Asymmetric Control in the Pictet–Spengler Reaction by Means of *N*-Protected Amino Acids as Chiral Auxiliary Groups

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Abstract: Aromatic and aliphatic Schiff bases of tryptamine react with Fmoc- or phthaloyl-protected amino acid chlorides to form *N*-acyliminium intermediates, which, in the presence of titanium alkoxides at room temperature, undergo Pictet–Spengler reactions to give tetrahydro-β-carbolines with diastereomeric ratios of up to 99:1. The chiral auxiliary can be removed from the Pictet–Spengler adducts by means of a simple reduction. To rationalize the observed stereoselectivity a transition-state model is proposed in which the titanium atom coordinates both the carbonyl group of the *N*-acyliminium ion and the amino acid protecting group.

Keywords
amino acids · asymmetric syntheses · carbolines · chiral auxiliaries · Pictet Spengler reaction

Introduction

Various naturally occurring alkaloids of the tetrahydroisoquinoline and β-carboline type have interesting physiological and pharmaceutical effects and are used for medicinal purposes. To synthesize these chiral *N*-heterocycles and their analogues with modified biological properties, efficient methods for the construction of the underlying heterocyclic framework in enantiomerically pure form are needed. One of the most important synthetic methods for this purpose, which has been successfully employed in numerous alkaloid syntheses, is the Pictet–Spengler reaction,[1] that is, the formation of a heterocycle by intramolecular attack of an electron-rich aromatic ring on the C=N double bond of a Schiff base derived from an arylethylamine and an aldehyde. In the light of the prominent position that the Pictet–Spengler reaction occupies in heterocycle chemistry, the development of methods that allow direction of the steric course of this transformation is of great interest to organic synthesis in general and to heterocyclic and medicinal chemistry in particular. It is, therefore, surprising, that the use of chiral auxiliary groups, which can be removed after reaction, for this important transformation has been investigated in only a few cases and with rather limited success.[2] We now report that *N*-protected amino acids are efficient chiral auxiliaries for Pictet–Spengler reactions with aromatic or aliphatic Schiff bases derived from tryptamine.[3]

In the context of a program directed at the use of the readily accessible amino acid esters as chiral mediators of selectivity in the asymmetric synthesis of carbo- and heterocycles,[4] we had found that these auxiliaries can also be employed to direct the steric course of the Pictet–Spengler reaction.[5] In the method developed *N*-alkyliminium intermediates are generated in situ from indolylethyl-substituted amino acid esters and aldehydes. The subsequent cyclization of these only weakly activated electrophiles unfortunately is rather slow. Consequently, only aromatic aldehydes give preparatively useful results; aliphatic carbonyl compounds undergo competitive self-aldolization and further undesired side reactions, and cannot be employed in this synthetic method. In addition, to remove the amino acid ester auxiliary from the cyclization products, the chemically very stable bond between the amino acid nitrogen and the α-carbon has to be broken by a laborious multistep sequence.

To overcome these drawbacks we reasoned that the intermediate generation of *N-acyl*iminium ions instead of *N-alkyl*iminium intermediates might provide a solution to the difficulties encountered. On the one hand, the electron-withdrawing effect of the *N*-acyl group should greatly enhance the electrophilicity of the iminium intermediates[6] and lead to a rapid cyclization. On the other, the chiral auxiliary would be linked to the resulting tetrahydro-β-carboline system by an amide bond, which should be cleavable by hydrolysis or reduction in a single step.

Results and Discussion

In our initial experiments aimed at steric control in the Pictet–Spengler reaction, Fmoc- and Z-protected prolines were investigated as chiral auxiliary groups, since proline had been found to be a superior mediator of chirality in asymmetric Diels–Alder reactions[7] and 1,3-dipolar cycloadditions[8] than amino acids carrying sterically demanding side chains. To generate the iminium intermediates **3**, the imines **1**, obtained from tryptamine and the aldehyde in the presence of a dehydrating agent, were treated with the *N*-protected acid chlorides **2**[9] in the presence of a

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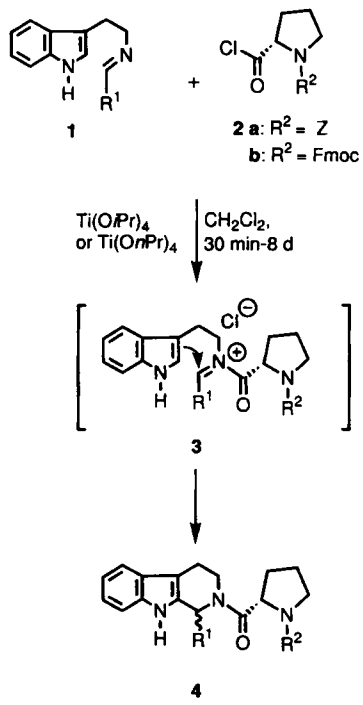


Scheme 1. Asymmetric Pictet–Spengler cyclizations employing *N*-protected proline derivatives as chiral auxiliary groups (Fmoc: 9-fluorenylmethoxycarbonyl, Z: benzyloxycarbonyl).

base or a Lewis acid, or without any further additive (Scheme 1). The electron-rich aromatic ring in **3** then attacked the $C=N^+$ double bond to give the desired tetrahydro-β-carbolines **4**. Whereas this transformation proceeded smoothly in the presence of pyridine, the use of strong Lewis acids like $TiCl_4$ or $EtAlCl_2$ resulted in the formation of complex reaction mixtures. The highest selectivities and yields were, however, recorded in the presence of titanium alkoxides. Aliphatic imines underwent the Pictet–Spengler cyclization at -16 to 25 °C within several hours to yield the heterocycles **4** in moderate yields and with isomeric ratios of between 60:40 and 89:11 (Table 1). The absolute configuration of the major diastereomer was not determined (vide infra).

