

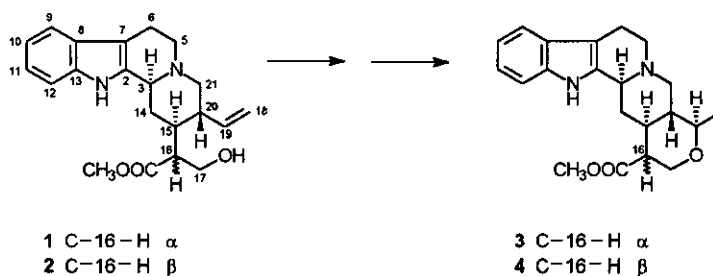
PREPARATION AND CONFORMATIONAL STUDY OF Z-ISOSITSIRIKINE
 MODEL COMPOUNDS AND THEIR *cis-N_b*-OXIDES. DETERMINATION OF
 THE C-16 CONFIGURATION

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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 configuration¹ in indole alkaloids of sitsirikine/isositsirikine type is a problem of general interest.²⁻⁴ Zenk *et al.*⁵ have presented some preliminary ¹H-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.

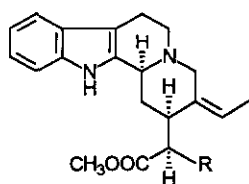


Scheme 1

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

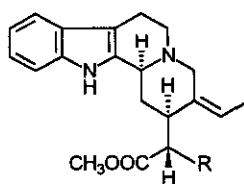
Enormous progress in nmr spectroscopy during the last decade has been achieved, thus making the time ripe for a direct determination of the C-16 configuration in compounds of the present type.

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.



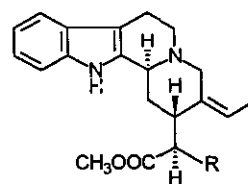
5 R = CH₃

7 R = CH₂-CH₃



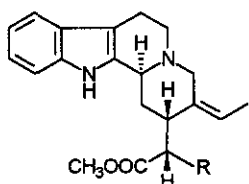
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8 R = CH₂-CH₃



