Pergamon

Tetrahedron Vol. 50, No. 41, pp. 11865-11884, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00753-5

Asymmetric Steering of the Pictet-Spengler Reaction by Means of Amino Acid Esters as Chiral Auxiliary Groups

Herbert Waldmann*, Gunther Schmidt

Universität Karlsruhe, Institut für Organische Chemie, Richard-Willstätter-Allee 2, D-76128 Karlsruhe

Martin Jansen and Jutta Geb

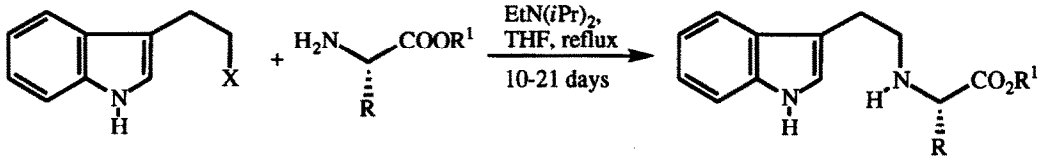
Universität Bonn, Institut für Anorganische Chemie, Gerhard-Domagk-Straße 1, D-53121 Bonn

Abstract: N-β-(3-Indolyl)ethyl amino acid esters and differently substituted aromatic aldehydes in the presence of acetic acid form iminium intermediates which at 6 °C to 40 °C undergo Pictet-Spengler cyclizations to give tetrahydro-β-carbolines with diastereomer ratios up to 98.5:1.5. The chiral auxiliary group is removed from the heterocycles by employing a retro Strecker reaction as the key transformation.

Numerous naturally occurring alkaloids embodying the β-carboline or the tetrahydroisoquinoline framework mediate pharmacologically useful physiological effects. Therefore, the synthesis of these natural products as well as analogues thereof in enantiomerically pure form is of widespread interest to both organic synthesis and medicinal chemistry. One of the most powerful methods for the construction of these heterocyclic compounds is the Pictet-Spengler cyclization.[1] In the context of total synthesis this key step usually is carried out asymmetrically in the sense of "ex-chiral-pool" syntheses employing chiral aldehydes[2] or tryptophan esters[3] as enantiomerically pure starting materials. However, despite the widespread use of subsequently removable chiral auxiliary groups to effect asymmetric transformations this principle has been applied to the steric steering of the Pictet-Spengler reaction only in a few isolated cases.[4] Thus, a generally applicable method for the execution of this important reaction of alkaloid chemistry in an asymmetric manner has not been developed. The purpose of this paper is to report in detail on the finding that the easily available amino acid esters which have already proven to be viable mediators of chirality in carbo- and aza-Diels-Alder reactions, 1,3-dipolar cycloadditions, radical reactions and Mannich reactions[5] can advantageously be applied as efficient chiral auxiliary groups in asymmetric Pictet-Spengler reactions.[6]

To study the influence of the stereogenic center present in amino acid esters on the stereoselection in the Pictet-Spengler reaction, the N-alkylated amino acid esters **3** were chosen as starting materials. These tryptamine derivatives are readily available by N-alkylation of the amino acid esters **2** with β-(3-indolyl)ethyl bromide **1a**[7]

or iodide **1b**[8] at elevated temperature and in the presence of N-ethyl-diisopropylamine (Scheme 1, Table 1). However, even under these conditions the nucleophilic attack by the amines on the alkyl halides proceeds only slowly and requires ca. two weeks to make the desired secondary amines **3** available in satisfactory yields. Quite unexpectedly, the sterically more demanding valine and leucine esters generally form the alkylation products in higher yields than the corresponding alanine ester. In neither case was a further alkylation of the secondary amines **3** to the corresponding tertiary amines observed.



1a: X = Br
1b: X = I

2

3

Scheme 1

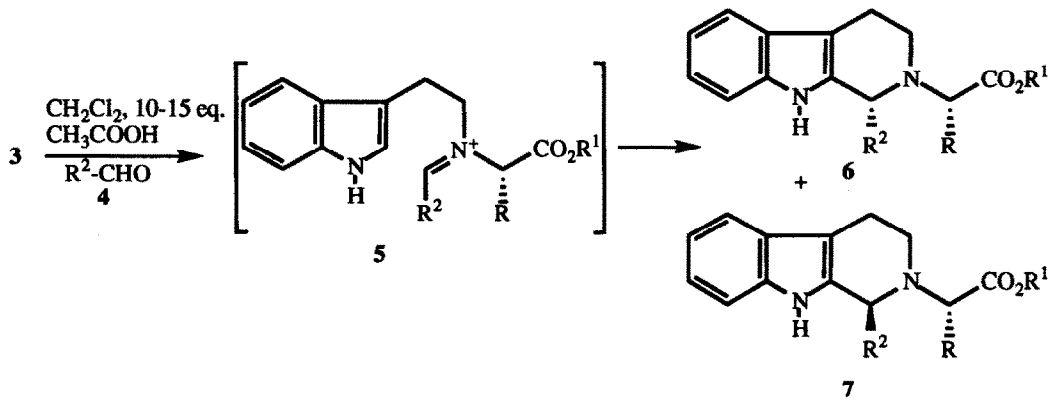
Table 1. Results of the N-Alkylation of the Amino Acid Esters with 2-(3-Indolyl)ethyl Halides **1a,b**.

Entry	3	Amino Acid Ester 2	R	R^1	Indolylethyl Halide	Reaction Time [d]	Yield [%]
1	**a**	Val-OMe	*i*-Pr	Me	**1a**	13	57
2	**b**	Val-O-*t*-Bu	*i*-Pr	*t*-Bu	**1a**	11	55
3	**c**	Ala-OMe	Me	Me	**1a**	13	16
4	**d**	Ile-OMe	*sec*-Bu	Me	**1a**	21	19
5	**e**	Leu-OAll	*i*-Bu	All	**1b**	10	67

To generate the iminium intermediates **5**, the amines **3** were treated with different aldehydes **4** in methylene chloride and in the presence of different acids. Unexpectedly, the application of trifluoroacetic acid which is often used as an efficient promotor of the Pictet-Spengler reaction,[3,4] resulted in the formation of complex product mixtures which were not analyzed in detail. However, in the presence of 10-15 equivalents of acetic acid the desired cyclization reaction proceeded without formation of undesired byproducts. In the course of these transformations the iminium intermediates **5** are formed *in situ* and subsequently are subject to a spontaneous intramolecular attack of the indole nucleus on the iminium group. Thereby the tetrahydro-β-carbolines **6** and **7** are generated in satisfactory yields and with diastereomer ratios up to 98.5:1.5 (Scheme 2, Table 2). The absolute configuration of the major diastereomers **6** which are isolated in a straigthforward way by simple flash chromatography and recrystallization from ether/petroleum ether (see the Experimental Part) was unambiguously proven by an X-ray analysis for the 4-nitrophenyl derivative **6b** (see Figure 1 and the Experimental Part for details).

Since the iminium intermediates **5** are only moderately reactive their cyclization to give **6** and **7** is a relatively slow process which requires several days to go to completion. Therefore, the reaction temperature should not be lowered too much to avoid undesirably long reaction times. Consequently, depending on the size of

the amino acid ester and the electronic properties of the imine substituents, the Pictet-Spengler reactions were carried out at temperatures of 6 °C to 40 °C.



Scheme 2

Table 2. Results of the Asymmetric Pictet-Spengler Reaction Employing the Amino Acid Derivatives **3a-e** and Various Aldehydes.

Entry	6	Amino Acid Ester	R	R^1	R^2	T [°C]	Yield [%]	dr 6:7[a]
1	**a**	Val-OMe	*i*-Pr	Me	Ph	25	76	90:10
2	**a**	Val-OMe	*i*-Pr	Me	Ph	6	51	93:7
3	**b**	Val-OMe	*i*-Pr	Me	4-NO_2-Ph	25	54	80:20
4	**c**	Val-O-*t*-Bu	*i*-Pr	*t*-Bu	4-NO_2-Ph	25	71	73:27
5	**d**	Val-OMe	*i*-Pr	Me	2-NO_2-Ph	25	59	98.5:1.5
6	**e**	Val-OMe	*i*-Pr	Me	4-Cl-Ph	25	69	78:22
7	**f**	Val-OMe	*i*-Pr	Me	2,4-di-Cl-Ph	25	78	93.5:6.5
8	**g**	Val-OMe	*i*-Pr	Me	4-MeO-Ph	25	24	96:4
9	**h**	Val-OMe	*i*-Pr	Me	2,4-di-MeO-Ph	40	81	89:11
10	**i**	Val-OMe	*i*-Pr	Me	4-EtO-Ph	40	85	93:7
11	**j**	Val-OMe	*i*-Pr	Me	4-Me-Ph	25	48	92:8
12	**k**	Val-OMe	*i*-Pr	Me	2-Naphthyl-	25	51	82:18
13	**l**	Ala-OMe	Me	Me	Ph	25	47	70:30
14	**m**	Ile-OMe	*sec*-Bu	Me	Ph	25	69	89:11
15	**n**	Leu-OAll	*i*-Bu	All	Ph	25	69	72:28
16	**o**	Ile-OMe	*sec*-Bu	Me	Ph-CH=CH_2	25	53	86:14
17	**p**	Val-OMe	*i*-Pr	Me	Me	25	82[b]	50:50
18	**q**	Val-OMe	*i*-Pr	Me	Cl_3C	40	72[b]	60:40

[a] Determined from the crude reaction mixtures by HPLC or by integration of the respective signals found for 1-H of the diastereomers **6** and **7**. [b] Yield of both isomers.

The long reaction times required for the formation of **6** and **7** from **3** and **4** are responsible for the fact that the process highlighted in Scheme 2 works best for aromatic but not for aliphatic aldehydes. If benzaldehyde derivatives are employed, in the majority of the cases the desired tetrahydro-β-carbolines are formed with satisfactory yields and with good to excellent isomer ratios (Table 2, entries 1-16; *vide infra*). If, however, aliphatic aldehydes like propionaldehyde and isobutyraldehyde are introduced into this reaction sequence the respective heterocycles **6** and **7** in the majority of the cases are formed only to a minor extent or not at all (see however Table 2, entry 17). Under the conditions of the relatively slow conversion of **3** to **6** and **7** these C-H acidic compounds probably are subject to competing self-aldolization. Furthermore, the aliphatic Pictet-Spengler adducts appear to be only moderately stable. Thus, at 40 °C chloral hydrate and **3a** undergo the cyclization to give **6q/7q** in 72% yield and with an isomer ratio of 60:40 (Table 2, entry 18), however, the product decomposes within several days. It should be noted though, that the successful formation of Pictet-Spengler adducts derived from aliphatic aldehydes under similar conditions has been reported.[9] Similar to the behaviour of aliphatic aldehydes, the α,β-unsaturated carbonyl compounds crotonic aldehyde and acrolein did not react in the desired manner. However, if cinnamic aldehyde which may be addressed as a vinylogous analogue of a benzaldehyde is used the heterocycles **6o** and **7o** are obtained in 53% yields (Table 2, entry 16).

