PREPARATION AND CONFORMATIONAL STUDY OF *Z*-ISOSITSIRIKINE MODEL COMPOUNDS AND THEIR *CIS*-N_b-OXIDES. DETERMINATION OF THE C-16 CONFIGURATION

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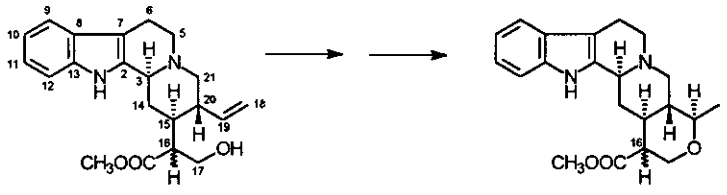
Abstract - Preparation of *Z*-isositsirikine derivatives (**5** - **12**) from the allylic alcohols (**21**) and (**22**) by the orthoester Claisen rearrangement and their oxidation to the corresponding *cis*-N_b-oxides (**13** - **20**) are described. Nmr methods were applied to determine the configuration at C-16 of *Z*-isositsirikine derivatives and their *cis*-N_b-oxides. A general, nmr based conformational study of compounds (**5** - **20**) is presented.

The determination of the correct C-16 configuration[1] in indole alkaloids of sitsirikine/isositsirikine type is a problem of general interest.[2-4] Zenk *et al.*[5] have presented some preliminary ^{1}H-nmr results based on the difference in chemical shifts between the C-17 methylene protons in the C-16 epimers (**1**) and (**2**) of sitsirikine. The results were later strongly contested by Brown and Leonard,[6] who based their own determination on an antecedent transformation of the sitsirikine epimers to the corresponding cyclositsirikines (16,17-dihydroheteroyohimbines) (**3**) and (**4**) (Scheme 1), in order to restrict the rotation about the C-15 - C-16 bond.



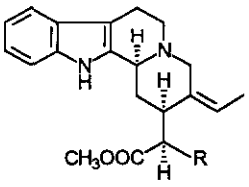
1 C−16−H α
2 C−16−H β

3 C−16−H α
4 C−16−H β

Scheme 1

Chemical transformations like these are exceedingly tedious and time consuming, however, and make a direct determination of the C-16 configurations desirable.

Enormous progress in nmr spectroscopy during the last decade has been achieved, thus making the time ripe for a direct determination of the C-16 configuration in compounds of the present type. The most reliable approach seemed to be the use of NOE difference spectroscopy. Simultaneously a general conformational analysis of the prepared compounds, which are indolo[2,3-*a*]quinolizidine derivatives, was deemed desirable. Further of interest was the conformational behaviour of the corresponding N_b-oxides.



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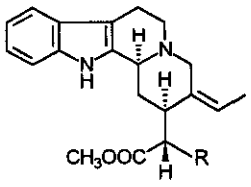
7 R= CH_2-CH_3



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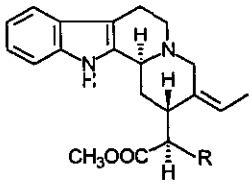

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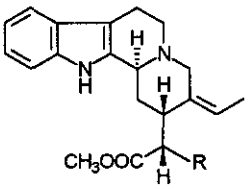

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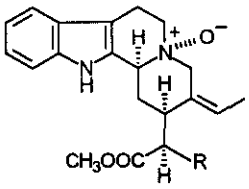
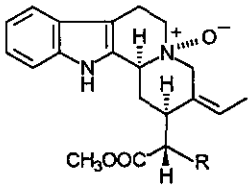
12 R= CH_2-CH_3



13 R= CH_3
15 R= CH_2-CH_3



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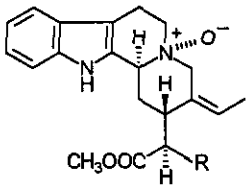
16 R= CH_2-CH_3



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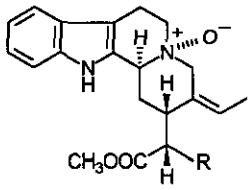
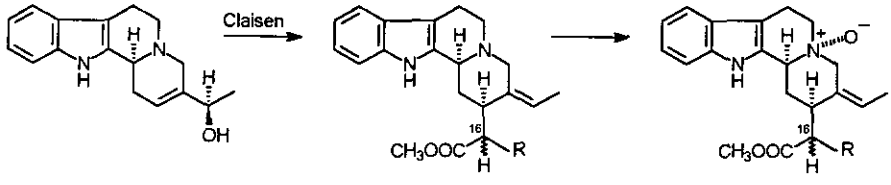
19 R= CH_2-CH_3



18 R= CH_3
20 R= CH_2-CH_3

RESULTS AND DISCUSSION

Recently we described a stereoselective preparation of deformyl-*Z*-geissoschizine derivatives (dehydroxymethyl-*Z*-isositsirikine derivatives) by the Claisen rearrangement using trimethyl orthoacetate and allylic alcohols (**21**) and (**22**).[7] Replacing trimethyl orthoacetate with trimethyl orthopropionate or trimethyl orthobutyrate permitted us, after careful separations (*cf.* Experimental), access to compounds (**5** - **12**), which are good model compounds for the determination of C-16 configurations in the *Z*-isositsirikine series. Oxidation of compounds (**5** - **12**) with either H_2O_2 or m-chloroperbenzoic acid (mCPBA) (*cf.* Experimental) led to the corresponding *cis*-N_b-oxides (**13** - **20**)[8,9] (Schemes 2 and 3).



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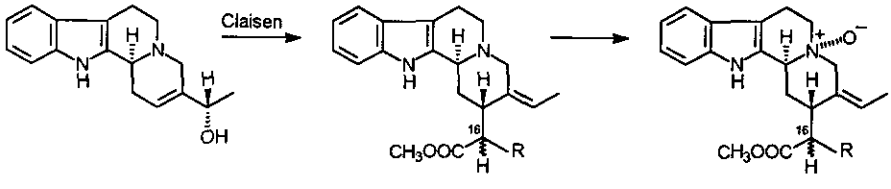
5 R= CH_3 , C - 16 -H α
6 R= CH_3 , C - 16 -H β
7 R= CH_2 - CH_3 , C - 16 -H α
8 R= CH_2 - CH_3 , C - 16 -H β

13 R= CH_3 , C - 16 -H α
14 R= CH_3 , C - 16 -H β
15 R= CH_2 - CH_3 , C - 16 -H α
16 R= CH_2 - CH_3 , C - 16 -H β

Scheme 2.



