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Claisen Orthoester Rearrangement in the Direct Preparation of Z-Isositsirikine and Z-Geissoschizine Derivatives Possessing the Right Oxidation State at C-17

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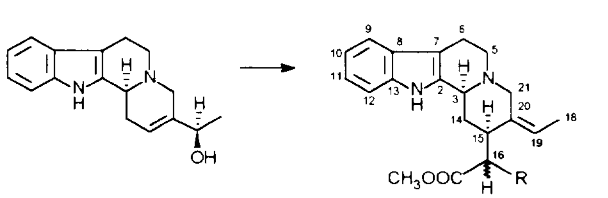
Abstract: The Claisen orthoester rearrangement utilizing allylic alcohol **1** (or **2**) and trimethyl 3-methoxyorthopropionate **13a** leads to *Z*-isositsirikine derivatives **21a-22a** (or **23a-24a**) possessing one RO-function at C-17. In the cases of trialkyl 3,3-dialkoxyorthopropionates [triethyl 3,3-diethoxyorthopropionate **14b** (or 3,3-diethoxymethylketene diethylacetal **20b**) and trimethyl 3,3-dimethoxyorthopropionate **14a** (or 3,3-dimethoxymethylketene dimethylacetal **20a**)], the intermediate ketene acetals **25a,b** do not rearrange according to the Claisen mechanism to form compounds **26a,b** and/or **27a,b** possessing two RO-functions at C-17. Syntheses of the intermediate orthoesters, trimethyl 3-methoxyorthopropionate **13a**, trimethyl 3,3-dimethoxyorthopropionate **14a**, trimethyl *trans*-3-methoxyorthoacrylate **20c**, and triethyl 3,3-diethoxyorthopropionate **14b** are described.

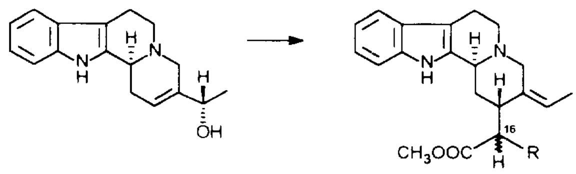
The Claisen rearrangement[1-3] provides a versatile synthetic method for the preparation of carbon-carbon bonds. Recently we described the stereoselective preparation of *Z*-isositsirikine derivatives **3a** and **4a**[4] from allylic alcohols **1** and **2**.[5] Replacing trimethyl orthoacetate with trimethyl orthopropionate and trimethyl orthobutyrate permitted us to prepare compounds **5a-12a** (Schemes 1 and 2).[6]



1

3a R=H
5a R=CH_3, C-16-H β
7a R=CH_3, C-16-H α
9a R=CH_3CH_2, C-16-H β
11a R=CH_3CH_2, C-16-H α

Scheme 1.



2

4a R=H
6a R=CH_3, C-16-H β
8a R=CH_3, C-16-H α
10a R=CH_3CH_2, C-16-H β
12a R=CH_3CH_2, C-16-H α

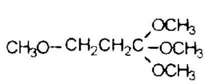
Scheme 2.

Although compounds **3a**-**12a** are relatively good model compounds for isositsirikine isomers, the presence of one or two functional groups at C-17 was desirable. One feasible way of achieving this would be to utilize, in the Claisen rearrangement, orthoesters possessing one or two RO-functions at the β-position and which would lead directly to *Z*-isositsirikine and *Z*-geissoschizine derivatives possessing one or two RO-functions (corresponding to alcohol and aldehyde oxidation states, respectively) at C-17. Another possibility would be to use allylic alcohols **1** and **2** with propiolic acid esters to obtain the corresponding vinyl allyl ethers, which then would rearrange according to the Claisen mechanism.[7,8] Reduction of the resulting aldehyde function with $NaBH_4$ or its reaction with trialkyl orthoformate (*vide infra*) or other similar compound would permit access to compounds possessing one and two functional groups, respectively, at C-17.

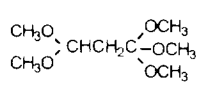
The present paper reports our results concerning the applicability of the Claisen orthoester rearrangement in the preparation of *Z*-isositsirikine and *Z*-geissoschizine derivatives possessing one or two RO-functions at C-17. Also described is the preparation of *Z*-geissoschizine derivatives possessing two RO-functions at C-17 from appropriate vinyl allyl ethers, achieved *via* the normal Claisen rearrangement and subsequent triethyl orthoformate treatment.

RESULTS AND DISCUSSION

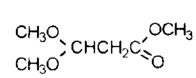
As orthoesters to be examined we chose trimethyl 3-methoxyorthopropionate **13a** and trimethyl 3,3-dimethoxyorthopropionate **14a**.



13a

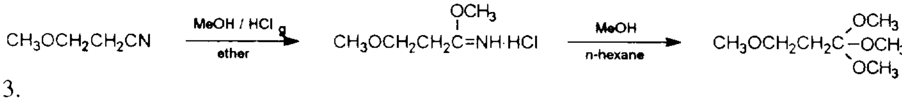


14a



14c

Compound **13a** was easily prepared from the commercially available 3-methoxypropionitrile[9] by the "Pinner method" (Scheme 3).[10,11]

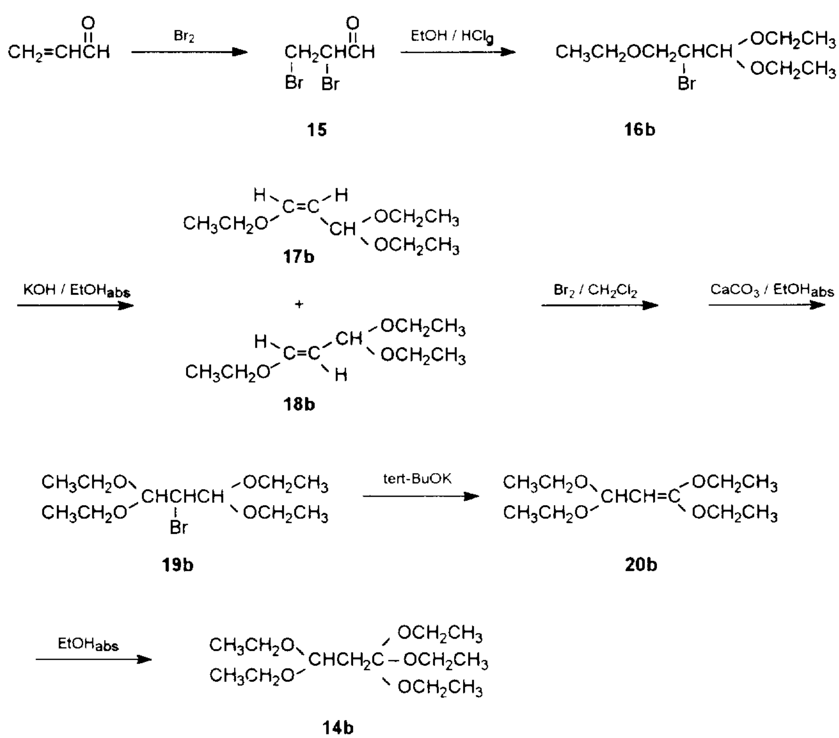


Scheme 3.

13a

As expected, application of the "Pinner method" to 3,3-dimethoxypropionitrile[12], possessing two 3-substituents, was less successful leading only to methyl 3,3-dimethoxypropionate **14c.** This route was therefore abandoned and an alternative method for the preparation of compound **14a** sought.

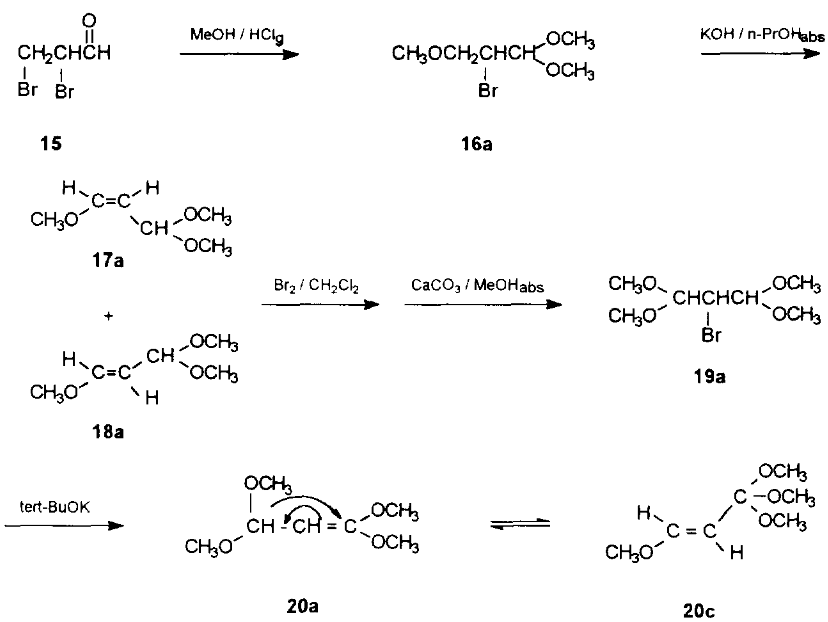
According to the literature, the corresponding ethyl derivative, triethyl 3,3-diethoxyorthopropionate **14b**, can be prepared *via* the corresponding ketene acetal (*vide infra*).[13] Before applying this "ketene acetal method" to the preparation of trimethyl 3,3-dimethoxyorthopropionate **14a**, however, we decided first to confirm it in the preparation of the ethyl derivative, **14b**, at the same time identifying the intermediates by modern analytical methods. Treatment of acrolein with molecular bromine afforded 2,3-dibromopropionaldehyde **15**, which was transformed to 2-bromo-3-ethoxypropionaldehyde diethylacetal **16b** with EtOH/HCl_g. Refluxing compound **16b** in EtOH with KOH led to a mixture of 3-ethoxy-*cis*- and 3-ethoxy-*trans*-acrolein diethylacetals **17b** and **18b**. Treatment of the mixture of compounds **17b** and **18b** in CH_2Cl_2 with molecular bromine, and then with $CaCO_3$ in EtOH, yielded bromomalonaldehyde tetraethylacetal **19b**, which was transformed to 3,3-diethoxymethylketene diethylacetal **20b** by potassium *tert*-butoxide. Finally, compound **20b** was transformed with abs. EtOH, containing traces of HCl_g, to triethyl 3,3-diethoxyorthopropionate **14b** (Scheme 4).



Scheme 4.

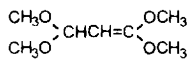
Our success in the preparation of triethyl 3,3-diethoxyorthopropionate **14b** encouraged us to apply the "ketene acetal method" (*vide supra)* to the preparation of the methyl derivative **14a**. This time 2,3-dibromopropionaldehyde **15** was transformed to 2-bromo-3-methoxypropionaldehyde dimethylacetal **16a** with

$MeOH/HCl_g$. Refluxing compound **16a** in propanol (which turned out to be better than MeOH) with KOH led to a mixture of 3-methoxy-*cis*- and 3-methoxy-*trans*-acrolein dimethylacetals **17a** and **18a**, although in lower yield (*cf.* Experimental) than for the ethyl derivative. Treatment of the mixture of compounds **17a** and **18a** in CH_2Cl_2 with molecular bromine, followed by $CaCO_3$ in MeOH, afforded bromomalonaldehyde tetramethylacetal **19a**, which was treated with potassium *tert*-butoxide in order to transform it to 3,3-dimethoxymethylketene dimethylacetal **20a**. However, under the reaction conditions used compound **20a** rearranged to trimethyl *trans*-3-methoxyorthoacrylate **20c**, and only small amounts of **20a** were detected by nmr (*cf.* Experimental)(Scheme 5).

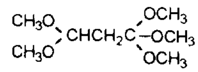


Scheme 5.

Reaction of trimethyl *trans*-3-methoxyorthoacrylate **20c** with trimethyl orthoformate in the presence of *p*-toluenesulfonic acid did not yield trimethyl 3,3-dimethoxyorthopropionate **14a** but led instead to methyl 3,3-dimethoxypropionate **14c**. Fortunately, treatment of compound **20c** with dry methanol containing traces of dry HCl gas provided access to a ≈ 4/6 mixture of 3,3-dimethoxymethylketene dimethylacetal **20a** and trimethyl 3,3-dimethoxyorthopropionate **14a**. When the separation of compounds **20a** and **14a** turned out to be uneconomical, we proceeded to use this 4/6 mixture as such in our experiments concerning the orthoester Claisen rearrangement.

