SHORT, STEREOSELECTIVE SYNTHESIS OF N$_a$-BOC-5β-CYANO-DEFORMYL-Z-GEISSOSCHIZINE, A PROTOTYPE OF POTENTIAL SYNTHONS IN THE PREPARATION OF SARPAGAN AND AJMALAN RING SYSTEMS

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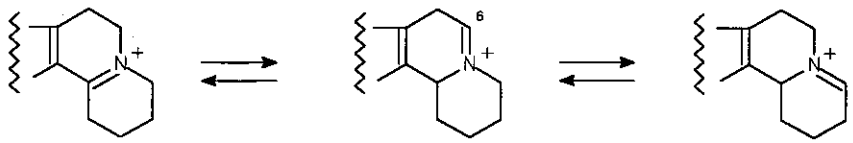
Abstract - This paper describes a short, easy synthesis of N$_a$-Boc-5β-cyano-deformyl-Z-geissoschizine (4), a prototype of potential synthons in the preparation of sarpagan and ajmalan ring systems.

INTRODUCTION

Very few synthetic approaches have been reported for sarpagine-ajmaline type indole alkaloids.[1-3] One interesting approach to the preparation of sarpagan and ajmalan ring systems seems to be the formation of iminium ions (or their equivalents) at $\Delta^{5(6)}$ from appropriate indolo[2,3-a]quinolizidine derivatives.

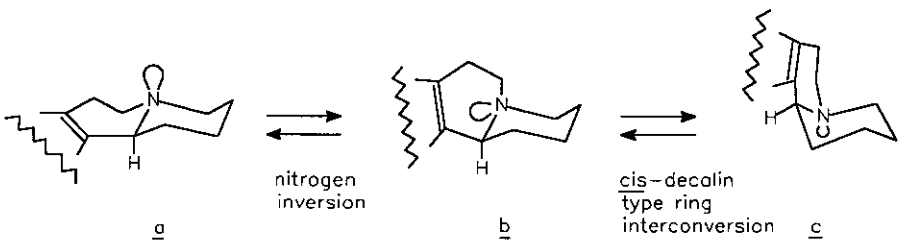
Until now, the synthetic use of $\Delta^{5(6)}$ indolo[2,3-a]quinolizidine iminium species for such purposes has been complicated by the long and tedious routes needed for their preparation,[4-6] and by the formation of mixtures of iminium ions containing only traces of the desired $\Delta^{5(6)}$-iminium ions. Yet a further problem is the easy

isomerization of iminium ions of this type (Scheme 1).



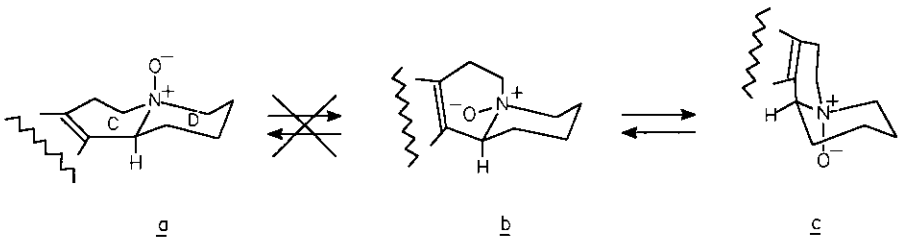
Scheme 1. Possible isomerization of the iminium ions.

An indolo[2,3-a]quinolizidine system can exist in three conformations, with equilibration by nitrogen inversion and cis-decalin type ring interconversion (Scheme 2).[7-9]



Scheme 2. Conformational equilibrium of indoloquinolizidines.

In the corresponding indoloquinolizidine N_b-oxides the C/D ring juncture (trans or cis) is fixed, so that there is no equilibrium between conformations (a) and (b/c) (Scheme 3). Transition between the conformations (b) and (c) continues to be possible, however.[7-9] The contribution of conformations (b) and (c) to the conformational equilibrium is strongly influenced by the substitution pattern of the molecule in question.

