114. A Reinvestigation of the Oxidative Rearrangement of Yohimbane-Type Alkaloids

Part B[1])

Formation of Oxindol (= 1,3-Dihydro-2*H*-indol-2-one) Derivatives

by **Reto Stahl** and **Hans-Jürg Borschberg***

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH–8092 Zürich

and **Pierre Acklin**[2])

Ciba-Geigy AG, K-136.5.82, CH–4002 Basel

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The methanolysis of the epimeric 7-chloro-7*H*-yohimbine derivatives **2** and **3** was reinvestigated. In case of the 7α-epimer **2**, the reaction was uneventful and conformed with earlier observations, *i.e.*, under sufficiently mild conditions, only the imino ether **4** (= imino ether A) was produced. Under the same conditions, the less reactive β-isomer **3** furnished a mixture of both imino ethers **4** and **5**, accompanied by the elimination product **11**, and by equal amounts of yohimbine (**1**) and 3,4,5,6-tetradehydroyohimbine (**12**), which are believed to arise through a disproportionation process of the putative intermediate 5,6-didehydroyohimbine (**23**). The nature of this divergent reactivity and of the ready equilibration of **4** and **5** was investigated by means of extensive force-field and semi-empirical calculations (AM1 and PM3) of various conformers of the compounds **2**–**5** and of some possible reaction intermediates.

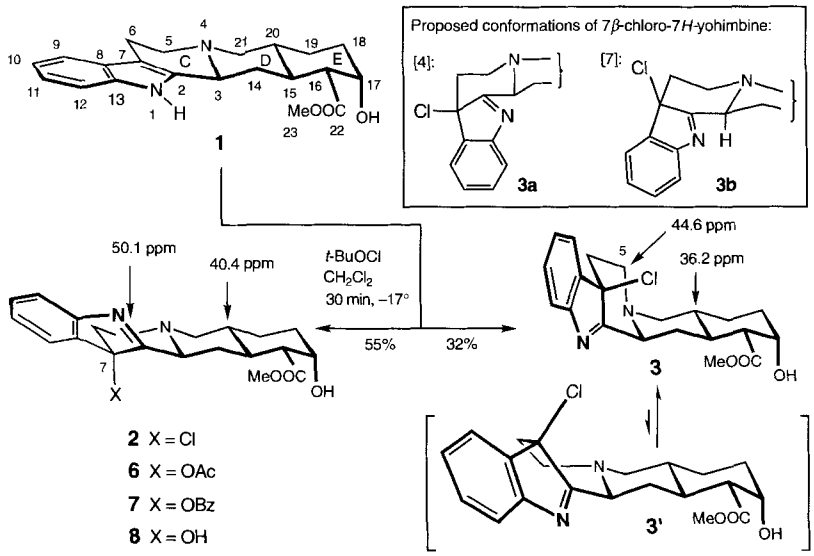
1. Introduction. – The standard method for the oxidative rearrangement of indole alkaloids into the corresponding oxindoles consists of exposure of the former to a halogenating agent, such as *t*-BuOCl or *N*-bromosuccinimide (NBS), followed by acid or base treatment in a protic solvent (for reviews, see [2]). *Godtfredsen* and *Vangedal* were the first to treat yohimbine (**1**; *Scheme 1*) and related alkaloids with *t*-BuOCl in CH_2Cl_2 [3], but their structure proposal for a chlorinated intermediate was questioned by *Saxton* [4] who proposed alternatively the chloroindolenine **2**. Subsequently, *Finch* and *Taylor* [5] as well as *Shavel* and *Zinnes* [6] independently showed this assumption to be correct. While reinvestigating this reaction some twenty years later, *Awang* and coworkers succeeded in separating and characterizing these two epimers [7][3]). In addition, they demonstrated that the α-isomer **2** can be transformed stereoselectively into **4** (*Scheme 2*) when heated in MeOH with or without added KOH. On the other hand, the β-epimer was found to react in a much more sluggish fashion, producing only small amounts, if any, of the epimeric imino ether **5**.

[1]) Part A: [1].

[2]) Author to whom correspondence regarding the various calculations should be addressed.

[3]) In that publication, all yohimbine structures were inadvertently drawn incorrectly as derivatives of β-yohimbine with opposite configuration at C(17).

Scheme 1



In the light of our recent findings within the *Aristotelia* alkaloid family [8], this result was difficult to rationalize, as one would have anticipated rather the opposite outcome. The rationale behind this contention being that chloroindolenine **3b**, in its twist-type conformation[4]), should be more strained than the α-epimer **2** which assumes an all-chair ground-state conformation. Extrapolating from the precedent case [8], one would have predicted that chloride **3b** should add MeOH and rearrange at a faster rate than its diastereoisomer **2**. However, in opposition to the rigid bridged, cage-like structures of the pentacyclic *Aristotelia* alkaloids, the yohimbane skeleton is endowed with much more conformational freedom; therefore, complications arising through this added flexibility are to be expected in the latter case. Hence, we decided to re-examine the question concerning the divergent reactivity of **3** as compared to **2**.

2. Results. – Chlorination of yohimbine (**1**) with *t*-BuOCl at −19° furnished a 2:1 mixture of (+)-**2** and (−)-**3**, which were separated by chromatography (previously claimed ratios were 1:1 [4] and 3:1 [7], resp.). The less polar, dextrorotatory isomer was assigned the 7α-configuration by *Finch et al.*, because its chiroptical properties paralleled the ones of 7α-acetoxy-7*H*-yohimbine (**6**), whose structure had been determined by X-ray crystallography of the corresponding methiodide [9]. The similarities between the NMR spectra of imino derivatives **2** and **6**–**8** clearly point to a common relative configuration at C(7) and to the same all-chair ground-state conformation for these compounds (see *Tables 1* and *2*).

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[4]) Formula **3b** in the present contribution is a facsimile drawing of the representation of **3** in *Scheme 2* within [7]. This conformation is roughly equivalent to our preferred representation **3'**, but different from the earlier, clearly unrealistic drawing **3a** [4].

Table 1. *^{1}H-NMR Chemical-Shift Values δ* [ppm]. In $CDCl_3$, unless stated otherwise.

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**[a]	**12**[a][b]
H–N(1)	7.77	–	–	–	–	–	–	–	8.82	8.95	–	–
H–C(3)	3.32	3.43	3.93	2.45	2.38	2.95	3.04	3.10	2.52	2.31	–	–
H_α–C(5)	2.61	2.88	2.55	2.41	2.44	2.65	2.78	2.77	2.50	2.45	2.99	8.29
H_β–C(5)	3.07	2.79	3.45	3.28	3.32	2.75	2.84	2.60	3.27	3.36	3.16	
H_α–C(6)	2.71	2.56	1.89	2.25	2.42	2.68	2.89	2.38	2.37	2.45	2.81	8.42
H_β–C(6)	2.98	1.82	2.74	2.00	2.01	1.47	1.61	1.45	2.00	2.00	2.92	
H–C(9)	7.46	7.48	7.44	7.35	7.18	7.38	7.42	7.38	7.38	7.17	7.38	8.31
H–C(10)	7.07	7.28	7.26	7.06	7.09	7.20	7.20	7.18	7.02	7.03	6.94	7.43
H–C(11)	7.12	7.39	7.37	7.22	7.24	7.37	7.38	7.28	7.20	7.17	7.05	7.76
H–C(12)	7.29	7.62	7.53	7.30	7.29	7.61	7.66	7.43	6.91	6.87	7.25	7.70
H_{ax}–C(14)	1.36	1.71	2.22	0.65	1.02	1.82	1.87	1.60	0.68	1.28	–[c]	3.08
H_{eq}–C(14)	1.99	2.13	1.64	0.88	1.02	2.05	2.11	1.98	1.07	1.17		4.03
H–C(15)	2.02	1.98	2.01	1.69	1.66	1.94	1.95	1.83	1.73	1.67	2.77	2.59
H–C(16)	2.34	2.37	2.36	2.11	2.23	2.37	2.38	2.31	2.11	2.27	2.33	2.64
H–C(17)	4.22	4.21	4.19	4.06	4.09	4.19	4.17	4.15	4.09	4.11	4.27	4.44
H_{ax}–C(18)	1.56	1.54	1.57	1.45	1.46	1.50	1.50	1.49	1.43	1.49	1.70	1.82
H_{eq}–C(18)	1.97	1.98	2.01	1.94	1.94	1.96	1.95	1.93	1.92	1.93	1.95	2.04
H_{ax}–C(19)	1.56	1.60	1.51	1.54	1.54	1.50	1.50	1.49	1.55	1.49	1.54	1.71
H_{eq}–C(19)	1.42	1.38	1.31	1.38	1.40	1.39	1.35	1.32	1.38	1.49	1.51	1.75
H–C(20)	1.55	1.41	1.59	1.29	1.40	1.46	1.50	1.32	1.29	1.49	1.70	2.11
H_{ax}–C(21)	2.23	2.26	2.55	1.90	1.86	2.18	2.16	2.14	1.92	1.83	2.80	4.43
H_{eq}–C(21)	2.94	2.91	2.94	3.11	3.20	2.92	2.93	2.75	3.10	3.19	3.07	4.79
COOMe	3.81	3.77	3.71	3.56	3.58	3.76	3.75	3.75	3.57	3.59	3.78	3.82
MeO–C(7)	–	–	–	4.06	4.09	–	–	–	–	–	–	–

[a]) In CD_3OD. [b]) Assignments of the aromatic protons in accordance with *Hesse* and coworkers [14]. [c]) Exchanged, appearing at 4.92 ppm in (D_8)THF.