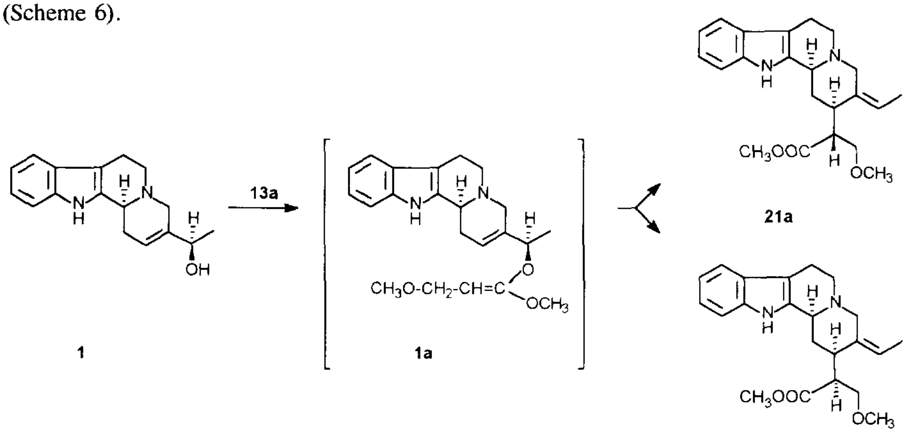


20a



14a

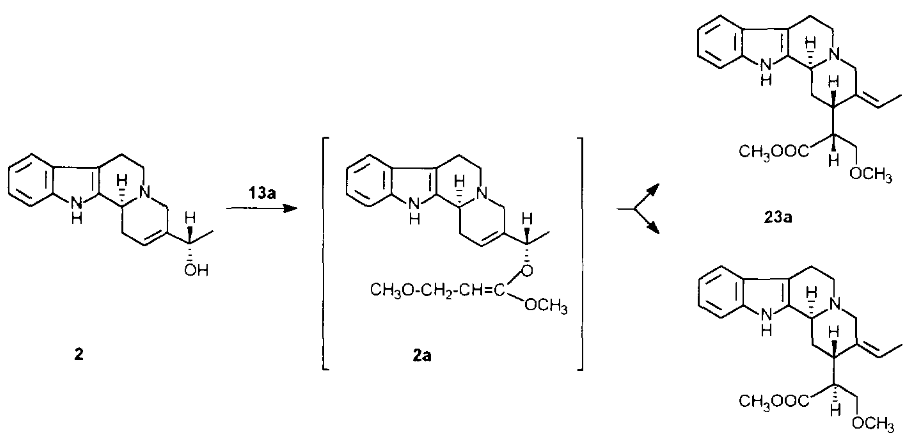
We began our Claisen orthoester rearrangement experiments with allylic alcohol **1** and trimethyl 3-methoxyorthopropionate **13a**. Heating the mixture of compounds **1** and **13a** in dry dioxane led, *via* vinyl allyl ether (= ketene acetal) **1a** (*Z*- and *E*-isomers), to a mixture of (*R**)- and (*S**)-*O*-methyl-*Z*-isositsirikines **21a** and **22a** (Scheme 6).



22a

Scheme 6.

Similarly, treatment of allylic alcohol **2** with trimethyl 3-methoxyorthopropionate **13a** afforded, *via* vinyl allyl ether (= ketene acetal) **2a** (*Z*- and *E*-isomers), a mixture of (16*R**)- and (16*S**)-*O*-methyl-15-epi-*Z*-isositsirikines [= (16*S**)- and (16*R**)-*O*-methyl-3-epi-*Z*-isositsirikines][14] **23a** and **24a** (Scheme 7).

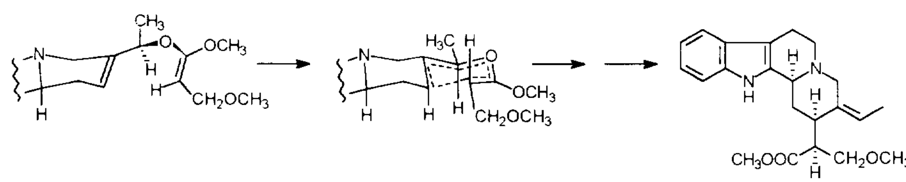


24a

Scheme 7.

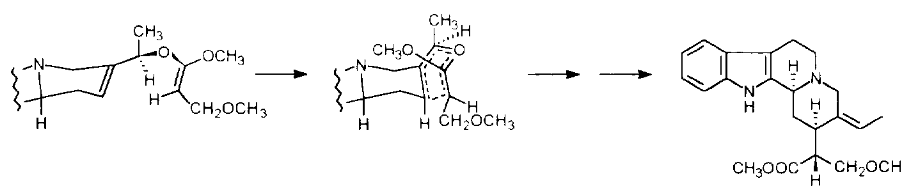
Although the Claisen rearrangement generally prefers a chair-like transition state, steric reasons may force the molecule to adopt a boat-like transition state if the reaction is to take place. It is generally assumed that the latter is higher in energy than the former.[15]

For ketene acetal **1a**-***E*** (***E,E*** isomer[3]), one can predict transition states *a* and *b*.[16] Of these, the chair-like transition state *a*, which is strongly favoured (equatorial CH_3OCH_2 group), leads to compound **22a**[17] (Scheme 8). The less favoured boat-like transition state *b* leads to compound **21a**[17] (Scheme 9). For ketene asetal **1a**-***Z***



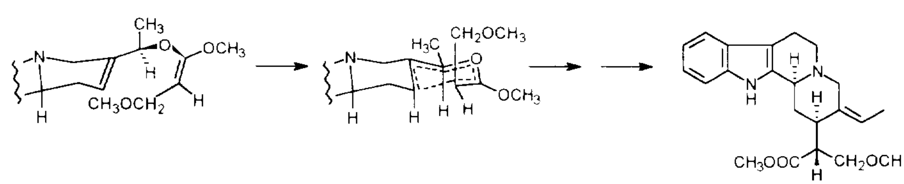
1a - *E* *a* **22a**

Scheme 8.



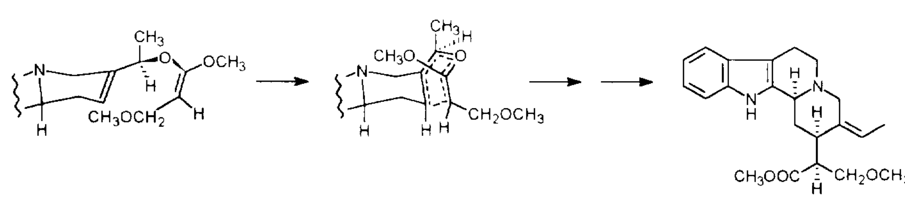
1a - *E* *b* **21a**

Scheme 9.



1a - *Z* *a'* **21a**

Scheme 10.

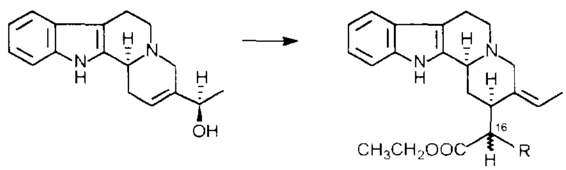


1a - *Z* *b'* **22a**

Scheme 11.

(***E,Z*** isomer[3]), transition states *a'* and *b'* can be predicted.[16] Of these, the chair-like transition state *a'*, which is strongly unfavoured for steric reasons, should lead, if present in any appreciable amount, to compound **21a**[17] (Scheme 10). The boat-like transition state *b'*, which is sterically less unfavoured, leads to compound **22a**[17] (Scheme 11). All this means that the formation of compound **22a** should be favoured over that of compound **21a**. Similar reasoning can be presented in favour of compound **23a** over compound **24a**. Our results (*cf.* Experimental) are in agreement with these conclusions.

In order to have "appropriate" model compounds in the ethyl ester series we next prepared the ethyl analogues **3b**, **5b** and **7b** of dehydroxymethyl-Z-isositsirikine **3a**, (16*R**)-17-deoxy-Z-isositsirikine **5a** and (16*S**)-17-deoxy-Z-isositsirikine **7a**, by Claisen orthoester method utilizing allylic alcohol **1** and commercially available triethyl orthoacetate[18] and triethyl orthopropionate[19] (Scheme 12).

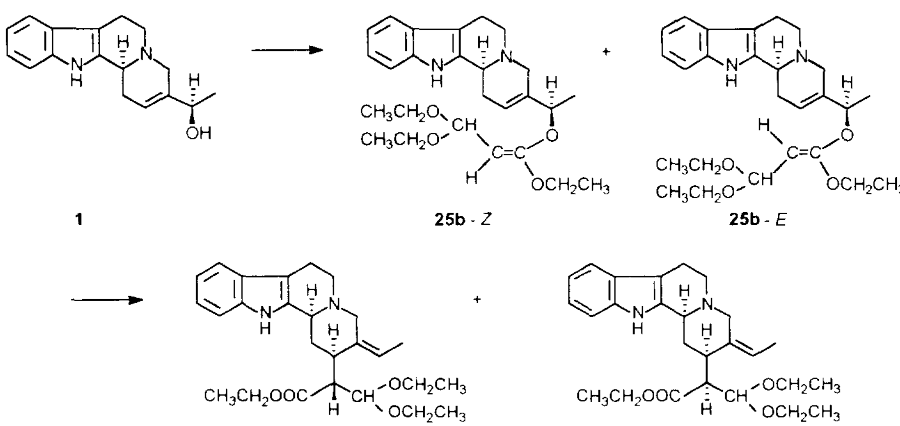


1

3b R=H
5b R=CH_3, C-16-H β
7b R=CH_3, C-16-H α

Scheme 12.

We continued our Claisen orthoester rearrangement experiments with allylic alcohol **1** and triethyl 3,3-diethoxyorthopropionate **14b**. Heating of compounds **1** and **14b** in dry dioxane, in the presence of traces of acetic acid, was expected to produce, *via* compound **25b** (*Z*- and *E*-isomers), a mixture of ethyl analogues of (16*R**)- and (16*S**)-*Z*-geissoschizine diethylacetals **26b** and **27b** (Scheme 13). However, purification of the



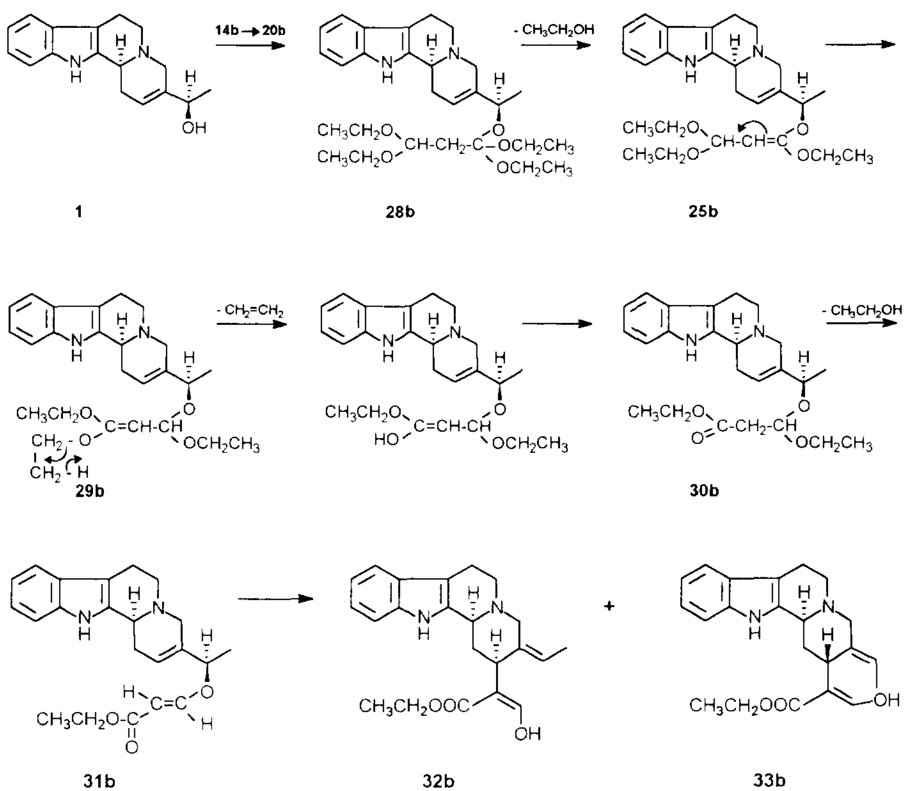
1 **25b** - *Z* **25b** - *E*

26b **27b**

Scheme 13.

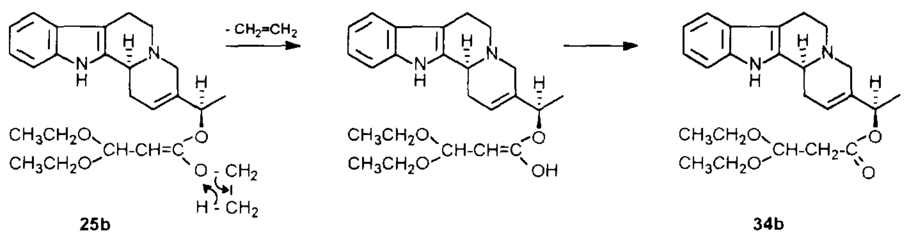
complex reaction mixture, followed by careful separations, permitted the isolation and identification only of compounds **1**, **25b** and/or **29b** (tentatively identified), **30b**, **31b**, **32b**, **33b**, **34b**, and **35b**. The resulting reaction mixture did not contain the desired compounds **26b** and **27b** (*vide infra*).

The formation of compounds **25b**, **29b**, **30b**, **31b**, **32b** and **33b** can be rationalized as presented in Scheme 14. Orthoester **14b** is transformed to the corresponding ketene acetal **20b** (*vide infra*), which reacts with allylic alcohol **1** to form mixed orthoester **28b**. This is then transformed, through loss of ethanol to mixed ketene acetal **25b** (*Z- and E*-isomers). The ketene acetal **25b** does not rearrange according to the Claisen mechanism but isomerizes to the new ketene acetal **29b**. Loss of ethylene, followed by tautomerization, yields compound **30b**. Cleavage of ethanol leads to compound **31b**, which was isolated from the reaction mixture and identified. Finally, the Claisen rearrangement of compound **31b** affords compounds **32b** and **33b**.

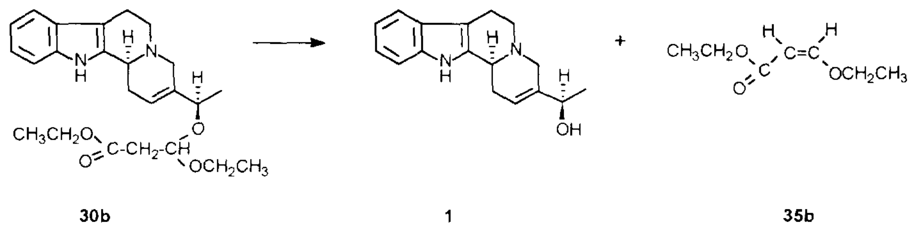


Scheme 14.

