Pergamon

Tetrahedron Vol. 50, No. 11, pp. 3537-3556, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0044-T

The Claisen Rearrangement in the Preparation of Geissoschizine Isomers

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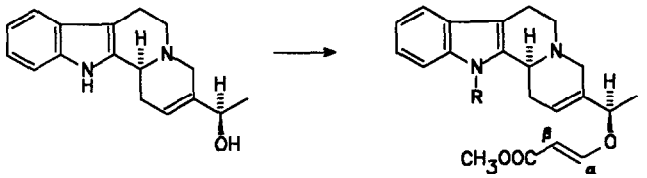
Abstract - The Claisen rearrangement of vinyl allyl ether **3** in refluxing toluene leads to a mixture of (±)-Z-geissoschizine **5** and (±)-15-epi-E-geissoschizine **6** [= (±)-3-epi-E-geissoschizine **6'**], whereas vinyl allyl ether **4**, under the same reaction conditions, affords only (±)-15-epi-Z-geissoschizine **15** [= (±)-3-epi-Z-geissoschizine **15'**]. No (±)-E-geissoschizine **16** was formed. However, the formation of (±)-15-epi-E-geissoschizine **6** [= (±)-3-epi-E-geissoschizine **6'**], which has earlier been transformed to (±)-E-geissoschizine **16**, represents a new, formal total synthesis of (±)-E-geissoschizine **16**. A conformational study of the prepared compounds, mainly based on nmr measurements, is presented.

The Claisen rearrangement,[1-4] in its most general form, consists of thermally induced transposition of vinyl allyl ethers to the corresponding homoallylic carbonyl compounds (a [3,3]-sigmatropic reaction). Winterfeldt and coll.[5] have used the method for the preparation of (±)-Z-geissoschizine **5** and (±)-15-epi-Z-geissoschizine **15** [= (±)-3-epi-Z-geissoschizine **15'**]. The authors claimed the reaction to be stereoselective and stereospecific; however, only the stereochemical mixture of the allylic alcohols **1** and **2**, and therefore the stereochemical mixture of the corresponding vinyl allyl ethers **3** and **4**, was used.

RESULTS AND DISCUSSION

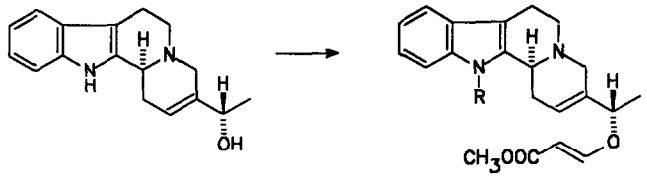
We recently developed a method that permits an efficient separation of the allylic alcohols **1** and **2**.[6] Thus, the time seemed ripe for a detailed examination of the stereoselectivity and stereospecificity of the reaction.

Carefully separated allylic alcohols **1** and **2** were transformed by propiolic acid methyl ester treatment to the corresponding vinyl allyl ethers **3** and **4**,[7] respectively. The corresponding Boc-protected vinyl allyl ethers **3a** and **4a**[7] were prepared for comparative ^{13}C-nmr measurements (*vide infra*) (Schemes 1 and 2).



1 **3** R = H
3a R = Boc

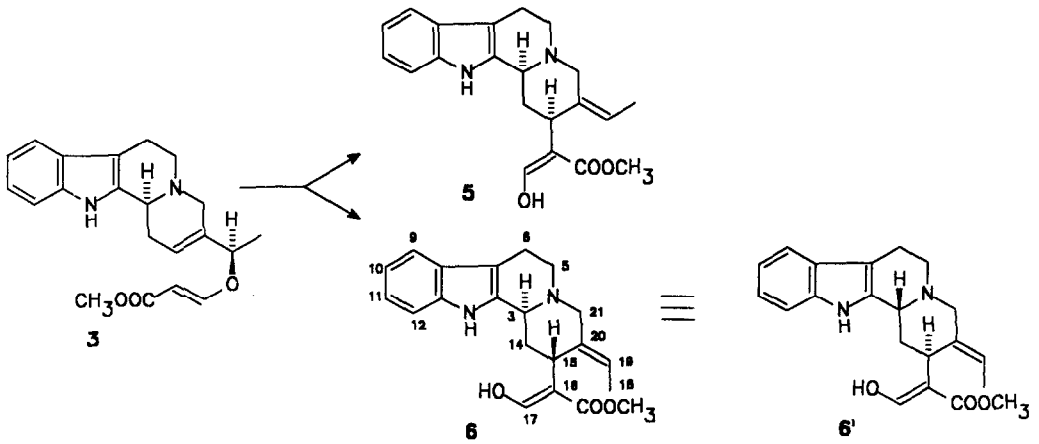
Scheme 1.



2 **4** R = H
4a R = Boc

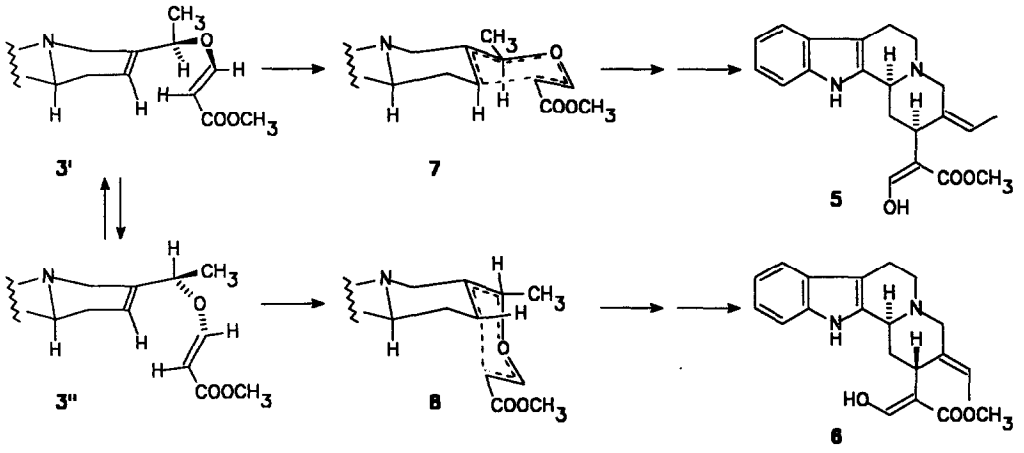
Scheme 2.

We began our experiments with the vinyl allyl ether **3**. Heating of compound **3** in refluxing toluene, carefully excluding the presence of water, led in 32% yield to a mixture of two geissoschizine isomers, (±)-Z-geissoschizine **5** and (±)-15-epi-E-geissoschizine **6** [= (±)-3-epi-E-geissoschizine **6'**] (presented below in the dominating tautomeric form) in about 5/4 ratio (Scheme 3).



Scheme 3.

The simultaneous formation of geissoschizine isomers **5** and **6** from the same vinyl allyl ether **3** (characterized by conformational forms **3'** and **3"**) means, that, contrary to earlier conclusions,[5] two transition states **7** and **8** are involved (Scheme 4). The transition state **7**, possessing an equatorial methyl group, seems to be slightly favoured over the transition state **8**, possessing an axial methyl group.