The diastereoselectivity depends only to a minor extent on the size of the aldehyde substituent R^1 (Table 1, entries 5 and 8).

Table 1. Results of the Pictet–Spengler reactions employing Z- or Fmoc-proline as chiral auxiliary groups.

No.	4	R^1	R^2	T/°C	Lewis acid/Base	Yield [%] [a]	d.r. [b]
1	a	*i*Pr	Z	−16	–	58	81:19
2	a	*i*Pr	Z	0 → 25	pyridine	41	82:18
3	a	*i*Pr	Z	−16	$Ti(OiPr)_4$	60	84:16
4	a	*i*Pr	Z	25	$Ti(OiPr)_4$	50	84:16
5	a	*i*Pr	Z	25	$Ti(OnPr)_4$	50 [c]	89:11
6	b	*t*Bu	Z	−16	–	38	87:13
7	b	*t*Bu	Z	25	–	37	82:18
8	b	*t*Bu	Z	25	$Ti(OnPr)_4$	57	88:12
9	c	Ph	Z	25	$Ti(OnPr)_4$	28	60:40
10	d	*i*Pr	Fmoc	25	$Ti(OnPr)_4$	96	84:16
11	d	*i*Pr	Fmoc	25	–	88	78:22

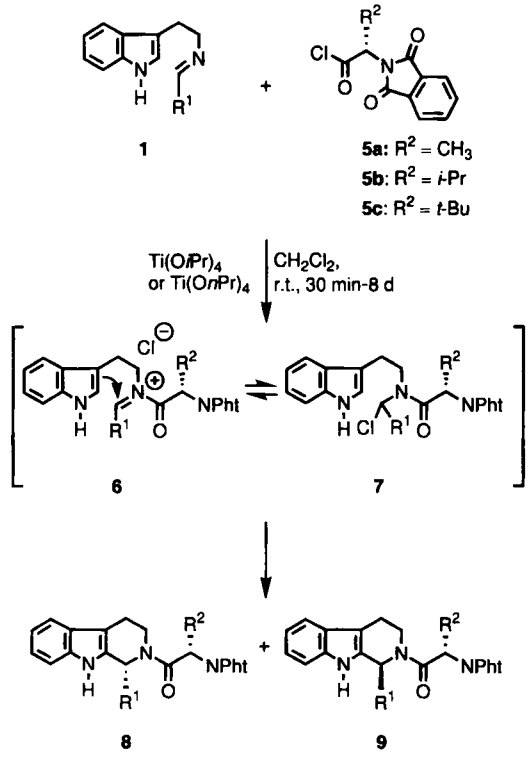
[a] The yields are based on diastereomeric mixture **4**. [b] Diastereomeric ratios determined from the crude reaction mixture by HPLC. [c] Yield of the pure diastereomer.

The use of the *N*-terminal Z protecting group resulted in a small but significant increase in the isomeric ratio (entries 5 and 10). $Ti(OnPr)_4$ gave slightly better results than $Ti(OiPr)_4$ (entries 4 and 5). Decreasing the reaction temperature does not increase the stereoselectivity (entries 3 and 4). In general, the isomeric ratio was lower when the Pictet–Spengler reaction was performed without addition of a Lewis acid (cf. entries 1, 2, and 7 with entries 5 and 8). The tetrahydro-β-carboline **4c** derived from benzaldehyde was obtained with a markedly lower selectivity than its aliphatic analogues (entry 9).

Overall, the use of a proline-derived chiral auxiliary led to only moderate levels of stereoselectivity and, in addition, the Pictet–Spengler adducts **4** were obtained as diastereomeric mixtures that could not be separated by crystallization or by means of chromatographic techniques.

In order to investigate whether the use of bulky amino acids with sterically more demanding side chains (e.g., *i*Pr in valine or *t*Bu in *tert*-leucine) would lead to more efficient stereodiscrimination, *N*,*N*-phthaloyl-protected amino acids were chosen as chiral auxiliary groups. The phthaloyl group is readily introduced by treatment of the amino acids with *N*-ethoxycarbonylphthalimide.[10] The acid chlorides of phthaloyl-protected amino acids are not prone to racemization[11] and can be generated in a straightforward manner by activation of the carboxylic acids with thionyl chloride.

Two equivalents of the activated amino acid derivatives was treated with two equivalents of a titanium alkoxide in methylene chloride at room temperature followed by one equivalent of the Schiff base. The tetrahydro-β-carbolines **8** and **9** were obtained in satisfactory yields and with excellent stereoselectivity (Scheme 2, Table 2).



Scheme 2. Asymmetric Pictet–Spengler cyclizations employing *N*,*N*-phthaloyl amino acids as chiral auxiliaries.

