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Preparation and Conformational Study of *Z*- and *E*-Isositsirikine Epimers and Model Compounds. Determination of their C-16 Configurations

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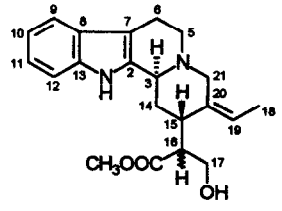
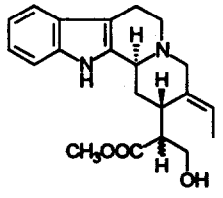
Abstract - Syntheses are reported for isositsirikine isomers **1** - **6** and (16S*)- and (16R*)-17-deoxy-*E*-isositsirikines **9** and **10** (model compounds[1,2] for the "synthetically missing" (16R)- and (16S)-*E*-isositsirikines **7** and **8**, respectively). Predominant conformations of the compounds, and of their C-16 configurations were determined on the basis of nmr measurements, especially NOE difference spectroscopy. The large difference in chemical shifts (δ 4.31 ppm *versus* δ 3.9 ppm), between the C-3-H-signals of (16R)- and (16S)-*E*-isositsirikines **7** and **8** is explained. The ^{13}C-nmr data confirm the non-identity of compounds **1** - **6** with rhazimanine and bhimberine, alkaloids isolated from *Rhazya stricta*.

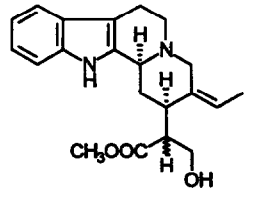
The isositsirikine skeleton allows the existence of eight stereoisomers **1** - **8**, which all have been treated in the literature,[3-5] but surprisingly little has been accomplished by spectroscopic methods. The enormous progress in nmr spectroscopy during the last decade makes in our view nmr the *méthode de choix* for the stereochemical determination of isositsirikine (and similar) structures.



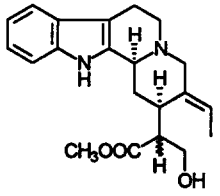
1 C-16-H β
2 C-16-H α



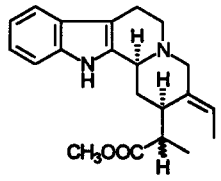
3 C-16-H β
4 C-16-H α



5 C-16-H β
6 C-16-H α

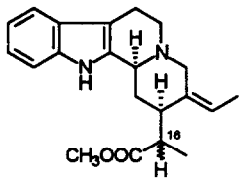


7 C-16-H β
8 C-16-H α

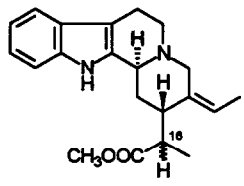


9 C-16-H β
10 C-16-H α

In a recent paper[6] we described our determination by nmr methods of the C-16 configuration and general conformational aspects of 17-deoxy-Z-isositsirikines **11** - **14**.



11 C-16-H β
12 C-16-H α



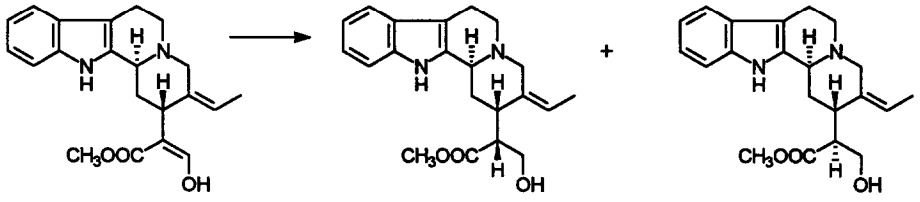
13 C-16-H β
14 C-16-H α

The determination of the predominant conformation and the correct C-16 configuration in indole alkaloids of sitsirikine/isositsirikine type is a problem of general interest.[3-8] Moreover, surprise has been expressed[9] over the relatively large difference in the chemical shifts of H-3 in the ^{1}H-nmr values, found earlier[10] for (16R)-*E*-isositsirikine **7** (δ 4.31 ppm) and (16S)-*E*-isositsirikine **8** (δ 3.9 ppm). Finally, the confusion over the structures of two "isositsirikine stereoisomers" rhazimanine[11] and bhimberine[12], based mainly on nmr measurements, makes a thorough analytical, especially ^{1}H- and ^{13}C-nmr spectral study of different isositsirikine structures highly desirable.

A preparation of the six isositsirikine isomers **1** - **6** made six of the eight stereoisomers available to us for nmr measurements. For the "missing" stereoisomers, (16R)-*E*-isositsirikine **7** and (16S)-*E*-isositsirikine **8**, ^{1}H-nmr values were taken from Ref. 10 and ^{13}C-nmr values from Refs. 13 (for compound **7**) and 14 (for compound **8**). In addition, the preparation of the (16S*)- and (16R*)-17-deoxy-*E*-isositsirikines **9** and **10** provided "model compounds" for comparison with compounds **7** and **8**.[1,2] In the present paper we describe a conformational study of compounds **1** - **10** and a detailed determination of their C-16 configurations.