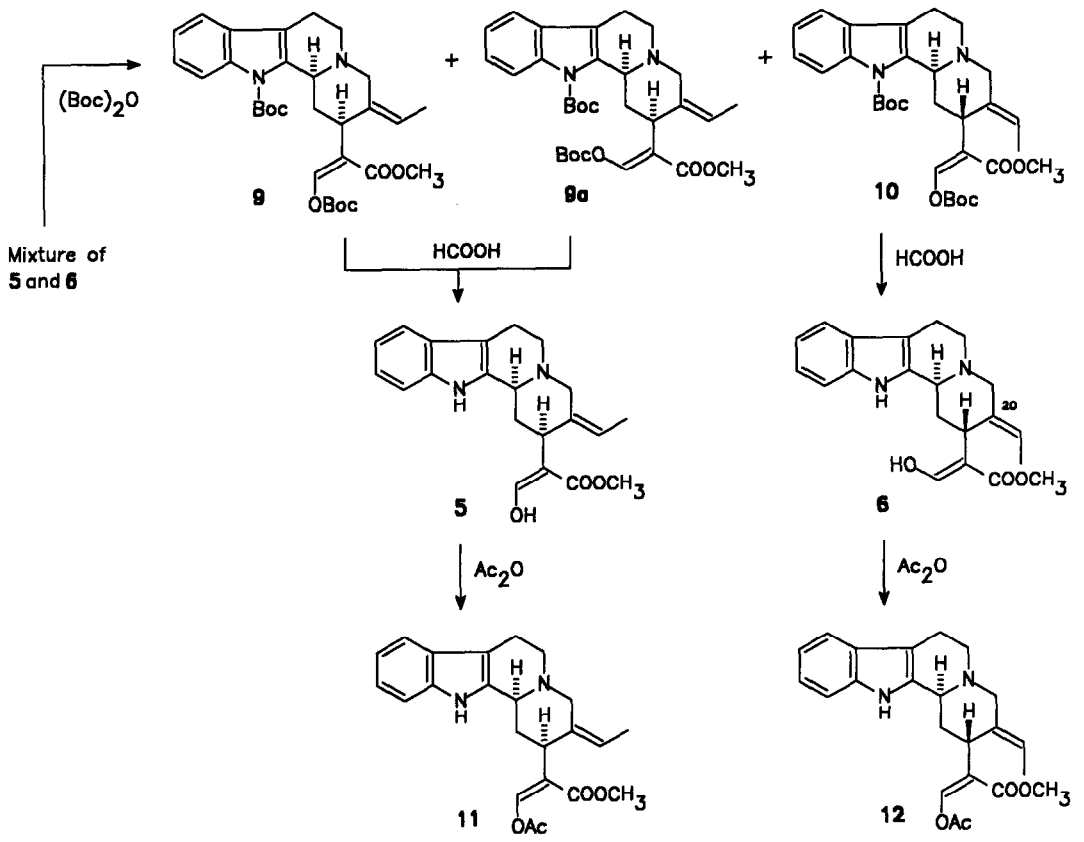


Scheme 4.

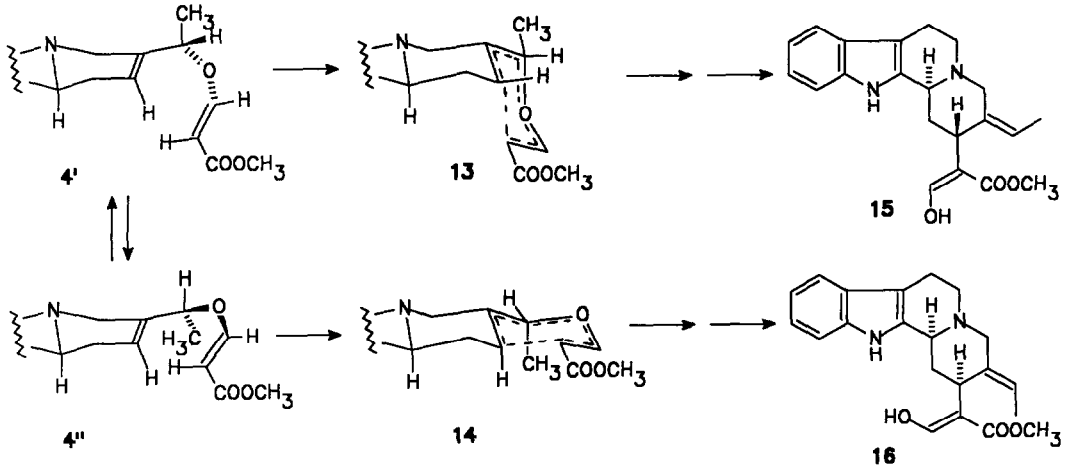
The formation of (±)-15-epi-E-geissoschizine **6** is of great importance because it shows that the Claisen rearrangement of an appropriate vinyl allyl ether can be used for the preparation of indolo[2,3-*a*]-quinolizidine derivatives possessing the E-ethylidene side-chain at position 20 (biogenetic numbering[6]) present in many indole alkaloids.

Compounds **5** and **6** exist in several tautomeric forms, although one (**5a** and **6b**, respectively; *vide infra*) is clearly dominating. This complicates their structural analysis (especially nmr-analysis). Since their separation also turned out to be difficult, the mixture of compounds **5** and **6** was treated with $(Boc)_2O$, which transformed them to the corresponding di-Boc derivatives **9** and **9a** (traces), and **10**, respectively. The di-Boc derivatives **9** (containing **9a**) and **10** were easily separated, analysed (*vide infra*), and retransformed by HCOOH treatment to the initial β-ketoesters **5** and **6**. In order to put the presented structures on a more solid basis, compounds **5** and **6** were also transformed by Ac_2O to the corresponding enol acetates **11** and **12** (*vide infra*), respectively (Scheme 5).

The formation of (±)-15-epi-E-geissoschizine **6**, which necessitates the contribution of transition state **8** (*vide supra*) with an axial methyl group, led us to hope that, also in the case of vinyl allyl ether **4** (characterized by conformational forms **4'** and **4"**), the two transition states **13** (with an equatorial methyl group) and **14** (with an axial methyl group) would be involved in reasonable amount. If this were the case, (±)-15-epi-Z-geissoschizine **15** and, most interestingly, (±)-E-geissoschizine **16** (presented in the dominating tautomeric form[9]), would be formed as a result (Scheme 6).

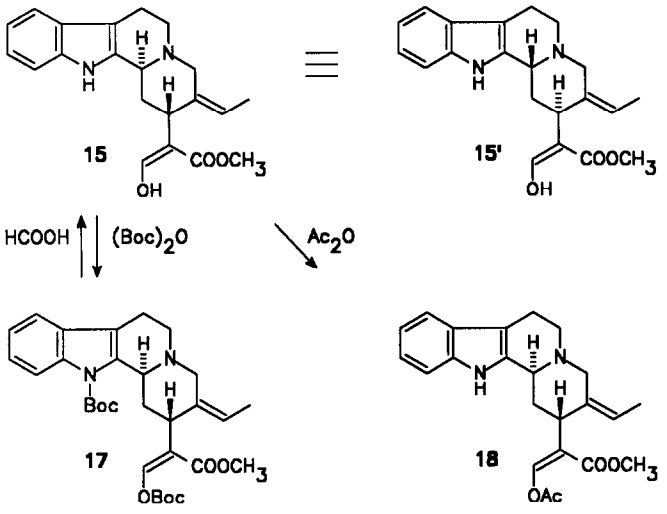


Scheme 5.



Scheme 6.

Unfortunately, the only geissoschizine isomer, obtained in 43% yield by the Claisen rearrangement of vinyl allyl ether **4** in refluxing toluene, was (±)-15-epi-Z-geissoschizine **15** [= (±)-3-epi-Z-geissoschizine **15'**]. No traces of (±)-E-geissoschizine **16** were detected in the reaction mixture (*vide infra*). Since compound **15** existed in several tautomeric forms (**15a** - **15d**; *vide infra*), it was treated with $(Boc)_2O$ and Ac_2O to yield di-Boc derivative **17** and enol acetate **18**, respectively, which were easier to analyse. Treatment of **17** with HCOOH regenerated (±)-15-epi-Z-geissoschizine **15** (Scheme 7).

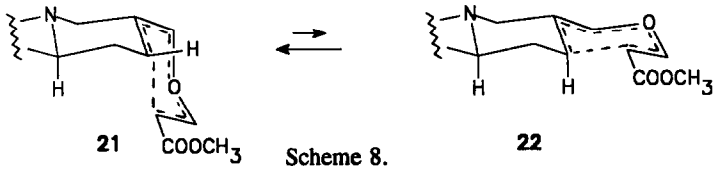


Scheme 7.

The absence of (±)-E-geissoschizine **16** in the reaction mixture (*vide supra*) indicated that the transition state **14**, a prerequisite for the formation of compound **16**, was not present in appreciable amount in the reaction mixture.

The Claisen rearrangement has earlier been regarded as highly stereoselective. However, our results (*vide supra*) indicate that, at least in the present case, it should rather be considered to involve competitive rearrangements. Regarding the different transition states (**7**, **8**, **13**, and **14**; chair-like conformation), two aspects should be taken into consideration as a first approximation:

1°. "Transition state skeleton" **21** (*cf.* **7** and **13**) is favoured over "skeleton" **22** (*cf.* **8** and **14**) owing to an incipient $A^{(1,3)}$ interaction in the formation of the C-15 - C-16 bond in the latter (Scheme 8).[3]



Scheme 8.