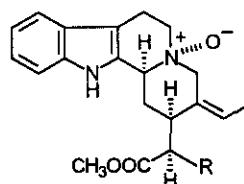
9 R = CH₃

11 R = CH₂-CH₃



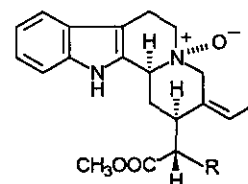
10 R = CH₃

12 R = CH₂-CH₃



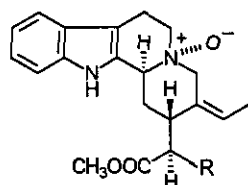
13 R = CH₃

15 R = CH₂-CH₃



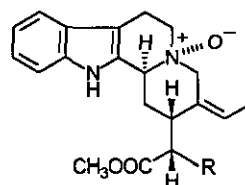
14 R = CH₃

16 R = CH₂-CH₃



17 R = CH₃

19 R = CH₂-CH₃

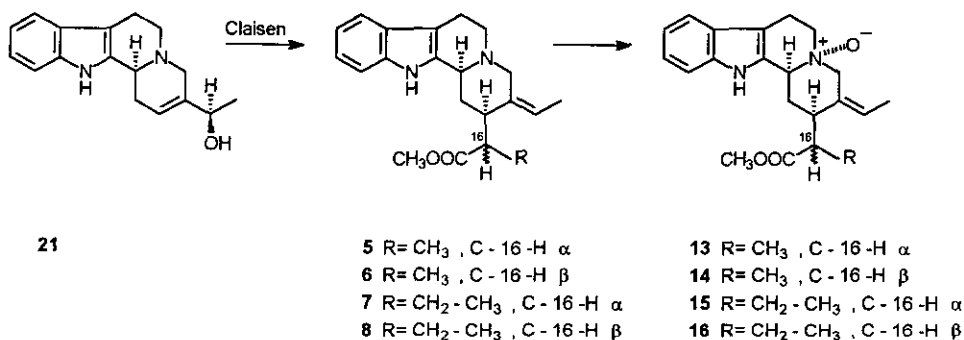


18 R = CH₃

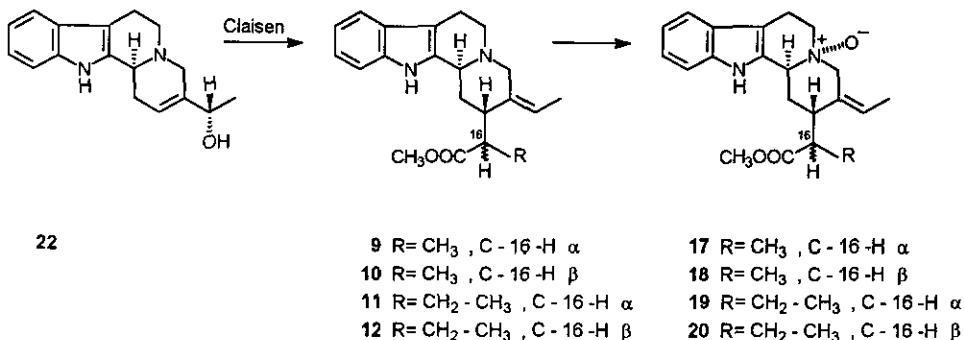
20 R = CH₂-CH₃

RESULTS AND DISCUSSION

Recently we described a stereoselective preparation of deformed-*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 H₂O₂ or *m*-chloroperbenzoic acid (mCPBA) (*cf.* Experimental) led to the corresponding *cis*-*N*_b-oxides (13 - 20)^{8,9} (Schemes 2 and 3).



Scheme 2.



Scheme 3

Table 1. ¹H-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-5 α	2.68 ddd	2.7 m	2.68 ddd	2.72 ddd	2.71 ddd
H-5 β	3.15 ddd	3.16 ddd	3.12 ddd	3.14 ddd	3.13 m
H-6 α	2.75 m	2.8 m	2.7 m	2.7 m	2.7 m
H-6 β	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-14 α	2.15 ddd	2.12 ddd	1.96 br d	2.20 br d	1.9 m
H-14 β	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-21 α	2.78 br d	2.85 br d	2.74 br d	3.0 m	2.81 br d
H-21 β	3.89 d	3.75 d	3.66 d	3.65 d	3.68 d
CO ₂ Me	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). ¹H-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-5 α	2.8 m	3.12 m	3.15 m	3.2 m	3.19 m
H-5 β	3.17 m	3.5 m	3.5 m	3.7 m	3.8 m
H-6 α	2.8 m	3.5 m	3.5 m	3.5 m	3.7 m
H-6 β	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-14 α	2.22 br d	2.4 m	2.14 m	2.1 m	2.38 m
H-14 β	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-21 α	3.05 br d	3.52 d	3.6 m	3.91 br d	4.10 br d
H-21 β	3.68 d	4.41 d	4.36 d	4.38 br d	4.34 br
CO ₂ Me	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). ¹H-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; $J_{14\beta,15} = 4$ Hz; $J_{17,CH_3} = 7.5$ 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; $J_{17,CH_3} = 7$ 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