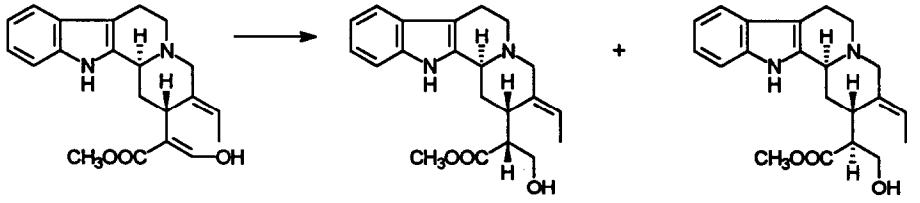
RESULTS AND DISCUSSION

We recently showed[15] that geissoschizine isomers **15**, **16**, and **17** can easily be prepared by exploiting the Claisen rearrangement of appropriate vinyl allyl ethers. Subsequent sodium borohydride reduction of the isomers led to isositsirikine C-16 epimer mixtures of **1** and **2**, **3** and **4**, and **5** and **6**, respectively (Schemes 1, 2, and 3). After careful chromatographic separations each diastereoisomer was obtained in pure state.



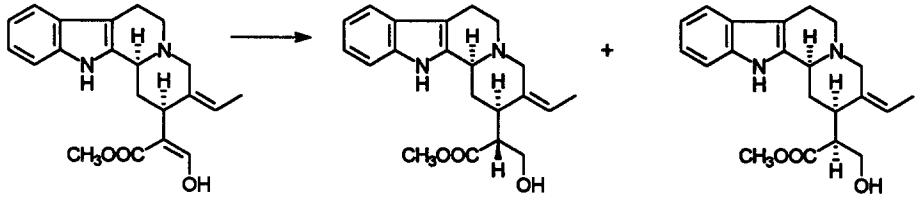
15 **1** **2**

Scheme 1.



16 **3** **4**

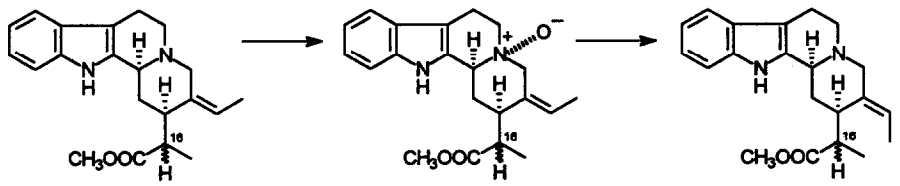
Scheme 2.



17 **5** **6**

Scheme 3.

The (16S*)- and (16R*)-17-deoxy-*E*-isositsirikines **9** and **10** (corresponding to (16R)- and (16S)-*E*-isositsirikines **7** and **8**)[1] were prepared from their *Z*-ethylidene counterparts **11** and **12**,[6] *via cis*-N_b-oxides **18** and **19**, by modified Polonovski reaction initiated isomerization[16,17] (Scheme 4).



11 C-16-H β
12 C-16-H α

18 C-16-H β
19 C-16-H α

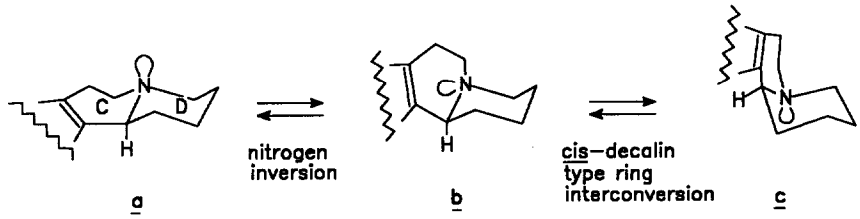
9 C-16-H β
10 C-16-H α

Scheme 4.

With the isositsirikine isomers **1**, **2**, **3**, **4**, **5**, and **6**, and their deoxy analogues **9** and **10** in hand, we proceeded to a detailed conformational and ethylidene- and C-16-configurational examination of these eight basic structures.

CONFORMATIONAL CONSIDERATIONS

The indolo[2,3-*a*]quinolizidine skeleton can exist in three main conformations,[18-22] owing to nitrogen inversion and *cis*-decalin type ring interconversion (Scheme 5).



a b c

Scheme 5.

The spectral data (Table 1; Figure 1) and comparison with earlier results[23-26] clearly indicate the predominance of conformation a for compounds **1** - **6** (though in somewhat less amount for compound **5**).

Table 1.^{1}H-nmr data of compounds **1** - **10**.

	1	**2**	**3**	**4**	**5**
H-1	8.53 br s	7.80 br s	8.20 br s	7.75 br s	8.49 br s
H-3	3.53 br d	3.7 br d	3.6 m	3.7 br d	3.7 br d
H-5α	2.6 m	2.68 ddd	2.58 m	2.66 ddd	2.7 m
H-5β	3.1 m	3.1 m	3.0 m	3.1 m	3.19 m
H-6α	2.68 br d	2.8 br d	2.71 br d	2.75 br d	2.79 br d
H-6β	3.0 m	3.0 m	3.0 m	3.00 dddd	3.0 m
H-9	7.42 d	7.45 d	7.44 d	7.45 d	7.44 d
H-10	7.05 t	7.07 t	7.07 t	7.08 t	7.07 t
H-11	7.11 t	7.13 t	7.13 t	7.13 t	7.13 t
H-12	7.27 d	7.30 d	7.31 d	7.31 d	7.32 d
H-14α	2.12 br d	1.94 br d	2.26 br d	1.97 br d	2.23 ddd
H-14β	1.76 ddd	1.88 ddd	1.7 m	1.80 ddd	1.74 ddd
H-15	2.6 m	2.8 m	3.1 m	3.27 br dd	2.62 m
H-16	3.1 m	3.1 m	3.0 m	3.1 m	3.0 m
H-17	3.86 br d	3.73 br d	4.0 br s	3.7 m	3.89 dd
H-17'	3.86 br d	3.73 br d	4.0 br s	3.7 m	3.81 dd
H-18	1.60 d	1.70 d	1.57 d	1.68 d	1.68 d
H-19	5.29 q	5.49 q	5.51 q	5.64 q	5.45 q
H-21α	2.95 br d	2.86 br d	3.32 br d	3.21 s	2.89 br d
H-21β	3.61 d	3.69 d	3.18 d	3.21 s	3.78 d
CO_2Me	3.56 s	3.84 s	3.64 s	3.87 s	3.70 s