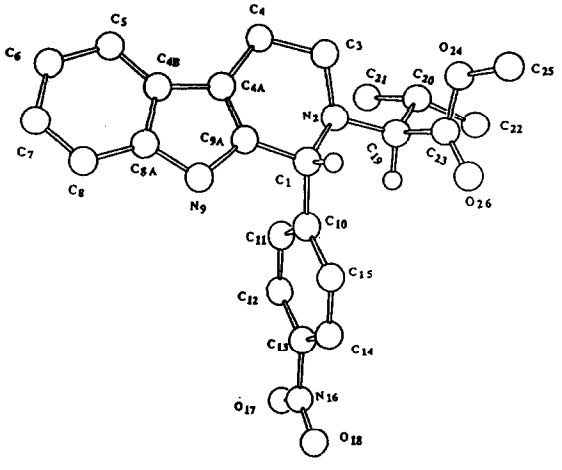


Figure 1.
Structure of the Pictet-Spengler adduct **6b** as determined by X-ray analysis (see the Experimental Part for details).

The diastereoselectivity recorded for the above mentioned Pictet-Spengler reactions is particularly influenced by the size of the amino acid side chain. Thus, the derivatives of valine and isoleucine esters give the highest diastereomer ratios whereas the sterically less demanding esters of leucine and alanine display inferior results (Table 2; compare entries 1 and 14 with entries 13 and 15). An increased size of the ester group, however, does not have a positive effect on the diastereoselectivity of the process, i.e. valine tert-butyl ester even gives a lower isomer ratio than the corresponding methyl ester (Table 2, entries 3 and 4). In contrast, the isomer ratio significantly increases with decreasing reaction temperature. Thus, at 25 °C the phenyl derivatives **6a** and **7a** are formed in a ratio of 90:10 whereas at 6 °C this value is raised to 93:7 (Table 2, entries 1 and 2), and also the 4-ethoxy substituted heterocycle **6i** is obtained at 40 °C with an isomer ratio of 93:7 whereas the 4-methoxy analogue is formed at 25 °C with a diastereoselectivity of 96:4 (Table 2, entries 8 and 10). If the aromatic aldehydes carry substituents in the *ortho* position, the isomer ratios recorded for the Pictet-Spengler adducts are

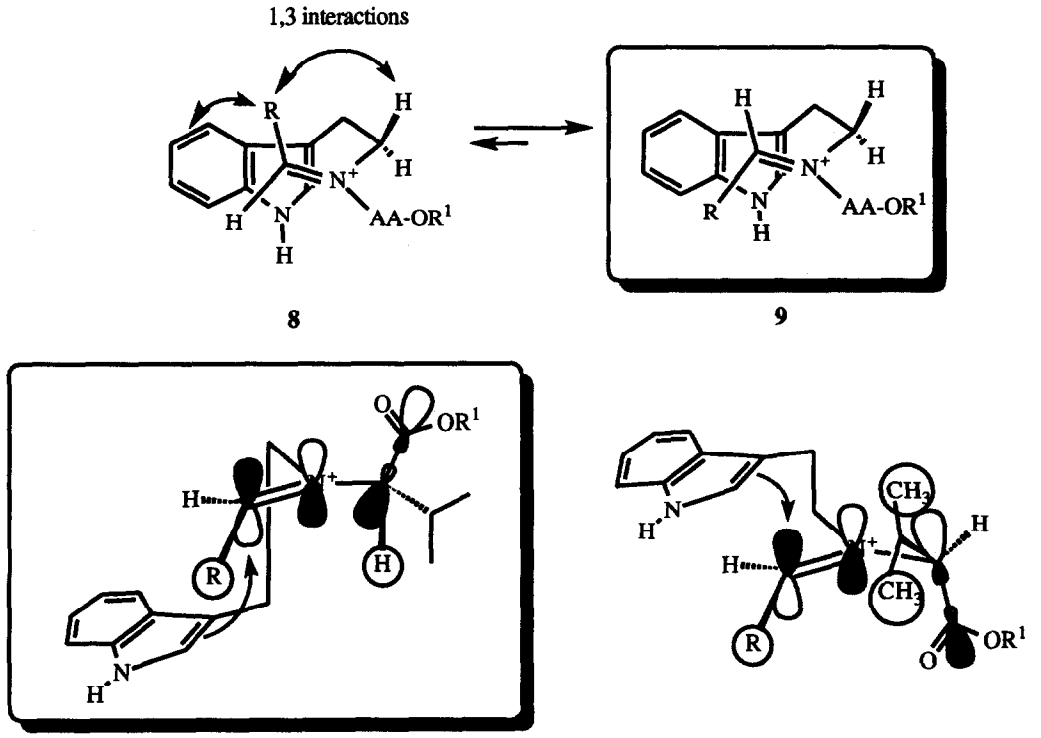
higher than for *para*- or unsubstituted carbonyl compounds. For instance, the 2-nitrophenyl derivative **6d** and the 2,4-dichloro compound **6f** are obtained with isomer ratios of 98.5:1.5 and 93.5:6.5, respectively (Table 2, entries 5 and 7), but for the phenyl substituted tetrahydro-β-carboline **6a** and the 4-nitrophenyl analogue **6b** the respective values are 90:10 and 80:20, respectively (Table 2, entries 1 and 3). In addition, iminium intermediates **5** carrying electron donating substituents react with a better stereodiscrimination than the corresponding electrophiles embodying -M substituents or no further functional group at all. Thus, the 4-methoxy, the 4-ethoxy and the 4-methyl compounds **6g**, **6i** and **6j** are formed with ratios of 96:4, 93:7 and 92:8, respectively (Table 2, entries 8, 10 and 11), whereas for the phenyl analogue **6a** and the 4-nitrophenyl derivative **6b** the ratios are 90:10 and 80:20, respectively (Table 2, entries 1 and 3).

The tetrahydro-β-carboline **6o** which is derived from cinnamic aldehyde and the benzaldehyde derivative **6a** are obtained with comparable isomer ratios of 86:14 and 90:10, respectively (Table 2, entries 1 and 16), i.e. the introduction of a double bond between the aromatic ring and the C=N-group does not lead to a major decrease of the stereoselectivity.

To rationalize the stereochemical outcome of related Pictet-Spengler cyclizations employing tryptophan derivatives in the presence of acid, it was proposed that in these transformations the product ratios are determined by thermodynamic control.[10,11] In an attempt to investigate if this is also the case in the cyclizations described above, or if the diastereomeric ratios are the results of kinetically controlled reactions, the minor stereoisomer **7b** obtained from p-nitrobenzaldehyde was treated with acetic acid in benzene at 80 °C for three days. Under these conditions **7b** was converted nearly quantitatively to the diastereomer **6b**. However, at 25 °C this epimerization could not be observed at all. From these observations it must be concluded that at least the formation of **6b** and **7b** highlighted in scheme 2 is kinetically controlled, but that the isomer formed in excess also is the thermodynamically more stable compound. This question was not investigated in further detail but we assume that this finding is also valid for the formation of the other tetrahydro-β-carbolines **6/7**.

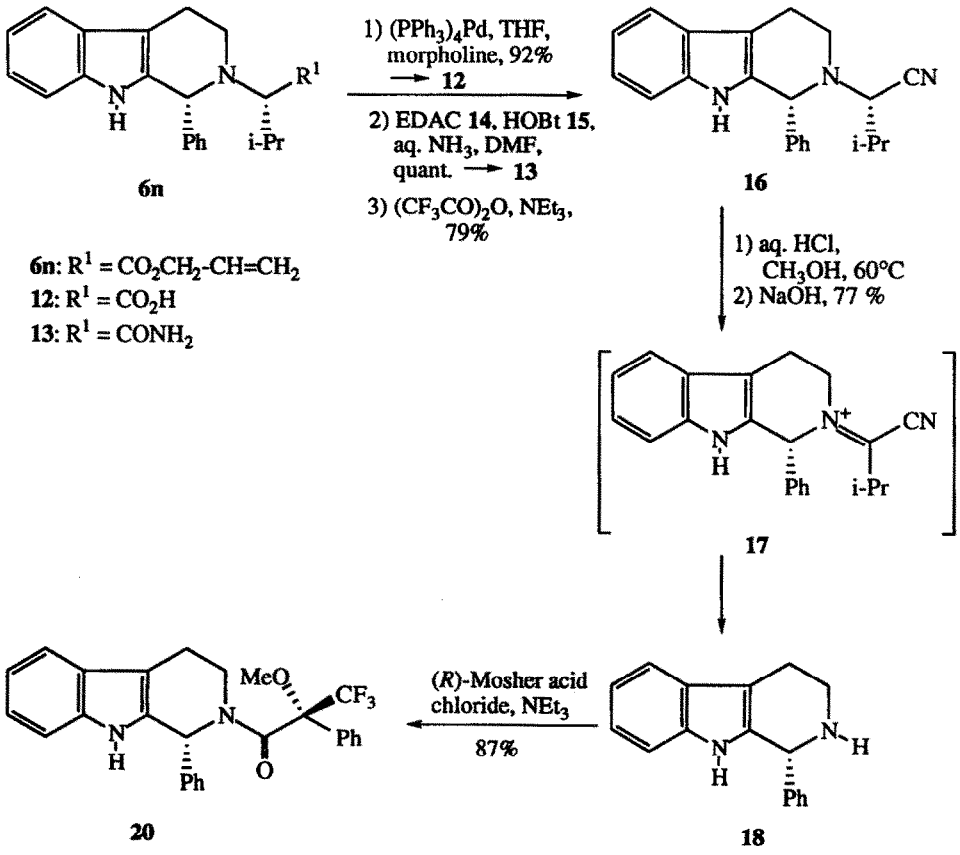
To rationalize the steric course of the Pictet-Spengler cyclization, first the configuration of the C=N double bond has to be addressed. By analogy to an analysis given by Cook et al.[12] for related cyclizations the two iminium intermediates **8** and **9** have to be compared. In **8** the steric repulsion between the imine substituent "R" and the indole moiety is more pronounced than the corresponding interaction between the aromatic nucleus and the imine hydrogen in **9** (Scheme 3). Furthermore, in **8** a 1,3-interaction between "R" and the protons of a CH_2 group would develop upon ring closure, whereas this would not be the case for **9**. Therefore, the Pictet Spengler cyclization most probably proceeds via the iminium intermediate **9**.