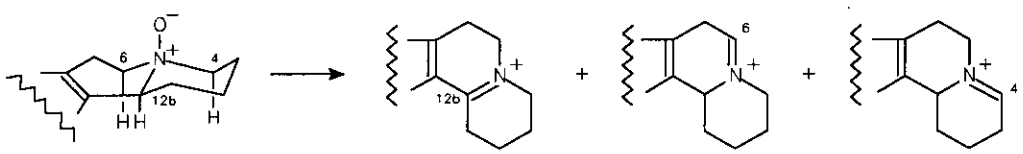


a b c

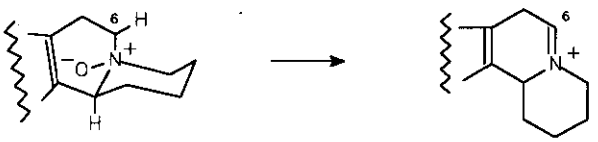
Scheme 3. Conformational equilibrium of indoloquinolizine N_b-oxides.

The modified Polonovski reaction (Polonovski-Potier reaction)[10-14] is widely used in the preparation of indolo[2,3-a]quinolizidine iminium ions from the corresponding indolo[2,3-a]quinolizidine N_b-oxides. It is known that the thermodynamically most stable iminium ion will be formed as the main product when stereoelectronic requirements for E2-type trans-diaxial elimination are fulfilled.[15,16]

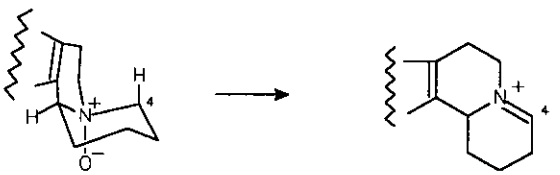
In theory, conformation (a) (C/D trans ring juncture) should lead to iminium ion formation toward C(4), C(6) and C(12b), of which C(12b) is strongly favored (Scheme 4); conformation (b) (C/D cis ring juncture), on the other hand, should lead to iminium ion formation toward C(6) (Scheme 5), and conformation (c) (C/D cis ring juncture) to iminium ion formation toward C(4) (Scheme 6). Knowledge of the exact conformation of the indolo[2,3-a]quinolizidine N_b-oxide in question is thus a prerequisite to predicting its behavior in iminium ion formation.



Scheme 4. Iminium ion formation from conformation (a).



Scheme 5. Iminium ion formation from conformation (b).

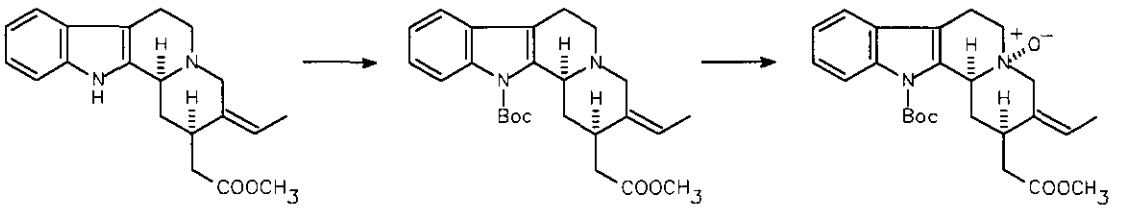


Scheme 6. Iminium ion formation from conformation (c).

We have previously shown[7] that the mCPBA oxidation of N_a-Boc protected 2-substituted indolo[2,3-a]quinolizidines leads mainly, and in several cases exclusively, to cis-N_b-oxides. Where the substitution pattern permits, these exist predominantly in conformation (b). Thus the prerequisites seemed to be fulfilled for a successful preparation of N_a-Boc-indolo[2,3-a]quinolizidine $\Delta^{5(6)}$-iminium ion (= N_a-Boc-deformyl-Z-geissoschizine $\Delta^{4(5)}$-iminium ion)[17] (**6**) [or its chemical equivalent (**4**)] from N_a-Boc-indolo[2,3-a]quinolizidine cis-N_b-oxide (= N_a-Boc-deformyl-Z-geissoschizine cis-N_b-oxide) (**3**) (vide infra).