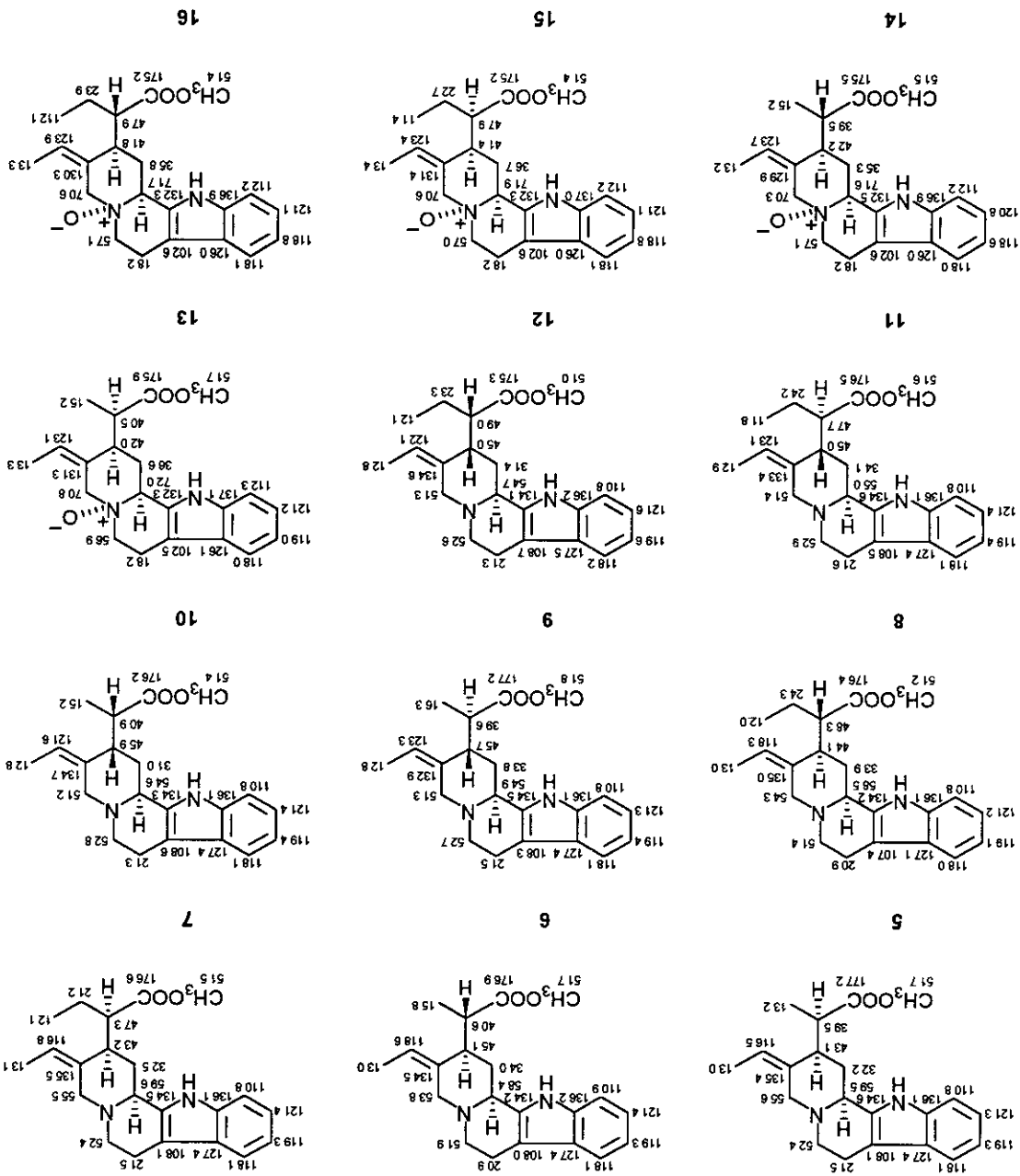


Figure 1 (continues on next page). ¹³C-Nmr data of compounds (5 - 20).

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*_p-oxides).