Table 1 (continued). ^{1}H-nmr data of compounds **1** - **10**.

	6	**7**[a]	**8**[a]	**9**	**10**
H-1	8.14 br s	8.67 br s	8.23 br s	9.03 br s	8.37 br s
H-3	3.47 br d	4.31 br s	3.9 br	4.45 br s	4.17 br
H-5α	2.65 ddd	3.15 ddd	2.84 ddd	3.25 ddd	3.0 m
H-5β	3.13 ddd	3.27 dd	3.17 dd	3.33 ddd	3.18 ddd
H-6α	2.74 br d	2.65 br d	2.68 br d	2.69 br dd	2.72 br d
H-6β	3.0 m	3.0 m	3.0 m	3.00 ddd	3.0 m
H-9	7.45 d	7.48 d	7.48 d	7.48 d	7.46 d
H-10	7.07 t	7.10 t	7.09 t	7.11 t	7.10 t
H-11	7.12 t	7.17 t	7.14 t	7.17 t	7.15 t
H-12	7.29 d	7.38 d	7.31 d	7.40 d	7.33 d
H-14α	2.26 ddd	2.26[b] m	2.27[c] m	2.2 m	2.2 m
H-14β	1.42 ddd	2.22[b] m	2.25[c] m	2.30 ddd	2.2 m
H-15	2.83 m	3.10 m	3.38 m	2.93 ddd	2.93 m
H-16	2.9 m	2.52 m	2.66 m	2.2 m	2.54 m
H-17	3.95 dd	3.55 br dd	3.92 br dd	0.84 d	1.19 d
H-17'	3.88 dd	3.50 br dd	3.87 br dd	-	-
H-18	1.70 d	1.67 d	1.63 d	1.66 dd	1.59 dd
H-19	5.36 q	5.64 br q	5.52 br q	5.70 q	5.57 q
H-21α	2.78 br d	2.93[d] br d	3.08 br d	3.01 br d	3.14 br d
H-21β	3.87 d	3.54[d] br d	3.80 br d	3.48 d	3.73 d
CO_2Me	3.76 s	3.82[e] s	3.57 s	3.77 s	3.53 s

[a] Values taken from Ref. 10.
[b,c] Assignments may be interchanged.
[d] Earlier assignments[10] have been interchanged.
[e] The earlier given value 3.67 ppm[10] is erroneous and is corrected to 3.82 ppm.

Table 1 (continued). ^{1}H-nmr data of compounds **1** - **10**.

Coupling constants:

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

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

Compound **3**.
$J_{6\alpha,6\beta} = 15.5$ Hz; $J_{14\alpha,14\beta} = 13.5$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 13$ Hz

Compound **4**.
$J_{3,6\beta} \approx 2$ Hz; $J_{3,14\beta} \approx 11$ Hz; $J_{5\alpha,5\beta} = 11$ Hz; $J_{5\alpha,6\alpha} = 4.5$ Hz; $J_{5\alpha,6\beta} \approx 11$ Hz; $J_{5\beta,6\beta} = 6$ Hz; $J_{6\alpha,6\beta} = 15.5$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\beta,15} \approx 5.5$ Hz; $J_{16,17} = 6$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 13$ Hz

Compound **5**.
$J_{3,14\alpha} \approx 4$ Hz; $J_{3,14\beta} \approx 11$ Hz; $J_{6\alpha,6\beta} \approx 15$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\alpha,15} \approx 3.5$ Hz; $J_{14\beta,15} \approx 11$ Hz; $J_{16,17} = 7.5$ Hz; $J_{16,17'} = 4.5$ Hz; $J_{17,17'} = 11.5$ Hz; $J_{18,19} = 7$ 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; $J_{5\alpha,5\beta} \approx 11$ Hz; $J_{5\alpha,6\alpha} = 4.5$ Hz; $J_{5\alpha,6\beta} \approx 11$ Hz; $J_{5\beta,6\alpha} \approx 1.5$ Hz; $J_{5\beta,6\beta} \approx 5$ Hz; $J_{6\alpha,6\beta} \approx 15$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\alpha,15} \approx 3.5$ Hz; $J_{14\beta,15} \approx 11$ Hz; $J_{16,17} = 6.5$ Hz; $J_{16,17'} = 5$ Hz; $J_{17,17'} = 11.5$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 13$ Hz