RESULTS AND DISCUSSION

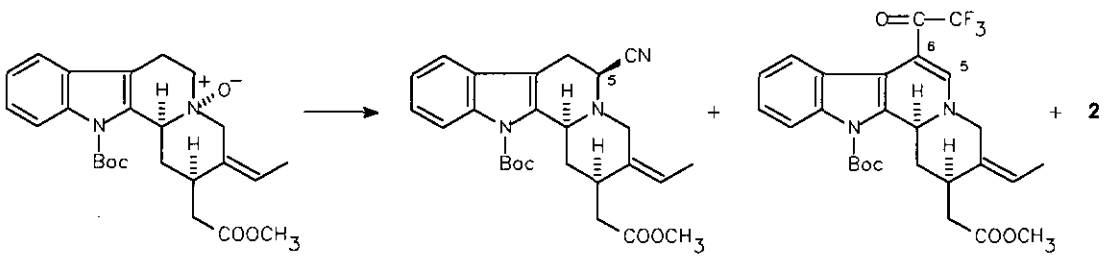
Treatment of the earlier described[18] deformyl-Z-geissoschizine (**1**) with di-t-butyl dicarbonate [$(Boc)_2O$] and p-dimethylaminopyridine (DMAP) in dry CH_2Cl_2 afforded the Boc-protected counterpart (**2**) in 83% yield. Oxidation of compound (**2**) with mCPBA in dry CH_2Cl_2 led exclusively to N_a-Boc-deformyl-Z-geissoschizine cis-N_b-oxide (**3**) in 93% yield (Scheme 7).



1 2 3

Scheme 7.

The easily accessible cis-N_b-oxide (**3**) was dissolved in dry CH_2Cl_2 and cooled to -17°C. Trifluoroacetic anhydride (TFAA) (2.5 equiv.) was added during 5 min and stirring was continued for 3 h until the temperature rose to 0°C. Thereafter a solution of KCN (3 equiv.) in H_2O was added and the pH of the aqueous layer was adjusted to pH 5 by addition of solid NaOAc. The mixture was stirred at room temperature for 45 min, basified to pH 10 with 10% Na_2CO_3 solution and extracted with CH_2Cl_2. After normal work-up and careful chromatographic purification the desired cyano derivative (**4**) (N_a-Boc-5β-cyano-deformyl-Z-geissoschizine) was obtained in 35% yield. Small amounts of compounds (**2**) (N_a-Boc-deformyl-Z-geissoschizine) and (**5**) (N_a-Boc-6-trifluoroacetyl-5,6-didehydro-deformyl-Z-geissoschizine) were isolated (Scheme 8).



3 4 5 + 2

Scheme 8.

The ^{13}C-Nmr data for compounds (**2**), (**3**), (**4**), and (**5**) are given in Figure 1. Comparison of the chemical shifts found, taking into account the conformational considerations relevant for indolo[2,3-a]quinolizidines in general[19-25], provides clear evidence of the stereostructures depicted in the formulae.