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9 R= CH_3 , C - 16 -H α
10 R= CH_3 , C - 16 -H β
11 R= CH_2 - CH_3 , C - 16 -H α
12 R= CH_2 - CH_3 , C - 16 -H β

17 R= CH_3 , C - 16 -H α
18 R= CH_3 , C - 16 -H β
19 R= CH_2 - CH_3 , C - 16 -H α
20 R= CH_2 - CH_3 , C - 16 -H β

Scheme 3

Table 1. ^{1}H-Nmr data of compounds (**5**, **6**, **9**, **10**, **11**, **12**, **13**, **14**, **17**, and **18**).

	5	**6**	**9**	**10**	**11**
H-1	7.89 br s	8.22 br s	7.94 br s	7.86 br s	7.69 br s
H-3	3.51 br d	3.62 br d	3.7 br d	3.6 br d	3.73 br d
H-5α	2.68 ddd	2.7 m	2.68 ddd	2.72 ddd	2.71 ddd
H-5β	3.15 ddd	3.16 ddd	3.12 ddd	3.14 ddd	3.13 m
H-6α	2.75 m	2.8 m	2.7 m	2.7 m	2.7 m
H-6β	3.0 m	3.0 m	3.00 m	3.0 m	3.01 m
H-9	7.46 d	7.46 d	7.45 d	7.46 d	7.45 d
H-10	7.07 t	7.08 t	7.06 t	7.08 t	7.07 t
H-11	7.12 t	7.13 t	7.11 t	7.13 t	7.12 t
H-12	7.30 d	7.31 d	7.28 d	7.30 d	7.29 d
H-14α	2.15 ddd	2.12 ddd	1.96 br d	2.20 br d	1.9 m
H-14β	1.45 ddd	1.66 ddd	1.86 ddd	1.85 ddd	1.9 m
H-15	2.7 m	2.40 m	2.53 ddd	2.52 ddd	2.59 ddd
H-16	2.90 m	2.8 m	2.89 m	2.9 m	2.8 m
H-17	1.21 d	1.21 d	1.07 d	1.28 d	1.49 m
H-18	1.70 d	1.71 d	1.70 d	1.63 d	1.71 d
H-19	5.27 q	5.36 q	5.41 q	5.33 q	5.42 q
H-21α	2.78 br d	2.85 br d	2.74 br d	3.0 m	2.81 br d
H-21β	3.89 d	3.75 d	3.66 d	3.65 d	3.68 d
CO_2Me	3.72 s	3.70 s	3.79 s	3.60 s	3.80 s
C-17-CH_3					0.89 t

Table 1 (continued). ^{1}H-Nmr data of compounds (**5**, **6**, **9**, **10**, **11**, **12**, **13**, **14**, **17**, and **18**).

	12	**13**	**14**	**17**	**18**
H-1	7.83 br s	12.29 br s	12.34 br s	11.43 br s	12.01 br s
H-3	3.7 br d	4.06 br	3.95 br	4.6 br	4.51 br
H-5α	2.8 m	3.12 m	3.15 m	3.2 m	3.19 m
H-5β	3.17 m	3.5 m	3.5 m	3.7 m	3.8 m
H-6α	2.8 m	3.5 m	3.5 m	3.5 m	3.7 m
H-6β	3.0 m	2.80 br d	2.83 br d	2.9 m	2.89 br d
H-9	7.46 d	7.44 def d	7.49 def d	7.4 m	7.43 d
H-10	7.08 t	7.03 t	7.00 t	7.0 m	7.03 t
H-11	7.14 t	7.05 t	7.01 t	7.0 m	7.05 t
H-12	7.31 d	7.17 br	7.08 br	7.3 br	7.29 br
H-14α	2.22 br d	2.4 m	2.14 m	2.1 m	2.38 m
H-14β	1.86 ddd	1.1 m	1.50 m	1.8 m	1.8 m
H-15	2.55 m	2.04 br s	1.8 m s	2.3 m	2.2 m
H-16	2.8 m	2.4 m	2.45 m	2.1 m	2.2 m
H-17	1.6 m	1.11 d	1.10 d	0.68 br	1.00 br
H-18	1.63 d	1.74 d	1.76 d	1.80 d	1.71 d
H-19	5.35 q	5.39 q	5.31 q	5.67 q	5.55 q
H-21α	3.05 br d	3.52 d	3.6 m	3.91 br d	4.10 br d
H-21β	3.68 d	4.41 d	4.36 d	4.38 br d	4.34 br
CO_2Me	3.60 s	3.63 s	3.61 s	3.70 s	3.46 s
C-17-CH_3	0.96 t				

Peak sharpness was reduced for several signals in the spectra of compounds (**13**, **14**, **17**, and **18**) (*cis*-N_b-oxides).

Table 1 (continued). ^{1}H-Nmr data of compounds (**5, 6, 9, 10, 11, 12, 13, 14, 17,** and **18**).

