# CONFORMATIONAL STUDY OF GEISSOSCHIZINE ISOMERS AND THEIR MODEL COMPOUNDS

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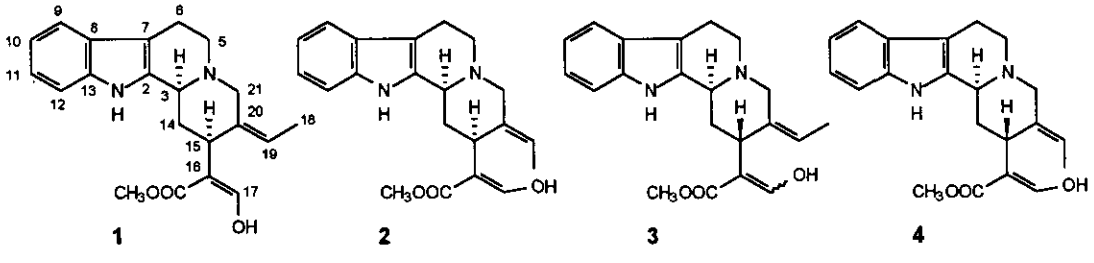
**Abstract** - Study was made of the major factors affecting the conformational equilibrium between the C and D rings of geissoschizine isomers (**1** - **4**) and several of their model compounds (**5** - **24**). Conclusions are mainly based on $^{13}C$ NMR data.

## INTRODUCTION

Geissoschizine (**2**) has played an important role in the development of biogenetic formation schemes for many indole alkaloids, although in some cases it is evidently merely a shunt metabolite.[1-4] Its structure was elucidated about 30 years ago,[5-7] but the stereochemical question as to which of the different possible conformations is the preponderant one, has been the subject of a long debat.[8-12] The three other geissoschizine isomers, *Z*-geissoschizine (**1**), 15-epi-*Z*-geissoschizine (**3**),[13] and 15-epi-*E*-geissoschizine (**4**),[13] also present interesting conformational aspects (*vide infra*).[14-17]

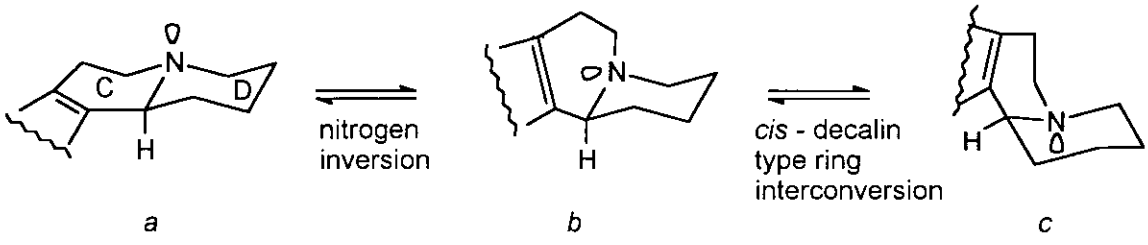



During our synthetic studies on indole alkaloids[18-27] the four geissoschizine isomers (**1** - **4**), as well as the deformyl derivatives (methyl geissoschizoates) (**5** - **8**) and their reduction products (geissoschizols) (**9** - **12**), became available to us. The 16,17-dihydro derivatives (16*R*- and 16*S*-isositsirikines) (**13** - **20**), and the geissoschizine *O*-methyl ethers (**21**) and (**22**) and geissoschizine acetates (**23**) and (**24**) were also studied. In contrast to geissoschizine isomers (**1** - **4**), no stabilization by intramolecular hydrogen bonding between the acidic enol hydroxyl and $N_b$ is possible for compounds (**21** - **24**) (*vide infra*).

Considering the analytical data of these compounds (**1** - **24**), the time appeared to be ripe for a general examination of the conformational behavior in the geissoschizine series. Our conclusions are mainly based on $^{13}C$ NMR results.[14]

## GENERAL CONFORMATIONAL EXAMINATION

Owing to nitrogen inversion and *cis*-decalin type ring interconversion (ring D in chair conformation), the indolo[2,3-*a*]quinolizidine skeleton present in geissoschizine isomers and their model compounds can exist in three main conformations (Scheme 1).[21,22,27] Moreover, the existence of ring D in boat and twist-boat conformations, in addition to the normal chair conformation, has to be taken into consideration.




Scheme 1. Conformational equilibrium of the indolo[2,3-*a*]quinolizidine skeleton.

Conformation *a* can be considered to be ~11 kJ/mol (~2.6 kcal/mol) more stable than conformation *c*.[28] The contribution of conformation *b* is generally small.[29] However, the contribution of the different conformations to the conformational equilibrium is strongly influenced by the substituents. It is noteworthy that the D ring substituents which in conformations *a* and *b* are axial become equatorial in conformation *c*, and *vice versa*.

The situation may be still further complicated by the presence of different tautomeric forms of the compounds since each tautomer has its own conformational equilibrium. If one tautomer is clearly dominating, its conformational behavior can be relatively easily interpreted. But if this is not the case, the experimental procedure becomes considerably more complicated (*vide infra*).

Before going into the details concerning the conformational behaviour of geissoschizine isomers (**1** - **4**), we examine the simple model compounds (**5** - **24**). In regard to the conformational behavior of these compounds, four main aspects should initially be taken into consideration:

1°. The stability of conformation *a per se* is higher than that of conformation *c*. The contribution of

conformation *b* is generally small (*vide supra*).

2°. Interaction between an equatorial C-15 substituent and the C-20 *E*-ethylidene side chain is energetically unfavorable and has a marked effect on the conformational equilibrium.

3°. An equatorial C-15 substituent is generally favored over an axial C-15 substituent.

4°. Intramolecular hydrogen bonding between the C-15 substituent and $N_b$ would exert a strong effect on the conformational equilibrium.

## RESULTS AND DISCUSSION

The $^{13}C$ NMR shift values of compounds (**25**)[29-31] (indole alkaloid present in *Dracontomelum magniferum*), (**26**)[32] (*Z*-deplancheine), and (**27**)[18] (*E*-deplancheine) were used as base values in the conformational analysis (Figure 1). All three compounds exist preponderantly in conformation *a*, as indicated by the characteristic signals at about δ 60 (C-3), 53 (C-5), and 21.6 ppm (C-6). The approximate α-, β-, and γ-effects (*trans* and *cis* positions) of the C-20 ethylidene side chain are given in Table 1.