2°. The presence of an equatorial methyl group in the transition state is favoured over an axial methyl group.

Considering the four transition states **7**, **8**, **13**, and **14**, these can be classified as in Table 1.

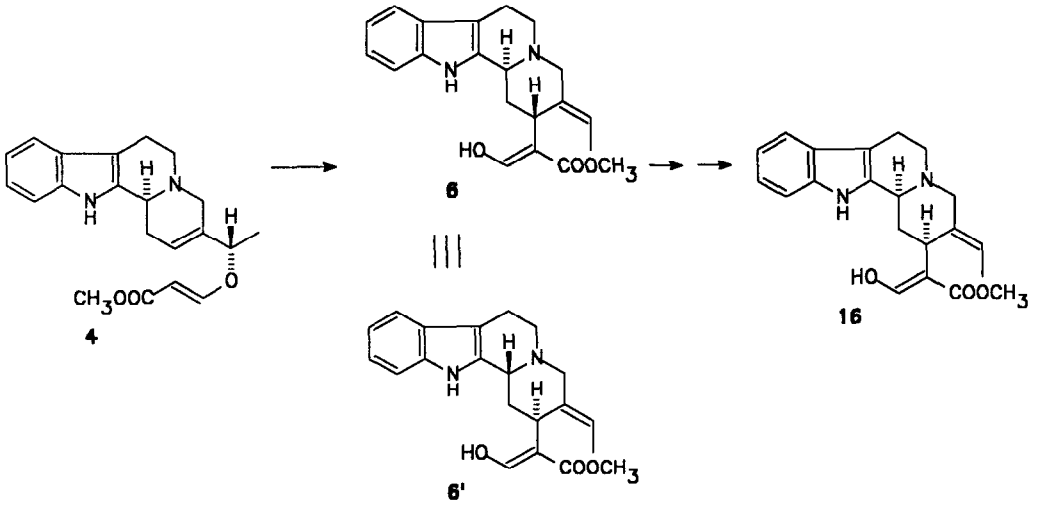
Table 1. Comparison of the four transition states **7**, **8**, **13**, and **14**.

Transition state		
	7	(us,fm)
	8	(fs,um)
	13	(fs,fm)
	14	(us,um)

f = favoured; u = unfavoured; s = "skeleton"; m = methyl; *e.g.* us,fm = unfavoured "skeleton", favoured methyl.

Thus, in the case of vinyl allyl ether **3**, the transition states in question (**7** and **8**) would seem to be *en gros* equally favoured (or unfavoured), whereas in the case of vinyl allyl ether **4**, the transition state **13** is strongly favoured over **14**.

On the other hand, since (±)-15-epi-E-geissoschizine **6** [= (±)-3-epi-E-geissoschizine **6'**] has earlier been transformed to (±)-E-geissoschizine **16**,[10] the preparation of (±)-15-epi-E-geissoschizine **6** by the Claisen rearrangement (*vide supra*) represents a new way to synthesise (±)-E-geissoschizine **16** (Scheme 9).



Scheme 9.

The ^{1}H-nmr data of compounds **3, 3a, 4, 4a, 9, 10, 11, 12, 17,** and **18** are given in Table 2 and the ^{13}C-nmr data of compounds **3, 3a, 4, 4a, 5, 6, 9, 10, 11, 12, 17,** and **18** in Figure 1.

Table 2. ^{1}H-nmr data of compounds **3, 3a, 4, 4a, 9, 10, 11, 12, 17,** and **18.**

Atom	3	3a	4	4a	9
1	8.13 s		8.57 s		
3	3.44 br d	4.15 d	3.39 br d*	4.11 d	4.58 d
5 α	2.63 ddd	2.7 m	2.63 ddd	2.8 m	2.8 m
5 β	3.18 ddd	3.11 m	3.18 ddd	3.13 m	3.28 m
6 α	2.75 br d	2.8 m	2.75 br d	2.8 m	2.8 m
6 β	2.99 ddd	2.85 m	3.00 ddd	2.90 m	2.8 m
9	7.48 d	7.42 d	7.48 d	7.42 d	7.41 d
10	7.08 t	7.22 t	7.08 t	7.23 t	7.26 t
11	7.13 t	7.27 t	7.13 t	7.28 t	7.21 t
12	7.29 d	8.03 d	7.29 d	8.07 d	8.15 d
14 α	2.51 br d	2.8 m	2.41 br d	2.8 m	1.98 ddd
14 β	2.30 m	2.18 m	2.15 m	2.14 m	2.47 ddd
15	5.82 br s	5.84 d	5.52 br s	5.82 d	3.81 br d
17					8.17 s
18	1.42 d	1.43 d	1.37 d	1.45 d	1.67 d*
19	4.42 q	4.46 q	4.39 q	4.50 q	5.12 q
21 α	3.04 br d	3.49 br d	2.90 br d	3.31 br d	3.47 d
21 β	3.38 d	3.33 d	3.43 d	3.40 d	4.01 d
CO_2Me	3.68 s	3.69 s	3.71 s	3.70 s	3.71 s
CH(α)=	7.50 d	7.52 d	7.52 d	7.53 d	
CH(β)=	5.29 d	5.30 d	5.33 d	5.31 d	
-N-Boc		1.66 s		1.66 s	1.66 s
-O-Ac					
-O-Boc					1.52 s

* Partly masked.

Table 2. ^{1}H-nmr data of compounds **3**, **3a**, **4**, **4a**, **9**, **10**, **11**, **12**, **17**, and **18** (continued).

Atom	**10**	**11**	**12**	**17**	**18**
1		7.89 br s	7.90 br s		8.27 br s
3	4.38 br d	3.48 d	3.54 br d*	4.18 br s	4.19 br s
5 α	2.8 m	2.68 ddd	2.62 ddd	2.7 m	2.9 ddd
5 β	3.08 ddd	3.16 ddd	3.10 ddd	3.13 m	3.32 ddd
6 α	2.8 m	2.74 m	2.7 m	2.7 m	2.71 ddd
6 β	2.8 m	3.01 m	3.0 m	2.88 m	3.1 m
9	7.40 d	7.47 d	7.46 d	7.41 d	7.48 d
10	7.23 t	7.08 d	7.07 t	7.23 t	7.09 t
11	7.20 t	7.12 t	7.11 t	7.20 t	7.14 t
12	7.96 d	7.26 d	7.26 d	7.99 d	7.33 d
14 α	2.23 br d	2.04 ddd	2.3 m	2.56 ddd	2.64 ddd
14 β	1.86 ddd	2.33 ddd	1.96 ddd	1.85 ddd	2.11 ddd
15	4.05 d	3.68 br d	4.16 dd	3.86 m	3.63 m
17	8.11 s	8.42 s	8.30 s	8.12 s	8.33 s
18	1.55 br d	1.66 br d	1.55 br d	1.61 d	1.63 d
19	5.44 q	5.06 q	5.52 q	5.22 q	5.14 q
21 α	4.12 br d	2.85 d	3.52 br d*	3.55 d	3.47 d
21 β	3.38 d	3.94 d	3.44 d	3.77 d	3.52 d
CO_2Me	3.78 s	3.75 s	3.81 s	3.76 s	3.73 s
CH(α)=					
CH(β)=					
-N-Boc	1.63 s			1.64 s	
-O-Ac		2.15 s	2.22 s		2.18 s
-O-Boc	1.51 s			1.50 s	

* Partly masked

Table 2. ^{1}H-nmr data of compounds **3, 3a, 4, 4a, 9, 10, 11, 12, 17,** and **18** (continued).

Coupling constants:

Compound **3.**
$J_{3,14\alpha}$ = 4 Hz; $J_{3,14\beta}$ = 10 Hz; $J_{5\alpha,5\beta}$ = 11.5 Hz; $J_{5\alpha,6\alpha}$ = 4 Hz; $J_{5\alpha,6\beta}$ = 11 Hz; $J_{5\beta,6\alpha}$ = 1 Hz; $J_{5\beta,6\beta}$ = 4.5 Hz; $J_{6\alpha,6\beta}$ = 15 Hz; $J_{14\alpha,14\beta}$ = 16 Hz; $J_{14\alpha,15}$ = 5 Hz; $J_{14\beta,15}$ ≈ 1 Hz; $J_{18,19}$ = 7 Hz; $J_{21\alpha,21\beta}$ = 16 Hz; $J_{CH(\alpha),CH(\beta)}$ = 12.5 Hz.