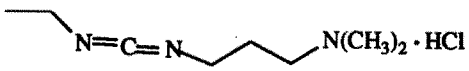
To explain the facial selectivity governing the attack of the indole nucleus on the $C=N^+$ double bond we assume that the iminium salts preferably adapt the conformations **10** and **11** (Scheme 3, a valine derivative is used as an example). These conformations should be energetically favourable since - by analogy to the Felkin-Anh model for nucleophilic attack on carbonyl groups - in these arrangements the π^*-orbital of the C=N bond and the σ^*-orbital of the α-C-COOR[1] bond are orientated parallel to each other.[13] In **10**, however, the sterically demanding substituent R and the small α-H of the amino acid ester are in a 1,3-relationship (Felkin-Anh type attack), whereas in **11** an unfavourable interaction with the bulky amino acid side chain would occur (anti Felkin-Anh type attack). Since **10** clearly is energetically more favourable than **11** and accounts for the formation of the major stereoisomers **6** we assume that the Pictet-Spengler cyclization of **5** predominantly follows this pathway. A rationalization along similar lines has also been forwarded by us to explain the steric steering of hetero Diels-Alder and Mannich reactions by amino acid esters as chiral auxiliary groups.[5b,c]

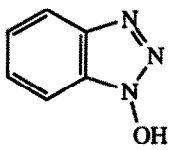


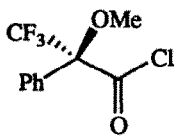
Scheme 3

To remove the mediator of selectivity from the heterocycles **6** the chemically stable bond between the amino acid α-C and the nitrogen atom has to be cleaved. For this purpose we have drawn from a method developed by Yamada et al. for the removal of COOR groups from tetrahydro-β-carbolines derived from tryptophane esters via the corresponding α-amino nitriles (Scheme 4).[14] To this end, in a representative example the N-alkylated amino acid allyl ester **6n** was converted in high yield into the corresponding amino acid **12** via Pd(0)-catalyzed transfer of the allyl group to morpholine as accepting nucleophile.[15] The carboxylic acid was activated by means of the carbodiimide **14** and N-hydroxybenzotriazole **15**[16] and transformed into the amide **13** by subsequent addition of aqueous ammonia. The amide was dehydrated to the α-amino nitrile upon treatment with trifluoroacetic acid in the presence of triethylamine. When heated in a 5:3 (v:v) mixture of 2N aqueous HCl and methanol the amino nitrile was subject to a retro Strecker reaction thereby generating the iminium intermediate **17** which under the reaction conditions was further converted to the desired secondary amine **18.** Its enantiomeric homogeneity was ascertained by conversion into the amide **20** of *(R)*-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid) and subsequent nmr spectroscopic investigation of this compound. We would particularly like to stress that all steps involved in the conversion of the amino acid ester derivative **6n** into the tetrahydro-β-carboline **18** proceed with high yield and are operationally simple.



EDAC =  **14**

HOBt =  **15**

(*R*)-Mosher acid chloride =  **19**

Scheme 4

Experimental

All melting points reported are uncorrected. Infrared spectra were recorded on a Perkin Elmer spectrometer Model 1430 or 882 and mass spectra on a Finnigan MAT MS 70 spectrometer. Specific optical rotation values were measured on a Perkin Elmer polarimeter 241. Proton and carbon NMR spectra were measured on a Bruker AC-200, a Bruker AM-400 or a Cryospec WM 250-MHz spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane. High-pressure liquid chromatography (HPLC) was performed on a Merck Hitachi instrument equipped with a L-3000 diode array detector, using a LiChrospher 100 RP18 250x4mm column, a mixture of methanol/water 85:15 or 80:20 (v/v) and a solvent flow-rate of 0.6 ml/min.

General Procedure for the Preparation of the N-alkylated Amino Acid Esters (3a-e)

ß-(3-Indolyl)ethyl halide **1a,b**, amino acid ester **2a-e** and N-ethyldiisopropylamine were dissolved in anhydrous THF, and the mixture was refluxed for several days. The solution was cooled to room temperature, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography to afford the chiral tryptamine derivatives **3a-e**.

N_b((*S*)-1-Methoxycarbonyl-2-methylpropyl)-tryptamine (3a)

A mixture of ß-(3-indolyl)ethyl bromide **1a** (16 g, 71.4 mmol), L-valine methyl ester **2a** (11 g, 83.8 mmol) and N-ethyldiisopropylamine (9.88 g, 76.4 mmol) in 100 ml THF was refluxed for 13 days. Chromatography of the residue on silica gel using petroleum ether/ethyl acetate (3:1 [v/v]) and recrystallization from diethyl ether/petroleum ether afforded 11.23 g (57%) of the product **3a** as colourless crystals. $[\alpha]_D^{22}$ = -19.9° (c= 1.0, $CHCl_3$); m.p.: 64 °C; IR ($CHCl_3$): 3410 and 1732 cm^{-1}; 200-MHz-^{1}H NMR ($CDCl_3$): δ = 8.20 (s, 1 H, N_a-H), 7.64-7.01 (m, 5 H, aromatic), 3.66 (s, 3 H, O-CH_3), 3.10 (d, J = 6.2 Hz, 1 H, α-H), 3.03-2.78 (m, 4 H, 2 CH_2), 1.97-1.84 (m, 1 H, β-H), 1.64 (s, 1 H, NH), 0.96 (d, J = 6.5 Hz, 3 H, CH_3) and 0.93 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 175.63 (C=O), 136.24, 127.45, 121.81, 121.71, 119.07, 118.79, 113.83, 111.03, 67.63 (α-C), 51.28 (O-CH_3), 48.81 (N-CH_2), 31.54 (β-C), 25.91 (aryl-CH_2), 19.03 and 18.87 (2 CH_3); Anal. calcd. for $C_{16}H_{22}N_2O_2$ (274.4); C 70.04, H 8.08, N 10.21, Found C 70.15, H 8.02, N 10.13.

N_b((*S*)-1-(1,1-Dimethylethoxycarbonyl)-2-methylpropyl)-tryptamine (3b)

A mixture of ß-(3-indolyl)ethyl bromide **1a** (2 g, 8.9 mmol), L-valine tert.-butylester **2b** (2 g, 11.6 mmol) and N-ethyldiisopropylamine (1.50 g, 11.6 mmol) in 30 ml THF was refluxed for 11 days. Chromatography of the residue on silica gel using petroleum ether/ethyl acetate (4:1 [v/v]) and recrystallization from diethyl ether/petroleum ether afforded 1.54 g (55%) of the product **3b** as colourless crystals. $[\alpha]_D^{22}$ = -15.1° (c= 1.1, $CHCl_3$); m.p.: 103 °C; IR ($CHCl_3$): 3303 and 1713 cm^{-1}; 200-MHz-^{1}H NMR ($CDCl_3$): δ = 8.38 (s, 1 H, N_a-H), 7.65-7.02 (m, 5 H, aromatic), 3.03-2.82 (m, 5 H, α-H and 2 CH_2), 1.97-1.83 (m, 1 H, β-H), 1.77 (s, 1 H, NH), 1.44 (d, J = 1.6 Hz, 9 H, 3 CH_3) and 0.98 (m, 6 H, 2 CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 174.64

(C=O), 136.36, 127.84, 121.83, 119.09, 118.88, 113.93, 111.16, 80.87 (O-C(CH$_3$)$_3$), 68.15 (α-C), 48.89 (N-CH$_2$), 31.71 (β-C), 28.10 (3 CH$_3$), 26.08 (CH$_2$), 19.10 and 19.02 (2 CH$_3$); Anal. calcd. for $C_{19}H_{28}N_2O_2$ (316.4) C 72.12, H 8.92, N 8.85, Found C 72.14, H 8.93, N 8.83.

N_b((*S*)-1-Methoxycarbonyl-ethyl)-tryptamine (3c)

A mixture of ß-(3-indolyl)ethyl bromide **1a** (7.0 g, 31.2 mmol), L-alanine methyl ester **2c** (4.1 g, 39.8 mmol) and N-ethyldiisopropylamine (4.00 g, 31.2 mmol) in 50 ml THF was refluxed for 13 days. Chromatography of the residue on silica gel using petroleum ether/ethyl acetate (2:1 [v/v]) afforded a colourless oil (1.2 g, 16%). $[\alpha]_D^{22}$ = -20.3° (c= 1.24, $CHCl_3$); IR ($CHCl_3$): 3410 and 1735 cm^{-1}; 200-MHz-^{1}H NMR ($CDCl_3$): δ = 8.61 (s, 1 H, N_a-H), 7.63-6.98 (m, 5 H, aromatic), 3.65 (s, 3 H, O-CH$_3$), 3.44 (q, J = 7.0 Hz, 1 H, α C-H), 3.01-2.84 (m, 4 H, 2 CH$_2$), 1.86 (s, 1 H, NH) and 1.31 (d, 3 H, CH$_3$); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 175.94 (C=O), 136.26, 127.24, 121.92, 121.67, 118.93, 118.61, 113.13, 111.07, 56.51 (α C), 51.61 (O-CH$_3$), 47.83 (N-CH$_2$), 25.77 (aryl-CH$_2$) and 18.77 (CH$_3$); Anal. calcd. for $C_{14}H_{18}N_2O_2$ (246.3); C 68.27, H 7.37, N 11.37, Found C 67.90, H 7.40, N 11.30.

N_b((*S*)-1-Methoxycarbonyl-2-methylbutyl)-tryptamine (3d)

A mixture of ß-(3-indolyl)ethyl bromide **1a** (7.0 g, 31.2 mmol), L-isoleucine methyl ester **2d** (9.8 g, 67.5 mmol) and N-ethyldiisopropylamine (4.00 g, 31.2 mmol) in 50 ml THF was refluxed for 21 days. Chromatography of the residue on silica gel using petroleum ether/ethyl acetate (3:1 [v/v]) yielded a colourless oil (1.69 g, 19%). $[\alpha]_D^{22}$ = -12.7° (c= 1.24, $CHCl_3$); IR ($CHCl_3$): 3414 and 1732 cm^{-1}; 200-MHz-^{1}H NMR ($CDCl_3$): δ = 8.33 (s, 1 H, N_a-H), 7.64-7.59 (m, 1 H), 7.35-6.99 (m, 4 H, aromatic), 3.66 (s, 3 H, O-CH$_3$), 3.21 (d, J = 6.0 Hz, 1 H, α-H), 3.03-2.79 (m, 4 H, 2 CH$_2$), 1.77-1.48 (m, 3 H, N-H, CH$_2$), 1.27-1.12 (m, 1 H, C-H), 0.90 (t, J = 7.2 Hz, 3 H, CH$_2$-C<u>H</u>$_3$) and 0.89 (d, J = 6.7 Hz, 3 H, CH-C<u>H</u>$_3$); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 175.50 (C=O), 136.20, 127.35, 121.72, 118.97, 118.71, 113.59, 111.02 (8 C), 66.16 (α-C), 51.21 (O-CH$_3$), 48.71 (N-CH$_2$), 38.16 (β-C), 25.85 (CH$_2$), 25.72 (CH$_2$), 15.31 (CH-<u>C</u>H$_3$) and 11.36 (CH$_2$-<u>C</u>H$_3$); Anal. calcd. for $C_{17}H_{24}N_2O_2$ (288.4); C 70.80, H 8.39, N 9.71, Found C 70.64, H 8.42, N 9.50.

