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Preparation and Determination of Stereochemical Properties of Epimeric Z-Geissoschizine and 19,20-Dihydrogeissoschizine Acetals

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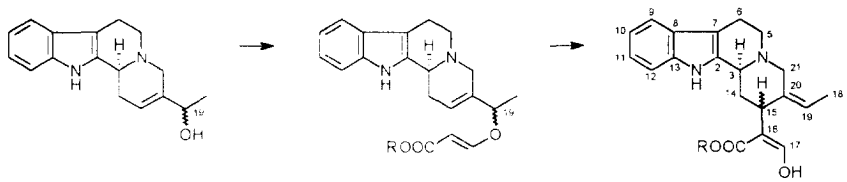
Abstract - Preparation and determination of stereochemical properties of epimeric Z-geissoschizine and 19,20-dihydrogeissoschizine acetals are described. The determination of the stereochemical properties is mainly based on nmr measurements.

C-17 acetal intermediates are widely used in the synthesis of geissoschizine derivatives.[1-4] Surprisingly little is known about their stereochemistry. The enormous progress in nmr spectroscopy during the last decade makes nmr the *méthode de choix* for the stereochemical determination of geissoschizine derivatives and similar structures.[5,6] In the present paper we describe our results for epimeric *Z*-geissoschizine and 19,20-dihydrogeissoschizine acetals.

RESULTS AND DISCUSSION

Allylic alcohols **1** and **2** can be transformed with methyl and ethyl propiolates to the corresponding vinyl allyl ethers **1a** and **2a**, and **1b** and **2b**.[7] The thermally induced transposition of compounds **1a,b** and **2a,b** to the corresponding homoallylic carbonyl compounds (Claisen rearrangement, a [3,3]sigmatropic reaction) permits easy access to (±)-*Z*-geissoschizines **3a,b** and **4a,b** (Scheme 1),[8,9] of which the corresponding methyl and ethyl acetals can be obtained by trimethyl and triethyl orthoformate treatment.[10,11] Catalytic hydrogenation of the acetals permits the preparation of the corresponding 19,20-dihydrogeissoschizine derivatives[12] (*vide infra*).



1 C-19 *S**
2 C-19 *R**

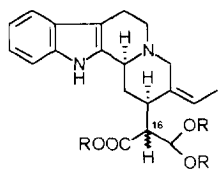
1a C-19 *S**, R= CH_3
1b C-19 *S**, R= CH_3CH_2
2a C-19 *R**, R= CH_3
2b C-19 *R**, R= CH_3CH_2

3a 15-H α ; R= CH_3
3b 15-H α ; R= CH_3CH_2
4a 15-H β ; R= CH_3
4b 15-H β ; R= CH_3CH_2

Scheme 1.

Four stereoisomers exist for the (±)-*Z*-geissoschizine acetals, all which were prepared in both the "methyl series" (**5a-8a**) and the "ethyl series" (**5b-8b**) (Table 1). Eight stereoisomers exist for the (±)-19,20-dihydrogeissoschizine acetals prepared in the "methyl series" (**9-16**) by catalytic reduction (Table 2). All these compounds possess the indolo[2,3-*a*]quinolizidine skeleton (*vide infra*).

Because compounds **5a-8a, 5b-8b,** and **9-16** contain at C-17 an acetal group (two methoxyl or ethoxyl groups), which is bulkier than in earlier cases (*cf.* Refs. 13 and 14), one would expect the preference of the C-15 - C-16 bond to exist in a conformation where H-15 and H-16 are approximately in *anti* position to each other to be less pronounced than in the earlier cases (*vide infra*).



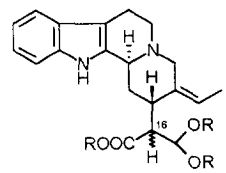
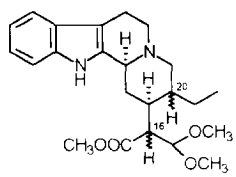


Table 1.

	16-H	
5a	β	R= CH_3
6a	α	R= CH_3
5b	β	R= CH_3CH_2
6b	α	R= CH_3CH_2

	16-H	
7a	β	R= CH_3
8a	α	R= CH_3
7b	β	R= CH_3CH_2
8b	α	R= CH_3CH_2



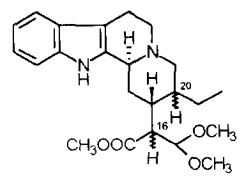
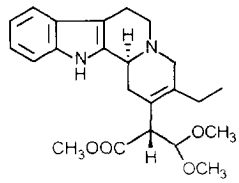


Table 2.

	16-H	20-H
9	β	α
10	α	α
11	β	β
12	α	β

	16-H	20-H
13	β	β
14	α	β
15	β	α
16	α	α

In addition to compounds **9** - **16**, small amounts of *"didehydro"* compounds **17** and **18** were formed during the catalytic reduction (*vide supra*). The formation of these compounds occurs through the hydrogen migration, which transforms the *exocyclic* C(19)H-C(20)H double bond to an *endocyclic* C(15)H-C(20)H double bond. Since the *endocyclic* double bond is tetrasubstituted, it is not reduced under the conditions used (*cf.* Experimental).



