Synthesis and Conformational Analysis of All Eight Diastereoisomers of 5-Methylyohimbane

by **Christian Lohse**[1]), **Richard Detterbeck**[2]), **Pierre Acklin**[3]), and **Hans-Jürg Borschberg***

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, HCl, ETH-Hönggerberg, CH-8093 Zürich

Some time ago, *Siddiqui et al*. proposed structure **1** for the naturally occurring indole alkaloid yohambinine, which they had isolated from *Rauwolfia serpentina* BENTH. In the present paper, enantioselective syntheses of all eight diastereoisomers endowed with the proposed 5-methylyohimbane structure are disclosed. However, none of the synthetically prepared compounds showed spectroscopic properties identical with those reported for the natural product yohambinine, which, therefore, must possess an altogether different constitutional formula. The ground-state conformations of the diastereoisomers **1**, **14**, **18**, **19**, **21**, **22**, **25**, and **26** were deduced by spectroscopic methods, and the outcome was compared with the results of extensive force-field, semi-empirical, and *ab-initio* calculations.

1. Introduction. – In 1987, *Siddiqui et al*. reported the isolation of a novel crystalline monoterpenoid indole alkaloid from the roots of *Rauwolfia serpentina* BENTH [3]. Its molecular formula was shown to be $C_{20}H_{26}N_2$ by combustion analysis, and this composition was confirmed by high-resolution EI-MS. The unexpected presence of a Me group at a tertiary C-atom was indicated by a *doublet* ($\delta = 1.12$ ppm, *d*, $J = 6.7$ Hz (3 H)) in the ^{1}H-NMR spectrum of yohambinine. The absence of *Bohlmann* bands in the IR spectrum and the appearance of H–C(3) as a broad *singlet* at 4.12 ppm in the ^{1}H-NMR spectrum pointed to a *cis*-quinolizidine system for rings C and D. The equatorial orientation of H–C(5) ($\delta = 3.42$ ppm, *qdd*, $J = 6.7$, 5.3, 2.8 Hz)[4]) was evident from the vicinal couplings with H–C(6). The multiplicities of the deshielded CH_2 H-atoms at C(21) pointed to a β-orientation of H–C(20) (J(H–C(21α), H–C(20)) = 12 Hz). The configuration at the remaining stereogenic center C(15) was inferred to be α due to biogenetic reasons. Therefore, the structural formula **1** was proposed for yohambinine (*Scheme 1*) [3].

Structure **1**, devoid of any functional groups in ring E and presenting the former carboxy group C(22) in a fully reduced form, is unique among the *Yohimbine* and seco-*Yohimbine* alkaloids (for reviews, see [4]). Therefore, we set out to synthesize yohambinine (**1**) in an enantioselective fashion according to the retrosynthetic plan presented in *Scheme 1*. A disconnection along the dashed line leads to (*R*)-2′-methyltryptamine (**2**), a known compound, readily prepared from L-tryptophane [5].

---

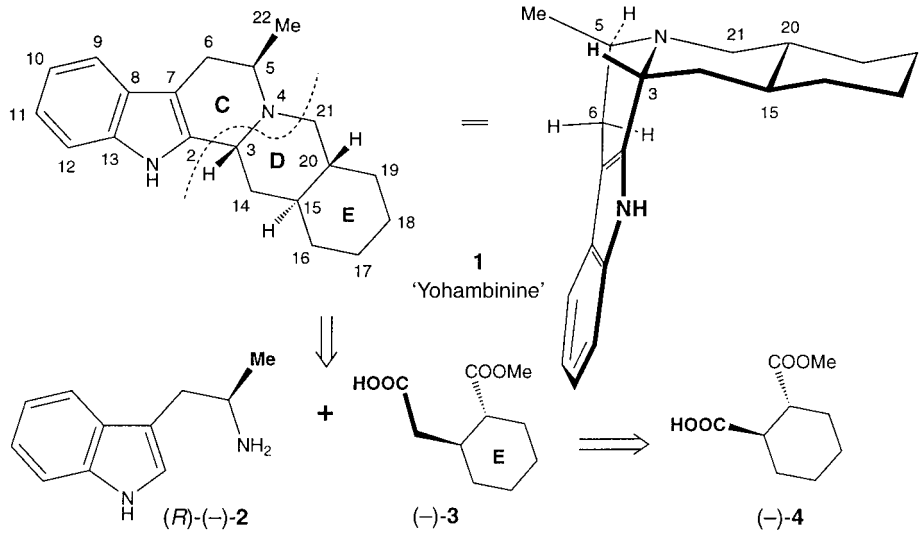
[1]) Taken in part from the Ph.D. thesis of *C.L.* [1].

[2]) Taken in part from the diploma thesis of *R.D.*, on leave from the University of Erlangen (FRG) [2].

[3]) Author to whom correspondence regarding the various calculations should be addressed at *Novartis Pharma AG*, WSJ-88.103, CH-4002 Basel.

[4]) In the cited paper, this signal was incorrectly interpreted as '*ddd*' [3].

Scheme 1

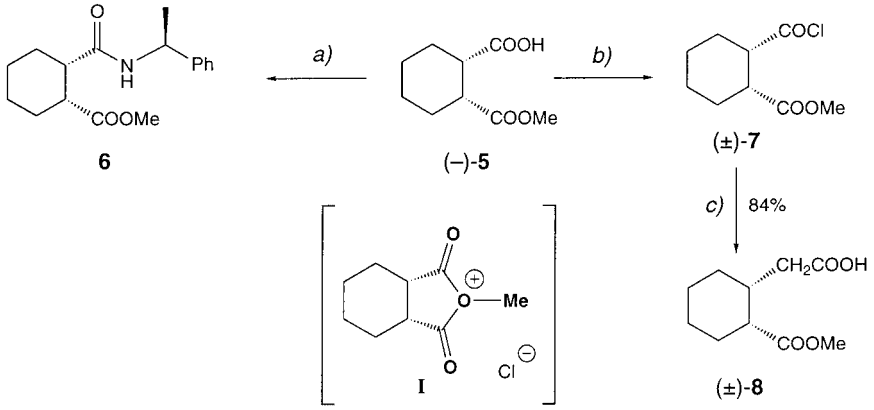


The other building block, containing the remaining C-atoms including the intact ring E, is represented by the chiral cyclohexane derivative (–)-**3**. This can be derived from the known intermediate (–)-**4** with established absolute configuration [6]) through *Arndt-Eistert* synthesis. The original straightforward plan envisaged a *Bischler-Napieralski* condensation to build ring C, followed by lactamization/reduction for the construction of ring D.

2. Synthesis. – The building block (–)-**2** was prepared essentially according to *Repke* and *Ferguson* [5] with some modifications [1][2] of the original procedure. The preparation of the other half ((–)-**3**) was uneventful and, for reasons detailed below, we prepared the optical antipode (+)-**3** as well. A similar reaction sequence was applied to the optically pure *cis*-monoester (–)-**5** [6] as well, but, surprisingly, the *Arndt-Eistert* product **8** turned out to be optically inactive (*Scheme 2*). Control experiments showed that the racemization occurred during the preparation of the acid chloride **7**, a finding that is in contrast with results reported by *Turbanti et al.* [7]. In many attempts, this compound was invariably obtained in optically inactive form, and it repeatedly furnished (±)-**5** after hydrolysis. Among several possible intermediates in the step (–)-**5** → (±)-**7**, the acylated oxonium ion **I** seems to be the only candidate that contains a second-order element of symmetry.

The assembly of the seco-compound (–)-**11** from the components (–)-**2** and (–)-**3** according to the protocol of *Mukaiyama et al.* [8] was straightforward (*Scheme 3*). However, all attempts to lactamize this intermediate to **12** failed. Therefore, the alternative route *via* amino alcohol (–)-**13** was chosen. Gratifyingly, this intermediate could be cyclized in good yield to (–)-**14** by the method of *Lange* and *Gottardo* [9]. As compound (–)-**14** (*normal* yohimbane skeleton) represents the C(3)-epimer of the alleged yohambinine structure (*pseudo*-type), it was equilibrated with (+)-**1** under

Scheme 2



a) (*S*)-2-Phenylethylamine, 2-chloro-1-methylpyridinium iodide, Bu_3N, CH_2Cl_2, 2 h reflux. *b*) $(COCl)_2$, 25°. *c*) 1. CH_2N_2, Et_2O; 2. Ag_2O, 1,4-dioxane/H_2O.

acidic conditions to furnish a 2:1 mixture in favor of the latter (for a discussion of the mechanism, see [10]). Surprisingly, the properties of our synthetic (+)-**1** clearly did not match the data reported for natural yohambinine [3] (see *Table 1*). As the straightforward nature of our synthetic approach undoubtedly led to compounds endowed with the structures **14** and **1**, we are forced to conclude that the originally proposed structural formula for yohambinine is incorrect. Hoping to clarify the matter, we set out to synthesize the remaining six diastereoisomers of **1**, each of them in only one antipodal form[5]).

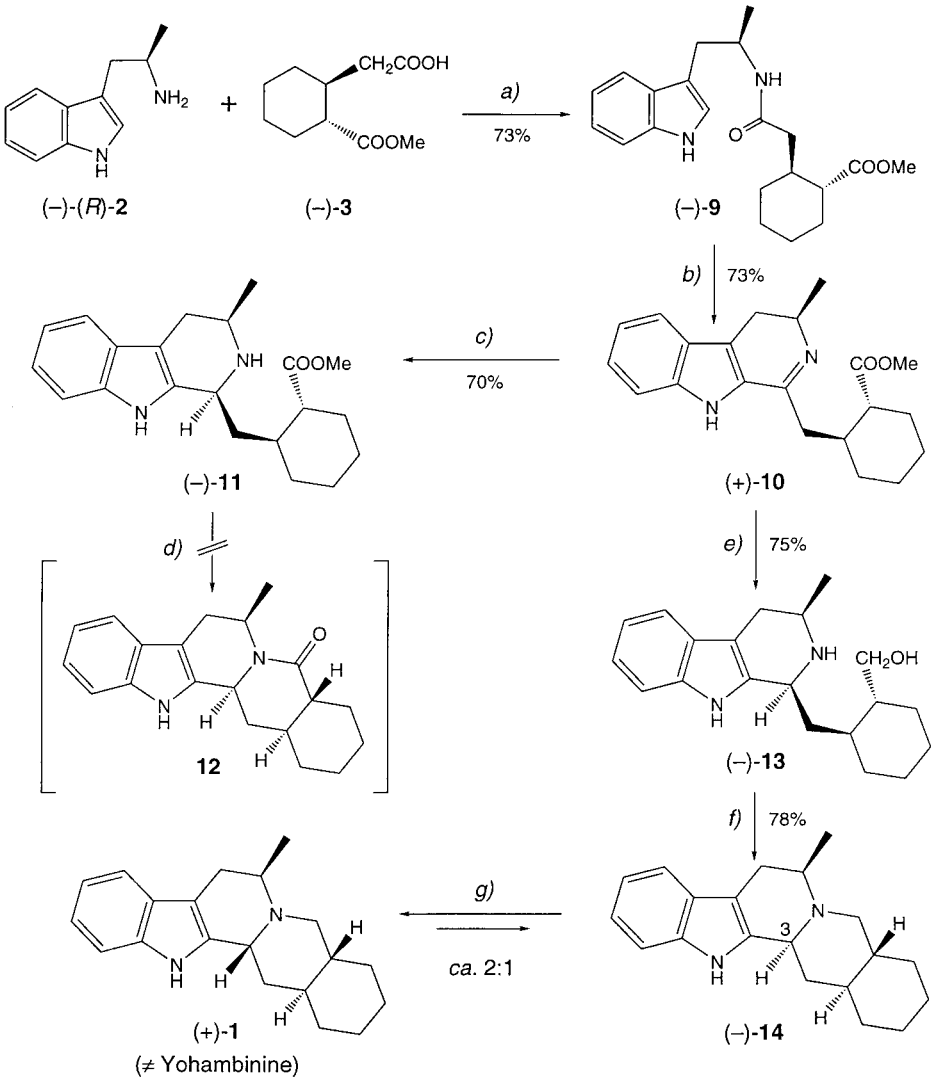
The four isomers with unnatural (15*R*)-configuration were prepared from (−)-**2** and from (+)-**3** as shown in *Scheme 4*. With the same methodology as described above, we obtained the *ent-pseudo* derivative (+)-**18**, the optical antipode of the C(5)-epimer of **1**. The corresponding *ent-normal* compound (+)-**19** was prepared through equilibration with (+)-**18** or reduction of lactam **17**, which was isolated as a by-product in the *Bischler-Napieralski* reaction, leading to (−)-**16**. When the latter was treated with DIBAH, the imine (+)-**20** was obtained in low yield, which, upon reduction with $NaBH_4$, furnished a 1:4 mixture of (+)-**18** and of the D/E *cis*-fused diastereoisomer (−)-**21**. This compound represents the *ent-epiallo* type, and it could be equilibrated with the corresponding *ent-allo* derivative (+)-**22**. As it turned out, none of the four yohambinine-type alkaloids displayed in *Scheme 5* was identical with the natural product (see *Table 1*).