Lowering the temperature to −40 °C reduces the rate of reaction, but does not improve the diastereoselectivity. The ring closure reaction presumably proceeds by attack of the indole nucleus on the $C=N^+$ double bond of the *N*-acyliminium intermediates **6**, which are formed in situ from the acid chlorides **5** and the imines **1**. It is generally believed that the Pictet–Spengler cyclization to give tetrahydro-β-carbolines proceeds by attack of C-3 of the indole on the $C=N^+$ bond giving rise to a spiro intermediate.[11] Although we share this opinion, we could not find any evidence for this pathway in the reaction studied, and we therefore cannot rule out an alternative mechanism that involves the direct attack of C-2 on the iminium ion. Whereas

Table 2. Results of the Pictet-Spengler reactions employing *N,N*-phthaloyl amino acids as chiral auxiliary groups.

No.	8	R^1	R^2	Lewis acid	Yield [%] [a]	8:9 [b]
1	a	Ph	Me	Ti(O*n*Pr)$_4$	30	84:16
2	b	Ph	*i*Pr	Ti(O*n*Pr)$_4$	52	90:10
3	b	Ph	*i*Pr	Ti(O*i*Pr)$_4$	58	96:4
4	c	Ph	*t*Bu	Ti(O*n*Pr)$_4$	60	>99:1
5	d	4-NO_2-C_6H_4	*i*Pr	Ti(O*n*Pr)$_4$	56	86:14
6	d	4-NO_2-C_6H_4	*i*Pr	Ti(O*i*Pr)$_4$	58	81:19
7	e	4-NO_2-C_6H_4	*t*Bu	Ti(O*n*Pr)$_4$	54	93:7
8	e	4-NO_2-C_6H_4	*t*Bu	Ti(O*i*Pr)$_4$	48	82:18
9	f	4-Cl-C_6H_4	*t*Bu	Ti(O*n*Pr)$_4$	44	89:11
10	f	4-Cl-C_6H_4	*t*Bu	Ti(O*i*Pr)$_4$	60	96:4
11	g	Me	*i*Pr	Ti(O*n*Pr)$_4$	31	83:17
12	g	Me	*i*Pr	Ti(O*i*Pr)$_4$	33	85:15
13	h	Me	*t*Bu	Ti(O*n*Pr)$_4$	66	96:4
14	h	Me	*t*Bu	Ti(O*i*Pr)$_4$	50	89:11
15	i	Et	*i*Pr	Ti(O*n*Pr)$_4$	57	97:3
16	i	Et	*i*Pr	Ti(O*i*Pr)$_4$	58	87:13
17	j	Et	*t*Bu	Ti(O*n*Pr)$_4$	59	95:5
18	k	*i*Pr	*i*Pr	Ti(O*n*Pr)$_4$	99	>99:1
19	k	*i*Pr	*i*Pr	- [d]	55 [c]	84:16
20	l	*i*Pr	*t*Bu	Ti(O*n*Pr)$_4$	52	84:16

[a] The yields are based on pure diastereomer **4**. [b] Determined from the crude reaction mixture by HPLC. [c] Yield of the diastereomeric mixture. [d] 1 equiv of NEt_3 was added as acid scavenger.

the reactions employing aliphatic imines are complete within several minutes, 8 to 9 days is required for aromatic Schiff bases. This may be explained by the resonance stabilization of the iminium intermediates in the latter case. Furthermore, ^{1}H NMR spectroscopic investigations by Bolognese et al. on the reaction between benzalanilines and phenylacetyl chloride suggest that, in the case of aromatic Schiff bases, the equilibrium between the iminium species **6** and the α-chloroalkylamines **7**, formed by addition of the chloride anion to the C=N$^+$ bond, is shifted towards the amines **7**.[12] Consequently, the concentration of the iminium intermediates **6**, which are prone to cyclization, decreases. Most of the aliphatic and aromatic imines afforded the Pictet-Spengler adducts in yields of 50-60% (see entries 3, 4, 7, 10, 13, 17, and 18 in Table 2); however, in the cases of 2-methoxy- and 2-nitrobenzylidenetryptamine and when α,β-unsaturated Schiff bases were employed, the desired heterocycles could not be isolated. To reach yields of 50-60% the use of the titanium alkoxide was essential; otherwise, significantly less product was formed. The major diastereomers were readily isolated from the product mixtures by simple flash chromatography and recrystallizaton from ether/*n*-hexane or ethyl acetate/*n*-hexane. Crystals suitable for X-ray structure analysis were obtained for the tetrahydro-β-carboline **8d** (R^1 = *p*-NO_2-C_6H_4-, R^2 = *i*Pr; Fig. 1; see the Experimental Procedure), and this enabled a rigorous determination of the configuration of the newly formed stereocenter.

The stereoselectivity observed in the Pictet-Spengler cyclizations employing the phthaloyl-protected amino acid chlorides **5** depends markedly on the steric demand of the amino acid side chain, the nature of the imine substituent, and the alcohol incorporated into the titanium Lewis acid. With aromatic imines, the diastereomeric ratio increases with the size of the amino acid side chain. For instance, the sterically less demanding alanine acid chloride **5a** gave a **8a**:**9a** ratio of 84:16 (Table 2, entry 1), whereas **8a**:**9a** ratios ranging from 90:10 to >99:1 were obtained with the analogous valine and *tert*-leucine derivatives (entries 2-4). With all aromatic Schiff bases the highest ratios were recorded with the *tert*-leucine-based chiral auxiliary (entries 4, 7, and 10). The same observation was made for aliphatic