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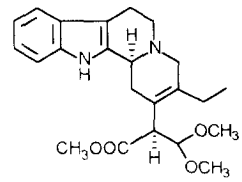

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Table 3. ^{1}H-nmr data for *compounds* 5a - 16.

	5a		5b		6a		6b		7a[a)]		7b		8a[a)]		8b	
H-1	8.12	br s	8.28	br s	7.98	br s	7.90	br s	7.72	br s	7.63	br s	7.80	br s	7.71	br s
H-3	3.7	m	3.8	m	3.48	br d	3.5	m	3.6	m	3.7	m	3.7	m	3.8	m
H-5α	2.80	ddd	2.9	m	2.68	ddd	2.7	m	2.7	m	2.7	m	2.7	m	2.7	m
H-5β	3.18	ddd	3.22	ddd	3.14	ddd	3.15	ddd	3.1	m	3.1	m	3.1	m	3.14	ddd
H-6α	2.7	m	2.7	m	2.7	m	2.7	m	2.7	m	2.7	m	2.7	m	2.7	m
H-6β	3.0	m	3.0	m	3.00	ddd	3.01	ddd	3.0	m	3.0	m	3.0	m	3.0	m
H-9	7.47	d	7.47	d	7.45	d	7.45	d	7.45	d	7.46	m	7.44	d	7.45	d
H-10	7.08	t	7.08	t	7.07	t	7.07	t	7.07	t	7.07	t	7.06	t	7.07	t
H-11	7.13	t	7.13	t	7.13	t	7.13	t	7.12	t	7.13	t	7.11	t	7.12	t
H-12	7.31	d	7.30	d	7.31	d	7.32	d	7.30	d	7.29	d	7.28	d	7.29	d
H-14α	2.40	ddd	2.38	ddd	2.28	ddd	2.28	ddd	2.56	ddd	2.65	ddd	1.9	m	1.9	m
H-14β	1.80	ddd	2.02	ddd	1.72	ddd	1.78	ddd	1.78	ddd	1.77	ddd	1.87	ddd	1.87	ddd
H-15	2.8	m	2.8	m	2.6	m	2.6	m	2.85	ddd	2.86	ddd	2.9	m	2.9	m
H-16	3.01	dd	2.92	dd	3.30	dd	3.26	dd	3.26	dd	3.25	dd	3.26	d	3.25	dd
H-17	4.66	d	4.81	d	4.82	d	4.93	d	4.67	d	4.79	d	4.35	d	4.48	d
H-18	1.68	d	1.66	d	1.71	d	1.70	d	1.64	d	1.63	d	1.71	d	1.70	d
H-19	5.41	q	5.44	q	5.66	q	5.70	q	5.38	q	5.39	q	5.49	q	5.48	q
H-21α	2.91	br d	2.99	br d	2.79	br d	2.79	br d	2.98	br d	3.00	br d	2.90	br d	2.98	br d
H-21β	3.75	d	3.68	d	3.88	d	3.88	d	3.66	d	3.66	d	3.68	d	3.67	d
OCH_3	3.35	s			3.33	s			3.41	s			3.31	s		
OCH_3	3.43	s			3.42	s			3.47	s			3.40	s		
CO_2CH_3	3.65	s			3.63	s			3.61	s			3.80	s		
OCH_2CH_3[b)]			3.47	dq			3.54	dq			3.58	dq			3.37	dq
OCH_2CH_3[b)]			3.56	dq			3.78	dq			3.74	dq			3.62	dq
OCH_2CH_3[c)]			3.64	dq			3.56	dq			3.66	dq			3.53	dq
OCH_2CH_3[c)]			3.76	dq			3.63	dq			3.80	dq			3.73	dq
$CO_2CH_2CH_3$			4.05	q			4.10	dq			4.05	dq			4.24	dq
$CO_2CH_2CH_3$			4.10	q			4.10	dq			4.10	dq			4.28	dq
OCH_2CH_3[b)]			1.12	dd			1.19	dd			1.18	dd			1.14	dd
OCH_2CH_3[c)]			1.30	dd			1.24	dd			1.32	dd			1.17	dd
$CO_2CH_2CH_3$			1.20	dd			1.21	dd			1.23	dd			1.33	dd