Compound **3a.**
$J_{3,14\alpha}$ = 4 Hz; $J_{3,14\beta}$ = 10 Hz; $J_{5\alpha,5\beta}$ = 11.5 Hz; $J_{5\beta,6\alpha}$ = 5 Hz; $J_{5\beta,6\beta}$ = 5 Hz; $J_{6\alpha,6\beta}$ = 15 Hz; $J_{14\alpha,14\beta}$ = 16 Hz; $J_{14\alpha,15}$ = 5 Hz; $J_{14\beta,15}$ ≈ 1 Hz; $J_{18,19}$ = 6.5 Hz; $J_{21\alpha,21\beta}$ = 16 Hz; $J_{CH(\alpha),CH(\beta)}$ = 12.5 Hz.

Compound **4.**
$J_{3,14\alpha}$ = 4 Hz; $J_{3,14\beta}$ ≈ 10 Hz; $J_{5\alpha,5\beta}$ = 12 Hz; $J_{5\alpha,6\alpha}$ = 4 Hz; $J_{5\alpha,6\beta}$ = 11.5 Hz; $J_{5\beta,6\alpha}$ ≈ 1 Hz; $J_{5\beta,6\beta}$ = 4.5 Hz; $J_{6\alpha,6\beta}$ = 15 Hz; $J_{14\alpha,14\beta}$ ≈ 16 Hz; $J_{14\alpha,15}$ ≈ 5 Hz; $J_{14\beta,15}$ ≈ 1 Hz; $J_{18,19}$ = 7 Hz; $J_{21\alpha,21\beta}$ = 16 Hz; $J_{CH(\alpha),CH(\beta)}$ = 12.5 Hz.

Compound **4a.**
$J_{3,14\alpha}$ ≈ 4 Hz; $J_{3,14\beta}$ ≈ 10 Hz; $J_{5\alpha,5\beta}$ = 11.5 Hz; $J_{5\beta,6\alpha}$ ≈ 5.5 Hz; $J_{5\beta,6\beta}$ ≈ 5.5 Hz; $J_{6\alpha,6\beta}$ ≈ 15 Hz; $J_{14\alpha,14\beta}$ ≈ 15 Hz; $J_{14\alpha,15}$ = 5 Hz; $J_{14\beta,15}$ ≈ 1 Hz; $J_{18,19}$ = 6.5 Hz; $J_{21\alpha,21\beta}$ = 16 Hz; $J_{CH(\alpha),CH(\beta)}$ = 12.5 Hz.

Compound **9.**
$J_{3,14\alpha}$ = 4.5 Hz; $J_{3,14\beta}$ ≈ 10 Hz; $J_{5\alpha,5\beta}$ ≈ 12 Hz; $J_{14\alpha,14\beta}$ = 13 Hz; $J_{14\alpha,15}$ = 2.5 Hz; $J_{14\beta,15}$ = 12 Hz; $J_{18,19}$ = 7 Hz; $J_{21\alpha,21\beta}$ = 15 Hz.

Compound **10.**
$J_{3,14\alpha}$ ≈ 1 Hz; $J_{3,14\beta}$ = 11 Hz; $J_{14\alpha,14\beta}$ = 14 Hz; $J_{14\alpha,15}$ ≈ 1 Hz; $J_{14\beta,15}$ = 7.5 Hz; $J_{18,19}$ = 7 Hz; $J_{21\alpha,21\beta}$ = 13.5 Hz.

Compound **11.**
$J_{3,14\alpha}$ ≈ 4 Hz; $J_{3,14\beta}$ = 12 Hz; $J_{5\alpha,5\beta}$ = 11 Hz; $J_{5\alpha,6\alpha}$ = 4.5 Hz; $J_{5\alpha,6\beta}$ = 11 Hz; $J_{5\beta,6\alpha}$ ≈ 1 Hz; $J_{5\beta,6\beta}$ = 4.5 Hz; $J_{6\alpha,6\beta}$ = 15 Hz; $J_{14\alpha,14\beta}$ ≈ 13 Hz; $J_{14\alpha,15}$ ≈ 2.5 Hz; $J_{14\beta,15}$ = 12 Hz; $J_{18,19}$ = 7 Hz; $J_{21\alpha,21\beta}$ = 12.5 Hz.

Compound **12.**
$J_{3,14\alpha}$ = 2.5 Hz; $J_{3,14\beta}$ = 12 Hz; $J_{5\alpha,5\beta}$ = 11 Hz; $J_{5\alpha,6\alpha}$ = 4.5 Hz; $J_{5\alpha,6\beta}$ = 11 Hz; $J_{5\beta,6\alpha}$ = 1 Hz; $J_{5\beta,6\beta}$ = 5 Hz; $J_{6\alpha,6\beta}$ ≈ 14.5 Hz; $J_{14\alpha,14\beta}$ = 13.5 Hz; $J_{14\alpha,15}$ ≈ 1 Hz; $J_{14\beta,15}$ = 7 Hz; $J_{18,19}$ = 7 Hz; $J_{21\alpha,21\beta}$ = 13 Hz.

Compound **17.**
$J_{3,14\alpha}$ = 5 Hz; $J_{3,14\beta}$ = 10 Hz; $J_{5\alpha,5\beta}$ ≈ 11 Hz; $J_{14\alpha,14\beta}$ = 13.5 Hz; $J_{14\alpha,15}$ = 6.5 Hz; $J_{14\beta,15}$ = 7.5 Hz; $J_{18,19}$ = 7 Hz; $J_{21\alpha,21\beta}$ = 15 Hz.

Compound **18.**
$J_{3,14\alpha}$ = 5 Hz; $J_{3,14\beta}$ = 6.5 Hz; $J_{5\alpha,5\beta}$ = 11.5 Hz; $J_{5\alpha,6\alpha}$ = 4.5 Hz; $J_{5\alpha,6\beta}$ ≈ 11 Hz; $J_{5\beta,6\alpha}$ ≈ 1 Hz; $J_{5\beta,6\beta}$ ≈ 4 Hz; $J_{6\alpha,6\beta}$ ≈ 15 Hz; $J_{14\alpha,14\beta}$ = 14 Hz; $J_{14\alpha,15}$ = 9.5 Hz; $J_{14\beta,15}$ ≈ 5 Hz; $J_{18,19}$ = 7 Hz; $J_{21\alpha,21\beta}$ = 12 Hz.