The formation of compound **34b** can be explained by the loss of ethylene from ketene acetal **25b** (*Z*- and *E*-isomers)(Scheme 15), and the formation of compounds **1** and **35b** by cleavage of allylic alcohol **1** from compound **30b** (Scheme 16).

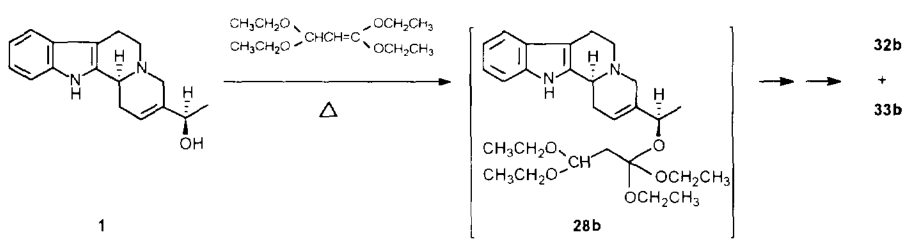


Scheme 15.



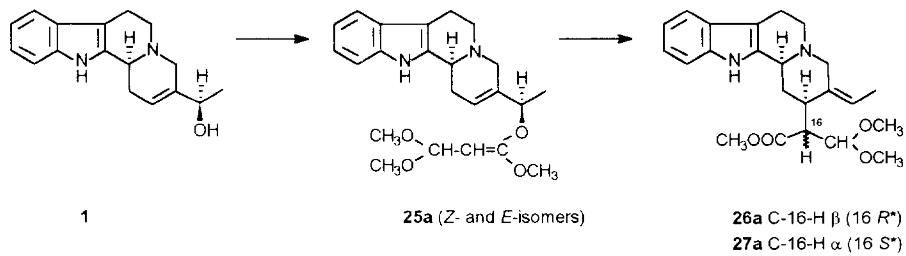
Scheme 16.

The intermediate orthoester **28b**, and thereafter compounds **32b** and **33b** (*vide supra*), would also be expected to form with 3,3-diethoxymethylketene diethylacetal **20b** and allylic alcohol **1** used as starting materials in the reaction (Scheme 17).[22] To test this, compounds **1** and **20b** were heated in toluene (Experimental). The results were essentially the same as for compounds **1** and **14b** (Scheme 14).



Scheme 17.

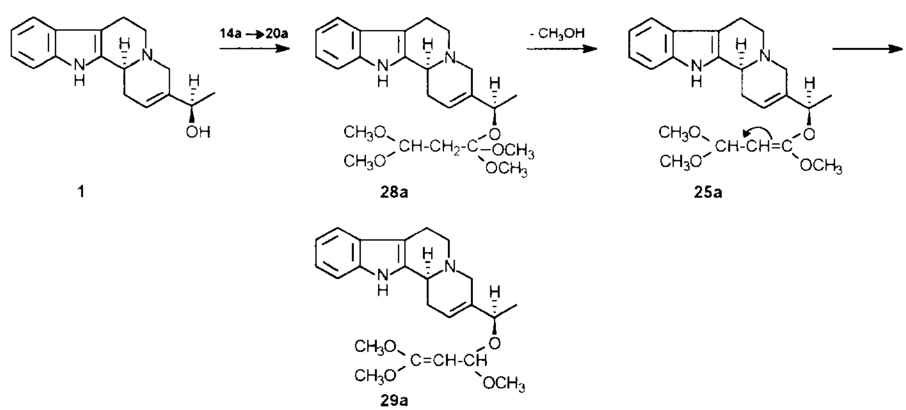
We next became interested in the Claisen orthoester rearrangement in the methyl series, utilizing allylic alcohol **1** and the 6/4 mixture (*vide supra*) of trimethyl 3,3-dimethoxyorthopropionate **14a** and 3,3-dimethoxymethylketene dimethylacetal **20a**. The Claisen orthoester rearrangement, were it to take place, would produce, *via* compound **25a** (*Z*- and *E*-isomers), a mixture of (16*R**)- and (16*S**)-*Z*-geissoschizine dimethylacetals **26a** and **27a** (Scheme 18).



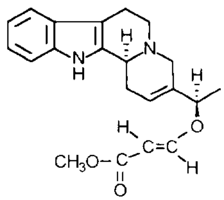
Scheme 18.

Although our results in the ethyl series (*vide supra*) had cast some doubt on the possible success in the direct Claisen rearrangement, we decided to attempt the reaction. Compound **1** and the 6/4 mixture of trimethyl 3,3-dimethoxyorthopropionate **14a** and 3,3-dimethoxymethylketene dimethylacetal **20a** in dry dioxane were heated in the presence of traces of acetic acid. Purification of the reaction mixture, followed by separations, permitted the isolation and identification only of compounds **1** (starting material), **25a** and/or **29a** (tentatively identified) and **34a.** As in the ethyl series, the resulting reaction mixture did not contain the desired compounds **26a** and **27a** (*vide infra*).

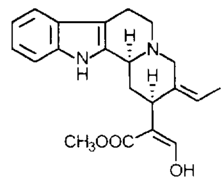
In analogy with the ethyl series, the formation of compounds **25a**, **29a**, **30a** (not isolated), and **34a**, can be rationalized as presented in Schemes 19 and 20. Orthoester **14a** is transformed to the corresponding ketene acetal (already present in the 6/4 mixture), and this reacts with the allylic alcohol **1** to form mixed orthoester **28a**. This is then transformed, through loss of methanol, to mixed ketene acetal **25a** (*Z*- and *E*-isomers). Again by analogy with the ethyl series, the ketene acetal **25a** does not rearrange according to the Claisen mechanism but can isomerize to the new ketene acetal **29a** (Scheme 19). Since the transformation of **29a** to **30a** by a mechanism similar to that operating in the ethyl series (**29b** → **30a**; loss of ethylene) is not possible, compounds **31a**, **32a,** and **33a** are not formed.



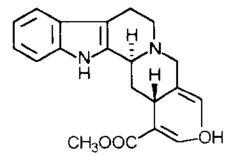
Scheme 19.



31a

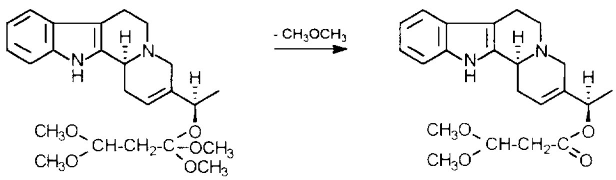


32a



33a

The presence of compound **34a,** formed in small amounts, can be explained by the loss of dimethylether from mixed orthoester **28a** (Scheme 20).



28a **34a**

Scheme 20.

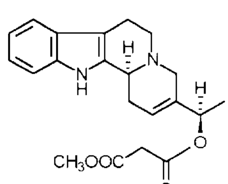
We next decided to replace the 6/4 mixture of trimethyl 3,3-dimethoxyorthopropionate **14a** and 3,3-dimethoxymethylketene dimethylacetal **20a** with trimethyl *trans*-3-methoxyorthoacrylate **20c**, which can be considered chemically equivalent to compound **20a** (Scheme 21).

20c **20a**

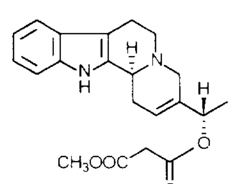
Scheme 21.

Compounds **1** and **20c** were heated in dioxane (*cf.* Experimental). The results were essentially the same as for the 6/4 mixture of compounds **14a** and **20a**, but the crude product that was obtained was cleaner.

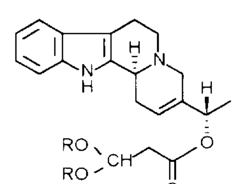
Treatment of the allylic alcohols **1** and **2** with methyl malonyl chloride[20] yielded compounds **36a** and **37a**, respectively. These were used as "model compounds" for compounds **34a,b** and their possible[21] epimers **38a,b** in the comparison of the nmr data (*vide infra*).



36a

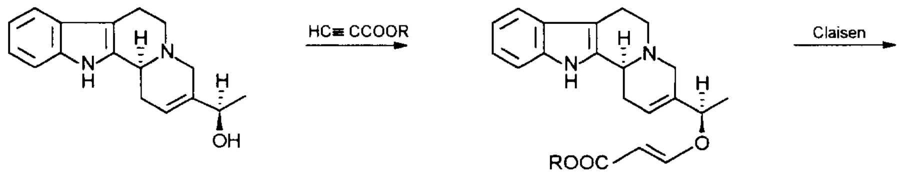


37a



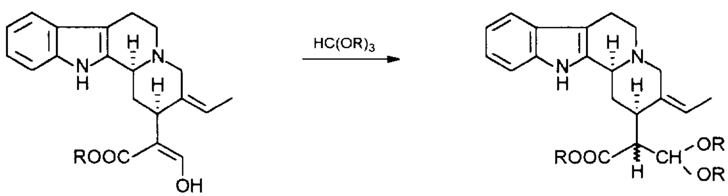
38a R= CH_3
38b R= CH_3CH_2

Finally, in order to be quite sure about the non-formation of compounds **26a,b** and **27a,b** [(16*R**)- and (16*S**)-*Z*-geissoschizine dialkylacetals] and/or their possible[21] epimers **39a,b** and **40a,b** [(16*R**)- and (16*S**)-3-epi-*Z*-geissoschizine dialkylacetals] in the above reactions, these compounds were prepared *via* compounds **31a,b** and **32a,b**, and **41a,b** and **42a,b**, respectively. The propiolic acid ester method (*vide supra*) was used, applying successively methyl or ethyl propiolate[23] treatment, Claisen rearrangement and trimethyl or triethyl



1

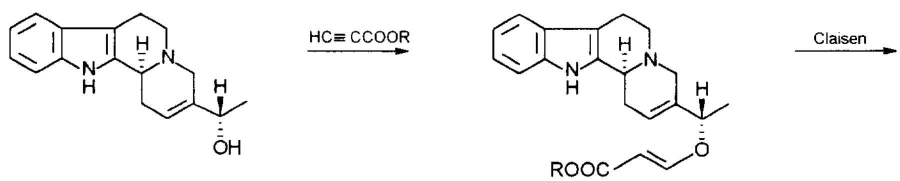
31a R= CH_3
31b R= CH_3CH_2



32a R= CH_3
32b R= CH_3CH_2

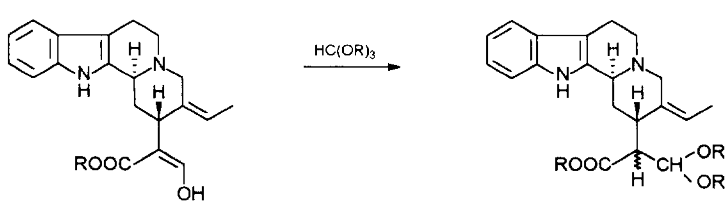
26a C-16-H β (16*R**), R= CH_3
27a C-16-H α (16*S**), R= CH_3
26b C-16-H β (16*R**), R= CH_3CH_2
27b C-16-H α (16*S**), R= CH_3CH_2

Scheme 22.



2

41a R= CH_3
41b R= CH_3CH_2



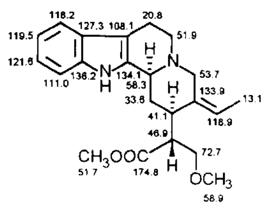
42a R= CH_3
42b R= CH_3CH_2

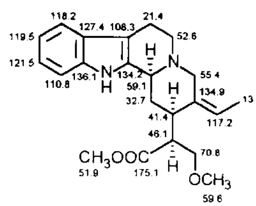
39a C-16-H β (16*R**), R= CH_3
40a C-16-H α (16*S**), R= CH_3
39b C-16-H β (16*R**), R= CH_3CH_2
40b C-16-H α (16*S**), R= CH_3CH_2

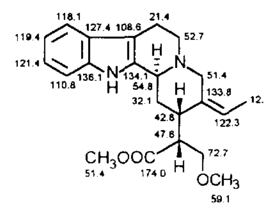
Scheme 23.

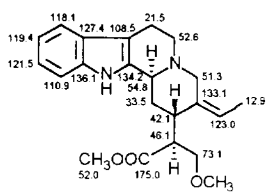
orthoformate treatment (Schemes 22 and 23). The spectral data, especially the ^{13}C-nmr data (*Cf.* Figure 1 and Experimental), confirmed that compounds **26a,b**, **27a,b**, **39a,b**, and **40a,b** were not among the products of reactions between allylic alcohol **1** and either trialkyl 3,3-dialkoxyorthopropionates **14a,b**, 3,3-dialkoxymethylketene dialkylacetal **20a,b** or trimethyl *trans*-3-methoxyorthoacrylate **20c**.

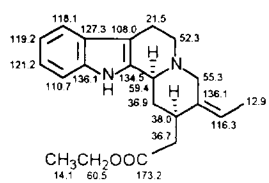
The ^{1}H- and ^{13}C-nmr data (Experimental and Figure 1), taking into account the conformational considerations relevant for indolo[2,3-*a*]quinolizidines in general,[24-26] provided clear evidence for the stereostructures depicted in the formulae. Comparison of the ^{1}H- and ^{13}C-nmr data of compounds **21a-24a** with those of the corresponding *Z*-isositsirikines (ref. 27, compounds **1**, **2**, **5** and **6**) permitted immediate choice of the C-16 configuration. A similar comparison permitted choice of the C-16 configuration in compounds **26a,b-27a,b** and **39a,b-40a,b**.