Table 3 (continued). **^{1}H-nmr data for compounds 5a - 16.**

	9		**10**		**11**		**12**		**13**		**14**		**15**		**16**	
H-1	7.73	br s	7.79	br s	7.89	br s	7.78	br s	8.00	br s	7.98	br s	8.16	br s	8.74	br s
H-3	3.19	br d	3.21	br d	3.2	m	3.2	m	4.15	br s	4.13	br s	4.50	br s	4.80	br s
H-5α	2.55	ddd	2.6	m	2.58	ddd	2.58	ddd	3.0	m	3.0	m	3.3	m	3.4	m
H-5β	2.9	m	3.0	m	3.1	m	3.1	m	3.2	m	3.2	m	3.3	m	3.4	m
H-6α	2.68	ddd	2.7	m	2.73	ddd	2.72	ddd	2.7	m	2.63	m	2.67	br d	2.85	br d
H-6β	2.9	m	2.9	m	3.0	m	3.0	m	3.0	m	3.0	m	3.0	m	3.0	m
H-9	7.46	d	7.45	d	7.47	d	7.46	d	7.47	d	7.48	d	7.50	d	7.50	d
H-10	7.07	t	7.06	t	7.09	t	7.08	t	7.10	t	7.10	t	7.12	t	7.14	t
H-11	7.12	t	7.11	t	7.14	t	7.14	t	7.16	t	7.16	t	7.18	t	7.21	t
H-12	7.31	d	7.29	d	7.32	d	7.32	d	7.35	d	7.39	d	7.38	d	7.41	d
H-14α	2.28	ddd	1.7	m	2.32	def d	2.14	br d	2.2	m	2.1	m	2.08	ddd	2.26	ddd
H-14β	1.48	ddd	1.53	ddd	1.7	m	1.65	ddd	2.3	m	1.74	ddd	2.29	ddd	2.49	ddd
H-15	2.21	ddd	2.23	dddd	1.9	m	1.6	m	1.7	m	2.0	m	1.35	ddd	1.42	ddd
H-16	2.91	dd	2.88	dd	3.05	d	3.18	dd	3.12	br dd	2.84	dd	3.04	dd	2.99	dd
H-17	4.65	d	4.54	d	4.71	d	4.90	d	4.67	d	4.48	br d	4.97	d	4.99	d
H-18	0.88	t	0.93	t	0.93	t	0.94	t	0.84	t	0.96	t	0.80	t	0.79	t
H-19[d]	1.3	m	1.3	m	1.22	dq	1.23	dq	1.3	m	1.3	m	0.9	m	1.0	m
H-19[e]	1.7	m	1.7	m	1.7	m	1.7	m	1.7	m	1.7	m	1.7	m	1.7	m
H-20	1.4	m	1.7	m	1.7	m	1.8	m	1.7	m	1.7	m	1.5	m	1.7	m
H-21α	2.37	br d	2.39	br d	2.08	dd	2.13	dd	2.81	br d	2.80	br d	2.85	dd	3.03	dd
H-21β	2.99	dd	3.03	dd	3.12	br d	3.14	dd	2.57	br d	2.6	m	2.41	dd	2.59	dd
OCH_3	3.38	s	3.30	s	3.34	s	3.36	s	3.41	s	3.31	s	3.17	s	3.24	s
OCH_3	3.41	s	3.42	s	3.41	s	3.43	s	3.43	s	3.35	s	3.41	s	3.42	s
CO_2CH_3	3.72	s	3.76	s	3.73	s	3.64	s	3.69	s	3.76	s	3.70	s	3.64	s

[a] Values taken from the spectrum of the 2/3 mixture of compounds **7a** and **8a**

[b], [c] Methylene protons in OCH_2CH_3 and $CO_2CH_2CH_3$ groups are not equivalent.

[d], [e] Methylene protons in the CH_2CH_3 side chain are not equivalent.

Table 3 (continued). **Coupling constants for compounds 5a - 16.**

Compound **5a**.
$J_{3,14\alpha} \approx 3$ Hz; $J_{3,14\beta} \approx 11$ Hz; $J_{5\alpha,5\beta} = 11$ Hz; $J_{5\alpha,6\alpha} = 4.5$ Hz; $J_{5\alpha,6\beta} \approx 11$ Hz; $J_{5\beta,6\alpha} \approx 2$ Hz; $J_{5\beta,6\beta} = 5$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\alpha,15} \approx 3$ Hz; $J_{14\beta,15} \approx 11$ Hz; $J_{15,16} = 9.5$ Hz; $J_{16,17} = 7$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 12.5$ Hz

Compound **5b**.
$J_{3,14\alpha} \approx 3$ Hz; $J_{3,14\beta} \approx 11$ Hz; $J_{5\alpha,5\beta} = 11$ Hz; $J_{5\beta,6\alpha} \approx 2$ Hz; $J_{5\beta,6\beta} = 5$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\alpha,15} \approx 3$ Hz; $J_{14\beta,15} \approx 11$ Hz; $J_{15,16} = 10$ Hz; $J_{16,17} = 7$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 12$ Hz; $J_{b)OCH2CH3} = 9$ Hz and 7 Hz; $J_{c)OCH2CH3} = 9$ Hz and 7 Hz; $J_{CO2CH2CH3} \approx 11$ Hz and 7 Hz

Compound **6a**.
$J_{3,14\alpha} \approx 3$ Hz; $J_{3,14\beta} \approx 11$ Hz; $J_{5\alpha,5\beta} = 11$ Hz; $J_{5\alpha,6\alpha} = 4.5$ Hz; $J_{5\alpha,6\beta} \approx 11$ Hz; $J_{5\beta,6\alpha} = 1.5$ Hz; $J_{5\beta,6\beta} = 5$ Hz; $J_{6\alpha,6\beta} = 15$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\alpha,15} \approx 3$ Hz; $J_{14\beta,15} \approx 11$ Hz; $J_{15,16} = 3$ Hz; $J_{16,17} = 9$ Hz; $J_{18,19} = 6.5$ Hz; $J_{21\alpha,21\beta} = 12.5$ Hz