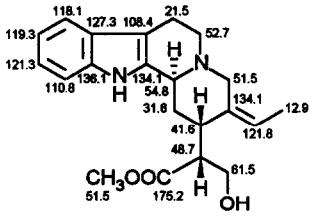
Compound **7**[a].
$J_{5\alpha,5\beta} = 12$ Hz; $J_{5\alpha,6\beta} = 4$ Hz; $J_{5\alpha,6\beta} = 12$ Hz; $J_{5\beta,6\alpha} \approx 1$ Hz; $J_{5\beta,6\beta} = 5.5$ Hz; $J_{6\alpha,6\beta} = 15$ Hz; $J_{16,17} = 7$ Hz; $J_{16,17'} = 5$ Hz; $J_{17,17'} = 12$ Hz; $J_{18,19} = 6.5$ Hz; $J_{21\alpha,21\beta} = 12$ Hz

Compound **8**[a].
$J_{5\alpha,5\beta} = 12$ Hz; $J_{5\alpha,6\alpha} = 4$ Hz; $J_{5\alpha,6\beta} = 12$ Hz; $J_{5\beta,6\alpha} \approx 1$ Hz; $J_{5\beta,6\beta} = 5.5$ Hz; $J_{6\alpha,6\beta} = 15$ Hz; $J_{16,17} = 5$ Hz; $J_{16,17'} = 5$ Hz; $J_{17,17'} = 12$ Hz; $J_{18,19} = 6.5$ Hz; $J_{21\alpha,21\beta} = 12$ Hz

Compound **9**.
$J_{3,14\alpha} = 3$ 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; $J_{6\alpha,6\beta} \approx 15$ Hz; $J_{14\alpha,14\beta} \approx 14$ Hz; $J_{14\alpha,15} = 6$ Hz; $J_{14\beta,15} = 2.5$ Hz; $J_{15,16} = 11.5$ Hz; $J_{16,17} = 6.5$ Hz; $J_{18,19} = 6.5$ Hz; $J_{21\alpha,21\beta} = 12$ Hz

Compound **10**.
$J_{6\alpha,6\beta} \approx 15$ Hz; $J_{16,17} = 6.5$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 12$ Hz

[a] Values taken from Ref. 10.



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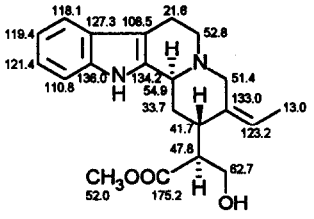

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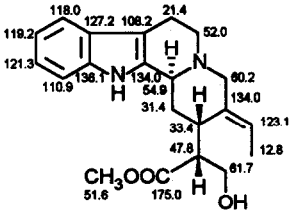

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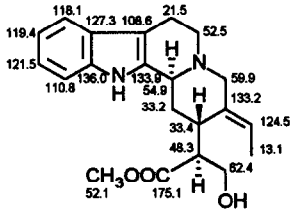

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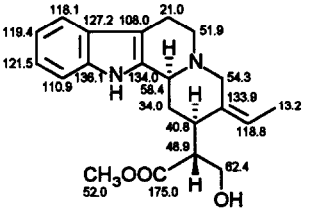

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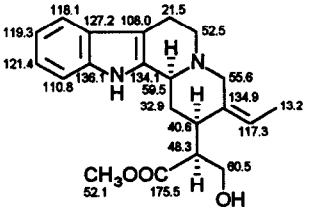

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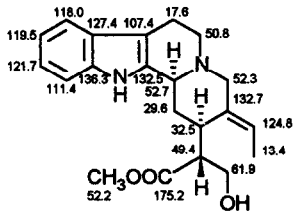

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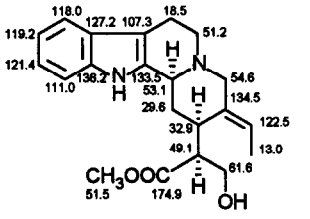
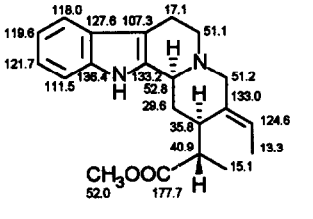


8[b]



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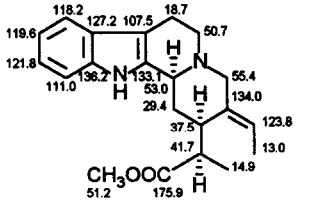


10

Figure 1. ^{13}C-nmr data of compounds **1** - **10**.

[a] Values taken from Ref. 13.
[b] Values taken from Ref. 14. Earlier assignments of C-17 and C-21 signals have been interchanged.

The situation is completely different for compounds **7** - **10**. In conformations a and b there would be a strong interaction between C-19-CH_3 and C-15-R [R = $CH(CH_2OH)COOCH_3$ or $CH(CH_3)COOCH_3$]. There are two ways in which this interaction can be avoided: the indolo[2,3-*a*]-quinolizidine skeleton exists in conformation c or ring D adopts the boat (or twisted boat) conformation. The latter alternative is experimentally excluded, however, by the presence of an NOE between H-16 and H-21β (Table 2).