N_b((*S*)-1-Allyloxycarbonyl-3-methylbutyl)-tryptamine (3e)

A mixture of ß-(3-indolyl)ethyl iodide **1b** (14.00 g, 51.5 mmol), L-leucine allyl ester **2e** (15.00 g, 43.6 mmol) and N-ethyldiisopropylamine (15.30 g, 59.2 mmol) in 200 ml THF was refluxed for 10 days. Then the solution was cooled to room temperature, filtered and concentrated *in vacuo*. Chromatography of the residue on silica gel using petroleum ether/ethyl acetate (5:1 [v/v]) yielded a colourless oil (10.75 g, 66%). $[\alpha]_D^{22}$ = -10.9° (c= 1.02, $CHCl_3$); IR ($CHCl_3$): 3489, 3017, 2964 and 1741 cm^{-1}; 250-MHz ^{1}H NMR ($CDCl_3$): δ = 8.19 (br, 1 H, N_a-H), 7.60 (d, J = 7.4 Hz, 1 H, aromatic), 7.34-7.31 (m, 1 H, aromatic), 7.24-7.08 (m, 2 H, aromatic), 7.01 (d, J = 2.2 Hz, 1 H, aromatic), 5.92-5.77 (m, 1 H, C<u>H</u>=CH$_2$), 5.32-5.18 (m, 2H, CH=C<u>H</u>$_2$), 4.57-4.55 (m, 2 H, OCH$_2$), 3.38 (t, J = 7.2 Hz, 1 H, α-CH), 3.00-2.82 (m, 4 H, CH$_2$), 1.79 (s, 1 H, NH), 1.75-1.62 (m, 1 H, CH), 1.52-1.49 (m, 2 H, CH$_2$), 0.92 (d, J = 6.6 Hz, 3 H, CH$_3$) and 0.89 (d, 3 H, CH$_3$); 62.9-MHz-^{13}C NMR ($CDCl_3$): δ = 175.60 (C=O), 136.37, 132.04, 127.49, 121.93, 121.86, 119.19, 118.86, 118.53

(C=$\underline{C}H_2$), 113.71, 111.15, 65.18 (OCH_2), 60.22 (α-CH), 48.25 (N-CH_2), 42.74 (CH_2), 26.00 (CH_2), 24.98 and 22.56 (CH_3); Anal. calcd. for $C_{19}H_{26}N_2O_2$ (314.4); C 72.58, H 8.33, N 8.91, Found C 72.45, H 8.32, N 8.94.

General Method for the Pictet-Spengler Reaction Employing the Amino Acid Esters (3a-e)

A solution of the N-alkylated amino acid ester **3a-e**, aldehyde **4a-j** and acetic acid in 50 ml methylene chloride was stirred for several days. After extraction with 100 ml sat. $NaHCO_3$ solution, the organic layer was dried with $MgSO_4$, the organic solvent removed *in vacuo*, the residue taken up in diethyl ether and extracted with an aqueous solution of sodium bisulfite in order to remove remaining aldehyde. The organic layer was washed with sat. aqueous $NaHCO_3$, the solvent dried with $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography with petroleum ether/ethyl acetate (10:1 [v/v]) and, if possible, recrystallized from diethyl ether/petroleum ether to afford the pure, major diastereomer **6a-m**. The diastereomeric ratio was determined by HPLC or ^1H NMR of the crude product.

2-((*S*)-1-Methoxycarbonyl-2-methylpropyl)-1-(*R*)-phenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6a)

After 9 days at room temperature N-alkylated L-valine methyl ester **3a** (0.3 g, 1.1 mmol), benzaldehyde **4a** (0.4 g, 3.8 mmol) and acetic acid (2 g, 33.3 mmol) yielded the carboline **6a** as colourless crystals (0.3 g, 76%). The diastereomeric ratio was determined by HPLC to be 90:10.

The same procedure was carried out for 8 days at 6 °C to yield 51% of **6a** and the isomeric ratio increased to 93:7. $[\alpha]_D^{22}$ = -240.0° (c= 1.13, $CHCl_3$); m.p.: 123 °C; IR ($CHCl_3$): 3403 and 1721 cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$): δ = 7.59-7.08 (m, 10 H, aromatic), 4.88 (s, 1 H, CH), 3.79 (s, 3 H, OCH_3), 3.49-3.40 (m, 1 H, CH_{2a}), 3.13-2.63 (m, 3 H, CH_2 and CH_{2a}), 2.85 (d, J = 11.0 Hz, 1 H, α-H), 2.31-2.19 (m, 1 H, β-H), 0.92 (d, J = 6.7 Hz, 3 H, CH_3) and 0.79 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 171.97 (C=O), 140.92, 136.39, 135.89, 129.72, 128.68, 128.35, 127.13, 121.48, 119.38, 118.28, 110.84, 109.10, 68.05 (α-C), 63.31 (C_6H_5-CH), 50.77 (OCH_3), 44.50 (NCH_2), 27.13 (β-C), 22.39 (CH_2), 20.07 and 19.24 (2 CH_3); Anal. calcd. for $C_{23}H_{26}N_2O_2$ (362.5); C 76.21, H 7.23, N 7.73, Found C 76.16, H 7.20, N 7.70.

2-((*S*)-1-Methoxycarbonyl-2-methylpropyl)-1-(*R*)-p-nitrophenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6b)

After 9 days at room temperature N-alkylated L-valine methyl ester **3a** (0.3 g, 1.1 mmol), p-nitrobenzaldehyde **4b** (0.4 g, 2.7 mmol) and acetic acid (2 g, 33.3 mmol) yielded the carbolines as a yellow oil (0.3 g, 67%). Recrystallization from diethyl ether/petroleum ether gave the main isomer **6b** (0.24 g, 54%) as yellow crystals. The diastereomeric ratio was determined by HPLC to be 80:20. $[\alpha]_D^{22}$ = -240.9° (c= 1.00, $CHCl_3$); m.p.: 208 °C; IR ($CHCl_3$): 3429, 1721 and 1349 cm^{-1}; 200-MHz ^1H NMR ($CDCl_3$): δ = 8.20-8.16 (m, 2 H, aromatic), 7.61-7.51 (m, 3 H, aromatic), 7.35 (s, 1 H, N_a-H), 7.21-7.07 (m, 3 H, aromatic), 4.99 (s, 1 H, CH), 3.78 (s, 3 H, OCH_3), 3.47-3.39 (m, 1 H, CH_2), 3.04-2.62 (m, 3 H, 2 CH_2), 2.66 (d, J = 10.9 Hz, 1 H, α-H), 2.31-2.16 (m, 1 H, β-H), 0.88 (d, J = 6.6 Hz, 3 H, CH_3) and 0.78 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 171.45 (C=O), 148.96, 147.86, 136.58, 133.98, 130.47, 126.81, 123.89, 121.98, 119.64,

118.43, 110.96, 109.80, 68.73 (α-C), 62.57 (C_6H_4-CH), 50.98 (OCH_3), 44.16 (NCH_2), 27.07 (β-C), 22.23 (CH_2), 19.97 and 19.15 (2 CH_3); Anal. calcd. for $C_{23}H_{25}N_3O_4$ (407.5); C 67.80, H 6.18, N 10.31, Found C 67.67, H 6.22, N 10.25.

Crystal data[17]: $C_{23}H_{25}N_3O_4$ crystallizes orthorhombic, space group $P2_12_12_1$ (Nr. 19), with a = 10.204(5) Å, b = 11.4678(6) Å, c = 18.48(1) Å, Z = 4, μ = 0.51 cm^{-1}. 3746 refl. were measured (on a diffractometer Enraf-Nonius CAD-4, MoKα-radiation, graphite monochromator), 2717 thereof independent with $I>2\sigma(I)$. The structure determination was carried out by means of direct methods (SHELX-76 and SHELXS-86 [G. M. Sheldrick, SHELX-76, Program for Crystal Structure Determination, University of Cambridge, 1976. G. M. Sheldrick, SHELXS-86, Göttingen 1986.]), R = 0.0425, R_w = 0.048, $w = 1 / \sigma^2(F) + 0.0001 * F^2$. All C, N, and O-atoms were refined anisotropically. The H atoms are in the calculated locations with equal isotropic temperature factors for CH, CH_2, CH_3 and phenyl-H.

Table 3: Fractional Coordinates of Atoms with Standard Deviations and Equivalent Isotropic Displacement Parameters for Compound **6b**[a].

Atom	x	y	z	U(eq)	Atom	x	y	z	U(eq)
C(1)	0.2530(2)	0.0967(2)	0.5534(1)	0.047(11)	C(20)	0.5463(3)	-0.1126(2)	0.5507(1)	0.065(9)
H(1)	0.2292(2)	0.1098(2)	0.4970(1)	0.089(3) [b]	C(21)	0.5489(3)	-0.1221(3)	0.6337(2))	0.089(13)
N(2)	0.3289(2)	-0.0121(2)	0.5637(1)	0.049(14)	C(22)	0.6829(3)	-0.0930(3)	0.5210(2)	0.092(28)
C(3)	0.2481(3)	-0.1168(2)	0.5553(1)	0.059(16)	C(23)	0.4432(3)	-0.0078(2)	0.4447(1)	0.057(14)
C(4)	0.1543(3)	-0.1272(2)	0.6196(2)	0.067(19)	O(24)	0.4002(2)	-0.1068(1)	0.4162(1)	0.067(18)
C(4A)	0.0871(2)	-0.0131(2)	0.6306(1)	0.052(9)	C(25)	0.3855(3)	-0.1135(3)	0.3383(1)	0.075(20)
C(4B)	-0.0263(2)	0.0178(2)	0.6719(1)	0.054(4)	O(26)	0.4682(3)	0.0747(2)	0.4087(1)	0.096(51)
C(5)	-0.1098(3)	-0.0432(3)	0.7200(1)	0.068(1)	C(10)	0.3328(2)	0.2010(2)	0.5779(1)	0.046(9)
C(6)	-0.2075(3)	0.0166(3)	0.7532(2)	0.081(9)	C(11)	0.3856(3)	0.2031(2)	0.6480(1)	0.061(15)
C(7)	-0.2294(3)	0.1354(3)	0.7403(2)	0.078(16)	C(12)	0.4555(3)	0.2965(2)	0.6721(1)	0.069(3)
C(8)	-0.1510(3)	0.1976(3)	0.6949(2)	0.067(7)	C(13)	0.4718(3)	0.3903(2)	0.6253(2)	0.069(15)
C(8A)	-0.0476(2)	0.1378(2)	0.6612(1)	0.053(2)	C(14)	0.4216(3)	0.3912(2)	0.5562(2)	0.068(18)
N(9)	0.0507(2)	0.1785(2)	0.6155(1)	0.052(6)	C(15)	0.3516(2)	0.2961(2)	0.5329(1)	0.058(9)
C(9A)	0.1299(2)	0.0854(2)	0.5979(1)	0.048(7)	N(16)	0.5440(3)	0.4930(3)	0.6516(2)	0.104(12)
C(19)	0.4551(2)	-0.0125(2)	0.5261(1)	0.052(10)	O(17)	0.5962(4)	0.4871(3)	0.7106(2)	0.159(30)
H(19)	0.5014(2)	0.0681(2)	0.5422(1)	0.089(3) [b]	O(18)	0.5461(4)	0.5796(3)	0.6139(2)	0.170(57)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor, [b] isotropic U.