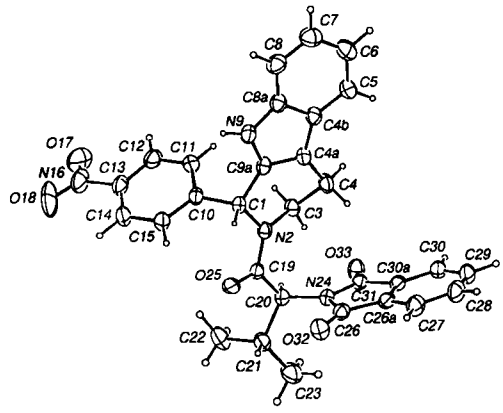


Fig. 1. Structure of the Pictet-Spengler adduct **8d** determined by X-ray analysis (see Experimental Procedure for details).

electrophiles with small aliphatic substituents (e.g., methyl; entries 11 and 13). However, for larger alkyl substituents this trend was reversed. For instance, already in the case of the ethyl-substituted imine **1i** (R^1 = Et), the result for the valine-derived auxiliary (**8i**:**9i** = 97:3, entry 15) was better than that for the *tert*-leucine-derived auxiliary (**8j**:**9j** = 95:5; entry 17). In the case of the isopropyl-substituted Schiff base **1k** (R^1 = *i*Pr), the phthaloyl-protected valine was a much more efficient auxiliary (**8k**:**9k** > 99:1, entry 18) than the *tert*-leucine derivative (**8l**:**9l** = 84:16, entry 20).

To reach a high level of diastereoselectivity the presence of titanium alkoxides is necessary. This is highlighted by the observation that for the valine derivative **8k** the isomeric ratio dropped from >99:1 to 84:16 when titanium tetra-*n*-propylate was omitted (Table 2, entries 18 and 19). The size of the alkyl groups of the titanium Lewis acids employed can have a distinct influence on the diastereoselectivity. Thus, for Pictet-Spengler reactions with aliphatic Schiff bases, titanium tetra-*n*-propylate gave better results than the isopropylate (entry 13 vs. 14 and 15 vs. 16). With aromatic imines, this trend persisted in some cases (entries 7 and 8), but, at least for the *p*-chlorobenzaldimine, the more bulky isopropylate gave a higher ratio (entries 9 and 10).

To explain the observed efficiency and direction of the stereoselection several factors must be considered, namely, the configuration of the C=N$^+$ double bond, the cisoid or transoid conformation of the 1-oxa-3-azabutadiene system in the *N*-acyliminium intermediate **6**, and the preference for attack on the *Re* or *Si* faces of the double bond. Concerning the configuration of the C=N$^+$ double bond, we assume that (*Z*)-isomer **11** is energetically more favorable than the (*E*)-isomer **10** (Scheme 3), in accord with the analysis of Cook et al.[13] (see also ref. [1b, 5]). In **10** destabilizing interactions of the imine substituent R^1 may occur with the aromatic ring and, upon ring closure, with the ethylene bridge to the indole nucleus. These interactions are absent in **11** and, consequently, the Pictet-Spengler cyclization is expected to proceed via the (*Z*)-isomer **11**.

We assume that in the course of the reaction the titanium alkoxide coordinates to the carbonyl oxygen atoms of the amino acid and the phthaloyl group to give rise to octahedral complexes (e.g., **12**, **13**, and **14**; Scheme 3). In **12** the acyliminium system, which can be regarded as a 1-oxa-3-azabutadiene, adopts a *trans* conformation whereas **13** and **14** are *cis* isomers. Intermediate **12** is disfavored owing to steric interactions between the imine substituent R^1 and the α-substituents of the amino acid side chain. This is avoided in the *cis* arrangements present in **13** and

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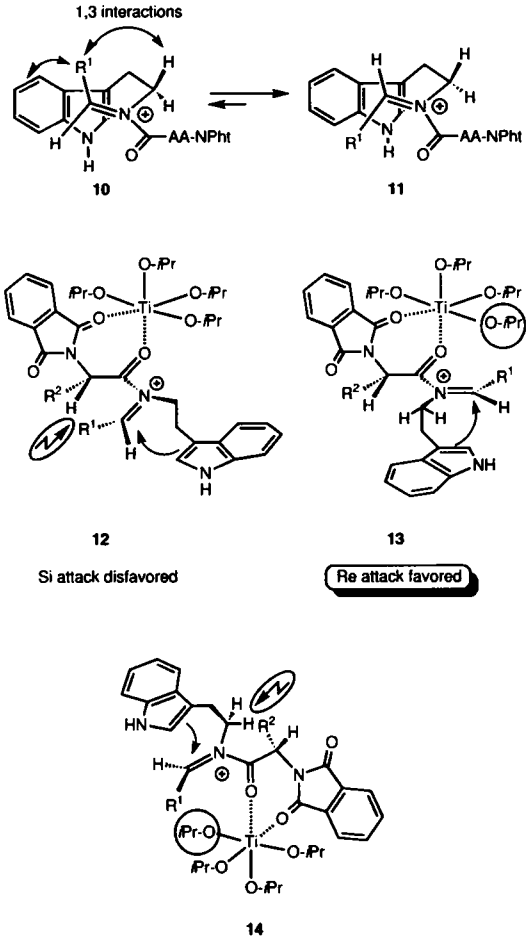
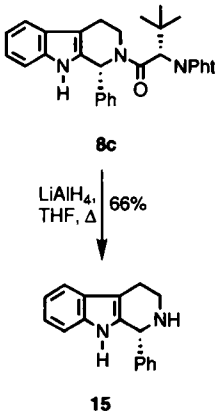


Scheme 3. Possible transition states of the Pictet–Spengler reaction.