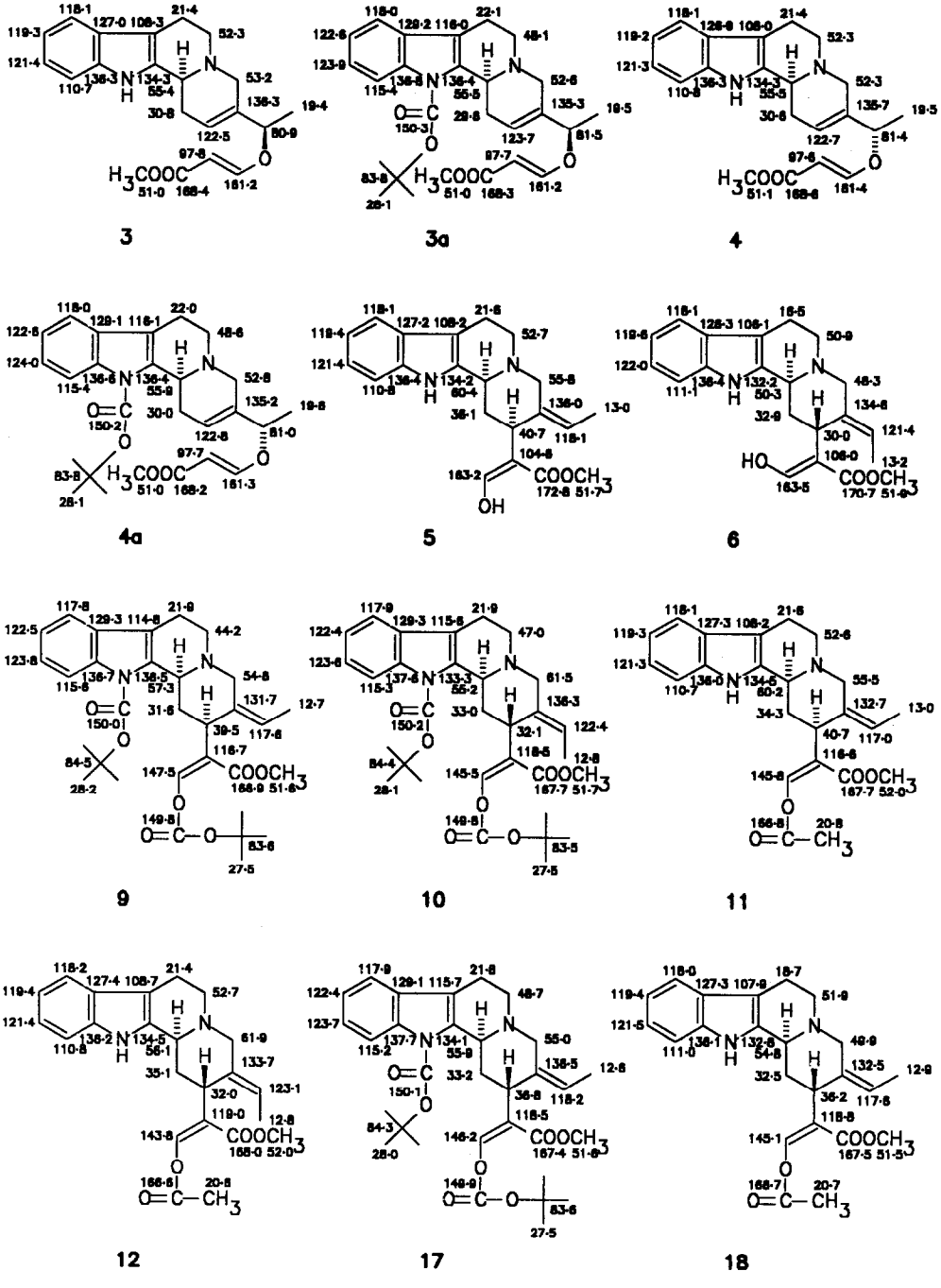
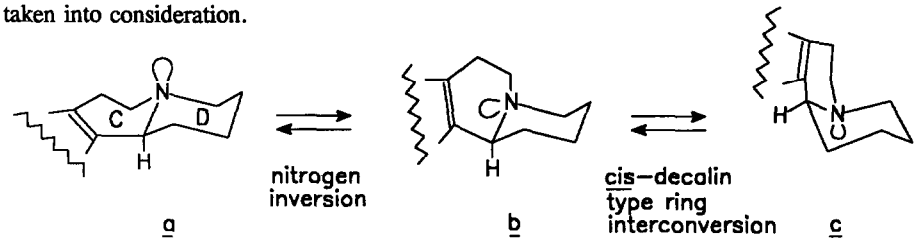


Figure 1. ^{13}C-nmr data of compounds **3**, **3a**, **4**, **4a**, **5**, **6**, **9**, **10**, **11**, **12**, **17**, and **18**.

CONFORMATIONAL EXAMINATION

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



Scheme 10. Conformational equilibrium of the indolo[2,3-*a*]quinolizidine skeleton.

The situation may be still further complicated by the presence of different tautomeric forms of the compounds (here compounds **5**, **6**, and **15**) since each tautomer has its own conformational equilibrium. If one tautomer is clearly dominating, as **5a** and **6b** for compounds **5** and **6** (Figures 2 and 3), the conformational behaviour can be relatively easily interpreted. But if this is not the case, as in compound **15**, the experimental procedure becomes more complicated (*vide infra*).

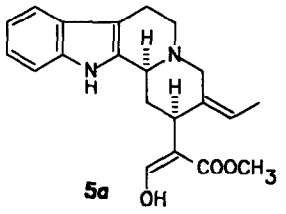


Figure 2. Dominating tautomeric form **5a** of compound **5**.

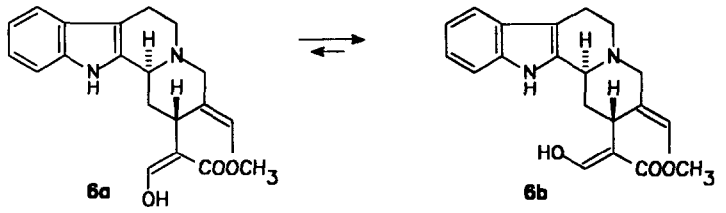


Figure 3. Equilibrium between tautomeric enols **6a** (present in small amounts; *cf.* acetylation of compound **6**) and **6b** (dominating) of compound **6**.

Table 3. ^{1}H-nmr data of the dominating tautomeric forms **5a** and **6b** of compounds **5** and **6**. The coupling constants between the aromatic protons are omitted.

Atom	**5a**	**6b**
1	8.21 br s	8.79 br s
3	3.50 br d	4.43 dd
9	7.46	7.48
10	7.10	7.11
11	7.14	7.14
12	7.28	7.28
14α	2.12 ddd	2.43 ddd
14β	1.83 ddd	1.86 ddd
15	3.2 m	4.13 ddd
17	7.95 s	8.06 s
18	1.67 d	1.52 d
19	5.14 q	5.40 q
21α	2.83 d	3.13 d
21β	3.92 d	3.7 d*
CO_2Me	3.75 s	3.76 s

* Partly masked.

Coupling constants:

Tautomer **5a**.
$J_{3,14\alpha} \approx 2$ Hz; $J_{3,14\beta} = 11$ Hz; $J_{14\alpha,14\beta} \approx 13$ Hz; $J_{14\alpha,15} \approx 2$ Hz; $J_{14\beta,15} \approx 12$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 13$ Hz.

Tautomer **6b**.
$J_{3,14\alpha} \approx 8$ Hz; $J_{3,14\beta} \approx 10$ Hz; $J_{14\alpha,14\beta} = 14$ Hz; $J_{14\alpha,15} = 2$ Hz; $J_{14\beta,15} = 5$ Hz; $J_{18,19} = 6.5$ Hz; $J_{21\alpha,21\beta} = 14$ Hz.

Estimation of the vicinal dihedral angles (Φ) for tautomers **5a** and **6b**, based on the observed coupling constants and using the Karplus equation,[11,12] gave the values in Table 4.

Table 4. Vicinal dihedral angles (Φ) for tautomers **5a** and **6b**.

	Tautomer **5a**	Tautomer **6b**
$H_{(3)}$-C-C-$H_{(14\alpha)}$	Φ ≈ 60°	Φ ≈ 25°
$H_{(3)}$-C-C-$H_{(14\beta)}$	Φ ≈ 180°	Φ ≈ 160°
$H_{(14\alpha)}$-C-C-$H_{(15)}$	Φ ≈ 60°	Φ ≈ 65°
$H_{(14\beta)}$-C-C-$H_{(15)}$	Φ ≈ 180°	Φ ≈ 40°

These values are compatible only if ring D of the dominating tautomeric form **5a** of compound **5** exists predominantly in chair conformation and ring D of the dominating tautomeric form **6b** of compound **6** in a slightly modified twisted boat conformation. Confirmation that this was so was obtained through NOE difference measurements. In the case of compound **5**, irradiation at H-21β resulted in an NOE at H-18 (9%), and irradiation at H-3 in NOEs at H-21α (≈3%) and H-5α (≈2%). When H-19 was irradiated no NOEs were observed at H-21α or H-21β. In the case of compound **6**, irradiation at H-14β resulted in NOEs at H-15 (6%) and H-21β (3%). Irradiation at H-19 showed an NOE at H-21α (3%). Moreover, no NOE was observed at H-18 when H-17 was irradiated.

The ^{13}C-nmr results (Figure 1) and the presence and the absence of the Bohlmann bands (see Experimental), respectively, further confirmed that compound **5** exists mainly in the tautomeric form **5a**, which prefers conformation a with ring D in chair conformation (Figure 4), whereas compound **6** exists almost exclusively in the tautomeric form **6b**, which prefers conformation c with ring D in twisted boat conformation (Figure 5; for the minor existence of the tautomeric form **6a**, see Figure 3). The twisted boat conformation for compound **6** permits a strong intramolecular hydrogen bonding between the acidic enolic hydroxyl group and N_b.

