Tetrahedron Vol. 46, No. 3, pp. 833-846, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00
Pergamon Press plc

Syntheses of 1,3-disubstituted N-oxy-β-carbolines by the Pictet-Spengler reactions of N-oxy-tryptophan and -tryptamine derivatives.

Pedro H.H. Hermkens†, Jan H. van Maarseveen†, Peter L.H.M. Cobben†, Harry C.J. Ottenheijm†, Chris G Kruse‡, Hans W. Scheeren†*

† Department of Organic Chemistry, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands.

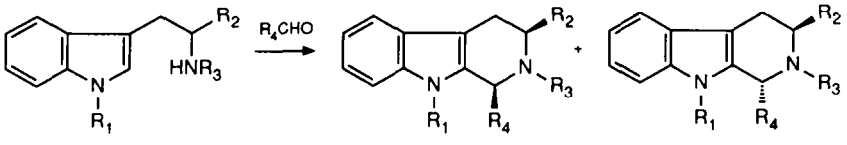
‡ Duphar Research Laboratories, P.O.B. 2, 1380 AA, Weesp, The Netherlands.

(*Received in UK* 26 *October* 1989)

Abstract: A general and simple approach for the synthesis of N-hydroxy and N-alkoxytryptophan and tryptamine derivatives is presented. Key-intermediates are nitro compounds which are easily accessible from gramine (**16**) and RCH_2NO_2. Reduction with Al-amalgam gave in high yields the corresponding hydroxylamines. The N-alkoxy derivatives are accesible by a regioselective O-alkylation of oxime **12** followed by a reduction with borane-trimethylamine complex. The influence of the substituents R_1-R_3 on the reactivity and the relative stereochemistry in the Pictet-Spengler condensation with aldehydes (R_4CHO) has been studied. The increased electrophilic character of the C=N double bond in the intermediate **38** due to the oxygen substituent on the nitrogen increases the reactivity and alters the stereoselectivity.

The tetrahydro-β-carboline nucleus is a structural feature present in many indole alkaloids, and the Pictet-Spengler reaction (Scheme I) is the most widely used method for synthesizing this tricyclic system. Recent examples are the total synthesis of Pyridindolol[1], Fumitremorgin-Verruculogen[2] and Eudistomins[3]. For obvious reasons much attention has been focussed on stereochemical[1b,2,3b,4,5] and mechanistic[4b,6] aspects of this reaction.

Scheme I



1 R_1=H, R_2=COOMe, R_3=H
2 R_1=H, R_2=COOMe, R_3=Bn
3: R_1=H, R_2=COOEt, R_3=OH
4 R_1=H, R_2=COOEt, R_3=OBn
5: R_1=H, R_2=H, R_3=OH

6 *(cis)*

7 *(trans)*

Generally, tryptophan methyl ester (**1**) and aldehydes in aprotic solvents yield both *cis* and *trans* 1,3-disubstituted-1,2,3,4-tetrahydro-β-carbolines **6** and **7** (Scheme I). It has been demonstrated[4g] that high *cis*-selectivity can be achieved if the Pictet-Spengler reaction is conducted at low temperatures (0°C). High or complete *trans*-selectivity was observed when N-benzyl tryptophan methyl ester **2** was condensed with aldehydes.[4b,4h]

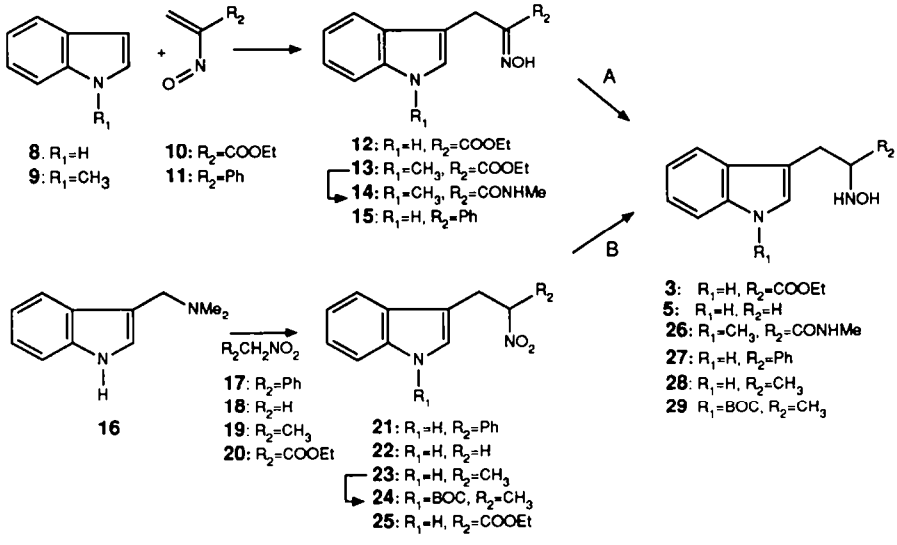
In contrast, Pictet-Spengler reactions of derivatives of N-hydroxytryptophans[3b] (*i.e.* **3** and **4**) and N-hydroxytryptamine[3a,d,e] (*i.e.* **5**) have been investigated only incidentally. The preliminary results of these studies indicate a different behaviour with respect to the reactivity and stereochemistry. Therefore we have studied the chemical scope and the stereochemical implications of this reaction for R_3=hydroxy or alkoxy in more detail by variations of R_1, R_2 and R_4 (Scheme I).

Synthesis of N-oxy-tryptophan and -tryptamine derivatives

N-hydroxy derivatives: (Scheme II) The synthesis of N-hydroxytryptophan derivatives like **3** is well documented.[7] Cycloaddition[8] of the nitroso-olefin **10** -prepared *in situ* from ethyl α-(hydroxyimino)-β-bromopropanoate- with an excess of **8** gives an adduct which after ring opening and rearomatization affords **12**. Subsequent reduction of the oxime double bond of **12** with borane-trimethylamine complex and acid gives **3** (Route A).

By the same procedure oxime **15** is obtained from **8** and **11**[9] in only 20% yield. The poor yield is a

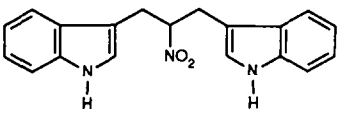
Scheme II



result of the lower reactivity of nitroso-olefin **11** compared with **10** due to the lower electron-withdrawing ability of the phenyl group.[9,10] Reduction of the oxime double bond of **15** failed with borane-trimethylamine complex or Al-amalgam. However, reduction with sodium cyano borohydride in acidic solvent gave the N-hydroxy tryptamine derivative **27** in 95% yield.

Since Route A seems to be only efficiently applicable if strongly electron withdrawing R_2 groups are present in the nitroso-olefin we studied an alternative route. Heath-Brown *et.al.*[11] prepared the nitro compound **23** (R_2=CH_3) from gramine (**16**) and nitroethane (**19**) by treatment with dimethylsulfate and base.[11a] Following the same procedure with α-nitrotoluene (**17**)[12] and nitromethane (**18**) we isolated the nitro compounds **21** (R_2=Ph) and **22** (R_2=H) in 63% and 86% yield, respectively. In the latter case a large excess of nitromethane was necessary in order to suppress the formation of the bisindole compound **30** (Chart I), which has not been reported before. Reduction of the nitro

Chart I



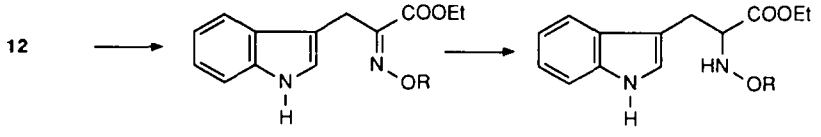
30

functionality of **21-23** into the hydroxylamine group proceeded smoothly with Al-amalgam in ethyl acetate saturated with water to give **5**, **27** and **28** in high to excellent yields.[13] This method appeared to be also very suited for the preparation of **3**. By simply heating gramine and ethyl nitroacetate (**20**) in xylene (100°C) the nitro compound **25** (R_2=COOEt) was obtained in 90% yield,[14] which by reduction with Al-amalgam afforded **3** in 92% yield.[15] Thus, route B is a general and a simple approach to both N-hydroxytryptophan and tryptamine derivatives.

In this study we also investigated the two indole nitrogen substituted compounds **26** and **29**. The synthesis of **26** has been described (Route A, **9**→**13**→**14**→**26**).[7a] In Route B it was possible to protect the nitrogen of indole with *tert*-butyloxycarbonyl (BOC) at the nitro-stage, by following the procedure of Grehn.[16] Reaction of **23** with di-*tert*-butyl dicarbonate in the presence of triethylamine and 4-dimethylaminopyridine in acetonitrile gave **24** in 83% yield and subsequent reduction of the nitro with Al-amalgam gave **29** in 54% yield.