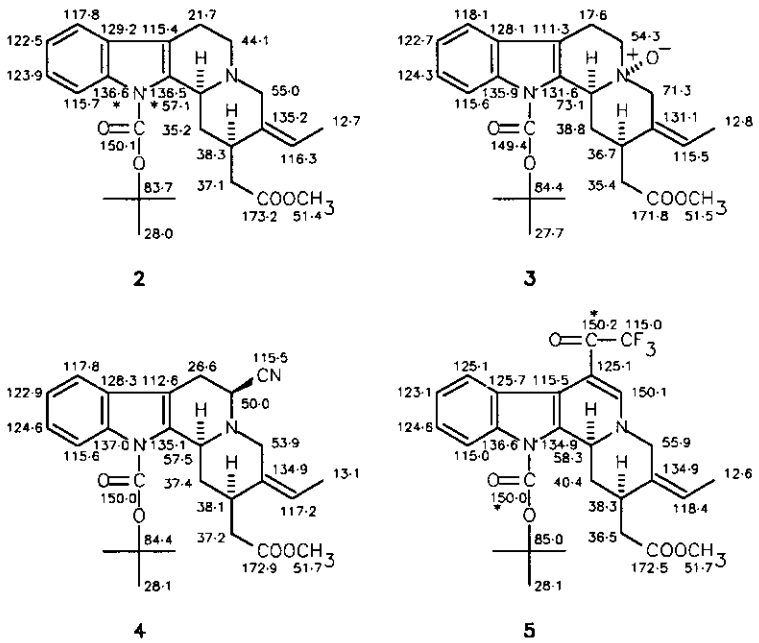


Figure 1. ^{13}C-Nmr data for compounds (**2**), (**3**), (**4**), and (**5**).

The stereostructure of compound (**4**) was further confirmed by complete ^{1}H-Nmr data (Table 1) and H, H-COSY, H,C-COSY, and NOE measurements.

The coupling constants in compound (**4**) between H-5 and H-6α and between H-5 and H-6β are 3 Hz and 5.5 Hz, respectively. Such values are only possible if H-5 is α. Further confirmation of this comes from the NOE difference measurements. Irradiation at H-14β resulted in NOE only at H-14α; no NOE was observed at H-5 [conformation (b)] and thus H-5 has to be α. Irradiation of H-19 gave a 7% NOE at H-16$_B$ (δ 2.74 ppm), which is in agreement with a chair conformation for ring D of compound (**4**) (Figure 2).

Table 1. ^{1}H-Nmr data for compound (4).

H-3	4.30	dd	**H-15**	2.86	m
H-5α	4.11	dd	**H-16$_A$**	2.27	dd
H-6α	3.01	dd	**H-16$_B$**	2.74	dd
H-6β	3.25	dd	**H-18**	1.72	br d
H-9	7.38	dd	**H-19**	5.28	q
H-10	7.30	dt	**H-21α**	3.24	d
H-11	7.23	dt	**H-21β**	3.93	d
H-12	8.08	dd	**Boc**	1.69	s
H-14α	2.48	ddd	**CO_2CH_3**	3.69	s
H-14β	1.23	dd			

Coupling constants:

$J_{3,14\alpha}$ = 2 Hz; $J_{3,14\beta}$ = 11 Hz; $J_{5\alpha,6\alpha}$ = 3 Hz; $J_{5\alpha,6\beta}$ = 5.5 Hz; $J_{6\alpha,6\beta}$ = 16 Hz; $J_{9,10}$ = 7.5 Hz; $J_{9,11}$ = 1.5 Hz; $J_{10,11}$ = 7.5 Hz; $J_{10,12}$ = 1.5 Hz; $J_{11,12}$ = 7.5 Hz; $J_{14\alpha,14\beta}$ = 12.5 Hz; $J_{14\alpha,15}$ = 4 Hz; $J_{14\beta,15}$ = 12 Hz; $J_{15,16A}$ = 8 Hz; $J_{15,16B}$ = 6.5 Hz; $J_{16A,16B}$ = 15 Hz; $J_{18,19}$ = 7 Hz; $J_{21\alpha,21\beta}$ = 13 Hz.

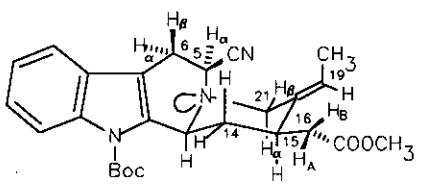


Figure 2. Predominant conformation of N$_a$-Boc-5β-cyano-deformyl-Z-geissoschizine (4). The stereochemistry at C(16) may be inverse.

CONCLUSIONS

The present work shows that the use of $\underline{N_a}$-Boc-deformyl-$\underline{Z}$-geissoschizine $\underline{cis}$-$\underline{N_b}$-oxide (**3**) under the described conditions permits a stereospecific formation of $\underline{N_a}$-Boc-5β-cyano-deformyl-$\underline{Z}$-geissoschizine (**4**), which is the synthetic equivalent of $\underline{N_a}$-Boc-deformyl-$\underline{Z}$-geissoschizine $\Delta^{4(5)}$-iminium ion (**6**). The method should be useful in the preparation of compounds possessing the sarpagan or ajmalan ring system ($\underline{vide\ supra}$). Further studies are in progress.