14. In these complexes opposite diastereotopic faces of the $C=N^+$ double bond are shielded by a substituent of the activating Lewis acid. A similar situation has been observed for $TiCl_4$-mediated Diels–Alder reactions of α,β-unsaturated proline ester amides.[7] In **13** the bulky amino acid side chain R^2 points away from the ethylene bridge between the indole nucleus and the iminium nitrogen, whereas these two functional groups are in close proximity in **14**, creating unfavorable steric interactions. Therefore, the reaction is expected to proceed via arrangement **13**; this explains correctly the predominant formation of the major diastereomers **8**.



Scheme 4. Removal of the chiral auxiliary from the Pictet–Spengler adduct **8c**.

The chiral auxiliary can readily be removed from the Pictet–Spengler adducts **8** by cleavage of the amide bond with reducing agents. In a representative experiment the enantiomerically pure phenyl-substituted tetrahydro-β-carboline **15** was obtained in a single step by treatment of the amide **8c** with $LiAlH_4$ in refluxing THF (Scheme 4). The use of other reducing agents like aluminum hydride, triethoxyaluminum hydride, or Red-Al® was less efficient and all attempts to hydrolyze the amide bond under acidic or basic conditions, including the use of hydrazine, were unsuccessful.

Conclusion

The *N*,*N*-phthaloyl amino acids are the first generally applicable chiral auxiliary groups for the Pictet–Spengler reaction that efficiently control the stereochemical course of this important transformation of alkaloid and heterocycle chemistry. They allow access to the desired heterocycles in high diastereomeric ratios, with aliphatic or aromatic aldehydes as starting materials, and can be removed by means of a simple method.

Experimental Procedure

General: All melting points were recorded on a Büchi melting point apparatus and are uncorrected. Infrared spectra were taken with a Bruker IFS88 spectrometer. Proton and carbon NMR spectra were measured on a Bruker AC-250 and a Bruker AM-400 spectrometer. Chemical shifts are expressed in ppm downfield relative to tetramethylsilane as an internal standard. Specific optical rotation values were determined on a Perkin–Elmer polarimeter 241. Elemental analyses were performed on an Elementar CHN-Rapid analyzer. 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 250 × 4 mm column, a LiChrospher 60 RP-select B 125 × 4 mm column, various mixtures of methanol/water (*v*/*v*), and a solvent flow rate of 0.6 mL min^{-1}.

Materials: Tryptamine was purchased from Fluka and $LiAlH_4$ as a 1 M solution in THF from Aldrich. The Schiff bases were prepared by condensation of tryptamine with the aldehydes in the presence of magnesium sulfate in dichloromethane. Filtration, followed by evaporation of the solvent in vacuo afforded the imines as yellowish oils or crystals. The solid imines were recrystallized from diethyl ether/*n*-hexane. *N*,*N*-Phthaloyl-protected amino acids were prepared using *N*-(ethoxycarbonyl)phtalimide according to the method of McArthur et al. [10]. Fmoc- and Z-proline were prepared by the method of Carpino et al. and Sheehan et al., respectively [14]. The amino acid chlorides were obtained by treatment of the amino acids with thionyl chloride/DMF according to the method of Perlow et al. [15].

General Procedures for the Preparation of the Tetrahydro-β-carbolines (4):

Procedure A: To a stirred solution of amino acid chloride **2** (2 equiv) in dry dichloromethane (50 mL) was added dropwise titanium alkoxide (2 equiv), and after 5 min a solution of the Schiff base (1 equiv) in dichloromethane (15 mL) at the temperature given in Table 1. Stirring was continued in the case of aliphatic Schiff bases for 5 min to 15 h and for the aromatic Schiff bases for 8–9 d. Merck silica gel (20 g), grade 60 (35–70 mesh ASTM), was then added, the solvent removed in vacuo, and the solid residue chromatographed on silica gel with mixtures of EtOAc/*n*-hexane as eluent. The diastereomeric ratios of the products were determined by hplc using samples that were directly taken from the crude reaction mixtures. The reaction conditions as well as the results are given in Table 1.

Procedure B: To a stirred solution of amino acid chloride **2** (0.3 g, 1 equiv) in dry dichloromethane (50 mL) was added dropwise a solution of the Schiff base (1 equiv) in dichloromethane (15 mL) at the temperature given in Table 1. Workup was as described for procedure A.