The two remaining isomers were prepared by combining (−)-**2** with (±)-**8** as shown in *Scheme 5*. The resulting 1:1 mixture of the two amides **23** and **24** could not be separated, but, after the standard transformation of this mixture, the resulting alkaloids

---

[5]) Only the four isomers derived from (−)-**3** and from (+)-**5** represent alkaloids endowed with the natural (15*S*)-configuration. The other four diastereoisomers were obtained in the antipodal (15*R*)-configuration and are labelled with the prefix *ent*. However, this was not considered to cause serious problems for an unambiguous identification of any of the latter compounds with natural yohambinine.

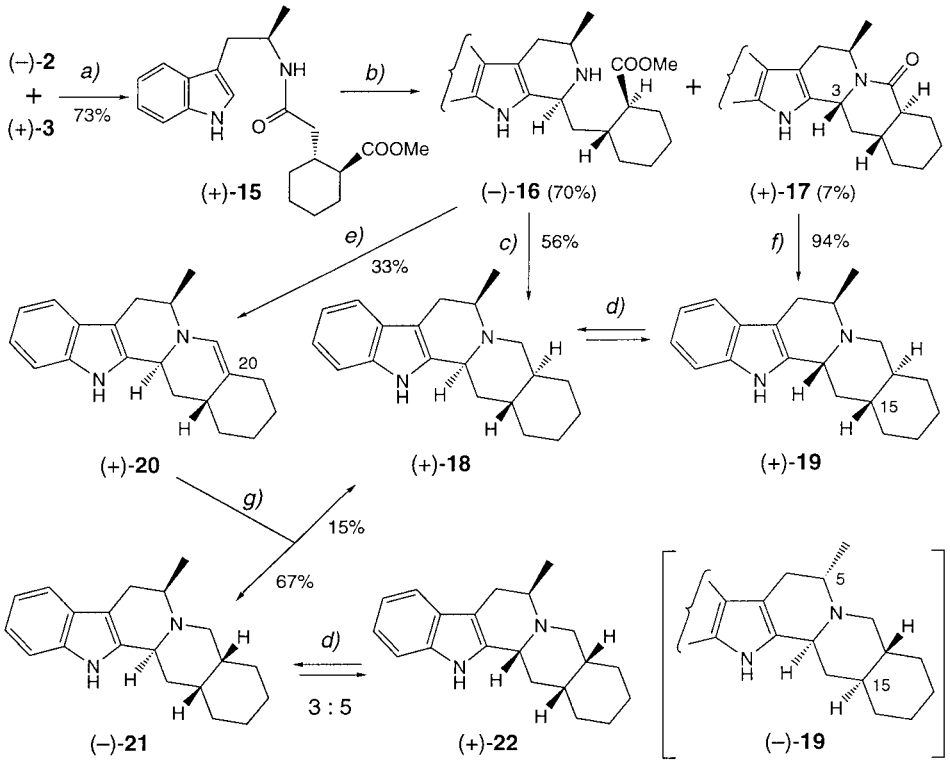
Scheme 3



a) 2-Chloro-1-methylpyridinium iodide, Bu_3N, CH_2Cl_2, 2 h reflux. *b*) $POCl_3$, toluene, 3 h reflux. *c*) $NaBH_4$, MeOH/H_2O. *d*) K_2CO_3, MeOH, 9 h reflux. *e*) $LiAlH_4$, THF. *f*) PPh_3, I_2, imidazole, CH_2Cl_2, 15 h 25°. *g*) CF_3COOH, 20 h 100°.

(–)-**21** and the new isomer (–)-**25** endowed with the *allo* skeleton were separated by chromatography. The still missing *epiallo* isomer (+)-**26** was once more generated through equilibration of (–)-**25**. Since neither of these 5-methylyohimbanes was identical to natural yohambinine (*Table 1*), we have to conclude that the latter is not a stereoisomer of **1**, but, rather, it must possess an altogether different, as yet unknown constitutional formula.

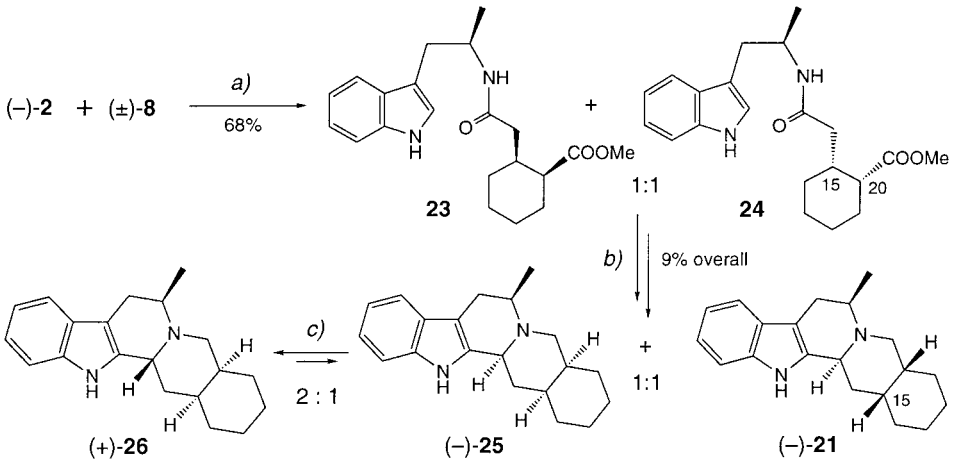
Scheme 4



a) 2-Chloro-1-methylpyridinium iodide, Bu_3N, CH_2Cl_2, 2 h reflux. *b*) 1. $POCl_3$, toluene, 3 h reflux; 2. $NaBH_4$, MeOH/H_2O. *c*) 1. $LiAlH_4$, THF, 18 h 25°; 2. PPh_3, I_2, imidazole, CH_2Cl_2, 15 h 25°. *d*) CF_3COOH, 20 h 100°. *e*) DIBAH, THF, 18 h 40°. *f*) $LiAlH_4$, THF, 18 h 25°. *g*) $NaBH_4$, MeOH/H_2O.

3. Conformational Analysis. – The ground-state conformations of all eight 5-methylyohimbanes were deduced through analyses of their spectral data. The following features were most helpful in this respect: *a*) the axial or equatorial orientation of H–C(3) is readily apparent from the half-width and chemical shift of the respective signal in the ^{1}H-NMR spectrum; *b*) the presence of *Bohlmann* bands in the IR spectrum indicates the presence of a *trans*-quinolizidine part system for rings C and D with a least two α-H-atoms *antiperiplanar* to the lone-pair of N(4) [11]; c) the axial or equatorial position of the Me group follows from its chemical shift in both the ^{1}H- and ^{13}C-NMR spectra (see *Table 1* and *2*). In the cases where rings D and E form a *trans*-decalin system (compounds **1**, **14**, **18**, and **19**), the ^{1}H-NMR spectra (500 MHz, $CDCl_3$) could be analyzed by first-order methods, and, in all cases, only the conformer displayed in *Fig. 1* could be discerned. However, in the *cis*-fused representatives **21**, **22**, **25**, and **26**, many signals in the ^{1}H- and ^{13}C-NMR spectra were considerably broadened at 25°, pointing to a dynamic process taking place within the NMR time-scale. Most likely, this involves simultaneous N(4)-inversion and chair-chair transitions of rings D and E. Recording of the spectra at 80° (300 MHz, C_6D_6) led to sharp signals in all cases,

Scheme 5



a) 2-Chloro-1-methylpyridinium iodide, Bu_3N, CH_2Cl_2, 2 h reflux. *b*) 1. $POCl_3$, toluene, 3 h reflux; 2. $NaBH_4$, $MeOH/H_2O$; 3. $LiAlH_4$, THF, 18 h 25°; 4. PPh_3; I_2, imidazole, CH_2Cl_2, 15 h 25°. *c*) CF_3COOH, 20 h 100°.

Table 1. *^{1}H-NMR Chemical-Shift Values* δ [ppm] (in $CDCl_3$)

Compound	**A**[a])	**14**	**1**	**18**	**19**	**25**	**26**	**21**	**22**
Type		*normal*	*pseudo*	*ent-pseudo*	*ent-normal*	*allo*	*epiallo*	*ent-epiallo*	*ent-allo*
H–C(3)	4.12	3.30	4.42	4.46	3.53	3.31	3.76	3.60	3.49
H–C(5)	3.42	2.57	3.32	3.30	3.34	2.55	3.30	2.88	3.22
H_α–C(6)	3.54	2.71	3.12	2.64	3.14	2.58	3.15	2.62	3.10
H_β–C(6)	3.20	2.60	2.35	2.66	2.52	2.71	2.50	2.76	2.52
H–C(9)	7.37	7.50	7.50	7.48	7.45	7.44	7.45	7.45	7.45
H–C(10)	6.96	7.12	7.12	7.11	7.07	7.08	7.09	7.08	7.09
H–C(11)	7.04	7.17	7.17	7.15	7.12	7.11	7.12	7.12	7.13
H–C(12)	7.28	7.36	7.36	7.35	7.29	7.29	7.28	7.29	7.29
H_{ax}–C(14)		1.30	1.73	1.81	1.34				
H_{eq}–C(14)	2.74	2.03	2.06	2.01	2.00				
H–C(15)	2.35	1.10	0.90	0.87	1.16				
H_{ax}–C(16)		0.92	1.03	1.03	1.07				
H_{eq}–C(16)		1.63	1.68	1.67	1.70				
H_{ax}–C(17)		1.24	1.14	1.12	1.29				
H_{eq}–C(17)		1.68	1.68	1.67	1.75				
H_{ax}–C(18)		1.25	1.25	1.23	1.29				
H_{eq}–C(18)		1.68	1.68	1.67	1.75				
H_{ax}–C(19)		1.01	0.76	0.76	1.02				
H_{eq}–C(19)		1.55	1.50	1.50	1.62				
H–C(20)	2.09	1.25	1.34	1.25	1.41				
H_{ax}–C(21)	2.77	1.75	2.36	2.05	2.39	2.23	3.02	2.44	2.61
H_{eq}–C(21)	3.04	3.12	2.54	2.65	2.72	3.10	2.44	2.67	2.86
CH_3(22)	1.12	1.24	1.26	1.36	1.01	1.24	1.06	1.31	0.98
M.p.	189–190°	168°	105–107°	78°	231°	152–154°	183–186°	122–124°	oil
$[\alpha]_D$	+98	−165	+24	+5	+110	−134	+51	−51	+123

[a]) Data reported for natural yohambinine [3].

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

Compound	**14**[a])	**1**[a])	**18**[a])	**19**[a])	**25**[d])	**26**[d])	**21**[d])	**22**
Type	*normal*	*pseudo*	*ent-pseudo*	*ent-normal*	*allo*	*epiallo*	*ent-epiallo*	*ent-allo*
C(2)	134.4	132.2	133.7	134.3	135.5	134.5	135.7	134.7
C(3)	61.0	47.6	56.4	53.0	60.6	47.2	56.2	52.9
C(5)	56.1	53.7	55.4	54.0	55.3	54.1	56.1	54.3
C(6)	30.8	21.9	24.6	28.5	31.2	22.1	23.7	26.4
C(7)	107.2	106.3	109.2	106.6	108.1	106.8	109.6	106.4
C(8)	126.9	128.4	127.6	128.2	127.4	128.2	127.4	128.1
C(9)	117.8	117.9	118.0	118.0	118.0	118.0	118.8	118.0
C(10)	118.9	119.3	119.4	119.2	119.2	119.1	120.2	119.2
C(11)	120.9	121.3	121.2	121.1	121.1	121.1	121.9	121.1
C(12)	110.7	110.8	110.8	110.6	110.6	110.6	111.4	110.6
C(13)	136.0	135.8	135.8	136.2	135.5	136.2	137.3	136.2
C(14)	36.7	34.9	35.1	37.9	31.6	35.7	35.1	31.4
C(15)	41.2	37.1	37.1	42.0	34.8[b])	34.4[b])	33.6[b])	34.7[b])
C(16)	32.4	32.9	33.0	32.9	31.2	28.3	30.6	29.7
C(17)[c])	26.2	26.2	26.3	26.5	26.6	26.4	28.3	26.2
C(18)[c])	25.8	25.9	25.9	26.0	26.6	26.4	25.9	26.0
C(19)	30.5	30.2	30.5	30.4	21.1	29.3	29.6	20.9
C(20)	41.5	41.8	41.5	42.1	36.5[b])	34.9[b])	36.4[b])	36.7[b])
C(21)	56.4	54.7	44.9	58.6	56.4	51.6	48.9	58.5
C(22)	20.0	19.3	19.5	10.2	20.8	10.6	20.5	9.7

[a]) Assignments corroborated through HETCOR experiments. [b])[c]) Respective assignments may be interchanged. [d]) In C_6D_6 at 80°. Values reported for yohambinine: C(3): 50.42, C(15): 38.52, C(20): 41.21 [3].

which allowed a determination of the prevailing ground-state conformations (see *Fig. 2*).