2-((*S*)-1-2,2-Dimethylethoxycarbonyl-2-methylpropyl)-1-(*R*)-p-nitrophenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6c)

After 8 days at room temperature N-alkylated L-valine tert. butyl ester **3b** (1.0 g, 3.2 mmol), p-nitrobenzaldehyde **4b** (1.0 g, 6.8 mmol) and acetic acid (2 g, 33.3 mmol) yielded the carboline **6c** as yellow crystals (1.00 g, 70%). The diastereomeric ratio was determined by 200-MHz ^{1}H NMR to be 73:27. $[\alpha]_D^{22}$ = -49.5° (c= 0.49, $CHCl_3$); m.p.: 213 °C; IR ($CHCl_3$): 3370, 1699, 1520 and 1347 cm^{-1}; 200-MHz ^{1}H NMR ($CDCl_3$): δ = 8.25-7.07 (m, 9 H, aromatic, and N_a-H), 5.42 (s, 1 H, CH), 3.25-2.62 (m, 4 H, 2 CH_2), 2.85 (d, J = 10.2 Hz, 1 H, α-H), 1.95-1.83 (m, 1 H, β-H), 1.11 (s, 9 H, CH_3), 1.06 (d, J = 6.6 Hz, 3 H, CH_3) and 0.75 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 172.89 (C=O), 150.11, 147.01, 136.04, 132.56, 129.63, 127.29, 123.24, 121.86, 119.37, 118.12, 111.01, 110.22, 81.05 (O<u>C</u>$(CH_3)_3$),.72.31 (α-C), 56.70 (C_6H_4-CH), 45.50 (NCH_2), 30.02 (β C), 27.51 (3 C, CH_3), 20.26 (CH_3), 19.96 (CH_2) and 18.83 (CH_3); Anal. calcd. for $C_{26}H_{31}N_3O_4$ (449.6); C 69.47, H 6.95, N 9.35, Found C 69.24, H 7.13, N 9.42.

2-((*S*)-1-Methoxycarbonyl-2-methylpropyl)-1-(*R*)-o-nitrophenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6d)

After 14 days at room temperature N-alkylated L-valine methyl ester **3a** (0.4 g, 1.5 mmol), o-nitrobenzaldehyde **4c** (0.4 g, 2.7 mmol) and acetic acid (0.4 g, 6.7 mmol) yielded the carboline **6d** as yellow crystals (0.35 g, 59%). The diastereomeric ratio was determined by 250-MHz ^{1}H NMR to be 98.5:1.5. $[\alpha]_D^{22}$ = -76.5° (c= 1.04, $CHCl_3$); m.p.: 184 °C; IR ($CHCl_3$): 3455, 1735, 1527 and 1356 cm^{-1}; 200-MHz-^{1}H NMR ($CDCl_3$): δ = 8.05-7.07 (m, 9 H, aromatic and N_a-H), 5.34 (s, 1 H, CH), 3.67 (s, 3 H, OCH_3), 3.44-3.36 (m, 1 H, CH_2), 3.14-2.65 (m, 3 H, 2 CH_2), 2.49 (d, J = 11.0 Hz, 1 H, α-H), 2.35-2.20 (m, 1 H, β-H), 0.93 (d, J = 6.5 Hz, 3 H, CH_3) and 0.75 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 170.95 (C=O), 151.52, 136.52, 136.33, 134.08, 132.92, 131.44, 128.58, 126.64, 123.17, 121.78, 119.37, 118.26, 110.88, 109.44, 68.70 (α-C), 57.02 (C_6H_4-CH), 50.51 (OCH_3), 43.83 (NCH_2), 26.84 (β-C), 22.18 (CH_2), 20.01 and 18.81 (2 CH_3); Anal. calcd. for $C_{23}H_{25}N_3O_4$ (407.5); C 67.80, H 6.18, N 10.31, Found C 67.83, H 6.19, N 10.23.

2-((*S*)-1-Methoxycarbonyl-2-methylpropyl)-1-(*R*)-p-chlorophenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6e)

After 17 days at room temperature N-alkylated L-valine methyl ester **3a** (0.3 g, 1.1 mmol), p-chlorobenzaldehyde **4d** (0.3 g, 2.1 mmol) and acetic acid (1.0 g, 16.7 mmol) yielded the carboline **6e** as colourless crystals (0.30 g, 69%). The diastereomeric ratio was determined by HPLC to be 78:22. $[\alpha]_D^{22}$ = -220.0° (c= 1.0, $CHCl_3$); m.p.: 160 °C; IR ($CHCl_3$): 3403 and 1721 cm^{-1}; 200-MHz-^{1}H NMR ($CDCl_3$): δ = 7.53-7.49 (m, 1 H, aromatic), 7.24-7.04 (m, 8 H, aromatic and N_a-H), 4.82 (s, 1 H, CH), 3.74 (s, 3 H, OCH_3), 3.42-3.35 (m, 1 H, CH_2), 3.05-2.57 (m, 3 H, CH_2 and CH_2), 2.73 (d, J = 10.9 Hz, 1 H, α-H), 2.26-2.14 (m, 1 H, β H), 0.85 (d, J = 6.6 Hz, 3 H, CH_3) and 0.75 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 171.64 (C=O), 139.39, 136.29, 135.09 133.93, 130.90, 128.81, 126.90, 121.59, 119.40, 118.22, 110.73, 109.29, 68.02 (α-C), 62.47 (C_6H_4-CH), 50.72 (O-CH_3), 44.28 (NCH_2), 26.96 (β-C), 22.18 (CH_2), 19.90 and 19.07 (2 CH_3); Anal. calcd. for $C_{23}H_{25}N_2O_2Cl$ (396.9); C 69.60, H 6.35, N 7.06, Cl 8.93, Found C 69.41, H 6.46, N 6.94, Cl 8.82.

2-((*S*)-1-Methoxycarbonyl-2-methylpropyl)-1-(*R*)-(2,4-dichloro-phenyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6f)

After 16 days at room temperature N-alkylated L-valine methyl ester **3a** (0.3 g, 1.1 mmol), 2,4-dichlorobenzaldehyde **4e** (0.3 g, 1.7 mmol) and acetic acid (1.0 g, 16.7 mmol) yielded the carboline **6f** upon dissolving in diethyl ether and precipitation with petroleum ether as a colourless oil (0.37 g, 78%). The diastereomeric ratio was determined by HPLC to be 93.5:6.5. $[\alpha]_D^{22}$ = -205.3° (c= 1.16, $CHCl_3$); IR ($CHCl_3$): 3403 and 1721 cm^{-1}; 200-MHz-^{1}H NMR ($CDCl_3$): δ = 7.53-7.39 (m, 4 H, N_a-H and aromatic), 7.24-7.04 (m, 4 H, aromatic), 5.50 (s, 1 H, CH), 3.73 (s, 3 H, OCH_3), 3.46-3.39 (m, 1 H, CH_2), 2.98-2.72 (m, 3 H, CH_2 and CH_2), 2.75 (d, J = 10.9 Hz, 1 H, α-H), 2.33-2.21 (m, 1 H, β-H), 0.97 (d, J = 6.7 Hz, 3 H, CH_3) and 0.81 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 171.83 (C=O), 137.63, 136.28, 134.53, 134.16, 134.05, 131.95, 129.42, 127.90, 126.72, 121.75, 119.46, 118.23, 110.75 and 109.27, 68.64 (α-C), 58.08 (C_6H_3-CH), 50.81 (OCH_3), 43.94 (NCH_2), 27.25 (β-C), 22.05 (CH_2), 20.04 and 19.16 (2 CH_3); Anal. calcd. for $C_{23}H_{24}N_2O_2Cl_2$ (431.3); C 64.04, H 5.61, N 6.49, Cl 16.44, Found C 64.20, H 5.55, N 6.54, Cl 16.23.

2-((*S*)-1-Methoxycarbonyl-2-methylpropyl)-1-(*R*)-p-methoxyphenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6g)

After 22 days at room temperature N-alkylated L-valine methyl ester **3a** (0.4 g, 1.5 mmol), p-methoxybenzaldehyde **4f** (0.4 g, 2.9 mmol) and acetic acid (1 g, 16.7 mmol) yielded the carboline **6g** as colourless crystals (0.14 g, 24%). The diastereomeric ratio was determined by HPLC to be 96:4. $[\alpha]_D^{22}$ = -219.4° (c= 1.13, $CHCl_3$); m.p.: 132 °C; IR ($CHCl_3$): 3392, 2837 and 1721 cm^{-1}; 200-MHz-^{1}H NMR ($CDCl_3$): δ = 7.53-7.48 (m, 1 H, aromatic), 7.31-7.25 (m, 2 H, aromatic), 7.15-7.05 (m, 4 H, aromatic and N_a-H), 6.91-6.85 (m, 2 H, aromatic), 4.78 (s, 1 H, CH), 3.82 (s, 3 H, OCH_3) and 3.74 (s, 3 H, OCH_3), 3.42-3.34 (m, 1 H, CH_2), 2.98-2.61 (m, 3 H, CH_2 and CH_2), 2.81 (d, J = 10.9 Hz, 1 H, α-H), 2.21-2.16 (m, 1 H, β-H), 0.85 (d, J = 6.7 Hz, 3 H, CH_3) and 0.75 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 172.00 (C=O), 159.51, 136.31, 136.20, 132.67, 130.80, 127.18, 121.39, 119.31, 118.21, 113.95, 110.79, 109.01, 67.78 (α-C), 62.60 (C_6H_4-CH), 55.27 (OCH_3), 50.72 (OCH_3), 44.56 (NCH_2), 27.08 (β-C), 22.39 (CH_2), 20.06 and 19.24 (2 CH_3); Anal. calcd. for $C_{24}H_{28}N_2O_3$ (392.5); C 73.44, H 7.19, N 7.14, Found C 73.23, H 6.96, N 7.07.

2-((*S*)-1-Methoxycarbonyl-2-methylpropyl)-1-(*R*)-(2,4-dimethoxyphenyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6h)

After 9 days at 40 °C N-alkylated L-valine methyl ester **3a** (0.4 g, 1.5 mmol), 2,4-dimethoxy-benzaldehyde **4g** (0.4 g, 2.4 mmol) and acetic acid (1 g, 16.7 mmol) yielded 0.58 g (94%) as a colourless oil. The diastereomeric ratio was determined by 400-MHz-^{1}H NMR to be 89:11. Crystallization from petroleum ether/diethyl ether gave the product **6h** as colourless crystals (81%). $[\alpha]_D^{22}$ = -181.9° (c= 1.10, $CHCl_3$); m.p.: 107 °C; IR ($CHCl_3$): 3396, 2839 and 1727 cm^{-1}; 200-MHz-^{1}H NMR ($CDCl_3$): δ = 200-MHz-^{1}H NMR ($CDCl_3$): δ = 7.54-7.05 (m, 6 H, aromatic and N_a-H), 6.60-6.44 (m, 2 H), 5.39 (s, 1 H, CH), 3.94 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.46-3.42 (m, 1 H, CH_2), 2.93 (d, J = 10.9 Hz, 1 H, α-H), 2.91-2.78 (m, 3 H, CH_2 and CH_2), 2.35-2.16 (m, 1 H, β-H), 1.01 (d, J = 6.7 Hz, 3 H, CH_3) and 0.82 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 172.47 (C=O), 160.01, 158.75, 136.56, 135.98, 130.51, 126.99, 121.56, 120.94, 118.95, 117.89, 110.54, 108.34, 105.44, 98.54, 68.08 (α-C), 55.79, 55.23, 54.26, 50.46,

44.24 (NCH_2), 27.38 (β-C), 22.22 (CH_2), 20.07 (CH_3) and 19.20 (CH_3); Anal. calcd. for $C_{25}H_{30}N_2O_4$ (422.5); C 71.07, H 7.16, N 6.63, Found C 71.03, H 7.16, N 6.56.