Coupling constants:

Compound (**5**).
$J_{3,14\alpha} \approx 4$ Hz; $J_{3,14\beta} \approx 11$ Hz; $J_{5\alpha,5\beta} = 11$ Hz; $J_{5\alpha,6\alpha} = 5$ Hz; $J_{5\alpha,6\beta} \approx 11$ Hz; $J_{5\beta,6\alpha} = 1.5$ Hz; $J_{5\beta,6\beta} = 6$ Hz; $J_{6\alpha,6\beta} = 15.5$ Hz; $J_{14\alpha,14\beta} = 12$ Hz; $J_{14\alpha,15} \approx 3.5$ Hz; $J_{14\beta,15} = 12$ Hz; $J_{16,17} = 7$ Hz; $J_{18,19} = 6.5$ Hz; $J_{21\alpha,21\beta} = 12.5$ Hz

Compound (**6**).
$J_{3,14\alpha} \approx 4$ Hz; $J_{3,14\beta} \approx 11$ Hz; $J_{5\alpha,5\beta} = 11$ Hz; $J_{5\beta,6\alpha} = 2$ Hz; $J_{5\beta,6\beta} = 6$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\alpha,15} \approx 3.5$ Hz; $J_{14\beta,15} = 12$ Hz; $J_{16,17} = 7$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 12.5$ Hz

Compound (**9**).
$J_{3,14\beta} \approx 11$ Hz; $J_{5\alpha,5\beta} = 11$ Hz; $J_{5\alpha,6\alpha} = 4.5$ Hz; $J_{5\alpha,6\beta} \approx 11$ Hz; $J_{5\beta,6\alpha} = 1.5$ Hz; $J_{5\beta,6\beta} = 6$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\alpha,15} \approx 2$ Hz; $J_{14\beta,15} = 5$ Hz; $J_{16,17} = 6.5$ Hz; $J_{18,19} = 6.5$ Hz; $J_{21\alpha,21\beta} = 13$ Hz

Compound (**10**).
$J_{3,14\beta} = 12$ Hz; $J_{5\alpha,5\beta} = 11$ Hz; $J_{5\alpha,6\alpha} = 4.5$ Hz; $J_{5\alpha,6\beta} \approx 11$ Hz; $J_{5\beta,6\alpha} \approx 1$ Hz; $J_{5\beta,6\beta} = 6$ Hz; $J_{14\alpha,14\beta} = 13.5$ Hz; $J_{14\alpha,15} \approx 2$ Hz; $J_{14\beta,15} = 5$ Hz; $J_{16,17} = 7$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 13$ Hz

Compound (**11**).
$J_{5\alpha,5\beta} = 11$ Hz; $J_{5\alpha,6\alpha} = 5$ Hz; $J_{5\alpha,6\beta} \approx 11$ Hz; $J_{14\alpha,15} \approx 2$ Hz; $J_{14\beta,15} \approx 4$ Hz; $J_{17,CH3} = 7.5$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 12.5$ Hz

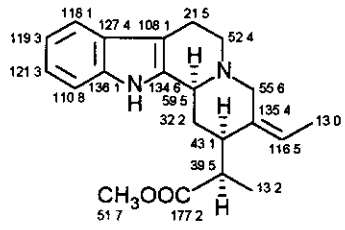
Compound (**12**).
$J_{3,14\beta} \approx 12.5$ Hz; $J_{5\alpha,5\beta} = 11$ Hz; $J_{14\alpha,14\beta} = 14$ Hz; $J_{14\beta,15} = 5$ Hz; $J_{17,CH3} = 7$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 13$ Hz

Compound (**13**).
$J_{16,17} = 7$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 12.5$ Hz

Compound (**14**).
$J_{6\alpha,6\beta} = 15.5$ Hz; $J_{16,17} = 7$ Hz; $J_{18,19} = 7$ Hz

Compound (**17**).
$J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 13$ Hz

Compound (**18**).
$J_{6\alpha,6\beta} = 15.5$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 13$ Hz



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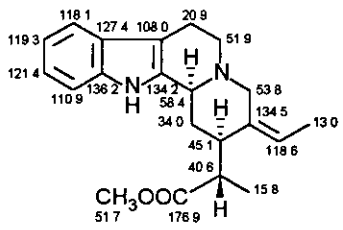

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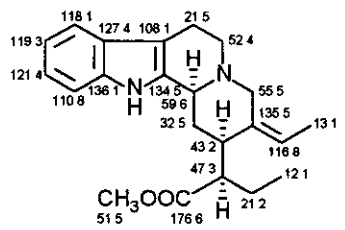

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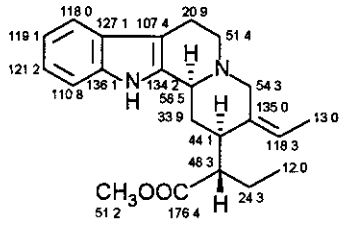

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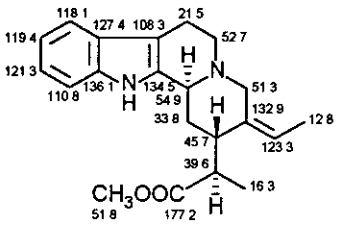

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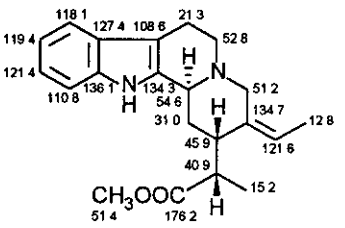

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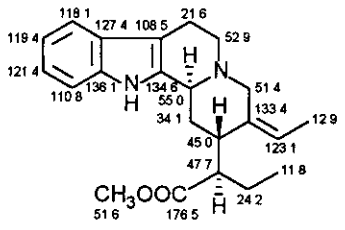

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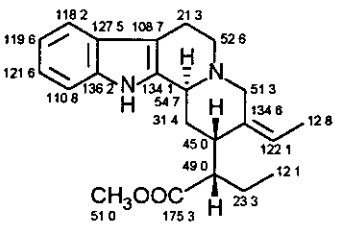

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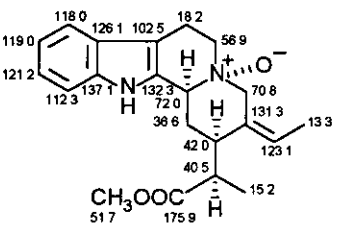

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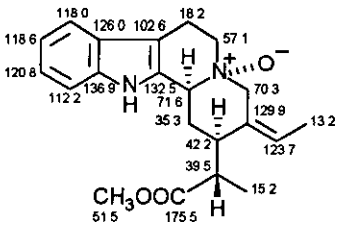

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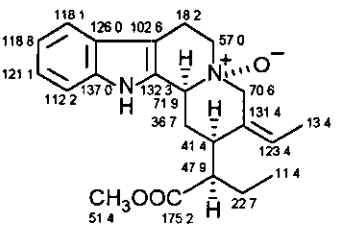

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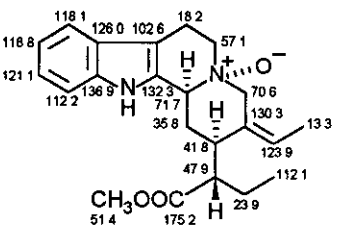
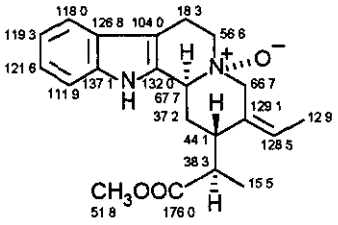


16

Figure 1 (continues on next page). ^{13}C-Nmr data of compounds (**5 - 20**).