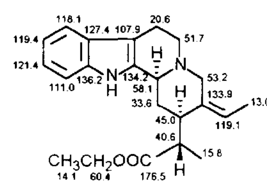

21a

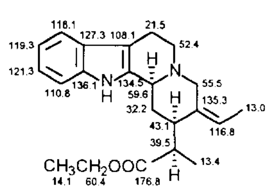

22a

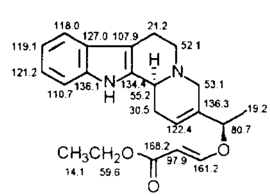

23a

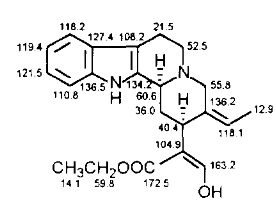

24a

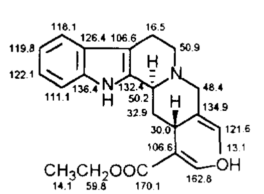

3b

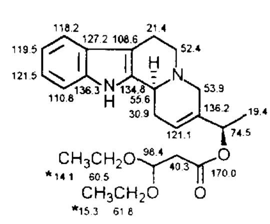

5b

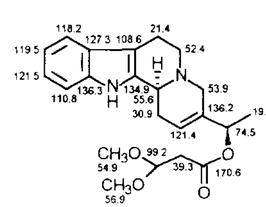

7b

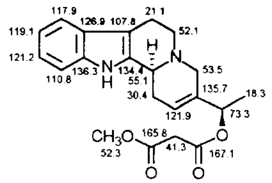

31b


32b

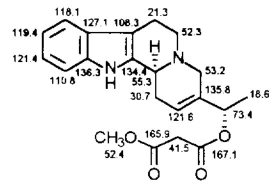

33b


34b

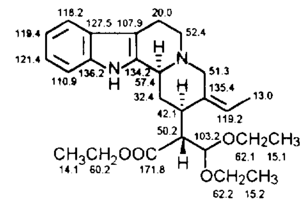

34a



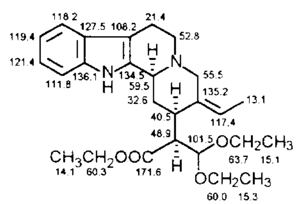
36a



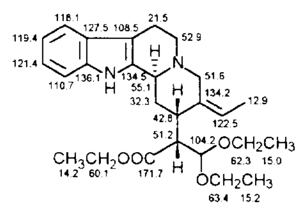
37a



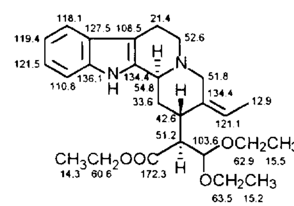
26b



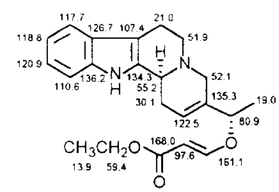
27b



39b



40b



41b

Figure 1. ^{13}C-nmr data.

CONCLUSIONS

Our results show that the Claisen orthoester rearrangement, using appropriate orthoesters, can successfully be applied to the direct preparation of *Z*-isositsirikine derivatives **21a**-**24a** possessing one RO-function at C-17. In the case of two RO-functions, however, the intermediate mixed ketene acetals **25a,b** are incapable of rearranging according to the Claisen mechanism and thus of leading directly to the *Z*-geissoschizine dialkylacetals **26a,b** and **27a,b.** The intermediate ketene acetals **25a,b** may isomerize to ketene acetals **29a,b**. Elimination and isomerization of compound **29b** leads to enol ether **31b**, which can then take part in another Claisen rearrangement leading to compounds **32b** and **33b**. Because an analogous elimination in the methyl series (compound **29a**) is not possible, the desired enol ether **31a**, and as a consequence *Z*-geissoschizine derivatives **32a** and **33a**, are not formed.

Syntheses were developed for the intermediate orthoesters, trimethyl 3-methoxyorthopropionate **13a**, trimethyl 3,3-dimethoxyorthopropionate **14a**, trimethyl *trans*-3-methoxyorthoacrylate **20c**, and triethyl 3,3-diethoxyorthopropionate **14b.** The desired *Z*-geissoschizine dialkylacetals **26a,b** and **27a,b**, and their C-15 epimers **39a,b** and **40a,b**, were prepared by a route utilizing allylic alcohols **1** and **2** and alkyl propiolates.

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}). ^1H-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 (^1H-nmr; δ_H=0.00 ppm) and $CDCl_3$ (^{13}C-nmr; δ_C=77.00 ppm). Signal assignments were confirmed by APT and DEPT experiments. Abbreviations s, d, t, q, m, def, and br are used to designate singlet, doublet, triplet, quartet, multiplet, deformed, and broad, respectively. Mass spectrometry (EIms and HRms) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of trimethyl 3-methoxyorthopropionate 13a by the "Pinner method".
Dry hydrogen chloride gas was passed into a cooled (0°C) solution of 22 ml (242.2 mmol) of 3-methoxypropionitrile[9] (dried over calcium chloride and distilled) and 10.3 ml of methanol in anhydrous ether (48.5 ml), until an increase in weight of 9.8 g (268.8 mmol) was obtained. This solution was stored at 10°C for 3 days, during which time a large amount of imidate hydrochloride crystallized from the solution. These crystals were filtered under argon, washed with ether and dried in vacuo to give 32.5 g methyl 3-methoxypropionimidate hydrochloride (212.3 mmol, 88%).
The imidate hydrochloride (32.2 g, 210.3 mmol) was suspended in dry hexane (46 ml), methanol (20.2 ml) was added and the mixture was stirred at room temperature for 3 days (Ar atm). Triethylamine (0.5 ml) was added, the mixture filtered, the hexane solution dried (K_2CO_3), the hexane removed in vacuo, and the residue distilled to give trimethyl 3-methoxyorthopropionate **13a**.
Compound **13a**. Y. 23.0 g (140.0 mmol, 67%). Oil. Bp. 45-46°C/2 mm. ^1H-Nmr: 2.10 [2H, t, J=7 Hz, -CH_2-*CH_2*-$C(OCH_3)_3$], 3.26 [9H, s, -CH_2-C(O*CH_3*)$_3$], 3.34 (3H, s, *CH_3*O-), 3.44 (2H, t, J=7 Hz, CH_3O*CH_2*-CH_2-). ^{13}C-Nmr: 30.4, 49.3 (3C), 58.6, 67.6, 114.6. Ms: 164 (M^+, <1%), 133 (100%), 105, 101. HRms: Found: 133.0864. Calcd for $C_6H_{13}O_3$ (= $C_7H_{16}O_4$ - CH_3O): 133.0865.

Attempt to prepare trimethyl 3,3-dimethoxyorthopropionate 14a by the "Pinner method". Formation of methyl 3,3-dimethoxypropionate 14c.
Dry hydrogen chloride gas was passed into a cooled (0°C) solution of 22 ml (196.1 mmol) of 3,3-dimethoxypropionitrile[12] (dried over calcium chloride and distilled) and 8.3 ml of methanol in anhydrous ether (40 ml), until an increase in weight of 7.7 g (210.2 mmol) was obtained. This solution was stored at 10°C for 3 days. Crystals were filtered under argon, washed with ether and dried in vacuo to give 14.4 g methyl 3,3-dimethoxypropionimidate hydrochloride (78.7 mmol, 40%).
The imidate hydrochloride (14.4 g, 78.7 mmol) was suspended in dry hexane (25 ml), methanol (13 ml) was added and the mixture was stirred at room temperature for 3 days (Ar atm). Triethylamine (0.5 ml) was added, the mixture filtered, the hexane solution dried (K_2CO_3), the hexane removed in vacuo, and the residue distilled to give methyl 3,3-dimethoxypropionate **14c**.
Compound **14c**. Y. 5.17 mg (18%). Oil. Bp. 40-40.5°C/2 mm. Ir: 1735 (C=O). ^1H-Nmr: 2.66 (2H, d, J=6 Hz, -CH-*CH_2*-C=O), 3.37 (6H, s, 2x*CH_3*O-), 3.71 (3H, s, *CH_3*O-), 4.84 [1H, t, J=6 Hz, -CH_2-*CH*$(OCH_3)_2$]. ^{13}C-Nmr: 38.6, 51.6, 53.4 (2C), 101.2, 170.3. Ms: 148 (M^+, <1%), 117, 75 (100%). HRms: Found: 117.0546. Calcd for $C_5H_9O_3$ (= $C_6H_{12}O_4$ - CH_3O): 117.0551.

Preparation of 2-bromo-3-ethoxypropionaldehyde diethylacetal 16b.
26.8 ml (0.4 mol) of freshly distilled acrolein was stirred rapidly and cooled to -5°C in an ice-salt bath. Bromine (20.4 ml, 0.4 mol) was added at a rate such that the temperature remained at 0-5°C, until a permanent red colour indicated a slight exess of bromine. Acidic ethanol (140 ml, containing 1 w-% of dry HCl gas) was added to the formed 2,3-dibromopropionaldehyde **15** and the solution was refluxed for 40 h (Ar atm). After cooling, water was added and the solution extracted with ether. The ether layer was stirred with NaOH (pH

10) for 0.5 h. After separating, the ether layer was washed with water and dried over anhydrous Na_2SO_4. Distillation through a Vigreux column gave 2-bromo-3-ethoxypropionaldehyde diethylacetal **16b**.
Compound **16b**. Y. 42.7 g (0.17 mol, 42%). Oil. Bp. 89-91°C/3.5 mm. (lit.[28] 103-104°C/14 mm). ^{1}H-Nmr: 1.24 (9H, m, 3x$CH_3$$CH_2$O-), 3.50-3.85 (8H, m, 3x$CH_3$$CH_2$-O-, $CH_3CH_2O$$CH_2$-), 4.09 (1H, q, J=6 Hz, -CH-*CH*Br-CH_2O-), 4.65 [1H, d, J=6 Hz, $(CH_3CH_2O)_2$*CH*-CH-]. ^{13}C-Nmr: 14.9, 15.1 (2C), 52.4, 63.7, 64.0, 66.6, 71.0, 102.1. Ms: 256 (M^+, ^{81}Br, <1%), 254 (M^+, ^{79}Br, <1%), 211, 209, 167, 165, 163, 103 (100%), 59. HRms: Found: 209.0183. Calcd for $C_7H_{14}O_2{}^{79}Br$ (= $C_9H_{19}O_3{}^{79}Br$ - C_2H_5O): 209.0177.

Preparation of the mixture of *cis*- and *trans*-3-ethoxyacrolein diethylacetals 17b and 18b.
12.71 g (226.6 mmol) of potassium hydroxide in 40 ml of absolute ethanol was added 20.05 g (78.9 mmol) of 2-bromo-3-ethoxypropionaldehyde diethylacetal **16b** and the mixture was refluxed for 2 h (Ar atm). Insoluble solids were filtered off and the filtrate was distilled under vacuum. The residue from the distillation was extracted with ether and the extract combined with the first distillate. Redistillation yielded the mixture of *cis*- and *trans*-3-ethoxyacrolein diethylacetals **17b** and **18b**, which was used without further purification.
Mixture of compounds **17b** and **18b**. Y. 8.76 g (50.3 mmol, 64%). Oil. Bp. 56-66°C/2 mm (lit. 99-104°C/25 mm[13]; 94-96°C/20 mm[29]). Ms: 175 (M^++1), 147, 129, 103 (100%), 101, 73. HRms: Found: 175.1342. Calcd for $C_9H_{19}O_3$ (= $C_9H_{18}O_3$ + H): 175.1334.

Preparation of bromomalonaldehyde tetraethylacetal 19b.
To 8.23 g (47.3 mmol) of the mixture of *cis*- and *trans*-3-ethoxyacrolein diethylacetals **17b** and **18b** in 13 ml of dry dichloromethane, 2 ml (39.0 mmol) of bromine in 7 ml of dry dichloromethane was added dropwise until a red colour persisted; a temperature of 0-5°C was maintained during the addition. Then 3.82 g (38.2 mmol) of precipitated calcium carbonate was added, followed by 26 ml of absolute ethanol. The mixture was stirred and refluxed for 0.5 h (Ar atm), after which it was cooled and filtered. The filtrate was neutralized with a saturated $NaHCO_3$ solution, the dichloromethane layer separated, and the aqueous layer washed twice with ether. The ether layer washings and the organic layer were combined and dried over anhydrous Na_2SO_4. Distillation gave bromomalonaldehyde tetraethylacetal **19b**.
Compound **19b**. Y. 9.65 g (32.4 mmol, 68%). Oil. Bp. 92-100°C/5 mm (lit.[13] 95-102°C/0.4 mm). ^{1}H-Nmr: 1.25 (12H, t, J=7 Hz, 4x$CH_3$$CH_2$O-), 3.5-3.9 (8H, m, 4x$CH_3$$CH_2$O-)[30], 4.03 (1H, t, J=5.5 Hz, -CH-*CH*Br-CH-), 4.60 (2H, d, J=5.5 Hz, -*CH*-CHBr-*CH*-). ^{13}C-Nmr: 14.9 (2C), 15.0 (2C), 54.7, 63.4 (2C), 63.6 (2C), 101.2 (2C). Ms: 300 (M^+, ^{81}Br, <1%), 298 (M^+, ^{79}Br, <1%), 173, 103 (100%), 75, 45. HRms: Found: 173.1183. Calcd for $C_9H_{17}O_3$ [= $C_{11}H_{23}O_4Br$ - (C_2H_5O + HBr)] 173.1178.