In the case of the minor, more polar isomer, the situation is more complex: while the configuration at C(7) is undoubtedly (*R*) (7β-chloro) by application of the exclusion principle, the problem posed by its conformation is less trivial. An inspection of molecular models reveals that a chair conformation (see **3a**) for ring C is not feasible as long as the C/D ring-junction is *trans*, but rather that geometric constraints tend to force ring C into a twist-boat conformation (see **3'**). However, a hitherto seemingly overlooked possibility that avoids at least part of the imposed strain consists in an inversion at N(4), which leads to a *cis*-quinolizidine derivative with ring C in a chair conformation (see **3**). The following observations strongly support the hypothesis that conformer **3** is the major conformer in solution: *1*) The ^{1}H-NMR coupling pattern within the $CH_2(5)/CH_2(6)$ fragment is more consistent with a staggered than with an eclipsed arrangement. *2*) In a difference NOE experiment, both H–C(20) and H_β–C(14) showed enhanced intensity, when the (axial) H_β–C(5) was irradiated. *3*) In the ^{13}C-NMR spectrum, C(20) showed up at 36.2 ppm, *i.e.*, shielded by 4 ppm compared to all other yohimbine derivatives mentioned in this paper, where C(20) invariably absorbed at 40.4 ± 0.4 ppm. A similar shielding was observed for C(5) which appeared 5.5 ppm upfield compared to isomer **2**. These mutual shieldings are most likely caused by a *syn-γ* effect which operates only in the *cis*-quinolizidine conformer **3** (for similar observations, see [10] [11]). *4*) In contrast to **2**, the β-epimer **3** showed no *Bohlmann* band in the IR spectrum [12]. *5*) Extensive force-field

Table 2. *^{13}C-NMR Chemical-Shift Values* δ [ppm]. In $CDCl_3$, unless stated otherwise.

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**[a])	**12**[a])[b])
C(2)	134.5	179.7	179.7	182.1	183.3	179.7	179.6	183.9	181.9	182.0	138.2	135.5
C(3)	59.9	59.2	62.8	69.5	73.0	60.4	60.5	60.0	71.4	74.3	128.2	145.2
C(5)	52.9	50.1	44.6	53.4	54.4	49.9	50.0	50.0	53.4	54.5	52.5	133.9
C(6)	21.8	37.7	36.9	32.9	33.0	36.2	36.3	36.4	35.3	35.0	22.4	116.7
C(7)	108.3	68.8	67.2	59.6	59.2	84.8	85.1	80.2	56.8	56.0	110.3	132.3
C(8)	127.4	140.3	140.6	152.3	152.4	137.2	137.2	141.0	133.8	135.5	131.6	121.4
C(9)	118.1	122.6	122.3	123.4	121.5	122.0	122.2	122.2	125.0	123.0	119.1	123.1
C(10)	119.4	126.7	126.8	123.3	123.9	126.1	126.2	126.2	122.4	122.7	119.8	124.0
C(11)	121.4	130.0	129.9	127.6	128.1	129.8	129.9	129.6	127.5	128.0	123.0	132.7
C(12)	110.7	121.5	121.2	118.0	118.0	121.5	121.6	121.1	109.6	109.6	111.9	113.9
C(13)	136.0	152.7	152.2	140.6	140.2	153.9	154.1	153.0	140.3	141.0	138.8	141.5
C(14)	34.4	31.3	29.7	30.2	29.7	31.0	31.1	31.0	30.4	29.7	98.8[c])	31.2[d])
C(15)	36.7	36.1	37.9	36.3	36.7	36.2	36.2	36.1	36.1	36.6	35.7	31.1
C(16)	52.4	52.2	52.1	52.2	52.3	52.0	52.0	52.0	52.4	52.3	54.4	53.5
C(17)	67.0	66.9	66.5	66.7	66.6	66.7	66.7	67.0	66.7	66.7	69.0	68.2
C(18)	31.5	31.4	31.2	31.3	31.3	31.1	31.1	31.2	31.3	31.3	34.2	32.6
C(19)	23.3	23.1	23.0	23.4	23.4	23.1	23.1	23.1	23.4	23.4	24.9	23.0
C(20)	40.8	40.4	36.2	40.4	40.4	40.4	40.4	40.2	40.4	40.0	39.6	36.8
C(21)	61.4	61.5	59.8	59.0	59.0	61.5	61.4	61.4	58.8	58.8	58.1	61.0
C(22)	175.6	175.5	175.8	175.8	175.8	175.8	175.9	175.5	175.5	175.8	175.5	174.3
COO*Me*	52.0	52.0	51.9	51.7	51.8	52.0	52.0	51.9	51.7	51.7	52.2	52.5
*Me*O–C(7)	–	–	–	56.5	56.4	–	–	–	–	–	–	–

[a]) In CD_3OD.

[b]) Assignments in the aromatic section according to [15].

[c]) Appears as a 1:1:1 *t* (^1J = 23.8 Hz) of low intensity due to coupling with D–C(14).

[d]) Appears as a 1:2:3:2:1 *quint.* (^1J = 18 Hz) of low intensity due to coupling with 2 D–C(14) (for a similar observation, see [14]).

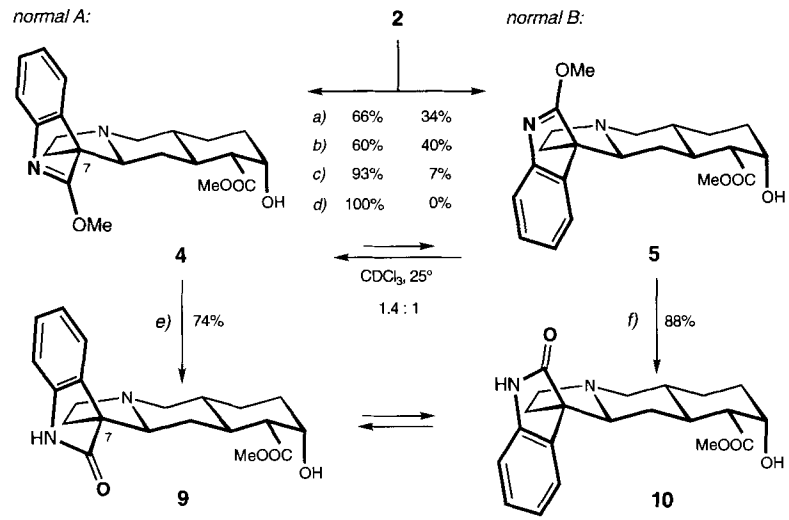
calculations disclosed **3** to represent the ground-state conformer of this compound, being some 5 kcal/mol more stable than the next-higher lying twist conformer **3′** (see *Appendix, Table 7*)[5]).

When re-examining the rearrangement of imino chloride **2**, we noticed that the standard conditions (KOH, 30 min reflux in MeOH [5] [6]) led to diminished yields of the epimeric imino ethers **4** and **5** (*Scheme 2*) due to partial saponification of the methyl-ester moiety (see *Table 3, Entry 1* (and *5*))[6]). This side reaction could be suppressed if NaOMe was employed as the base, and – in accordance with earlier work [7] – the rearrangement

[5]) Possibly, *Awang* and coworkers [7] did not consider conformation **3**, because they misassigned several ^{13}C-NMR signals, including the one for C(20). In the light of the above conclusions, a re-interpretation of an earlier model study by *Dolby* and *Gribble* [13] seems warranted: their deduction of the relative configuration of two epimeric chloroindolenines, obtained through oxidation of 1,2,3,4,7,12,12b-octahydroindolo[2,3-*a*]-quinolizine, was shown to be erroneous [7]. It now seems that their slower moving diastereoisomer had a conformation analogous to **3** (equivalent to formula **3aiii** in their Scheme IV [13]), because in both compounds H–C(3) shows a similar chemical shift (δ 3.87 *vs.* 3.93 ppm). The observed deshielding by 0.5 ppm compared to **2** is most likely caused by the anisotropy effect exerted by the coplanar C=N bond, and not by the Cl substituent as assumed before [13].

[6]) In the case of related 21-oxo derivatives, additional complications arose due to concomitant lactam ring opening processes [16].

Scheme 2



a) KOH, MeOH, 30 min reflux. *b*) MeOH, 40 h reflux. *c*) 0.5N NaOMe, MeOH, 2 min reflux. *d*) 0.5N NaOMe, MeOH, 30 min 25°. *e*) 10% aq. CF_3COOH, 30 min reflux. *f*) CF_3SO_3H, CH_2Cl_2/H_2O, 6 h 25°.

was found to be kinetically controlled under sufficiently mild conditions, producing exclusively imino ether **4** (= imino ether A; *Table 3*, *Entry 4*). The known [7] [11] equilibration of **4** to furnish a 1.4:1 mixture of the spiro epimers **4** and **5** is a very facile process which takes place readily at room temperature in MeOH or $CHCl_3$. From the data detailed in *Table 4*, the activation energy of this reversible first-order reaction can be estimated to amount to *ca.* 24 kcal/mol at 25° in either direction. This equilibration process closely resembles the well-known epimerization of the corresponding oxindoles within the tetrahydro-β-carboline alkaloid series [17] [18], and its mechanism will be discussed in more detail below.

Table 3. *Solvolysis of* **2** *and* **3**. Product composition, as determined by ^{1}H-NMR spectroscopy (300 MHz, $CDCl_3$) of the crude material (Σ), isolated after workup.

Entry	Starting material	Conditions	Σ [%]	**4** [%]	**5** [%]	**1** [%]	**11** [%]	**12** [%]
1	**2**	KOH, MeOH, 30 min reflux	78	32[a])	35[a])			
2		MeOH, 40 h reflux	98	60	40			
3		0.5N NaOMe, MeOH, 2 min reflux	98	93	7			
4		0.5N NaOMe, MeOH, 30 min 25°	98	100	0			
5	**3**	KOH, MeOH, 30 min reflux[b])	50	22	21	30		
6		MeOH, 3 d 25°	88	55	45			
7		0.5N NaOMe, MeOH, 2 min reflux	86	7	44	11	25	13
8		0.5N NaOMe, MeOH, 40 min reflux	90	22	27	18	16	17
9		0.5N NaOMe, MeOH, 3 h 25°[c])	95	20	60			

[a]) Yield of isolated material (after chromatography). [b]) Unreacted **3**: 27%. [c]) Unreacted **3**: 20%.