4. Calculations. – Extensive calculations were performed to help us understand the experiments and predict the most stable conformations of the different isomers. Conformational analysis of all possible stereoisomers was performed in the continuum model for $CHCl_3$ with the AMBER* force field [12] in MacroModel [13], using the truncated *Newton* conjugate gradient (TNCG) [14] as the minimizing method. In accordance with the NMR observations, a single minimum-energy conformation was found for isomers **1**, **14**, **18**, and **19**, two conformations were found for isomer **21** and **22**, and three conformations for isomers **25** and **26** within an energy window of 10 kcal above the global minimum. Even though molecular-mechanics methods cannot be used to compare energies of different molecules, they allow for ranging of conformers and stereoisomeric structures. However, the result depends on the accuracy of the force field for the calculated compounds. As we were not sure how well the AMBER* parameters fit these indole alkaloids, we decided to verify the data with semi-empirical methods. All low-energy conformations within a 10-kcal window were calculated with the PM3 [15] and AM1 [16] Hamiltonians in *Mopac 93* [17]. As it turned out, the energies resulting from the force-field calculations strongly deviated from the semi-empirically determined enthalpies of formation for the isomers, as well as for different

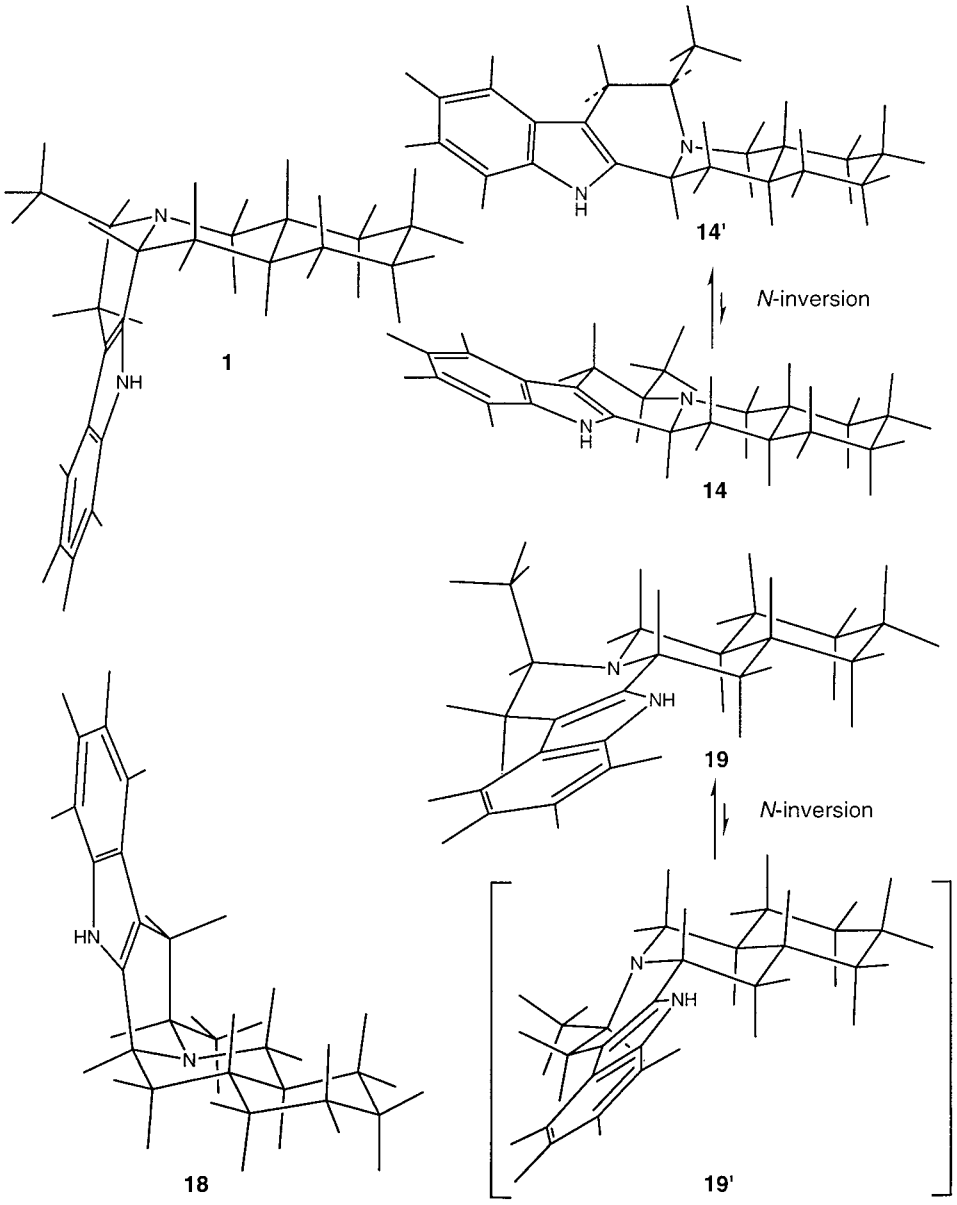


Fig. 1. *Lowest-energy conformations of the four diastereoisomers of 5-methylyohimbane with* trans-*fused rings D and E as calculated by PM3.* Unlabelled substituents represent H-atoms.

conformations of each isomer. Some of the resulting low-energy conformations are listed in *Table 3*.

To obtain more reliable energies, the calculations were repeated with more and more sophisticated *ab initio* methods, although these are quite time-consuming for this

Table 3. *Calculated Energy Minima* (relative energies compared to **23**, in kcal/mol)

Method	Macromodel	Mopac[a])	Mopac[a])	Gaussian[b])	Gaussian[b])	Gaussian[b])	Gaussian[b])
Type	Force field Amber	Semi-empiric AM1	Semi-empiric PM3	HF-*ab initio* 6-31G	HF-*ab initio* 6-31G**	RHF-*ab initio* 6-31G**PCM/ SCRF	DFT *Becke-Lyp3* (B3LYP)
Solvent	$CHCl_3$	*in vacuo*	*in vacuo*	*in vacuo*	*in vacuo*	$CHCl_3$	*in vacuo*
1	1.00	−1.02	0.43	2.55	2.30	1.25	0.43
14	0.69	0.56	1.87	1.39	0.80	0.58	0.95
18	1.09	0.00	0.17	2.14	1.76	0.76	−0.10
19	0.00	0.00	0.00	0.00	0.00	0.00	0.00
19′	1.61	−1.16	−0.25	3.01	2.98	2.26	1.24
21	2.42	2.64	3.47	4.80	4.36	3.83	3.25
21′	2.44	0.16	2.23	4.90	4.63	6.76	1.65
22	0.85	1.30	1.52	2.31	2.44	2.51	4.25
25	1.60	2.05	2.38	3.67	3.22	3.09	2.44
26	1.71	1.59	1.40	3.45	3.62	3.25	2.33
26′	2.37	0.38	1.69	5.33	5.18	4.49	2.18

[a]) H_f.
[b]) Ground-state electronic and internuclear repulsion energy, neglecting 0-K residual vibration energy.

size of molecule. The conformational geometries determined by molecular mechanics were used as starting points for Gaussian 94 [18]. In a first step, they were optimized on 6-31G level of theory. The relaxed geometries were taken as the basis for the calculations at the 6-31G** level before applying the solvation model for $CHCl_3$ at the same level of theory. Finally the molecular-mechanics geometries were optimzed *in vacuo* with density-functional theory, using the *Becke-Lyp3* extension in Gaussian. The relative enthalpy differences resulting from all these calculations are listed in *Table 3*, where the relative enthalpy has been set to 0 for the minimal-energy conformation of isomer **18**. Interestingly, although the values of the relative enthalpies differ substantially, the ranking of the different conformations of single diastereoisomers is identical for all pure *ab initio* and the force-field calculations. This is not entirely so for the density functionals and not at all the case for the semi-empirical energies.

Under thermodynamic control, the relative stabilities (ΔG°) of reaction products can be determined from experimentally determined product ratios. This was possible for all four pairs of C(3)-epimers, and the observed ratios of *ca.* 1:2 in favor of **14**, **18**, **22**, and **16**, respectively, translate into $\Delta\Delta G^\circ$ values of less than 0.5 kcal/mol at 110°. Even though the experimental differences in ΔG° are not directly correlated with the calculated differences in heat of formation (ΔH_f°), they seem to be best reflected by the density-functional calculations (*Becke-Lyp3*). Whereas the *Hartree-Fock* ΔH_f° values calculated *in vacuo* deviate substantially from the experimental values, optimization in $CHCl_3$ appears to improve the model.

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

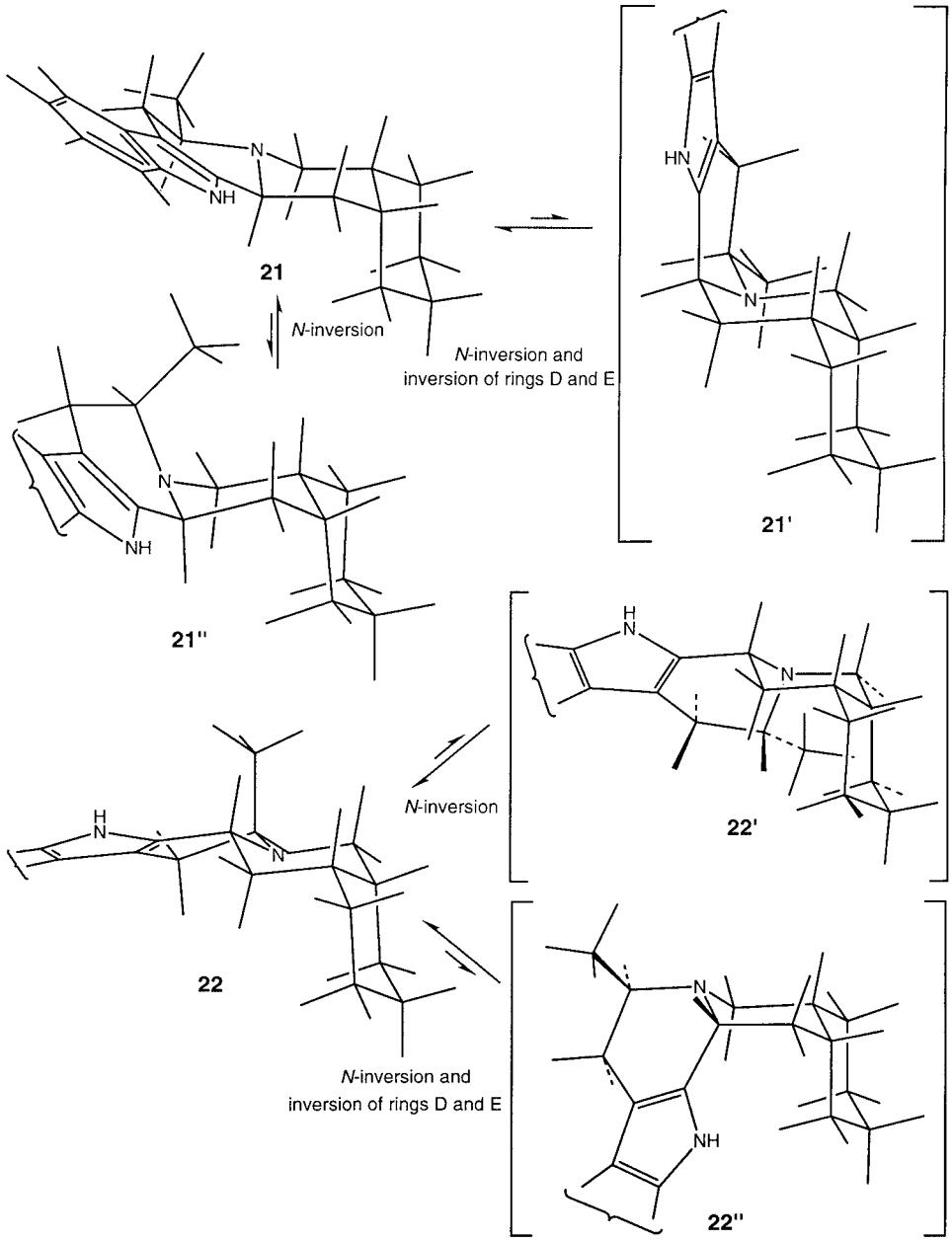


Fig. 2. *Lowest-energy conformations of the four diastereoisomers of 5-methylyohimbane with* cis*-fused rings D and E as calculated by PM3.* Unlabelled substituents represent H-atoms. Formulae in square brackets represent calculated, energetically higher lying conformers.