Preparation of 3,3-diethoxymethylketene diethylacetal 20b.
Bromomalonaldehyde tetraethylacetal **19b** (8.26 g, 27.7 mmol), potassium *tert*-butoxide (6.92 g, 61.8 mmol, 2.2 equiv.) and *tert*-butanol (1.03 g, 13.9 mmol) were stirred for 7 h at 100°C (Ar atm). After cooling, anhydrous ether was added and the mixture was filtered. Distillation gave 3,3-diethoxymethylketene diethylacetal **20b**.
Compound **20b**. Y. 3.00 g (13.8 mmol, 50%). Oil. Bp. 60-74°C/0.7 mm (lit.[13] 104-105°C/9.5 mm). ^{1}H-Nmr: 1.20 (6H, t, J=7 Hz, 2x$CH_3$$CH_2$O-), 1.21 (6H, t, J=7 Hz, 2x$CH_3$$CH_2$O-), 3.40-3.75 (4H, m, 2x$CH_3$$CH_2$O-), 3.80 (2H, q, J=7 Hz, $CH_3$$CH_2$O-C=CH-), 3.81 [1H, d, J=7.5 Hz, $(CH_3CH_2O)_2$*CH*-CH=C-], 3.98 (2H, q, J=7 Hz, $CH_3$$CH_2$O-C=CH-), 5.29 [1H, d, J=7.5 Hz, $(CH_3CH_2O)_2$CH-*CH*=C-]. ^{13}C-Nmr: 13.9, 14.6, 15.0 (2C), 60.4, 61.1, 63.3, 63.4, 98.7, 100.1, 160.2. Ms: 219 (M^++1), 189, 173 (100%), 147, 103. HRms: Found: 219.1613. Calcd for $C_{11}H_{23}O_4$ (= $C_{11}H_{22}O_4$ + H): 219.1596.

Preparation of triethyl 3,3-diethoxyorthopropionate 14b.
A solution of 3,3-diethoxymethylketene diethylacetal **20b** (3.06 g, 13.1 mmol), absolute ethanol (10.5 ml) and acidic ethanol (1 ml, containing 0.5 w-% dry HCl) was warmed to 50°C for 10 min (Ar atm) and allowed to cool to room temperature. After the alcohol was removed, the residue was distilled through a Vigreux column

to give triethyl 3,3-diethoxyorthopropionate **14b**.
Compound **14b**. Y. 2.55 g (9.65 mmol, 69%). Oil. Bp. 70-75°C/1.5 mm (lit.[13] bp. 103-106°C/6 mm). ^{1}H-Nmr: 1.20 (15H, t, J=7 Hz, 5x*CH*$_3$CH$_2$O-), 2.16 [2H, d, J=4.5 Hz, -CH-*CH*$_2$-C(OCH$_2$CH$_3$)$_3$], 3.45-3.75 (10H, m, 5xCH$_3$*CH*$_2$O-), 4.69 [1H, t, J=4.5 Hz, (CH$_3$CH$_2$O)$_2$*CH*-CH$_2$-]. ^{13}C-Nmr: 14.7 (3C), 15.1 (2C), 37.0, 57.0 (3C), 61.4 (2C), 99.9, 113.9. Ms: 264 (M$^+$, <1%), 219, 173, 147, 117, 103 (100%), 45. HRms: Found: 219.1583. Calcd for $C_{11}H_{23}O_4$ (= $C_{13}H_{28}O_5$ - C_2H_5O) 219.1596.

Preparation of 2-bromo-3-methoxypropionaldehyde dimethylacetal 16a.
13.4 ml (0.2 mol) of freshly distilled acrolein was stirred rapidly and cooled to -5°C in an ice-salt bath. Bromine (10.2 ml, 0.2 mol) was added until a permanent red color indicates a slight exess of bromine. The temperature was maintained at 0-5°C through adjusting the rate of bromine addition at a rate such that the temperature is kept at 0-5°C. Acidic methanol (48.8 ml, containing 1 w-% of dry HCl) was added and the solution was refluxed for 40 h (Ar atm). After cooling, water was added and the solution was extracted with ether. The ether layer was stirred with NaOH (pH 10) for 0.5 h. After separating, the ether layer was washed with water and dried over anhydrous Na_2SO_4. Distillation through a Vigreux column gave 2-bromo-3-methoxypropionaldehyde dimethylacetal **16a**.
Compound **16a**. Y. 22.3 g (0.11 mol, 53%). Oil. Bp. 72-77°C/10 mm. ^{1}H-Nmr: 3.41 (3H, s, *CH*$_3$O-), 3.45 (3H, s, *CH*$_3$O-), 3.47 (3H, s, *CH*$_3$O-), 3.72 (2H, d, J=10 Hz, -CHBr-*CH*$_2$O-), 4.10 (1H, td, J_1=10 Hz, J_2=5.5 Hz, -CH-*CH*Br-CH$_2$O-), 4.50 [H, d, J=5.5 Hz, (CH$_3$O)$_2$*CH*-CHBr-]. ^{13}C-Nmr: 50.9, 55.2, 55.7, 58.9, 73.0, 104.0. Ms: 214 (M$^+$, ^{81}Br, <1%), 212 (M$^+$, ^{79}Br, <1%), 183, 181, 151, 149, 75 (100%), 43. HRms: Found: 180.9858. Calcd for $C_5H_{10}O_2{}^{79}Br$ (= $C_6H_{13}O_3{}^{79}Br$ - CH_3O) 180.9864.

Preparation of the mixture of *cis*- and *trans*-3-methoxyacrolein dimethylacetals 17a and 18a.
12.0 g (214 mmol) of potassium hydroxide in 20 ml of abs. propanol was added 10.00 g (47.2 mmol) of 2-bromo-3-methoxypropionaldehyde dimethylacetal **16a** and the mixture was refluxed for 2 h (Ar atm). Insoluble solids were filtered off and the filtrate was distilled under vacuum. The residue from the distillation was extracted with ether and the extract combined with the first distillate. Redistillation yielded a mixture of *cis*- and *trans*-3-methoxyacrolein dimethylacetals **17a** and **18a**, which was used without further purification.
Mixture of compounds **17a** and **18a**. Y. 2.03 g (15.3 mmol, 33%). Oil. Bp. 29-32°C/2.5 mm. Ms: 133 (M$^+$ + 1, 100%), 131, 117, 101, 85, 75. HRms: Found: 133.0872. Calcd for $C_6H_{13}O_3$ (=$C_6H_{12}O_3$ + H): 133.0864.

Preparation of bromomalonaldehyde tetramethylacetal 19a.
To 10.85 g (82.2 mmol) of the mixture of *cis*- and *trans*-3-methoxyacrolein dimethylacetals **17a** and **18a** in 10 ml of dry dichloromethane, 4.4 ml (85.9 mmol) of bromine in 5 ml of dry dichloromethane was added dropwise until a red colour persisted; a temperature of 0-5°C was maintained through adjustment of the rate of addition. Then 8.23 g (82.2 mmol) of precipitated calcium carbonate was added, followed by 34 ml of absolute methanol. The mixture was stirred and refluxed for 0.5 h (Ar atm), after which it was cooled and filtered. The filtrate was neutralized with a saturated $NaHCO_3$ solution, the dichloromethane layer separated, and the aqueous layer washed twice with ether. The ether layer washings and the organic layer were combined and dried over anhydrous Na_2SO_4. Distillation gave bromomalonaldehyde tetramethylacetal **19a**.
Compound **19a**. Y. 13.84 g (57.2 mmol), 70%). Oil. Bp. 60-80°C/2 mm. ^{1}H-Nmr: 3.45 and 3.48 (12H, 2s, 4x*CH*$_3$O-), 4.05 (1H, t, J=5 Hz, -CH-*CH*Br-CH-), 4.44 [2H, d, J=5 Hz, 2x(-*CH*-CHBr-)]. ^{13}C-Nmr: 52.5, 55.0 (4C), 103.0 (2C). Ms: 244 (M$^+$, ^{81}Br, <1%), 243, 242 (M$^+$, ^{79}Br, <1%), 241, 213, 211, 181, 179, 138, 136, 131, 103 (100%), 101, 85, 75. HRms: Found: 241.0045. Calcd for $C_7H_{14}O_4{}^{79}Br$ (= $C_7H_{15}O_4{}^{79}Br$ - H): 241.0075.

Attempt to prepare 3,3-dimethoxymethylketene dimethylacetal 20a from bromomalonaldehyde tetramethylacetal 19a. Formation of trimethyl *trans*-3-methoxyorthoacrylate 20c.

Bromomalonaldehyde tetramethylacetal **19a** (13.5 g, 55.9 mmol), potassium *tert*-butylate (15.65 g, 139.7 mmol, 2.5 equiv.) and *tert*-butanol (1.52 g, 20.5 mmol) were stirred for 7 h at 100°C (Ar atm). After cooling, anhydrous ether was added and the mixture filtered. Distillation gave trimethyl *trans*-3-methoxyorthoacrylate **20c**.[31]

Compound **20c**. Y. 1.02 g (11.3%). Oil. Bp. 28-30°C/3.5 mm. ^{1}H-Nmr: 3.20 [9H, s, -(OCH_3)$_3$], 3.58 (3H, s, -OCH_3), 4.54 [1H, d, J≈12 Hz, -CH=*CH*-C(OCH$_3$)$_3$], 6.80 (1H, d, J=12 Hz, CH$_3$O-*CH*=CH-). ^{13}C-Nmr: 49.2 (3C), 56.0, 98.5, 114.6, 153.9. Ms: 162 (M$^+$), 130, 102, 74 (100%). HRms: Found: 162.0894. Calcd for $C_7H_{14}O_4$: 162.0892.

Attempt to prepare trimethyl 3,3-dimethoxyorthopropionate 14a. Formation of methyl 3,3-dimethoxypropionate 14c.

Trimethyl *trans*-3-methoxyorthoacrylate **20c** (86.1 mg, 0.53 mmol), trimethyl orthoformate (0.23 ml, 2.12 mmol, 4 equiv.) and *p*-toluenesulfonic acid (24.7 mg) was stirred for 2h at 100°C. The mixture was cooled, evaporated and purified by column chromatography (alumina, CH_2Cl_2) to yield methyl 3,3-dimethoxypropionate **14c**.[32]

Compound **14c**. Y. 71.5 mg (91%). Oil. For the analytical data, see above.

Preparation of 3,3-dimethoxymethylketene dimethylacetal 20a and trimethyl 3,3-dimethoxyorthopropionate 14a from trimethyl *trans*-3-methoxyortho-acrylate 20c.

Trimethyl *trans*-3-methoxyorthoacrylate **20c** (394.0 mg, 2.43 mmol), dry methanol (2 ml, 20 equiv.), and dry acidic methanol (1 drop, containing 3 w% dry HCl_g) were stirred for 4 h under reflux (Ar atm). After cooling, the mixture was neutralized with $NaHCO_3$, filtered and evaporated in vacuum, yielding an approx. 4/6 mixture of 3,3-dimethoxymethylketene dimethylacetal **20a** and trimethyl 3,3-dimethoxyorthopropionate **14a**.

Mixture of compounds **20a** and **14a**. Y. 390 mg (≈90%). Oil. ^{1}H-Nmr (for compound **20a**): 3.26 [6H (rel. int.), s, 2xCH_3O-], 3.32 (3H, s, CH_3O-), 3.33 (3H, s, CH_3O-), 3.44 [1H, d, J=7 Hz, (CH$_3$O)$_2$*CH*-CH=], 5.15 [1H, d, J=7 Hz, -CH-*CH*=C-(OCH)$_2$]. ^{1}H-Nmr (for compound **14a**): 2.11 [2H (rel. int.), d, J=5 Hz, -CH-CH_2-(OCH$_3$)$_3$], 3.25 [9H, s, -(OCH_3)$_3$], 3.35 [6H, s, -(OCH_3)$_2$], 4.51 [1H, t, J=4.5 Hz, (CH$_3$O)$_2$*CH*-CH$_2$-]. ^{13}C-Nmr (for compound **20a**): 52.3 (2C), 52.8, 56.7, 95.2, 101.3, 162.9. ^{13}C-Nmr (for compound **14a**): 34.8, 48.9 (3C), 53.0 (2C), 101.6, 114.2. Ms: 194 (M$^+$ for compound **14a** , <1%), 163 (M$^+$ + 1 for compound **20a**, 194 - CH$_3$O for compound **14a**), 105, 87, 75 (100%). HRms: Found: 163.0981. Calcd for $C_7H_{15}O_4$ (= $C_8H_{18}O_5$ - CH$_3$O for compound **14a** and $C_7H_{14}O_4$ + H for compound **20a**): 163.0970.

Preparation of (16*R)-*O*-methyl-*Z*-isositsirikine 21a and (16*S**)-*O*-methyl-*Z*-isositsirikine 22a.**

A solution of allylic alcohol **1** (100 mg, 0.37 mmol), trimethyl 3-methoxyorthopropionate (425 mg, 2.59 mmol, 7 equiv.) and acetic acid (3 μl) in 1,4-dioxane (6 ml, Na dried and distilled) was stirred for 72 h at 100°C (Ar atm). The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, neutralized with a saturated $NaHCO_3$ solution, washed with water and dried with Na_2SO_4. The crude product was purified by column chromatography (alumina, CH_2Cl_2) to give a mixture of compounds **21a** and **22a** (81.6 mg; 60%; ≈25/75). The mixture was divided into its isomeric components by repeated PLC (silica, CH_2Cl_2/MeOH:95/5).