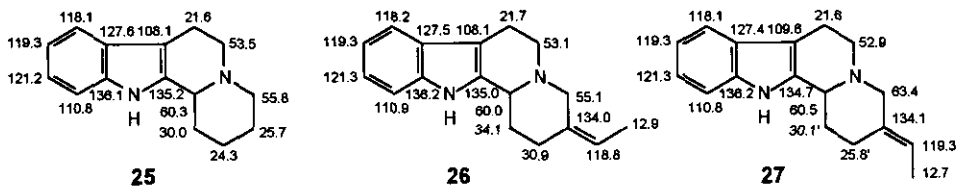



Figure 1. $^{13}C$ NMR shift values of compounds (**25**), (**26**), and (**27**).

Table 1. Approximative α-, β-, and γ-effects (*trans* and *cis* positions) of the C-20 ethylidene side chain.

| | | | | | | |
|---|---|---|---|---|---|---|
| α-effect | *trans* | 6-8 | ppm | *cis* | ± 1 | ppm |
| β-effect | *trans* | ~4 | ppm | *cis* | ~0 | ppm |
| γ-effect | *trans* | ~0 | ppm | *cis* | ~0 | ppm |

The estimated shift values given in Figure 2 are taken to represent with relatively good accuracy the shift values of compound (**25**) when it is totally in conformation *c*. The values are based on those measured for the *trans*-2-*tert*-butyl analogue of compound (**25**), which is estimated to exist ≥99.9% in conformation *c*,[31] and on the assumption that a *tert*-butyl group noticeably affects only the directly attached carbon.[33] In any event, the influence of the *trans*-2-*tert*-butyl group on the chemical shifts of ring C carbons is negligible.

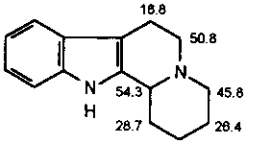



Figure 2. Estimated $^{13}C$ NMR shift values for conformation *c* of compound (**25**).

Although several other characteristic signals of compounds (**25** - **27**) (*e.g.* those of C-3 and C-21) were used as the basis for a first approximation of the contribution of conformations *a* and *c* to the equilibrium, for simplicity we refer in the discussion that follows only to the C-6 values δ 21.6 ppm and 16.8 ppm (*vide infra*).

**Methyl geissoschizoates**

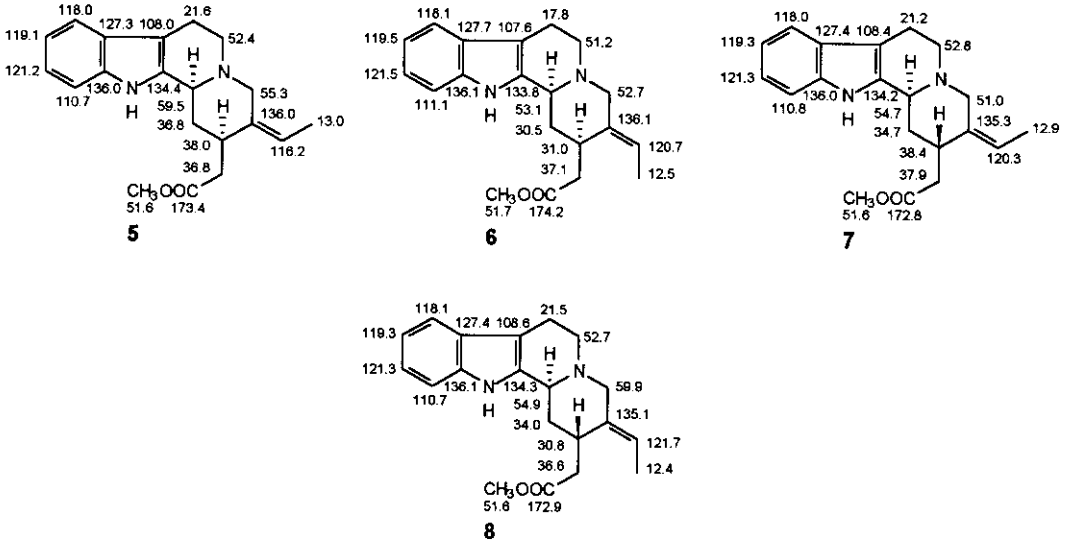



Figure 3. $^{13}C$ NMR shift values of methylgeissoschizoates (**5** - **8**).

Methyl *Z*-geissoschizoate (**5**)

Compound (**5**)[17,20,21,34,35] exists nearly totally in conformation *a* (C-6 δ 21.6 ppm) with ring D in chair conformation (Figure 4). The C-15 substituent is in equatorial position. There is practically no interaction between the C-15 substituent and the C-20 *Z*-ethylidene side chain.

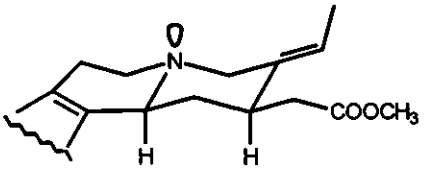



Figure 4. Compound (**5**) in conformation *a* with ring D in chair conformation.

Methyl *E*-geissoschizoate (**6**)

Comparison of the measured shift value δ 17.8 ppm of compound (**6**)[19,21,36] with the values δ 21.6 ppm and 16.8 ppm indicates that the contribution of conformers *a* and c to the conformational equilibrium (in $CDCl_3$ at rt) is about 20% and 80%, respectively. In conformation *a*, where the C-15 substituent is equatorial, there is a strong interaction between the C-15 substituent and the C-20 *E*-ethylidene side chain (Figure 5).

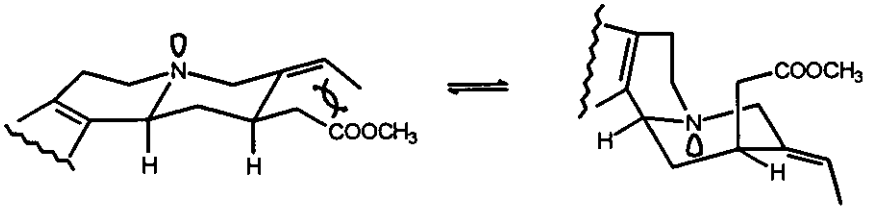



Figure 5. Conformational equilibrium of conformations *a* and *c* of compound (**6**).

Methyl 15-epi-*Z*-geissoschizoate (**7**)[13]

Compound (**7**)[20,34] exists preponderantly (≥90%) in conformation *a* (C-6 δ 21.2 ppm) with ring D in chair conformation and the C-15 substituent in axial position (Figure 6). There is practically no interaction between the C-15 substituent and the C-20 *Z*-ethylidene side chain.