2-((*S*)-1-Methoxycarbonyl-2-methylpropyl)-1-(*R*)-p-ethoxyphenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6i)

After 9 days at 40 °C N-alkylated L-valine methyl ester **3a** (0.3 g, 1.1 mmol), p-ethoxybenzaldehyde **4h** (0.3 g, 2.0 mmol) and acetic acid (1 g, 16.7 mmol) yielded the carboline **6i** as colourless crystals (0.38 g, 85%). The diastereomeric ratio was determined by HPLC to be 93:7. $[\alpha]_D^{22}$ = -199.2° (c= 0.96, $CHCl_3$); m.p.: 121 °C; IR ($CHCl_3$): 3398 and 1721 cm^{-1}; 200-MHz-^{1}H NMR ($CDCl_3$): δ = 7.57-7.51 (m, 1 H, aromatic), 7.33-7.24 (m, 3 H, aromatic), 7.18-7.06 (m, 3 H, aromatic and N_a-H), 6.91-6.84 (m, 2 H, aromatic), 4.80 (s, 1 H, CH), 4.05 (q, J = 7.0, 2 H, CH_2), 3.76 (s, 3 H, OCH_3), 3.45-3.37 (m, 1 H, CH_2), 3.06-2.59 (m, 3 H, CH_2 and CH_2), 2.85 (d, J = 10.8 Hz, 1 H, α-H), 2.27-2.15 (m, 1 H, β-H), 1.43 (t, 3 H, CH_3), 0.89 (d, J = 6.7 Hz, 3 H, CH_3) and 0.77 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 171.88 (C=O), 158.78, 136.17, 136.11, 132.37, 130.67, 127.03, 121.23, 119.16, 118.06, 114.28, 110.66, 108.84, 67.62 (α-C), 63.30 (O-CH_2), 62.47 (C_6H_4-CH), 50.57 (OCH_3), 44.43 (NCH_2), 26.94 (β-C), 22.25 (CH_2), 19.92 (CH_3) and 19.10 (CH_3) and 14.80 (CH_2-CH_3); Anal. calcd. for $C_{25}H_{30}N_2O_3$ (406.5); C 73.86, H 7.44, N 6.89, Found C 73.65, H 7.27, N 6.56.

2-((*S*)-1-Methoxycarbonyl-2-methylpropyl)-1-(*R*)-p-methylphenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6j)

After 16 days at room temperature N-alkylated L-valine methyl ester **3a** (0.3 g, 1.1 mmol), p-methylbenzaldehyde **4i** (0.6 g, 5.0 mmol) and acetic acid (1 g, 16.7 mmol) yielded the carboline **6j** 0.20 g (48%) as colourless crystals. The diastereomeric ratio was determined by HPLC to be 92:8. $[\alpha]_D^{22}$ = -245.3° (c= 0.9, $CHCl_3$); m.p.: 141 °C; IR ($CHCl_3$): 3393 and 1715 cm^{-1}; 200-MHz-^{1}H NMR ($CDCl_3$): δ = 7.59-7.54 (m, 1 H, aromatic), 7.34-7.09 (m, 8 H, aromatic and N_a-H), 4.84 (s, 1 H, CH), 3.79 (s, 3 H, OCH_3), 3.51-3.42 (m, 1 H, CH_2), 3.11-2.63 (m, 3 H, CH_2 and CH_2), 2.88 (d, J = 10.8 Hz, 1 H, α-H), 2.42 (m, 3 H, CH_3), 2.32-2.20 (m, 1 H, β-H), 0.94 (d, J = 6.7 Hz, 3 H, CH_3) and 0.81 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 171.87 (C=O), 137.83, 137.56, 136.16, 135.95, 129.42, 129.21, 127.00, 121.23, 119.16, 118.07, 110.65, 108.81, 67.75 (α-C), 62.87 (C_6H_4-CH), 50.57 (OCH_3), 44.38 (NCH_2), 26.97 (β-C), 22.24 (CH_2), 21.17 (CH_3), 19.90 (CH_3) and 19.09 (CH_3); Anal. calcd. for $C_{24}H_{28}N_2O_2$ (376.5); C 76.56, H 7.50, N 7.44, Found C 76.60, H 7.51, N 7.35.

2-((*S*)-1-Methoxycarbonyl-2-methylpropyl)-1-(*R*)-2-naphthyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6k)

After 16 days at room temperature N-alkylated L-valine methyl ester **3a** (0.3 g, 1.1 mmol), 2 naphthaldehyde **4i** (0.4 g, 1.9 mmol) and acetic acid (1 g, 16.7 mmol) yielded the carboline **6k** 0.19 g (51%) as colourless crystals. The diastereomeric ratio was determined by HPLC to be 92:8. $[\alpha]_D^{22}$ = -415.3° (c= 1.1, $CHCl_3$); m.p.: 180 °C; IR ($CHCl_3$): 3396 and 1720 cm^{-1}; 200-MHz-^{1}H NMR ($CDCl_3$): δ = 7.97-7.80 (m, 4 H, aromatic), 7.62-7.46 (m, 4 H, aromatic), 7.24-7.07 (m, 4 H, aromatic and N_a-H), 5.07 (s, 1 H, CH), 3.82 (s, 3 H, OCH_3), 3.54-3.47 (m, 1 H, CH_2), 3.13-2.70 (m, 3 H, CH_2 and CH_2), 2.92 (d, J = 11.0 Hz, 1 H, α-H), 2.35-2.23 (m, 1 H, β-H), 0.96 (d, J = 6.6 Hz, 3 H, CH_3) and 0.76 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR

($CDCl_3$): δ = 171.80 (C=O), 138.28, 136.27, 135.45, 133.43, 133.07, 128.77, 128.60, 127.83, 127.76, 127.02, 126.72, 126.16, 121.39, 119.26, 118.16, 110.71, 109.11, 68.05 (α-C), 63.30 (C_6H_4-CH), 50.67 (OCH_3), 44.29 (NCH_2), 26.99 (β-C), 22.30 (CH_2), 19.86 (CH_3) and 19.15 (CH_3); Anal. calcd. for $C_{27}H_{28}N_2O_2C$ (412.5); C 78.61, H 6.84, N 6.79, Found C 78.62, H 6.86, N 6.72.

2-((*S*)-1-Methoxycarbonyl-ethyl)-1-(*R*)-phenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6l)

After 14 days at room temperature N-alkylated L-alanine methyl ester **3c** (0.3 g, 1.2 mmol), benzaldehyde **4a** (0.5 g, 4.7 mmol) and acetic acid (3 g, 50.0 mmol) yielded 0.19 g (47%) of the product **6l** as colourless crystals. The diastereomeric ratio was determined to be 70:30 by integration of a 400-MHz ^1H NMR spectrum. $[\alpha]_D^{22}$ = -179.5° (c= 0.84, $CHCl_3$); m.p.: 158 °C; IR ($CHCl_3$): 3397 and 1723 cm^{-1}; 200-MHz-^1H NMR ($CDCl_3$): δ = 7.58-7.09 (m, 10 H, aromatic and N_a-H), 5.19 (s, 1 H, CH), 3.76 (s, 3 H, OCH_3), 3.50 (q, J = 7.0, 1 H, CH), 3.46-3.38 (m, 1 H, CH_2), 3.02-2.83 (m, 3 H, 2 CH_2), 2.85 (d, J = 11.0 Hz, 1 H, α-CH) and 1.30 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): 173.62 (C=O), 141.11, 136.35, 135.66, 129.28, 128.91, 128.39, 127.21, 121.46, 119.36, 118.29, 110.82, 108.93, 63.08 (α-C), 56.30 (C_6H_5-CH), 51.16 (OCH_3), 43.68 (NCH_2), 22.46 (CH_2) and 16.46 (CH_3); Anal. calcd. for $C_{21}H_{22}N_2O_2$ (334.4); C 75.42, H 6.63, N 8.38, Found C 75.31, H 6.62, N 8.37.

2-((*S*)-1-Methoxycarbonyl-2-methylbutyl)-1-(*R*)-phenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6m)

After 11 days at room temperature N-alkylated L-isoleucine methyl ester **3d** (0.3 g, 1.4 mmol), benzaldehyde **4a** (0.5 g, 34.7 mmol) and acetic acid (3 g, 50.0 mmol) yielded 0.23 g (69%) of the product **6m** as colourless crystals. The diastereomeric ratio was determined by HPLC to be 89:11. $[\alpha]_D^{22}$ = -218.3° (c= 1.0, $CHCl_3$); m.p.: 218 °C; IR ($CHCl_3$): 3400 and 1722 cm^{-1}; 200-MHz-^1H NMR ($CDCl_3$): δ = 7.59-7.35 (m, 6 H, aromatic and N_a-H), 7.25-7.11 (m, 4 H, aromatic), 4.84 (s, 1 H, CH), 3.79 (s, 3 H, OCH_3), 3.49-3.42 (m, 1 H, CH_2), 3.05-2.67 (m, 3 H, 2 CH_2), 2.97 (d, J = 10.9 Hz, 1 H, α-H), 2.09-2.06 (m, 1 H, CH_2), 1.91-1.79 (m, 1 H, CH_2), 0.96-0.85 (m, 1 H, β-H), 0.83-0.74 (m, 6 H, 2 CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): 171.82 (C=O), 140.66, 136.21, 135.70, 129.64, 128.49, 128.19, 126.94, 121.31, 119.21, 118.11, 110.66, 109.08, 66.62 (α-C), 63.16 (C_6H_5-CH), 50.60 (OCH_3), 44.39 (N-CH_2), 32.85 (β-C), 24.34 (CH_2), 22.19 (CH_2), 16.03 (CH-$\underline{C}H_3$) and 10.52 (CH_2-$\underline{C}H_3$); Anal. calcd. for $C_{24}H_{28}N_2O_2$ (376.5); C 76.56, H 7.50, N 7.44, Found C 76.81, H 7.12, N 7.45.

2-((*S*)-1-Allyloxycarbonyl-3-methylbutyl)-1-(*R*)-phenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6n)

After 11 days at room temperature N-alkylated L-leucine allyl ester **3e** (0.30 g, 1.0 mmol), benzaldehyde **4a** (0.5 g, 4.7 mmol) and acetic acid (5.0 g, 83.3 mmol) yielded the carboline **6n** (0.27 g, 69%) as colourless crystals. The diastereomeric ratio was determined by HPLC to be 72:28. $[\alpha]_D^{22}$ = -171.0° (c= 1.0, $CHCl_3$); m.p.: 110 °C; IR ($CHCl_3$): 3467, 3023, 2964 and 1734 cm^{-1}; 250-MHz ^1H NMR ($CDCl_3$): δ = 7.53-7.49 (m, 1 H, aromatic), 7.40-7.31 (m, 5 H, aromatic and N_a-H), 7.24-7.04 (m, 4 H, aromatic), 6.03-5.90 (m, 1 H, $C\underline{H}$=CH_2), 5.41-5.24 (m, 2H, CH=$C\underline{H}_2$), 5.07 (s, 1 H, CH), 4.67-4.62 (m, 2 H, OCH_2), 3.42-3.33 (m, 2 H, α-H and CH_2), 2.97-2.77 (m, 3 H, CH_2 and CH_2), 1.70-1.44 (m, 3 H, CH_2 and CH), 0.78 (d, J = 6.4 Hz, 3

H, CH_3) and 0.50 (d, 3 H, CH_3); 62.9-MHz-^{13}C NMR ($CDCl_3$): δ = 172.45 (C=O), 140.70, 136.23, 135.76, 132.31, 129.73, 128.59, 128.32, 127.07, 121.37, 119.28, 118.60 (C=$\underline{C}H_2$), 118.15, 110.69, 109.27, 64.79 (OCH_2), 63.09, 58.89, 43.86 (NCH_2), 38.90 (CH_2), 27.13, 24.11, 23.17 (CH_3), 22.37 (CH_2) and 21.66 (CH_3); Anal. calcd. for $C_{26}H_{30}N_2O_2$ (402.5); C 77.58, H 7.51, N 6.96, Found C 77.57, H 7.50, N 6.97.