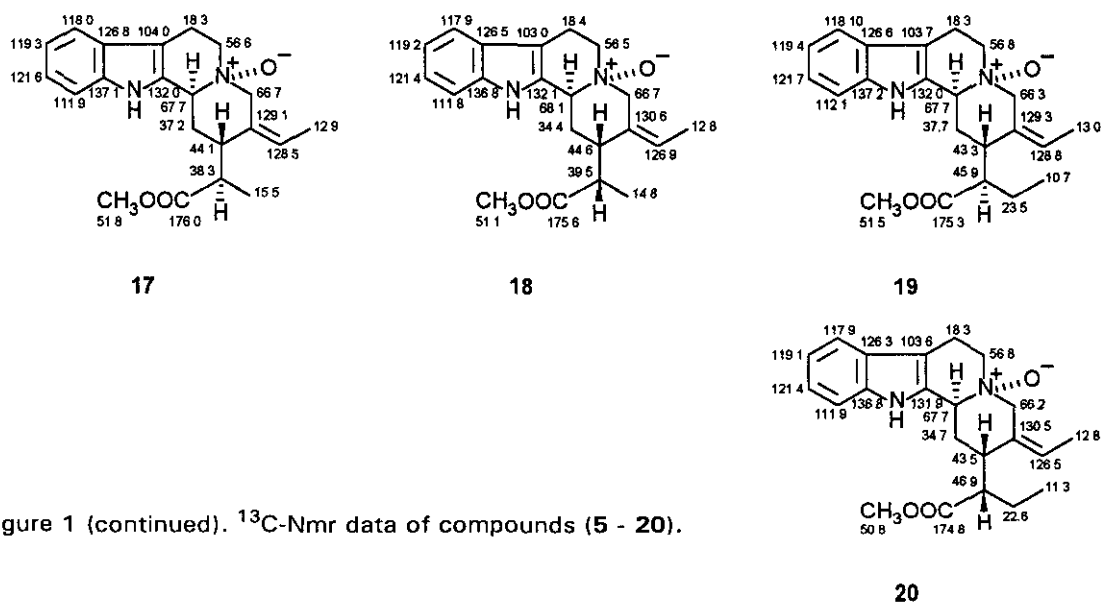
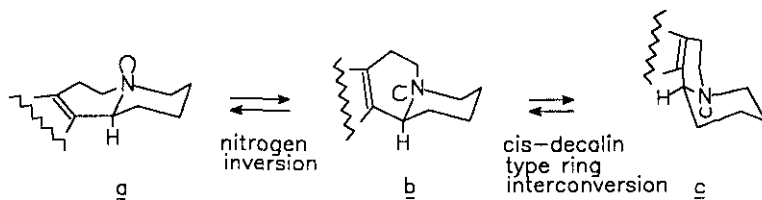


Figure 1 (continued). ^{13}C -Nmr data of compounds (5 - 20).

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 results¹²⁻¹⁴ 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-5 α when H-21 β was irradiated, indicating the preponderance of conformation b. By analogy, taking the ¹³C-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	<u>a</u> , chair	H-16(7%)	H-14 α (1.5%)	H-19(12%)	
6	<u>a</u> , 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	<u>a</u> , 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	<u>a</u> , chair	H-15(9%) H-16(2%) CO ₂ Me(< 1%)	H-14 α (1.5%) H-15(1.5%)		H-17(3.5%) H-19(18%)
11	<u>a</u> , chair	H-15(10.5%)	H-15(2.5%)		H-19(16%)
12	<u>a</u> , chair	H-15(9%) CO ₂ Me(< 1%)	H-15(1.5%)		H-19(18%)
13	<u>b</u> [*] , chair	H-15(< 1%) H-16(5.5%)		H-19(≈ 10%)	
14	<u>b</u> , chair	H-16(6%) H-17(1.5%)	H-15(≈ 1%) H-19(1.5%)	H-19(≈ 9%)	
17	<u>b</u> , chair	H-15(6%)	H-19(2%)	H-3(≈ 5%)	
18	<u>b</u> [*] , chair	H-15(7%)	H-14 α (≈ 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 ^1H - 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.

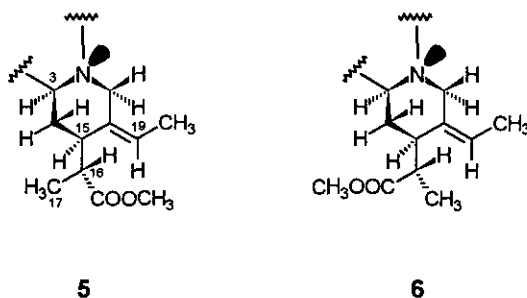


Figure 2. The approximate *anti* position between H-15 and H-16 in compound (5) (vicinal dihedral angle $\text{H}_{15}\text{-C-C-H}_{16}$ $\Phi \approx 150^\circ$) and in compound (6) (vicinal dihedral angle $\text{H}_{15}\text{-C-C-H}_{16}$ $\Phi \approx 145^\circ$) (representing the H-3 - H-15 *cis*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