N-alkoxytryptophan derivatives: (Scheme III) One of the approaches we explored for the synthesis of N-alkoxytryptophan derivatives (R_3 variation) starts with the oxime **12**.[17] Alkylation of oximes is known to occur both on oxygen and nitrogen to give mixtures of oxime ethers and nitrons.[18] Selective

Scheme III



31: R=Bn
32: R=i-C_3H_7
33: R=n-C_4H_9
34: R=CH_3

4 : R=Bn
35: R=i-C_3H_7
36: R=n-C_4H_9
37: R=CH_3

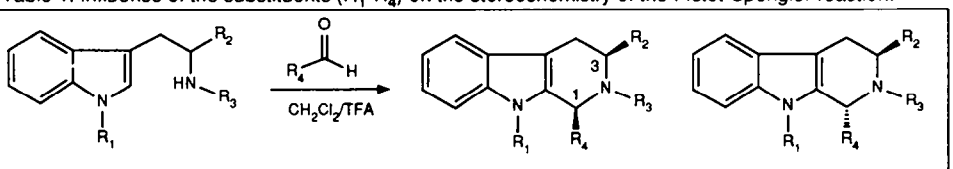
O-alkylation of oximes has been reported using phase transfer conditions[18a], but these conditions failed with **12**.[19] In our hands the method of choice for selective O-alkylation encompasses DMSO as solvent, potassium *tert*-butoxide as base and an alkyl chloride as alkylating agent and 50°C as the reaction temperature. Under these conditions reaction of **12** with benzylchloride, 2-chloropropane and 1-chlorobutane gave **31**, **32** and **33** in 68, 76 and 77% yield, respectively. In the case of the O-methyl derivative **34** we applied a general method[18b] for the preparation of methyloxime ethers -*viz.* reaction of **12** with methyliodide in acetone in the presence of suspended Ag_2O (86% yield).

Reduction of the oxime ethers was accomplished under standard conditions. Treatment of **31-34** with borane-trimethylamine complex afforded **4** and **35-37** in 73-91% yield.

Pictet-Spengler reactions

Reaction of the above described N-hydroxy(alkoxy)-tryptophan and -tryptamine derivatives (variation in R_1-R_3) with aldehydes (R_4CHO) in dichloromethane at room temperature in the presence

Table 1. Influence of the substituents (R_1-R_4) on the stereochemistry of the Pictet-Spengler reaction.



3-5, 26-29, 35-37 | 6 | 7

Entry	Product	R_1	R_2	R_3	R_4	Reaction Conditions	yield[a] (%)	Product ratio[b] 6/7	6-7 / 6+7 x100%
1	a[c]	H	COOEt	OH	CH_3	25°C, 5 h.	98	70 / 30	40
2	b				n-C_3H_7	2 d	98	60 / 40	20
3	c				$CH_2C_6H_5$	2 d	98	58 / 42	16
4	d				$C_2H_4SCOCH_3$	1 h	99	71 / 29	42
5	e[c]				C_6H_5	3 h.	85	43 / 57[b,d]	-14
6	f				2-thienyl	2 d.	79	58 / 42	16
7	g				3,4,5-$C_6H_2(OMe)_3$	4 d	76	50 / 50	0
8	h	H	C_6H_5	OH	CH_3	25°C, 2h	94	70/30	40
9	i		CH_3			12h	87	86/14	72
10	j[e]		H			24h	83	-	-
11	k		C_6H_5		C_6H_6	3h.	91	45/55	-10
12	l		CH_3			40°C, 24h	97	63/37	26
13	m		CH_3		3,4,5-$C_6H_2(OMe)_3$	40°C, 24h	97	66/34	32
14	n	CH_3	CONHCH$_3$	OH	C_6H_5	25°C, 3h	95	0/100	-100
15		Boc	CH_3			competition between deprotection and condensation			
16	o	H	COOEt	OCH_3	CH_3	25°C, 1h	95	47/53	-6
17	p[c]			$OCH_2C_6H_5$		3h	96	50/50[c]	0
18	q			O-i-C_3H_7		1h	80	42/58[d]	-16
19	r			O-n-C_4H_9		1h	87	43/57[d]	-14
20	s			OCH_3	C_6H_5	1h.	97	18/82	-64
21	t			O-i-C_3H_7		1h	96	21/79	-58
22	u			O-n-C_4H_9		1h	93	25/75	-50

a) based on isolated products b) based on isolated compounds c) see reference 3b d) product ratio determined by means of an analytical HPLC-technique e) see reference 3a

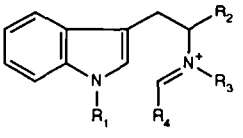
of trifluoroacetic acid (1 equiv.) gave a mixture of N-hydroxy(alkoxy)-1,2,3,4-tetrahydro-β-carbolines **6** and **7** (Table I). With the exception of entry 15 all variations of R_1-R_4 studied resulted in the desired β-carbolines in excellent yields. In order to establish the relative stereochemistry of the C(1) and C(3) protons, NOE difference studies were carried out. Irradiation of C(1)H of compounds **6** resulted in a ca. 10% NOE on C(3)H and *vice versa*. The absence of these NOE differences in compounds 7 indicates that the C(1) and C(3) protons in **6** and in **7** have a *cis*- and a *trans*-relationship, respectively. Although it has been argued that proton NMR shifts cannot be used for the assignment of the stereochemistry of 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines[4a], we found that in all the 1,3-disubstituted N-hydroxy(alkoxy)-β-carboline derivatives the chemical shifts of the C(1)H protons and in the 1,3-disubstituted N-hydroxy-β-carbolines the NOH protons of the *trans*-isomers (**7**) are consistently down-field (0.14-1.54 ppm) to the chemical shifts of the corresponding protons of the corresponding *cis*-isomers (**6**).

The influence of the substituent R_4 on the relative stereochemistry was studied by the reaction of **3** with different aldehydes (Table I, Entries 1-7). The tendency is a selectivity for the *cis*-isomer **6**. Exceptions are the reactions of benzaldehyde and 3,4,5-trimethoxybenzaldehyde (entries 5 and 7). It has been reported[4g] that in the case R_3=H under similar reaction conditions using butyraldehyde or benzaldehyde the *cis* product is formed dominantly (*cis*/*trans*=80/20). The decrease of this selectivity we observed for N-hydroxytryptophan (R_3=OH, entries 2 and 5) is in agreement with results observed for tryptophan derivatives in which R_3=alkyl.[4b,c,h]

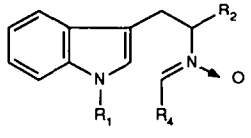
The observed stereochemistry seems to be the result of a kinetically controlled reaction. Prolonged treatment of either the *cis*-isomers **6b** and **6e** or the *trans*-isomers **7b** and **7e** respectively under the reaction conditions used for their formation did not cause the formation of the other isomer. Higher temperature (65°C) led to serious decomposition of the starting materials. In the resulting reaction mixtures the other isomer could be detected only in less than 5% by means of analytical HPLC techniques

The influence of the α-substituent R_2 on the reactivity and relative stereochemistry was studied by reaction of the N-hydroxy compounds **3**, **5** and **27-28** (R_2=COOEt, H, Ph and CH_3, respectively) with acetaldehyde and benzaldehyde derivatives (Table I, Entries, 1, 5 and 8-13). The substituents R_2=COOEt and R_2=Ph (Entries 1, 8, 5, 11) have a comparable influence on the stereochemistry, whereas R_2=CH_3 (Entries 9, 12, 13) causes a shift towards *cis*-selectivity. Based on the minimal reaction times mentioned in Table I, the reactivities of the compounds with R_2=COOEt (Entries 1 and 5) and R_2=Ph (Entries 8 and 11) are also comparable, whereas with R_2=H (Entry 10) and R_2=CH_3 (Entry 9) a decrease in reactivity is observed. The smooth reaction of N-hydroxytryptamine (**5**) with acetaldehyde (Entry 10[3a]) is surprising in view of the fact that tryptamine itself (R_3=H) cyclizes only under much more severe reaction conditions.[1b,4d]

Chart II



38



39

It is generally excepted that the Pictet-Spengler reaction involves the intermediacy of the imminium ion **38** (Chart II) and that the electrophilic character of the C=N bond this intermediate explains differences in reactivity.[1b] Electron withdrawing groups (R_2 *e.g.* COOR) destabilize the iminium ion and will accelerate the reaction. In the same way the higher reactivity of N-hydroxytryptamine (R_3=OH) *versus* tryptamine (R_3=H) can be attributed to the electron withdrawing ability of the hydroxy group. This increased reactivity is also reflected in a lower stereoselectivity.

The influence of R_1 on the relative stereochemistry was studied by the reaction of the N-hydroxy compounds **26** and **29** with benzaldehyde (Table I, Entries 14-15). Examination of molecular models indicated that in the β-carboline **6** the $A_{(1,2)}$-strain[4a] between the substituents R_1 (CH_3 or BOC) and R_4

(Ph) will be so pronounced that mainly the *trans*-isomer will be formed. Indeed, reaction of **26** (R_1=CH_3) with benzaldehyde gave a single diastereomer of which the relative stereochemistry was established as *trans* (Entry 14). On the basis of this observation, we reasoned that the introduction of a protective group at the indole nitrogen could lead to a highly stereoselective approach for *trans* 1,3-disubstituted N-hydroxy-1,2,3,4-tetrahydro-β-carbolines (**7**: R_1=H). However, treatment of the N-BOC protected compound **29** with benzaldehyde under the acidic reaction conditions employed previously did not yield the desired ringclosed product as ringclosure is so slow now that N-deprotection becomes a competitive reaction. This result can be rationalized by the decreased electron density of the indole C(2)-C(3) double bond due to the electron-withdrawing BOC group.