Compound **6b**.
$J_{3,14\alpha} \approx 3$ Hz; $J_{3,14\beta} \approx 11$ Hz; $J_{5\alpha,5\beta} = 11$ Hz; $J_{5\alpha,6\beta} \approx 11$ Hz; $J_{5\beta,6\alpha} \approx 2$ Hz; $J_{5\beta,6\beta} = 5$ Hz; $J_{6\alpha,6\beta} = 15$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\alpha,15} \approx 3$ Hz; $J_{14\beta,15} \approx 11$ Hz; $J_{15,16} = 3$ Hz; $J_{16,17} = 9$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 12.5$ Hz; $J_{b)OCH2CH3} = 9$ Hz and 7 Hz; $J_{c)OCH2CH3} = 9$ Hz and 7 Hz; $J_{CO2CH2CH3} = 7$ Hz

Compound **7a**.
$J_{3,14\alpha} \approx 3$ Hz; $J_{3,14\beta} \approx 11$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\alpha,15} \approx 3$ Hz; $J_{14\beta,15} = 5$ Hz; $J_{15,16} = 10.5$ Hz; $J_{16,17} = 7$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 12.5$ Hz

Compound **7b**.
$J_{3,14\alpha} \approx 3$ Hz; $J_{3,14\beta} \approx 11$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\alpha,15} \approx 3$ Hz; $J_{14\beta,15} = 5$ Hz; $J_{15,16} = 10.5$ Hz; $J_{16,17} = 7$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 12.5$ Hz; $J_{b)OCH2CH3} = 9$ Hz and 7 Hz; $J_{c)OCH2CH3} = 9$ Hz and 7 Hz; $J_{CO2CH2CH3} \approx 11$ Hz and 7 Hz

Compound **8a**.
$J_{3,14\beta} \approx 11$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\beta,15} = 5$ Hz; $J_{15,16} = 10.5$ Hz; $J_{16,17} = 7$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 12.5$ Hz

Compound **8b**.
$J_{3,14\beta} \approx 11$ Hz; $J_{5\alpha,5\beta} \approx 11$ Hz; $J_{5\beta,6\alpha} \approx 2$ Hz; $J_{5\beta,6\beta} = 5$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\beta,15} = 4$ Hz; $J_{15,16} = 10$ Hz; $J_{16,17} = 7$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 12$ Hz; $J_{b)OCH2CH3} = 9$ Hz and 7 Hz; $J_{c)OCH2CH3} = 9$ Hz and 7 Hz; $J_{CO2CH2CH3} \approx 11$ Hz and 7 Hz

Compound **9**.
$J_{3,14\alpha} \approx 3$ Hz; $J_{3,14\beta} = 12$ Hz; $J_{5\alpha,5\beta} \approx 12$ Hz; $J_{5\alpha,6\alpha} = 4.5$ Hz; $J_{5\alpha,6\beta} \approx 11$ Hz; $J_{5\beta,6\alpha} \approx 2$ Hz; $J_{6\alpha,6\beta} \approx 15$ Hz; $J_{14\alpha,14\beta} = 12.5$ Hz; $J_{14\alpha,15} \approx 3$ Hz; $J_{14\beta,15} = 12$ Hz; $J_{15,16} = 10.5$ Hz; $J_{16,17} = 7$ Hz; $J_{18,19} = 7$ Hz; $J_{20,21\beta} = 2$ Hz; $J_{21\alpha,21\beta} = 12$ Hz

Compound **10**.
$J_{3,14\beta} = 12$ Hz; $J_{14\alpha,14\beta} = 12.5$ Hz; $J_{14\alpha,15} = 3$ Hz; $J_{14\beta,15} = 12$ Hz; $J_{15,16} = 8.5$ Hz; $J_{15,20} \approx 4$ Hz; $J_{16,17} = 7$ Hz; $J_{18,19} = 7$ Hz; $J_{20,21\beta} = 2.5$ Hz; $J_{21\alpha,21\beta} = 12$ Hz

Compound **11**.
$J_{5\alpha,5\beta} = 11$ Hz; $J_{5\alpha,6\alpha} = 4.5$ Hz; $J_{5\alpha,6\beta} \approx 11$ Hz; $J_{5\beta,6\alpha} \approx 2$ Hz; $J_{6\alpha,6\beta} = 15.5$ Hz; $J_{15,16} < 1$ Hz; $J_{16,17} = 8.5$ Hz; $J_{18,19} = 7$ Hz; $J_{19,20} = 7$ Hz; $J_{20,21\alpha} \approx 11$ Hz; $J_{21\alpha,21\beta} \approx 12$ Hz