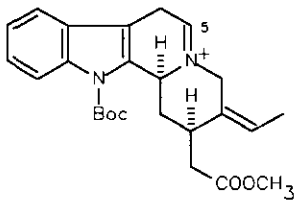


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Figure 3. $\underline{N_a}$-Boc-deformyl-$\underline{Z}$-geissoschizine $\Delta^{4(5)}$-iminium ion (= $\underline{N_a}$-Boc-indolo[2,3-$\underline{a}$]quinolizidine $\Delta^{5(6)}$-iminium ion) (**6**).

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 spectrophotometer in $CHCl_3$. Ir absorption bands are expressed in reciprocal centimeters (cm^{-1}). ^1H- and ^{13}C-Nmr spectra were measured with a Varian Gemini-200 spectrometer working at 199.975 MHz (^1H-Nmr) and 50.289 MHz (^{13}C-Nmr) [compounds (**2**), (**3**), and (**5**)] and a Varian Unity-400 NMR spectrometer working at 399.952 MHz (^1H-Nmr) and 100.577 MHz (^{13}C-Nmr) [compound (**4**)]. The spectra were recorded in $CDCl_3$. Chemical shift data are given in ppm by reference to

TMS (^{1}H-Nmr; δ_H = 0.0 ppm) and $CDCl_3$ (^{13}C-Nmr; δ_C = 77.0 ppm). Abbreviations s, d, t, q, m, and br are used to designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. In ^{1}H measurements the spectral width was 6000 Hz, acquisition time 3.774 s, and pulse width 7.5 μs. NOE difference spectroscopy was done at 30°C. Spectra were obtained by direct subtraction using a 90° composite pulse. For the ^{13}C-nmr data, see Figure 1. Mass spectrometry (EIms and HRms) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of deformyl-Z-geissoschizine (1):

Deformyl-Z-geissoschizine (**1**) was prepared according to our earlier described method.[18]

Preparation of N_a-Boc-deformyl-Z-geissoschizine (2):

A solution of deformyl-Z-geissoschizine (**1**) (210 mg, 0.65 mmol), di-t-butyl dicarbonate [$(Boc)_2O$] (170 mg, 1.2 equiv.), and p-dimethylaminopyridine (DMAP) (8 mg, 0.1 equiv.) in dry CH_2Cl_2 (3 ml) was stirred at room temperature for 2 h (Ar atm). Evaporation and purification by flash chromatography (silica gel, CH_2Cl_2/MeOH:99/1) gave compound (**2**).

Compound (**2**): Y. 230 mg (83%). Amorphous material. Ir: 1730 br (2 x C=O). ^{1}H-Nmr: 1.69 [9H, s, -C(CH_3)$_3$], 1.70 (3H, d, J=7 Hz, H-18), 3.39 (1H, d, J=14 Hz, H-21α), 3.68 (3H, s, -CO_2CH_3), 3.97 (1H, d, J=14 Hz, H-21β), 4.63 (1H, br d, J=10 Hz, H-3), 5.29 (1H, q, J=7 Hz, H-19), 7.16-7.30 (2H, m, H-10, H-11), 7.39 (1H, d, J=8 Hz, H-9), 8.14 (1H, d, J=8 Hz, H-12). Ms: 424 (M^+), 367 (100%), 323, 295, 251, 169, 156. HRms found: 424.2349. Calcd for $C_{25}H_{32}O_4N_2$: 424.2362.

Preparation of N_a-Boc-deformyl-Z-geissoschizine cis-N_b-oxide (3):

A solution of compound (**2**) (130 mg, 0.31 mmol) and m-chloroperbenzoic acid (mCPBA) (58 mg, 1.1 equiv.) in dry CH_2Cl_2 (7 ml) was stirred at room temperature for 4 h (Ar atm). Normal work-up and purification by column chromatography (alumina, CH_2Cl_2/MeOH:98/2) yielded compound (**3**).