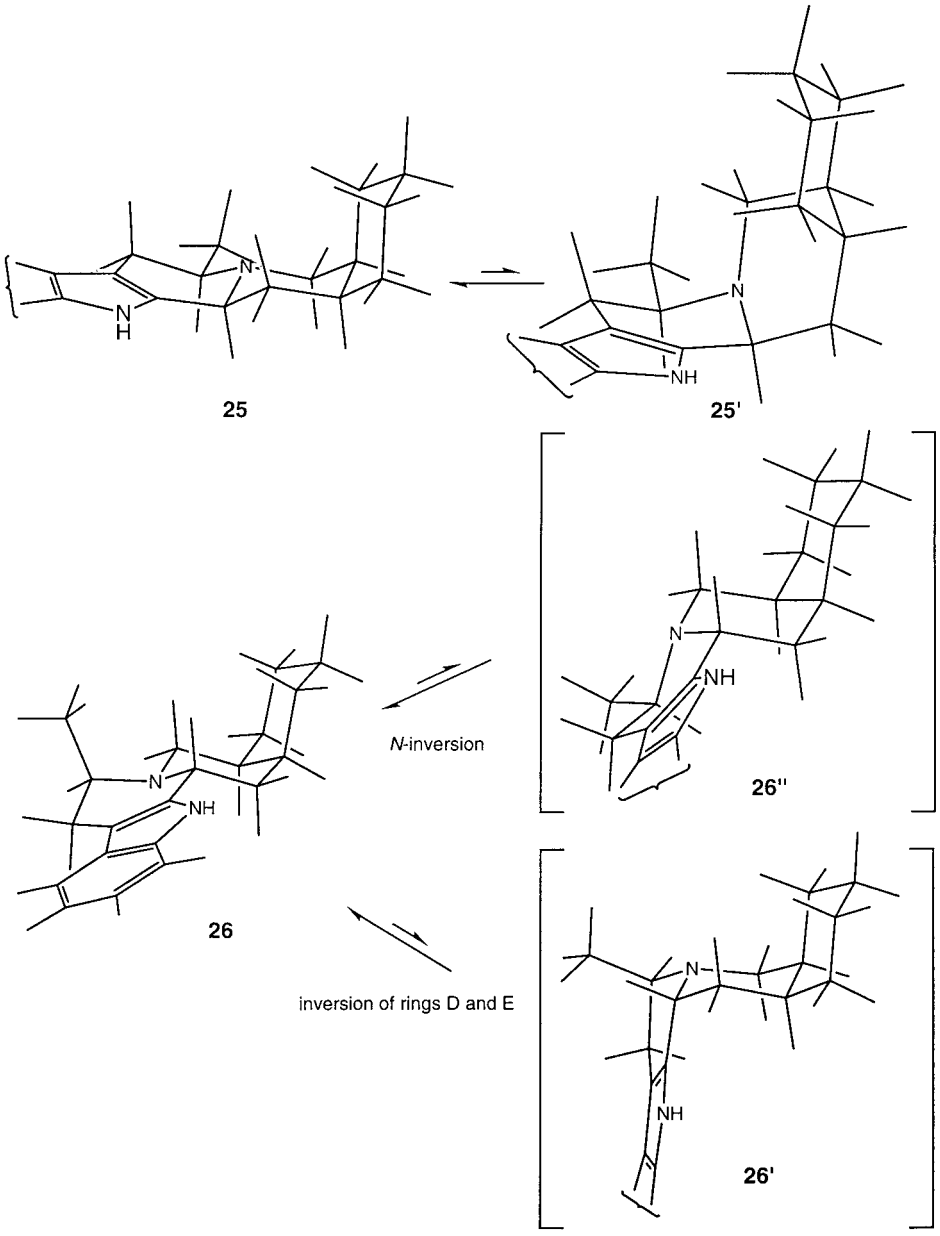

N
H
25
N
NH
25'
N
NH
26
N-inversion
N
NH
26''
inversion of rings D and E
N
NH
26'

Fig. 2 (cont.)

Experimental Part

General. See [19].

Calculations. All calculations were performed on *Silicon Graphics Onyx, Power Challenge*, and *Indy*. MacroModel V. 5.0 [13] and the AMBER* force field [12] were used for all molecular-mechanics calculations. To this end, 5000 conformations of each compound were generated according to the systematic *Monte Carlo* procedure [20] and minimized *in vacuo* with the truncated *Newton* conjugate gradient (TNCG) method [14]. The resulting conformations were then relaxed in the GB/SA solvation model for $CHCl_3$ [21] with the same minimization method.

The global minima and all conformations within an energy window of 10 kcal above, found by the molecular-mechanics method, were used as starting point for semi-empirical calculations. The ΔH_f values were calculated with Mopac 93 by means of both Hamiltonians AM1 [16] and PM3 [15].

The same set of conformations were optimized with HF methods in Gaussian 94 [18] on 6-31G and 6-31G** theory levels. In addition, the resulting 6-31-G** geometries were used as starting points for *ab initio* solvation calculation at the same level of theory. Furthermore, the original *z*-matrices were minimized with density function theory on the *Becke-Lyp3* level in Gaussian 94.

General Procedures. Method 1 [8]. To a stirred soln. of 1.2 equiv. of 2-chloro-1-methylpyridinium iodide (*Fluka*, *purum*) in 8 ml of CH_2Cl_2 was added a soln. of 1 equiv. of *(*R*)-3-(2-aminopropyl)indole* ((−)-**2**) [5], 2.4 equiv. of Bu_3N, and 1 equiv. of the designated carboxylic acid in 15 ml of CH_2Cl_2. The mixture was refluxed for 1 h, cooled to 25°, diluted with 100 ml of CH_2Cl_2, and extracted with 5% aq. HCl. The org. phase was dried (Na_2SO_4), evaporated, and the residue was chromatographed (silca gel; hexane/AcOEt 1:1) to furnish the desired amides.

Method 2. The amides obtained according to *Method 1* were dissolved in $POCl_3$ (1 mmol/ml) and refluxed for 2 h. The resulting black mixture was evaporated (40°/18 Torr), and the residue was poured onto ice. The mixture was rendered basic by addition of 2N aq. NaOH soln. and extracted with CH_2Cl_2 (3×). The org. phase was dried (Na_2SO_4) and evaporated. The residue was chromatographed (silica gel; hexane/AcOEt, gradient 3:1 to 1:1) to furnish the desired 3,4-dihydro-*β*-carbolines.

Method 3. The intermediates obtained by *Method 2* were dissolved in MeOH (0.5 mmol/ml, treated with 10–20 equiv. of $NaBH_4$ and stirred for 16 h at 25°. After addition of 3 ml of 2N aq. NaOH soln., MeOH was removed by evaporation (40°/18 Torr), and the residue was extracted with CH_2Cl_2 (3×). The org. phase was dried (Na_2SO_4) and evaporated. The residue was chromatographed (silica gel; hexane/AcOEt 1:1) to furnish the desired 1,2,3,4-tetrahydro-*β*-carbolines.

Method 4. The intermediates obtained by *Method 3* were dissolved in THF (5 ml/mmol) and added *via* syringe to a suspension of 15 equiv. of $LiAlH_4$ in 10 ml of THF at 0° under Ar. The mixture was stirred at 0° for 30 min and then refluxed for 16 h. After cooling to 0°, sat. aq. $NaHCO_3$ soln. was added dropwise until excess reagent was decomposed. Most of the THF was removed *in vacuo* and the residue was rendered basic by addition of 6N aq. NaOH soln. and extracted with Et_2O (4×). The org. phase was dried (Na_2SO_4) and evaporated. The residue was chromatographed (silica gel; Et_2O/hexane/MeOH/Et_2NH 60:40:10:3) to furnish the desired primary alcohols.

Method 5 [9]. To a stirred suspension of 1.5 equiv. of polymer-bound Ph_3P (*Fluka*, *purum*), 1.5 equiv. of imidazole (*Fluka*, *puriss.*), and 1.5 equiv. of I_2 (*Fluka*, *purum*) in 10 ml of CH_2Cl_2 was added a soln. of 1 equiv. of the primary alcohol in 2 ml of CH_2Cl_2. After stirring at 25° for 15 h, the mixture was distributed between H_2O and CH_2Cl_2. The org. extracts were pooled, dried (Na_2SO_4), and evaporated. The residue was chromatographed (silica gel; Et_2O/hexane/MeOH/Et_2NH 60:40:10:3) to furnish the desired (5*S*)-5-methylyohimbanes.

Method 6. A soln. of the designated 5-methylyohimbane in CF_3COOH (*Fluka*, *puriss.*) (0.05 mmol/ml) was heated to 110° under Ar for 18 h. The cold mixture was poured onto ice/H_2O, rendered basic with 2N aq. NaOH soln., and extracted with Et_2O. The org. extracts were pooled, dried (Na_2SO_4), and evaporated. The residue was chromatographed (silica gel; Et_2O/hexane/MeOH/Et_2NH, 60:40:10:3) to furnish the starting material and the desired C(3)-epimeric (5*S*)-5-methylyohimbane.

*(+)-(1*S*,2*R*)-2-(Methoxycarbonyl)cyclohexanecarboxylic Acid* ((+)-**3**). The compound (+)-**4** [6] (2.05 g, 11 mmol) was stirred with 2 equiv. of oxalyl chloride (*Fluka*, *purum*) for 40 min at 25°. The excess reagent was removed *in vacuo* at 25°, and the oily residue was added to 150 ml of ethereal CH_2N_2. Stirring was continued until no more N_2 evolution was perceptible. After destruction of excess CH_2N_2 with the required amount of AcOH, the mixture was evaporated and then dissolved in 40 ml of 1,4-dioxane (*Fluka*, *puriss.*). To this soln. was added a suspension of 180 mg (0.78 mmol) of freshly precipitated Ag_2O in 12 ml of H_2O. The mixture was stirred for 20 min at 60° and for 10 min at reflux. The cold mixture was filtered through *Celite*™ and evaporated. The

residue was distributed between 1N aq. HCl soln. and Et_2O. The combined org. extracts were dried (Na_2SO_4) and evaporated to give 1.97 g (9.84 mmol, 89%) of crude (+)-**3**, which was used for the next step without further purification. Yellow oil. $[\alpha]_D = +39$ ($c = 0.28$, acetone). IR ($CHCl_3$): 2930, 2860, 1720, 1450, 1430, 1370, 1255, 1160, 1110. ^{1}H-NMR (300 MHz, $CDCl_3$): 9.20 (br. *s*, 1 H); 3.63 (*s*, 3 H); 2.41 (*dd*, *J* = 15.0, 3.3, 1 H); 2.20–2.04 (*m*, 3 H); 1.90 (*m*, 2 H); 1.74 (*m*, 2 H); 1.48 (*qd*, *J* = 12.6, 3.5, 1 H); 1.26 (*tt*, *J* = 12.6, 3.3, 2 H); 1.06 (*qd*, *J* = 12.4, 3.9, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 179.2 (*s*); 178.1 (*s*); 51.8 (*q*); 48.9 (*d*); 39.6 (*t*); 35.9 (*d*); 31.6 (*t*); 30.0 (*t*); 25.5 (*t*); 25.3 (*t*). EI-MS: 200 (0.3, M^+), 182 (34), 168 (81), 150 (25), 122 (39), 100 (100), 81 (85).

*(−)-(1*R*,2*S*)-2-(Methoxycarbonyl)cyclohexaneacetic Acid* ((−)-**3**). Same procedure as above, starting with (−)-**4** [6], the optical purity of which having been shown to exceed 95% through an analysis ofthe ^{1}H-NMR spectrum of its (*S*)-phenethylamide derivative. Yield of (−)-**3**: 90%. $[\alpha]_D = -37$ ($c = 0.35$, acetone).