Peak sharpness was reduced for several signals (C-5, C-14, C-19, and C-21) in the spectra of compounds (**13 - 20**) (*cis*-N_b-oxides).



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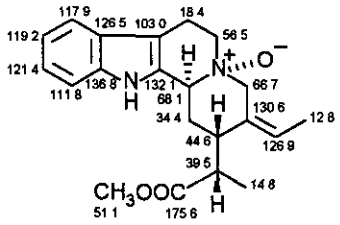

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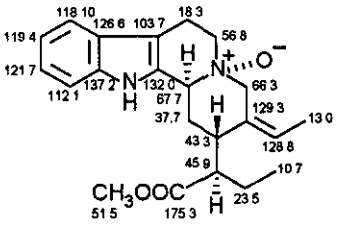

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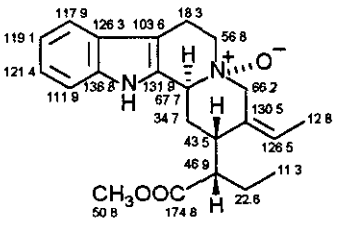

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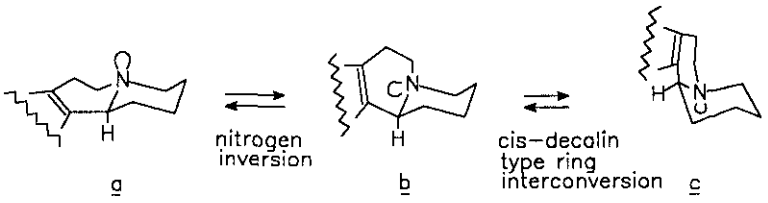
Figure 1 (continued). ^{13}C-Nmr data of compounds (**5** - **20**).

CONFORMATIONAL EXAMINATION

In general, the indolo[2,3-*a*]quinolizidine skeleton (*vide supra*) can exist in three main conformations, owing to nitrogen inversion and *cis*-decalin type ring interconversion (Scheme 4).[10-12] In addition to the normal chair conformation, the existence of ring D in boat and twisted boat conformations has to be taken into consideration.[10,11]



Scheme 4. Conformational equilibrium of the indolo[2,3-*a*]quinolizidine skeleton.

The spectral data (Table 1; Figure 1) and comparison with earlier results[12-14] clearly indicate that *compounds* (**5** - **12**) *exist predominantly in conformation* a.

The situation is different for the *cis*-N_b-oxides (**13** - **20**). Since these compounds can not exist in conformation a, only the competition between conformations b and c has to be taken into consideration.[15,16] NOE difference measurements (Table 2) of compounds (**13**), (**14**), (**17**), and (**18**) showed an NOE (2 - 2.5%) at H-5α when H-21β was irradiated, indicating the preponderance of conformation b. By analogy, taking the ^{13}C-nmr values (Figure 1) into account, the predominance of conformation b was also evident for compounds (**15**), (**16**), (**19**), and (**20**).

Table 2. Predominant conformations and observed NOE values for compounds (**5**, **6**, **9**, **10**, **11**, **12**, **13**, **14**, **17**, and **18**).

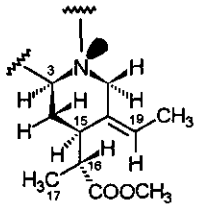
Comp.	Predominant *conformation*	Observed NOEs H-19 *irradiated*	Observed NOEs H-17 *irradiated*	Observed NOEs H-16 irradiated	Observed NOEs H-15 irradiated
5	a, chair	H-16(7%)	H-14α(1.5%)	H-19(12%)	
6	a, chair	H-15(2%) H-16(9%) H-17(3%)	H-15(2%) H-19(2%)		H-17(3.5%) H-19(3.5%)
9	a, chair	H-15(10%) H-17(1.5%)	H-15(2.5%) H-19(2%)	H-3(11%)	H-17(3%) H-19(18%)
10	a, chair	H-15(9%) H-16(2%) CO_2Me(<1%)	H-14α(1.5%) H-15(1.5%)		H-17(3.5%) H-19(18%)
11	a, chair	H-15(10.5%)	H-15(2.5%)		H-19(16%)
12	a, chair	H-15(9%) CO_2Me(<1%)	H-15(1.5%)		H-19(18%)
13	b*, chair	H-15(<1%) H-16(5.5%)		H-19(≈10%)	
14	b, chair	H-16(6%) H-17(1.5%)	H-15(≈1%) H-19(1.5%)	H-19(≈9%)	
17	b, chair	H-15(6%)	H-19(2%)	H-3(≈5%)	
18	b*, chair	H-15(7%)	H-14α(≈1%)	H-3(≈5%)	

*Accentuated contribution of conformation c

However, the contribution of conformation c to the conformational equilibrium between conformations b and c was clearly observable for compounds (**13**) and (**18**), appearing as reduced peak sharpness in both ^{1}H- and ^{13}C-nmr spectra (*cf.* footnotes in Tables 1 and 2, and Figure 1).

CONFIGURATIONAL EXAMINATION

Although in principle there is free rotation about the C-15 - C-16 bond, rotamers where C-15-H and C-16-H are approximately in an *anti* position to each other (Figures 2 and 3) can be expected to be favoured.[17] This should facilitate the use of NOE difference measurements for the determination of the C-16 configuration. The results of our NOE difference measurements are given in Table 2.