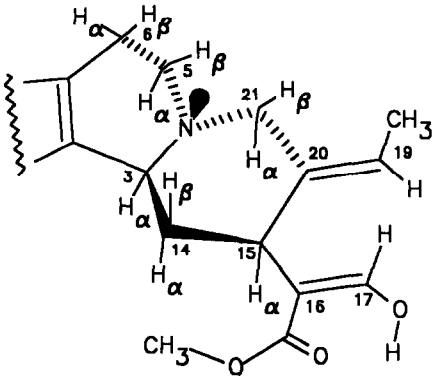


Figure 4. Predominant conformation of the dominating tautomer **5a** of compound **5**.

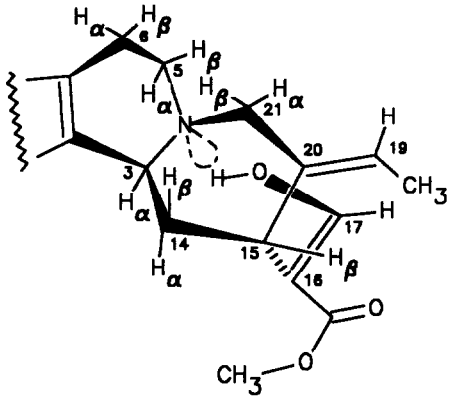
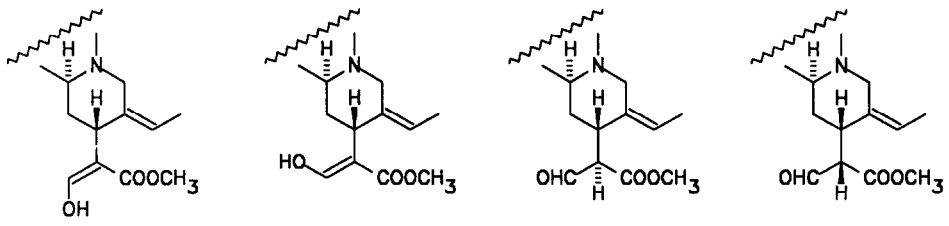


Figure 5. Predominant conformation of the dominating tautomer **6b** of compound **6**.

The existence of the hydrogen bonding is the prerequisite for the predominance of the presented tautomeric form **6b** and the presented conformation (Figure 5) for compound **6**. If compound **6** is acetylated (Ac_2O), it reacts under the minor tautomeric form **6a** (Figure 3) leading to compound **12** (structure confirmed by NOE (2%) at H-17 when H-15 is irradiated). The acetyl derivative **12** exists predominantly in conformation a with ring D in a twisted boat conformation. On the other hand, acetylation of compound **5** leads to compound **11** which prefers conformation a with ring D in a boat conformation. In the di-Boc-derivatives **9** and **10**, where the N_a-Boc group forces the C/D relationship to be b, ring D exists predominantly in boat and twisted boat conformations, respectively (*cf.* Table 2).

The spectral data for compound **15** are more equivocal. Existence of compound **15** in at least four spectrally detectable tautomeric forms, **15a** - **15d** (Figure 6), makes exact measurement of the contribution of the different conformations of each tautomer to their conformational equilibrium difficult.



15a **15b** **15c** **15d**

Figure 6. Tautomeric forms **15a** - **15d** of compound **15**.

Considering the main tautomer **15a**, a contribution of conformation **15a'** (conformation c with ring D in chair conformation) to the conformational equilibrium can be expected. The ^{1}H-nmr data of tautomer **15a**

(Table 5) taken from the spectrum of the tautomeric mixture showed, however, a considerable contribution of conformation **15a"** [conformation c with ring D in twisted boat conformation; vicinal dihedral angles (Φ), $H_{(3)}$-C-C-$H_{(14\alpha)}$, Φ ≈ 25°; $H_{(3)}$-C-C-$H_{(14\beta)}$, Φ ≈ 160°; estimated using the Karplus equation and the coupling constants taken from Table 5] (Figure 7). This large contribution was further confirmed by NOE difference measurements. Irradiation at H-14α resulted in NOEs at H-15 (≈2%) and H-17 (≈4%). When H-15 was irradiated there were NOEs at H-19 (≈6%) and H-17 (≈3%).

Table 5. ^{1}H-nmr data of tautomer **15a** (taken from the spectrum of the tautomeric mixture).

H-3	4.20 dd
H-14α	2.40 ddd
H-14β	1.9 m
H-15	3.96 br s
H-17	7.99 s
H-18	1.57 d
H-19	5.46 q
CO_2Me	3.73 s

Coupling constants:

$J_{3,14\alpha}$ = 8 Hz; $J_{3,14\beta}$ ≈ 10 Hz; $J_{14\alpha,14\beta}$ = 13 Hz; $J_{14\alpha,15}$ = 2 Hz; $J_{18,19}$ = 7 Hz.

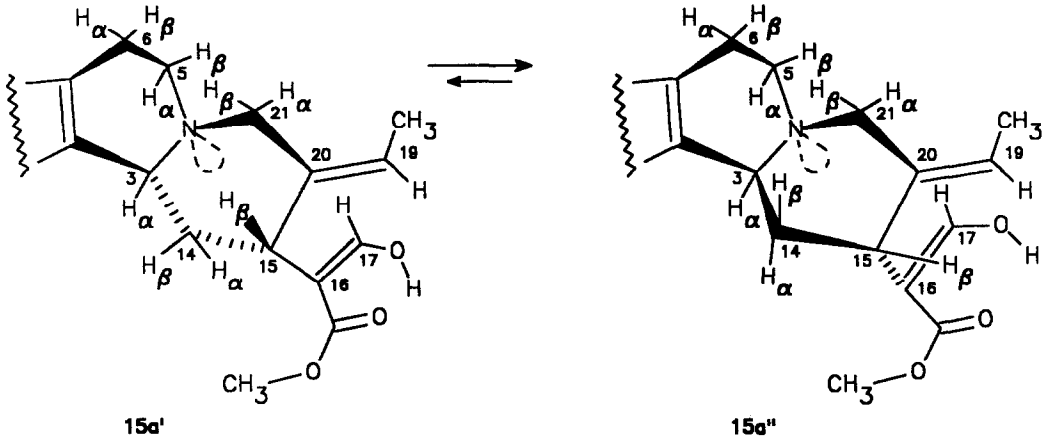
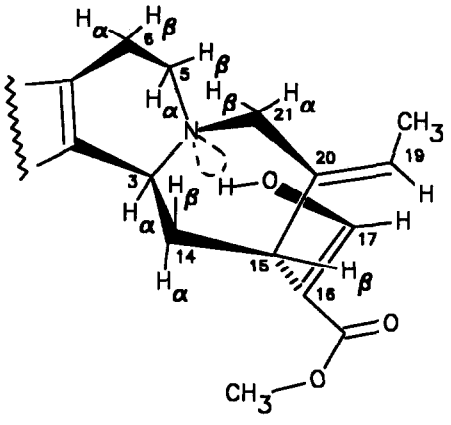


Figure 7. Equilibrium between conformations **15a'** and **15a"** of tautomeric form **15a**.

For tautomer **15b**, in analogy with compound **6** (*vide supra*), a contribution of conformation **15b'** can be predicted (Figure 8). The presence of tautomers **15c** and **15d** is supported by weak signals in the ^{1}H-nmr spectrum of compound **15** at 9.79 and 9.83 ppm and in the ^{13}C-nmr spectrum at 196.4 and 198.1 ppm.



15b'

Figure 8. Predominant conformation **15b'** of tautomer **15b.**

The acetyl and di-Boc derivatives **18** and **17** of compound **15** exist predominantly in conformations c and b, respectively, with ring D in chair conformation in **18** and in twisted boat conformation in **17** (*cf.* Table 2).

CONCLUSIONS

The present results show, contrary to earlier indications,[5] that the Claisen rearrangement of vinyl allyl ether **3** permits the preparation of both (±)-Z-geissoschizine **5** and (±)-15-epi-E-geissoschizine **6.** However, the epimeric vinyl allyl ether **5** affords only (±)-15-epi-Z-geissoschizine **15.** The "missing" compound, (±)-E-geissoschizine **16,** has to be prepared in an alternative way (*cf.* Refs 10, 13-18). Our synthesis of (±)-15-epi-E-geissoschizine **6,** which earlier[10] has been transformed to compound **16,** means nevertheless that a new, formal total synthesis of (±)-E-geissoschizine **16** has been developed.