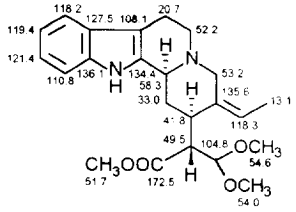
Compound **12**.
$J_{3,14\beta} \approx 12$ Hz; $J_{5\alpha,5\beta} = 11$ Hz; $J_{5\alpha,6\alpha} = 4.5$ Hz; $J_{5\alpha,6\beta} \approx 11$ Hz; $J_{5\beta,6\alpha} \approx 2$ Hz; $J_{6\alpha,6\beta} \approx 15.5$ Hz; $J_{14\alpha,14\beta} \approx 13$ Hz; $J_{14\beta,15} \approx 12$ Hz; $J_{15,16} = 3$ Hz; $J_{16,17} = 9$ Hz; $J_{18,19} = 7$ Hz; $J_{19,20} = 7$ Hz; $J_{20,21\alpha} \approx 11$ Hz; $J_{20,21\beta} = 3.5$ Hz; $J_{21\alpha,21\beta} \approx 12$ Hz

Compound **13**.
$J_{15,16} \approx 6$ Hz; $J_{16,17} = 7.5$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 12$ Hz

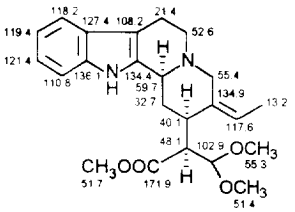
Compound **14**.
$J_{3,14\beta} \approx 4$ Hz; $J_{14\alpha,14\beta} = 13$ Hz; $J_{14\beta,15} \approx 4$ Hz; $J_{15,16} \approx 7$ Hz; $J_{16,17} = 7$ Hz; $J_{18,19} = 7$ Hz; $J_{21\alpha,21\beta} = 12$ Hz

Compound **15**.
$J_{3,14\alpha} = 4.5$ Hz; $J_{3,14\beta} \approx 2$ Hz; $J_{6\alpha,6\beta} = 16$ Hz; $J_{14\alpha,14\beta} = 14$ Hz; $J_{14\alpha,15} \approx 12$ Hz; $J_{14\beta,15} \approx 2.5$ Hz; $J_{15,16} = 4.5$ Hz; $J_{16,17} = 9$ Hz; $J_{18,19} = 7$ Hz; $J_{20,21\alpha} = 4$ Hz; $J_{20,21\beta} = 12$ Hz; $J_{21\alpha,21\beta} = 12$ Hz

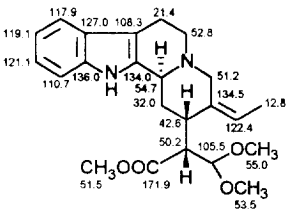
Compound **16**.
$J_{3,14\alpha} = 4.5$ Hz; $J_{3,14\beta} \approx 2$ Hz; $J_{6\alpha,6\beta} = 16$ Hz; $J_{14\alpha,14\beta} = 14$ Hz; $J_{14\alpha,15} \approx 12$ Hz; $J_{14\beta,15} \approx 2$ Hz; $J_{15,16} = 4$ Hz; $J_{16,17} = 9$ Hz; $J_{18,19} = 7$ Hz; $J_{20,21\alpha} = 3.5$ Hz; $J_{20,21\beta} = 12$ Hz; $J_{21\alpha,21\beta} = 12$ Hz



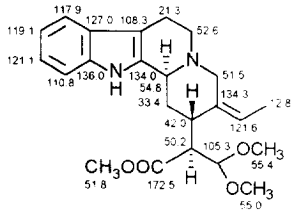
5a



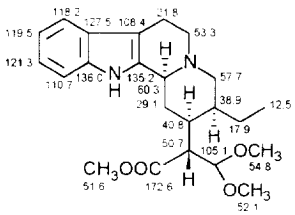
6a



7a [a)]



8a [a)]



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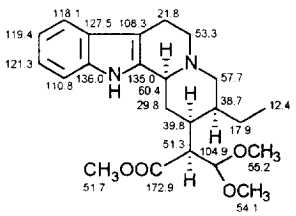

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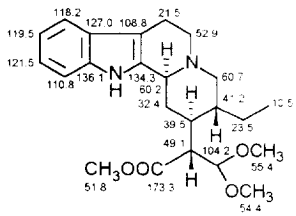

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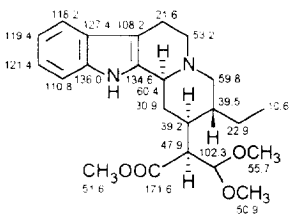

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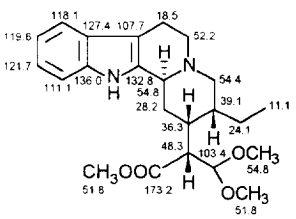

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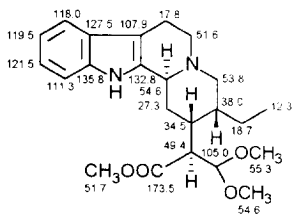

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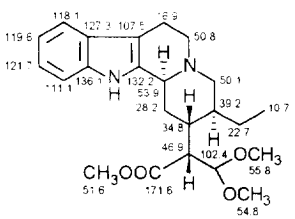