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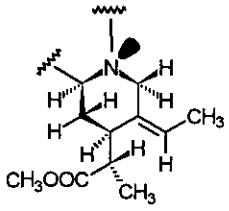

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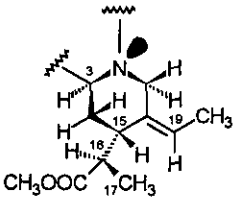
Figure 2. The approximate *anti* position between H-15 and H-16 in compound (**5**) (vicinal dihedral angle H_{15}-C-C-H_{16} $\Phi \approx 150^{\circ}$) and in compound (**6**) (vicinal dihedral angle H_{15}-C-C-H_{16} $\Phi \approx 145^{\circ}$)(representing the H-3 - H-15 *cis* series).



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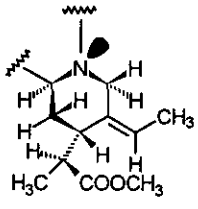

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Figure 3. The approximate *anti* position between H-15 and H-16 in compound (**9**) (vicinal dihedral angle H_{15}-C-C-H_{16} $\Phi \approx 180^{\circ}$) and in compound (**10**) (vicinal dihedral angle H_{15}-C-C-H_{16} $\Phi \approx 170^{\circ}$)(representing the H-3 - H-15 *trans* series).

In compounds (**5**), (**6**), (**13**), and (**14**) (H-3 - H-15 *cis* series) an appreciable NOE was observed at H-19 when H-16 was irradiated, and *vice versa*. This indicates the spacial proximity of these two protons (Figure 2, Table 2). In addition, in compounds (**6**) and (**14**), an NOE was observed at H-15 when H-17 was irradiated, and *vice versa,* indicating that the C-16 configuration is S*. In compounds (**5**) and (**13**), showing an NOE at H-14α when H-17 was irradiated, the C-16 configuration is R*.

For compounds (**9** - **12**) and (**17** - **18**) (H-3 - H-15 *trans* series) an NOE at H-3, when H-16 was irradiated, was observed and measured when possible [compounds (**9**), (**17**), and (**18**)]. The approximate *anti* position between H-15 and H-16 is thereby supported. In addition, in compounds (**10**) and (**18**) an NOE was observed at H-14α when H-17 was irradiated, and this confirms the S*-configuration of C-16. In compounds (**9**) and (**17**), which showed an NOE at H-19 when H-17 was irradiated, the C-16 configuration is R*. The C-16 configuration in compound (**12**) was determined by taking into account the small NOE (<1%) observed at the methyl protons of the methoxycarbonyl group when H-19 was irradiated. This showed the C-16 configuration to be S*. From this it follows that the C-16 configuration in compound (**11**) is R*.

The C-16 configurations in compounds (**7**), (**8**), (**15**), (**16**), (**19**), and (**20**) were determined by comparing their ^{1}H- and ^{13}C-nmr values with those of compounds whose configurations had already been determined.

CONCLUSIONS

Isositsirikine derivatives (**5** - **12**) were prepared by the Claisen rearrangement using trimethyl orthopropionate or trimethyl orthobutyrate together with the allylic alcohol (**21**) or (**22**) and oxidized

by H_2O_2 or mCPBA to the corresponding *cis*-N_b-oxides (**13** - **20**). The predominant conformation and C-16 configuration of *Z*-isositsirikine model compounds (**5** - **12**) and their N_b-oxides (**13** - **20**) could be fixed by nmr measurements. NOE difference spectroscopy was especially useful in the rapid determination of their stereochemistry.

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 IR spectrophotometer using $CHCl_3$ as solvent. Ir absorption bands are expressed in reciprocal centimetres (cm^{-1}). ^{1}H-Nmr spectra were measured with a Varian Unity-400 NMR spectrometer working at 399.952 MHz and ^{13}C-nmr spectra with a Varian Gemini-200 spectrometer working at 50.289 MHz using $CDCl_3$ as solvent. Chemical shifts are given in ppm with reference to TMS (^{1}H-nmr; $\delta_H = 0.00$ ppm) and $CDCl_3$ (^{13}C-nmr; $\delta_C = 77.00$ ppm). Signal assignments were confirmed by APT, DEPT, COSY, and HETCOR experiments. Abbreviations s, d, t, q, m, def and br are used to designate singlet, doublet, triplet, quartet, multiplet, deformed and broad, respectively. NOE difference spectroscopy was measured with the Varian Unity-400 NMR spectrometer at 30°C. Spectra were obtained by direct subtraction using a 90° composite pulse. Mass spectrometry (Elms and HRms) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compounds (**5**) [(16R*)-17-deoxy-*Z*-isositsirikine] and (**6**) [(16S*)-17-deoxy-*Z*-isositsirikine]

A solution of the allylic alcohol (**21**) (1000 mg, 3.73 mmol), trimethyl orthopropionate (4.2 ml, freshly distilled) and acetic acid (25 μl) in 1,4-dioxane (50 ml, Na dried and distilled) was stirred for 72 h at 100°C (Ar atm). The MeOH formed during the reaction was distilled off. The solvent was evaporated, the residue dissolved in CH_2Cl_2, neutralized with a saturated $NaHCO_3$ solution, washed with water and dried with Na_2SO_4. The crude product was purified by column chromatography (alumina, CH_2Cl_2, CH_2Cl_2/MeOH: 98/2) to give a mixture (953 mg, 76%) of compounds (**5**) and (**6**).[18] The mixture was divided into its isomeric components by repeated plc (silica gel, CH_2Cl_2/MeOH: 95/5).

Compound (**5**). Y. 203 mg (16%). Amorphous material. Ir: 1720 (C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 338 (M^+), 337, 251 (100%), 169, 156. HRms: Found: 338.2037. Calcd for $C_{21}H_{26}N_2O_2$: 338.1994.

Compound (**6**). Y. 174 mg (14%). Amorphous material. Ir: 1730 (C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 338 (M^+), 337, 251 (100%), 169, 156. HRms: Found: 338.2010. Calcd for $C_{21}H_{26}N_2O_2$: 338.1994.