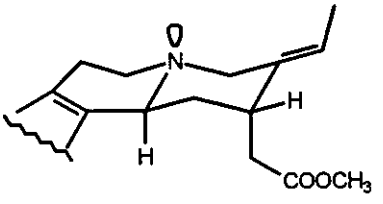



Figure 6. Compound (**7**) in conformation *a* with ring D in chair conformation.

There is also practically no interaction between the equatorial C-15 substituent and the C-20 *Z*-ethylidene side chain in conformation *c*, and it permits a small contribution (≤10%) to the conformational equilibrium. In this situation the C-15 substituent assumes the energetically more favorable equatorial position (Figure 7).

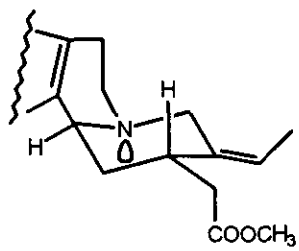



Figure 7. Compound (7) in conformation *c* with ring D in chair conformation.

Methyl 15-epi-*E*-geissoschizoate (**8**)[13]

Compound (**8**)[26,34] exists nearly totally in conformation *a* (C-6 δ 21.5 ppm) with ring D in chair conformation. The C-15 substituent is in axial position (Figure 8). There is practically no interaction between the C-15 substituent and the C-20 *E*-ethylidene side chain.

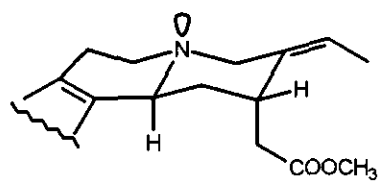



Figure 8. Compound (**8**) in conformation *a* with ring D in chair conformation.

In conformation *c* the C-15 substituent would be equatorial and there would be a strong interaction with the C-20 *E*-ethylidene side chain (Figure 9). Although an equatorial C-15 substituent is energetically more favorable than an axial one, the loss of stability due to interaction with the C-20 *E*-ethylidene side chain makes it the poorer choice.

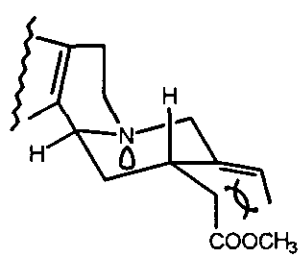



Figure 9. Compound (**8**) in conformation *c* with ring D in chair conformation.

**Geissoschizols**

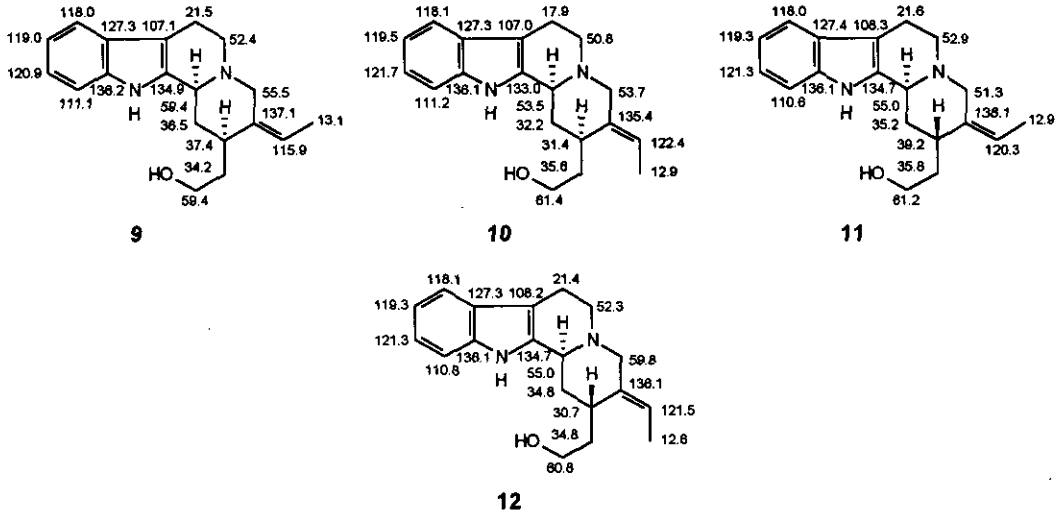



Figure 10. $^{13}C$ NMR shift values of geissoschizols (**9** - **12**).

*Z*-Geissoschizol (**9**)

Compound (**9**)[20] exists nearly totally in conformation *a* (C-6 δ 21.5 ppm) with ring D in chair conformation (Figure 11). The C-15 substituent is in equatorial position. There is practically no interaction between the C-15 substituent and the C-20 *Z*-ethylidene side chain. The situation is similar to that of compound (**5**).

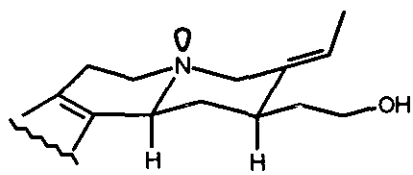



Figure 11. Compound (**9**) in conformation *a* with ring D in chair conformation.

*E*-Geissoschizol (**10**)

Comparison of the measured shift value δ 17.9 ppm (C-6) of compound (**10**)[17,36,37] with the values δ 21.6 ppm and δ 16.8 ppm indicates that the contribution of conformers *a* and *c* to the conformational equilibrium (in $CDCl_3$ at 25 °C) is about 20% and 80%, respectively (Figure 12). The smaller proportion of conformer *a* can be explaned by the strong interaction between the equatorial C-15 substituent and the *E*-ethylidene side. The situation is very similar to that of compound (**6**).

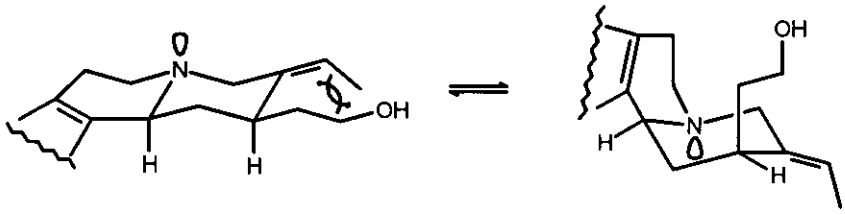


Figure 12. Conformational equilibrium of conformations *a* and *c* of compound (**10**).

15-Epi-*Z*-geissoschizol (**11**)[13]

Compound (**11**)[20] exists nearly exclusively in conformation *a* (C-6 δ 21.6 ppm) with ring D in chair conformation (Figure 13). The C-15 substituent is in axial position. There is practically no interaction between the C-15 substituent and the C-20 *Z*-ethylidene side chain.

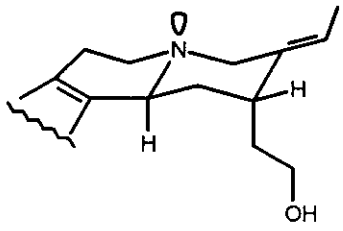


Figure 13. Compound (**11**) in conformation *a* with ring D in chair conformation.