2-((*S*)-1-Methoxycarbonyl-2-methylbutyl)-1-(*R*)-(2-phenylvinyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6o)

After 20 days at room temperature N-alkylated L-isoleucine methyl ester **3d** (0.2 g, 0.7 mmol), cinnamonaldehyde **4j** (0.2 g, 1.5 mmol) and acetic acid (0.7 g, 11.7 mmol) yielded the carboline **6o** (0.15 g, 53%) as colourless crystals.The diastereomeric ratio was determined by integration of a 400-MHz-^{1}H NMR spectrum to be 86:14. $[\alpha]_D^{22}$ = -213.6° (c= 0.15, $CHCl_3$); m.p.: 174 °C; IR ($CHCl_3$) 3403 and 1721 cm^{-1}; 200-MHz-^{1}H NMR ($CDCl_3$): δ = 7.68-6.83 (m, 10 H, aromatic and N_a-H), 6.17-6.04 (m, 2 H, CH=CH), 4.52 (d, J = 9 Hz, 1 H, CH), 3.76 (s, 3 H, OCH_3), 3.39-3.32 (m, 1 H, CH_2), 3.42 (d, J = 11.0 Hz, 1 H, α-H), 2.89-2.53 (m, 3 H, 2 CH_2), , 2.12-2.09 (m, 1 H, CH_2), 1.85-1.77 (m, 1 H, CH_2), 1.28-1.18 (m, 1 H, β-H), 0.93-0.85 (m, 6 H, 2 CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): 171.87 (C=O), 136.26, 136.13, 134.61, 133.65, 129.72, 128.76, 128.11, 127.45, 126.65, 121.56, 119.39, 118.22, 110.77, 109.14, 67.02 (α-C), 61.74 (C_6H_5-CH), 50.62 (OCH_3), 44.02 (NCH_2), 32.77 (β-C), 24.74 (CH_2), 22.18 (CH_2), 16.08 (CH-$\underline{C}H_3$) and 10.22 (CH_2-$\underline{C}H_3$); Anal. calcd. for $C_{26}H_{30}N_2O_2$ (402.5); C 77.58, H 7.51, N 6.96, Found C 77.96, H 7.66, N 7.08.

2-((*S*)-1-Methoxycarbonyl-2-methylpropyl)-1-methyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6p/7p)

After 2 days at room temperature N-alkylated L-valine methyl ester **3a** (0.3 g, 1.1 mmol), acetaldehyde **4p** (0.5 g, 11.4 mmol) and acetic acid (0.50 g, 8.3 mmol) yielded the carbolines **6p/7p** as a yellow oil (0.27 g, 82%).The diastereomeric ratio was determined by 200-MHz ^{1}H NMR to be 50:50. The products could not be separated by chromatography. 200-MHz ^{1}H NMR ($CDCl_3$): δ = 8.02 (s, 1 H, N_a-H) and 7.90 (s, 1 H, N_a-H), 7.56-7.49 (m, 1 H, aromatic), 7.33-7.02 (m, 3 H, aromatic), 4.24 (q, 1 H, J = 6.7 Hz, CH) and 3.97 (q, 1 H, J = 6.1 Hz, CH), 3.74 (s, 3 H, OCH_3) and 3.43 (s, 3 H, OCH_3), 3.31 (d, J = 10.4 Hz, 1 H, α-H), 3.03 (d, J = 10.1 Hz, 1 H, α-H), 3.41-2.52 (m, 4 H, 2 CH_2), 2.44-2.11 (m, 1 H, β-H), 1.50 (d, J = 6.3, 3 H), 1.39 (d, J = 6.7, 3 H), 1.12 (d, J = 6.7 Hz, 3 H, CH_3), 1.07 (d, 3 H, CH_3) 1.02 (d, 3 H, CH_3) and 0.95 (d, 3 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 174.95 (C=O), 172.18 (C=O), 137.49, 136.62, 135.91, 135.56, 127.24, 127.11, 121.11, 121.03, 119.14, 118.92, 117.91, 117.77, 110.63, 108.63, 107.46, 72.42 (α-C), 67.93 (α-C), 52.06, 50.97, 50.65, 50.06, 43.83 (N-CH_2), 42.84 (N-CH_2), 28.92 (β-C), 27.04 (β-C), 22.00 (CH_2), 20.53 (CH_2), 20.03 (CH_3), 19.87 (CH_3), 19.25 (CH_3), 19.14 (CH_3).

2-((*S*)-1-Methoxycarbonyl-2-methylpropyl)-1-trichloromethyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (6q/7q)

After 11 days at 40 °C N-alkylated L-valine methyl ester **3a** (0.3 g, 1.1 mmol), chloral **4q** (0.5 g, 3.0 mmol) and acetic acid (4.00 g, 66.4 mmol) yielded the carboline **6q/7q** as a yellow oil (0.32 g, 72%).The diastereomeric ratio was determined by 200-MHz ^{1}H NMR to be 60:40. The products could not be separated by chromatography. 200-MHz ^{1}H NMR ($CDCl_3$): δ = 7.59-7.01 (m, 5 H, aromatic), 6.36 (s, 1 H, CH) and 6.32

(s, 1 H, CH), 3.62 (s, 3 H, OCH_3) and 3.54 (s, 3 H, OCH_3), 3.07-2.64 (m, 5 H, 2 CH_2 and α-H), 1.89-1.76 (m, 1 H, β-H), 0.87-0.76 (m, 6 H, CH_3); 50.3-MHz-^{13}C NMR ($CDCl_3$): δ = 174.76 (C=O), 174.47 (C=O), 137.08, 136.23, 127.99, 127.96, 122.17, 121.83, 119.95, 119.07, 118.92, 118.87, 118.65, 113.90, 113.87, 113.08, 111.07, 102.00, 85.52, 85.43, 67.17 (α-C), 67.02 (α-C), 51.46 (OCH_3), 51.36 (OCH_3), 48.30 (N-CH_2), 31.11 (β C), 25.32 (CH_2), 18.95 (CH_3), 18.38 (CH_3) and 18.29 (CH_3).

2-((*S*)-1-Carboxy-3-methylbutyl)-1-(*R*)-phenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (12)

To a solution of allylic ester **6n** (6.73 g, 17.70 mmol) in anhydrous THF (50 ml) tetrakis(triphenylphosphine)-palladium(0) (0.6 g, 0.52 mmol) and then morpholine (17 ml, 0.195 mol) were given under an argon atmosphere and with exclusion of light. After stirring for three days, the solvent was removed *in vacuo*, the residue was taken up in CH_2Cl_2 and extracted with diluted HCl. The organic layer was dried over $MgSO_4$, the solvent evaporated under reduced pressure and the residue was purified by flash chromatography using petroleum ether/ethyl acetate (1:1[v/v]) to provide 5.57 g (92%) of the desired product **12**. The carboxylic acid is sensitive to air and should be stored under nitrogen at -18 °C. $[\alpha]_D^{22}$ = -171.5° (c= 1.0, $CHCl_3$); m.p.: 173 °C; IR ($CHCl_3$): ν 3465 and 1706 cm^{-1}; 250-MHz-^{1}H NMR ($CDCl_3$): δ = 9.45 (br, 1H, COOH), 7.54-7.50 (m, 1 H, aromatic), 7.40-7.33 (m, 5 H, aromatic and N_a-H), 7.10-7.06 (m, 4 H, aromatic), 5.21 (s, 1 H, CH), 3.42-3.36 (m, 2 H, α-CH and CH_2), 2.99-2.80 (m, 3 H, CH_2), 1.73-1.43 (m, 3 H, CH and CH_2), 0.79 (d, J = 6.3 Hz, 3 H, CH_3) and 0.63 (d, 3 H, CH_3); 62.9-MHz-^{13}C NMR ($CDCl_3$): δ = 177.83 (C=O), 139.97, 136.24, 135.12, 129.89, 128.56, 128.43, 126.90, 121.40, 119.23, 118.12, 110.75, 109.03, 62.69 (C_6H_5-CH), 59.19 (α-C), 43.55 (N-CH_2), 38.52 (CH_2), 24.14 (CH), 22.99 (CH_3), 22.05 (CH_3), 21.75 (CH_2); Anal. calcd. for $C_{23}H_{26}N_2O_2$ (362.5); C 76.21, H 7.23, N 7.73, Found C 76.07, H 7.24, N 7.75.

2-((*S*)-1-Carbamoyl-3-methylbutyl)-1-(*R*)-phenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (13)

To a solution of the organic acid **12** (0.6 g, 1.66 mmol) in anhydrous DMF (20 ml) N-(dimethyl-aminopropyl)-N′-ethylcarbodiimide hydrochloride (DEAC) **14** (1.0 g, 5.22 mmol) and N-hydroxy-benzotriazole **15** (0.67 g, 4.96 mmol) were added. The reaction mixture was stirred for 30 minutes and 1 ml of an aqueous solution of NH_3 was injected with a syringe and stirring was continued for 24 h. The solvent was evaporated under reduced pressure, the residue was taken up in 200 ml of CH_2Cl_2 and extracet five times with water (100 ml), the organic layer was dried over $MgSO_4$, concentrated *in vacuo* and the residue was purified by flash chromatography using petroleum ether/ethyl acetate (2/1 [v/v]) to yield 0.6 g (quant.) of the amide **13**. $[\alpha]_D^{22}$ = -108.4° (c= 1.0, $CHCl_3$); m.p.: 161 °C; IR ($CHCl_3$): 3172 and 1669 cm^{-1}; 250-MHz-^{1}H NMR ($CDCl_3$): δ = 7.54-7.50 (m, 1 H, aromatic), 7.39-7.33 (m, 5 H, aromatic and N_a-H), 7.18-7.07 (m, 4 H, aromatic), 5.49 (br, 2H, NH_2), 5.03 (s, 1 H, CH), 3.50-3.41 (m, 1 H, CH_2), 3.20 (t, J = 6.7 Hz, 1 H, α-CH), 3.03-2.86 (m, 3 H, CH_2), 1.73-1.43 (m, 3 H, CH and CH_2), 0.83 (d, J = 6.3 Hz, 3 H, CH_3) and 0.65 (d, 3 H, CH_3); 62.9-MHz-^{13}C NMR ($CDCl_3$): δ = 175.17 (C=O), 140.89, 136.18, 135.17, 129.14, 128.68, 128.18, 126.96, 121.24, 119.09, 118.09, 110.73, 109.07, 62.29 (C_6H_5-CH), 60.13 (α-C), 43.41 (N-CH_2), 39.17 (CH_2), 24.36, 22.97, 22.13, 21.92 (CH_2); Anal. calcd. for $C_{23}H_{27}N_3O$ (361.5); C 76.42, H 7.53, N 11.62, Found C 76.22, H 7.56, N 11.54.