Compound (**3**): Y. 125 mg (93%). Amorphous material. Ir: 1730 br (2 x C=O). ^{1}H-Nmr: 1.60 [9H, s, -

C($C\underline{H}_3$)$_3$], 1.71 (3H, d, J=7 Hz, H-18), 3.59 (3H, s, -$CO_2C\underline{H}_3$), 3.96 (1H, d, J=14 Hz, H-21α), 4.52 (1H, d, J=14 Hz, H-21β), 5.05 (1H, br d, J=13 Hz, H-3), 5.42 (1H, q, J=7 Hz, H-19), 7.09-7.23 (2H, m, H-10, H-11), 7.33 (1H, d, J=8 Hz, H-9), 8.01 (1H, d, J=8 Hz, H-12). Ms: 440 (M^+), 340, 324, 251, 170, 169, 156 (100%). HRms found: 440.2303. Calcd for $C_{25}H_{32}O_5N_2$: 440.2311.

Preparation of N_a-Boc-5β-cyano-deformyl-Z-geissoschizine (4) and N_a-Boc-6-trifluoroacetyl-5,6-didehydro-deformyl-Z-geissoschizine (5):

Compound (3) (602 mg, 1.37 mmol) was dissolved in dry CH_2Cl_2 (40 ml) and cooled to -17°C. Trifluoroacetic anhydride (TFAA) (0.50 ml, 2.5 equiv.) was added with a syringe during 5 min and stirring was continued for 3 h until the temperature rose to 0°C. Then KCN (27 mg, 3 equiv.) in H_2O (2 ml) was added and the pH of the aqueous layer was adjusted to pH 5 by addition of solid NaOAc. The mixture was stirred at room temperature for 45 min, basified to pH 10 with 10% Na_2CO_3 and extracted with CH_2Cl_2. Normal work-up and purification by flash silica chromatography gave compound (5) (CH_2Cl_2/hexane:25/75), compound (4) (CH_2Cl_2), and compound (2) (CH_2Cl_2/MeOH:99/1).

Compound (5): Y. 71 mg (10%). Amorphous material. Ir: 1730 br (3 x C=O). ^{1}H-Nmr: 1.72 [9H, s, -C($C\underline{H}_3$)$_3$], 1.79 (3H, d, J=7 Hz, H-18), 3.69 (3H, s, -$CO_2C\underline{H}_3$), 3.72 (1H, d, J=14 Hz, H-21α), 4.51 (1H, d, J=14 Hz, H-21β), 5.38 (1H, q, J=8 Hz, H-19), 5.70 (1H, br d, J=11 Hz, H-3), 7.21-7.32 (2H, m, H-10, H-11), 7.52 (1H, s, H-5), 8.08 (1H, d, J=9 Hz, H-12), 8.47 (1H, d, J=9 Hz, H-9). Ms: 518 (M^+), 462, 418, 343, 264 (100%). HRms found: 518.2021. Calcd for $C_{27}H_{29}O_5N_2F_3$: 518.2028.

Compound (4): Y. 215 mg (35%). Amorphous material. Ir: 2300 (CN), 1730 br (2 x C=O). ^{1}H-Nmr: See Table 1. Ms: 449 (M^+), 422, 392, 366 (100%), 348, 321, 293, 212, 169, 168. HRms found: 449.2328. Calcd for $C_{26}H_{31}O_4N_3$: 449.2315.

Compound (2): Y. 41 mg (7%). For analytical data, see above.