The situation is similar to that of compound (**7**). No participation of conformation *c* to the conformational equilibrium was found, even though, here, if ring D were to adopt a twist-boat conformation, stabilization would be possible by intramolecular hydrogen bonding between the alcoholic hydroxyl group and $N_b$ (Figure 14).

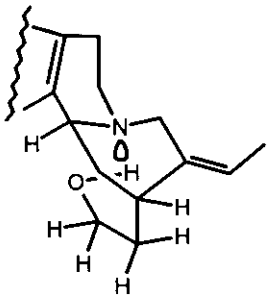


Figure 14. Compound (**11**) in conformation *c* with ring D in twist-boat conformation.

15-Epi-*E*-geissoschizol (**12**)[13]

Compound (**12**)[9,38,39] exists nearly totally in conformation *a* (C-6 δ 21.4 ppm) with ring D in chair conformation and the C-15 substituent in axial position (Figure 15). There is practically no interaction

between the C-15 substituent and the C-20 *E*-ethylidene side chain.

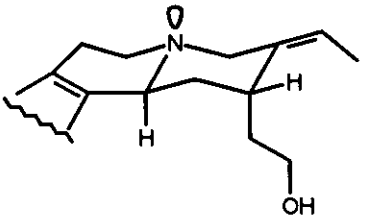


Figure 15. Compound (**12**) in conformation *a* with ring D in chair conformation.

The situation is very similar to that of compound (**8**), except that here, in conformation *c*, intramolecular hydrogen bonding would be possible if ring D were to adopt twist-boat conformation (Figure 16).

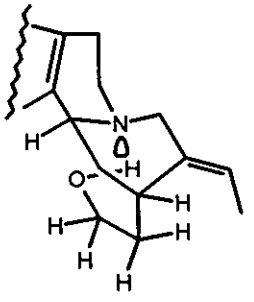
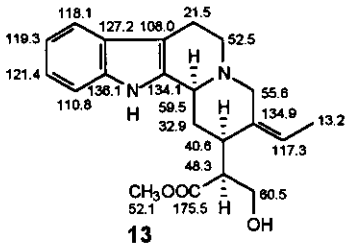
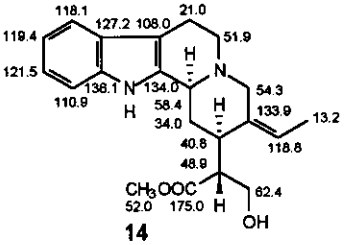


Figure 16. Compound (**12**) in conformation *c* with ring D in twist-boat conformation.

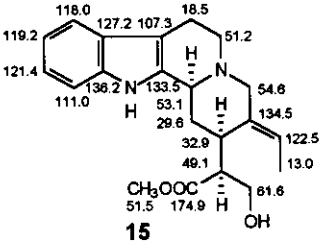
**Isositsirikines** (16,17-dihydrogeissoschizines)



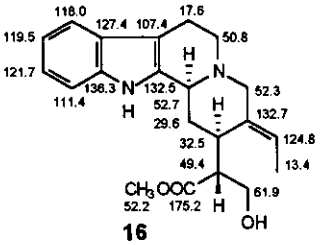
**13**



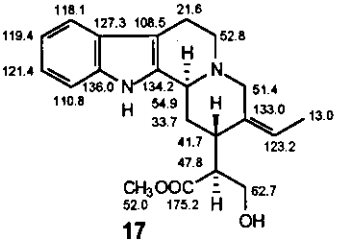
**14**



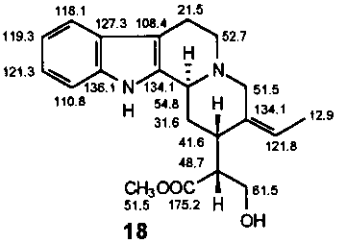
**15**



**16**



**17**



**18**

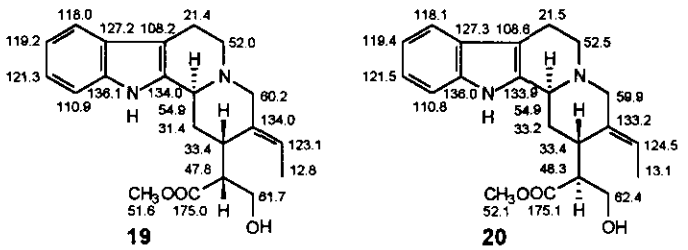



Figure 17. $^{13}C$ NMR shift values of compounds (**13** - **20**).

16*S*-*Z*-Isositsirikine (**13**) and 16*R*-*Z*-isositsirikine (**14**)

Compounds (**13** )and (**14**)[17,24,34,40] exist nearly totally in conformation *a* (C-6 δ 21.5 ppm and δ 21.0 ppm, respectively) and the D rings are in chair conformations (Figure 18). In both cases, the C-15 substituent is in equatorial position and there is practically no interaction between the C-15 substituent and the C-20 *Z*-ethylidene side chain. The situation is similar to that of compounds (**5**) and (**9**).

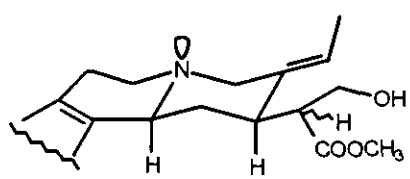



Figure 18. Compounds (**13**) and (**14**) in conformation *a* with ring D in chair conformation.

There is a slight difference between compounds (**13**) and (**14**) in the contribution (≤1% *versus* ~7-8%) of conformation *c* to the conformational equilibrium. The difference is apparently due to a stronger interaction of the C-15 substituent with the indolic part in compound (**13**) than in compound (**14**) (Figure 19).


Figure 19. Compound (**13**) (left) and compound (**14**) (right) in conformation *c* with ring D in chair conformation.

16*S*-*E*-Isositsirikine (**15**) and 16*R*-*E*-Isositsirikine (**16**)

For compounds (**15**) and (**16**)[34,40,41] C-6 shift values δ 18.5 ppm for compound (**15**) and δ 17.6 ppm for compound (**16**) indicate that the contribution of conformation *c* to the conformational equilibrium (in $CDCl_3$ at rt) is about 65% for (**15**) and 83% for (**16**). The strong interaction in conformation *a* between the equatorial C-15 substituent and the *E*-ethylidene side chain pushes the equilibrium towards conformation *c* (Figure 20). Interaction of the C-15 substituent with the indolic part in conformation *c* seems to be weaker in compound (**15**) than in compound (**16**).