*(±)-(1*RS*,2*RS*)-2-(Methoxycarbonyl)cyclohexaneacetic Acid* ((±)-**8**). Same procedure as described above, starting with (−)-**5** [6]. Yield: 82%. $[\alpha]_D = \pm 0$ ($c = 0.4$, acetone). IR ($CHCl_3$): 3600–2300 (br.), 2920, 2860, 1720, 1680, 1440, 1300, 1120, 1035, 1000, 930, 870. ^{1}H-NMR (200 MHz, $CDCl_3$): 9.80 (br. *s*, 1 H); 3.64 (*s*, 3 H); 2.66 (*m*, 1 H); 2.40 (*m*, 2 H); 1.90–1.20 (*m*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 178.4 (*s*); 174.4 (*s*); 50.9 (*q*); 43.7 (*d*); 35.6 (*t*); 33.5 (*d*); 28.4 (*t*); 25.8 (*t*); 22.8 (*t*); 22.7 (*t*).

When the intermediate acid chloride (±)-**7** ($[\alpha]_D = \pm 0$ ($c = 0.4$, acetone) was hydrolyzed back to the half ester **5**, the isolated compound was racemic. This contention could be verified best by checking the ^{1}H-NMR (300 MHz, C_6D_6) of the derived (*S*)-phenethylamide **6**, which showed two MeO signals of equal intensities between 3.6 and 3.7 ppm, whereas the corresponding derivative of the starting material (−)-**5** displayed only one signal in this region.

*(−)-(1*R*,2*S*)-Methyl 2-{*N*-[(1*R*)-2-(Indol-3-yl)-1-methylethyl]acetamido}cyclohexane-1-carboxylate* ((−)-**9**). Prepared from (−)-**2** [5] and (−)-**3** according to *Method 1*. Yield: 73%. M.p. 68–69° (foam). $[\alpha]_D = -44$ ($c =$ 0.2, acetone). ^{1}H-NMR (500 MHz, $CDCl_3$): 8.34 (*s*, 1 H); 7.64 (*dm*, *J* = 7.9, 1 H); 7.34 (*ddd*, *J* = 8.0, 1.1, 0.7, 1 H); 7.17 (*ddd*, *J* = 8.0, 7.0, 1.2, 1 H); 7.10 (*ddd*, *J* = 8.0, 7.0, 1.10, 1 H); 7.02 (*d*, *J* = 2.5, 1 H); 5.58 (br. *d*, *J* = 8.2, 1 H); 4.37 (*m*, 1 H); 3.63 (*s*, 3 H); 2.96 (*ddd*, *J* = 14.5, 6.0, 0.7, 1 H); 2.86 (*ddd*, *J* = 14.4, 7.0, 0.6, 1 H); 2.16 (*dd*, *J* = 13.8, 3.6, 1 H; 2.03 (*td*, *J* = 11.5, 3.5, 1 H); 1.95 (*m*, 1 H); 1.83 (*dd*, *J* = 13.8, 4.5, 1 H); 1.75 (*dmd*, *J* = 13.4, 3.2, 1 H); 1.70 (*dm*, *J* = 13.0, 1 H); 1.63 (*dm*, *J* = 13.0, 1 H); 1.43 (*tdd*, *J* = 13.0, 12.0, 3.5, 1 H); 1.21 (*qt*, *J* = 13.0, 3.5, 1 H); 1.16 (*d*, *J* = 6.6, 3 H); 1.11 (*qt*, *J* = 13.0, 3.5, 1 H); 0.88 (*tdd*, *J* = 13.0, 11.5, 3.6, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 176.1 (*s*); 170.7 (*s*); 136.2 (*s*); 127.9 (*s*); 122.7 (*d*); 122.0 (*d*); 119.4 (*d*); 119.0 (*d*), 112.1 (*s*); 111.1 (*d*); 51.5 (*q*); 49.1 (*d*); 45.5 (*d*); 42.3 (*t*); 36.9 (*d*); 32.1 (*t*); 31.2 (*t*); 29.8 (*t*); 25.4 (*t*); 25.2 (*t*); 20.6 (*q*). HETCOR: 122.7/7.02; 122.0/7.17; 119.4/7.10; 119.0/7.64; 111.1/7.34; 51.5/3.63; 49.1/2.03; 45.5/4.37; 42.3/2.16 (expected cross-peak with 1.83 missing), 36.9/1.95; 32.1/2.96 and 2.86; 20.6/1.16 (no significant cross-peaks for the remaining CH_2 groups). EI-MS: 356 (1, M^+), 325 (1), 226 (1), 200 (2), 184 (3), 183 (24), 158 (20), 157 (100), 130 (26), 123 (10).

*(+)-(1*R*,2*S*)-Methyl 2-[(3,4-Dihydro-3-methyl-β-carbolin-1-yl)methyl]cyclohexane-1-carboxylate* ((+)-**10**). Prepared from (−)-**9** according to *Method 2*. Yield: 73%. M.p. 85–87° (foam). $[\alpha]_D = +33$ ($c = 0.13$, acetone). ^{1}H-NMR (500 MHz, $CDCl_3$): 9.94 (*s*, 1 H); 7.59 (*dm*, *J* = 8.0, 1 H); 7.51 (*dt*, *J* = 8.2, 0.9, 1 H); 7.27 (*ddd*, *J* = 8.2, 7.0, 1.2, 1 H); 7.13 (*ddd*, *J* = 8.0, 7.0, 1.0, 1 H); 3.88 (*ddq*, *J* = 11.8, 7.0, 6.8, 1 H); 3.82 (*s*, 3 H); 2.99 (*dd*, *J* = 16.2, 11.8, 1 H); 2.84 (*ddd*, *J* = 12.8, 2.4, 1.4, 1 H); 2.61 (*dd*, *J* = 16.2, 11.8, 1 H); 2.27 (*td*, *J* = 11.5, 3.7, 1 H); 2.14 (*dd*, *J* = 13.0, 11.0, 1 H); 2.09–1.95 (*m*, 2 H); 1.78 (*dm*, *J* = 12.5, 1 H); 1.68 (*dm*, *J* = 13.0, 1 H); 1.46 (*d*, *J* = 6.8, 3 H); 1.39–1.25 (*m*, 2 H); 1.13–0.99 (*m*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 178.5 (*s*); 158.2 (*s*); 136.8 (*s*); 128.2 (*s*); 125.5 (*s*); 124.0 (*d*); 119.8 (*d*); 119.6 (*d*); 115.7 (*s*); 112.4 (*d*); 53.9 (*d*); 52.1 (*q*); 49.1 (*d*); 42.4 (*t*); 36.6 (*d*); 30.9 (*t*); 30.6 (*t*); 26.3 (*t*); 25.7 (*t*); 25.2 (*t*); 22.3 (*q*). HETCOR: 124.0/7.27; 119.8/7.59; 119.6/7.13; 112.4/7.51; 53.9/3.88; 52.1/3.82; 49.1/2.27; 42.4/2.84 and 2.14; 36.6/1.98; 30.9/2.08 and 1.32; 30.6/1.95 and 1.02; 26.3/2.99 and 2.61; 25.7/1.78 and 1.30; 25.2/1.68 and 1.06; 22.3/1.46. EI-MS: 338 (7, M^+), 291 (3), 279 (7), 263 (4), 199 (15), 198 (100), 183 (22), 155 (20).

*(−)-(1*R*,2*S*,1*S*)-Methyl 2-[(1,2,3,4-Tetrahydro-3-methyl-β-carbolin-1-yl)methyl]cyclohexane-1-carboxylate* ((−)-**11**). Prepared from (+)-**10** according to *Method 3*. Yield: 70%. M.p. 192°. $[\alpha]_D = -187$ ($c = 0.15$, acetone). UV (EtOH): 289 (2.82), 280 (2.87), 225 (3.50). IR ($CHCl_3$): 3470, 3370, 3000, 2930, 2854, 1724, 1461, 1447, 1433, 1370, 1310, 1268, 1166, 1128. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.17 (*s*, 1 H); 7.46 (*dm*, *J* = 7.9, 1 H); 7.33 (*dt*, *J* = 8.0, 0.8, 1 H); 7.14 (*ddd*, *J* = 8.1, 7.1, 1.2, 1 H); 7.08 (*ddd*, *J* = 7.8, 7.1, 1.1, 1 H); 4.21 (*m*, 1 H); 3.67 (*s*, 3 H); 3.04 (*ddq*, *J* = 10.5, 3.9, 6.4, 1 H); 2.78 (*ddd*, *J* = 15.1, 3.9, 1.9, 1 H); 2.37 (*ddd*, *J* = 15.1, 10.5, 2.6, 1 H); 2.15 (*ddd*, *J* = 12.0, 11.0, 3.5, 1 H); 2.12 (*ddm*, *J* = 13.5, 3.0, 1 H); 2.02 (*m*, 1 H); 1.95 (*ddd*, *J* = 13.0, 3.3, 1.6, 1 H); 1.77 (*m*, 2 H); 1.64 (*m*, 2 H); 1.48 (*qd*, *J* = 12.5, 3.5, 1 H); 1.30–1.20 (*m*, 2 H); 1.32 (*d*, *J* = 6.4, 3 H); 1.01 (*qd*, *J* = 12.3, 3.5, 1 H). NOE: *a*) irrad. at 4.21 (H–C(3)) → 8.17 (H–N(1)), 3.04 (H–C(5)), 2.12 (H_{eq}–C(16)), 2.02 (H–C(15)), 1.64 (CH_2(14)); *b*) irrad. at 3.04 (H–C(5)) → 4.21 (H–C(3)), 2.78 H_{eq}–C(6), 1.32 (CH_3(22)). ^{13}C-NMR (125 MHz, $CDCl_3$): 176.9 (*s*); 136.4 (*s*); 136.02 (*s*); 127.5 (*s*); 121.3 (*d*); 119.2 (*d*); 117.9 (*d*); 110.8 (*d*); 109.7 (*s*); 51.6 (*q*); 50.7

(*d*); 50.3 (*d*); 50.1 (*d*); 40.6 (*t*); 34.9 (*d*); 31.5 (*t*); 30.7 (*t*); 30.2 (*t*); 25.5 (*t*), 25.4 (*t*); 22.7 (*q*). HETCOR: 121.3/7.14; 119.2/7.08; 117.9/7.46; 110.8/7.33; 51.6/3.67; 50.7/4.21; 50.3/2.16; 50.1/3.04; 40.6/1.64; 34.9/2.02; 31.5/2.12 and 1.01; 30.7/2.78 and 2.36; 30.2/1.95 and 1.48; 25.5/1.77 and 1.25; 25.4/1.77 and 1.25; 22.7/1.32. EI-MS: 340 (9, M^+), 308 (13), 297 (16), 196 (11), 185 (100), 156 (26).

*(−)-(1*R*,2*S*,1*S*)-{2-[(1,2,3,4-Tetrahydro-3-methyl-β-carbolin-1-yl)methyl]cyclohex-1-yl}methanol* ((−)-**13**). Prepared from (+)-**10** according to *Method 4*. Yield: 75%. M.p. 125°. $[\alpha]_D = -107$ ($c = 0.09$, acetone). UV (EtOH): 290 (3.19), 282 (3.26), 226 (3.91). IR ($CHCl_3$): 3620, 3470, 3000, 2960, 2920, 2850, 1460, 1447, 1380, 1309, 1270, 1144, 1123, 1086, 1045, 1009, 963. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.31 (*s*, 1 H); 7.43 (*dm*, $J = 7.7$, 1 H); 7.25 (*dt*, $J = 7.9$, 0.8, 1 H); 7.11 (*ddd*, $J = 7.9$, 7.2, 1.2, 1 H); 7.06 (*ddd*, $J = 7.7$, 7.2, 1.2, 1 H); 4.2 (*m*, 1 H); 3.68 (*dd*, $J = 11.5$, 3.9, 1 H); 3.41 (*dd*, $J = 11.5$, 3.1, 1 H); 3.06 (*ddq*, $J = 10.6$, 4.0, 6.4, 1 H); 2.77 (*ddd*, $J = 15.3$, 4.0, 1.8, 1 H); 2.39 (*ddd*, $J = 15.3$, 10.6, 2.5, 1 H); 1.94 (*dm*, $J = 13.0$, 1 H); 1.85 (*m*, 1 H); 1.75–1.65 (*m*, 3 H); 1.59–1.50 (*m*, 2 H); 1.37 (br. *qd*, $J = 12.4$, 3.6, 1 H); 1.30 (*d*, $J = 6.4$, 3 H); 1.26–1.20 (*m*, 2 H); 1.15–1.05 (*m*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 136.1 (*s*); 136.0 (*s*); 127.4 (*s*); 121.4 (*d*); 119.3 (*d*); 118.0 (*d*); 110.8 (*d*); 109.1 (*s*); 64.5 (*t*); 52.1 (*d*); 50.3 (*d*); 45.0 (*d*); 38.7 (*t*); 35.0 (*d*); 33.1 (*t*); 30.5 (*t*); 30.0 (*t*); 26.2 (*t*); 26.1 (*t*); 22.5 (*q*). HETCOR: 121.4/7.11; 119.3/7.05; 118.0/7.43; 110.8/7.25; 64.5/3.68 and 3.41; 52.1/4.12; 50.3/3.06; 45.0/1.10; 38.7/1.85 and 1.55; 35.0/1.55; 33.1/1.94 and 1.05; 30.5/2.77 and 2.39; 30.0/1.72 and 1.37; 26.2/1.69 and 1.23; 26.1/1.69 and 1.23; 22.5/1.30. EI-MS: 312 (3, M^+), 294 (4), 198 (4), 186 (14), 185 (100), 156 (18).