Of special interest is the influence of R_3 on the relative stereochemistry. We studied the reaction of N-alkoxytryptophan derivatives **4** and **35-37** with acetaldehyde and benzaldehyde (Table I, Entries 16-22). It is striking that the N-alkoxytryptophans are more reactive than the N-hydroxy counterpart **3**. This can be rationalized by two lines of reasoning. Firstly, N-alkoxy amines are known to be less basic than the corresponding N-hydroxy amines[20] and therefore the intermediates **38** containing a positively charged N are more reactive with R_3=alkoxy. Secondly, the intermediate **38** with R_3=OH is in equilibrium with the nitrone **39** (Chart II). In the case of R_3=alkoxy such an equilibrium is not possible.

Another interesting feature is that the reaction with acetaldehyde as well as with benzaldehyde shows a shift of *de* towards *trans* selectivity in going from NOH to NOR_3 derivatives (Compare entries 1 with 16 and 5 with 20). However, in contrast with the complete *trans*-selectivity observed for the reaction of N-benzyltryptophan with benzaldehyde[4b], the N-alkoxytryptophans showed no complete selectivity. This can again be rationalized by the increased reactivity of intermediate **38** as a result of the electronic effect exerted by the oxygen atom.

Conclusions

An efficient route to the N-hydroxytryptophan and tryptamine derivatives has been described via the corresponding nitro compounds (**21-25**), prepared from gramine and nitromethane derivatives (**17-20**) (Route B). Reduction of the nitro-group with Al-amalgam gave the N-hydroxy compounds (**3**, **5**, and **27-29**) in high yields.

N-alkoxytryptophans can be conveniently prepared by a regioselective O-alkylation of oxime **12** (Route B) followed by reduction with $Me_3N.BH_3$.

In our study on the influence of the substituents R_1-R_4 on the course of the Pictet-Spengler reaction we found that:

i) reactions of N-hydroxytryptophan **3** with aldehydes (R_4CHO) in general show a moderate selectivity for the *cis*-isomer.

ii) the reactivity and stereochemistry is influenced by the α-substituent R_2; compounds with R_2=COOEt or Ph are more reactive than compounds with R_2=H or CH_3; in the case of R_2=CH_3 the most pronounced *cis*-selectivity is observed.

iii) for R_3-substituents the reactivity and the *trans*-selectivity increase in the row H < OH < OR.

iv) the presence of a substituent other than H at the indole nitrogen (R_1) causes complete *trans*--selectivity.

Acknowledgement
This work was supported by the Technology Foundation of the Netherlands (STW).

Experimental Section
Melting points were taken on a Koefler hot stage (Leitz-Wetzlar) and are uncorrected. Ultraviolet spectra were measured with a Perkin Elmer spectrometer, Model lambda 5. Proton magnetic resonance spectra were measured on a Bruker WH-90 or on a Bruker AM 400 spectrometer. Chemical shifts are reported as δ-values relative to tetramethylsilane as an internal standard; deuteriochloroform was used as solvent unless stated otherwise. Mass spectra were obtained with a double-focusing VG 7070E spectrometer. Thin-layer chromatography (TLC) was carried out by using silica gel F-254 plates (thickness 0.25 mm). Spots were visualized with a UV hand lamp, iodine vapor, or Cl_2-TDM.[21] For column chromatography Merck silica gel (type 60H) was used.

3-(2-Hydroxyimino-2-phenylethyl)indole (15)
A solution of α-(hydroxyimino)-α-phenyl-β-bromoethane[9] (21.4 g, 100 mmol) in dry dichloromethane (400 mL) was added dropwise in 4 hours to a solution of indole (**8**) (35.1 g, 300 mmol) and Na_2CO_3 (21.1 g, 200 mmol) in dry dichloromethane (250 mL). Stirring was continued for 40 h. at room temperature in an argon atmosphere. The reaction mixture was filtered and subsequently washed with 0.1 N HCl and brine. The organic layer was dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was subjected to column chromatography (CH_2Cl_2/MeOH, 98/2, v/v) to give 5 g (20%) of **15**: mp 167-171°C; Rf 0.29 (CH_2Cl_2/MeOH, 98/2, v/v) ; EIMS (70 eV) m/z (relative intensity) 250 (M^+, 48), 233 ([M-OH]$^+$, 13), 130 ([C_9H_8N]$^+$, 100); ^{1}H NMR δ 8.22-7.00 (m, 10H, C(4)-C(7)H, indole NH and C_6H_5), 6.89 (m, 1H, C(2)H), 4.27 (s, 2H, indole C(3)-CH_2); Anal.Calcd. for $C_{16}H_{14}N_2O$ (Mw 250.303): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.78; H, 5.60; N, 10.96.

3-(2-Nitro-2-phenylethyl)indole (21)
Following the same procedure as described by Heath-Brown[11] for **23**, with gramine (5.8 g, 30 mmol), sodium (0.76 g, 33 mmol) and dimethylsulfate (7.56 g, 60 mmol) in ethanol (25 mL) and α-nitrotoluene (**17**)[13] (5.1 g, 37 mmol) gave after column chromatography ($CHCl_3$/n-hexane, 70/30, v/v) 5.0 g (63%) of **21**. Recrystallized from CH_2Cl_2/n-hexane: mp 98-100°C; Rf 0.58 ($CHCl_3$); EIMS (70 eV) m/z (relative intensity) 266 (M^+, 29), 220 ([$C_{16}H_{14}N$]$^+$, 100), 130 ([C_9H_8N]$^+$, 36); ^{1}H NMR δ 8.00 (br s, 1H, NH), 7.56-7.04 (m, 9H, indole C(4)-C(7)H and C_6H_5), 6.91 (d, 1H, indole C(2)H), 5.77 (X part of ABX spectrum, 1H, J=5.5Hz, J=9.3Hz, CH_2CHNO_2), 3.95 and 3.47 (AN part of ABX spectrum, 2H, ^{2}J=14.7Hz, J=5.5Hz, J=9.3Hz, CH_2CHNO_2); Anal.Calcd. for $C_{16}H_{14}N_2O_2$ (Mw 266.302): C, 72.16; H, 5.30; N, 10.52. Found: C, 71.80; H, 5.24; N, 10.36.

3-(2-Nitroethyl)indole (22) and 3-[2-Nitro-2-(3-indolyl-methyl)ethyl]indole (30)
This synthesis is a modification of Heath-Brown's procedure.[11]
Sodiummethoxide which was fresh made from 4.35 g (189 mmol) sodium in dry methanol (300 mL) was added to a stirred solution of gramine (**16**) (30 g, 172 mmol), dimethylsulfate (43.4 g, 344 mmol) in nitromethane/methanol, 1/1, v/v (500 mL). The reaction mixture was stirred for 24h, after which the reaction was completed. The solution was concentrated to near dryness. The residue dissolved in dichloromethane and subsequently washed with 5% NH_3 and 1N HCl and brine. The organic layer was dried (Na_2SO_4) en the solvent evaporated in vacuo. The crystalline residue was subjected to column chromatography ($CHCl_3$/n-hexane, 75/25, v/v) to yield 28g (86%) of **22** and 2.8g (5%) of **30**.
Compound 22: Spectrocopic data are identical with earlier published results.[3a,d]
Compound 30: Recrystallized from CH_2Cl_2/MeOH/n-hexane: mp 213-214°C; Rf 0.29 ($CHCl_3$); EIMS (70 eV), m/z (relative intensity) 319 (M^+, 67), 272 ([M-HNO_2]$^+$, 22), 130 ([C_9H_8N]$^+$, 100); ^{1}H NMR (DMSO-d^6) δ 10.96 (br s, 2H, 2xNH), 7.60-6.92 (m, 10H, 2x indoleC(2)H and 2xindoleC(4)-C(7)H), 5.22 (X part of ABX spectrum, 1H, $CHNO_2$), 3.50 (AB part of ABX spectrum, 4H, 2x indoleC(3)-CH_2); Anal Calcd. for $C_{19}H_{17}N_3O_2$ (Mw 319.364): C, 71.46; H, 5.37; N, 13.16. Found: C, 71.21; H, 5.32; N, 12.97.

N(1)[(*tert*-Butyloxy)carbonyl]-3-(2-Nitropropyl)indole (24)
To a stirred solution of **23**[11] (204 mg, 1 mmol) and DMAP (12.2 mg, 0.1 mmol) in dry acetonitrile (3 mL) was added di-*tert*-butyl dicarbonate (260 mg, 1.2 mmol). After completion of the reaction as was monitored by TLC ($CHCl_3$/MeOH, 99/1, v/v) the reaction mixture was diluted with ethyl acetate and subsequently washed with 10% NH_3, water and brine. The organic layer was dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was subjected to column chromatography (CH_2Cl_2/n-hexane, 90/10, v/v) to give 250 mg (83%) of **24**. Recrystallized from CH_2Cl_2/n-hexane; mp 117-119°C; Rf 0.82 ($CHCl_3$); UV (MeOH) λmax 225, 257, 262.5, 273 (sh), 284.5, 292.5 nm; EIMS (70 eV) m/z (relative

intensity) 304 (M^+, 34), 248 (16), 201 (38), 157 ($[C_{11}H_{11}N]^+$, 54), 57 ($[C_4H_9]^+$, 100); ^1H NMR δ 8.07 (m, 1H, C(2)H), 7.51-7.12 (m, 4H, C(4)-C(7)H), 4,86 (m, 1H, CH_2CHCH_3), 3.43 and 3.12 (AB part of ABX spectrum, 2H, ^2J=14.7Hz, J=6.3Hz, J=5.4Hz, indole C(3)-CH_2), 1.67 (s, 9H, $C(CH_3)_3$), 1.60 (d, 3H, J=6.3Hz, $CHCH_3$); Anal.Cald. for $C_{16}H_{20}N_2O_4$ (Mw 304.349): C, 63.14; H, 6.62; N, 9.20. Found: C, 63.24; H, 6.59; N, 9.13.