Table 4. *Equilibration of the Imino Ethers* **4** *and* **5** *in* $CDCl_3$ *at 25°*

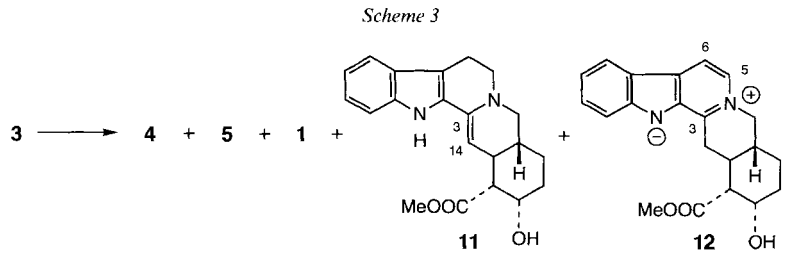
Starting material	Products	10 min	24 h	48 h	120 h	192 h
4	**4/5**	98:2	80:20	75:25	60:40	58:42
5	**4/5**	7:93	31:69	38:62	54:46	58:42

Table 5. *Hydrolysis of the Imino Ethers* **4** *and* **5**

Entry	Starting material	Conditions	**9** [%]	**10** [%]	**9/10**
1	**4**	10% aq. AcOH, 2 h reflux	56	44	3:2
2		10% aq. CF_3COOH, 4 h reflux	> 99	< 1	> 100:1
3	**5**	10% aq. AcOH, 2 h reflux	56	44	3:2
4		10% aq. CF_3COOH, 3 h reflux	34	66	1:2
5		5 equiv. CF_3SO_3H, CH_2Cl_2/H_2O 6:1, 6 h 25°	< 5	> 95	< 1:20

The acid-catalyzed hydrolysis of imino ether **4** under the classical conditions (10% aqueous AcOH, 4 h reflux [5]) is known to lead to the equilibrium mixture of the two corresponding oxindoles **9** and **10**. Subsequently, *Herlem* and *Khuong-Huu* reported that under the same conditions, this starting material yielded oxindole **10** (= oxindole B) in 59% yield (probably accompanied by an unspecified amount of **9**), and that a similar treatment of imino ether **4** with CF_3COOH produced a 68% yield of **9** [11]. Their explanation was that – under kinetic control – **4** should yield only **9**, and that a subsequent epimerization of the resulting oxindoles *via* a *retro-Mannich* process is prevented in the presence of a sufficiently strong acid which permanently protonates N(4)[7]). This interpretation met with scepticism ([7], footnote 17), but our results, displayed in *Table 4*, are fully consistent with the reasoning of the French group. Indeed, we were able to demonstrate for the first time that it is possible to hydrolyze the more labile imino ether **5** (= imino ether B) with complete retention of configuration at C(7) to oxindole **10**, if an even stronger acid (CF_3SO_3H) is employed (*Table 5, Entry 5*).

Scheme 3



[7]) In anticipation to this explanation, *Finch* and *Taylor* had shown before that hydrolysis of the methiodide of **4** produced exclusively the methiodide of **9** [5]. This correlation formed the basis for their assignment of configuration to **4**.

The solvolytic behavior of the 7β-isomer **3** was investigated next (*Scheme 3*). While treatment with KOH in MeOH (90 min reflux) was reported to yield none of the imino ethers **4** and **5**, but only 'very polar, probably polymeric' products [7], we found that after 30 min reflux, a 1:1 mixture of the imino ethers was detectable, albeit in only *ca.* 20% combined yield (*Table 3, Entry 5*). Surprisingly, significant amounts of yohimbine (**1**) were produced at the same time. Whereas a solvolysis in neat MeOH furnished the equilibrium mixture of **4** and **5** in excellent yield, and uncontaminated with yohimbine (**1**) (*Table 3, Entry 6*), this side product was formed again when NaOMe was added to the mixture (*Entries 7* and *8*). Under these conditions, a fourth compound was obtained that was shown by TLC and ^{1}H-NMR spectroscopy to be the known elimination product **11**, which is generally prepared by treatment of **2** or **3** with ethanolic HCl [3]. As the reduced product, yohimbine (**1**), most likely arose through some disproportionation process, we looked out for a fifth component being situated on a higher oxidation level than the starting material **3**. Indeed, a strongly fluorescent by-product was detected in the crude mixture and identified as 3,4,5,6-tetradehydroyohimbine (**12**) [19] by comparison with a reference sample which was prepared according to the method of *Janot et al.* [20].

3. Discussion. – Under stereoelectronic control [21], the addition of MeOH or other nucleophiles to imine double bonds that are positioned endo- or exocyclic with respect to a six-membered ring is known to take place from an axial direction (for recent examples, see [22]). In the case of the α-configurated chloroindolenine **2**, this would mean that the favored product resulting from MeOH addition to its ground-state conformation **2** should be the *trans*-adduct **13** (*Scheme 4*). As pointed out before, however, this intermediate – if formed at all[8]) – cannot adopt a conformation in which a concerted ring contraction with expulsion of Cl^- can take place, because the C(2)–C(3) bond that should undergo migration is always synclinal or orthogonal to the leaving group at C(7) [7]. This is not so in the case of the *cis*-addition product which can readily assume at least two conformations (**14** and **14″**) where the bonds in question are not far from being correctly aligned for a concerted ring contraction. Maybe not surprisingly, none of the 41 unique conformations (local minima) found for the *cis*-adduct **14** by force-field calculations possessed an acceptable dihedral angle of 180 ± 20° between the crucial bonds. To get some idea how much additional strain is imposed by the required distortion of **14** and **14″**, the critical torsion angle was arbitrarily set to 180 ± 3° by imposing a high artificial torsion potential well (for details, see *Appendix*). The conformers **14*** and **14″*** that were created by this procedure now have perfectly aligned bonds for a concerted ring contraction, and the additional strain imposed by the required conformational change from **14** to **14*** and from **14″** to **14″*** is quite substantial (12.8 and 5.3 kcal/mol, resp.). However, these values certainly represent upper limits, as the stereoelectronic requirements for the observed rearrangement are in all likelihood less stringent than imposed for these calculations.

As the pathway **2** → **14′** → **14** → **14*** → **4** would involve an unfavorable MeOH addition step from an equatorial direction, we prefer the alternative route **2** → **2′** → **14″** → **14″*** → **4′** → **4** that proceeds under strict stereoelectronic control. The activation energy of the

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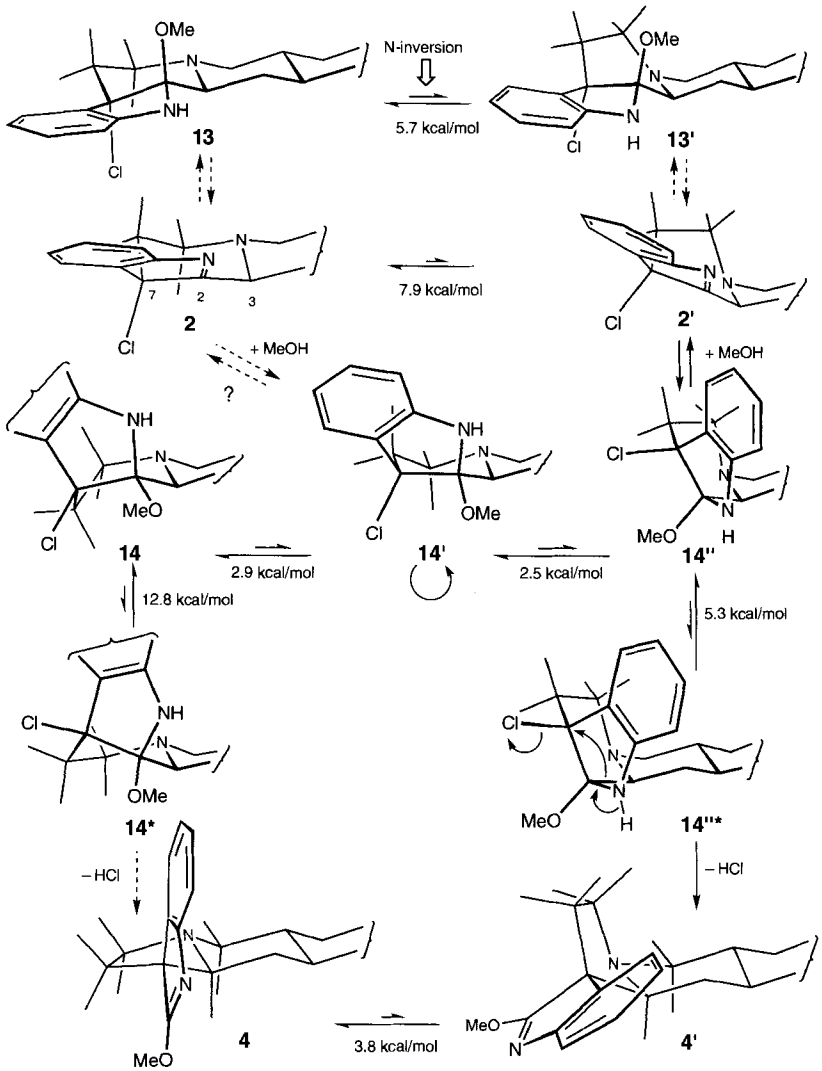
[8]) Semi-empirical calculations at the AM1 and PM3 level indicated a very substantial difference between the heat of formation of **13** and **14** (11.4 kcal/mol in favor of the *cis*-adduct **14**; see *Appendix, Table 6*).