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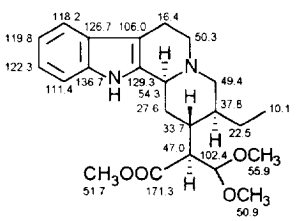
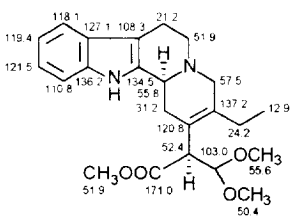


16



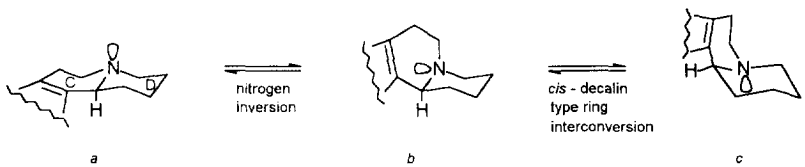
18

Figure 1. ^{13}C-nmr data for compounds 5a - 16 and 18.

[a)] Values taken from the spectrum of the 2/3 mixture of compounds **7a** and **8a.**

CONFORMATIONAL CONSIDERATIONS

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



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

According to the ^{1}H- and ^{13}C-nmr chemical shifts the predominant conformation of the *Z*-geissoschizine acetals **5a, 5b, 6a**, **6b**, **7a**, **7b**, **8a**, **8b** and of compounds **9**, **10** (*allo*) and **11**, **12** (*normal*) is a, where ring D adopts a chair conformation. Compounds **15** and **16** (*pseudo*) exist predominantly in conformation c with ring D in chair conformation (H-3: δ 4.50 and 4.80 ppm; C-6: δ 16.9 and 16.4 ppm). The conformations of the two *epiallo* compounds **13** and **14**, where no conformation is heavily dominating, are more difficult to establish. The conformational equilibrium is seen as strong ^{13}C peak broadening, especially in the spectrum of compound **14**.

Comparison of the chemical shifts with those given earlier,[8,9,13-15] taking into account the conformational considerations relevant for indolo[2,3-*a*]quinolizidines, provides evidence of the stereostructures depicted in the formulae. An important assistance in the determination of the H-16 stereochemistry was that compounds **9** and **11** were prepared from compound **5a**, and compounds **10** and **12** from compound **6a**. This allowed us to assume that, if no epimerization takes place, the H-16 stereochemistry of compounds **5a**, **9** abd **11**,would be identical, and likewise the H-16 stereochemistry of compounds **6a**, **10** and **12**. Because compounds **13-16** were prepared from a ~2:3 mixture of compounds **7a** and **8a** (H-16 *R** and *S**) (*cf.* Experimental), no similar assistance was available for the interpretation of the H-16 stereochemistry of these compounds. However, the ~2:3 relationship gave useful information in the interpretation of their spectra.

CONCLUSIONS

Epimeric *Z*-geissoschizine acetals **5a-8a** ("methyl series") and **5b-8b** ("ethyl series"), and 19,20-dihydrogeissoschizine acetals **9-16** ("methyl series") were synthesised. The predominant conformations of the prepared compounds were determined by nmr technique. It is hoped that the furnished data will prove useful in future structural determinations of acetals of the present type.

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 IR spectrophotometer using $CHCl_3$ as solvent. Ir absorption bands are expressed in reciprocal centimetres (cm^{-1}). ^{1}H-Nmr spectra were measured with a Varian Unity-400 NMR spectrometer working at 399.952 MHz and ^{13}C-nmr spectra with a Varian Gemini-200 spectrometer working at 50.289 MHz. $CDCl_3$ was used as solvent. Chemical shifts are given in ppm by reference to TMS (^{1}H-nmr; δ_H=0.00 ppm) and $CDCl_3$ (^{13}C-nmr; δ_C=77.00 ppm). 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. Spectra were obtained by direct substraction using a 90° composite pulse. Mass spectrometry (EIms and HRms) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compounds 1a, 2a, 3a, and 4a.
For the preparation of compounds **1a**, **2a**, **3a**, and **4a**, see Ref. 8 (compounds **3**, **4**, **5**, and **15**, respectively).

Preparation of compounds 1b, 2b, 3b, 4b, 5b, 6b, 7b, and 8b.
For the preparation of compounds **1b**, **2b**, **3b**, **4b**, **5b**, **6b**, **7b**, and **8b**, see Ref. 9 (compounds **31b**, **41b**, **32b**, **42b**, **26b**, **27b**, **39b**, and **40b**, respectively).