Preparation of compounds (**7**) [(16R*)-17-methyl-17-deoxy-*Z*-isositsirikine] and (**8**) [(16S*)-17-methyl-17-deoxy-*Z*-isositsirikine]

A solution of the allylic alcohol (**21**) (1000 mg, 3.73 mmol), trimethyl orthobutyrate (4.16 ml, freshly distilled) and acetic acid (25 μl) in 1,4-dioxane (50 ml, Na dried and distilled) was stirred for 72 h at 100°C (Ar atm). The MeOH formed during the reaction was distilled off. After normal work-up [*vide supra*; compounds (**5**) and (**6**)] the crude mixture was purified by column chromatography (alumina, CH_2Cl_2, CH_2Cl_2/MeOH: 98/2) to give a mixture (775 mg, 59%) of compounds (**7**) and (**8**). The mixture was fractionated by plc (silica gel, CH_2Cl_2/MeOH: 90/10).

Compound (**7**) [contaminated with compound (**8**)]. Y. 263 mg (20%). Amorphous material. Ir: 1725 (C=O). ^{1}H-Nmr: 0.93 (3H, t, J=7 Hz, C-17-CH_3), 1.45 (1H, br d, J=12 Hz, H-14β), 1.70 (3H, d, J=7 Hz, H-18), 2.21 (1H, br dd, J=12 Hz, J≈3 Hz, H-14α), 2.74 (1H, d, J=12.5 Hz, H-21α), 3.72 (3H, s, -$COOCH_3$), 3.87 (1H, d, J=12.5 Hz, H-21β), 5.29 (1H, q, J=7 Hz, H-19), 7.07 (1H, t, J=7 Hz, H-10), 7.12 (1H, t, J=7 Hz, H-11), 7.30 (1H, d, J=7 Hz, H-12), 7.46 (1H, d, J=7 Hz, H-9), 8.05 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 352 (M^+), 323, 293, 251 (100%), 169, 156. HRms: Found: 352.2170. Calcd for $C_{22}H_{28}N_2O_2$: 352.2151.

Compound (**8**) [contaminated with compound (**7**)]. Y. 210 mg (16%). Amorphous material. Ir: 1725 (C=O). ^{1}H-Nmr: 0.90 (3H, t, J=7 Hz, C-17-CH_3), 1.72 (3H, d, J=7 Hz, H-18), 2.08 (1H, br dd, J=12 Hz, J≈3 Hz, H-14α), 3.70 (3H, s, -$COOCH_3$), 3.79 (1H, d, J=12.5 Hz, H-21β), 5.38 (1H, q, J=7 Hz, H-19), 7.08 (1H, t, J=7 Hz, H-10), 7.13 (1H, t, J=7 Hz, H-11), 7.31 (1H, d, J=7 Hz, H-12), 7.46 (1H, d, J=7 Hz, H-9), 8.08 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 352 (M^+), 323, 293, 251 (100%), 169, 156. HRms: Found: 352.2172. Calcd for $C_{22}H_{28}N_2O_2$: 352.2151.

Preparation of compounds (**9**) [(16R*)-17-deoxy-15-epi-*Z*-isositsirikine] and (**10**) [(16S*)-17-deoxy-15-epi-*Z*-isositsirikine]

A solution of the allylic alcohol (**22**) (1000 mg, 3.73 mmol), trimethyl orthopropionate (3.7 ml, freshly distilled) and acetic acid (25 μl) in 1,4-dioxane (50 ml, Na dried and distilled) was stirred for 72 h at 100°C (Ar atm). The MeOH formed during the reaction was distilled off. After normal work-up [*vide supra*; compounds (**5**) and (**6**)] the crude mixture was purified by column chromatography (alumina, hexane/CH_2Cl_2: 50/50, CH_2Cl_2, CH_2Cl_2/MeOH: 98/2) to give a mixture

(895 mg, 71%) of compounds (**9**) and (**10**). The mixture was divided into its isomeric components by plc (silica gel, CH_2Cl_2/MeOH: 95/5).

Compound (**9**). Y. 269 mg (21%). Amorphous material. Ir: 1730 (C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 338 (M^+), 337, 251 (100%), 169, 156. HRms: Found: 338.1974. Calcd for $C_{21}H_{26}N_2O_2$: 338.1994.

Compound (**10**). Y. 400 mg (32%). Amorphous material. Ir: 1730 (C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 338 (M^+), 337, 251 (100%), 169, 156. HRms: Found: 338.1996. Calcd for $C_{21}H_{26}N_2O_2$: 338.1994.

Preparation of compounds (**11**) [(16R*)-17-methyl-17-deoxy-15-epi-*Z*-isositsirikine] and (**12**) [(16S*)-17-methyl-17-deoxy-15-epi-*Z*-isositsirikine]

A solution of the allylic alcohol (**22**) (2000 mg, 7.44 mmol), trimethyl orthobutyrate (8.4 ml, 52.16 mmol, freshly distilled) and acetic acid (40 μl) in 1,4-dioxane (100 ml, Na dried and distilled) was stirred for 72 h at 100°C (Ar atm). The MeOH that formed during the reaction was distilled off. After normal work-up [*vide supra*; compounds (**5**) and (**6**)] the crude mixture was purified by column chromatography (alumina, CH_2Cl_2/n-hexane: 50/50; CH_2Cl_2) to give a mixture of compounds (**11**) and (**12**) (1990 mg, 76%). The mixture was divided into its isomeric components by plc (silica gel, CH_2Cl_2/MeOH: 90/10). Compound (**11**) was further purified by recrystallization from CH_2Cl_2.

Compound (**11**). Y. 262 mg (10%). mp 216-218°C (CH_2Cl_2). Ir: 1725 (C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 352 (M^+), 323, 293, 251 (100%), 169, 156. HRms: Found: 352.2191. Calcd for $C_{22}H_{28}N_2O_2$: 352.2151.

Compound (**12**). Y. 785 mg (30%). Amorphous material. Ir: 1730 (C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 352 (M^+), 323, 293, 251 (100%), 169, 156. HRms: Found: 352.2139. Calcd for $C_{22}H_{28}N_2O_2$: 352.2151.