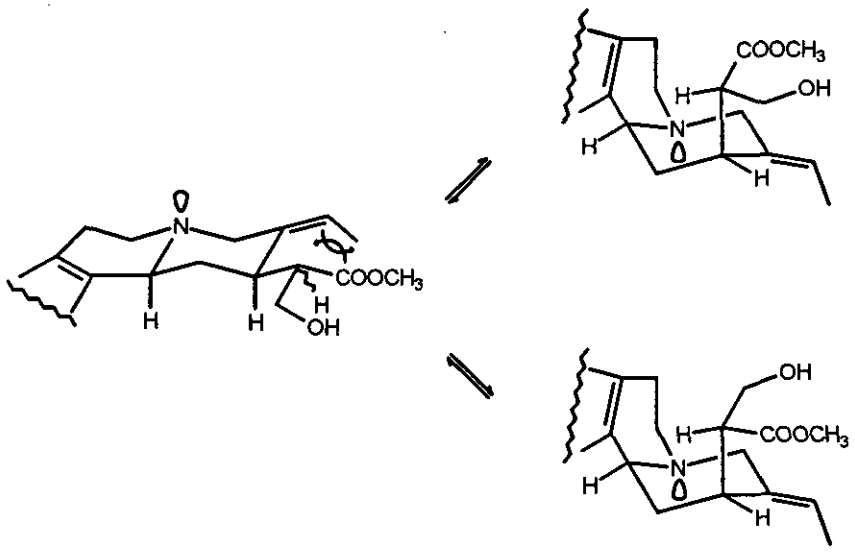



Figure 20. Compounds (**15**) and (**16**) in conformational equilibrium between conformations *a* and *c*.

16*S*-15-Epi-*Z*-isositsirikine (**17**) and 16*R*-15-Epi-*Z*-isositsirikine (**18**)

Compounds (**17**) and (**18**)[24] exist nearly totally in conformation *a* (C-6 δ 21.6 ppm and δ 21.5 ppm, respectively) with the D ring in chair conformation and the C-15 substituent in axial position (Figure 21). Similarly to compounds (**7**) and (**11**), there is practically no interaction between the C-15 substituent and the C-20 *Z*-ethylidene side chain.

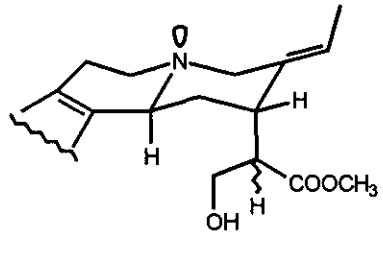



Figure 21. Compounds (**17**) and (**18**) in conformation *a* with ring D in chair conformation.

No participation of conformation *c* in the conformational equilibrium was found, even though if the D ring were to adopt a twist-boat conformation, some stabilization might be achieved by intramolecular hydrogen bonding between the alcoholic hydroxyl group and $N_b$ (Figure 22).

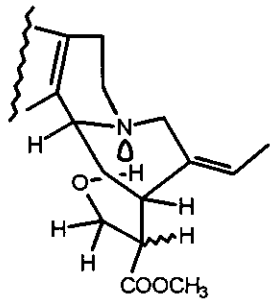



Figure 22. Compounds (**17**) and (**18**) in conformation *c* with ring D in twist-boat conformation.

16*S*-15-Epi-*E*-isositsirikine (**19**)[13] and 16*R*-15-Epi-isositsirikine (**20**)[13]

Compounds (**19**) and (**20**)[34,36,41] exist nearly totally in conformation *a* (C-6 δ 21.4 ppm and δ 21.5 ppm, respectively) with the D ring in chair conformation and the C-15 substituent in axial position (Figure 23). There is practically no interaction between the C-15 substituent and the C-20 *E*-ethylidene side chain. The situation is similar to that of compound (**8**).

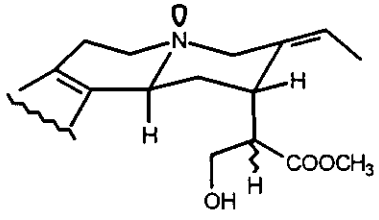



Figure 23. Compounds (**19**) and (**20**) in conformation *a* with ring D in chair conformation.

In conformation *c* with the D ring in chair conformation the C-15 substituent would be equatorial and there would be a strong interaction with the C-20 *E*-ethylidene side chain (Figure 24). Although an equatorial C-15 substituent would be energetically more favorable than an axial one, the loss of stability due interaction with the C-20 *E*-ethylidene side chain makes it a poorer choice.

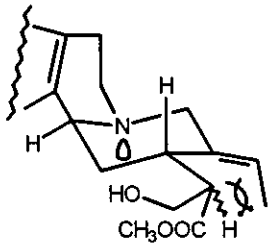



Figure 24. Compounds (**19**) and (**20**) in conformation *c* with ring D in chair conformation.

The strong interaction between the C-15 substituent and the 20-*E*-ethylidene side chain when the D ring of compounds (**19**) and (**20**) is in chair conformation could, one might think, be avoided if the D ring adopted not the chair but a boat conformation, which could be stabilized by intramolecular hydrogen bonding (Figure 25). The experimental data do not, however, show any appreciable contribution of conformation *c* to the conformational equilibrium.

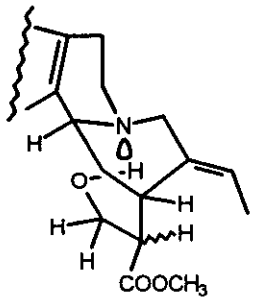



Figure 25. Compounds (**19**) and (**20**) in conformation *c* with ring D in twist-boat conformation.