Ethyl α-(Hydroxyamino)-β-(indol-3-yl)propanoate (3)

Procedure A: Reduction of oxime **12** as described earlier.[7]

Procedure B: This synthesis is a modification of Cohen's procedure.[13] To a stirred solution of **25**[14] (524 mg, 2 mmol) in ethyl acetate (saturated with water) (100 mL) was added at 0°C portionwise freshly prepared Al(Hg) until starting material was finished. The reaction mixture was filtered and the filtrate dried ($MgSO_4$) and the solvent evaporated in vacuo. The residue was subjected to column chromatography ($CHCl_3$/MeOH, 98/2, v/v) to give 455 mg (92%) of **3**. Spectroscopic data are identical with earlier published results.[7]

3-(2-Hydroxyamino-2-phenylethyl)indole (27)

Procedure A: To a solution of **15** (1.63 g, 6.5 mmol) in dry methanol (150 mL) was added a small part of a solution of $NaCN.BH_3$ (4 g, 63.7 mmol) in dry methanol (50 mL). Then with HCl in ethanol (7N solution) the solution was kept at pH 1~2 (electronic pH-meter) untill the pH did not change anymore. This process was repeated until all the $NaCN.BH_3$ was added (48 hours). The reaction mixture was filtered and the residue concentrated to dryness. The residue was dissolved in ethylacetate/water, 1/1, v/v. The aqueous layer was washed again with ethyl acetate. The combined organic layers were subsequently washed with a saturated $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and the solvent evaporated in vacuo. Recrystallization from CH_2Cl_2/n-hexane gave 1.6 g (95%) of **27**.: mp 112-115°C; Rf 0.75 (EtOAc/n-hexane, 9/1, v/v); ^1H NMR δ 7.93 (br s, 1H, NH), 7.71-6.95 (m, 9H,indole C(4)-C(7)H and C_6H_5), 6.82 (d, 1H, C(2)H), 4.64 (br s, 2H, HNOH), 4.27 (X part of ABX spectrum, 1H, J=14.1Hz, indole C(3)CH_2**CH**), 3.17 and 3.05 (AB part of ABX spectrum, 2H, ^2J=14.4Hz, J=6.0Hz, J=8.6Hz, indole C(3)CH_2CH); Anal.Calcd. for $C_{16}H_{16}N_2O$ (Mw 252.319): C, 76.16; H, 6.39: N, 11.10. Found: C, 76.18; H, 6.42; N, 10.86.

Procedure B: : The same procedure was followed as was described for **3**. Reaction of **21** (2.14 g, 8 mmol) gave after column chromatography ($CHCl_3$/MeOH, 98/2, v/v) 1.54 g (76%) of **27**.

3-(2-Hydroxyaminoethyl)indole (5)

Procedure B was followed as described for **3**. Reaction with **22** (1.5 g, 7.9 mmol) gave after evaporation of the solvent crude **5**. The residue was not purified because of the instability of the compound. Spectroscopic data are identical with earlier published results.[3]

3-(2-Hydroxyaminopropyl)indole (28)

Procedure B was followed as described for **3**. Reaction with **23**[11a] (8,23 g, 40.3 mmol) gave after column chromatography ($CHCl_3$/MeOH, 96/4, v/v) 7.5 g (98%) of **28**. Spectroscopic data are identical with earlier published results.[11b]

N(1)-[(*tert*-Butyloxy)carbonyl]-3-(2-hydroxyaminopropyl)indole (29)

Procedure B was followed as described for **3**. reaction with **24** (145 mg, 0.48 mmol) gave after column chromatography ($CHCl_3$/MeOH, 99/1, v/v) 74 mg (54%) of **29**. Rf 0.20 ($CHCl_3$/MeOH, 97/3, v/v); EIMS (70 eV) m/z (relative intensity) 290 (M^+, 21), 189 (38), 130 ($[C_9H_8N]^+$,100); ^1H NMR δ 8.17 (m, 1H, C(2)H), 7.67-7.19 (m, 4H, C(4)-C(7)H), 6.21 (br s, 2H, HNOH), 3.31 (m, 1H, CH_2CHCH_3), 2.85 (t, 2H, indole C(3)-CH_2), 1.68 (s, 9H, $C(CH_3)_3$), 1.15 (d, 3H, $CHCH_3$).

Ethyl α-(2-propyloximino)-β-(indol-3-yl)propanoate (32)

To a stirred solution of **12**[7] (375 mg, 1.52 mmol) and 2-chloropropane (235 mg, 3 mmol) in DMSO (7 ML) at 50°C was added portionwise KOtBu (188 mg, 1.68 mmol). After completion of the reaction (3 hours) the reaction mixture was worked-up under identical conditions as with procedure A, to give 330 mg (76%) of **32**.. Oil; Rf 0.37 ($CHCl_3$/MeOH, 97/3, v/v); EIMS (70 eV) m/z (relative intensity) 288 (M^+, 32), 229 ($[M-OC_3H_7]^+$, 51), 155 (100), 130 ($[C_9H_8N]^+$, 93); ^1H NMR δ 8.12 (br s, 1H, NH), 7.90-7.79 (m, 1H, indole (4)H), 7.34-7.06 (m, 4H, indole C(2)H and C(5)-C(7)H), 4.68 (m, 1H, $NOCH(CH_3)_2$), 4.27 (q, 2H, OCH_2CH_3), 4.07 (s, 2H, indole C(3)CH_2), 1.40 (d, 6H, $NOCH(CH_3)_2$), 1.29 (t, 3H, OCH_2CH_3).

Ethyl α-(1-butyloximino)-β-(indol-3-yl)propanoate (33)

The same procedure was followed as described for **32**. Reaction with **12**[7] (984 mg, 4 mmol), 1-chlorobutane (1.2 g, 12 mmol) and KOtBu (0.5 g, 4.4 mmol) in DMSO at 50°C gave after column

chromatography ($CHCl_3$) 930 mg (77%) of **33**. Oil; Rf 0.83 ($CHCl_3$/MeOH, 97/3, v/v); EIMS (70 eV) m/z (relative intensity) 302 (M^+, 30), 229 ([M-COOEt]$^+$, 60), 155 (100), 130 ([C_9H_8N]$^+$, 80); ^{1}H NMR δ 8.09 (br s, 1H, indole NH), 7.76-7.03 (m, 5H, C(2)H and C(4)-C(7)H), 4.30 (t, 1H, $NOCH_2$),4.21 (q, 2H, OCH_2CH_3), 4.02 (d, 2H, indole C(3)CH_2), 1.88-1.13 (m, 4H, $OCH_2CH_2CH_2CH_3$), 1.24 (t, 3H, OCH_2CH_3), 0.92 (t, 3H, $OCH_2CH_2CH_2CH_3$).

Ethyl α-(methyloximino)-β-(indol-3-yl)propanoate (34)
To a stirred solution of **12**[7] (246 mg, 1 mmol) and methyliodide (1 mL) in aceton (3 mL) was added Ag_2O (250 mg, 1.08 mmol). After completion of the reaction (30 minutes) as was monitored by TLC ($CHCl_3$/MeOH, 97/3, v/v) the reaction mixture was filtered and the filtrate evaporated in vacuo. The residue was subjected to column chromatography ($CHCl_3$) to give 224 mg (86%) of **34**. Oil; Rf 0.67 ($CHCl_3$/MeOH, 97/3, v/v); EIMS (70 eV) m/z (relative intensity) 260 (M^+, 46), 229 ([$C_{13}H_{13}N_2O_2$]$^+$, 55), 155 ([$C_{10}H_7N_2$]$^+$, 100), 130 ([C_9H_8N]$^+$, 100); ^{1}H NMR δ 8.03 (br s, 1H, NH), 7.69-7.00 (m, 5H, C(2)H and C(4)-C(7)H), 4.25 (q, 2H, OCH_2CH_3), 4.13 (s, 3H, OCH_3), 4.04 (s, 2H, indole C(3)-CH_2), 1.31 (t, 3H, OCH_2CH_3).