Preparation of compound (**13**) [(16R*)-17-deoxy-*Z*-isositsirikine *cis*-N_b-oxide]

A solution of compound (**5**) (92.6 mg, 0.27 mmol) and H_2O_2 (30%; 82 μl) in $CHCl_3$/MeOH (1/1, 1.35 ml) was stirred for 22 h at 60°C (Ar atm). More H_2O_2 (25 μl + 25 μl) was added in two lots and the reaction mixture was stirred for 2.5 h (1.5 h + 1 h). The reaction mixture and Pd/C (10%) (12 mg) were stirred for 1 h at 60°C to destroy the excess H_2O_2. Pd/C was filtered off and washed with MeOH. The filtrate was evaporated and purified by column chromatography (alumina, CH_2Cl_2/MeOH: 95/5, CH_2Cl_2/MeOH: 93/7) to give compound (**13**).

Compound (**13**). Y. 38 mg (39%). Amorphous material. Ir: 1730 (C=O). For the ^{1}H-nmr data, see

Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 354 (M^+), 338, 249, 169, 156 (100%). HRms: Found: 354.1995. Calcd for $C_{21}H_{26}N_2O_3$: 354.1943.

Preparation of compound (14) [(16S*)-17-deoxy-*Z*-isositsirikine *cis*-N_b-oxide]

A solution of compound (6) (176.4 mg, 0.52 mmol) and H_2O_2 (30%; 157 μl) in $CHCl_3$/MeOH (1/1, 3 ml) was stirred for 20 h at 60°C (Ar atm). More H_2O_2 (50 μl + 50 μl) was added in two lots and the reaction mixture stirred for 2.5 h (1.5 h + 1 h). The reaction mixture and Pd/C (10%) (24 mg) were stirred for 1 h at 60°C to destroy the excess H_2O_2. After normal work-up [*vide supra*; compound (13)] the crude mixture was purified by column chromatography (alumina, CH_2Cl_2/MeOH: 98/2, CH_2Cl_2/MeOH: 97.5/2.5, CH_2Cl_2/MeOH: 95/5) to give compound (14).

Compound (14). Y. 96.3 mg (52%). Amorphous material. Ir: 1730 (C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 354 (M^+), 338, 337, 251, 249, 169, 156 (100%). HRms: Found: 354.1946. Calcd for $C_{21}H_{26}N_2O_3$: 354.1943.

Preparation of compounds (15) [(16R*)-17-methyl-17-deoxy-*Z*-isositsirikine *cis*-N_b-oxide] and (16) [(16S*)-17-methyl-17-deoxy-*Z*-isositsirikine *cis*-N_b-oxide]

A solution of mCPBA (300 mg, 1.74 mmol) in CH_2Cl_2 (3 ml) was added in portions to the mixture of compounds (7) and (8) (400 mg, 1.14 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred at room temperature (Ar atm) for 3 h. The solvent was evaporated and the crude mixture purified by column chromatography (alumina, CH_2Cl_2/MeOH: 98/2, CH_2Cl_2/MeOH: 95/5) to give a mixture of compounds (15) and (16) (152 mg, 36 %). The mixture was fractionated by plc (silica gel, CH_2Cl_2/MeOH: 90/10).

Compound (15) [contaminated with compound (16)]. Y. 63 mg (15%). Amorphous material. Ir: 1730 (C=O). ^{1}H-Nmr: 0.83 (3H, t, J=7 Hz, C-17-CH_3), 1.74 (3H, *d*, J=7 Hz, H-18), 3.64 (3H, s, -$COOCH_3$), 4.41 (1H, d, J=12.5 Hz, H-21β), 5.49 (1H, q, J=7 Hz, H-19), 7.0-7.2 (3H, m, H-10, H-11, H-12), 7.46 (1H, d, J=7 Hz, H-9), 12.02 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 368 (M^+), 351, 323, 267, 249, 169, 156 (100%). HRms: Found: 368.2088. Calcd for $C_{22}H_{28}N_2O_3$: 368.2100.

Compound (16) [contaminated with compound (15)]. Y. 50 mg (12%). Amorphous material. Ir: 1730 (C=O). ^{1}H-Nmr: 0.83 (3H, t, J=7 Hz, C-17-CH_3), 1.77 (3H, d, J=7 Hz, H-18), 3.60 (3H, s, -$COOCH_3$), 4.35 (1H, d, J=12.5 Hz, H-21β), 5.36 (1H, q, J=7 Hz, H-19), 7.0-7.2 (3H, m, H-10, H-11, H-12), 7.46 (1H, d, J=7 Hz, H-9), 12.14 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 368 (M^+), 351, 323, 267, 249, 169, 156 (100%). HRms: Found: 368.2084. Calcd for $C_{22}H_{28}N_2O_3$: 368.2100.

Preparation of compound (17) [(16R*)-17-deoxy-15-epi-*Z*-isositsirikine *cis*-N_b-oxide]

A solution of compound (9) (80.5 mg, 0.24 mmol) and H_2O_2 (30%; 71 μl) in $CHCl_3$/MeOH (1/1: 2.0 ml) was stirred for 22 h at 60°C (Ar atm). More H_2O_2 (20 μl + 20 μl) was added in two lots and the reaction mixture stirred for 2.5 h (1.5 h + 1 h). The reaction mixture and Pd/C (10%) (10.9 mg) were stirred for 1 h at 60°C to destroy the excess H_2O_2. After normal work-up [*vide supra*; compound (13)] the crude mixture was purified by PLC (silica, CH_2Cl_2/MeOH: 90/10) to give compound (17) and small amounts of compound (18), due to epimerization.

Compound (17). Y. 28 mg (33 %). Amorphous material. Ir: 1730 (C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 354 (M^+), 337, 267, 249, 184, 169, 156 (100%). HRms: Found: 354.1950. Calcd for $C_{21}H_{26}N_2O_3$: 354.1943.

Compound (18). Y. 4.3 mg (5%). For the analytical data, see below.