**Geissoschizines**

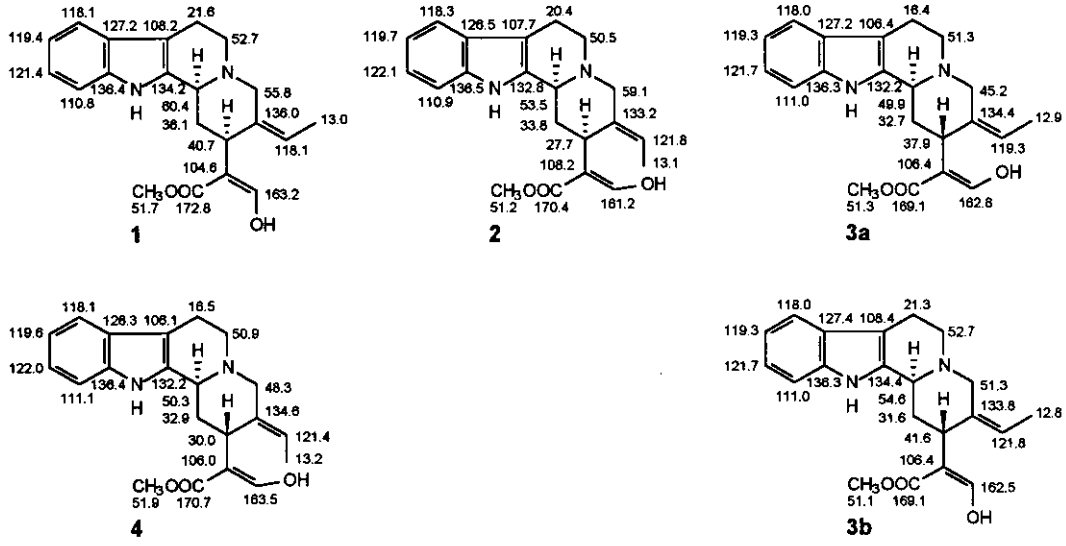



Figure 26. $^{13}C$ NMR shift values of compounds (**1** - **4**).

*Z*-Geissoschizine (**1**)

Compound (**1**)[15,17,23] exists nearly totally in conformation *a* (C-6 δ 21.6 ppm) with the D ring in chair conformation and the C-15 substituent in an equatorial position (Figure 27). There is practically no interaction between the C-15 substituent and the C-20 *Z*-ethylidene side chain.

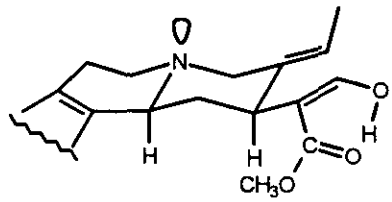


Figure 27. Compound (**1**) in conformation *a* with ring D in chair conformation.

*E*-Geissoschizine (**2**)[8]

Compound (**2**) has long been the subject of debate.[9-12] If compound (**2**) were in conformation *a* with the D ring in chair conformation, there would be a strong interaction between the C-15 substituent and the C-20 *E*-ethylidene side chain (Figure 28).

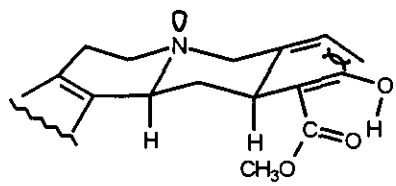


Figure 28. Compound (**2**) in conformation *a* with ring D in chair conformation.

If compound (**2**) were in conformation *c*, it could avoid interaction between the C-15 substituent and the C-20 *E*-ethylidene side chain, but, in contrast to the isositsirikines (**15**) and (**16**) (*vide supra*), there then would be a relatively strong interaction between the C-15 substituent and the indolic part of the molecule. Release of this, would be provided if the D ring existed, not in chair but in twist-boat conformation. However, this would recreate the energetically unfavorable interaction between the C-15 substituent and the C-20 *E*-ethylidene side chain (Figure 29).

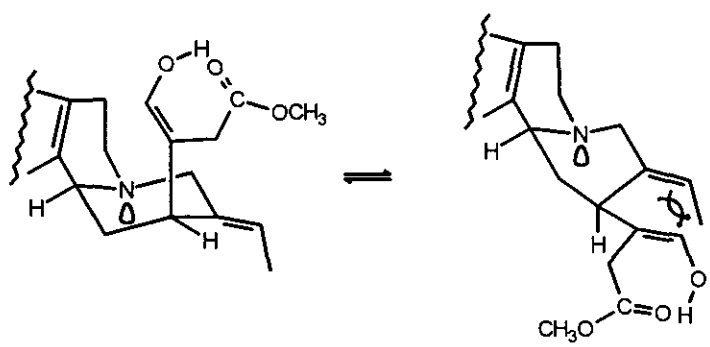


Figure 29. Compound (**2**) in conformation *c* with ring D in chair and twist-boat conformation.

In fact, as shown by Sakai and his group,[12] the least unfavorable situation for compound (**2**) is when it

exists preponderantly in conformation *a* with the D ring in twist-boat conformation (C-6 value δ 20.4 ppm). The C-15 substituent is then in a flagpole position,[42] which permits a stabilizing intramolecular hydrogen bonding between the acidic enol hydroxyl and $N_b$. This, in turn, releases the interaction between the C-15 substituent and the C-20 *E*-ethylidene side chain (Figure 30). Evidently, then, in its conformational preference the molecule is behaving in accordance with Socrates' precept to choose the lesser evil (*Cf.* Ref. 43).

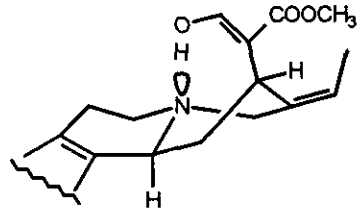
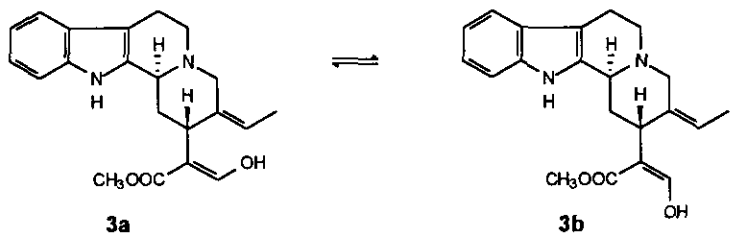



Figure 30. Compound (**2**) in conformation *a* with ring D in twist-boat conformation.

15-Epi-*Z*-geissoschizine (**3**)[13]

Compound (**3**)[15] exists in several tautomeric forms, of which **3a** and **3b** are predominant (Scheme 2).[15,44] Both **3a** and **3b** are in a conformational equilibrium of their own.




Scheme 2. Predominant tautomeric forms (**3a**) and (**3b**) of compound (**3**).

Tautomer (**3a**) exists nearly totally in conformation *c* (C-6 δ 16.5 ppm) with the D ring in twist-boat conformation (Figure 31).[45] The C-15 substituent is in a flagpole position,[42] which permits stabilizing intramolecular hydrogen bonding between the acidic enol hydroxyl and $N_b$. There is no interaction between the C-15 substituent and the C-20 *Z*-ethylidene side chain.

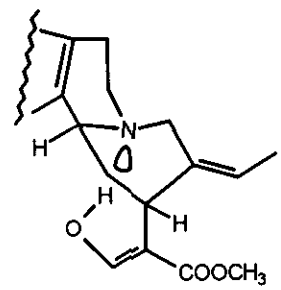



Figure 31. Tautomer (**3a**) in conformation *c* with ring D in twist-boat conformation.