Compound **21a**. Y. 9.5 mg (7%). Amorphous material. Ir: 1720 (s, C=O). ^{1}H-Nmr: 1.73 (3H, d, J=7 Hz, CH_3CH=C-), 3.31 (3H, s, CH_3O-), 3.73 (3H, s, CH_3OOC-), 3.80 (1H, d, J=12 Hz, H-21β), 5.48 (1H, q, J=7 Hz, CH$_3$*CH*=C-), 7.08 (1H, t, J=7 Hz, H-10), 7.14 (1H, t, J=7 Hz, H-11), 7.32 (1H, d, H-12), 7.46 (1H, d, J=7 Hz, H-9), 8.01 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 368 (M$^+$), 353, 337, 323, 251 (100%), 169. HRms: Found: 368.2127. Calcd for $C_{22}H_{28}N_2O_3$: 368.2099.

Compound **22a**. Y. 14.5 mg (11%). Amorphous material. Ir: 1720 (s, C=O). ^{1}H-Nmr: 1.72 (3H, d, J=7 Hz, CH_3CH=C-), 3.35 (3H, s, CH_3O-), 3.48 (1H, br d, J≈11 Hz, H-3), 3.76 (3H, s, CH_3OOC-), 3.88 (1H, d, J=12 Hz, H-21β), 5.37 (1H, q, J=7 Hz, CH$_3$*CH*=C-), 7.07 (1H, t, J=7 Hz, H-10), 7.14 (1H, t, J=7 Hz, H-11), 7.30 (1H, d, J=7 Hz, H-12), 7.47 (1H, d, J=7 Hz, H-9), 7.91 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 368 (M$^+$), 353, 337, 323, 251 (100%), 169. HRms: Found: 368.2107. Calcd for

$C_{22}H_{28}N_2O_3$: 368.2099.

Preparation of (16*R)-*O*-methyl-15-epi-*Z*-isositsirikine 23a and (16*S**)-*O*-methyl-15-epi-*Z*-isositsirikine 24a.**
A solution of allylic alcohol **2** (200 mg, 0.75 mmol), trimethyl 3-methoxyorthopropionate (742 mg, 4.48 mmol, 6 equiv.) and acetic acid (5 μl) in 1,4-dioxane (10 ml, Na dried and distilled) was stirred for 72 h at 100°C (Ar atm). The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, neutralized with a saturated $NaHCO_3$ solution, washed with water and dried with Na_2SO_4. The crude product was purified by column chromatography (alumina, CH_2Cl_2) to give a mixture of compounds **23a** and **24a** (188.0 mg; 68%; ≈80/20). The mixture was divided into its isomeric components by PLC (silica, CH_2Cl_2/MeOH; 95/5).
Compound **23a**. Y. 84.6 mg (41%). Amorphous material. Ir: 1720 (C=O). ^{1}H-Nmr: 1.63 (3H, d, J=7 Hz, CH_3CH=C-), 3.39 (3H, s, CH_3O-), 3.61 (3H, s, CH_3O-), 3.67 (1H, d, J=12 Hz, H-21β), 5.34 (1H, q, J=7 Hz, CH_3CH=C-), 7.08 (1H, t, J=7 Hz, H-10), 7.14 (1H, t, J=7 Hz, H-11), 7.30 (1H, d, J=7 Hz, H-12), 7.46 (1H, d, J=7 Hz, H-9), 7.89 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 368 (M^+), 353, 337, 323, 251 (100%), 169. HRms: Found: 368.2116. Calcd for $C_{22}H_{28}N_2O_3$: 368.2099.
Compound **24a**. Y. 35.6 mg (17%). Amorphous material. Ir: 1720 (C=O). ^{1}H-Nmr: 1.70 (3H, d, J=7 Hz, CH_3CH=C-), 3.31 (3H, s, CH_3O-), 3.71 (1H, d, J=12.5 Hz, H-21β), 3.83 (3H, s, CH_3O-), 5.43 (1H, q, J=7 Hz, CH_3CH=C-), 7.07 (1H, t, J=7 Hz, H-10), 7.13 (1H, t, J=7 Hz, H-11), 7.30 (1H, d, J=7 Hz, H-12), 7.46 (1H, d, J=7 Hz, H-9), 7.80 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 368 (M^+), 353, 337, 323, 251 (100%), 169. HRms: Found: 368.2123. Calcd for $C_{22}H_{28}N_2O_3$: 368.2099.

Preparation of the ethyl analogue 3b of dehydroxymethyl-Z-isositsirikine.
A solution of allylic alcohol **1** (216 mg, 0.81 mmol), triethyl orthoacetate[17] (790 mg, 4.87 mmol, 7 equiv.) and acetic acid (3 μl) in 1,4-dioxane (15 ml, Na dried and distilled) was stirred for 72 h at 100°C (Ar atm). The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, neutralized with a saturated $NaHCO_3$ solution, washed with water and dried with Na_2SO_4. The crude product was purified by column chromatography (alumina, CH_2Cl_2, CH_2Cl_2/MeOH; 99.5/0.5) to give compound **3b**. Compound **3b**: Y. 142 mg (52%). Amorphous material. Ir: 1720 (C=O). ^{1}H-Nmr: 1.29 (3H, t, J=7 Hz, CH_3CH$_2$O-), 1.69 (3H, d, J=6.5 Hz, CH_3CH=C-), 3.46 (1H, br d, J≈11 Hz, H-3), 3.86 (1H, d, J=12 Hz, H-21β), 4.20 (2H, q, J=7 Hz, CH_3CH_2O-), 5.22 (1H, q, J=6.5 Hz, CH_3CH=C-), 7.07 (1H, t, J=7 Hz, H-10), 7.11 (1H, t, J=7 Hz, H-11), 7.24 (1H, d, J=7 Hz, H-12), 7.45 (1H, d, J=7 Hz, H-9), 7.99 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 338 (M^+), 337, 309, 293, 251 (100%), 170, 169, 156. HRms: Found: 388.1996. Calcd for $C_{21}H_{26}N_2O_2$: 338.1994.

Preparation of ethyl analogues 5b and 7b of (16*R)-17-deoxy-*Z*-isositsirikine and (16*S**)-17-deoxy-*Z*-isositsirikine.**
A solution of allylic alcohol **1** (195 mg, 0.73 mmol), triethyl orthopropionate[18] (773 mg, 6 equiv.) and acetic acid (2 μl) in 1,4-dioxane (15 ml) was stirred for 72 h at 100°C (Ar atm).The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, neutralized with a saturated $NaHCO_3$ solution, washed with water and dried with Na_2SO_4. The crude product was purified by column chromatography (alumina, CH_2Cl_2, CH_2Cl_2/MeOH; 99.5/0.5, CH_2Cl_2/MeOH:99/1) to give a mixture (167 mg, 65%, ≈ 1/1) of compounds **5b** and **7b**. The mixture was divided into its isomeric components by PLC (silica, CH_2Cl_2/MeOH; 95/5).
Compound **5b**. Y. 69 mg (27%). Amorphous material. Ir: 1720 (s, C=O). ^{1}H-Nmr: 1.18 (3H, d, J=7 Hz, CH_3CH-), 1.27 (3H, t, J=7 Hz, CH_3CH$_2$O-), 1.72 (3H, d, J=7 Hz, CH_3CH=C-), 3.70 (1H, br d, J≈11 Hz, H-3), 3.73 (1H, d, J=12 Hz, H-21β), 4.17 (2H, q, J=7 Hz, CH_3CH_2O-), 5.38 (1H, q, CH_3CH=C-), 7.08 (1H, t, J=7 Hz, H-10), 7.14 (1H, t, J=7 Hz, H-11), 7.32 (1H, d, J=7 Hz, H-12), 7.46 (1H, d, J=7 Hz, H-9), 8.24 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 352 (M^+), 337, 323, 307, 251 (100%), 169. HRms: Found: 352.2171. Calcd for $C_{22}H_{28}N_2O_2$: 352.2150.
Compound **7b**. Y. 64 mg (25%). Amorphous material. Ir: 1720 (s, C=O). ^{1}H-Nmr: 1.21 (3H, d, J=7 Hz, CH_3CH-), 1.28 (3H, t, J=7 Hz, CH_3CH$_2$O-), 1.70 (3H, d, J=7 Hz, CH_3CH=C-), 3.48 (1H, br d, J≈11 Hz,

H-3), 3.88 (1H, d, J=12 Hz, H-21β), 4.18 (2H, q, J=7 Hz, CH_3*CH_2*O-), 5.30 (1H, q, J=7 Hz, CH_3*CH*=C-), 7.07 (1H, t, J=7 Hz, H-10), 7.13 (1H, t, J=7 Hz, H-11), 7.28 (1H, d, J=7 Hz, H-12), 7.46 (1H, d, J=7 Hz, H-9), 8.02 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 352 (M^+), 337, 323, 307, 251 (100%), 169. HRms: Found: 352.2151. Calcd for $C_{22}H_{28}N_2O_2$: 352.2150.

Reaction between allylic alcohol 1 and triethyl 3,3-diethoxyorthopropionate 14b.
A solution of allylic alcohol **1** (103 mg, 0.384 mmol), triethyl 3,3-diethoxyorthopropionate **14b** (411 mg, 4 equiv.) and acetic acid (2 μl) in 1,4-dioxane (20 ml) was stirred for 72 h at 100°C (Ar atm). The solvent was evaporated and the residue fractionated and purified by repeated PLC (silica, CH_2Cl_2/MeOH; 95/5) to yield compounds **1**, **30b**, **31b**, **32b**, **33b**, **34b** and **35b**. In addition, a substance, tentatively identified as compound **25b** and/or compound **29b**, was isolated in trace amount.
Compound **1**. Y. 52 mg (50%). For the analytical data, see ref. 5.
Compound **25b** and/or compound **29b**: Traces (<1%). Amorphous material. Ms: 440 (M^+), 411, 395, 337, 251 (100%), 250, 184, 170, 169, 156. HRms: Found: 440.2693. Calcd for $C_{26}H_{36}N_2O_4$: 440.2675.
Compound **30b**: Y. 3.2 mg (2%). Amorphous material. Ir: 1735 (C=O). ^{1}H-Nmr: 1.17 (3H, t, J=7 Hz, *CH_3*CH_2O-), 1.24 (3H, t, J=7 Hz, *CH_3*CH_2O-), 1.34 (3H, d, J=7 Hz, *CH_3*CH-O-), 4.08 (2H, q, J=7 Hz, CH_3*CH_2*O-), 4.22 (1H, q, J=7 Hz, CH_3-*CH*-O-), 4.32 (2H, q, J=7 Hz, CH_3*CH_2*O-), 5.77 (1H, br d, J=4 Hz, -CH_2-*CH*=C-), 5.81 [1H, br t, J$\approx$6 Hz, -CH_2-*CH*(OCH_2CH_3)$_2$], 7.12 (1H, td, J_1=7 Hz, J_2=1.5 Hz, H-10), 7.16 (1H, td, J_1=7 Hz, J_2=1.5 Hz, H-11), 7.47 (1H, dd, J_1=7 Hz, J_2=1.5 Hz, H-9), 7.73 (1H, br d, J=7 Hz, H-12). Ms: 412 (M^+), 367, 170 (100%). HRms: Found 412.2389. Calcd for $C_{24}H_{32}N_2O_4$: 412.2362.
Compound **31b**: Y. 11.2 mg (8%). For the analytical data, see below.
Compound **32b**: Y. 4.2 mg (3%). For the analytical data, see below.
Compound **33b**: Y. Traces (<1%). For the analytical data, see below.
Compound **34b**: Y. 12.7 mg (8%). Amorphous material. Ir: 1730 (C=O). ^{1}H-Nmr: 1.26 (3H, t, J=7 Hz, *CH_3*CH_2O-), 1.30 (3H, t, J=7 Hz, *CH_3*CH_2O-), 1.38 (3H, d, J=7 Hz, *CH_3*CH-O-), 4.15 (4H, q, J=7 Hz, 2xCH_3*CH_2*O-), 4.43 (1H, q, J=7 Hz, CH_3*CH*-O-), 5.76 (1H, br, -CH_2-*CH*=C-), 7.09 (1H, t, J=7.5 Hz, H-10), 7.14 (1H, t, J=7.5 Hz, H-11), 7.31 (1H, d, J=7.5 Hz, H-12), 7.49 (1H, d, J=7.5 Hz, H-9), 7.87 (1H, s, NH). For the ^{13}C-Nmr data, see Figure 1. Ms: 412 (M^+), 367, 267, 251 (100%), 170, 169. HRms: Found: 412.2341. Calcd for $C_{24}H_{32}N_2O_4$: 412.2362.
Compound **35b**: Y. 5.5 mg (10%). Oil. Ir: 1735 (C=O). ^{1}H-Nmr: 1.35 (3H, t, J=7 Hz, -OCH_2*CH_3*), 1.40 (3H, t, J=7 Hz, -OCH_2*CH_3*), 4.02 (2H, q, J=7 Hz, -O*CH_2*CH_3), 4.23 (2H, q, J=7 Hz, -O*CH_2*CH_3), 4.62 (1H, d, J=8 Hz, -CH=*CH*-$COOCH_2CH_3$, *cis*), 9.73 (1H, d, J=8 Hz, CH_3CH_2O-*CH*=CH-, *cis*). ^{13}C-Nmr: 13.7, 14.4, 63.8, 65.9, 85.0, 172.3, 189.4. Ms: 144 (M^+), 115, 88, 71, 70 (100%), 69. HRms: Found: 144.0794. Calcd for $C_7H_{12}O_3$: 144.0786.