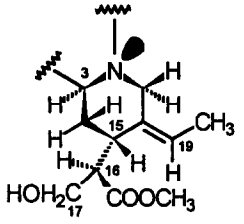
NOE difference measurements (Table 2) of compounds **9** and **10** showed an NOE (2 - 4%) at H-15 when H-18 was irradiated, arguing for the preponderance of conformation c. The preponderance was further supported by an NOE (2 - 3%) at H-21β when H-16 was irradiated, and by the ^{1}H-nmr chemical shift values of H-3, 4.45 and 4.17 ppm for compounds **9** and **10**, respectively (Table 1), and the ^{13}C-nmr chemical shift values of C-6, 17.1 and 18.7 ppm, respectively (Figure 1).

Table 2. Predominant conformations and observed NOE values for compounds **1-6**, **9**, and **10**.

Comp.	Predominant conformation	Observed NOEs H-19 irradiated	Observed NOEs H-17 irradiated	Other noteworthy NOEs observed
1	a, chair	H-15(4%) H-16(<1%) CO_2Me(<1%)	H-14α(2%) H-15(1.5%)	
2	a, chair	H-15(9%) H-17(1.5%)	H-19(1.5%)	
3	a, chair	CO_2Me(<1%) H-21β(2.5%)	H-14α(1%)	
4	a, chair	H-21β($\approx$7%)	H-15(3%) H$\approx$18(1.5%)	
5	a, chair	H-15(1.5%) H-16(9%)	H-15($\approx$1%) H-19($\approx$2%)	
6	a, chair	H-15(<1%) H-16(9.5%)	H-14α($\approx$1%)	
9	c, chair	H-21α(5.5%)	H-15(2%) H-18(2%) H-19($\approx$1%)	H-18→H-15(2%) H-16→H-21β(2.5%)
10	c, chair	H-21α(6%)	H-15(2.5%)	H-18→H-15(4%); CO_2Me($\approx$1%) H-16→H-21β(3%) H-21β→H-16(5.5%)

CONFIGURATIONAL EXAMINATION

In principle there is free rotation about the C-15 - C-16 bond. However, rotamers where C-15-H and C-16-H are approximately in an *anti* position to each other (Figures 2 - 5) are expected to be favoured.[6,27] This facilitates 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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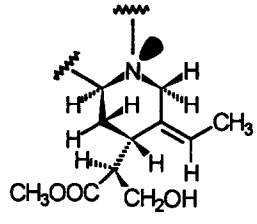
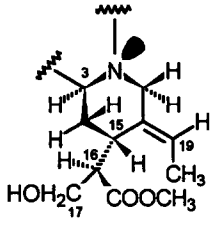


2

Figure 2. The approximate *anti* position between H-15 and H-16 in compound **1** (vicinal dihedral angle H_{15}-C-C-H_{16} $\Phi \approx 180°$) and in compound **2** (vicinal dihedral angle H_{15}-C-C-H_{16} $\Phi \approx 180°$).



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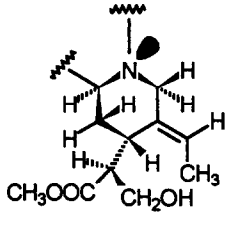

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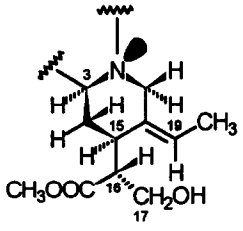
Figure 3. The approximate *anti* position between H-15 and H-16 in compound **3** (vicinal dihedral angle H_{15}-C-C-H_{16} $\Phi \approx 180°$) and in compound **4** (vicinal dihedral angle H_{15}-C-C-H_{16} $\Phi \approx 180°$).



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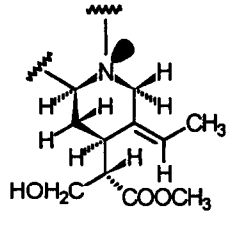
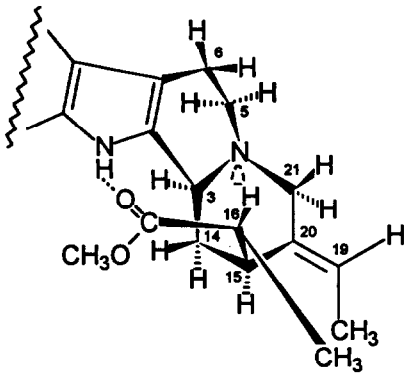


6

Figure 4. The approximate *anti* position between H-15 and H-16 in compound **5** (vicinal dihedral angle H_{15}-C-C-H_{16} $\Phi \approx 150°$) and in compound **6** (vicinal dihedral angle H_{15}-C-C-H_{16} $\Phi \approx 155°$).



9

Figure 5. The approximate *anti* position between H-15 and H-16 in compound **9** (vicinal dihedral angle H_{15}-C-C-H_{16} $\Phi \approx 160°$). Hydrogen bonding between the methoxycarbonyl group and the indolic NH group.

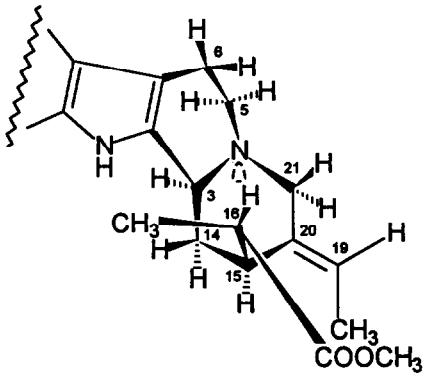


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Figure 6. The approximate *anti* position between H-15 and H-16 in compound **10** (vicinal dihedral angle H_{15}-C-C-H_{16} $\Phi \approx 150°$).