1-Isopropyl-2-Z-prolyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (4a): M.p. 164 °C; $[\alpha]_D^{22} = -55.6$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.56$ (s, 1H, NH), 7.45–7.29 (m, 7H, aryl), 7.14–7.05 (m, 2H, aryl), 5.51 (d, $^3J(H,H) = 7.9$ Hz, 1H, NCH), 5.32–4.95 (m, 2H, OCH_2), 4.91–4.86 (m, 1H, α-CH), 4.32–4.19 (m, 1H, NCH_2), 3.68–3.42 (m, 3H, NCH_2), 2.84–2.78 (m, 2H, CH_2), 2.17–1.83 (m, 5H, CH and CH_2), 1.15 (d, $^3J(H,H) = 6.6$ Hz, 3H, CH_3), 1.05 (d, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 171.17$ (C=O), 154.51 (C=O), 136.74, 135.97, 134.20, 128.36, 128.04, 127.69, 126.37, 121.53, 119.14, 117.64, 111.12, 106.57, 66.85 (CH_2), 57.17 (CH), 55.15 (CH), 46.66 (CH_2), 40.10 (CH_2), 33.03 (CH), 32.91 (CH_2), 24.38 (CH_2), 22.48 (CH_2), 19.86 (CH_3), 19.77 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu} = 3284$ (N–H), 1702 (C=O), 1640 (C=O); $C_{27}H_{31}N_3O_3$ (445.6): calcd C 72.78, H 7.01, N 9.43; found C 72.81, H 7.07, N 9.27.

1-(2,2)-Dimethylethyl-2-Z-prolyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (4b): ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 8.51$ (s, 1H, NH), 7.45–7.18 (m, 7H, aryl), 7.14–7.05 (m, 2H, aryl), 5.13 (s, 1H, NCH), 5.38–4.70 (m, 3H, OCH_2 and α-CH), 4.23–4.00 (m, 1H, NCH_2), 3.82–3.50 (m, 3H, NCH_2), 2.84–2.71 (m, 2H, CH_2), 2.30–1.71 (m, 4H, CH_2), 1.06 (s, 9H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 171.79$ (C=O), 154.47 (C=O), 136.87, 136.12, 132.65, 128.38, 128.10, 127.68, 126.35, 121.75, 119.28, 117.61, 111.08, 108.29, 66.83 (CH_2), 57.47 (CH), 57.23 (CH), 46.90 (CH_2), 40.82 (CH_2), 37.34 (C), 30.46 (CH_3), 28.20 (CH_3), 24.29 (CH_2), 22.24 (CH_2); MS (70 eV, EI): *m*/*z* (%): 459.3 (5.4) [M^+], 91 (100) [$C_7H_7^+$]; IR (KBr, cm^{-1}): $\tilde{\nu} = 3327$ (NH), 1699 (C=O), 1651 (C=O); $C_{28}H_{33}N_3O_3$ (459.6): calcd C 73.18, H 7.24, N 9.14; found C 72.81, H 7.07, N 9.27.

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1-Phenyl-2-Z-prolyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (4c): ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.05 (s, 1H, NH), 7.53–7.51 (m, 1H, aryl), 7.38–7.27 (m, 7H, aryl), 7.24–6.95 (m, 7H, aryl and CH), 5.23–5.06 (m, 2H, OCH_2), 4.76–4.71 (m, 1H, α-CH), 3.97–3.88 (m, 1H, NCH_2), 3.75–3.48 (m, 3H, NCH_2), 2.97–2.87 (m, 2H, CH_2), 2.28–1.86 (m, 4H, CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.24 (C=O), 154.44 (C=O), 139.69, 136.39, 131.59, 128.66, 128.44, 128.38, 128.24, 127.94, 127.79, 127.63, 126.39, 122.09, 119.47, 117.91, 111.40, 108.96, 66.89 (CH_2), 56.68 (CH), 52.50 (CH), 47.16 (CH_2), 39.31 (CH_2), 31.16 (CH_2), 22.19 (CH_3), 23.66 (CH_2), 22.42 (CH_2); MS (70 eV, EI): *m/z* (%): 479.3 (0.8) [M^+], 91 (100) [$C_7H_7^+$]; IR (cm^{-1}): $\tilde{\nu}$ = 3304 (NH), 1705 (C=O), 1647 (C=O); $C_{30}H_{29}N_3O_3$ (479.6): calcd C 75.13, H 6.09, N 8.76; found C 73.95, H 6.03, N 8.58.

1-Isopropyl-2-Fmoc-prolyl-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (4d): ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.72 (s, 1H, NH), 7.75–7.69 (m, 2H, aryl), 7.68–7.61 (m, 1H, aryl), 7.60–7.51 (m, 1H, aryl), 7.47–7.23 (m, 6H, aryl), 7.15–6.95 (m, 2H, aryl), 5.50 (d, ^3J(H,H) = 7.9 Hz, 1H, NCH), 4.91–4.85 (m, 1H, α-CH), 4.43–4.10 (m, 4H, CH, OCH_2, NCH_2), 3.91–3.30 (m, 3H, CH_2, NCH_2), 2.84–2.70 (m, 2H, CH_2), 2.20–1.63 (m, 5H, CH and CH_2), 1.06 (d, ^3J(H,H) = 6.6 Hz, 3H, CH_3), 0.98 (d, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.26 (C=O), 154.76 (C=O), 143.85, 141.21, 135.96, 134.18, 127.62, 126.99, 126.44, 125.18, 121.67, 119.80, 119.30, 117.74, 111.07, 107.13, 67.40 (OCH_2), 57.18 (CH), 55.29 (CH), 47.16 (CH), 46.74 (CH_2), 40.18 (CH_2), 33.08 (CH), 29.99 (CH_2), 24.46 (CH_2), 22.51 (CH_2), 19.93 (CH_3), 19.80 (CH_3); IR (cm^{-1}): $\tilde{\nu}$ = 3304 (NH), 1701 (C=O), 1646 (C=O); $C_{34}H_{35}N_3O_3$ (533.7): calcd C 76.52, H 6.61, N 7.88; found C 75.81, H 6.75, N 7.50.