Scheme 4[a])



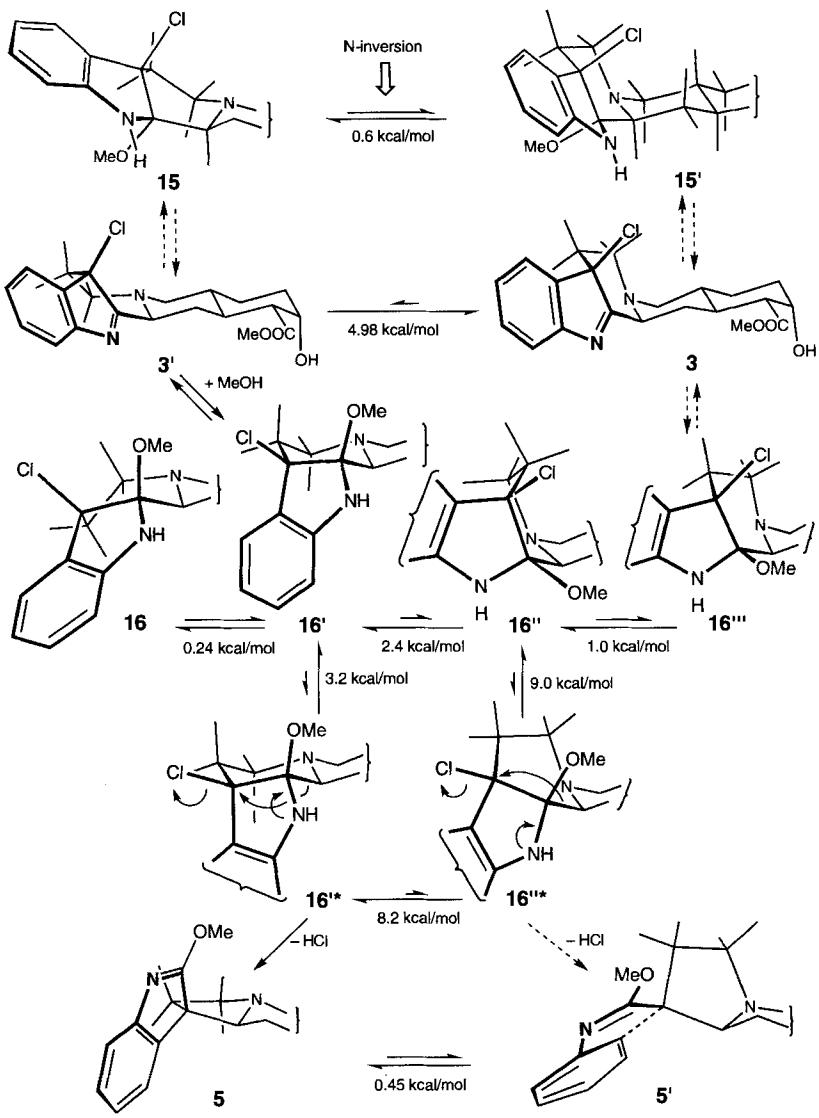
[a]) The energy values, taken from *Table 7*, represent calculated differences in strain energy ($\Delta\Delta H$) between various conformers. Unlabelled substituents are H-atoms.

global transformation **2** → **4** can be estimated to amount to 21–22 kcal/mol[9]), and the fact that the MeOH adduct **14** did not accumulate and could never be detected in the NMR spectra when monitoring the progress of the reaction, points to the MeOH addition process as being the rate-determining step in this sequence.

[9]) An upper limit of *ca.* 22 kcal/mol follows from the fact that the consecutive epimerization of **4** to **5**, whose activation energy was determined to be *ca.* 24 kcal/mol, is suppressed to the extent of at least 97% (*Table 3, Entry 4*).

Similar arguments can be put forward to explain the preferential formation of **5**, under mild conditions, when starting with the 7β-epimer **3**. Again, the *trans*-addition product **15** (*Scheme 5*) represents a cul-de-sac, whereas the *cis*-diastereoisomer **16** can rearrange to **5** or **5′** through either of its conformers **16′** or **16″**, respectively. The stereoelectronic requirements discussed above would seem to indicate that the preferred pathway again involves an initial conformational change of the starting material **3** to **3′**,

Scheme 5[a])

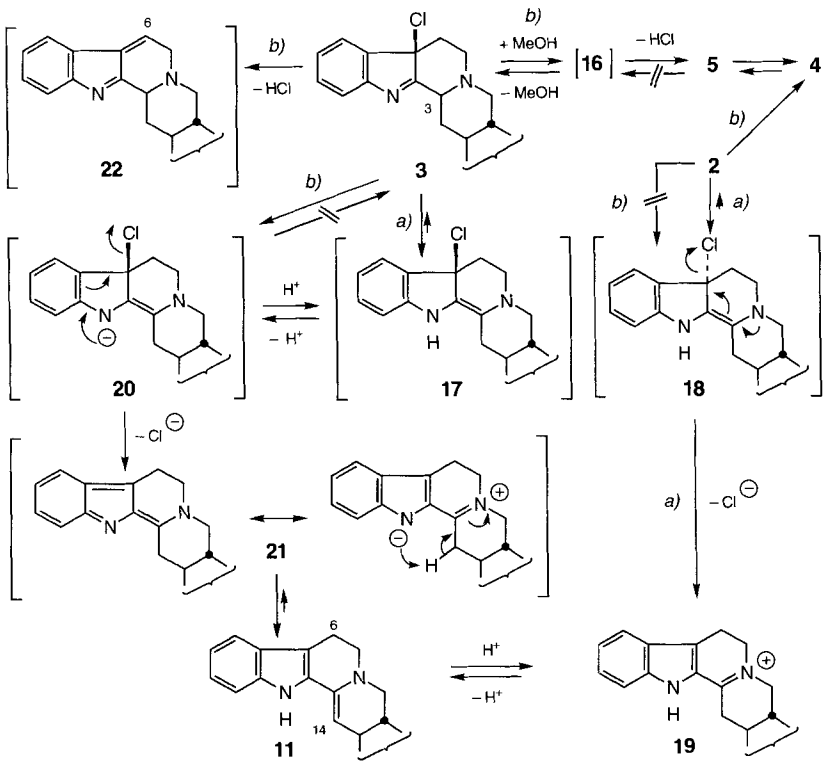


[a]) The energy values, taken from *Table 7*, represent calculated differences in strain energy ($\Delta\Delta H$) between various conformers. Unlabelled substituents are H-atoms.

followed by MeOH addition from the axial direction to furnish the intermediate **16′**. In this conformer, the calculated torsion angle between the crucial bonds C(2)–C(3) and C(7)–Cl amounts to 158° and, therefore, comparatively little energy is required to reach the optimum conformation **16′*** (τ 178°) for the subsequent ring contraction.

In the case of the 7β-epimer **3**, the situation is more complex as compared to **2**, due to the formation of the by-products **1**, **11**, and **12** under conditions where **2** very cleanly furnished a 93:7 mixture of **4** and **5**. The detailed pathways, through which these by-products are formed, are not known with certainty at present, and the routes displayed in *Scheme 6* are speculative. Under acidic conditions, the formation of the elimination product **11** from **2** and **3** is believed to proceed *via* the enamine tautomers **17** and **18**, respectively, that undergo a vinylogous β-elimination to give iminium ion **19**, the protonated form of **11** [5]. Under basic conditions, however, only **3** seems to be deprotonated to give **20** that, upon elimination, yields the delocalized species **21**, a tautomer of **11**. When the same reaction was performed in deuterated methanol, the isolated imino ethers **4** and **5** showed no D-incorporation into position 3 indicating that the deprotonation step **3** → **20** is essentially irreversible, either because protonation at N(1) to yield **17**, or elimination of Cl^- to give **21**, are faster processes.

Scheme 6

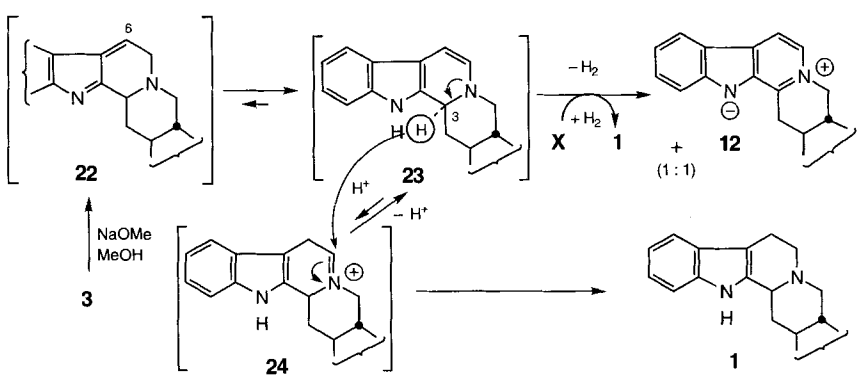


a) HCl, MeOH. *b*) NaOMe, MeOH.

As borne out by control experiments, the elimination product **11** is stable under the basic conditions that lead to its formation. Therefore, it cannot represent the precursor for the two remaining products **1** and **12**. A more likely candidate for the required disproportionation would seem to be the elusive[10]) 5,6-didehydroyohimbine (**23**) that could be formed from **3** by an *E*2 *anti*-elimination process *via* **22**, a metastable tautomer of enamine **23** (*Scheme 7*). Whereas **23**, and even more so the corresponding anion derived by deprotonation of H–N(1), can be expected to be a good hydride donor, vaguely resembling NADPH, the nature of the hydride acceptor **X** that is reduced to yohimbine (**1**) is more obscure. In principle, all compounds being situated on the same oxidation level as the starting material **3** have to be considered as possible candidates, but the following experiment strongly points to **24**, the protonated form of **23**, as the substrate that is reduced. When the known [24] reduction of **12** with $NaBH_4$ in MeOH was repeated using less than stoichiometric amounts of reducing agent, monitoring of the reaction by ^{1}H-NMR spectroscopy showed that only the signals of the starting material **12** and the final product **1** were detectable, but none that could be ascribed to the expected intermediate **23**. This means that **24** is reduced at a considerably faster rate than **12** despite the unfavorable position of the equilibrium **23**/**24** in a basic medium[11]). Accordingly, when the same experiment was carried out with $NaBH_4$ in CD_3OD as the solvent, the isolated yohimbine (**1**) was deuterated regioselectively at the expected position C(6).