The preponderant conformation of the dominating tautomer **5a** of (±)-Z-geissoschizine **5** was shown to be conformation a with ring D in chair conformation, and the preponderant conformation of the dominating tautomer **6b** of (±)-15-epi-E-geissoschizine **6** was conformation c with ring D in a twisted boat conformation (Figures 2 and 3).

In the case of compound **15,** which exists in at least four different tautomeric forms (**15a** - **15d**),

determination of the preponderant conformation for each tautomer is more difficult. However, a considerable contribution of conformation **15a''** (Figure 7) to the conformational equilibrium of tautomer **15a** was shown, and a contribution of conformation **15b'** (Figure 8) to the conformational equilibrium of tautomer **15b** was predicted.

In several cases transformation of the reaction products to the corresponding di-Boc and/or acetyl derivatives is advantageous for isolational and analytical purposes.

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}). Abbreviations s, m, w, and br are used to designate strong, medium, weak, and broad, respectively. ^{1}H- and ^{13}C-nmr spectra were measured with a Varian Unity-400 NMR spectrometer working at 399.952 MHz (^{1}H-nmr) and 100.577 MHz (^{13}C-nmr). 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). 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 done at 399.952 MHz (^{1}H-nmr) and 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 compound 3:
A solution of alcohol **1** (3.041 g, 11.35 mmol), methylpropiolate (3.04 ml, 3 equiv.) and *N*-methylmorpholine (1.52 ml) in dry 1,4-dioxane (25 ml) was stirred for 3 days in dark at room temperature (N_2 atm). The reaction mixture was evaporated and purified by flash chromatography (silica, CH_2Cl_2/MeOH, 98:2) followed by precipitation from CH_2Cl_2/n-hexane (twice) to give compound **3**.
Compound **3**: Y. 3.68 g (92%). Amorphous material. Ir: 3360 (w, NH), 2810, 2770 (w, Bohlmann bands), 1710 (s, C=O), 1650 (s, -C=C-), 1630 (s, -C=C-). For the ^{1}H-nmr data, see Table 2. For the ^{13}C-nmr data, see Figure 1. Ms: 352 (M^+), 323, 251 (100%), 184, 171, 170, 169, 156. HRms: Found: 352.1814. Calcd for $C_{21}H_{24}N_2O_3$: 352.1787.

Preparation of compound 3a:
To compound **3** (100 mg, 0.28 mmol) in abs. CH_2Cl_2 (5 ml) was added *p*-dimethylamino pyridine (DMAP) (3 mg, 0.1 equiv.) and di-*t*-butyl dicarbonate [$(Boc)_2O$] (82 mg, 1.3 equiv.) with stirring at room temperature (Ar atm). After 3 h the mixture was evaporated and purified by flash chromatography (silica, CH_2Cl_2/MeOH, 99:1) to afford compound **3a**.
Compound **3a**: Y. 105 mg (82%). Amorphous material. Ir: 1710 (s, br, 2 x C=O), 1650 (s, -C=C-), 1630 (s, -C=C-). For the ^{1}H-nmr data, see Table 2. For the ^{13}C-nmr data, see Figure 1. Ms: 452 (M^+), 395, 351, 295 (100%), 251, 169. HRms: Found: 452.2286. Calcd for $C_{26}H_{32}N_2O_5$: 452.2311.

Preparation of compound 4:
Reaction of alcohol **2** (200 mg, 0.75 mmol), methylpropiolate (0.20 ml, 3 equiv.) and *N*-methylmorpholine (0.10 ml) in dry 1,4-dioxane (10 ml) using the procedure described for compound **3** afforded compound **4**, which was purified by flash chromatography (silica, CH_2Cl_2/MeOH, from 99.5:0.5 to 98.5:1.5).
Compound **4**: Y. 247 mg (94%). Mp. 156-157°C (toluene), lit. (for the diastereoisomeric mixture) 151°C[5]. Ir: 3350 (w, NH), 2830, 2770 (w, Bohlmann bands), 1700 (s, C=O), 1640 (s, -C=C-), 1625 (s, -C=C-). For the ^{1}H-nmr data, see Table 2. For the ^{13}C-nmr data, see Figure 1. Ms: 352 (M^+), 323, 251 (100%), 184, 171, 170, 169, 156. HRms: Found: 352.1812. Calcd for $C_{21}H_{24}N_2O_3$: 352.1787.

Preparation of compound 4a:
Reaction of compound **4** (95 mg, 0.27 mmol) in abs. CH_2Cl_2 (4 ml) with DMAP (3 mg, 0.1 equiv.) and $(Boc)_2O$ (77 mg, 1.3 equiv.) for 4 h, following the procedure described for compound **3a**, led to compound **4a**, which was purified by flash chromatography (silica, CH_2Cl_2/MeOH, 99:1).
Compound **4a**: Y. 92 mg (75%). Amorphous material. Ir: 1720 (s, C=O), 1700 (s, C=O), 1640 (m, -C=C-), 1620 (m, -C=C-). For the ^{1}H-nmr data, see Table 2. For the ^{13}C-nmr data, see Figure 1. Ms: 452 (M^+), 395, 351, 295 (100%), 251, 169. HRms: Found: 452.2275. Calcd for $C_{26}H_{32}N_2O_5$: 452.2311.

Preparation of (±)-Z-geissoschizine 5 and (±)-15-epi-E-geissoschizine 6:
Compound **3** (713 mg, 2.03 mmol) was dissolved in dry toluene (25 ml) and refluxed for 2 h under Ar atm (the reaction is moisture sensitive). Evaporation and purification by flash chromatography (silica, CH_2Cl_2:MeOH, 98:2) afforded a mixture of compounds **5** and **6** (5:4). Attempts to separate compounds **5** and **6** were not successful.
Compounds **5** and **6**: Y. 228 mg (32%). For the analytical data of compounds **5** and **6**, see below.

Preparation of (±)-N_a,O-di-Boc-Z-geissoschizine (cis-isomer) 9, (±)-N_a,O-di-Boc-Z-geissoschizine (trans-isomer) 9a, and (±)-N_a,O-di-Boc-15-epi-E-geissoschizine 10:
Reaction of a mixture of compounds **5** and **6** (326 mg, 0.93 mmol, 5:4) with DMAP (11.4 mg, 0.1 equiv.) and $(Boc)_2O$ (454 mg, 2.2 equiv.) in abs. CH_2Cl_2 (2.0 ml), following the procedure described for compound **3a**, led to a crude mixture of compound **9**, **9a** (traces), and **10** which was purified by flash chromatography (silica, CH_2Cl_2/MeOH, from 99:1 to 98.5:1.5). Separation of compounds **9** and **9a** did not succeed.
Compound **9** (containing traces of compound **9a**): Y. 242 mg (47%). Amorphous material. Ir: 1765 (s, C=C-O-C=O), 1720 (s, br, 2 x C=O). For the ^{1}H-nmr data, see Table 2. For the ^{13}C-nmr data, see Figure 1. Ms: 552 (M^+), 496, 452, 440, 439, 395 (100%), 379, 295, 281, 169. HRms: Found: 552.2835. Calcd for $C_{31}H_{40}N_2O_7$: 552.2836.
Compound **9a** (containing compound **9**): Traces. For the ^{13}C-nmr data, see Note 19.
Compound **10**: Y. 202 mg (40%). Amorphous material. Ir: 1760 (s, C=C-O-C=O), 1710 (s, br, 2 x C=O). For the ^{1}H-nmr data, see Table 2. For the ^{13}C-nmr data, see Figure 1. Ms: 552 (M^+), 496, 452,440, 439, 395 (100%), 379, 337, 295, 281, 169. HRms: Found: 552.2794. Calcd for $C_{31}H_{40}N_2O_7$: 552.2836.