General Procedure for the Preparation of the Tetrahydro-β-carbolines 8: To a stirred solution of amino acid chloride **5** (2 equiv) in dry dichloromethane (50 mL) was added dropwise titanium alkoxide (2 equiv), and after 5 min a solution of the Schiff base (1 equiv) in dichloromethane (15 mL). Stirring was continued in the case of aliphatic Schiff bases for 5 min to 4 h and for aromatic Schiff bases for 8–9 d. Merck silica gel (20 g), grade 60 (35–70 mesh ASTM), was then added, the solvent removed in vacuo, and the solid residue chromatographed on silica gel with mixtures of EtOAc/*n*-hexane as eluents. The pure diastereomer **8** was obtained by rerystallization from diethyl ether/hexane or EtOAc/*n*-hexane. The diastereomeric ratios of the products were determined by hplc on samples that were directly taken from the crude reaction mixtures. The reaction conditions and the results are listed in Table 2.

1-(*R*)-Phenyl-2-(phthaloylalanyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (8a): M.p. 247–250 °C; $[\alpha]_D^{22}$ = −102 (*c* = 0.5 in CH_2Cl_2); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.32 (s, 1H, NH), 7.80–7.78 (m, 2H, aryl), 7.69–7.67 (m, 2H, aryl), 7.35 (d, ^3J(H,H) = 7.6 Hz, 1H, aryl), 7.27–7.20 (m, 5H, aryl), 7.16–7.01 (m, 3H, aryl), 6.95 (s, 1H, CH), 5.19 (q, ^3J(H,H) = 7.0, 1H, α-CH), 3.81 (dd, ^2J(H,H) = 14.2 Hz, ^3J(H,H) = 4.6 Hz, 1H, NCH_2), 3.45–3.37 (m, 1H, NCH_2), 2.74 (dd, ^2J(H,H) = 15.2 Hz, ^3J(H,H) = 3.2 Hz, 1H, CH_2), 2.63–2.55 (m, 1H, CH_2), 1.69 (d, 3H, CH_3); ^{13}C NMR (100.6 MHz, ($CDCl_3$, 25 °C, TMS): δ = 168.06 (C=O), 167.55 (C=O), 139.60, 136.27, 134.25, 131.56, 131.37, 128.79, 128.49, 128.1, 126.34, 123.55, 121.94, 119.32, 117.96, 111.26, 109.25, 52.92 (CH), 47.03 (CH), 39.88 (CH_2), 21.96 (CH_2), 15.57 (CH_3), IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3305 (NH), 1781 (C=O), 1721 (C=O), 1656 (C=O); $C_{28}H_{23}N_3O_3$ (449.5): Calcd C 74.82, H 5.16, N 9.35; found C 74.76, H 5.23, N 9.22.

1-(*R*)-Phenyl-2-(phthaloylvalyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (8b): M.p. 265 °C; $[\alpha]_D^{22}$ = −150 (*c* = 1 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.24 (s, 1H, NH), 7.83–7.78 (m, 2H, aryl), 7.73–7.68 (m, 2H, aryl), 7.41–7.27 (m, 7H, aryl), 7.14 (s, 1H, CH), 7.11–7.02 (m, 2H, aryl), 4.82 (d, ^3J(H,H) = 10.6 Hz, 1H, α-CH), 4.17 (dd, ^2J(H,H) = 14.2 Hz, ^3J(H,H) = 4.8 Hz, 1H, NCH_2), 3.49–3.36 (m, 1H, NCH_2), 3.30–3.20 (m, 1H, β-CH), 2.79 (dd, ^2J(H,H) = 15.4 Hz, ^3J(H,H) = 3.5 Hz, 1H, CH_2), 2.61 (m, 1H, CH_2), 0.96 (d, ^3J(H,H) = 6.6 Hz, 3H, CH_3), 0.90 (d, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 167.80 (C=O), 167.25 (C=O), 139.89, 136.31, 134.26, 131.39, 131.33, 128.79, 128.47, 127.53, 126.41, 123.60, 121.97, 119.38, 118.00, 111.33, 109.53, 56.67 (CH), 52.52 (CH), 40.13 (CH_2), 27.79 (CH_3), 22.19 (CH_2), 20.17 (CH_3), 19.31 (CH_3); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3335 (NH), 1771 (C=O), 1719 (C=O), 1648 (C=O); $C_{30}H_{27}N_3O_3$ (477.6): calcd C 75.45, H 5.70, N 8.80; found C 75.49, H 5.70, N 8.80.

1-(*R*)-Phenyl-2-(phthaloyl-*tert*-leucyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (8c): M.p. 298 °C; $[\alpha]_D^{22}$ = −209 (*c* = 0.9 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.85–7.84 (m, 2H, aryl), 7.79 (s, 1H, NH), 7.76–7.75 (m, 2H, aryl), 7.35–7.26 (m, 7H, aryl), 7.13 (t, ^3J(H,H) = 6.0 Hz, 1H, aryl), 7.04–7.00 (m, 2H, CH and aryl), 4.79 (s, 1H, α-CH), 3.76 (dd, ^2J(H,H) = 14.5 Hz, ^3J(H,H) = 4.8 Hz, 1H, NCH_2), 3.37 (m, 1H, NCH_2), 2.61–2.58 (m, 1H, CH_2), 2.16–2.10 (m, 1H, CH_2), 1.18 (s, 9H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 167.77 (C=O), 165.83 (C=O), 140.21, 139.82, 136.31, 134.40, 131.94, 131.16, 128.69, 128.31, 127.78, 126.36, 123.70, 121.70, 119.04, 117.73, 111.48, 108.74, 57.06 (CH), 52.24 (CH), 40.03 (CH_2), 37.20 (C), 27.90 (CH_3), 21.90 (CH_2); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3377 (NH), 1775 (C=O), 1719 (C=O), 1654 (C=O); $C_{31}H_{29}N_3O_3$ (491.6): calcd C 75.74, H 5.95, N 8.55; found C 75.63, H 6.05, N 8.47.