Preparation of compound (18) [(16S*)-17-deoxy-15-epi-*Z*-isositsirikine *cis*-N_b-oxide]

A solution of compound (10) (80.5 mg, 0.24 mmol) and H_2O_2 (30%; 71 μl) in $CHCl_3$/MeOH (1/1: 2.0 ml) was stirred for 22 h at 60°C (Ar atm). More H_2O_2 (20 μl + 20 μl) was added in two lots and the reaction mixture stirred for 2.5 h (1.5 h + 1 h). The reaction mixture and Pd/C (10%) (10.9 mg) were stirred for 1 h at 60°C to destroy the excess H_2O_2. After normal work-up [*vide supra*; compound (13)] the crude mixture was purified by column chromatography (alumina, CH_2Cl_2/MeOH: 98.5/1.5, CH_2Cl_2/MeOH: 98/2) to give compound (18).

Compound (18). Y. 34 mg (40%). Amorphous material. Ir: 1730 (C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 354 (M^+), 337, 267, 251, 187, 184, 169, 156 (100%). HRms: Found: 354.1945. Calcd for $C_{21}H_{26}N_2O_3$: 354.1943.

Preparation of compounds (19) [(16R*)-17-methyl-17-deoxy-15-epi-*Z*-isositsirikine *cis*-N_b-oxide] and (20) [(16S*)-17-methyl-17-deoxy-15-epi-*Z*-isositsirikine *cis*-N_b-oxide]

A solution of mCPBA (300 mg, 1.74 mmol) in CH_2Cl_2 (10 ml) was added in portions to a mixture of compounds (11) and (12) (300 mg, 0.85 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred at room temperature (under Ar atm) for 3 h. After normal work-up [*vide supra*; compounds (15) and (16)] the crude mixture was purified by column chromatography (alumina, CH_2Cl_2/MeOH: 98/2, CH_2Cl_2/MeOH: 95/5) to give compounds (19) and (20) as a ~4:6 mixture (142 mg; 45%). The mixture was fractionated by plc (silica gel, CH_2Cl_2/MeOH: 90/10). Compound (20) was further purified by recrystallization from CH_2Cl_2.

Compound (19) [contaminated with compound (20)]. Y. ~55 mg (~18%). Amorphous material. Ir: 1730 (C=O). ^{1}H-Nmr: 0.50 (3H, t, J=7 Hz, C-17-CH_3), 1.80 (3H, d, J=7 Hz, H-18), 3.70 (3H,

s, -$COOCH_3$), 4.5 (1H, br, H-3), 5.67 (1H, q, J=7 Hz, H-19), 7.0-7.5 (4H, m, H-9, H-10, H-11, H-12), 11.54 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 368 (M^+), 351, 323, 267 (100%), 251, 184, 170, 156. HRms: Found: 368.2080. Calcd for $C_{22}H_{28}N_2O_3$: 368.2100.

Compound (**20**). Y. 38 mg (12%). mp 216-220°C (CH_2Cl_2). Ir: 1730 (C=O). ^{1}H-Nmr: 0.72 (3H, t, J=7 Hz, C-17-CH_3), 1.69 (3H, d, J=7 Hz, H-18), 3.48 (3H, s, -$COOCH_3$), 4.5 (1H, br, H-3), 5.55 (1H, q, J=7 Hz, H-19), 7.05 (1H, t, H-10), 7.07 (1H, t, J=7 Hz, H-11), 7.30 (1H, d, J=7 Hz, H-12), 7.44 (1H, d, J=7 Hz, H-9), 11.74 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 368 (M^+), 351, 323, 267 (100%), 251, 184, 170, 156. HRms: Found: 368.2086. Calcd for $C_{22}H_{28}N_2O_3$: 368.2100.

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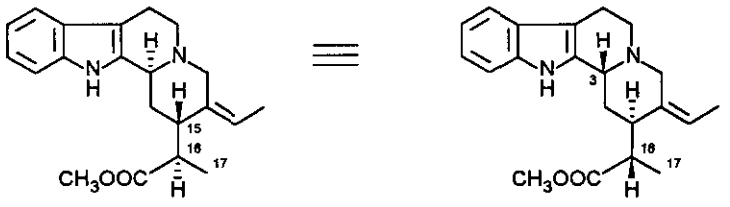
8. Small amounts of the corresponding *trans*-N_b-oxides were also formed.
9. Compound (**9**), (±)-(16R*)-17-deoxy-15-epi-*Z*-isositsirikine is identical with (±)-(16S*)-17-deoxy-3-epi-*Z*-isositsirikine (**9'**). Likewise, the same situation holds for compounds (**10** - **12**)



9 **9'**

and (**17** - **20**). Since the compounds are formed by the Claisen rearrangement from the allylic alcohol (**22**),[19] for mechanistic reasons we preferred their presentation as shown (*vide supra*), even though the C-15-H in formulae (**9** - **12**) and (**17** - **20**), being β, is unnatural.

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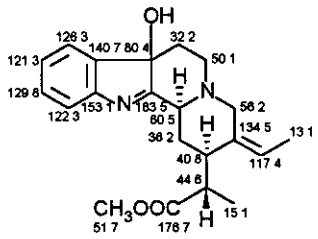
18. During the purification of compound (**6**) small amounts of the corresponding hydroxyindolenine (**6a**) were formed, due to autoxidation.
    Compound (**6a**): Amorphous material. ^{1}H-Nmr: 1.29 (3H, d, J = 7 Hz, H-17), 1.67 (3H, d, J = 7 Hz, H-18), 2.11 (1H, br d, J = 12.5 Hz, H-14α), 3.70 (3H, s, -COOCH$_3$), 3.85 (1H, d, J = 12 Hz, H-21β), 5.27 (1H, q, J = 7 Hz, H-19), 7.16-7.29 (2H, m, H-10, H-11), 7.41 (1H, d, J = 7 Hz, H-9), 7.51 (1H, d, J = 7 Hz, H-12). For the ^{13}C-nmr data, see formula (**6a**) below. Ms: 355 ($M^+ + 1$), 354 (M^+), 338, 284, 268, 252, 250. HRms: Found: 354.1926. Calcd for $C_{21}H_{26}N_2O_3$: 354.1943.



6a

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