Preparation of (±)-Z-geissoschizine 5 by Boc cleavage:
Compound **9** (21 mg, 0.038 mmol; containing traces of isomer **9a**) was dissolved in HCOOH (1.0 ml). The reaction mixture was stirred for 22 h at room temperature (Ar atm). It was then evaporated, dissolved in CH_2Cl_2, shaken with 10% Na_2CO_3 for 20 min, and extracted with CH_2Cl_2. The combined organic phases were washed with H_2O and dried (Na_2SO_4) to afford compound **5**.
Compound **5**: Y. 11 mg (82%). Mp. 137-138°C (ether/hexane), lit. 137-138°C[17]. Ir: 3400 (br, NH, OH), 2820, 2770 (w, Bohlmann bands), 1730, 1680 (s, br, C=O), 1660 (s, br, -C=C-). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 352 (M^+, 100%), 323, 251, 184, 171, 170, 169, 156. HRms: Found: 352.1805. Calcd for $C_{21}H_{24}N_2O_3$: 352.1787.

Preparation of (±)-15-epi-E-geissoschizine 6 by Boc cleavage:
Treatment of compound **10** (18 mg, 0.033 mmol) with HCOOH, following the procedure described for compound **5**, gave compound **6** .
Compound **6**: Y. 11 mg (96%). Amorphous material, lit. amorphous material[10], oil[17]. Ir: 3350 (m, br, NH, OH), 1730, 1680 (s, br, C=O), 1660 (s, br, -C=C-). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 352 (M^+), 323, 251 (100%), 184, 171, 170, 169, 156. HRms: Found: 352.1796. Calcd for $C_{21}H_{24}N_2O_3$: 352.1787.

Preparation of (±)-O-acetyl-Z-geissoschizine 11:
Compound **5** (64 mg, 0.18 mmol) was dissolved in abs. CH_2Cl_2 (0.75 ml). Freshly distilled Ac_2O (0.56 ml,

33 equiv.) and a catalytic amount of dry pyridine were added. The reaction mixture was stirred for 20 hours at room temperature (Ar atm). After evaporation H_2O was added to the residue at 0°C and the mixture was stirred for 20 minutes at room temperature. After filtration CH_2Cl_2 was added to the filtrate and the solution was neutralized with saturated $NaHCO_3$ solution, followed by usual work-up to yield compound **11**.
Compound **11**: Y. 47 mg (66%). Viscous oil. Ir: 3400 (m, br, NH), 2830, 2770 (w, Bohlmann bands), 1765 (s, C=C-O-C=O), 1710 (s, br, 2 x C=O). For the ^{1}H-nmr data, see Table 2. For the ^{13}C-nmr data, see Figure 1. Ms: 394 (M^+), 351, 335, 170, 169 (100%), 156. HRms: Found: 394.1938. Calcd for $C_{23}H_{26}N_2O_4$: 394.189 3.

Preparation of (±)-O-acetyl-15-epi-E-geissoschizine 12:
Reaction of compound **6** (41 mg, 0.12 mmol) with Ac_2O (0.36 ml, 33 equiv.) and a catalytic amount of pyridine in abs. CH_2Cl_2 (0.48 ml), following the procedure described for compound **11**, led to compound **12**.
Compound **12**: Y. 20 mg (44%). Viscous oil. Ir: 3300 (m, br, NH), 2830, 2770 (w, Bohlmann bands), 1765 (s, C=C-O-C=O), 1710 (s, br, 2 x C=O). For the ^{1}H-nmr data, see Table 2. For the ^{13}C-nmr data, see Figure 1. Ms: 394 (M^+), 351, 335, 170, 169 (100%), 156. HRms: Found: 394.1866. Calcd for $C_{23}H_{26}N_2O_4$: 394.1893.

Preparation of (±)-15-epi-Z-geissoschizine 15:
Compound **4** (610 mg, 1.73 mmol) was dissolved in dry toluene (18 ml) and refluxed for 1 h under Ar atm (the reaction is moisture sensitive). Evaporation and purification by flash chromatography (silica, CH_2Cl_2:MeOH, 97:3) led to compound **15** (present in different tautomeric forms).
Compound **15**: Y. 261 mg (43%). Amorphous material. Ir: 3370 (m, NH, OH), 1720, 1670 (s, br, C=O). ^{1}H-nmr: 1.57, 1.64, 1.66 (d, J=7 Hz, H-18 of different tautomeric forms), 1.7 - 2.1 (m, H-14β of different tautomeric forms, H-14α of two tautomeric forms), 2.24 (ddd, J_1=13 Hz, J_2=8 Hz, J_3=2 Hz, H-14α of one tautomeric form), 2.40 (ddd, J_1=13 Hz, J_2=8 Hz, J_3=2 Hz, H-14α of one tautomeric form), 3.68, 3.73, 3.79, 3.83 (s, -CO_2CH_3 of different tautomeric forms), 3.96 (br s, H-15), 4.20 (dd, $J_1 \approx 10$ Hz, J_2=8 Hz, H-3), 5.46 (q, J=7 Hz, H-19), 7.06-7.16 (2H, m, H-10, H-11), 7.27 (d, J= 7.5 Hz, H-12), 7.45 (d, J=7.5 Hz, H-9), 7.84, 7.93, 8.11 (br s, H-1 of different tautomeric forms), 7.99 (s, H-17), 9.79, 9.83 (s, -CHO of keto forms). ^{13}C-nmr: 12.8, 12.9, 13.0, 16.4, 20.0, 21.3, 21.5, 28.1, 31.6, 32.7, 33.0, 33.9, 34.2, 37.9, 41.6, 41.7, 45.2, 48.7, 49.9, 51.1, 51.3, 52.0, 52.1, 52.6, 52.7, 54.5, 54.6, 58.5, 60.3, 106.0, 106.4, 108.4, 111.0, 118.0, 119.2, 119.3, 121.2, 121.7, 121.8, 126.3, 127.1, 127.2, 127.4, 132.1, 132.2, 133.7, 133.8, 134.4, 135.9, 136.0, 136.3, 162.5, 162.8, 168.8, 169.1, 171.0, 172.5, 196.4, 198.2. Ms: 352 (M^+, 100%), 351, 323, 251, 250, 171, 170, 169, 156. HRms: Found: 352.1786. Calcd for $C_{21}H_{24}N_2O_3$: 352.1787.

Preparation of (±)-N_a,O-di-Boc-15-epi-Z-geissoschizine 17:
Reaction of compound **15** (137 mg, 0.39 mmol) with DMAP (5.0 mg, 0.1 equiv.) and $(Boc)_2O$ (186 mg, 2.2 equiv.) in abs. CH_2Cl_2 (1.5 ml) for 2.5 h, following the procedure described for compound **3a**, led to compound **17**, which was purified by flash chromatography (silica, CH_2Cl_2/MeOH, 99.5:0.5).
Compound **17**: Y. 174 mg (81%). Amorphous material. Ir: 1760 (s, C=C-O-C=O), 1720 (s, br, 2 x C=O). For the ^{1}H-nmr data, see Table 2. For the ^{13}C-nmr data, see Figure 1. Ms: 552 (M^+), 496, 440, 439 (100%), 395, 379, 295, 281, 169. HRms: Found: 552.2866. Calcd for $C_{31}H_{40}N_2O_7$: 552.2836.

Preparation of (±)-O-acetyl-15-epi-Z-geissoschizine 18:
Reaction of compound **15** (61 mg, 0.17 mmol) with Ac_2O (0.54 ml, 33 equiv.) and a catalytic amount of pyridine in abs. CH_2Cl_2 (0.72 ml), following the procedure described for compound **11**, led to compound **18**.
Compound **18**: Y. 54 mg (79%). Viscous oil. Ir: 3400 (w, br, NH), 1760 (s, C=C-O-C=O), 1710 (s, C=O). For the ^{1}H-nmr data, see Table 2. For the ^{13}C-nmr data, see Figure 1. Ms: 394 (M^+), 352, 351, 335, 251, 249, 237, 184 (100%), 171, 170, 169, 156. HRms: Found: 394.1861. Calcd for $C_{23}H_{26}N_2O_4$: 394.1893.

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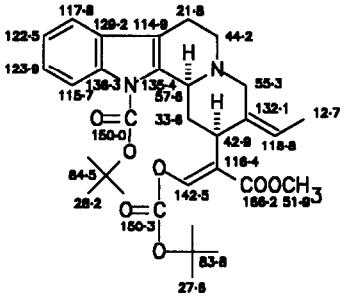
19. ^{13}C-nmr data of compound **9a**, taken from the spectrum of a mixture of compounds **9** and **9a**.



9a

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(*Received in UK* 29 *November* 1993; *revised* 23 *December* 1993; *accepted* 7 *January* 1994)