Some comments regarding the question of the startling differences between the reactivities of **2** and **3** seem warranted. Judging from the isolated amounts of products in the latter case, the difference in activation energies for the concurring parallel reactions cannot be more than 0.5 kcal/mol at 64°, but must amount to at least 1.7 kcal/mol in favor of the reaction **3** → **5** at 25° (see *Table 3*, *Entries 7–9*). Evidently, considerable differences between the activation entropies in the respective rate-limiting steps in the sequences **3** → **11** and **3** → **1** + **12**, as compared to **3** → **5**, must be responsible for the

Scheme 7

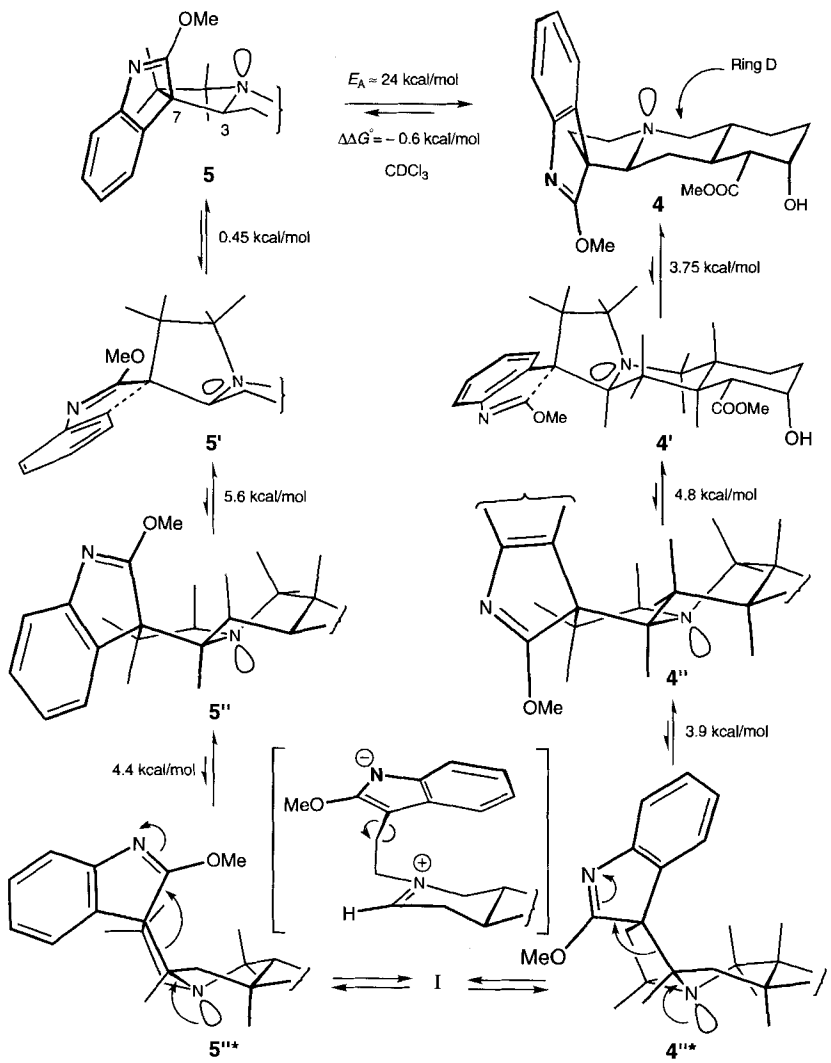


[10]) All 1,2-dihydro-β-carboline derivatives described so far in the literature are endowed with a π-acceptor substituent at C(3), such as –COOMe [23], which seems to be essential for stabilizing this system.

[11]) Certain enamines, like **11** *e.g.*, are known to be readily reduced with $NaBH_4$ in MeOH [25], in spite of their reactive iminium forms, such as **19**, being present in rather low concentrations at a pH in the vicinity of 10.

remarkable temperature dependence of the observed product distribution. On the other hand, **2** was found to react 13 times faster than **3** (0.5N NaOMe in CD_3OD at 25°, progress of reaction monitored by ^{1}H-NMR), and this amounts to a 1.5 kcal/mol difference in the respective activation energies. Taken together, it seems as if this additional lability of **2** towards rearrangement to **4** serves to protect this compound from the concurring side reactions that were observed in the case of **3**. The difference in reactivity is also reflected in the semi-empirical calculations, as the transition **2** → **14** is predicted to be 3.4 (PM3) to

Scheme 8[a])



[a]) The energy values, taken from *Table 7*, represent calculated differences in strain energy ($\Delta\Delta H$) between various conformers. Unlabelled substituents are H-atoms.

3.8 kcal/mol (AM1) more favorable than the alternative reaction **3** → **16**, and it seems as if at least part of this variance in the differences of the heats of formation is reflected in the respective transition states.

The facile equilibration of the imino ethers **4** and **5** is believed to proceed through the ring-opened zwitterionic intermediate **I** (*Scheme 8*), which is formed by a *retro*-aza-*Mannich* reaction [5]. However, this type of fragmentation requires the lone-pair of N(4) to be aligned in an *anti*-periplanar fashion to the C(3)–C(7) bond which is not the case in the respective ground-state conformations of either **4** or **5** (see [21] and ref. cit. therein). The same holds for the N(4)-inverted conformers **4′** and **5′**, and the only way to properly align the orbitals in question consists in transforming ring D into a twist-boat form which renders the molecules more flexible, so that the stereoelectronically required geometries **4″** and **5″** can readily be assumed. Again, these pathways were mapped out with the aid of force-field calculations, and the resulting relative strain energies of the intermediate conformers **4″*** and **5″*** indicate that the required conformational changes represent energetically feasible processes at room temperature.

Appendix: Calculations. – All conformations were calculated with Batchmin V. 5.0 in MacroModel V. 5.0, using the force-field AMBER [26]. To this end, 5000 conformations of each compound were generated according to the systematic Monte Carlo procedure [27] and minimized *in vacuo* by means of the TNCG method [28]. The resulting conformations were then relaxed in the continuum model for $CHCl_3$ [29] with the same minimization method. Some of the resulting low-energy conformations are listed in *Table 7*. To calculate the strain energy of the starred conformers that do not represent local minima, the crucial torsion angle was set to 180° and a rotational barrier of 600 kcal/degree^2 was imposed on the bond in question (C(2)–C(7) for **14** and **16**, C(3)–N(4) for **4** and **5**). The created conformers were minimized using the force-field AMBER (continuum model for $CHCl_3$) and the resulting energies calculated after removal of the imposed constraints

Table 6. *Calculated Heats of Formation* ΔH_f [kcal/mol]

	No. of unique conformers	ΔH_f	
		PM3	AM1
1	23	−102.19	−93.82
2	17	−97.31	−90.45
3	11	−99.09	−91.33
4	19	−129.05	−117.80
5	23	−128.58	−116.92
9	12	−150.57	−139.91
10	22	−151.58	−142.12
11	27	−83.88	−73.18
13	23	−143.33	−137.02
14	46	−154.84	−148.42
15	20	−142.53	−136.55
16	40	−153.24	−145.53
17	10	−105.38	−96.92
18	11	−106.37	−98.00
22	33	−69.57	−60.88
23	19	−82.27	−72.93

Table 7. *Calculated Relative Strain Energies* ΔΔH [kcal/mol] *of Some Conformers*

	Conformation	CDE[a])	l.p.[b])	$\Delta\Delta H$	τ[c])		Conformation	CDE[a])	l.p.[b])	$\Delta\Delta H$	τ[c])
2	**2**	ccc	β	0.00		**3**	**3**	ccc	α	0.00	
	2′	tcc	α	7.94			**3′**	bcc	β	4.98	
4	**4**	-cc	β	0.00	71.6	**5**	**5**	-cc	β	0.00	70.5
	4′	-cc	α	3.76	70.0		**5′**	-cc	α	0.45	76.1
	4″	-tc	α	8.54	129.5		**5″**	-tc	α	6.08	132.4
	4″*	-tc	α	12.44	173.4		**5″***	-tc	α	10.50	177.0
13	**13**	ccc	β	0.00	52.8	**15**	**15**	tcc	β	0.00	53.0
	13′	tcc	α	5.65	48.8		**15′**	ccc	α	0.60	60.5
14	**14**	bcc	β	0.00	116.7	**16**	**16**	bcc	β	0.00	131.4
	14′	ccc	β	2.85	94.3		**16′**	ccc	β	0.24	158.4
	14″	ccc	α	5.38	153.8		**16″**	bcc	α	2.63	116.5
							16‴	ccc	α	3.64	89.7
	14*	tcc	β	12.76	177.2		**16′***	bcc	β	3.46	178.0
	14″*	ccc	α	10.70	177.4		**16″***	bcc	α	11.63	178.4

[a]) Conformations of rings C, D, and E in this order (c = chair, b = boat, t = twist).
[b]) Orientation of the N(4) lone pair (l.p.).
[c]) Dihedral angle, defined by the fragment C(3)–C(7)/N(4)–lone pair for compounds **4** and **5**, and by the fragment C(3)–C(2)/C(7)–Cl for compounds **13**–**16**.

without further minimization. This procedure resulted in dihedral angles of 178 ± 1° for the crucial bonds in all cases.

In addition, for each compound, the ΔH_f of the found global minimum was calculated with Mopac 93 using both the Hamiltonians AM1 [30] and PM3 [31] with the results shown in *Table 6*.

We thank the *Forschungskommission der ETH Zürich* and the *Swiss National Science Foundation* for financial support.

Experimental Part

General. See [1].