Preparation of (16*R)- and (16*S**)-*Z*-geissoschizine dimethylacetals 5a and 6a.**
Z-Geissoschizine[8] **3a** (64.0 mg, 0.18 mmol), trimethylorthoformate (0.34 ml, 1.7 equiv.) and *p*-toluenesulfonic acid (~40 mg) in methanol (5 ml) were stirred under reflux for 4 h (Ar atm, the reaction is sensitive to humidity). The solvent was evaporated and the residue was neutralized with Na_2CO_3 (5%), washed with water and dried with Na_2SO_4. The crude product, a mixture of compounds **5a** and **6a** (70.9 mg, 99%, ~1:1), was divided into its isomeric components by successive PLC treatments (silica, CH_2Cl_2/MeOH; 95/5).
Compound **5a**. Y. 18.2 mg (25%). Mp. 142°C (toluene). Ir: 1730 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 398 (M^+), 397, 383, 367, 323, 251 (100%), 250, 249. Hrms: Found: 398.2191. Calcd for $C_{23}H_{30}N_2O_4$: 398.2206.
Compound **6a**. Y. 16.4 mg (23%). Amorphous material. Ir: 1735 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 398 (M^+), 397, 383, 367, 323, 251 (100%), 250, 249. HRms: Found: 398.2218. Calcd for $C_{23}H_{30}N_2O_4$: 398.2206.

Preparation of (16*R)- and (16*S**)-15-epi-*Z*-geissoschizine dimethylacetals 7a and 8a.**
15-Epi-*Z*-geissoschizine[8] **4a** (240.8 mg, 0.68 mmol), trimethylorthoformate (1.25 ml, 1.7 equiv.) and *p*-toluenesulfonic acid (~150 mg) in methanol (10 ml) were stirred under reflux for 3.5 h (Ar atm). The solvent was evaporated and the residue was neutralized with NaOH (5%), washed with water and dried with Na_2SO_4. The crude product, a mixture of compounds **7a** and **8a** (230.0 mg, 85%, ~2:3) was purified by column chromatography (silica, CH_2Cl_2/MeOH; 99/1; 98/2).
Mixture of compounds **7a** and **8a** (separation did not succeed). Y. 168 mg (62%). Amorphous material. Ir: 1730 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 398 (M^+), 397, 383, 367, 323, 251 (100%), 250, 249. HRms: Found: 398.2197. Calcd for $C_{23}H_{30}N_2O_4$: 398.2206.

Catalytic hydrogenation of (16*R)-*Z*-geissoschizine dimethylacetal 5a.**
Compound **5a** (27.5 mg, 0.07 mmol) was hydrogenated [MeOH, PtO_2 (31 mg)] during 3 h at rt. Filtration and evaporation of the solvent yielded the crude product (26 mg, 0.07 mmol), which was purified by PLC treatment (silica, CH_2Cl_2/MeOH; 95/5) to yield compounds **9** (*allo*), **11** (*normal*), and **17** (*didehydro*).
Compound **9**. Y. 8.1 mg (29%). Amorphous material. Ir: 1735 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 400 (M^+, 100%), 399, 385, 369, 253, 251. HRms: Found: 400.2361. Calcd for $C_{23}H_{32}N_2O_4$: 400.2362.
Compound **11**. Y. 6.2 mg (22%). Amorphous material. Ir: 1735 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 400 (M^+, 100%), 399, 385, 369, 253, 251. HRms: Found: 400.2378. Calcd for $C_{23}H_{32}N_2O_4$: 400.2362.

Compound **17**. Y. Traces (not quite pure). Amorphous material. Ir: 1730 (C=O). ^{1}H-nmr: 1.07 (3H, t, J=8 Hz, -CH_2CH$_3$), 3.26 (3H, s, -OCH_3), 3.41 (3H, s, -OCH_3), 3.74 (3H, s, -COOCH_3), 3.93 [1H, d, J=9 Hz, -CHCH(OCH$_3$)$_2$], 4.87 [1H, d, J=9 Hz, -CHCH(OCH$_3$)$_2$], 7.08 - 7.17 (2H, m, H-10, H-11), 7.33 (1H, d, J=8 Hz, H-12), 7.49 (1H, d, J=8 Hz, H-9), 7.94 (1H, br s, NH). Ms: 398 (M$^+$), 367, 323, 251, 170 (100%), 169. HRms: Found: 398.2188. Calcd for $C_{23}H_{30}N_2O_4$: 398.2206.

Catalytic hydrogenation of (16*S)-*Z*-geissoschizine dimethylacetal 6a.**

Compound **6a** (29 mg, 0.07 mmol) was hydrogenated [MeOH, PtO_2 (35 mg)] during 3 h at rt. Filtration and evaporation of the solvent yielded the crude product (28 mg, 0.07 mmol), which was purified by PLC treatment (silica, CH_2Cl_2/MeOH; 95/5) to yield compounds **10** (*allo*), **12** (*normal*), and **18** (*didehydro*).

Compound **10**. Y. 8 mg (27%). Amorphous material. Ir: 1735 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 400 (M$^+$, 100%), 399, 385, 369, 253, 251. HRms: Found: 400.2355. Calcd for $C_{23}H_{32}N_2O_4$: 400.2362.

Compound **12**. Y. 2.4 mg (8%). Amorphous material. Ir: 1735 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 400 (M$^+$, 100%), 399, 385, 369, 253, 251. HRms: Found: 400.2351. Calcd for $C_{23}H_{32}N_2O_4$: 400.2362.