Tautomer (**3b**) exists in conformation *a* (C-6 δ 21.4 ppm) and the D ring in chair conformation.[45] The C-15 substituent is in an axial position (Figure 32).

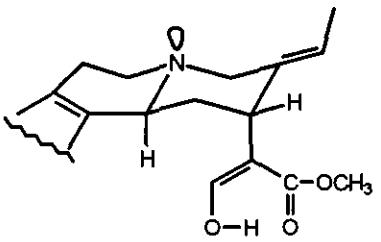



Figure 32. Tautomer (**3b**) in conformation *a* with ring D in chair conformation.

15-Epi-*E*-geissoschizine (**4**)[13]

Compound (**4**)[15,22,34,36] exists almost totally in conformation *c* (C-6 δ 16.5 ppm) with the D ring in twist-boat conformation (Figure 33). The C-15 substituent is in a flagpole position,[42] wich permits stabilizing intramolecular hydrogen bonding between the acidic enol hydroxyl and $N_b$. There is no interaction between the C-15 substituent and the C-20 *E*-ethylidene side chain.

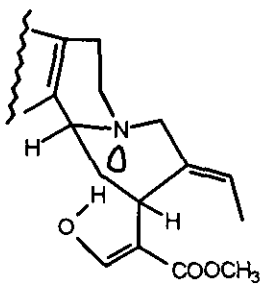



Figure 33. Compound (**4**) in conformation *c* with ring D in twist-boat conformation.

**Geissoschizine methyl ethers**

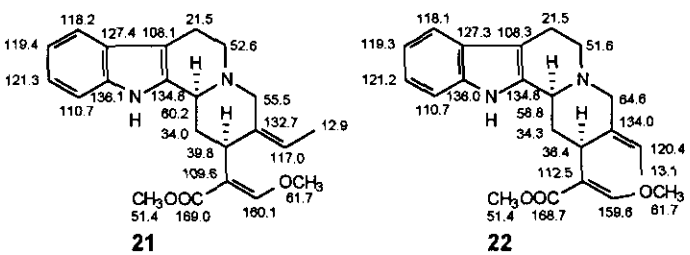



Figure 34. $^{13}C$ NMR shift values of compounds (**21**) and (**22**).

*Z*-Geissoschizine methyl ether (**21**)

Compound (**21**)[23] exists nearly totally in conformation *a* (C-6 δ 21.5 ppm) with the D ring in chair conformation. The C-15 substituent is in equatorial position (Figure 35). Interaction between the C-15 substituent and the C-20 *Z*-ethylidene side chain is weak if any.

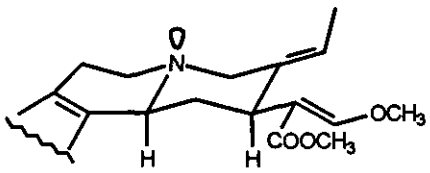



Figure 35. Compound (**21**) in conformation *a* with ring D in chair conformation.

*E*-Geissoschizine methyl ether (**22**)[8]

The case of *E*-geissoschizine methyl ether (**22**)[10,12] is puzzling. If compound (**22**) were in conformation *a* and ring D in chair conformation, the C-15 substituent would be in equatorial position and there would be a strong interaction with the C-20 *E*-ethylidene side chain (Figure 36). A strong contribution of conformation *c* would accordingly be expected.

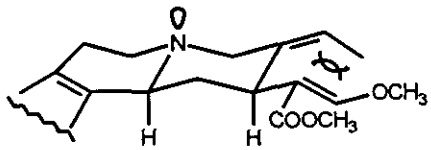



Figure 36. Compound (**22**) in conformation *a* with ring D in chair conformation.

In conformation *c* (Figure 37), compound (**22**) could avoid interaction between the C-15 substituent and the C-20 *E*-ethylidene side chain, as do the corresponding 16,17-dihydro derivatives (**15**) and (**16**) (*vide supra*). In compound (**22**), however, conformation *c* appears to be energetically less favorable due to stronger interaction between the C-15 substituent and the indolic part of the molecule.

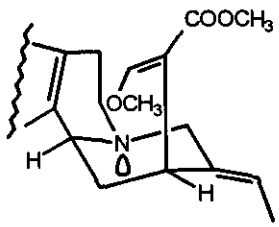



Figure 37. Compound (**22**) in conformation *c* with ring D in chair conformation.

According to the spectral data, compound (**22**) exists nearly totally in conformation *a* (C-6 value δ 21.5 ppm). To avoid the interaction between the C-15 substituent and the C-20 *E*-ethylidene side chain, ring D apparently adopts a twist-boat conformation (Figure 38). In contrast to *E*-geissoschizine (**2**), however, stabilization by intramolecular hydrogen bonding is not possible. Once again, then, the choice appears to be made for the lesser evil (*vide supra*).

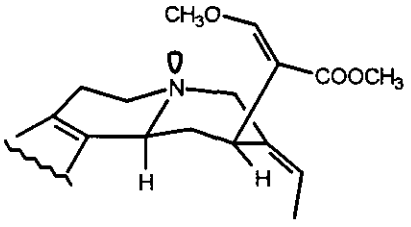



Figure 38. Compound (**22**) in conformation *a* with ring D in twist-boat conformation.

**15-Epi-geissoschizine acetates**[13]

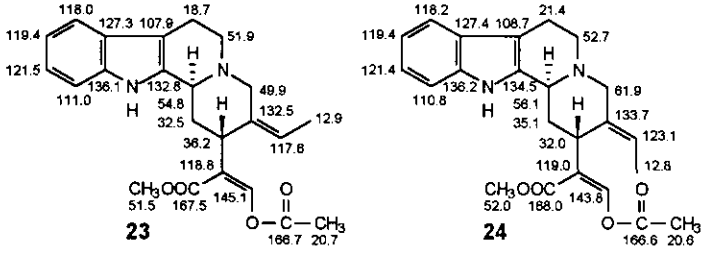



Figure 39. $^{13}C$ NMR shift values of compounds (**23**) and (**24**).

15-Epi-*Z*-geissoschizine acetate (**23**)[13]

Comparison of the shift value δ 18.7 ppm (C-6) for compound (**23**)[15] with the values δ 21.6 ppm and δ 16.8 ppm indicates that the contributions of conformers *a* and *c* to the conformational equilibrium (in $CDCl_3$ at rt) are about 40% and 60%, respectively. The C-15 substituent is axial in conformation *a* and equatorial in conformation *c* (Figure 40). In both cases there is practically no interaction between the C-15 substituent and the C-20 *Z*-ethylidene side chain. In contrast to the 15-epi-*Z*-geissoschizine (**3**), in compound (**23**) there is no possibility for either to tautomery or intramolecular hydrogen bonding stabilization.