Chlorination of Yohimbine (**1**) (Method: [11]). To a cold (−17°) soln. of yohimbine (**1**; *Fluka, purum*; 210 mg, 0.6 mmol) in CH_2Cl_2 (8 ml) was added 0.1M *t*-BuOCl in CCl_4 (4 ml) within 15 min. After stirring for 30 min at −17°, H_2O (5 ml) was added and the mixture worked up with CH_2Cl_2. The resulting material (230 mg of a yellow foam) was chromatographed (silica gel, cyclohexane/THF/Et_3N 100:40:15): 123.3 mg (55%) of (+)-**2** and 73.5 mg (32%) of (+)-**3**.

*(+)-7α-Chloro-7*H*-yohimbine* (= *Methyl 7α-Chloro-17α-hydroxy-7*H*-yohimban-16α-carboxylate*; (+)-**2**): M.p. 77° (MeOH) ([7]: 78–82°). $[\alpha]_D$ = +130.5 (*c* = 1.1, $CHCl_3$). UV (EtOH): 293 (3.27), 267 (3.26), 225 (4.21). IR ($CHCl_3$): 3610, 3500, 2940, 2820, 2755, 1710, 1592, 1456, 1437, 1340, 1149, 1107, 1013, 960, 902, 870, 662. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.62 (*dt*, *J* = 7.7, 0.8, 1 H); 7.48 (*ddd*, *J* = 7.3, 1.2, 0.6, 1 H); 7.39 (*td*, *J* = 7.7, 1.3, 1 H); 7.28 (*td*, *J* = 7.5, 1.0, 1 H); 4.21 (*m*, 1 H); 3.77 (*s*, 3 H); 3.43 (*dd*, *J* = 11.0, 2.6, 1 H); 2.99 (br. *s*, 1 H); 2.91 (*dd*, *J* = 11.1, 3.3, 1 H); 2.88 (*td*, *J* = 12.0, 2.4, 1 H); 2.79 (*ddd*, *J* = 12.0, 4.4, 2.3, 1 H); 2.56 (*dt*, *J* = 14.6, 2.4, 1 H); 2.37 (*dd*, *J* = 11.6, 2.2, 1 H); 2.26 (*dd*, *J* = 11.1, 10.7, 1 H); 2.13 (*dt*, *J* = 13.2, 3.0, 1 H); 2.02–1.95 (*m*, 2 H); 1.82 (*ddd*, *J* = 14.6, 12.0, 4.4, 1 H); 1.71 (*ddd*, *J* = 13.2, 12.1, 11.0, 1 H); 1.64–1.49 (*m*, 2 H); 1.45–1.34 (*m*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 179.7 (*s*); 175.5 (*s*); 152.7 (*s*); 140.3 (*s*); 130.0 (*d*); 126.7 (*d*); 122.6 (*d*); 121.5 (*d*); 68.8 (*s*); 66.9 (*d*); 61.5 (*t*); 59.2 (*d*); 52.2 (*d*); 52.0 (*q*); 50.1 (*t*); 40.4 (*d*); 37.7 (*t*); 36.1 (*d*); 31.4 (*t*); 31.3 (*t*); 23.1 (*t*). HETCOR: 130.0/7.39; 126.7/7.28; 122.6/7.48; 121.5/7.62; 66.9/4.21; 61.5/2.91, 2.26; 59.2/3.43; 52.2/2.37; 52.0/3.77; 50.1/2.88, 2.79;

40.4/1.41; 37.7/2.56, 1.82; 36.1/1.98; 31.4/2.13, 1.71; 31.3/1.98, 1.54; 23.1/1.60, 1.38. FAB-MS: 391 (36, $[M + 3]^+$), 390 (35), 389 (100, $[M + 1]^+$), 388 (38), 387 (29), 354 (28), 353 (69), 352 (46), 351 (30), 289 (12).

*(+)-7β-Chloro-7*H*-yohimbine* (= *Methyl 7β-Chloro-17α-hydroxy-7*H*-yohimban-16α-carboxylate*; (+)-**3**): M.p. 82–85° (MeOH) ([7]: 85–90°). $[\alpha]_D = +10$ ($c = 0.9$, $CHCl_3$). UV (EtOH): 291 (3.35), 262 (3.35), 226 (4.21). IR ($CHCl_3$): 3640, 3460, 2950, 2870, 1714, 1633, 1591, 1454, 1437, 1363, 1260, 1169, 1018. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.53 (*ddd, J* = 7.7, 1.0, 0.7, 1 H); 7.44 (*ddd, J* = 7.4, 1.3, 0.6, 1 H); 7.37 (*td, J* = 7.7, 1.3, 1 H); 7.26 (*td, J* = 7.5, 1.0, 1 H); 4.19 (*m*, 1 H); 3.93 (*dd, J* = 12.3, 2.9, 1 H); 3.71 (*s*, 3 H); 3.45 (*dd, J* = 4.4, 1.8, 1 H); 3.45 (*dt, J* = 16.3, 4.4, 1 H); 2.94 (*dd, J* = 13.3, 3.6, 1 H); 2.74 (*dt, J* = 14.5, 4.3, 1 H); 2.55 (*dd, J* = 13.0, 11.2, 1 H); 2.55 (*ddd, J* = 11.5, 5.3, 4.0, 1 H); 2.36 (*dd, J* = 11.5, 2.0, 1 H); 2.22 (*q, J* = 12.3, 1 H); 2.04–1.96 (*m*, 2 H); 1.89 (*ddd, J* = 14.5, 9.0, 5.4, 1 H); 1.64 (*dt, J* = 13.1, 3.2, 2 H); 1.62–1.49 (*m*, 3 H); 1.31 (*m*, 1 H). NOE: 3.45 (H_β–C(5)) → 2.74 (H_β–C(6)), 2.55 (H_α–C(5)), 2.22 (H_β–C(14)), 1.59 (H–C(20)). ^{13}C-NMR (125 MHz, $CDCl_3$): 179.7 (*s*); 175.8 (*s*); 152.2 (*s*); 140.6 (*s*); 129.9 (*d*); 126.8 (*d*); 122.3 (*d*); 121.2 (*d*); 67.2 (*s*); 66.5 (*d*); 62.8 (*t*); 59.8 (*d*); 52.1 (*d*); 51.9 (*q*); 44.6 (*t*); 37.9 (*d*); 36.9 (*t*); 36.2 (*d*); 31.2 (*t*); 29.7 (*t*); 23.0 (*t*). HETCOR: 129.9/7.37; 126.8/7.26; 122.3/7.44; 121.2/7.53; 66.5/4.19; 62.8/3.93; 59.8/2.94, 2.55; 52.1/2.36; 51.9/3.71; 44.6/3.45, 2.55; 37.9/2.01; 36.9/2.74, 1.89; 36.2/1.59; 31.2/2.01, 1.57; 29.7/2.22, 1.64; 23.0/1.51, 1.31. FAB-MS: 391 (37, $[M + 3]^+$), 390 (34), 389 (100, $[M + 1]^+$), 388 (28), 387 (29), 354 (27), 353 (48), 352 (23), 351 (21), 289 (47).

*Methanolysis of (+)-***2** [5]. To a soln. of (+)-**2** (90.6 mg, 0.233 mmol) in MeOH (2.5 ml) was added 0.5N aq. KOH (0.5 ml). The mixture was refluxed under Ar for 30 min. After cooling to 0°, H_2O (8 ml) was added and the mixture worked up with $CHCl_3$. The combined org. extracts were dried (K_2CO_3) and evaporated to give 68.1 mg of a brownish foam which was chromatographed (silica gel, benzene/Et_2O/Et_3N 7:2:1): 27.8 mg (32%) of (+)-**4** (imino ether A) and 28.8 mg (35%) of (−)-**5** (imino ether **B**).

Data of the more polar (+)-**4**: M.p. 184–186° (MeOH) ([5]: 198–199°). $[\alpha]_D = +88$ ($c = 0.9$, $CHCl_3$) ([5]: +109). UV (EtOH): 253 (3.88), 211 (4.58). IR ($CHCl_3$): 3510, 2950, 2930, 2800, 1710, 1616, 1580, 1458, 1437, 1360, 1166, 1011, 1000, 969. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.35 (*dm, J* = 7.1, 1 H); 7.30 (*dm, J* = 7.6, 1 H); 7.22 (*td, J* = 7.6, 1.3, 1 H); 7.06 (*ddd, J* = 7.6, 7.1, 1.0, 1 H); 4.06 (*s*, 3 H); 4.06 (*m*, 1 H); 3.56 (*s*, 3 H); 3.28 (*td, J* = 8.5, 2.3, 1 H); 3.11 (*dd, J* = 10.8, 3.6, 1 H); 3.02 (br. *s*, 1 H); 2.45 (*dd, J* = 11.1, 2.5, 1 H); 2.41 (*q, J* = 8.8, 1 H); 2.25 (*ddd, J* = 13.0, 9.2, 2.4, 1 H); 2.11 (*dd, J* = 11.6, 2.0, 1 H); 2.00 (*dt, J* = 13.0, 8.5, 1 H); 1.94 (*m*, 1 H); 1.90 (*q, J* = 10.7, 1 H); 1.69 (*qd, J* = 11.2, 3.2, 1 H); 1.55–1.33 (*m*, 3 H); 1.29 (*m*, 1 H); 0.88 (*dt, J* = 12.4, 3.0, 1 H); 0.65 (*q, J* = 11.8, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 182.1 (*s*); 175.8 (*s*); 152.3 (*s*); 140.6 (*s*); 127.6 (*d*); 123.4 (*d*); 123.3 (*d*); 118.0 (*d*); 69.5 (*d*); 66.7 (*d*); 59.6 (*s*); 59.0 (*t*); 56.5 (*q*); 53.4 (*t*); 52.2 (*d*); 51.7 (*q*); 40.4 (*d*); 36.3 (*d*); 32.9 (*t*); 31.3 (*t*); 30.2 (*t*); 23.4 (*t*). HETCOR: 127.6/7.22; 123.4/7.35; 123.3/7.06; 118.0/7.30; 69.5/2.45; 66.7/4.06; 59.0/3.11, 1.90; 56.5/4.06; 53.4/3.28, 2.41; 52.2/2.11; 51.7/3.56; 40.4/1.29; 36.3/1.69; 32.9/2.25, 2.00; 31.3/1.94, 1.45; 30.2/0.88, 0.65; 23.4/1.54, 1.38. FAB-MS: 385 (100, $[M + 1]^+$), 384 (61), 383 (52), 367 (10), 225 (36), 176 (33), 174 (20).