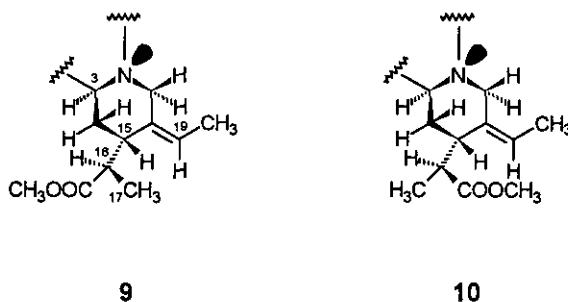


Figure 3. The approximate *anti* position between H-15 and H-16 in compound (9) (vicinal dihedral angle $\text{H}_{15}\text{-C-C-H}_{16}$ $\Phi \approx 180^\circ$) and in compound (10) (vicinal dihedral angle $\text{H}_{15}\text{-C-C-H}_{16}$ $\Phi \approx 170^\circ$) (representing the H-3 - H-15 *trans* 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-14 α 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-14 α 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 ^1H - 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 H₂O₂ or mCPBA to the corresponding *cis*-N₆-oxides (13 - 20). The predominant conformation and C-16 configuration of *Z*-isositsirikine model compounds (5 - 12) and their N₆-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 CHCl₃ as solvent. Ir absorption bands are expressed in reciprocal centimetres (cm⁻¹). ¹H-Nmr spectra were measured with a Varian Unity-400 NMR spectrometer working at 399.952 MHz and ¹³C-nmr spectra with a Varian Gemini-200 spectrometer working at 50.289 MHz using CDCl₃ as solvent. Chemical shifts are given in ppm with reference to TMS (¹H-nmr; δ_H = 0.00 ppm) and CDCl₃ (¹³C-nmr; δ_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 CH₂Cl₂, neutralized with a saturated NaHCO₃ solution, washed with water and dried with Na₂SO₄. The crude product was purified by column chromatography (alumina, CH₂Cl₂, CH₂Cl₂/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, CH₂Cl₂/MeOH: 95/5).

Compound (5). Y. 203 mg (16%). Amorphous material. Ir: 1720 (C=O). For the ¹H-nmr data, see Table 1. For the ¹³C-nmr data, see Figure 1. Ms: 338 (M⁺), 337, 251 (100%), 169, 156. HRms: Found: 338.2037. Calcd for C₂₁H₂₆N₂O₂: 338.1994.

Compound (6). Y. 174 mg (14%). Amorphous material. Ir: 1730 (C=O). For the ^1H -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 $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_2$: 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 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 98/2) to give a mixture (775 mg, 59%) of compounds (7) and (8). The mixture was fractionated by plc (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 90/10).

Compound (7) [contaminated with compound (8)]. Y. 263 mg (20%). Amorphous material. Ir: 1725 (C=O). ^1H -Nmr: 0.93 (3H, t, $J=7$ Hz, C-17- CH_3), 1.45 (1H, br d, $J=12$ Hz, H-14 β), 1.70 (3H, d, $J=7$ Hz, H-18), 2.21 (1H, br dd, $J=12$ Hz, $J\approx 3$ Hz, H-14 α), 2.74 (1H, d, $J=12.5$ Hz, H-21 α), 3.72 (3H, s, - COOCH_3), 3.87 (1H, d, $J=12.5$ Hz, H-21 β), 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 $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_2$: 352.2151.

Compound (8) [contaminated with compound (7)]. Y. 210 mg (16%). Amorphous material. Ir: 1725 (C=O). ^1H -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, $J\approx 3$ Hz, H-14 α), 3.70 (3H, s, - COOCH_3), 3.79 (1H, d, $J=12.5$ Hz, H-21 β), 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 $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_2$: 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 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 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, CH₂Cl₂/MeOH: 95/5).

Compound (9). Y. 269 mg (21%). Amorphous material. Ir: 1730 (C=O). For the ¹H-nmr data, see Table 1. For the ¹³C-nmr data, see Figure 1. Ms: 338 (M⁺), 337, 251 (100%), 169, 156. HRms: Found: 338.1974. Calcd for C₂₁H₂₆N₂O₂: 338.1994.