Ethyl α-(benzyloxamino)-β-(indol-3-yl)propanoate (4)
A solution of HCl in ethanol (5 mL of a 7N solution) was added to a stirred solution of **31**[7] (672 mg, 2.0 mmol) and borane-trimethylamine complex (TMA.BH_3:Aldrich Chemical Co., 210 mg, 2.9 mmol) in ethanol (5 mL) at room temperature. Stirring was continued for 24h at room temperature. The reaction mixture was then concentrated to dryness in vacuo. The residue was dissolved in dichloromethane and subsequently washed with saturated $NaHCO_3$, water and brine. The organic layer was dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was subjected to column chromatography ($CHCl_3$/MeOH, 98/2, v/) to give 566 mg (84%) of **4**. Spectroscopic data are identical with earlier published results.[7]

Ethyl α-(2-propyloxamino)-β-(indol-3-yl)propanoate (35)
The same procedure was followed as described for **4**. Reaction with **32** (1008 mg, 3.5 mmol) and TMA.BH_3 (281 mg, 3.85 mmol) gave after column chromatography ($CHCl_3$/MeOH, 99/1, v/v) 673 mg (74%) of **35**. Oil; Rf 0.27 ($CHCl_3$/MeOH, 99/1, v/v); EIMS (70 eV) m/z (relative intensity) 290 (M^+, 53), 217 ([$C_{13}H_{17}N_2O$]$^+$, 22), 130 ([C_9H_8N]$^+$, 100); ^{1}H NMR δ 8.03 (br s, 1H, indole NH), 7.66-7.02 (m, 5H, C(2)H and C(4)-C(7)H), 4.11 (q, 2H, OCH_2CH_3), 4.03-3.3.74 (m, 2H, $OCH(Me)_2$ and CHCOOEt), 3.09 (d, 2H, indole C(3)CH_2CH), 1.14 (t, 3H, OCH_2CH_3), 1.10 (d, 6H, $CH(CH_3)_2$.

Ethyl α-(1-butyloxamino)-β-(indol-3-yl)propanoate (36)
The same procedure was followed as described for **4**. Reaction with **33** (900 mg, 3.0 mmol) and TMA.BH_3 (460 mg, 6.3 mmol) gave after column chtomatography ($CHCl_3$) 833 mg (91%) of **36**. Oil; Rf 0.35 ($CHCl_3$/MeOH, 99/1, v/v); EIMS (70 EV) m/z (relative intensity) 304 (M^+, 52), 231 ([M-COOEt]$^+$, 24), 130 ([C_9H_8N]$^+$, 100); ^{1}H NMR δ 8.06 (br s, 1H, indole NH), 7.67-7.04 (m, 5H, C(2)H and C(4)-C(7)H), 4.14 (q, 2H, OCH_2CH_3), 4.01 (t, 1H, CHCOOEt), 3.70 (t, 1H, $NOCH_2$), 3.10 (d, 2H, indole C(3)CH_2CH), 1.62-1.13 (m, 4H, $OCH_2CH_2CH_2CH_3$), 1.13 (t, 3H, OCH_2CH_3), 0.89 (t, 3H, $OCH_2CH_2CH_2CH_3$).

Ethyl α-(methyloxamino)-β-(indol-3-yl)propanoate (37)
The same procedure was followed as described for **4**. Reaction with **34** (624 mg, 2.4 mmol) and TMA.BH_3 (210 mg, 2.9 mmol) gave after column chromatography ($CHCl_3$/MeOH, 98/2, v/) 456 mg (73%) of **37**. Oil; Rf 0.20 ($CHCl_3$/MeOH, 97/3, v/v); EIMS (70 eV) m/z (relative intensity) 262 (M^+, 41), 189 ([$C_{11}H_{13}N_2O$]$^+$, 18), 130 ([C_9H_8N]$^+$, 100); ^{1}H NMR δ 8.12 (br s, 1H, indole NH), 7.66-7.07 (m, 5H, C(2)H and C(4)-C(7)H), 4.78 (br s, 1H, HNOMe), 4.11 (q, 2H, OCH_2CH_3), 4.02 (t, 1H, CHCOOEt), 3.49 (s, 3H, OCH_3), 3.09 (d, 2H, indole C(3)CH_2CH), 1.14 (t, 3H, OCH_2CH_3).

General procedure Pictet-Spengler reaction.
To a stirred solution of a N-hydroxy(alkoxy)tryptophan or tryptamine derivative (variation R_1-R_3, see Table I) (1 mmol) and aldehyde (R_4CHO), see Table I) (1.25 mmol) in dry dichloromethane (10 mL) was added trifluoroacetic acid (1 mmol). Stirring was continued at the appropriate temperature and reaction time (see Table I). After completion of the reaction the solvent was evaporated and the residue subjected to column chromatography to separate the compounds **6** and **7**. Spectroscopic data of the β-carbolines **6** and **7**, see Table II.

Table II. Spectroscopic data of the β-carbolines **6** and **7**

Prod.	mp (°C)	Rf (Solv.Sys)[a]	Mass Spectrum	^{1}H NMR δ (ppm)
6b[b]	178-181	0.75 (D)	302 (M^+, 36), 285 ([M-OH]$^+$, 8), 259 ([M-C_3H_7]$^+$, 100), 229 ([M-COOEt]$^+$, 17), 185 ([$C_{11}H_9N_2O$]$^+$, 51), 169 ([$C_{11}H_9N_2$]$^+$, 42)	7.76 (br s, 1H,NH), 7.58-7.04 (m, 4H, C(5)-C(8)H), 5.64 (br s, 1H, NOH), 4.32 (q, 2H, OCH_2CH_3), 4.13 (br s, 1H, C(1)H), 3.86 (t, 1H, C(3)H), 3.10 (d, 2H, C(4)H_2), 2.22-1.53 (m, 4H, C(1)$CH_2CH_2CH_3$), 1.36 (t, 3H, OCH_2CH_3), 1 00 (t, 3H, C(1)$CH_2CH_2CH_3$).
7b[b]	141-144	0 45 (D)	302 (M^+, 46), 285 ([M-OH]$^+$, 86), 259 ([M-C_3H_7]$^+$, 100), 229 ([M-COOEt]$^+$, 29), 185 ([$C_{11}H_9N_2O$]$^+$, 45), 169 ([$C_{11}H_9N_2$]$^+$, 69)	7.62 (br s, 1H,NH), 7.47-6.89 (m, 4H, C(5)-C(8)H), 5.84 (br s, 1H, NOH), 4.27 (br t, 1H, C(1)H), 4.14 (q, 2H, OCH_2CH_3), 3 92 (X part of ABX spectrum, 1H, C(3)H), 3.11 and 2.97 (AB part of ABX spectrum, 2H, ^2J=15.4Hz, J=8.1 Hz, J-5.3 Hz, C(3)H), 1.96-1.49 (m, 4H, C(1)$CH_2CH_2CH_3$), 1.33 (t, 3H, OCH_2CH_3), 1.00 (t, 3H, C(1)$CH_2CH_2CH_3$)
6c[b]	160-162	0 71 (B)	350 (M^+, 5), 277 ([M-COOEt]$^+$, 3), 259 ([M-C_7H_7]$^+$, 100), 169 ([$C_{11}H_9N_2$]$^+$, 35)	7.71-6.87 (m, 10H, NH, C(5)-C(8)H and C_6H_5), 6.11 (br s, 1H, NOH), 4.49 (br s, 1H, C(1)H), 4.32 (q, 2H, OCH_2CH_3), 4.00-3.64 (m, 3H, C(3)H and C(1)CH_2), 3.16-2 87 (m, 2H, C(4)H_2), 1.33 (t, 3H, OCH_2CH_3).
7c[b]	155-159	0.57 (B)	350 (M^+, 3), 333 ([M-OH]$^+$, 11), 277 ([M-COOEt]$^+$, 2), 259 ([M-C_7H_7]$^+$, 100), 169 ([$C_{11}H_9N_2$]$^+$, 39)	7.60-6.76 (m, 10H, NH, C(5)-C(8)H and C_6H_5), 6.40 (br s, 1H, NOH), 4.69 (X part of ABX spectrum, 1H, C(1)H), 4.27 (q, 2H, OCH_2CH_3), 4.13 (t, 1H, C(3)H), 3.67-2.49 (m, 4H, C(4)H_2 and AB part of ABX spectrum of C(1)HCH_2), 1.32 (t, 3H, OCH_2CH_3).
6d	foam[c]	0.74 (D)	362 (M^+, 30), 345 ([M-OH]$^+$, 18), 289 ([M-COOEt]$^+$, 7), 259 ([M-C_4H_7OS]$^+$, 100), 169 ([$C_{11}H_9N_2$]$^+$, 87)	8 73 (br s, 1H, NH), 7 44-7.07 (m, 4H, C(5)-C(8)H), 6.08 (br s, 1H, NOH), 4.29 (q, 2H, OCH_2CH_3), 4.12 (br s, 1H, C(1)H,), 3.82 (X part of ABX spectrum, 1H, C(3)H), 3.24-2.76 (m, 4H, C(4)H_2 and CH_2S), 2.31 (s, 3H, $SCOCH_3$), 2 17-1.78 (m, 2H, C(1)CH_2), 1.36 (t, 3H, OCH_2CH_3)
7d	foam[c]	0 67 (D)	362 (M^+, 25), 345 ([M-OH]$^+$, 63), 301 (37), 289 ([M-COOEt]$^+$, 9), 259 ([M-C_4H_7OS]$^+$, 74), 169 ([$C_{11}H_9N_2$]$^+$, 100)	8.57 (br s, 1H, NH), 7.52-7.00 (m, 4H, C(5)-C(8)H), 6.27 (br s, 1H, NOH), 4.44 (t, 1H, C(1)H), 4.21 (q, 2H, OCH_2CH_3), 4.06 (t, 1H, C(3)H), 3.41-2.80 (m, 4H, C(4)H_2 and CH_2S), 2.34 (s, 3H, $SCOCH_3$), 2.34-1.81 (m, 2H, C(1)CH_2), 1.27 (t, 3H, OCH_2CH_3)
6f[d]	168-170	0 69 (D)	342 (M^+, 7), 325 ([M-OH]$^+$, 9), 269 ([M-COOEt]$^+$, 11), 251 ([$C_{15}H_{11}N_2$]$^+$, 36), 225 ([$C_{14}H_{11}N$]$^+$, 100), 169 ([$C_{11}H_9N_2$]$^+$, 8)	7 61-6.80 (m, 8H, NH, C(5)-C(8)H and C_4H_3S), 5.83 (br s, 1H, NOH), 5.34 (br s, 1H, C(1)H), 4 42 (q, 2H, OCH_2CH_3), 4.00 (t, 1H, C(3)H), 3.20 (d, 2H, J=7 9Hz, C(4)H_2), 1.36 (t, 3H, OCH_2CH_3)
7f[d]	214-217	0.57 (D)	342 (M^+, 7), 325 ([M-OH]$^+$, 35), 269 ([M-COOEt]$^+$, 16), 251 ([$C_{15}H_{11}N_2$]$^+$, 71), 225 ([$C_{14}H_{11}N$]$^+$, 100), 169 ([$C_{11}H_9N_2$]$^+$, 14)	7 61-6.80 (m, 8H, NH, C(5)-C(8)H and C_4H_3S), 5.80 (s, 1H, C(1)H), 4.22 (q, 2H, OCH_2CH_3), 4.12 (t, 1H, C(3)H), 3.44 (m, 2H, C(4)H_2), 1.29 (t, 3H, OCH_2CH_3)
6g[b]	225-227	0 76 (D)	426 (M^+, 16), 409 ([M-OH]$^+$, 19), 353 ([M-COOEt]$^+$, 13), 335 (34), 309 ([$C_{19}H_{19}NO_3$]$^+$, 61), 278 ([$C_{16}H_{16}NO_2$]$^+$, 65), 219 (100), 169 ([$C_{11}H_9N_2$]$^+$, 9)	7 67 (br s, 1H, NH), 7.60-7.10 (m, 4H, C(5)-C(8)H), 6.73 (s, 2H, $C_6H_2(OMe)_3$), 5.50 (s, 1H, NOH), 4.95 (s, 1H, C(1)H), 4.33 (q, 2H, OCH_2CH_3), 4.04 (X part of ABX spectrum, 1H, C(3)H), 3.88 (s, 3H, p-(OCH_3)), 3.82 (s, 6H, 2x m-(OCH_3)), 3.55-3 11 (m, 2H, C(4)H_2), 1.34 (t, 3H, OCH_2CH_3)