Preparation of "model compound" 36a.
A solution of allylic alcohol **1** (2.00 g, 7.46 mmol), methyl malonyl chloride[19] (1.6 ml, 2 equiv.) and acetic acid (20 μl) in 1,4-dioxane (50 ml) was stirred for 72 h at 100°C (Ar atm). The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, neutralized with a saturated $NaHCO_3$ solution, washed with water and dried with Na_2SO_4. The crude product was purified by column chromatography (alumina, CH_2Cl_2, CH_2Cl_2/MeOH; 99.5/0.5) to give compound **36a**.
Compound **36a**. Y. 2.42 g (88%). Amorphous material. Ir: 1760 (C=O), 1740 (C=O). ^{1}H-Nmr: 1.36 (3H, d, J=6.5 Hz, *CH_3*CH-O-), 3.38 (2H, s, -CO-*CH_2*-CO-), 3.73 (3H, s, *CH_3*OOC-), 5.37 (1H, q, J=6.5 Hz, CH_3*CH*-O-), 5.76 (1H, br, -CH_2-*CH*=C-), 7.06 (1H, t, J=7 Hz, H-10), 7.10 (1H, t, J=7 Hz, H-11), 7.25 (1H, d, J=7 Hz, H-12), 7.45 (1H, d, J=7 Hz, H-9), 8.47 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 368 (M^+), 251 (100%), 170, 169. HRms: Found: 368.1744. Calcd for $C_{21}H_{24}N_2O_4$: 368.1736.

Preparation of "model compound" 37a.

A solution of allylic alcohol **2** (2.00 g, 7.46 mmol), methyl malonyl chloride[19] (1.6 ml, 2 equiv.) and acetic acid (20 μl) in 1,4-dioxane (50 ml) was stirred for 72 h at 100°C (Ar atm).The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, neutralized with a saturated $NaHCO_3$ solution, washed with water and dried with Na_2SO_4. The crude product was purified by column chromatography (alumina, CH_2Cl_2, CH_2Cl_2/MeOH; 99.5/0.5) to give compound **37a**.

Compound **37a**. Y. 2.08 g (76 %). Amorphous material. Ir: 1760 (C=O), 1740 (C=O). ^{1}H-Nmr: 1.41 (3H, d, J=6.5 Hz, CH_3CH-O-), 3.40 (2H, s, -CO-CH_2-CO-), 3.75 (3H, s, CH_3OOC-), 3.77 (1H, d, J=12 Hz, H-21β), 5.44 (1H, q, J=6.5 Hz, CH_3*CH*-O-), 5.83 (1H, br, -CH_2-*CH*=C-), 7.08 (1H, t, J=7 Hz, H-10), 7.13 (1H, t, J=7 Hz, H-11), 7.29 (1H, d, J=7 Hz, H-12), 7.49 (1H, d, J=7 Hz, H-9), 7.99 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 368 (M^+), 251 (100%), 170, 169. HRms: Found: 368.1759. Calcd for $C_{21}H_{24}N_2O_4$: 368.1736.

Reaction between allylic alcohol 1 and 3,3-diethoxymethylketene diethylacetal 20b.

A solution of allylic alcohol **1** (200 mg, 0.75 mmol), 3,3-diethoxymethylketene diethylacetal **20b** (986 mg, 6 equiv.) and acetic acid (5 μl) in 1,4-dioxane (10 ml) was stirred for 72 h at 100°C (Ar atm). The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, neutralized with a saturated $NaHCO_3$ solution, washed with water and dried with Na_2SO_4. The solvent was evaporated and the residue fractionated and purified by repeated PLC (silica, CH_2Cl_2/MeOH; 95/5) to yield compounds **1**, **30b**, **31b**, **32b**, **33b**, **34b** and **35b**. In addition, a substance, tentatively identified as compound **25b** and/or compound **29b**, was isolated in trace amount.

Compound **1**. Y. 62 mg (31%). For the analytical data, see ref. 5.
Compound **25b** and/or compound **29b**. Y. Traces (<1%). For the analytical data, see above.
Compound **30b**. Y. 12.4 mg (4%). For the analytical data, see above.
Compound **31b**. Y. 16.5 mg (6%). For the analytical data, see below.
Compound **32b**. Y. 13.7 mg (5%). For the analytical data, see below.
Compound **33b**. Y. Traces (<1%). For the analytical data, see below.
Compound **34b**. Y. 43.9 mg (14%). For the analytical data, see above.
Compound **35b**. Y. 9.7 mg (9%). For the analytical data, see above.

Reaction between allylic alcohol 1 and the mixture (≈4/6) of 3,3-dimethoxymethylketene dimethylacetal 20a and trimethyl 3,3-dimethoxyorthopropionate 14a.

A solution of allylic alcohol **1** (80.8 mg, 0.30 mmol), the mixture (≈4/6) of 3,3-dimethoxymethylketene dimethylacetal **20a** and trimethyl 3,3-dimethoxyorthopropionate **14a** (258 mg, ≈5 equiv.), and acetic acid (1 μl) in 1,4-dioxane (10 ml) was stirred for 72 h at 100°C (Ar atm). The solvent was evaporated under vacuum. The residue (≈ 330 mg), which was fractionated by PLC (silica, CH_2Cl_2/MeOH; 95/5), consisted of the starting materials **1**, **14a** and **20a**, traces of compounds **25a** and/or **29a** (tentatively identified), and traces of compound **34a**.

Compounds **25a** and/or **29a**: Traces (<1%). Amorphous material. Ms: 398 (M^+). Compound **34a**: Traces (<1%). Amorphous material. For the analytical data, see below.

Reaction between allylic alcohol 1 and trimethyl *trans*-3-methoxyorthoacrylate 20c.

A solution of allylic alcohol **1** (99.8 mg, 0.37 mmol), trimethyl *trans*-3-methoxyorthoacrylate **20c** (306.7 mg, 5 equiv.) and acetic acid (1 μl) in 1,4-dioxane (10 ml) was stirred for 72 h at 100°C (Ar atm). The solvent was evaporated and the residue fractionated and purified by repeated PLC (silica, CH_2Cl_2/MeOH; 95/5) to yield compounds **1** (starting material), **25a** and/or **29a** (tentatively identified) and **34a**.

Compound **1**. Y. 69.5 mg (70%). For the analytical data, see ref. 5.

Compound **25a** and/or **29a:** Traces (<1%). Amorphous material. Ms: 398 (M^+). Compound **34a**: Y. 4.2 mg(3%). Amorphous material. Ir: 1730 (C=O). ^{1}H-Nmr: 1.34 (3H, d, J=7 Hz, CH_3CH-O-), 3.34 (3H, s,

CH_3O-), 3.37 (3H, s, CH_3O-), 5.78 (1H, br, -CH_2-CH=C-), 7.10 (1H, t, J=7.5 Hz, H-10), 7.14 (1H, t, J=7.5 Hz, H-11), 7.31 (1H, d, J=7.5 Hz, H-12), 7.49 (1H, d, J=7.5 Hz, H-9), 7.96 (1H, s, NH). For the ^{13}C-Nmr data, see Figure 1. Ms: 384 (M^+), 353, 267, 251 (100%), 170, 169. HRms: Found: 384.2060. Calcd for $C_{22}H_{28}N_2O_4$: 384.2049.

Preparation of vinyl allyl ether 31b.

A solution of allylic alcohol **1** (3.00 g, 11.2 mmol), ethylpropiolate[23] (3.4 ml, 3 equiv.) and *N*-methylmorpholine (1.5 ml) in 1,4-dioxane (25 ml) was stirred for 3 days in dark at room temperature (Ar atm). The reaction mixture was evaporated and purified by flash chromatography (silica, CH_2Cl_2/hexane: 50/50, CH_2Cl_2, CH_2Cl_2/MeOH; 99.5/0.5) to give compound **31b**.

Compound **31b**. Y. 3.58 g (87%). Amorphous material. Ir: 1710 (C=O). ^{1}H-Nmr: 1.25 (3H, t, J=7 Hz, CH_3CH_2O-), 1.37 (3H, d, J=6 Hz, CH_3CH-O-), 3.31 (1H, d, J=15.5 Hz, H-21β), 4.15 (2H, q, J=7 Hz, CH_3CH_2O-), 4.34 (1H, q, J=6 Hz, CH_3CH-O-), 5.29 (1H, d, J=12.5 Hz, -CH=CH-O-), 5.68 (1H, br s, -CH_2-CH=C-), 7.06 (1H, t, J=7 Hz, H-10), 7.10 (1H, t, J=7 Hz, H-11), 7.25 (1H, d, J=7 Hz, H-12), 7.46 (1H, d, J=7 Hz, H-9), 7.48 (1H, d, J=12.5 Hz, -CH=CH-O-), 8.55 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 366 (M^+), 251 (100%), 170, 169. HRms: Found: 366.1942. Calcd for $C_{22}H_{26}N_2O_3$: 366.1943.

Preparation of vinyl allyl ether 41b.

A solution of allylic alcohol **2** (1.42 g, 5.30 mmol), ethylpropiolate[23] (1.8 ml, 3 equiv.) and *N*-methylmorpholine (0.7 ml) in 1,4-dioxane (20 ml) was stirred for 3 days in dark at room temperature (Ar atm). The reaction mixture was evaporated and purified by flash chromatography (silica, CH_2Cl_2/hexane; 50/50, CH_2Cl_2, CH_2Cl_2/MeOH; 99.5/0.5) to give compound **41b**.

Compound **41b**. Y. 1.46 mg (75%). Amorphous material. Ir: 1710 (C=O). ^{1}H-Nmr: 1.25 (3H, t, J=7 Hz, CH_3CH_2O-), 1.29 (3H, d, J=6 Hz, CH_3CH-O-), 3.38 (1H, d, J=15.5 Hz, H-21β), 4.17 (2H, q, J=7 Hz, CH_3CH_2O-), 4.30 (1H, q, J=6 Hz, CH_3CH-O-), 5.33 (1H, d, J=12.5 Hz, -CH=CH-O-), 5.41 (1H, br s, -CH_2-CH=C-), 7.04 (1H, t, J=7 Hz, H-10), 7.10 (1H, t, J=7 Hz, H-11), 7.23 (1H, d, J=7 Hz, H-12), 7.45 (1H, d, J=7 Hz, H-9), 7.51 (1H, d, J=12.5 Hz, -CH=CH-O-), 9.07 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 366 (M^+), 251 (100%), 170, 169. HRms: Found: 366.1965. Calcd for $C_{22}H_{26}N_2O_3$: 366.1943.

Preparation of the ethyl analogues 32b and 33b of *Z*-geissoschizine and 15-epi-*E*-geissoschizine.

Compound **31b** (483 mg, 1.32 mmol) was dissolved in dry toluene (40 ml) and refluxed for 2 h under Ar atm. Evaporation and purification by flash chromatography (silica, CH_2Cl_2/EtOH; 99/1; CH_2Cl_2/EtOH: 98/2) afforded a mixture of compounds **32b** and **33b** (257.2 mg, 53%, ≈5/1), which was divided into its isomeric components by repeated PLC (CH_2Cl_2/EtOH; 95/5).

Compound **32b**. Y. 73.6 mg (15%). Amorphous material. Ir: 1715 (C=O). ^{1}H-Nmr (for the dominating tautomeric form): 1.27 (3H, t, J=7 Hz, CH_3CH_2O-), 1.67 (3H, d, J=6 Hz, CH_3CH=C-), 3.92 (1H, d, J=13.5 Hz, H-21β), 4.24 (2H, q, J=7 Hz, CH_3CH_2O-), 5.15 (1H, q, J=6 Hz, CH_3CH=C-), 7.09 (1H, t, J=7 Hz, H-10), 7.14 (1H, t, J=7 Hz, H-11), 7.29 (1H, d, J=7 Hz, H-12), 7.46 (1H, d, J=7 Hz, H-9), 7.97 (1H, s, -C=CH-OH), 8.18 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 366 (M^+), 337, 293, 251, 249, 171, 170, 169 (100%), 156. HRms: Found: 366.1938. Calcd for $C_{22}H_{26}N_2O_3$: 366.1943.

Compound **33b**. Y. 13.9 mg (3%). Amorphous material. Ir: 1710 (C=O). ^{1}H-Nmr (for the dominating tautomeric form): 1.31 (3H, t, J=7 Hz, CH_3CH_2O-), 1.53 (3H, d, J=6.5 Hz, CH_3CH=C-), 3.71 (1H, d, J=13.5 Hz, H-21β), 4.37 (2H, q, J=7 Hz, CH_3CH_2O-), 5.60 (1H, q, J=7 Hz, CH_3CH=C-), 7.10 (1H, t, J=7 Hz, H-10), 7.14 (1H, t, J=7 Hz, H-11), 7.28 (1H, d, J=7 Hz, H-12), 7.48 (1H, d, J=7 Hz, H-9), 8.02 (1H, s, -C=CH-OH), 8.29 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 366 (M^+), 337, 293, 251, 249, 171, 170, 169 (100%), 156. HRms: Found: 366.1944. Calcd for $C_{22}H_{26}N_2O_3$: 366.1943.

Preparation of the ethyl analogue 42b of 15-epi-*Z*-geissoschizine.