2-((*S*)-1-Cyano-3-methylbutyl)-1-(*R*)-phenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (16)

A solution of the amide **13** (0.48 g, 1.33 mmol) and triethylamine (0.4 ml, 2.86 mmol) in dry CH_2Cl_2 (50 ml) was cooled to 0 °C and treated with trifluoroacetic anhydride (0.2 ml, 1.41 mmol). The mixture was warmed to ambient temperature, stirred for 2 hours and extracted with a sat. solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* (bath temperature < 30 °C). Recrystallization of the residue from ether/petroleum ether afforded 0.36 g (79%) of the cyanide **16**.$[\alpha]_D^{22}$ = -165.6° (c= 1.0, $CHCl_3$); m.p.: 138 °C; IR ($CHCl_3$): 3058 and 2218 cm^{-1}; 250-MHz-^{1}H NMR ($CDCl_3$): δ =7.54-7.51 (m, 1 H, aromatic), 7.37 (s, 5 H, aromatic), 7.20-7.08 (m, 4 H, aromatic and N_a-H), 4.77 (s, 1 H, CH), 3.61 (t, J = 6.7 Hz, 1 H, α-CH), 3.36-3.30 (m, 1 H, CH_2), 3.13-2.81 (m, 3 H, CH_2), 1.79-1.56 (m, 3 H, CH and CH_2), 0.78 (d, J = 6.3 Hz, 3 H, CH_3) and 0.60 (d, 3 H, CH_3); 62.9-MHz-^{13}C NMR ($CDCl_3$): δ = 139.18, 136.32, 134.26, 129.31, 129.07, 129.03, 126.79, 121.76, 119.51, 118.30, 117.64, 110.86, 108.83, 64.36 (C_6H_5-CH), 50.85 (α-C), 44.68 (N-CH_2), 40.24 (CH_2), 24.30 (CH), 22.44 (CH_3), 21.67 (CH_2), 21.48 (CH_3); Anal. calcd. for $C_{23}H_{25}N_3$ (343.5); C 80.43, H 7.34, N 12.23, Found C 80.36, H 7.34, N 12.22.

1-(*R*)-Phenyl-1,2,3,4-tetrahydro-ß-carboline (18)

A solution of the α-amino nitrile **16** (0.5 g, 1.52 mmol) in 50 ml methanol and 30 ml 2N HCl was heated for 20 hours at 60 °C. The reaction mixture was extracted with 50 ml diethyl ether/petroleum ether (v/v), the pH of the aqueous layer was adjusted to 11 with 1N NaOH. After extraction with 100 ml CH_2Cl_2 the organic layer was dried with $MgSO_4$, the solvent was removed *in vacuo* and the residue purified by flash chromatography (CH_2Cl_2/methanol (20:1 [v/v]) to yield the tetrahydro-β-carboline **18** (0.29 g, 77%). $[\alpha]_D^{22}$ = -4.5° (c= 1.0, $CHCl_3$); m.p.: 167 °C; IR ($CHCl_3$): 3143, 2920 and 1454 cm^{-1}; 250-MHz-^{1}H NMR ($CDCl_3$): δ =7.90 (br, 1 H, N_a-H), 7.54-7.51 (m, 1 H, aromatic H), 7.32-7.20 (m, 5 H, aromatic H), 7.11-7.07 (m, 3 H, aromatic H), 5.05 (m, 1 H, CH), 3.34-3.25 (m, 1 H, N-CH_2), 3.12-3.01 (m, 1 H, N-CH_2), 2.94-2.75 (m, 2 H, CH_2), 1.92 (br, 1 H, N_b-H); 62.9-MHz-^{13}C NMR ($CDCl_3$): δ = 142.40, 136.52, 135.04, 129.42, 129.19, 128.81, 127.96, 122.30, 119.95, 118.83, 111.49, 110.77, 58.64 (CH), 43.37 (NCH_2) and 23.11 (CH_2); $C_{17}H_{16}N_2$ requires (248.1313). Found 248.1300.

(1 R), 2-((2 R)-2-Methoxy-2-trifluoro-phenylacetyl)-1-phenyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole (20)

A solution of tetrahydro-β-carboline **18** (80 mg, 0.32 mmol) and triethylamine (0.10 g, 1.0 mmol) in dry CH_2Cl_2 (20ml) was cooled to 0 °C and treated with *(R)*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride **19** (81 mg, 0.35 mmol). The reaction mixture was warmed to ambient temperature, stirred for 4 hours, extracted with aqueous HCl and with sat. aqueous $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (petroleum ether/ethyl acetate (4:1 [v/v]) of the residue provided the amide **20** (0.13 g, 87%) as colourless crystals. $[\alpha]_D^{22}$ = -114.2° (c= 0.8, $CHCl_3$); m.p.: 265 °C; IR ($CHCl_3$): 3391, 2941 and 1650 cm^{-1}; 250-MHz-^{1}H NMR ($CDCl_3$): δ =7.88 (br, 1 H, N_a-H), 7.56-7.53 (m, 2 H, aromatic H), 7.42-7.05 (m, 13 H, aromatic H and CH), 4.22 (dd, J = 5.2, 14.12 Hz, H, N-CH), 3.38 (s, 1H, OCH_3), 3.21 (td, J = 4.2, 13.1 Hz, 1 H, N-CH_2), 2.23 (dd, 3.4, 15.7 Hz, 1 H, CH_2), 1.50-1.40 (m, 1 H, CH_2); 62.9-MHz-^{13}C NMR ($CDCl_3$): δ = 165.22 (C=O), 139.74, 136.49, 134.05, 130.49, 129.46, 128.77, 128.62, 128.45, 126.77, 126.36, 126.24, 122.24, 119.48, 118.14, 111.37, 109.47, 84.67 (q, CF_3), 55.32 (CH),

52.47 (OCH_3), 38.55 (NCH_2) and 19.89 (CH_2); Anal. calcd. for $C_{27}H_{23}N_2O_2F_3$ (464.5); C 69.82, H 4.99, N 6.03, Found C 69.88, H 5.00, N 5.98.

Acknowledgement: This research was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

References and Notes

1. Whaley, W. M.; Govindachari, T. R. *Organic Reactions*; Wiley and Sons: New York, 1951, 6, pp. 151-206.
2. a) Czarnocki, Z.; MacLean, D. B.; Szarek, W. A. *Bull. Soc. Chim. Belg.* **1986**, 95, 749-770, and refs given; b) Melnyk, P.; Ducrot, P.; Thal, C. *Tetrahedron* **1993**, 49, 8589-8596.
3. a) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Morgan, K.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc., Perkin Trans., 1* **1993**, 431-439, and refs given.; b) Deng, L.; Czerwinski, K.; Cook, J. M. *Tetrahedron Lett.* **1991**, 32, 175-178, and refs given; c) Massiot, G; Mulumba, T. *J. Chem. Soc., Chem. Commun.* **1983**, 1147-1149; d) Peng, S.; Winterfeldt, E. *Liebigs Ann. Chem.* **1990**, 313-318; e) Zhang, L.-H.; Bi, Y.-Z.; Yu, F.-X.; Menzia, G.; Cook, J. M. *Heterocycles* **1992**, 34, 517-547.
4. a) Bohlmann, C.; Bohlmann, R.; Rivera, E. G.; Vogel, C.; Manandhar, M. D.; Winterfeldt, E. *Liebigs Ann. Chem.* **1985**, 1752-1763.; b) Comins, D. L.; Badawi, M. M. *Tetrahedron Lett.* **1991**, 32, 2995-2996; c) Amann, R.; Spitzner, D. *Angew. Chem.* **1991**, 103, 1373-1374; *Angew. Chem. Int. Ed. Engl.* **1991**, 103, 1320-1321.
5. Use of amino acid esters as chiral auxiliaries in a) carbo Diels-Alder reactions: Waldmann, H. *J. Org. Chem.* **1988**, 53, 6133-6136; *Liebigs Ann. Chem.* **1990**, 671-680; b) aza Diels-Alder reactions: Review: Waldmann, H. *Synthesis*, in press; Waldmann, H. *Angew. Chem.* **1988**, 100, 307-308; *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 274-275; *Liebigs Ann. Chem.* **1989**, 231-238; Waldmann, H.; Braun, M.; Dräger, M. *Angew. Chem.* **1990**, 102, 1445-1447; *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 1468-1471; *Tetrahedron: Asymmetry* **1991**, 2, 1231-1246; Waldmann, H.; Braun, M. *Liebigs Ann. Chem.* **1991**, 1045-1048; c) Mannich reactions: Waldmann, H.; Braun, M.; Dräger, M. *Angew. Chem.* **1990**, 102, 1445-1447; *Angew. Chem. Int. Ed. Engl.* **1990**, 102, 1468-1471; *J. Org.Chem.* **1992**, 57, 4444-4451; d) 1,3-dipolar cycloadditions: Waldmann, H. *Liebigs Ann. Chem.* **1990**, 1013-1017; Waldmann, H.; Bläser, E.; Jansen, M.; Letschert, H.-P. *Angew. Chem.* **1994**, 106, 717-719; *Angew. Chem. Int. Ed. Engl.* **1994**, 106, 683-685; e) radical reactions: Waldmann, H. *Synlett* **1990**, 627-628; *Liebigs Ann. Chem.* **1991**, 1317-1322; Reviews: Waldmann, H.; Braun, M. *Gazz. Chim. Ital.* **1991**, 121, 277-284; Waldmann, H. *Kontakte* **1993**, 1, 58-71; *Kontakte* **1993**, 2, 34-45; Waldmann H. *Synlett*, in press.
6. Part of this work has been published as a preliminary communication: Waldmann, H.; Schmidt, G.; Jansen, M.; Geb, J. *Tetrahedron Lett.* **1993**, 34, 5867-5870.
7. Hoskins, T.; Shimodaira, K. *Liebigs Ann. Chem.* **1935**, 520, 19-30.

8. Marshall, J. A.; Cleary, D. G. *J. Org. Chem.* **1986**, 51, 858-863.
9. Bailey, P. D.; Hollinshead, S. P.; McLay, N. R. *Tetrahedron Lett.* **1987**, 28, 5177-5180.
10. Bailey, P. D. *Tetrahedron Lett.* **1987**, 28, 5181-5184.
11. Deng, L.; Czerwinski, K.; Cook, J. M. *Tetrahedron Lett.* **1991**, 32, 175-178.
12. Ungemach, F.; DiPierro, M.; Weber R.; Cook, J. M. *J. Org. Chem.* **1981**, 46, 164-168.
13. Anh, N. T. *Top. Curr. Chem.* **1980**, 88, 145-162.
14. Yamada, S.; Akimoto, H. *Tetrahedron Lett.* **1969**, 3105-3108.
15. Friedrich-Bochnitschek, S.; Waldmann, H.; Kunz, H. *J. Org. Chem.* **1989**, 54, 751-756.
16. Chen, S. T.; Wu, S. H.; Wang, K. T. *Synthesis* **1989**, 37-38.
17. Furher details of the X-ray analysis are available from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, W-76344 Eggenstein-Leopoldshafen 2, by referring to the registration number CSD-57243, the authors and this paper.

(*Received in Germany* 20 *June* 1994; *revised* 22 *August* 1994; *accepted* 25 *August* 1994)