*(−)-(3*S*,5*R*,15*S*,20*R*)-5-Methylyohimbane* ((−)-**14**). Prepared from (−)-**13** according to *Method 5*. Yield: 78%. M.p. 168° (foam). $[\alpha]_D = -165$ ($c = 0.21$, acetone). UV (EtOH): 290 (3.84), 283 (3.91), 222 (4.61). IR ($CHCl_3$): 3475, 3055, 3000, 2960, 2920, 2845, 2780, 1469, 1447, 1371, 1333, 1310, 1162, 1146, 1120, 1009, 982. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.50 (*dm*, $J = 7.7$, 1 H); 7.36 (*dt*, $J = 8.0$, 0.9, 1 H); 7.17 (*ddd*, $J = 8.1$, 7.1, 1.2, 1 H); 7.12 (*ddd*, $J = 7.7$, 7.1, 1.1, 1 H); 3.30 (*dm*, $J = 11.7$, 1 H); 3.12 (*dd*, $J = 11.0$, 3.8, 1 H); 2.71 (*m*, 1 H); 2.60 (*td*, $J = 10.7$, 2.4, 1 H); 2.57 (*m*, 1 H); 2.03 (*dt*, $J = 12.7$, 3.1, 1 H); 1.75 (*t*, $J = 11.0$, 1 H); 1.68 (*m*, 2 H); 1.63 (*dm*, $J = 12.6$, 1 H); 1.55 (*dm*, $J = 12.9$, 1 H); 1.30 (*dt*, $J = 12.5$, 11.7, 1 H); 1.26–1.23 (*m*, 3 H); 1.24 (*d*, $J = 5.9$, 3 H); 1.10 (*qt*, $J = 11.5$, 3.4, 1 H); 1.01 (*qd*, $J = 12.0$, 3.0, 1 H); 0.92 (*qd*, $J = 12.2$, 3.2, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 136.0 (*s*); 134.4 (*s*); 126.9 (*s*); 120.9 (*d*); 118.9 (*d*); 117.8 (*d*); 110.7 (*d*); 107.2 (*s*); 61.0 (*d*); 56.4 (*t*); 56.1 (*d*); 41.5 (*d*); 41.2 (*d*); 36.7 (*t*); 32.4 (*t*); 30.8 (*t*); 30.5 (*t*); 26.2 (*t*); 25.8 (*t*); 20.0 (*q*). HETCOR: 120.9/7.12; 118.9/6.97; 117.8/7.35; 110.7/7.21; 61.0/3.30; 56.4/3.12 and 1.75; 56.1/2.57; 41.5/1.25; 41.2/1.10; 36.7/2.03 and 1.30; 32.4/1.63 and 1.02; 30.8: no cross-peaks with CH_2(6) detectable; 30.5/1.56 and 0.92; 26.2/1.70 and 1.25; 25.8/1.70 and 1.25; 20.0/1.24. EI-MS: 294 (100, M^+), 279 (40), 238 (17), 169 (9).

*(+)-(3*R*,5*R*,15*S*,20*R*)-5-Methylyohimbane* ((+)-**1**). Prepared from (−)-**14** according to *Method 6*. M.p. 103–107° (foam). $[\alpha]_D = +24$ ($c = 0.24$, acetone). UV (EtOH): 289 (3.78), 282 (3.85), 226 (4.54). IR ($CHCl_3$): 3475, 3000, 2960, 2920, 2850, 1448, 1374, 1332, 1324, 1305, 1277, 1162, 1148, 1127, 1009. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.82 (*s*, 1 H); 7.50 (br. *d*, $J = 7.8$, 1 H); 7.36 (*dt*, $J = 8.0$, 0.9, 1 H); 7.17 (*ddd*, $J = 7.8$, 7.0, 1.1, 1 H); 7.12 (*ddd*, $J = 8.0$, 7.0, 1.0, 1 H); 4.42 (*m*, $w_{1/2} = 10$, 1 H); 3.32 (*quint.*, $J = 7.0$, 1 H); 3.12 (*ddd*, $J = 16.0$, 6.2, 2.6, 1 H); 2.54 (*dd*, $J = 11.1$, 3.6, 1 H); 2.36 (*dd*, $J = 16.0$, 1.8, 1 H); 2.35 (*t*, $J = 11.3$, 1 H); 2.06 (*dt*, $J = 14.0$, 2.8, 1 H); 1.73 (*ddd*, $J = 14.0$, 12.4, 5.3, 1 H); 1.72–1.62 (*m*, 2 H); 1.50 (*dm*, $J = 13.0$, 1 H); 1.34 (*qt*, $J = 11.1$, 3.5, 1 H); 1.35–1.22 (*m*, 4 H, incl. 1.25 (*d*, $J = 7.0$, 3 H)); 1.14 (*m*, 1 H); 1.03 (*qd*, $J = 12.8$, 3.4, 1 H); 0.90 (*qt*, $J = 11.4$, 3.2, 1 H); 0.76 (*qd*, $J = 12.8$, 3.7, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 135.8 (*s*); 132.2 (*s*); 128.4 (*s*); 121.3 (*d*); 119.3 (*d*); 117.9 (*d*); 110.8 (*d*); 106.3 (*s*); 54.7 (*t*); 53.7 (*d*); 47.6 (*d*); 41.8 (*d*); 37.1 (*d*); 34.9 (*t*); 32.9 (*t*); 30.2 (*t*); 26.2 (*t*); 25.9 (*t*); 21.9 (*t*); 19.3 (*q*). HETCOR: 121.3/7.17; 119.3/7.12; 117.9/7.50; 110.8/7.36; 54.7/2.54 and 2.36; 53.7/3.32; 47.6/4.42; 41.8/1.25; 37.1/0.90; 34.9/2.06 and 1.73; 32.9/1.66 and 1.03; 30.2/1.50 and 0.76; 26.2/1.73 and 1.14; 25.9/1.66 and 1.25; 21.9/3.32 and 2.36; 19.3/1.25. EI-MS: 294 (100, M^+), 293 (72), 279 (55), 251 (33), 238 (54), 169 (82), 156 (54), 150 (98), 91 (72).

*(+)-(1*S*,2*R*)-Methyl 2-[*N*-[(1*R*)-2-(Indol-3-yl)-1-methylethyl]aceamido]cyclohexane-1-carboxylate* ((+)-**15**). Prepared from (−)-**2** and (+)-**3** according to *Method 1*. Yield: 73%. M.p. 72–74° (foam). $[\alpha]_D = +23$ ($c = 0.16$, acetone). UV (EtOH): 290 (3.00), 281 (3.02), 222 (3.81). IR ($CHCl_3$): 3475, 3355, 3008, 2935, 2860, 1719, 1461, 1450, 1437, 1376, 1312, 1261, 1171, 1123, 1009. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.33 (*s*, 1 H); 7.64 (*dm*, $J = 7.9$, 1 H); 7.35 (*dt*, $J = 8.0$, 0.9, 1 H); 7.18 (*ddd*, $J = 8.0$, 7.0, 1.1, 1 H); 7.11 (*ddd*, $J = 8.0$, 7.9, 1.1, 1 H); 7.01 (*d*, $J = 2.3$, 1 H); 5.54 (br. *d*, $J = 8.1$, 1 H); 4.36 (*m*, 1 H); 3.63 (*s*, 3 H); 2.95 (*ddd*, $J = 14.5$, 5.9, 0.8, 1 H); 2.86 (*ddd*, $J = 14.5$, 6.7, 0.6, 1 H); 2.17 (*dd*, $J = 13.5$, 3.5, 1 H); 2.10 (*ddd*, $J = 12.0$, 11.0, 3.5, 1 H); 1.96–1.86 (*m*, 2 H); 1.81 (*dd*, $J = 13.51$, 9.0, 1 H); 1.77–1.68 (*m*, 2 H); 1.65 (*m*, 1 H); 1.43 (*qd*, $J = 12.5$, 3.5, 1 H); 1.18 (*m*, 2 H); 1.16 (*d*, $J = 6.5$, 3 H); 1.01–0.87 (*m*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 176.1 (*s*); 170.7 (*s*); 136.2 (*s*); 127.9 (*s*); 122.6 (*d*); 121.9 (*d*); 119.4 (*d*); 119.0 (*d*); 112.1 (*s*); 111.1 (*d*); 51.5 (*q*); 49.1 (*d*); 45.5 (*d*); 42.3 (*t*); 36.8 (*d*); 31.9 (*t*); 31.1 (*t*); 29.8 (*t*); 25.3 (*t*); 25.2 (*t*); 20.5 (*q*). HETCOR: 122.6/7.01; 121.9/7.18; 119.4/7.11; 119.0/7.64; 111.1/7.35; 51.5/3.63; 49.1/2.10; 45.5/4.36; 42.3/2.17 and 1.81; 36.8/1.90; 31.9/2.95 and 2.86; 31.1/1.72 and 0.93; 29.8/1.86 and 1.43;

25.3/1.62 and 1.18; 25.2/1.72 and 1.18; 20.5/1.16. EI-MS: 357 (76, $[M+1]^+$), 325 (91), 200 (6), 187 (14), 186 (77), 183 (27), 158 (71), 157 (100), 130 (34), 123 (13).

*(−)-(1*S*,2*R*,1*S*)-Methyl 2-[(1,2,3,4-Tetrahydro-3-methyl-β-carbolin-1-yl)methyl]cyclohexane-1-carboxylate* ((−)-**16**). Prepared from (+)-**15** according to *Method 2*, followed by *Method 3*. Yield: 70%. M.p. 112°. $[\alpha]_D = -132$ ($c = 0.12$, acetone). IR ($CHCl_3$): 3475, 3355, 3008, 2935, 2860, 1719, 1461, 1450, 1437, 1376, 1312, 1261, 1171, 1123, 1009. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.99 (*s*, 1 H); 7.45 (*dm*, $J = 7.8$, 1 H); 7.41 (*dt*, $J = 8.0$, 0.8, 1 H); 7.15 (*ddd*, $J = 8.1$, 7.1, 1.2, 1 H); 7.08 (*ddd*, $J = 7.8$, 7.1, 1.1, 1 H); 4.04 (*m*, 1 H); 3.67 (*s*, 3 H); 3.13 (*ddq*, $J = 10.7$, 4.2, 6.3, 1 H); 2.79 (*ddd*, $J = 15.2$, 4.2, 1.9, 1 H); 2.41 (*ddd*, $J = 15.2$, 10.7, 2.5, 1 H); 2.21 (*ddd*, $J = 11.9$, 11.0, 3.7, 1 H); 2.13 (*dm*, $J = 13.5$, 1 H); 2.02 (*m*, 1 H); 1.96 (*m*, 1 H); 1.86–1.77 (*m*, 3 H, incl. 1.82 (*ddd*, $J = 10.7$, 8.1, 2.9, 1 H)); 1.51 (*qd*, $J = 12.7$, 3.6, 1 H); 1.40 (*ddd*, $J = 12.8$, 9.4, 3.3, 1 H); 1.36–1.29 (*m*, 5 H, incl. 1.32 (*d*, $J = 6.4$, 3 H)); 1.06 (*qd*, $J = 12.3$, 3.5, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 178.0 (*s*); 137.2 (*s*); 136.4 (*s*); 127.1 (*s*); 121.2 (*d*); 119.1 (*d*); 117.8 (*d*); 111.1 (*d*); 108.8 (*s*); 52.3 (*d*); 51.9 (*q*); 50.5 (*d*); 49.7 (*d*); 41.9 (*t*); 37.5 (*d*); 32.4 (*t*); 30.7 (*t*); 30.4 (*t*); 25.6 (*t*); 25.5 (*t*); 22.6 (*q*). HETCOR: 121.2/7.15; 119.1/7.08; 117.8/7.45; 111.1/7.41; 52.3/4.04; 51.9/3.67; 50.5/3.13; 49.7/2.21; 41.9/1.82 and 1.40; 37.5/2.02; 32.4/2.13 and 1.06; 30.7/2.10 and 1.51; 30.4/2.79 and 2.41; 25.6/1.82 and 1.31; 25.4/1.82 and 1.32; 22.6/1.33. EI-MS: 340 (13, M^+), 297 (25), 196 (8), 185 (100), 156 (13).