Compound **41b** (910.1 mg, 2.49 mmol) was dissolved in dry toluene (40 ml) and refluxed for 2 h under Ar

atm. Evaporation and purification by flash chromatography (silica, CH_2Cl_2/EtOH; 99/1, CH_2Cl_2/EtOH; 98/2) afforded compound **42b**.
Compound **42b**. Y. 279.2 mg (31%). Amorphous material. Ir: 1720 (C=O). 1H-Nmr: 1.21, 1.30, 1.31 (t, J=7 Hz, *CH_3*CH_2O- of different tautomeric forms), 1.56, 1.60, 1.63 (d, J=7 Hz, *CH_3*CH=C- of different tautomeric forms), 4.20, 4.28 (q, J=7 Hz, CH_3*CH_2*O- of different tautomeric forms), 5.39, 5.42, 5.45 (q, J=7 Hz, CH_3*CH*=C- of different tautomeric forms), 7.05-7.15 (2H, m, H-10, H-11), 7.29 (1H, d, J=7 Hz, H-12), 7.42 (1H, d, J=7 Hz, H-9), 8.05 (s, -C=*CH*-O-), 8.11, 8.47 (br s, NH of different tautomeric forms). ^{13}C-Nmr: 12.7, 12.8, 14.0, 16.3, 18.2, 20.2, 21.3, 30.9, 32.6, 33.8, 37.4, 40.6, 40.8, 41.4, 42.0, 45.0, 48.6, 49.9, 51.0, 51.2, 52.7, 52.8, 54.3, 54.6, 54.8, 58.1, 59.7, 61.3, 61.7, 105.7, 106,1, 108.7, 110.8, 111.1, 118.0, 119.3, 119.5, 121.3, 121.6, 121.9, 126.7, 127.4, 132.0, 132.1, 133.9, 134.0, 134.2, 136.2, 136.3, 162.4, 162.5, 168.6, 168.9, 170.8, 198.2. Ms: 366 (M^+), 337, 293, 251 (100%), 249, 184, 171, 170, 169, 156. HRms: Found: 366.1952. Calcd for $C_{22}H_{26}N_2O_3$: 366.1943.

Preparation of ethyl analogues 26b and 27b of (16*R)- and (16*S**)-*Z*-geissoschizine diethylacetals.**
The ethyl analogue of *Z*-geissoschizine **32b** (39.0 mg, 0.072 mmol), triethylorthoformate (280 μl, 16 equiv.) and *p*-toluenesulfonic acid (pH 2) in ethanol (20 ml) were stirred for 2 h at 90°C (Ar atm). The solvent was evaporated, and the residue was neutralized with NaOH (10%), washed with water and dried with Na_2SO_4. The crude mixture (32 mg, 68%, ≈ 1/2) of compounds **26b** and **27b** was divided into its isomeric components by PLC (silica, CH_2Cl_2/EtOH; 95/5).
Compound **26b**. Y. 2.4 mg (5%). Amorphous material. Ir: 1735 (C=O). ^{1}H-Nmr: 1.12 (3H, t, J=7 Hz, *CH_3*CH_2O-), 1.20 (3H, t, J=7 Hz, *CH_3*CH_2O-), 1.30 (3H, t, J=7 Hz, *CH_3*CH_2O-), 1.66 (3H, d, J=7 Hz, *CH_3*CH=C-), 3.5-3.8 (4H, m, 2xCH_3*CH_2*O-), 3.67 (1H, d, J=12 Hz, H-21β), 4.07 (2H, dq, J_1=9 Hz, J_2=7 Hz, CH_3*CH_2*O-), 4.81 [1H, d, J=7 Hz, -CH-*CH*(OCH_2CH_3)$_2$], 5.44 (1H, q, J=7 Hz, CH_3*CH*=C-), 7.08 (1H, t, J=7 Hz, H-10), 7.14 (1H, t, J=7 Hz, H-11), 7.30 (1H, d, J=7 Hz, H-12), 7.48 (1H, d, J=7 Hz, H-9), 8.28 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 440 (M^+), 411, 395, 337, 251 (100%), 250, 249, 184, 170, 169, 156. HRms: Found: 440.2686. Calcd for $C_{26}H_{36}N_2O_4$: 440.2675.
Compound **27b**. Y. 5.2 mg (11%). Amorphous material. Ir: 1720 (C=O). ^{1}H-Nmr: 1.19 (3H, t, J=7 Hz, *CH_3*CH_2O-), 1.22 (3H, t, J=7 Hz, *CH_3*CH_2O-), 1.24 (3H, t, J=7 Hz, *CH_3*CH_2O-), 1.70 (3H, d, J=7 Hz, *CH_3*CH=C-), 3.53 (2H, q, J=7 Hz, CH_3*CH_2*O-), 3.8 (4H, m, 2xCH_3*CH_2*O-), 3.89 (1H, d, J=12 Hz, H-21β), 4.10 (2H, q, J=7 Hz, CH_3*CH_2*O-), 4.94 [1H, d, J=9 Hz, -CH-*CH*(OCH_2CH_3)$_2$], 5.70 (1H, q, J=7 Hz, CH_3*CH*=C-), 7.07 (1H, t, J=7 Hz, H-10), 7.14 (1H, t, J=7 Hz, H-11), 7.32 (1H, d, J=7 Hz, H-12), 7.46 (1H, d, J=7 Hz, H-9), 7.83 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 440 (M^+), 411, 395, 337, 251, 250, 184, 170, 169, 156. HRms: Found: 440.2656. Calcd for $C_{26}H_{36}N_2O_4$: 440.2675.

Preparation of (16*R)- and (16*S**)-*Z*-geissoschizine dimethylacetals 26a and 27a.**
Z-Geissoschizine[8] **32a** was treated with trimethylorthoformate as described in Ref. 34.
Compound **26a.** For the analytical data, see Ref. 34.
Compound **27a**. For the analytical data, see Ref. 34.

Preparation of ethyl analogues 39b and 40b of (16*R)- and (16*S**)-15-epi-*Z*-geissoschizine diethylacetales.**
The ethyl analogue of 3-epi-Z-geissoschizine **42b** (279.2 mg, 0.76 mmol), triethylorthoformate (2.2 ml, 17 equiv.) and *p*-toluenesulfonic acid (pH 2) in ethanol (40 ml) was stirred for 4 h at 95°C (Ar atm). The solvent was evaporated, the residue neutralized with NaOH (10%), washed with water and dried with Na_2SO_4. The crude product, a mixture (102.3 mg, 31%, ≈ 1/2) of compounds **39b** and **40b** was divided into its isomeric components by two successive PLC treatments (silica, CH_2Cl_2/EtOH; 95/5 and 98/2).
Compound **39b**.[33] Y. 26.4 mg (8%). Amorphous material. Ir: 1720 (C=O). ^{1}H-Nmr: 1.18 (3H, t, J=7 Hz, *CH_3*CH_2O-), 1.23 (3H, t, J=7 Hz, *CH_3*CH_2O-), 1.32 (3H, t, J=7 Hz, *CH_3*CH_2O-), 1.63 (3H, d, J=7 Hz, *CH_3*CH=C-), 3.5-3.8 (4H, m, 2xCH_3*CH_2*-O-), 3.67 (1H, d, J=12 Hz, H-21β), 4.08 (2H, dq, J_1=11 Hz, J_2=7 Hz, CH_3*CH_2*O-), 4.79 [1H, d, J=7 Hz, -CH-*CH*(OCH_2CH_3)$_2$], 5.39 (1H, q, J=7 Hz, CH_3*CH*=C-),

7.07 (1H, t, J=7 Hz, H-10), 7.13 (1H, t, J=7 Hz, H-11), 7.29 (1H, d, J=7 Hz, H-12), 7.45 (1H, d, J=7 Hz, H-9), 7.66 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 440 (M^+), 411, 395, 337, 251, 250 (100%), 249, 235, 184, 169, 156. HRms: Found: 440.2673. Calcd for $C_{26}H_{36}N_2O_4$: 440.2675.
Compound **40b**. Y. 57.4 mg (17%). Amorphous material. Ir: 1720 (C=O). ^{1}H-Nmr: 1.14 (3H, t, J=7 Hz, CH_3CH$_2$O-), 1.17 (3H, t, J=7 Hz, CH_3CH$_2$O-), 1.33 (3H, t, J=7 Hz, CH_3CH$_2$O-), 1.70 (3H, d, J=7 Hz, CH_3CH=C-), 3.5-3.8 (≈4H, m, 2xCH$_3$$CH_2$-O-), 3.68 (1H, d, J=12 Hz, H-21β), 4.26 (2H, br q, J=7 Hz, CH$_3$$CH_2$O-), 4.48 [1H, d, J=7 Hz, -CH-CH(OCH$_2$CH$_3$)$_2$], 5.48 (1H, q, J=7 Hz, CH$_3$$CH$=C-), 7.06 (1H, t, J=7 Hz, H-10), 7.12 (1H, t, J=7 Hz, H-11), 7.30 (1H, d, J=7 Hz, H-12), 7.45 (1H, d, J=7 Hz, H-9), 7.69 (1H, s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 440 (M^+), 411, 395, 337, 251, 250 (100%), 249, 184, 169, 156. HRms: Found 440.2677. Calcd for $C_{26}H_{36}N_2O_4$: 440.2675.

Preparation of (16*R)- and (16*S**)-15-epi-Z-geissoschizine dimethylacetals 39a and 40a.**
15-Epi-Z-geissoschizine[8] **42a** was treated with trimethylorthoformate as described in Ref. 34.
Compound **39a**. For the analytical data, see Ref. 34.
Compound **40a**. For the analytical data, see Ref. 34.

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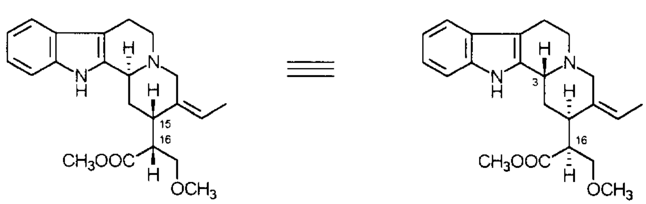
14. Compound **23a**, (±)-(16*R**)-*O*-methyl-15-epi-Z-isositsirikine, is identical with (±)-(16*S**)-*O*-methyl-3-epi-Z-isositsirikine **23a´**, and the corresponding situation holds for compounds **4a**, **6a**, **8a**, **10a**, **12a**, **24a**, **32a,b**, **33a,b**, **39a,b**, **40a,b**, and **42a,b**.



23a **23a'**

For mechanistic reasons we prefer to present these compounds as shown, even though the C-15-H in the formulae, being β, is unnatural.

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16. The CH_3-group should preferentially be equatorial (or nearly equatorial) in the transition state. See ref. 8 and Carruthers, W. *Some Modern Methods of Organic Synthesis,* 3rd Ed., Cambridge University Press, 1986, p. 167.
17. **Note!** In order to have a uniform presentation of the formed compounds with other formulae, a 180° rotation about the C-15 - C-16 bond has been effected.
18. Aldrich, Compound T6,040-2.
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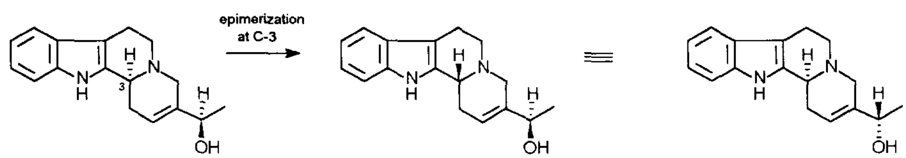
21. The C-3 epimerization in the present racemic series, which might take place in several compounds, would mean *e.g.* in the case of the allylic alcohol **1** the formation of allylic alcohol **2**.



1 **2**

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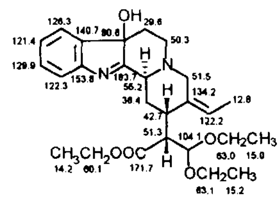
31. Small amounts of 3,3-dimethoxymethylketene dimethylacetal **20a** were detected in the reaction mixture by ^{1}H-nmr: 3.22 [6H (rel. int.), s, 2xCH_3O-)], 3.32 (3H, s, CH_3O-), 3.33 (3H, s, CH_3O-), 3.44 [1H, d, J=7 Hz, $(CH_3O)_2$-*CH*-CH=], 5.15 [1H, d, J=7 Hz, -CH-*CH*=C$(OCH)_2$].
32. Small amounts of trimethyl 3,3-dimethoxyorthopropionate **14a** were detected in the reaction mixture by ^{1}H-nmr: 2.12 [2H (rel. int.), d, J=4.5 Hz, -CH-CH_2-C-], 3.26 [9H, s, -$(OCH_3)_3$], 3.36 [6H, s, -$(CH_3)_2$], 4.51 [1H, t, J=4.5 Hz, $(CH_3O)_2$-*CH*-CH_2-].
33. During the purification of compound **39b** small amounts of the corresponding hydroxyindolenine **39c** were formed, due to autoxidation.
Compound **39c**. Amorphous material. Ir: 1720 (C=O). ^{1}H-Nmr: 1.12 (3H, t, J=7 Hz, CH_3CH_2O-), 1.16 (3H, t, J=7 Hz, CH_3CH_2O-), 1.23 (3H, t, J=7 Hz, CH_3CH_2O-), 1.60 (3H, d, J=7 Hz, CH_3CH=C-), 3.5-3.8 (≈5H, m, 2xCH_3CH_2O- and H-21β), 4.08 (2H, q, J=7 Hz, CH_3CH_2O-), 4.70 [1H, d, J=7 Hz, -CH-*CH*-$(OCH_2CH_3)_2$], 5.41 (1H, q, J=7 Hz, CH_3*CH*=C-), 7.22 (1H, t, J=7 Hz, H-10), 7.36 (1H, t, J=7 Hz, H-11), 7.42 (1H, d, J=7 Hz, H-9), 7.57 (1H, d, J=7 Hz, H-12). For the ^{13}C-nmr data, see formula **39c** below. Ms: 456 (M^+), 439, 411, 393, 267, 266, 265 (100%), 250, 249. HRms: 456.2637. Calcd for $C_{26}H_{36}N_2O_5$: 456.2624.



39c

34. Lounasmaa, M.; Jokela, R.; Bäck, M.; Hanhinen, P.; Laine, C. *In preparation* .

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