When H-17 in compound **9** was irradiated an NOE was observed at H-18 (2%) and H-15 (2%)(Table 2). Further, when H-16 was irradiated an NOE was observed at H-21β (2.5%) supporting the approximate *anti* position between H-15 and H-16. All this indicated that the C-16 configuration is S* in compound **9**. No NOE was observed at the methoxycarbonyl group when H-18 was irradiated.

By contrast, no NOE was observed at H-18 in compound **10** when H-17 was irradiated. However, an NOE was observed at H-15 (3.5%) when H-17 was irradiated and at H-21β (3%) when H-16 was irradiated, supporting the approximate *anti* position between H-15 and H-16 and thus the R*-configuration of C-16. Further evidence of the C-16 R*-configuration for compound **10** was provided by the NOE (1%) at the methoxycarbonyl group when H-18 was irradiated.

The contribution of conformation **c** to the conformational equilibrium is greater in compound **9** than in compound **10**, due to the hydrogen bonding between the methoxycarbonyl group and the indolic NH group. This is reflected *e.g.* by the difference in the ^{1}H-nmr chemical shift values of H-3 (δ 4.45 *versus* δ 4.17 ppm; Table 1).

A comparison of the ^{13}C-nmr values of compounds **9** and **10** with those of compounds **7** and **8**, respectively (Figure 1), shows a clear analogy between the compounds. The above conclusions regarding the preponderant conformations and C-16 configurations of compounds **9** and **10** are thus directly applicable to compounds **7** [(16R)-*E*- isositsirikine] and **8** [(16S)-*E*-isositsirikine]. The relatively large difference in the ^{1}H-nmr chemical shift values of H-3 for compounds **7** and **8** (δ 4.31 *versus* δ 3.9 ppm; Table 1), which has been regarded as surprising[9], obtains thereby a logical explanation.

CONCLUSIONS

Sodium borohydride reduction of our recently described[15] geissoschizine isomers **15**, **16**, and **17** permitted a rapid preparation of isositsirikine isomers **1** - **6**. The (16S*)- and (16R*)-17-deoxy-*E*-isositsirikines **9** and **10** were prepared from their *Z*-ethylidene counterparts **11** and **12**, by oxidation and by isomerization initiated by modified Polonovski reaction.[6,16,17]

The predominant conformations and the C-16 configurations were determined by nmr measurements, mainly by NOE difference spectroscopy. The relatively large difference in the chemical shifts of H-3 in the ^{1}H-nmr values for (16R)-*E*-isositsirikine **7** (δ 4.31 ppm) and (16S)-*E*-isositsirikine **8** (δ 3.9 ppm) finds explanation in the same large difference in the analogous compounds **9** (δ 4.45 ppm) and **10** (δ 4.17 ppm)(*vide supra*).

The ^{13}C-nmr results confirm the non-identity of compounds **1** - **6** with the "isositsirikine stereoisomers" rhazimanine[11] and bhimberine[12].

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 by reference to TMS (^{1}H-nmr; δ_H=0.00 ppm) and $CDCl_3$ (^{13}C-nmr; δ_C=77.00 ppm). 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 (EIms and HRms) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compounds 1 [(16R*)-15-epi-*Z*-isositsirikine] and 2 [(16S*)-15-epi-*Z*-isositsirikine].

Compound **15**[15] (214 mg, 0.61 mmol) was dissolved in dry MeOH (21 ml). The solution was cooled in an ice bath and $NaBH_4$ (25 mg, 1.1 equiv.) was added with stirring in small portions (Ar atm). Stirring was continued for 4 h at room temperature. Water was added and MeOH evaporated. Extraction with CH_2Cl_2 yielded the crude product, which was then fractionated by PLC (alumina, EtOAc/MeOH, 98/2) to give compounds **1** and **2**.

Compound **1**: Y. 105 mg (49%). Amorphous material, lit.[27] oil. Ir: 2820, 2770 (w, Bohlmann bands), 1720 (s, C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 354 (M^+), 353, 323, 251 (100%), 169, 156. HRms: Found: 354.1927. Calcd for $C_{21}H_{26}N_2O_3$: 354.1943.

Compound **2**: Y. 56 mg (26%). Mp. 227-229°C ($CHCl_3$), lit.[27] oil. Ir: 2820, 2765 (w, Bohlmann bands), 1720 (s, C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 354 (M^+), 353, 323, 251 (100%), 169, 156. HRms: Found: 354.1993. Calcd for $C_{21}H_{26}N_2O_3$: 354.1943.

Preparation of compounds 3 [(16R*)-15-epi-*E*-isositsirikine] and 4 [(16S*)-15-epi-*E*-isositsirikine].

Compound **16**[15] (139 mg, 0.395 mmol) was dissolved in dry MeOH (7 ml). The solution was cooled in an ice bath and $NaBH_4$ (17 mg, 1.1 equiv.) was added with stirring in small portions during 15 min (Ar atm). Stirring was continued for 2 h at room temperature. After normal work-up the crude product was fractionated by PLC (silica, CH_2Cl_2/MeOH, 90/10) to give compounds **3** and **4**.