a) A $CHCl_3$ B.$CHCl_3$/MeOH, 99/1 C: $CHCl_3$/MeOH, 97/3 D: $CHCl_3$/MeOH, 93/7 b) Satisfactory micro analyses were obtained for these compounds (C±0.5%, H±0.2%, N±0.4%)

c) These products resisted crystallization attempts d) Attempts to separate these isomers failed.

Table II. Spectroscopic data of the β-carbolines **6** and **7**

Prod	mp (°C)	Rf (Solv.Sys)[a]	Mass Spectrum	^{1}H NMR δ (ppm)
7g[b]	220-223	0 60 (D)	426 (M^+, 17), 409 ([M-OH]$^+$, 37), 353 ([M-COOEt]$^+$, 43), 309 ([$C_{19}H_{19}NO_3$]$^+$, 47), 278 ([$C_{18}H_{16}NO_2$]$^+$, 63), 219 (100), 169 ([$C_{11}H_9N_2$]$^+$, 27)	7.64 (br s, 1H, NH), 7.60-7.09 (m, 4H, C(5)-C(8)H), 6.62 (s, 2H, $C_6H_2(OMe)_3$), 6 03 (s, 1H, NOH), 5 69 (s, 1H, C(1)H), 4 40-4.07 (m, 3H, OCH_2CH_3 and C(3)H), 3 87 (s, 3H, p-(OCH_3)), 3.80 (s, 6H, 2x m-(OCH_3)), 3.44-3 14 (m, 2H, C(4)H_2), 1.28 (t, 3H, OCH_2CH_3)
6h[b]	101-103	0 10 (B)	278 (M^+, 20), 263 ([M-CH_3]$^+$, 2), 169 ([$C_{11}H_9N_2$]$^+$, 5), 159 (100)	7 73 (br s, 1H, NH), 7 61-6.96 (m, 9H, C(5)-C(8)H and C_6H_5), 4 73 (br s, 1H, NOH), 4.07 (br t, 2H, C(1)H and C(3)H), 3 04 (d, 2H, C(4)H_2), 1.62 (d, 3H, C(1)CH_3)
7h	foam[c]	0 05 (B)	278 (M^+, 21), 263 ([M-CH_3]$^+$, 7), 169 ([$C_{11}H_9N_2$]$^+$, 7), 159 (100)	7.78 (br s, 1H, NH), 7 63-7.02 (m, 9H, C(5)-C(8)H and C_6H_5), 5.02 (br s, 1H, NOH), 4.34 (q, 1H, C(1)H), 4 09 (X part of ABX soectrum, 1H, C(3)H), 3 38 and 3.08 (AB part of ABX spectrum, 2H, ^{2}J=14.9Hz, J=8.0 Hz, J=5.1Hz, C(4)H_2), 1 52 (d, 3H, C(1)CH_3)
6l	foam[c]	0 28 (D)	216 (M^+, 26), 157 ([$C_{11}H_{11}N$]$^+$, 100)	7 73 (br s, 1H, NH), 7.50-7 01 (m, 4H, C(5)-C(8)H), 5.08 (br s, 1H, NOH), 4.06 (br s, 1H, C(1)H), 3.14 (m, 1H, C(3)H), 2.74 (m, 2H, C(4)H_2), 1 61 (d, 3H, C(1)CH_3), 1.42 (d, 3H, C(3)CH_3)
7l	foam[c]	0.22 (D)	216 (M^+, 25), 157 ([$C_{11}H_{11}N$]$^+$, 100)	7 70 (br s, 1H, NH), 7 52-7.06 (m, 4H, C(5)-C(8)H), 4.32 (q, 1H, C(1)H), 3.50 (m, 1H, C(3)H), 2.77 (m, 2H, C(4)H_2), 1 51 (d, 3H, C(1)CH_3), 1 32 (d, 3H, C(3)CH_3)
6j[b]	191-193	0 17 (C)	202 (M^+, 42), 157 ([$C_{11}H_{11}N$]$^+$, 100)	7 70 (br s, 1H, NH), 7.51-7.06 (m, 4H, C(5)-C(8)H), 6.47 (s, 1H, NOH), 4.03 (m, 1H, C(1)H), 3 55 (m, 1H, C(3)H_A), 3.20 (m, 1H, C(3)H_B), 2 97 (m, 2H, C(4)H_2), 1.59 (d, 3H, C(1)CH_3)
6k[b]	191-193	0 62 (B)	340 (M^+, 11), 219 ([$C_{16}H_{13}N$]$^+$, 100)	7.64-6 91 (m, 15H, NH, C(5)-C(8)H and 2xC_6H_5), 5.10 (br s, 1H, C(1)H), 4 59 (br s, 1H, NOH), 4.27 (t, 1H, J=7.5Hz, C(3)H), 3.16 (d, 2H, J=7.5Hz, C(4)H_2)
7k[b]	192-195	0 29 (B)	340 (M^+, 4), 219 ([$C_{16}H_{13}N$]$^+$, 100)	7.73-7 02 (m, 15H, NH, C(5)-C(8)H and 2xC_6H_5), 6.64 (br s, 1H, C(1)H), 4.84 (br s, 1H, NOH), 4.11 (X part of ABX spectrum, 1H, C(3)H), 3.42 and 3.14 (AB part of ABX spectrum, 2H, ^{2}J=15.6Hz,J=8.0Hz, J=4.8Hz, C(4)H_2)
6l[b]	95-97	0 39 (B)	278 (M^+, 20), 258 ([$C_{18}H_{14}N_2$]$^+$, 25), 245 ([$C_{17}H_{13}N_2$]$^+$, 23), 219 ([$C_{16}H_{13}N$]$^+$, 100)	7 53-7.02 (m, 10H, NH, C(5)-C(8)H and C_6H_5), 4.94 (s, 1H, C(1)H), 4.82 (br s, 1H, NOH), 3.30 (m, 1H, C(3)H), 2.86 (m, 2H, C(4)H_2), 1 47 (d, 3H, C(3)CH_3)

a) A.$CHCl_3$ B.$CHCl_3$/MeOH, 99/1 C· $CHCl_3$/MeOH, 97/3 D. $CHCl_3$/MeOH, 93/7 b) Satisfactory micro analyses were obtained for these compounds (C±0.5%, H±0 2%, N±0 4%)
c) These products resisted crystallization attempts d) Attempts to separate these isomers failed