Compound **18**. Y. 1.6 mg (6%). Amorphous material. Ir: 1735 (C=O). ^{1}H-nmr: 1.09 (3H, t, J=7.5 Hz, -CH_2CH_3), 3.35 (3H, s, -OCH_3), 3.46 (3H, s, -OCH_3), 3.53 (1H, m, H-3), 3.61 (3H, s, -COOCH_3), 3.93 [1H, d, J=8 Hz, -CHCH(OCH$_3$)$_2$], 5.01 [1H, d, J=8 Hz, -CHCH(OCH$_3$)$_2$], 7.09 (1H, t, J=8 Hz, H-10), 7.15 (1H, t, J=8 Hz, H-11), 7.34 (1H, d, J=8 Hz, H-12), 7.49 (1H, d, J=8 Hz, H-9), 7.85 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. Ms: 398 (M$^+$), 367, 323, 251, 170 (100%), 169. HRms: Found: 398.2217. Calcd for $C_{23}H_{30}N_2O_4$: 398.2206.

Catalytic hydrogenation of the mixture of (16R*)- and (16*S)-15-*epi*-*Z*-geissoschizine dimethylacetals 7a and 8a.**

The mixture of compounds **7a** and **8a** (175.2 mg, 0.44 mmol) was hydrogenated [MeOH, PtO_2 (194 mg)] during 3 h at rt. Filtration and evaporation of the solvent yielded the crude product, which was divided by preliminary PLC (silica, CH_2Cl_2/MeOH; 93/7) into five mixture fractions: [**15** and **16** (*pseudo*) (27.9 mg, 16%)], [**11** and **12** (*normal*)[16] (38.3 mg, 22%)], [**13** and **14** (*epiallo*) (46.8 mg, 26%)], [**9** and **10** (*allo*)[16] (9.7 mg, 6%)], and [**17** and **18** (*didehydro*) (7.8 mg, 4%)]. The mixture fractions were further divided (or division was attempted) into their components by repeated PLC (silica, CH_2Cl_2/MeOH; 93/7).

Compound **15**. Y. 10.6 mg (6%). Amorphous material. Ir: 1735 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 400 (M$^+$, 100%), 399, 385, 369, 253, 251. HRms: Found: 400.2366. Calcd for $C_{23}H_{32}N_2O_4$: 400.2362.

Compound **16**. Y. 6.4 mg (4%). Amorphous material. Ir: 1735 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 400 (M$^+$, 100%), 399, 385, 369, 253, 251. HRms: Found: 400.2343. Calcd for $C_{23}H_{32}N_2O_4$: 400.2362.

Compound **11**. Y. 20.4 mg (12%). Amorphous material. Ir: 1730 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 400 (M$^+$, 100%), 399, 385, 369, 253, 251. HRms: Found: 400.2362. Calcd for $C_{23}H_{32}N_2O_4$: 400.2362.

Compound **12**. Y. 14.8 mg (8%). Amorphous material. Ir: 1730 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 400 (M$^+$, 100%), 399, 385, 369, 253, 251. HRms: Found: 400.2351. Calcd for $C_{23}H_{32}N_2O_4$: 400.2362.

Compound **13**. Y. 15.1 mg (9%). Amorphous material. Ir: 1730 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 400 (M$^+$), 399, 385, 369, 253, 251 (100%). HRms: Found: 400.2360. Calcd for $C_{23}H_{32}N_2O_4$: 400.2362.

Compound **14**. Y. 12.0 mg (7%). Amorphous material. Ir: 1730 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 400 (M$^+$, 100%), 399, 385, 369, 253, 251. HRms: Found: 400.2379. Calcd for $C_{23}H_{32}N_2O_4$: 400.2362.

Mixture of compounds **9** and **10** (separation did not succeed). Y. 9.7 mg (6%). Amorphous material. Ir: 1735 (C=O). For the ^{1}H-nmr data, see Table 3. For the ^{13}C-nmr data, see Figure 1. Ms: 400 (M$^+$, 100%), 399, 385, 369, 253, 251. HRms: Found: 400.2362. Calcd for $C_{23}H_{32}N_2O_4$: 400.2362.

Mixture of compounds **17** (minor) and **18** (major) (separation did not succeed). Y. 7.8 mg (4%). Amorphous material. Ir: 1735 (C=O). For the ^{1}H-nmr data, see above. For the ^{13}C-nmr data of compound **18**, see Figure 1. Ms: 398 (M^+), 367, 323, 251, 170 (100%), 169. HRms: Found: 398.2188. Calcd for $C_{23}H_{30}N_2O_4$: 398.2206.

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7. In conformity with our general presentation of the indoloquinolizidines under examination, compounds **1**, **1a**, and **1b**, and compounds **2**, **2a**, and **2b** are drawn in such a way that their relative configurations become 3*S**,19*S** and 3*S**,19*R**, respectively. This is done despite the convention that the centre of chirality which is first cited, and which has the lowest locant, generally is presented in such a way that its chirality descriptor becomes *R**. *A Guide to IUPAC Nomenclature of Organic Compounds, Recommendations 1993*. Panico, R.; Powell, W. H.; Richer, J.-C., Eds., Blackwell Scientific Publications, Oxford, 1993, p. 154.
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16. Due to C(3) epimerization.

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