*(+)-(3*S*,5*R*,15*R*,20*S*)-5-Methylyohimban-21-one* ((+)-**17**). Isolated as a by-product in 7% yield in the above reaction leading to (−)-**16**. M.p. 187–191° (subl.). $[\alpha]_D = +14$ ($c = 0.1$, acetone). IR ($CHCl_3$): 3470, 3000, 2925, 2855, 1629, 1460, 1447, 1408, 1346, 1304. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.80 (*s*, 1 H); 7.48 (*dm*, $J = 7.8$, 1 H); 7.32 (*dt*, $J = 8.0$, 0.8, 1 H); 7.18 (*ddd*, $J = 8.0$, 7.1, 1.2, 1 H); 7.12 (*ddd*, $J = 7.8$, 7.1, 1.1, 1 H); 5.55 (*qd*, $J = 7.0$, 5.8, 1 H); 4.74 (*m*, 1 H); 2.99 (*ddd*, $J = 15.5$, 5.8, 2.6, 1 H); 2.58 (*dt*, $J = 15.5$, 1.3, 1 H); 2.47 (*m*, 1 H); 2.36 (*ddm*, $J = 10.0$, 4.8, 1 H); 1.90–1.76 (*m*, 4 H); 1.63 (*m*, 2 H); 1.32–1.26 (*m*, 3 H); 1.19 (*d*, $J = 7.0$, 3 H); 1.10 (*m*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 170.8 (*s*); 136.4 (*s*); 132.2 (*s*); 127.6 (*s*); 122.1 (*d*); 119.7 (*d*); 118.4 (*d*); 110.8 (*d*); 107.2 (*s*); 49.2 (*d*); 47.5 (*d*); 42.5 (*d*); 36.7 (*d*); 35.8 (*t*); 33.2 (*t*); 27.7 (*t*); 26.3 (*t*); 26.2 (*t*); 25.6 (*t*); 17.1 (*q*). EI-MS: 308 (100, M^+), 293 (14), 279 (12), 183 (29), 168 (28), 156 (22).

*(+)-(3*S*,5*R*,15*R*,20*S*)-5-Methylyohimbane* ((+)-**18**). Prepared from (−)-**16** according to *Method 4*, followed by *Method 5*. Yield: 56%. M.p. 78° (foam). $[\alpha]_D = +5$ ($c = 0.11$, acetone). UV (EtOH): 289 (3.78), 282 (3.85), 226 (4.54). IR ($CHCl_3$): 3475, 3000, 2960, 2920, 2850, 1459, 1447, 1382, 1310, 1305, 1269, 1154, 1143, 1120, 1009. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.80 (*s*, 1 H); 7.48 (br. *d*, $J = 7.9$, 1 H); 7.35 (*dt*, $J = 7.8$, 1.0, 1 H); 7.15 (*ddd*, $J = 7.9$, 7.1, 1.3, 1 H); 7.11 (*ddd*, $J = 7.8$, 7.1, 1.2, 1 H); 4.46 (*m*, $w_{1/2} = 9.2$, 1 H); 3.30 (*m*, 1 H); 2.70–2.56 (*m*, 3 H, incl. 2.65 ((*dd*, $J = 11.0$, 2.7, 1 H)); 2.05 (*t*, $J = 11.0$, 1 H); 2.01 (*ddd*, $J = 14.0$, 3.3, 2.3, 1 H); 1.81 (*ddd*, $J = 13.9$, 12.4, 5.3, 1 H); 1.70–1.60 (*m*, 3 H); 1.50 (*dm*, $J = 13.0$, 1 H); 1.36 (*d*, $J = 6.8$, 3 H); 1.28–1.09 (*m*, 3 H); 1.03 (br. *qd*, $J = 12.0$, 3.1, 1 H); 0.87 (*m*, 1 H); 0.76 (*qd*, $J = 12.3$, 3.5, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 135.8 (*s*); 133.7 (*s*); 127.6 (*s*); 121.2 (*d*); 119.4 (*d*); 118.0 (*d*); 110.8 (*d*); 109.2 (*s*); 56.4 (*d*); 55.4 (*d*); 44.9 (*t*); 41.5 (*d*); 37.1 (*d*); 35.1 (*t*); 33.0 (*t*); 30.5 (*t*); 26.3 (*t*); 25.9 (*t*); 24.6 (*t*); 19.5 (*q*). HETCOR: 121.2/7.15; 119.4/7.11; 118.0/7.48; 110.8/7.35; 56.4/4.46; 55.4/3.30; 44.9/2.65 and 2.05; 41.5/1.23; 37.1/0.87; 35.1/1.81 (only 1 cross-peak detectable); 33.0/1.66 and 1.02; 30.5/1.51 and 0.76; 26.3/1.65 and 1.12; 24.6/2.65 and 2.63; 19.5/1.36. EI-MS: 294 (100, M^+), 293 (70), 279 (40), 251 (30), 236 (17), 169 (14), 156 (11), 150 (15).

*(+)-(3*S*,5*R*,15*R*,20*S*)-5-Methylyohimbane* ((+)-**19**). *Method A:* Prepared from (+)-**18** according to *Method 6*. Yield: 30% (and 62% of **18**). M.p. 231°. $[\alpha]_D = +110$ ($c = 0.13$, acetone). UV (EtOH): 290 (3.82), 281 (3.90), 226 (4.57). IR ($CHCl_3$): 3475, 3055, 3000, 2960, 2920, 2845, 2800, 2760, 1467, 1446, 1371, 1324, 1302, 1281, 1160, 1109, 1009. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.68 (br. *s*, 1 H); 7.45 (br. *d*, $J = 7.8$, 1 H); 7.29 (*dm*, $J = 8.0$, 1 H); 7.12 (*ddd*, $J = 7.8$, 7.1, 1.3, 1 H); 7.08 (*ddd*, $J = 8.0$, 7.1, 1.1, 1 H); 3.53 (*ddm*, $J = 11.0$, 1.8, 1 H); 3.34 (br. *quint.*, $J = 6.6$, 1 H); 3.15 (*ddd*, $J = 15.2$, 5.9, 2.3, 1 H); 2.74 (*dd*, $J = 11.1$, 3.8, 1 H); 2.53 (*dt*, $J = 15.2$, 1.5, 1 H); 2.39 (*t*, $J = 10.9$, 1 H); 2.00 (*dt*, $J = 12.1$, 3.1, 1 H); 1.80–1.74 (*m*, 2 H); 1.70 (*dm*, $J = 13.0$, 1 H); 1.62 (*dm*, $J = 13.0$, 1 H); 1.41 (*qt*, $J = 11.8$, 3.5, 1 H); 1.34 (*q*, $J = 11.7$, 1 H); 1.32–1.22 (*m*, 2 H); 1.16 (*qt*, $J = 11.8$, 3.4, 1 H); 1.07 (*qd*, $J = 12.0$, 2.8, 1 H); 1.03 (*m*, 1 H); 1.01 (*d*, $J = 6.6$, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 136.2 (*s*); 134.3 (*s*); 128.2 (*s*); 121.1 (*d*); 119.2 (*d*); 118.0 (*d*); 110.6 (*d*); 106.6 (*s*); 58.6 (*t*); 54.0 (*d*); 53.0 (*d*); 42.1 (*d*); 42.0 (*d*); 37.9 (*t*); 32.9 (*t*); 30.4 (*t*); 28.5 (*t*); 26.5 (*t*); 26.0 (*t*); 10.2 (*q*). HETCOR: 121.1/7.12; 119.2/7.12; 118.0/7.45; 110.6/7.29; 58.6/2.74 and 2.39; 54.0/3.34; 53.0/3.53; 42.1/1.41; 42.0/1.15; 37.9/2.00 and 1.34; 32.9/1.75 and 1.07; 30.4/1.61 and 1.03; 28.5/3.15 and 2.53; 26.5/1.75 and 1.26; 26.0/1.75 and 1.26; 10.2/1.01. EI-MS: 294 (100, M^+), 293 (72), 279 (61), 251 (20), 238 (30), 169 (28), 156 (11).

Method B: From (+)-**17** according to *Method 4*. Yield: 94%.

*(+)-(3*S*,5*R*,15*R*)-5-Methylyohimb-20-ene* ((+)-**20**). To a soln. of 400 mg (1.18 mmol) of (−)-**16** in 10 ml of dry THF were added 3.7 ml of an 1M soln. of DIBAH in hexane (3 equiv.) under Ar. After stirring for 18 h at 40°, the mixture was distributed between 2N aq. NaOH soln. and CH_2Cl_2. The combined org. extracts were dried (Na_2SO_4), evaporated, and chromatographed (silica gel; Et_2O/hexane/MeOH/Et_2NH, 60:40:10:3) to give

115 mg (0.39 mmol, 33%) of (+)-**20** and starting material. M.p. 193°. $[\alpha]_D = +155$ ($c = 0.10$, acetone). UV: 290 (3.73), 282 (3.79), 226 (4.48). IR ($CHCl_3$): 3470, 3060, 3000, 2920, 2850, 1661, 1460, 1448, 1431, 1397, 1311, 1270, 1260, 1175. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.91 (br. *s*, 1 H); 7.49 (br. *d*, $J = 7.8$, 1 H); 7.35 (*dt*, $J = 7.8$, 0.8, 1 H); 7.17 (*ddd*, $J = 7.8$, 7.2, 1.3, 1 H; 7.13 (*ddd*, $J = 7.8$, 7.2, 1.1, 1 H); 5.95 (br. *s*, $w_{1/2} = 4$, 1 H); 4.45 (br. *s*, $w_{1/2} = 9$, 1 H); 3.34 (*dqd*, $J = 10.5$, 6.8, 3.8, 1 H); 2.72 (*ddd*, $J = 15.0$, 4.8, 1.2, 1 H); 2.56 (*ddd*, $J = 15.0$, 10.5, 2.6, 1 H); 2.29 (*m*, 1 H); 2.07 (*dm*, $J = 13.6$, 1 H); 1.96 (*m*, 2 H); 1.85–1.20 (*m*, 4 H); 1.45 (*d*, $J = 6.8$, 3 H); 1.24 (*m*, 1 H); 1.24 (*qd*, $J =$ 13.0, 3.3, 1 H); 1.09 (*m*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 135.8 (*s*); 134.4 (*s*); 127.5 (*s*); 122.2 (*d*); 121.1 (*d*); 119.3 (*d*); 117.9 (*d*); 117.4 (*s*); 110.8 (*d*); 109.3 (*s*); 54.4 (*d*); 53.5 (*d*); 34.9 (*t*); 34.2 (*t*); 32.3 (*t*); 31.4 (*d*); 28.1 (*t*); 27.6 (*t*); 26.3 (*t*); 19.0 (*q*). CI-MS: 293 (100, $[M+1]^+$), 292 (68, M^+), 277 (32), 275 (15), 249 (17), 234 (18), 169 (11), 156 (14).