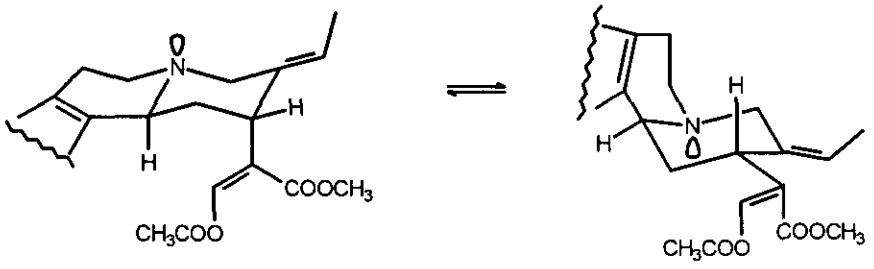



Figure 40. Equilibrium between conformations *a* and *c* of compound (**23**).

15-Epi-*E*-geissoschizine acetate (**24**)[13]

Compound (**24**)[15] exists in conformation *a* (C-6 δ 21.4 ppm) and ring D in chair conformation. The C-15 substituent is in an axial position (Figure 41). There is almost no interaction between the C-15 substituent and the C-20 *E*-ethylidene side chain.

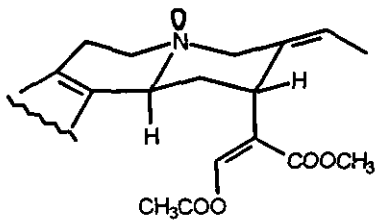



Figure 41. Compound (**24**) in conformation *a* with ring D in chair conformation.

In conformation *c* the C-15 substituent would be equatorial and in strong interaction with the C-20 *E*-ethylidene side chain (Figure 42).

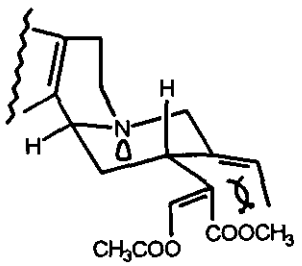



Figure 42. Compound (**24**) in conformation *c* with ring D in chair conformation.

As there is no hydroxyl group present in compound (**24**), stabilizing intramolecular hydrogen bonding is not possible (Figure 43). This is in contrast to the situation in 15-epi-*E*-geissoschizine (**4**) and strengthens the argument for the existence of compound (**4**) in conformation *c*.

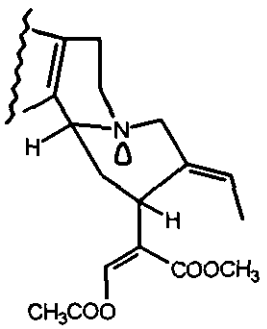



Figure 43. Compound (**24**) in conformation *c* with ring D in twist-boat conformation.

## SUMMARY

A general reasoning concerning the conformational behaviour of geissoschizine isomers (**1** - **4**) and their model compounds (**5** - **24**) is presented.

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13. In order to make uniform and clarify the conformational presentation of compounds C(3)Hα-C(15)Hα and C(3)Hβ-C(15)Hα compounds, we present the latter compounds (*trans* relationship) as

C(3)Hα-C(15)Hβ compounds, even though in most naturally occurring examples C(15)H is α.

14. For brevity, usually only the $^{13}C$ NMR shift value of C-6 (the most characteristic one for the conformational examination of compounds of the present type) is mentioned in the text. Other shift values are given in the formulae. Readers interested in details are referred to the original papers mentioned in the text.
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37. Preparation of *E*-geissoschizol (**10**): LAH (17.0 mg, 0.448 mmol, 6.7 equiv.) was added to a cold solution of compound (**6**)[19] (21.6 mg, 0.067 mmol) in THF (5 mL). The mixture was stirred for 1 h at rt after which LAH (27.1 mg, 0.714 mmol, 10.7 equiv.) was added and stirring was continued for 2 h (Ar atm). $H_2O$ was added, the solution was extracted with $CH_2Cl_2$, dried with $Na_2SO_4$, and the crude product was purified by flash chromatography (silica gel, $CH_2Cl_2$:$CH_3OH$ 90:10) to give compound (**10**) (6.1 mg, 31%). Amorphous. $^1$H-NMR ($CDCl_3$): δ 1.63 (3H, d, J = 7 Hz, H-18), 4.29 (1H, br s, H-3), 5.54 (1H, q, J = 7 Hz, H-19), 7.06-7.22 (2H, m, H-10, H-11), 7.36 (1H, d, J = 7 Hz, H-12), 7.46 (1H, d, J = 7 Hz, H-9), 8.76 (1H, br s, NH). Ms: 296 ($M^+$), 295, 170 (100 %), 169. HRms: Calcd for $C_{19}H_{24}N_2O$: 296.1890. Found: 296.1912.

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39. Preparation of 15-epi-*E*-geissoschizol (**12**): LAH (141.9 mg, 3.74 mmol, 11.7 equiv.) was added to a cold solution of compound (**8**)[26] (103.7 mg, 0.32 mmol) in THF (10 mL). The mixture was stirred for 1 h at rt after which LAH (132.5 mg, 3.49 mmol, 10.9 equiv.) was added and stirring was continued for 2 h (Ar atm). $H_2O$ was added, the solution was extracted with $CH_2Cl_2$, dried with $Na_2SO_4$, and the crude product was purified by flash chromatography (silica gel, $CH_2Cl_2$:$CH_3OH$ 98:2) to give compound (**12**) (77.8 mg, 82%). Amorphous. $^1$H-NMR ($CDCl_3$): δ 1.64 (3H, d, J = 7 Hz, H-18), 5.52 (1H, q, J = 7 Hz, H-19), 7.06-7.20 (2H, m, H-10, H-11), 7.32 (1H, d, J = 7 Hz, H-12), 7.46 (1H, d, J = 7 Hz, H-9), 7.90 (1H, br s, NH). Ms: 296 ($M^+$), 295 (100 %), 251, 170, 169. HRms: Calcd for $C_{19}H_{24}N_2O$: 296.1890. Found: 296.1906.

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44. Contrary to our earlier results[15] the $^{13}$C NMR data actually point to the preponderance of a chair conformation for ring D.

45. The tentative shift values for **3a** and **3b**, taken from the spectrum of the tautomeric mixture of 15-epi-*Z*-geissoschizine (**3**), were mainly assigned by using the spectra of compounds (**4**) and (**1**), respectively, as models.

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