during 5 min and the reaction mixture was stirred at -17°C for 5 min and then at rt for 2 h. After evaporation to dryness it was redissolved in MeOH. $NaBD_4$ (6.0 equiv.) was added in small portions during 20 min (0°C, Ar-atm) and the solution was stirred for 18 h at rt. Before extraction with CH_2Cl_2, water was added and MeOH was evaporated

in vacuo. The combined organic layers were washed with H_2O and 10% aq Na_2CO_3 and dried (Na_2SO_4).
After concentration the crude product was purified by column chromatography (silica, CH_2Cl_2-MeOH, 97:3).
Compounds 3-4-d_1 and 3-12b-d_1:
(1:1 mixture), Y. 82 mg, 65%.
MS: 253 (M^+). For the other analytical data, see compound 3.
Compound 5-4-d_1:
Y. 71 mg, 40%.
MS:353 (M^+). For the other analytical data, see compound 5.

Preparation of compounds 9 and 12
m-Chloroperbenzoic acid (mCPBA) (1.5 equiv.) in abs. CH_2Cl_2 (5 ml) was added during 10 min to a cooled (0°C), stirred solution of compound 8 or 11 (0.5 mmol) in abs. CH_2Cl_2 (5 ml) under argon. Stirring was continued at 0°C for 90 min and the solution was cooled to -15°C. Trifluoroacetic anhydride (TFAA) (2.5 equiv.) was added during 5 min and the reaction mixture was stirred at -15°C for 5 min and then at rt for 2 h. After evaporation to dryness the residue was redissolved in MeOH. $NaBH_4$ (6.0 equiv.) was added during 20 min (0°C, Ar-atm) and the solution was stirred for 18 h at rt. The crude product obtained after the normal work-up was purified by column chromatography (silica, CH_2Cl_2-MeOH, 97:3) to afford compound 9 or 12.
Compound 9:
Y. 76 mg, 60%. Mp. 159-161°C (EtOH) (lit. 157°C[11]; 160-161°C[20]).
The analytical data (IR, ^1H NMR, ^{13}C NMR, MS) were identical with those described earlier.[11,16]
Compound 12:
Y. 62 mg, 35%. Viscous oil.
IR: 2840, 2780 (Bohlmann bands), 1720 (C=O).
^1H NMR: 0.91 (3H, t, J=7.2 Hz, $-CH_2CH_3$), 1.65 (9H, s, $-C(CH_3)_3$), 3.95 (1H, m, H-12b), 7.12 - 7.33 (3H, m, H-8,9,10), 8.10 (1H, m, H-11).
MS: 354 (M^+), 298, 297 (100%), 253; exact mass: 354.2311 (calc. for $C_{22}H_{30}N_2O_2$: 354.2307).

Preparation of compounds 9-12b-d_1 and 12-12b-d_1
The procedure was identical to that described for compounds 9 and 12 except that $NaBD_4$ was used instead of $NaBH_4$ (vide supra).
Compound 9-12b-d_1:
Y. 70 mg, 55%.
MS: 255 (M^+). For the other analytical data, see compound 9.
Compound 12-12b-d_1:
Y. 53 mg, 30%.
MS: 355 (M^+). For the other analytical data, see compound 12.

Preparation of compounds 4, 6, 10 and 13
m-Chloroperbenzoic acid (mCPBA) (1.5 equiv.) in abs. CH_2Cl_2 (5 ml) was added with a syringe during 10 min to a cooled (0°C), stirred solution of compound 3, 5, 8 or 11 (0.5 mmol) in abs. CH_2Cl_2 (5 ml) under argon. Stirring was continued at 0°C for 90 min and then the solution was cooled to -17°C. Trifluoroacetic anhydride (TFAA) (2.5 equiv.) was added with a syringe during 5 min and the reaction mixture was stirred at -17°C for 5 min and then at rt for 2 h. KCN (1.15 equiv.) in H_2O was added and the pH of the aqueous layer was adjusted to pH 5 by addition of NaOAc. The mixture was stirred at rt for 0.5 h, basified to pH 10 with 10% Na_2CO_3, extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated. The crude product was purified through a column of silica (CH_2Cl_2-MeOH, 97:3) to afford compound 4, 6, 10 or 13.
Compound 4:
Y. 36 mg, 26%. Mp. 145-147°C (EtOH).

IR: 3440 (NH), 2270 (CN).
^{1}H NMR: 1.10 (3H, t, J=7.8 Hz, -$CH_2\underline{CH_3}$), 2.17 (2H, q, J=7.8 Hz, -$\underline{CH_2}CH_3$), 3.89 (1H, m, H-12b), 4.18 (1H, s, H-4), 5.68 (1H, m, H-2), 7.02 - 7.47 (4H, m, arom. H), 7.83 (1H, br s, NH).
MS: 277 (M^+), 250, 249, 170 (100%), 169; exact mass: 277.1572 (calc. for $C_{18}H_{19}N_3$: 277.1579).
Compound 6:
Y. 132 mg, 70%. Viscous oil.
IR: 2270 (CN), 1720 (C=O).
^{1}H NMR: 1.13 (3H, t, J=7.2 Hz, -$CH_2\underline{CH_3}$), 1.67 (9H, s, -$C(CH_3)_3$), 2.04 (2H, q, J=7.2 Hz, -$\underline{CH_2}CH_3$), 4.21 (1H, s, H-4), 4.28 (1H, br s, H-12b), 5.69 (1H, m, H-2), 7.20 - 7.63 (3H, m, H-8,9,10), 8.10 (1H, m, H-11). MS: 377 (M^+), 350, 320, 293, 249, 214 (100%), 170; exact mass: 377.2078 (calc. for $C_{23}H_{27}N_3O_2$: 377.2103).
Compound 10:
Y. 35 mg, 25%. Amorphous material.
IR: 3410 (NH), 2850 and 2780 (Bohlmann bands), 2260 (CN).
^{1}H NMR: 0.91 (3H, t, J=6.0 Hz, -$CH_2\underline{CH_3}$), 3.67-4.22 (2H, m, H-4, H-12b), 7.02 - 7.41 (4H, m, arom. H), 7.79 (1H, br s, NH).
MS: 279 (M^+, 100%) 252, 251, 250, 225, 169; exact mass: 279.1732 (calc. for $C_{18}H_{21}N_3$: 279.1735).
Compound 13:
Y. 95 mg, 50%. Viscous oil.
IR: 2270 (CN), 1730 (C=O).
^{1}H NMR: 0.83 (3H, t, J=5.4 Hz, -$CH_2\underline{CH_3}$), 1.61 (9H, s, -$C(CH_3)_3$), 7.17 - 7.26 (3H, m, H-8,9,10), 7.95 (1H, m, H-11).
MS: 379 (M^+), 352, 322, 296, 267 (100%), 252, 223, 212, 168; exact mass: 379.2234 (calc. for $C_{23}H_{29}N_3O_2$: 379.2260).

Preparation of compounds 6 and 7
The procedure for compounds 4, 6, 10 and 13 was modified so that the temperature after TFAA-addition at -17°C was allowed to rise to 0°C during 2 h. From compound 5 (380 mg, 1.08 mmol), mCPBA (0.28 g, 1.5 equiv.), TFAA (0.38 ml, 2.5 equiv.) and KCN (81 mg, 1.15 equiv.), a mixture (3:2 according to ^{13}C NMR) of products 6 and 7 was formed. Y. 110 mg, 27%.
MS: 377 (M^+), 350, 320, 293, 249, 239, 214 (100%), 195, 170; exact mass: 377.2106 (calc. for $C_{23}H_{27}N_3O_2$: 377.2103).

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