REFERENCES AND NOTES

1. J. A. Joule, "The Monoterpenoid Indole Alkaloids", ed. J. E. Saxton, John Wiley, New York, 1983, pp. 201-264.
2. A. Koskinen and M. Lounasmaa, "Progress in the Chemistry of Natural Products", eds. W. Herz, H. Grisebach, and G. W. Kirby, Vol. 43, Springer Verlag, Wien - New York, 1983, pp. 267-346.
3. J. E. Saxton, Nat. Prod. Rep., 1984, **1**, 21; 1985, **2**, 49; 1986, **3**, 353; 1987, **4**, 591; 1989, **6**, 1; 1990, **7**, 191; 1991, **8**, 251; 1992, **9**, 393.
4. E. E. van Tamelen and L. K. Oliver, J. Am. Chem. Soc., 1970, **92**, 2136. See also E. E. van Tamelen and L. K. Oliver, Bioorg. Chem., 1976, **5**, 309.
5. J. E. Johansen, B. D. Christie, and H. Rapoport, J. Org. Chem., 1981, **46**, 4914. See also, H. Rapoport, "Stereoselective Synthesis of Natural Products", eds. W. Bartmann and E. Winterfeldt, Excerpta Medica, Amsterdam - Oxford, 1979, pp. 37-49.
6. D. Herlem, A. Florès-Parra, F. Khuong-Huu, A. Chiaroni, and C. Riche, Tetrahedron, 1982, **38**, 271.
7. M. Lounasmaa and T. Tamminen, Tetrahedron, 1991, **47**, 2879.
8. M. Lounasmaa, "Studies in Natural Products Chemistry", ed. Atta-ur-Rahman, Vol. 1, Elsevier, Amsterdam, 1988, pp. 89-122.
9. M. Lounasmaa, "Studies in Natural Products Chemistry", ed. Atta-ur-Rahman, Vol. 14, Elsevier, Amsterdam, 1993, pp. xx-yy.
10. P. Potier, "Stereoselective Synthesis of Natural Products", eds. W. Bartmann and E. Winterfeldt, Excerpta Medica, Amsterdam - Oxford, 1979, pp. 19-27.
11. P. Potier, Rev. Latinoamer. Quim., 1978, **9**, 47.
12. M. Lounasmaa and A. Koskinen, Heterocycles, 1984, **22**, 1591.
13. D. Grierson, "Organic Reactions", ed. L. A. Paquette, Vol. 39, John Wiley, New York, 1990, pp. 85-295.

14. D. S. Grierson and H.-P. Husson, "Comprehensive Organic Synthesis", eds. B. M. Trost and I. Fleming, Vol. 6, Pergamon Press, Oxford, 1991, pp. 909-924.

15. M. Nakagawa, Y. Ogawa, Y. Miyake, K. Yamaguchi, T. Hina, C. C. Chiang, J. L. Flippen, and B. Witkop, Heterocycles, 1982, **19**, 663.

16. I. Moldvai, C. Szántay Jr, G. Tóth, A. Vedres, A. Kálmán, and C. Szántay, Rec. Trav. Chim. Pays-Bas, 1988, **107**, 335.

17. Note! Two numbering systems are used. The IUPAC numbering system is used for compounds whose names are based on the word "indolo[2,3-a]quinolizidine", and the biogenetic numbering system of Le Men and Taylor[26] for compounds whose names are based on the word "geissoschizine".

18. M. Lounasmaa, R. Jokela, B. Tirkkonen, J. Miettinen, and M. Halonen, Heterocycles, 1992, **34**, 321.

19. M. Lounasmaa and R. Jokela, Tetrahedron, 1989, **45**, 3975.

20. M. Lounasmaa and R. Jokela, Tetrahedron, 1989, **45**, 7449.

21. M. Lounasmaa, R. Jokela, B. Tirkkonen, and T. Tamminen, Tetrahedron, 1989, **45**, 7615.

22. M. Lounasmaa and R. Jokela, Tetrahedron, 1990, **46**, 615.

23. M. Lounasmaa, R. Jokela, P. Mäkimattila, and B. Tirkkonen, Tetrahedron, 1990, **46**, 2633.

24. M. Lounasmaa, R. Jokela, and L.-P. Tiainen, Tetrahedron, 1990, **46**, 7873.

25. M. Lounasmaa, R. Jokela, J. Miettinen, and M. Halonen, Heterocycles, 1992, **34**, 1497.

26. J. Le Men and W. Taylor, Experientia, 1965, **21**, 508.

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