Data of the less polar (−)-**5**: M.p. 95–96° (sinters at 85°). $[\alpha]_D = -49$ ($c = 1.0$, $CHCl_3$). UV (EtOH): 257 (3.64), 211 (4.33). IR ($CHCl_3$): 3510, 2930, 2795, 1710, 1616, 1576, 1460, 1437, 1359, 1276, 1168, 1012, 997, 969, 906. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.29 (*ddd, J* = 7.7, 1.2, 0.5, 1 H); 7.24 (*td, J* = 7.5, 1.3, 1 H); 7.18 (*ddd, J* = 7.4, 1.3, 0.5, 1 H); 7.09 (*td, J* = 7.3, 1.3, 1 H); 4.09 (*s*, 3 H); 4.09 (*m*, 1 H); 3.58 (*s*, 3 H); 3.32 (*m*, 1 H); 3.20 (*dd, J* = 10.8, 3.4, 1 H); 3.14 (br. *s*, 1 H); 2.46–2.33 (*m*, 3 H); 2.23 (*dd, J* = 11.6, 2.0, 1 H); 2.01–1.90 (*m*, 2 H); 1.86 (*t, J* = 10.5, 1 H); 1.66 (*qd, J* = 10.6, 4.5, 1 H); 1.58–1.33 (*m*, 4 H); 1.08–1.00 (*m*, 2 H). NOE: irrad. at 7.18 (H–C(9)) → 2.38 (H–C(3)), 2.01 (H_β–C(6)). ^{13}C-NMR (100 MHz, $CDCl_3$): 183.3 (*s*); 175.8 (*s*); 152.4 (*s*); 140.2 (*s*); 128.1 (*d*); 123.9 (*d*); 121.5 (*d*); 118.0 (*d*); 73.0 (*d*); 66.6 (*d*); 59.2 (*s*); 59.0 (*t*); 56.4 (*q*); 54.4 (*t*); 52.3 (*d*); 51.8 (*q*); 40.4 (*d*); 36.7 (*d*); 33.0 (*t*); 31.3 (*t*); 29.7 (*t*); 23.4 (*t*). HETCOR: 128.1/7.24; 123.9/7.09; 121.5/7.18; 118.0/7.29; 73.0/2.38; 66.4/4.09; 59.0/3.20, 1.86; 56.4/4.09; 54.4/3.32, 2.44; 52.3/2.23; 51.8/3.58; 40.4/1.40; 36.7/1.66; 33.0/2.42, 2.01; 31.3/1.94, 1.46; 29.7/1.02, 1.02; 23.4/1.54, 1.40. EI-MS: 384 (36, M^+), 226 (15), 225 (100), 224 (9).

*Methanolysis of (−)-***3**. As described for (+)-**2**. For conditions, products, and yields, see *Table 3*.

*Methanolysis of (−)-***3** *in CD_3OD. Method A:* To 0.5N $NaOCD_3$ in 5 ml of CD_3OD, (−)-**3** (161 mg) was added. The mixture was refluxed under Ar for 2 min. After cooling to 0°, H_2O (8 ml) was added and the mixture worked up with $CHCl_3$. The combined org. extract was dried (K_2CO_3) and evaporated and the residue chromatographed twice (silica gel, 1. cyclohexane/THF/Et_3N 100:60:15, 2. hexane/AcOEt/Et_3N/MeOH 12:8:1:1): 30 mg (20%) of (14,23,23,23-$^2H_4$)-3,14-didehydroyohimbine. ^{1}H- and ^{13}C-NMR: COO*Me* and *H*–C(14) replaced by D to ≥ 95%.

Method B: In an analogous experiment, the mixture was refluxed for 35 min. Workup and chromatography as above furnished 12% of (23,23,23-$^2H_3$)yohimbine. ^{1}H- and ^{13}C-NMR: no D-incorporation into the yohimbane skeleton.

*Hydrolysis of (−)-***5**. *Method A:* To a soln. of (−)-**5** (30.3 mg, 0.079 mmol) in CH_2Cl_2 (2 ml) was added CF_3SO_3H (*Fluka, purum*; 23 mg) in CH_2Cl_2 (1 ml). After stirring at 0° for 2 h, additional CF_3SO_3H (30 mg) and

H_2O (0.5 ml) were added, and stirring was continued for 4 h. The resulting mixture was rendered basic (pH 10) by addition of conc. aq. NH_3 soln. and extracted 3 times with CH_2Cl_2. The combined extracts were dried (K_2CO_3) and evaporated to yield 25.7 mg (88%) of crude material which was shown by ^{1}H-NMR spectroscopy to consist of 95% pure *yohimbine oxindole B* ((−)-**10**). An anal. sample was prepared by chromatography (silica gel, $CHCl_3$/MeOH 19:1). M.p. 215–218° ([5]: 222–224°). $[\alpha]_D = -8.8$ ($c = 1.25$, $CHCl_3$) ([5]: −9). UV (EtOH): 252 (3.65), 207 (4.28). IR ($CHCl_3$): 3440, 2930, 2800, 1711, 1618, 1469, 1437, 1350, 1339, 1166, 1015. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.95 (*s*, 1 H); 7.17 (*m*, 2 H); 7.03 (*td*, $J = 7.5, 0.9$, 1 H); 6.87 (*m*, 1 H); 4.11 (*m*, 1 H); 3.59 (*s*, 3 H); 3.36 (*m*, 1 H); 3.19 (*dd*, $J = 10.6, 2.8$, 1 H); 3.14 (*s*, 1 H); 2.50–2.41 (*m*, 2 H); 2.31 (*dd*, $J = 11.0, 2.6$, 1 H); 2.27 (*dd*, $J = 11.6, 2.0$, 1 H); 2.04–1.98 (*m*, 1 H); 1.93 (*dq*, $J = 9.9, 2.9$, 1 H); 1.83 (*t*, $J = 10.4$, 1 H); 1.67 (br. *qd*, $J = 11.2, 3.5$, 1 H); 1.55–1.37 (*m*, 4 H); 1.28 (*q*, $J = 11.6$, 1 H); 1.17 (*dt*, $J = 11.9, 3.1$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 182.0 (*s*); 175.8 (*s*); 141.0 (*s*); 133.5 (*s*); 128.0 (*d*); 123.0 (*d*); 122.7 (*d*); 109.6 (*d*); 74.3 (*d*); 66.7 (*d*); 58.8 (*t*); 56.0 (*s*); 54.5 (*t*); 52.3 (*d*); 51.7 (*q*); 40.0 (*d*); 36.6 (*d*); 35.0 (*t*); 31.3 (*t*); 29.7 (*t*); 23.4 (*t*). HETCOR: 128.0/7.17; 123.0/7.17; 122.7/7.03; 109.6/6.87; 74.3/2.31; 66.7/4.11; 58.8/3.19, 1.83; 54.5/3.36, 2.45; 52.3/2.27; 51.7/3.59; 40.0/1.49; 36.6/1.67; 35.0/2.45, 2.00; 31.3/1.93, 1.49; 29.7/1.28, 1.17; 23.4/1.49, 1.49. FAB-MS: 371 (100, $[M + 1]^+$), 370 (43), 369 (36), 225 (13), 176 (11).

Method B: A soln. of (−)-**5** (30 mg, 0.079 mmol) in 10% aq. CF_3COOH (3 ml) was refluxed under Ar for 3 h. Workup as above furnished 28.8 mg of (+)-**9**/(−)-**10** 1:2 (by ^{1}H-NMR).

Method C: A soln. of 173 mg of (+)-**4**/(−)-**5** 1:1 in 10% aq. AcOH (17 ml) was refluxed for 210 min. Workup as above and chromatography (silica gel, benzene/Et_2O/MeOH 7:2:1) gave 86.5 mg (33%) of (−)-**10** and 32.8 mg (13%) of (+)-**9**.