Compound (10). Y. 400 mg (32%). Amorphous material. Ir: 1730 (C=O). For the ¹H-nmr data, see Table 1. For the ¹³C-nmr data, see Figure 1. Ms: 338 (M⁺), 337, 251 (100%), 169, 156. HRms: Found: 338.1996. Calcd for C₂₁H₂₆N₂O₂: 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 orthobutyrates (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, CH₂Cl₂/n-hexane: 50/50; CH₂Cl₂) to give a mixture of compounds (11) and (12) (1990 mg, 76%). The mixture was divided into its isomeric components by plc (silica gel, CH₂Cl₂/MeOH: 90/10). Compound (11) was further purified by recrystallization from CH₂Cl₂.

Compound (11). Y. 262 mg (10%). mp 216-218°C (CH₂Cl₂). Ir: 1725 (C=O). For the ¹H-nmr data, see Table 1. For the ¹³C-nmr data, see Figure 1. Ms: 352 (M⁺), 323, 293, 251 (100%), 169, 156. HRms: Found: 352.2191. Calcd for C₂₂H₂₈N₂O₂: 352.2151.

Compound (12). Y. 785 mg (30%). Amorphous material. Ir: 1730 (C=O). For the ¹H-nmr data, see Table 1. For the ¹³C-nmr data, see Figure 1. Ms: 352 (M⁺), 323, 293, 251 (100%), 169, 156. HRms: Found: 352.2139. Calcd for C₂₂H₂₈N₂O₂: 352.2151.

Preparation of compound (13) [(16R*)-17-deoxy-Z-isositsirikine *cis*-N₆-oxide]

A solution of compound (5) (92.6 mg, 0.27 mmol) and H₂O₂ (30%; 82 μl) in CHCl₃/MeOH (1/1, 1.35 ml) was stirred for 22 h at 60°C (Ar atm). More H₂O₂ (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 H₂O₂. Pd/C was filtered off and washed with MeOH. The filtrate was evaporated and purified by column chromatography (alumina, CH₂Cl₂/MeOH: 95/5, CH₂Cl₂/MeOH: 93/7) to give compound (13).

Compound (13). Y. 38 mg (39%). Amorphous material. Ir: 1730 (C=O). For the ¹H-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 $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_3$: 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 $\text{CHCl}_3/\text{MeOH}$ (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, $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 98/2, $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 97.5/2.5, $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 95/5) to give compound (14).

Compound (14). Y. 96.3 mg (52%). Amorphous material. Ir: 1730 (C=O). For the ^1H -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 $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_3$: 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, $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 98/2, $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 95/5) to give a mixture of compounds (15) and (16) (152 mg, 36 %). The mixture was fractionated by plc (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$: 90/10).

Compound (15) [contaminated with compound (16)]. Y. 63 mg (15%). Amorphous material. Ir: 1730 (C=O). ^1H -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, $-\text{COOCH}_3$), 4.41 (1H, d, $J=12.5$ Hz, H-21 β), 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 $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3$: 368.2100.

Compound (16) [contaminated with compound (15)]. Y. 50 mg (12%). Amorphous material. Ir: 1730 (C=O). ^1H -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, $-\text{COOCH}_3$), 4.35 (1H, d, $J=12.5$ Hz, H-21 β), 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 $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3$: 368.2100.

Preparation of compound (17) [(16R*)-17-deoxy-15-epi-Z-isositsirikine *cis*-N₆-oxide]

A solution of compound (9) (80.5 mg, 0.24 mmol) and H₂O₂ (30%; 71 μ l) in CHCl₃/MeOH (1/1; 2.0 ml) was stirred for 22 h at 60°C (Ar atm). More H₂O₂ (20 μ l + 20 μ l) 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 H₂O₂. After normal work-up [*vide supra*; compound (13)] the crude mixture was purified by PLC (silica, CH₂Cl₂/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 ¹H-nmr data, see Table 1. For the ¹³C-nmr data, see Figure 1. Ms: 354 (M⁺), 337, 267, 249, 184, 169, 156 (100%). HRms: Found: 354.1950. Calcd for C₂₁H₂₆N₂O₃: 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*-N₆-oxide]