*(−)-(3*S*,5*R*,15*R*,20*R*)-5-Methylyohimbane* ((−)-**21**). Prepared from 100 mg (0.34 mmol) of (+)-**20** according to *Method 3*. The crude mixture was chromatographed (silica gel; Et_2O/hexane/MeOH/Et_2NH 60:40:10:3) to give 67 mg (67%) of (−)-**21** and 15 mg (15%) of (+)-**18**. Characterization of (−)-**21**: M.p. 122–124°. $[\alpha]_D = -51$ ($c = 0.21$, $CHCl_3$). IR ($CHCl_3$): 3630, 3475, 3055, 3005, 2965, 2920, 2850, 2800, 1463, 1448, 1371, 1337, 1312, 1288, 1275, 1260, 1158, 1111, 1074, 1013. ^{1}H-NMR (500 MHz, $CDCl_3$): sharp signals at: 7.70 (br. *s*, 1 H); 7.45 (br. *d*, $J = 7.6$, 1 H); 7.29 (*dm*, $J = 7.8$, 1 H); 7.12 (*m*, 1 H); 7.08 (*m*, 1 H); 2.44 (*t*, $J = 10.8$, 1 H); 1.31 (*q*, $J = 6.1$, 3 H); br. signals at: 3.60 (1 H); 2.88 (1 H); 2.75–2.60 (3 H); 2.10–1.40 (12 H). ^{1}H-NMR (300 MHz, C_6D_6, 80°): 7.54 (*m*, 1 H); 7.22–7.1 (*m*, 3 H); 6.83 (br. *s*, 1 H); 3.58 (*m*, $w_{1/2} = 17$, 1 H); 2.78 (*dd*, $J = 10.9$, 3.5, 1 H); 2.70–2.55 (*m*, 3 H); 2.32 (*dd*, $J = 10.9$, 9.6, 1 H); 1.92 (*m*, 1 H); 1.75-1.55 (*m*, 6 H); 1.50–1.20 (*m*, 5 H); 1.17 (*d*, $J = 5.9$, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): sharp signals at: 135.9 (*s*); 127.4 (*s*); 121.2 (*d*); 119.3 (*d*); 118.0 (*d*); 110.6 (*d*); 108.5 (*s*); 55.9 (*d*); 35.1 (*d*); 20.2 (*q*); br. signals at *ca.*: 135.0 (*s*); 55.0 (*d*); 49.1 (*t*); 36.3 (*t*); 33.2 (*t*); 30.8 (*t*); 29.5 (*t*); 26.3 (*t*); 21.9 (*t*). ^{13}C-NMR (75 MHz, C_6D_6, 80°): 137.3 (*s*); 135.7 (*s*); 127.4 (*d*); 121.9 (*d*); 120.2 (*d*); 118.8 (*d*); 111.4 (*d*); 109.6 (*s*); 56.2 (*d*); 56.1 (*d*); 48.9 (*t*); 36.4 (*d*); 35.1 (*t*); 33.6 (*d*); 30.6 (*t*); 29.6 (*t*); 28.3 (*t*); 25.9 (*t*); 23.7 (*t*); 20.5 (*q*). EI-MS: 294 (100, M^+), 293 (89), 279 (40), 251 (19), 238 (13), 236 (12), 183 (16), 169 (34), 156 (23), 150 (71), 143 (13), 130 (12).

*(+)-(3*R*,5*R*,15*R*,20*R*)-5-Methylyohimbane* ((+)-**22**). Prepared from (−)-**21** according to *Method 6*. Yield: 52% (and 33% of **21**). Yellow oil. $[\alpha]_D 0 + 123$ ($c = 0.10$, acetone). IR ($CHCl_3$): 3475, 3055, 3000, 2960, 2920, 2855, 2800, 2760, 1464, 1446, 1373, 1325, 1308, 1285, 1162, 1109, 1008, 905. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.77 (br. *s*, 1 H); 7.45 (br. *d*, $J = 7.8$, 1 H); 7.29 (*dm*, $J = 7.8$, 1 H); 7.13 (*ddd*, $J = 7.8$, 7.2, 1.3, 1 H); 7.09 (*ddd*, $J = 7.8$, 7.2, 1.1, 1 H); 3.49 (*m*, 1 H); 3.22 (br. *quint.*, $J = 6.6$, 1 H); 3.10 (*ddd*, $J = 15.0$, 5.9, 2.3, 1 H); 2.86 (br. *dd*, $J = 11.5$, 3.2, 1 H); 2.61 (br. *dm*, $J = 11.5$, 1 H); 2.52 (*dt*, $J = 15.0$, 1.4, 1 H); 1.98–1.85 (*m*, 2 H); 1.75–1.63 (*m*, 3 H); 1.60–1.52 (*m*, 2 H); 1.45–1.25 (*m*, 6 H); 0.98 (*d*, $J = 6.6$, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): sharp signals: 136.2 (*s*); 128.2 (*s*); 121.1 (*d*); 119.2 (*d*); 118.0 (*d*); 110.6 (*d*); 106.4 (*s*); 54.0 (*d*); 36.7 (*d*); 34.7 (*d*); 31.4 (*t*); 26.4 (*t*); 26.2 (*t*); 26.0 (*t*); br. signals: 134.7 (*s*); 58.5 (*t*); 52.9 (*d*); 31.5 (*t*); 20.9 (*t*); 9.7 (*q*). EI-MS: 294 (100, M^+), 293 (74), 279 (53), 251 (12), 238 (12), 170 (13), 169 (23), 156 (12), 150 (49).

*1:1-Mixture of Methyl (1*S*,2*S*)-2-{*N*-[(1*R*)-2-(Indol-3-yl)-1-methylethyl]acetamido}cyclohexane-1-carboxylate* (**23**) *and Methyl (1*R*,2*R*)-2-{*N*-[(1*R*)-2-(Indol-3-yl)-1-methylethyl]acetamidocyclohexane-1-carboxylate* (**24**). Prepared from (−)-**2** and (±)-**8** according to *Method 1*, followed by *Method 2*. Yield: 86%.

*(−)-(3*S*,5*R*,15*S*,20*S*)-5-Methylyohimbane* ((−)-**25**): Prepared from the 1:1 mixture **23**/**24** according to *Methods 3–5*. Overall yield: 16% (and 16% of (−)-**21**). Slightly yellow needles. M.p. 152–154° (dec.). $[\alpha]_D = -134$ ($c = 0.28$, $CHCl_3$). IR ($CHCl_3$): 3465, 3000, 2960, 2920, 2855, 2785, 2750, 1463, 1446, 1373, 1333, 1309, 1165, 1140, 1121, 1009. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.77 (br. *s*, 1 H); 7.44 (br. *d*, $J = 7.7$, 1 H); 7.29 (*dt*, $J = 7.7$, 1.1, 1 H); 7.11 (*ddd*, $J = 7.7$, 7.2, 1.3, 1 H); 7.08 (*ddd*, $J = 7.7$, 7.2, 1.1, 1 H); 3.32 (*m*, 1 H); 3.10 (*d*, $J = 11.0$, 1 H); 2.71 (*m*, 1 H); 2.62–2.50 (*m*, 2 H); 2.23 (*dd*, $J = 11.2$, 3.2, 1 H); 2.00–1.30 (*m*, 12 H); 1.24 (*d*, $J = 6.0$, 3 H). ^{1}H-NMR (300 MHz, C_6D_6, 80°): aliphatic region: 3.08 (*dm*, $J = 8.2$, 1 H); 3.01 (*dd*, $J = 11.0$, 2.7, 1 H); 2.70–2.50 (*m*, 2 H); 2.42 (*m*, 1 H); 2.08 (*dd*, $J = 11.2$, 3.3, 1 H); 1.98 (*m*, 1 H); 1.79–1.65 (*m*, 3 H); 1.60–1.52 (*m*, 3 H); 1.28–1.14 (*m*, 5 H); 1.10 (*d*, $J = 6.2$, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): sharp signals: 135.9 (*s*); 135.5 (*s*); 127.4 (*s*); 121.1 (*d*); 119.3 (*d*); 118.0 (*d*); 110.6 (*d*); 108.1 (*s*); 55.3 (*d*); 36.5 (*d*); 34.4 (*d*); 31.4 (*t*); 20.8 (*q*); br. signals: 60.6 (*d*); 56.4 (*t*); 31.5 (2*t*); 26.6 (2*t*); 21.1 (*t*). ^{13}C-NMR (75 MHz, C_6D_6, 80°): aliphatic region: 61.1 (*d*); 56.2 (*t*); 55.2 (*d*); 37.1 (*d*); 34.8 (*d*); 31.69 (*t*); 31.63 (*t*); 31.5 (*t*); 26.8 (*t*); 26.6 (*t*); 21.1 (*t*); 20.6 (*q*). EI-MS: 294 (97, M^+), 293 (75), 279 (41), 251 (15), 238 (15), 170 (23), 169 (33), 168 (21), 156 (26), 150 (100), 130 (13).

*(+)-(3*R*,5*R*,15*S*,20*S*)-5-Methylyohimbane* ((+)-**26**): Prepared from (−)-**25** according to *Method 6*. Yield: 57% (and 34% of **25**). M.p. 183–186° (dec.). $[\alpha]_D = +51.4$ ($c = 1.0$, $CHCl_3$). IR ($CHCl_3$): 3470, 3055, 3000, 2950, 2920, 2850, 2780, 1462, 1446, 1368, 1320, 1311, 1280, 1256, 1153. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.68 (br. *s*, 1 H); 7.45 (br. *d*, $J = 7.8$, 1 H); 7.28 (*dm*, $J = 7.8$, 1 H); 7.12 (*ddd*, $J = 7.8$, 7.2, 1.3, 1 H); 7.09 (*ddd*, $J = 7.8$, 7.2, 1.1, 1 H); 3.76 (*m*, 1 H); 3.30 (br. *quint.*, $J = 6.6$, 1 H); 3.15 (*ddd*, $J = 15.2$, 5.9, 2.3, 1 H); 3.02 (br. *t*, $J = 11.2$, 1 H); 2.50

(br. *d*, *J* = 15.2, 1 H); 2.44 (br. *dd*, *J* = 11.2, 4.0, 1 H); 2.12 (br. *m*, 1 H); 1.95 – 1.70 (*m*, 5 H); 1.65 – 1.23 (*m*, 5 H); 1.06 (*d*, *J* = 6.6, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): sharp signals: 136.2 (*s*); 128.2 (*s*); 121.1 (*d*); 119.2 (*d*); 118.0 (*d*); 110.6 (*d*); 106.8 (*s*); 54.1 (*d*); 51.6 (*t*); 47.2 (*d*); 34.9 (*d*); 34.4 (*d*); br. signals: 134.5 (*s*); 35.7 (*t*); 31.5 (*t*); 29.3 (*t*); 28.3 (*t*); 26.4 (2*t*); 22.1 (*t*); 10.6 (*q*). EI-MS: 294 (100, M^+), 293 (79), 279 (46), 251 (12), 238 (12), 170 (16), 169 (28), 156 (15), 150 (70).

REFERENCES

[1] C. Lohse, Ph.D. Thesis, ETH-Zürich, 1997, Nr. 12286.
[2] R. Detterbeck, Diplomarbeit, ETH-Zürich, 1997.
[3] S. Siddiqui, S. S. Ahmad, S. I. Haider, *Tetrahedron Lett*. **1987**, *28*, 1311.
[4] C. Szantay, K. Honty, 'The Monoterpene Indole Alkaloids', John Wiley & Sons Ltd., New York, 1994.
[5] D. B. Repke, W. J. Ferguson, *J. Heterocycl. Chem*. **1976**, 775.
[6] a) A. Werner, H. E. Conrad, *Chem. Ber*. **1899**, *32*, 3046; b) M. M. Vavon, P. Peignier, *Bull. Soc. Chim. Fr*. **1929**, *45*, 297; c) H.-J. Gais, K. L. Lukas, W. A. Ball, S. Braun, H.-J. Lindner, *Liebigs Ann. Chem*. **1986**, 693; d) G. Sabbioni, J. B. Jones, *J. Org. Chem*. **1987**, *52*, 4566.
[7] L. Turbanti, G. Cerbai, C. DiBugno, R. Giorgi, G. Garzelli, M. Criscuoli, A. R. Renzetti, A. Subissi, G. Bramanti, *J. Med. Chem*. **1993**, *36*, 699.
[8] T. Mukaiyama, Y. Aikawa, S. Kobayashi, *Chem. Lett*. **1976**, 57.
[9] G. L. Lange, C. Gottardo, *Synth. Commun*. **1990**, *20*, 1473.
[10] L.-H. Zhang, A. K. Gupta, J. M. Cook, *J. Org. Chem*. **1989**, *54*, 4708.
[11] F. Bohlmann, *Chem. Ber*. **1958**, *91*, 2157.
[12] a) D. Q. McDonald, W. C. Still, *Tetrahedron Lett*. **1992**, *33*, 7743; b) S. J. Weiner, P. A. Kollmann, D. Case, U. C. Singh, C. Alagona, S. Profeta, P. Weiner, *J. Am. Chem. Soc*. **1984**, *106*, 765; c) S. J. Weiner, P. A. Kollmann, N. T. Nguyen, D. A. Case, *J. Comput. Chem*. **1987**, *7*, 230.
[13] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem*. **1990**, *11*, 440.
[14] J. Ponder, F. M. Richards, *J. Comput. Chem*. **1987**, *8*, 1016.
[15] J. J. P. Stewart, *J. Comput. Chem*. **1989**, *10*, 209.
[16] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc*. **1985**, *107*, 3902.
[17] J. P. P. Stewart, *J. Comput.-Aided Mol. Des*. **1990**, *4*, 1.
[18] M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Peterson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, *Gaussian, Inc.*, Pittsburgh PA, 1995.
[19] R. Stahl, H.-J. Borschberg, *Helv. Chim. Acta* **1994**, *77*, 1331.
[20] J. M. Goodman, W. C. Still, *J. Comput. Chem*. **1991**, *12*, 1110.
[21] W. C. Still, A. Tempczyck, R. C. Hawley, T. Hendrickson, *J. Am. Chem. Soc*. **1990**, *112*, 6127.

Received January 5, 2002