Table II. Spectroscopic data of the β-carbolines 6 and 7

Prod.	mp (°C)	Rf (Solv.Sys)[a]	Mass Spectrum	^{1}H NMR δ (ppm)
7l[b]		0.19 (B)	278 (M^+, 24), 258 ($[C_{18}H_{14}N_2]^+$, 19), 245 ($[C_{17}H_{13}N_2]^+$, 24), 219 ($[C_{16}H_{13}N]^+$, 100)	7.59-7.08 (m, 10H, NH, C(5)-C(8)H and C_6H_5), 5.73 (br s, 1H, NOH), 5.18 (s, 1H, C(1)H), 3.56 (m, 1H, C(3)H), 3.03 and 2.81 (AB part of ABX spectrum, 2H, ^{2}J=15.5Hz, J=6.6Hz, J=8.5Hz, C(4)H_2), 1.29 (d, 3H, C(3)HCH_3)
6m[b]	230-232	0.62 (D)	368 (M^+, 24), 350 ($[M-H_2O]^+$, 43), 335 ($[C_{20}H_{19}N_2O_3]^+$, 57), 309 ($[C_{19}H_{19}NO_3]^+$, 100), 278 ($[C_{18}H_{16}NO_2]^+$, 94)	7.50-7.03 (m, 5H, NH and C(5)-C(8)H), 6.63 (s, 2H, C(1)$C_6H_2(OMe)_3$), 4.84 (br s, 2H, C(1)H and NOH), 3.89 (s, 3H, p-OCH_3), 3.83 (s, 6H, 2x m-OCH_3), 3.25 (m, 1H, C(3)H), 2.91 (m, 2H, C(4)H_2), 1.48 (d, 3H, C(3)HCH_3)
7m[b]	220-222	0.47 (D)	368 (M^+, 23), 350 ($[M-H_2O]^+$, 15), 335 ($[C_{20}H_{19}N_2O_3]^+$, 36), 309 ($[C_{19}H_{19}NO_3]^+$, 100), 278 ($[C_{18}H_{16}NO_2]^+$, 92)	7.56-7.06 (m, 5H, NH and C(5)-C(8)H), 6.54 (s, 2H, C(1)$C_6H_2(OMe)_3$), 5.50 (br s, 1H, NOH), 5.03 (s, 1H, C(1)H), 3.84 (s, 3H, p-OCH_3), 3.78 (s, 6H, 2x m-OCH_3), 3.64 (m, 1H, C(3)H), 3.11 and 2.78 (AB part of ABX spectrum, 2H, ^{2}J=15.5Hz, J=6.3Hz, J=4.5Hz, C(4)H_2), 1.29 (d, 3H, C(3)HCH_3)
7n[b]	211-223	0.26 (C)	335 (M^+, 8), 318 ($[M-OH]^+$, 46), 277 ($[M-CONHCH_3]^+$, 18), 259 ($[C_{18}H_{16}N_2]^+$, 100), 232 ($[C_{17}H_{14}N]^+$, 41)	7.70-7.10 (m, 4H, C(5)-C(8)H), 6.83 (br s, 1H, NHMe), 5.57 (s, 1H, C(1)H), 5.26 (br s, 1H, NOH), 3.78-3.04 (m, 3H, C(3)H and C(4)H_2), 3.41 (s, 3H, indole N-CH_3), 2.78 (d, 3H, $NHCH_3$)
6o	oil[c]	0.46 (B)	288 (M^+, 22), 257 ($[M-OCH_3]^+$, 68), 215 ($[M-COOEt]^+$, 18), 183 ($[C_{12}H_{11}N_2]^+$, 68), 157 ($[C_{11}H_{11}N]^+$, 100)	7.73 (br s, 1H, NH), 7.48-7.05 (m, 4H, C(5)-C(8)H), 4.33 (q, 2H, OCH_2CH_3), 4.21 (m, 1H, C(1)H), 3.92-3.57 (m, 1H, C(3)H), 3.76 (s, 3H, $NOCH_3$), 3.40-2.92 (m, 2H, C(4)H_2), 1.64 (d, 3H, C(1)HCH_3), 1.39 (t, 3H, OCH_2CH_3)
7o	oil[c]	0.40 (B)	288 (M^+, 21), 257 ($[M-OCH_3]^+$, 10), 231 (22), 215 ($[M-COOEt]^+$, 16), 183 ($[C_{12}H_{11}N_2]^+$, 24), 157 ($[C_{11}H_{11}N]^+$, 100)	7.68 (br s, 1H, NH), 7.50-7.02 (m, 4H, C(5)-C(8)H), 4.64 (q, 1H, C(1)HCH_3), 4.22 (q, 2H, OCH_2CH_3), 4.09 (X part of ABX spectrum, 1H, C(3)H), 3.61 (s, 3H, $NOCH_3$), 3.22 and 3.10 (AB part of ABX spectrum, 2H, ^{2}J=16.0Hz, J=7.5Hz, J=6.2Hz, C(4)H_2), 1.49 (t, 3H, OCH_2CH_3)
6q[d] 7q[d]	oil[c]	0.26 (B)	316 (M^+, 9), 257 ($[M-C_3H_7O]^+$, 51), 243 ($[M-COOEt]^+$, 11), 183 ($[C_{12}H_{11}N_2]^+$, 40), 157 ($[C_{11}H_{11}N]^+$, 100)	
6r[d] 7r[d]	oil[c]	0.31 (B)	330 (M^+, 9), 257 ([M-COOEt and M-C_4H_9O]$^+$, 25), 183 ($[C_{12}H_{11}N_2]^+$, 18), 157 ($[C_{11}H_{11}N]^+$, 100)	
6s	oil[c]	0.76 (B)	350 (M^+, 12), 319 ($[M-OCH_3]^+$, 14), 277 ($[M-COOEt]^+$, 8), 245 ($[C_{17}H_{13}N_2]^+$, 12), 219 ($[C_{16}H_{13}N]^+$, 100)	7.50-7.06 (m, 10H, NH, C(5)-C(8)H and C_6H_5), 4.96 (s, 1H, C(1)H), 4.28 (q, 2H, OCH_2CH_3), 3.93 (X part of ABX spectrum, 1H, C(3)H), 3.30-2.96 (m, 2H, C(4)H_2), 3.08 (s, 3H, OCH_3), 1.33 (t, 3H, OCH_2CH_3)

a) A $CHCl_3$ B $CHCl_3$/MeOH, 99/1 C: $CHCl_3$/MeOH, 97/3 D: $CHCl_3$/MeOH, 93/7. b) Satisfactory micro analyses were obtained for these compounds (C±0.5%, H±0.2%, N±0.4%)
c) These products resisted crystallization attempts. d) Attempts to separate these isomers failed.

Table II. Spectroscopic data of the β-carbolines **6** and **7**

Prod.	mp (°C)	Rf (Solv.Sys)[a]	Mass Spectrum	^{1}H NMR δ (ppm)
7s[b]	188-189	0.66 (B)	350 (M^+, 15), 319 ([M-OCH_3]$^+$, 68), 277 ([M-COOEt]$^+$, 21), 245 ([$C_{17}H_{13}N_2$]$^+$, 52), 219 ([$C_{16}H_{13}N$]$^+$, 96), 218 ([$C_{16}H_{12}N$]$^+$, 100)	7 58-7.07 (m, 10H, NH, C(5)-C(8)H and C_6H_5), 5.72 (s, 1H, C(1)H), 4.18 (q, 2H, OCH_2CH_3), 4.14 (t, 1H, C(3)H), 3.47 (s, 3H, OCH_3), 3.28 (d, 2H, C(4)H_2), 1.26 (t, 3H, OCH_2CH_3)
6t	oil[c]	0 54 (B)	378 (M^+, 14), 319 ([M-C_3H_7O]$^+$, 16), 305 ([M-COOEt]$^+$, 9), 245 ([$C_{17}H_{13}N_2$]$^+$, 17), 219 ([$C_{16}H_{13}N$]$^+$, 100)	7.52-7 04 (m, 10H, NH, C(5)-C(8)H and C_6H_5), 5 01 (s, 1H, C(1)H), 4.26 (q, 2H, OCH_2CH_3), 3 98 (X part of ABX spectrum, 1H, C(3)H), 3.61-2.96 (m, 3H, C(4)H_2 and $NOCHMe_2$), 1.36 (t, 3H, OCH_2CH_3), 0 87 (d, 3H, J=6.1Hz, $OCH(CH_3)_A(CH_3)_B$), 0.44 (d, 3H, J=6.1Hz, $OCH(CH_3)_A(CH_3)_B$)
7t[b]	151-153	0 46 (B)	378 (M^+, 16), 319 ([M-C_3H_7O]$^+$, 61), 305 ([M-COOEt]$^+$, 27), 245 ([$C_{17}H_{13}N_2$]$^+$, 48), 219 ([$C_{16}H_{13}N$]$^+$, 100)	7.56-7.03 (m, 10H, NH, C(5)-C(8)H and C_6H_5), 5 73 (s, 1H, C(1)H), 4.16 (t, 1H, C(3)H), 4.14 (q, 2H, OCH_2CH_3), 3.64 (m, 1H, $NOCHMe_2$), 3.28 (d, 2H, J=5 8Hz, C(4)H_2), 1.26 (t, 3H, OCH_2CH_3), 1 08 (d, 3H, J=6.1Hz, $OCH(CH_3)_A(CH_3)_B$), 0.87 (d, 3H, J=6 1Hz, $OCH(CH_3)_A(CH_3)_B$)
6u	oil[c]	0 64 (A)	392 (M^+, 9), 319 ([M-COOEt and M-C_4H_9O]$^+$, 18), 245 ([$C_{17}H_{13}N_2$]$^+$, 13), 219 ([$C_{16}H_{13}N$]$^+$, 100)	7.55-7/04 (m, 10H, NH, C(5)-C(8)H and C_6H_5), 5.00 (s, 1H, C(1)H), 4.28 (q, 2H, OCH_2CH_3), 3.97 (X part of ABX spectrum, 1H, C(3)H), 3.74-3 42 (m, 2H, $NOCH_2$), 3.40-2.71 (m, 2H, C(4)H_2), 1.37 (t, 3H, OCH_2CH_3), 1.21-0.83 (m, 4H, $OCH_2CH_2CH_2CH_3$), 0 69 (br t, 3H, $OCH_2CH_2CH_2CH_3$)
7u	oil[c]	0.53 (A)	392 (M^+, 12), 319 ([M-COOEt and M-C_4H_9O]$^+$, 72), 245 ([$C_{17}H_{13}N_2$]$^+$, 43), 219 ([$C_{16}H_{13}N$]$^+$, 100)	7.56-7.06 (m, 10H, NH, C(5)-C(8)H and C_6H_5), 5.76 (s, 1H, C(1)H), 4.19 (t, 1H, C(3)H), 4.15 (q, 2H, OCH_2CH_3), 3.78-3 41 (m, 2H, $NOCH_2$), 3.29 (d, 2H, J=6.0Hz, C(4)H_2), 1.47-1.00 (m, 4H, $OCH_2CH_2CH_2CH_3$), 1 26 (t, 3H, OCH_2CH_3), 0.79 (br t, 3H, $OCH_2CH_2CH_2CH_3$)