A solution of compound (10) (80.5 mg, 0.24 mmol) and H₂O₂ (30%; 71 μ l) in CHCl₃/MeOH (1/1; 2.0 ml) was stirred for 22 h at 60°C (Ar atm). More H₂O₂ (20 μ l + 20 μ l) 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 H₂O₂. After normal work-up [*vide supra*; compound (13)] the crude mixture was purified by column chromatography (alumina, CH₂Cl₂/MeOH: 98.5/1.5, CH₂Cl₂/MeOH: 98/2) to give compound (18).

Compound (18). Y. 34 mg (40%). Amorphous material. Ir: 1730 (C=O). For the ¹H-nmr data, see Table 1. For the ¹³C-nmr data, see Figure 1. Ms: 354 (M⁺), 337, 267, 251, 187, 184, 169, 156 (100%). HRms: Found: 354.1945. Calcd for C₂₁H₂₆N₂O₃: 354.1943.

Preparation of compounds (19) [(16R*)-17-methyl-17-deoxy-15-epi-Z-isositsirikine *cis*-N₆-oxide] and (20) [(16S*)-17-methyl-17-deoxy-15-epi-Z-isositsirikine *cis*-N₆-oxide]

A solution of mCPBA (300 mg, 1.74 mmol) in CH₂Cl₂ (10 ml) was added in portions to a mixture of compounds (11) and (12) (300 mg, 0.85 mmol) in CH₂Cl₂ (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, CH₂Cl₂/MeOH: 98/2, CH₂Cl₂/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, CH₂Cl₂/MeOH: 90/10). Compound (20) was further purified by recrystallization from CH₂Cl₂.

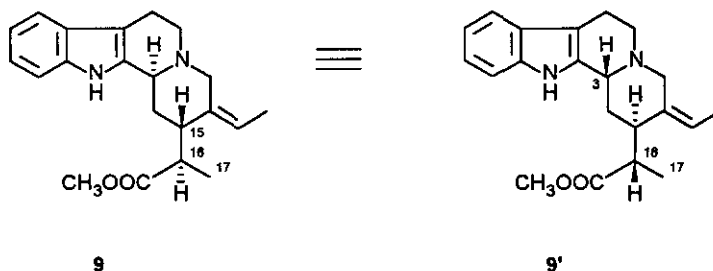
Compound (19) [contaminated with compound (20)]. Y. ~55 mg (~18%). Amorphous material. Ir: 1730 (C=O). ¹H-Nmr: 0.50 (3H, t, J=7 Hz, C-17-CH₃), 1.80 (3H, d, J=7 Hz, H-18), 3.70 (3H,

s, $-\text{COOCH}_3$), 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 $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3$: 368.2100.

Compound (20). Y. 38 mg (12%). mp 216-220°C (CH_2Cl_2). Ir: 1730 ($\text{C}=\text{O}$). ^1H -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, $-\text{COOCH}_3$), 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 $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3$: 368.2100.

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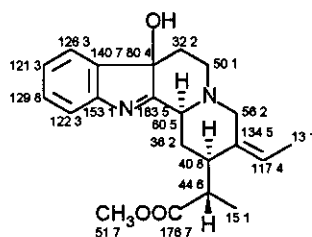
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8. Small amounts of the corresponding *trans*- N_6 -oxides were also formed.
9. Compound (9), (\pm)-(16R*)-17-deoxy-15-epi-Z-isositsirikine is identical with (\pm)-(16S*)-17-deoxy-3-epi-Z-isositsirikine (9'). Likewise, the same situation holds for compounds (10 - 12)



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. ¹H-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-14 α), 3.70 (3H, s, -COOCH₃), 3.85 (1H, d, J=12 Hz, H-21 β), 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 ¹³C-nmr data, see formula (6a) below. Ms: 355 (M⁺ + 1), 354 (M⁺), 338, 284, 268, 252, 250. HRms: Found: 354.1926. Calcd for C₂₁H₂₆N₂O₃: 354.1943.



6a

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