*Hydrolysis of (+)-***4**. *Method A:* A soln. of (+)-**4** (30.2 mg, 0.079 mmol) in 10% aq. CF_3COOH (3 ml) was refluxed for 210 min. Workup as above furnished 25.3 mg (86%) of *yohimbine oxindole A* ((+)-**9**), uncontaminated with (−)-**10** (by ^{1}H-NMR). An anal. sample was prepared by chromatography (silica gel, $CHCl_3$/MeOH 19:1), followed by recrystallization from AcOEt. M.p. 221–222° ([5]: 168–170°). $[\alpha]_D = +58.5$ ($c = 1.1$, $CHCl_3$) ([5]: +59). UV (EtOH): 282 (3.16), 251 (3.80), 208 (4.42). IR ($CHCl_3$): 3440, 2930, 2800, 1711, 1619, 1470, 1436, 1339, 1259, 1165, 1014. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.82 (*s*, 1 H); 7.38 (*dd*, $J = 7.2, 0.5$, 1 H); 7.20 (*td*, $J = 7.7, 1.3$, 1 H); 7.02 (*td*, $J = 7.5, 0.9$, 1 H); 6.91 (*dm*, $J = 7.5$, 1 H); 4.09 (*m*, 1 H); 3.57 (*s*, 3 H); 3.27 (*td*, $J = 8.6, 2.4$, 1 H); 3.13 (*s*, 1 H); 3.10 (*dd*, $J = 10.8, 3.6$, 1 H); 2.52 (*dd*, $J = 11.2, 2.5$, 1 H); 2.50 (*q*, $J = 8.5$, 1 H); 2.37 (*ddd*, $J = 13.0, 9.2, 2.5$, 1 H); 2.11 (*dd*, $J = 11.7, 2.1$, 1 H); 2.00 (*dt*, $J = 13.0, 8.4$, 1 H); 1.92 (*dq*, $J = 13.7, 2.9$, 1 H); 1.92 (*t*, $J = 10.7$, 1 H); 1.73 (*qd*, $J = 11.3, 3.2$, 1 H); 1.60–1.33 (*m*, 3 H); 1.29 (*qt*, $J = 11.0, 3.5$, 1 H); 1.07 (*dt*, $J = 12.3, 3.0$, 1 H); 0.68 (*q*, $J = 11.7$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 181.9 (*s*); 175.5 (*s*); 140.3 (*s*); 133.8 (*s*); 127.5 (*d*); 125.0 (*d*); 122.4 (*d*); 109.6 (*d*); 71.4 (*d*); 66.7 (*d*); 58.8 (*t*); 56.8 (*s*); 53.4 (*t*); 52.4 (*d*); 51.7 (*q*); 40.4 (*d*); 36.1 (*d*); 35.3 (*t*); 31.3 (*t*); 30.4 (*t*); 23.4 (*t*). HETCOR: 127.5/7.20; 125.0/7.38; 122.4/7.02; 109.6/6.91; 71.4/2.52; 66.7/4.09; 58.8/3.10, 1.92; 53.4/3.27, 2.50; 52.4/2.11; 51.7/3.57; 40.4/1.29; 36.1/1.73; 35.3/2.37, 2.00; 31.3/1.92, 1.43; 30.4/1.07, 0.68; 23.4/1.55, 1.38. FAB-MS: 371 (100, $[M + 1]^+$), 370 (60), 369 (51), 307 (11), 225 (11), 154 (41).

Method B: A soln. of (+)-**4** (30 mg, 0.079 mmol) in 10% aq. AcOH (3 ml) was refluxed for 150 min. Workup as above furnished 35.2 mg of (+)-**9**/(−)-**10** 1:2.3 (by ^{1}H-NMR).

*Equilibration of (+)-***9**. A soln. of (+)-**9** (15.5 mg) in 10% aq. AcOH (1.5 ml) was refluxed for 2 h. Workup as above furnished 15 mg of (+)-**9**/(−)-**10** 1:2.3 (by ^{1}H-NMR).

(+)-3,14-Didehydroyohimbine (= *Methyl 3,14-Didehydro-17α-hydroxy-7*H*-yohimban-16α-carboxylate*; (+)-**11**). A reference sample was prepared according to *Zinnes* and *Shavel* [6]. M.p. 154–159° (dec.), sinters at 137° ([3]: 176–178° (dec.)). $[\alpha]_D = +44$ ($c = 0.75$, $CHCl_3$). UV (EtOH): 352 (3.98), 320 (4.04), 308 (4.01), 245 (4.00), 228 (4.16). IR ($CHCl_3$): 3470, 2920, 2842, 1725, 1710, 1642, 1554, 1449, 1436, 1326, 1302, 1270, 1164, 1109, 1004. ^{1}H-NMR (500 MHz, CD_3OD): 7.38 (*dt*, $J = 7.7, 1.0$, 1 H); 7.25 (*dt*, $J = 8.1, 0.9$, 1 H); 7.05 (*ddd*, $J = 8.2, 7.1, 1.2$, 1 H); 6.94 (*ddd*, $J = 8.0, 7.1, 1.0$, 1 H); 4.27 (*q*, $J = 2.8$, 1 H); 3.78 (*s*, 3 H); 3.16 (*ddd*, $J = 10.5, 4.9, 2.1$, 1 H); 3.07 (*dd*, $J = 10.8, 2.9$, 1 H); 2.99 (*ddd*, $J = 11.5, 10.5, 4.5$, 1 H); 2.92 (*td*, $J = 11.1, 4.4$, 1 H); 2.91 (*m*, 1 H); 2.81 (*m*, 1 H); 2.80 (*t*, $J = 11.0$, 1 H); 2.77 (*m*, 1 H); 2.33 (*dd*, $J = 12.1, 2.7$, 1 H); 1.95 (*dq*, $J = 14.0, 3.1$, 1 H); 1.74–1.65 (*m*, 2 H); 1.58–1.47 (*m*, 2 H); the missing signal of H–C(14) appeared at 4.93 (*d*, $J = 1.6$, 1 H) in (D_8)THF. ^{13}C-NMR (125 MHz, CD_3OD): 175.5 (*s*); 138.8 (*s*); 138.2 (*s*); 131.6 (*s*); 128.2 (*s*); 123.0 (*d*); 119.8 (*d*); 119.1 (*d*); 111.9 (*d*); 110.3 (*s*); 98.8 (*t*, $^1J(^2H,^{13}C) = 23.8$ in broad-band decoupled spectrum); 69.0 (*d*); 58.1 (*t*); 54.4 (*d*); 52.5 (*t*); 52.2 (*q*); 39.6 (*d*); 35.7 (*d*); 34.2 (*t*); 24.9 (*t*); 22.4 (*t*). HETCOR: 123.0/7.05; 119.8/6.94; 119.1/7.38; 111.9/7.25; 69.0/4.27; 58.1/3.07, 2.80; 54.4/2.33; 52.5/3.16, 2.99; 52.2/3.78; 39.6/1.70; 35.7/2.77; 34.2/1.95, 1.70; 24.9/1.54, 1.51; 22.4/2.92, 2.81. EI-MS: 352 (100, M^+), 351 (64), 294 (20), 293 (70), 279 (11), 275 (20), 235 (20), 222 (17), 221 (71), 209 (11), 205 (18), 129 (13), 91 (13).

(+)-3,4,5,6-Tetradehydroyohimbine (= *Methyl 3,4,5,6-Tetradehydro-17α-hydroxy-7*H*-yohimban-16α-carboxylate*; (+)-**12**) (Method: [20]). To a soln. of yohimbine (**1**; 152 mg, 0.43 mmol) in AcOH (10 ml) was added

$Pb(OAc)_4$ (*Fluka, pract.* ≥95%; 430 mg, 0.97 mmol). After stirring at r.t. under Ar for 1 h, the solvent was evaporated (45°/70 Torr) and the residue distributed between 50% aq. NaOH soln. and $CHCl_3$. Evaporation of the org. phase furnished 132 mg of crude (+)-**12** that was used as such for the reduction experiments described below. An anal. sample was prepared by chromatography (basic alumina, acetone/$CHCl_3$/MeOH 2:1:1), followed by precipitation of the resulting material from MeOH/AcOEt at −20° and drying of the amorphous material at 25°/0.001 Torr. M.p. 260–264° ([19]: 256–265°). $[\alpha]_D$ = +180 (*c* = 1.44, MeOH) ([20]: +211 (*c* = 1, H_2O)). UV (EtOH): 364 (3.62), 306 (4.28), 252 (4.44), 208 (4.30). IR (KBr): 1728, 1631, 1231, 1015, 779, 758. ^{1}H-NMR (400 MHz, CD_3OD): 8.42 (*d, J* = 6.6, 1 H); 8.31 (*dd, J* = 8.2, 0.9, 1 H); 8.29 (*d, J* = 6.6, 1 H); 7.76 (*ddd, J* = 8.3, 6.8, 1.1, 1 H); 7.70 (*dt, J* = 8.3, 1.0, 1 H); 7.43 (*ddd, J* = 8.1, 6.8, 1.2, 1 H); 4.79 (*dd, J* = 13.8, 4.4, 1 H); 4.44 (*t, J* = 12.8, 1 H); 4.43 (*m*, 1 H); 4.03 (*dd, J* = 18.5, 4.8, 1 H); 3.82 (*s*, 3 H); 3.08 (*dd, J* = 18.5, 10.0, 1 H); 2.64–2.55 (*m*, 2 H); 2.11 (*m*, 1 H); 2.04 (*dq, J* = 13.5, 3.2, 1 H); 1.82 (*m*, 1 H); 1.75–1.65 (*m*, 2 H). ^{13}C-NMR (100 MHz, CD_3OD): 174.3 (*s*); 145.2 (*s*); 141.5 (*s*); 135.5 (*s*); 133.9 (*d*); 132.7 (*d*); 132.3 (*s*); 124.0 (*d*); 123.1 (*d*); 121.4 (*s*); 116.7 (*d*); 113.9 (*d*); 68.2 (*d*); 61.0 (*t*); 53.5 (*d*); 52.5 (*q*); 36.8 (*d*); 32.6 (*t*); 31.3 (*quint.*, $^1J(^2H,^{13}C)$ = 18.5 in broad-band decoupled spectrum); 31.2 (*d*); 23.0 (*t*). FAB-MS: 351 (100, $[M + 1]^+$), 289 (13), 155 (29), 152 (11).

*Reduction of (+)-***12** *with $NaBH_4$ in MeOH.* To a soln. of the above crude (+)-**12** (100 mg) in MeOH (5 ml) was added $NaBH_4$ (*Fluka, purum*; 10 mg). After stirring under Ar for 1 h, the solvent was evaporated and the residue chromatographed twice (silica gel, 1. cyclohexane/THF/Et_3N 100:60:15, 2. $CHCl_3$/Et_2O/Et_2NH 80:40:5): 81.3 mg (71% overall) of pure **1**.

*Reduction of (+)-***12** *with $NaBH_4$ in CD_3OD.* As above with CD_3OD (*Glaser AG*, 99.95%) as solvent: deuterated sample of yohimbine (**1**). ^{13}C-NMR (broad-band decoupled): the *s* of undeuterated **1** at 21.7 ppm (C(6)) showed only ¼ of the usual intensity and was replaced to some extent by a *m*, caused by coupling with D–C(6).

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