Compound **3**: Y. 30.5 mg (22%). Mp. 191-193°C (toluene/EtOH, 1/1), lit.[27] mp. 191-199°C (EtOH). Ir: 3270 (m, OH), 2820, 2775 (w, Bohlmann bands), 1720 (s, C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 354 (M^+), 353, 323, 295, 251 (100%), 169, 156. HRms: Found: 354.1974. Calcd for $C_{21}H_{26}N_2O_3$: 354.1943.

Compound **4**. Y. 33 mg (24%). Mp. 199-201°C (EtOH), lit.[27] mp. 202-203°C (CH_2Cl_2/MeOH). Ir: 3310 (m,

OH), 2815, 2775 (w, Bohlmann bands), 1715 (s, C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 354 (M^+), 353, 323, 295, 251 (100%), 169, 156. HRms: Found: 354.1943. Calcd for $C_{21}H_{26}N_2O_3$: 354.1943.

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

Compound **17**[15] (120 mg, 0.34 mmol) was dissolved in dry MeOH (12 ml). The solution was cooled in an ice bath and $NaBH_4$ (14 mg, 1.1 equiv.) was added with stirring in small portions (Ar atm). Stirring was continued for 4 h at room temperature. After normal work-up the crude product was fractionated by PLC (silica, CH_2Cl_2/MeOH, 93/7) to yield compounds **5** and **6**.

Compound **5**: Y. 36 mg (30%). Mp. 128-131°C ($CHCl_3$). Ir: 2820, 2750 (vw, Bohlmann bands), 1715 (s, C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 354 (M^+), 353, 323, 251 (100%), 169, 156. HRms: Found: 354.1961. Calcd for $C_{21}H_{26}N_2O_3$: 354.1943.

Compound **6**: Y. 37 mg (31%). Amorphous material. Ir: 2820, 2750 (vw, Bohlmann bands), 1720 (s, C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 354 (M^+), 353, 323, 251 (100%), 169, 156. HRms: Found: 354.1931. Calcd for $C_{21}H_{26}N_2O_3$: 354.1943.

Preparation of compound **9** [(16S*)-17-deoxy-*E*-isositsirikine].

A solution of compound **18**[6] (89.9 mg, 0.25 mmol) in dry CH_2Cl_2 (6.3 ml) was cooled to -15°C and trifluoroacetic anhydride (TFAA) (89 μl, 0.63 mmol, 2.5 equiv.) was added in portions during 5 min (Ar atm). The reaction mixture was stirred for 2 h at room temperature. The solvent was evaporated and the residue dissolved in MeOH/HCl_{aq} [6.3 ml MeOH + 25 μl HCl (16%)]. The mixture was stirred for 2 h at room temperature. $NaBH_4$ (56.7 mg, 1.50 mmol, 6 equiv.) was added to the mixture in small portions at -2°C during 15 min (N_2 atm). The mixture was stirred at room temperature overnight. H_2O (12.5 ml) was added, MeOH evaporated, and the mixture extracted with CH_2Cl_2. The crude product was fractionated by PLC (silica, CH_2Cl_2/MeOH, 90/10) to yield compounds **11** and **9**.

Compound **11**. Y. 41.8 mg (49%). For the analytical data, see Ref. 6.

Compound **9**. Y. 17 mg (20%). Amorphous material. Ir: 1725 (s, C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 338 (M^+), 337, 323, 307, 279, 251 (100%), 169, 156. HRms: Found: 338.2023. Calcd for $C_{21}H_{26}N_2O_2$: 338.1994.

Preparation of compound **10** [(16R*)-17-deoxy-*E*-isositsirikine].

A solution of compound **19**[6] (91.2 mg, 0.26 mmol) in dry CH_2Cl_2 (6.5 ml) was cooled to -15°C and trifluoroacetic anhydride (TFAA) (90 μl, 0.64 mmol, 2.5 equiv.) was added in portions during 5 min (Ar atm). The reaction mixture was stirred for 2 h at room temperature. The solvent was evaporated and the residue dissolved in MeOH/HCl_{aq} [6.5 ml MeOH + 25 μl HCl_{aq} (16%)]. The mixture was stirred for 2 h

at room temperature. $NaBH_4$ (59.0 mg, 1.56 mmol, 6 equiv.) was added to the mixture in small portions at 0°C during 15 min (N_2 atm). The mixture was stirred at room temperature overnight. After normal work-up (*vide supra*) the crude product was purified by column chromatography (alumina, CH_2Cl_2/MeOH, 99.5/0.5) and fractionated by PLC (silica, CH_2Cl_2/MeOH, 90/10) to yield compounds **12** and **10**.

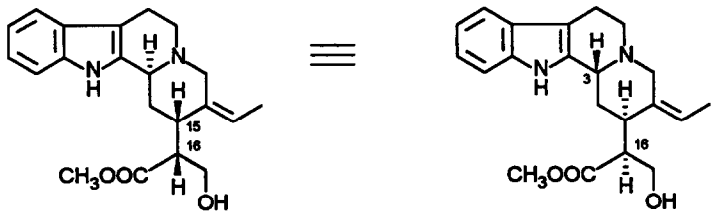
Compound **12**. Y. 25 mg (28%). For the analytical data, see Ref. 6.