a) A.$CHCl_3$ B·$CHCl_3$/MeOH, 99/1 C $CHCl_3$/MeOH, 97/3 D $CHCl_3$/MeOH, 93/7. b) Satisfactory micro analyses were obtained for these compounds (C±0.5%, H±0.2%, N±0.4%)
c) These products resisted crystallization attempts d) Attempts to separate these isomers failed.

References and Notes

1. a) Wu,G.; Yamanaka, E.; Cook, J.M. *Heterocycles*, **1978** *9*, 175. b) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook J.M. *J.Org.Chem.* **1979**, *44*, 535. c) Bieräugel, H.; Plemp, R.; Pandit, U.K. *Heterocycles* **1980**, *14*, 947. d) Bieräugel, H.; Plemp, R.; Pandit, U.K. *Tetrahedron* **1983**, *39*, 3987.
2. a) Harrison, D.M. *Tetrahedron Lett.* **1981**, *22*, 2501. b) Harrison, D.M.; Sharma, R.B. *Tetrahedron Lett.* **1986**, *27*, 521. c) Nakagawa, M.; Fukushima, H.; Kawate, T.; Hongu, S-I.; Teruaki, U.; Taniguchi, M.; Hino, T. *Tetrahedron Lett.* **1986**, *27*, 3235. d) Nakagawa, M.; Kodato, S-I.; Hongu, S-I.; Kawate, T.; Hino, T. *Tetrahedron Lett.* **1986**, *27*, 6217. e) O'Malley, G.J.; Cava, M.P. *Tetrahedron Lett.* **1987**, *28*, 1131. f) Boyd, S.A.; Thompson, W.J. *J.Org.Chem.* **1987**, *52*, 1790. g) Kodato, S-I.; Nakagawa, M.; Hongu, M.; Kawate, T.; Hino, T. *Tetrahedron*, **1988**, *44*, 359. h) Hino, T.; Kawate, T.; Nakagawa, M. *Tetrahedron* **1989**, *45*, 1941.
3. a) Han, S.Y.; Lakshmikantham, M.V.; Cava, M.P. *Heterocycles*, **1985**, *23*, 1671. b) Plate, R.; Hout, v.R.H.M.; Behm, H.; Ottenheijm, H.C.J. *J.Org.Chem.* **1987**, *52*, 555. c) Nakagawa, M.; Liu, J.J.; Ogata, K.; Hino, T. *J.Chem.Soc. Chem.Commun.* **1988**, 463. d) Still, I.W.J.; Strautmanis, J.R. *Tetrahedron Lett.* **1989**, *30*, 1041. e) Nakagawa, M.; Liu, J.J.; Hini, T. *J.Am.Chem.Soc.* **1989**, *111*, 2721. f) Hermkens, P.H.H.; Maarseveen, v.J.H.; Kruse, C.G.; Scheeren, J.W. *Tetrahedron Lett.* submitted. g) Hermkens, P.H.H.; Maarseveen, v.J.H.; Ottenheijm, H.C.J.; Kruse, C.G.; Scheeren, J.W. *J.Org.Chem.* submitted.
4. Reaction with aldehydes: a)Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J.M.; Silverton, J.V. *J.Am.Chem.Soc.* **1980**, *102*, 6976. b) Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J.M. *J.Org.Chem.* **1981**, *46*, 164. c) Massiot, G.; Mulamba, T. *J.Chem.Soc. Chem.Commun.* **1983**, 1147. d) Grigg, R.; Gunaratne, H.Q.N.; McNaghten, E. *J.Chem.Soc. Perkin Trans. I* **1983**, 185. e) Jawdosiuk, M.; Cook, J.M. *J.Org.Chem.* **1984**, *49*, 2699. f) Bailey, P.D.; Hollingshead, S.P. *J.Chem.Soc.Chem.Commun.* **1985**, 1575. g) Bailey, P.D.; Hollingshead, S.P.; McLay, N.R. *Tetrahedron Lett.* **1987**, *28*, 5177. h) Zhang, L-H.; Cook, J.M. *Heterocycles*, **1988**, *27*, 1357 and 2795.
5. Reaction with conjugated alkynoates: Bailey, P.D.; Hollinshead, S.P.; Dauter, Z. *J.Chem.Soc.Chem.Commun.* **1985**, 1507. b) Bailey, P.D.; Hollinshead, S.P. *Heterocycles*, **1987**, *26*, 389. c) Bailey, P.D.; Hollinshead, S.P. *J.Chem.Soc. Perkin Trans. I* **1988**, 739.
6. Bailey, P.D. *J.Chem.Res.(S)* **1987**, 202. b) Bailey, P.D. *Tetrahedron Lett.* **1987**, *28*, 5181.
7. a) Ottenheijm, H.C.J.; Plate, R.; Noordik, J.H.; Herscheid, J.D.M. *J.Org.Chem.* **1982**, *47*, 2147. b) Plate, R.; Hermkens, P.H.H.; Smits, J.M.M.; Ottenheijm, H.C.J. *J.Org.Chem.* **1986**, *51*, 309.
8. This versatile cycloaddition has been described for the first time by Gilchrist, T.L.; Longham, D.A.; Roberst, T.G. *J.Chem.Soc.Chem.Commun.* **1979**, 1089.
9. a) Faragher, R.; Gilchrist, T.L. *J.Chem.Soc. Perkin Trans. I* **1978**, 249. b) Davies, D.E.; Gilchrist, T.L.; Roberts, T.G. *J.Chem.Soc.Perkin Trans.I* **1983**, 1275.
10. a) Boger, D.L. *Tetrahedron*, **1983**, *39*, 2869. b) Davies, D.E.; Gilchrist, T.L. *J.Chem.Soc. Perkin Trans.I* **1983**, 1479.
11. a) Heath-Brown, B.; Philpott, P.G. *J.Chem.Soc.* **1965**, 7165. b) Cohen, A.; Heath-Brown, B. *J.Chem.Soc.* **1965**, 7179.
12. Kurz,M.E.; Chen, R.T.Y. *J.Chem.Soc. Chem.Commun.* **1976**, 968.
13. These reduction conditions are a modification of the procedure described by Cohen, A. (NH_4Cl and zinc-dust gave **28** in 74% yield, see ref. 11b)
14. Synthesis of Ethyl α-nitro-β-(indol-3-yl)propionate is described by a) Weisblat, D.I.; Lyttle, D.A. *J.Am.Chem.Soc.* **1949**, *71*, 3079. b) Lyttle, D.A.; Weisblat, D.I. *J. Am. Chem. Soc.* **1947**, *69*, 2118.
15. In contrast reduction of the oxime double bond of **12** under identical conditions gave complete overreduction to the amine derivative.
16. Grehn, L.; Ragnarsson, U. *Angew. Chem., Int.Ed.Engl.* **1984**, *23*, 296.
17. Recently we described an alternative approach starting directly with the N-hydroxytryptophan and tryptamines, see Hermkens, P.H.H.; Maarseveen, v.J.H.; Berens, H.W.; Smits, J.M.M.; Kruse, C.G.; Scheeren, J.W. *J.Org.Chem.*, submitted.
18. a) Shinozaki, H.; Yoshida, N.; Tajima, M. *Chemistry Lett.* **1980**, 869. b) Buehler, E. *J.Org.Chem.* **1967**, *32*, 261. c) Smith, P.A.; Robertson, J.E. *J.Am.Chem.Soc.* **1962**, *84*, 1197.
19. Standard phase transfer conditions were not suitable, because the ester functionality of oxime **12** sapofinied.
20. Perrin, D.; In *"Dissociation Constants of Organic Bases in Aqueous Solution"*, Butterworths, London, **1965**.
21. Arx, E.; Faupel, M. Bruggen, M. *J.Chromatogr.* **1976**, *120*, 224.