Compound **10**. Y. 6.3 mg (7%). Amorphous material. Ir: 1725 (s, C=O). For the ^{1}H-nmr data, see Table 1. For the ^{13}C-nmr data, see Figure 1. Ms: 338 (M^+), 337, 323, 307, 279, 251 (100%), 169, 156. HRms: Found: 338.2007. Calcd for $C_{21}H_{26}N_2O_2$: 338.1994.

REFERENCES AND NOTES

1. Owing to different priorities for the C-16 ligands the (16S*)-17-deoxy-*E*-isositsirikine **9** is the "model compound" for (16R)-*E*-isositsirikine **7** and the (16R*)-17-deoxy-*E*-isositsirikine **10** that for (16S)-*E*-isositsirikine **8**.

   Compound **1**, (±)-(16R*)-15-epi-*Z*-isositsirikine, is identical with (±)-(16S*)-3-epi-*Z*-isositsirikine **1'**, and the corresponding situation holds for compounds **2** - **4**. Since the compounds are formed by reduction from the geissoschizine isomers, which for mechanistic reasons (*cf.* Ref. 15) were presented as **15** and **16**, we preferred to present compounds **1** - **4** as shown, even though the C-15-H in formulae **1** - **4**, being β, is unnatural.



1 **1'**

2. Biogenetic numbering. Le Men J.; Taylor, W. *Experientia,* **1965**, 21, 508.
3. Brown, R. T. *"The Monoterpenoid Indole Alkaloids"*, (ed. Saxton, J. E.), 1st Edition, Wiley, New York, 1983, pp. 63-146.
4. Szántay, Cs.; Blasko, G.; Honty, K.; Dörnyei, G. *"The Alkaloids"*, (ed. Brossi, A.), Vol. 27, Academic Press, Orlando, 1986, pp. 131-268 and 407-410.

5. Lounasmaa, M.; Tolvanen, A. *"The Monoterpenoid Indole Alkaloids"*, (ed. Saxton, J. E.), 2nd Edition, Wiley, New York, 1994, (in press).
6. Hanhinen, P.; Nurminen, T.; Jokela, R.; Lounasmaa, M. *Heterocycles* (in press).
7. Stöckigt, J.; Rueffer, M.; Zenk, M. H.; Hoyer, G.-A. *Planta Medica*, **1978**, 3,188.
8. Brown, R. T.; Leonard, L. *Tetrahedron Lett.*, **1979**, 1805.
9. Atta-ur-Rahman; Zaman, K.; Perveen, S.; Habib-ur-Rehman; Muzaffar, A.; Choudhary, M. I.; Pervin, A. *Phytochemistry*, **1991**, 30, 1285.
10. Kan, C.; Kan, S.-K.; Lounasmaa, M.; Husson, H.-P. *Acta Chem. Scand.*, **1981**, B35, 269.
11. Atta-ur-Rahman; Malik, S.; Habib-ur-Rehman, *Phytochemistry*, **1986**, 25, 1731.
12. Atta-ur-Rahman; Habib-ur-Rehman; Malik, S. *Heterocycles*, **1986**, 24, 703.
13. Lounasmaa, M. *Unpublished results.*
14. van Beek, T. A.; Verpoorte, R.; Baerheim Svendsen, A. *Planta Medica*, **1983**, 47, 83.
15. Tirkkonen, B.; Miettinen, J.; Salo, J.; Jokela, R.; Lounasmaa, M. *Tetrahedron*, **1994**, 50, 3537.
16. Lounasmaa, M.; Jokela, R.; Miettinen, J.; Halonen, M. *Heterocycles*, **1992**, 34, 1497.
17. Jokela, R.; Halonen, M.; Lounasmaa, M. *Heterocycles*, **1994**, 38, 189.
18. Lounasmaa, M.; Johansson, C.-J. *Acta Chem. Scand.*, **1975**, B29, 655.
19. Lounasmaa, M.; Johansson, C.-J. *Tetrahedron*, **1977**, 33, 113.
20. Lounasmaa, M.; Tamminen, T. *Tetrahedron*, **1991**, 47, 2879.
21. Lounasmaa, M. *"Studies in Natural Products Chemistry"* (ed. Atta-ur-Rahman), Vol. 1, Elsevier, Amsterdam, 1988, pp. 89-122.
22. Lounasmaa, M. *"Studies in Natural Products Chemistry"* (ed. Atta-ur-Rahman), Vol. 14, Elsevier, Amsterdam, 1994, pp. 703-730.
23. Lounasmaa, M.; Jokela, R. *Tetrahedron*, **1989**, 45, 3975.
24. Lounasmaa, M.; Jokela, R. *Tetrahedron*, **1989**, 45, 7449.
25. Lounasmaa, M; Jokela, R.; Tirkkonen, B.; Tamminen, T. *Tetrahedron*, **1989**, 45, 7615.
26. Lounasmaa, M.; Jokela, R.; Tiainen, L.-P. *Tetrahedron*, **1990**, 46, 7873.
27. Ninomiya, I.; Naito, T.; Miyata, O.; Shinada, T.; Winterfeldt, E.; Freund, R.; Ishida, T. *Heterocycles*, **1990**, 30, 1031. See also, Winterfeldt, E.; Freund, R. *Liebigs Ann. Chem.*, **1986**, 1262, and Freund, R.; Winterfeldt, E. *Liebigs Ann. Chem.*, **1988**, 1007.

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