1-(*R*)-4-Nitrophenyl-2-(phthaloylvalyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (8d): M.p. 284 °C; $[\alpha]_D^{22}$ = −184.8 (*c* = 0.27 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.22 (s, 1H, NH), 8.13 (d, ^3J(H,H) = 8.7 Hz, 2H, aryl), 7.86–7.71 (m, 4H, aryl), 7.52 (d, 2H, aryl), 7.42–7.37 (m, 2H, aryl), 7.20 (s, 1H, CH), 7.19–7.06 (m, 2H, aryl), 4.81 (d, ^3J(H,H) = 10.5 Hz, 1H, α-CH), 4.23 (dd, ^2J(H,H) = 14.1 Hz, ^3J(H,H) = 4.7 Hz, 1H, NCH_2), 3.47–3.17 (m, 3H, β-CH and CH_2), 2.82 (dd, ^2J(H,H) = 15.7 Hz, ^3J(H,H) = 3.3 Hz, 1H, CH_2), 2.68–257 (m, 1H, CH_2), 0.95 (d, ^3J(H,H) = 6.6 Hz, 3H, CH_3), 0.90 (d, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 167.95 (C=O), 167.78 (C=O), 147.44, 147.34, 136.73, 134.44, 131.02, 129.39, 126.30, 123.57, 123.53, 122.22, 119.51, 118.10, 111.96, 109.47, 56.49 (CH), 52.00 (CH), 40.51 (CH_2), 27.81 (CH_3), 22.14 (CH_2), 20.07 (CH_3), 19.25 (CH_3); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3367 (NH), 1717 (C=O), 1348 (NO_2); $C_{30}H_{26}N_4O_5$ (522.6): Calcd C 68.95, H 5.02, N 10.72, found C 68.90, H 5.02, N 10.71.

Crystal data: $C_{30}H_{26}N_4O_5$ crystallizes noncentrosymmetric, monoclinic space group $P2_1$ (no. 4), with M_r = 522.19, a = 1201.3(1), b = 987.4(1), c = 1238.1(1) pm, β = 114.48(2)°, Z = 2, ρ_{calcd} = 1.298(1) g cm^{-3}. The diffracted intensities of 3256 unique reflexions were measured at −85 °C by the method of learnt profiles (Stoe single-crystal diffractometer, graphite monochromated $Mo_{K\alpha}$ radiation, $2\theta_{max}$ = 55°), using ω/θ scans. The structure was solved by direct methods (SHELXS-86) and refined on F_o^2 data (SHELXL-93) with anistropic temperature factors for C, N, O. All H atoms were localized by a difference Fourier synthesis. The absolute configuration of **8d** was determined based on the known chirality of the valine-derived chiral group. Final residuals: R_1 = 0.030 for 2713 $F_o > 4\sigma(F_o)$ and wR_2 = 0.079, 431 structure parameters [16].

1-(*R*)-(4-Nitrophenyl)-2-(phthaloyl-*tert*-leucyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]-indole (8e): M.p. 283 °C; $[\alpha]_D^{22}$ = −232 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.21 (s, 1H, NH), 8.15 (d, ^3J(H,H) = 8.8 Hz, 2H, aryl), 7.87–7.80 (m, 2H, aryl), 7.78–7.75 (m, 2H, aryl), 7.53 (d, 2H, aryl), 7.35–7.32 (m, 1H, aryl), 7.24 (s, 1H, CH), 7.20–7.13 (m, 2H, aryl), 7.06–6.84 (m, 1H, aryl), 4.80 (s, 1H, α-CH), 3.82 (dd, ^2J(H,H) = 14.4 Hz, ^3J(H,H) = 4.9 Hz, 1H, NCH_2), 3.33–3.21 (m, 1H, NCH_2), 2.63 (dd, ^2J(H,H) = 15.4 Hz, ^3J(H,H) = 2.9 Hz, 1H, CH_2), 2.21–2.08 (m, 1H, CH_2), 1.14 (s, 9H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 167.76 (C=O), 166.44 (C=O), 147.56, 147.45, 136.55, 134.62, 131.07, 130.39, 129.07, 126.24, 123.82, 123.49, 122.20, 119.41, 117.94, 111.73, 109.18, 56.93 (CH), 51.77 (CH), 40.36 (CH_2), 37.26 (C), 27.75 (CH_3), 21.81 (CH_2); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3354 (NH), 1773 (C=O), 1718 (C=O), 1655 (C=O); $C_{31}H_{28}N_4O_5$ (536.6): calcd C 69.39, H 5.26, N 10.44; found C 69.36, H 5.25, N 10.42.

1-(*R*)-4-Chlorphenyl-2-(phthaloyl-*tert*-leucyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]-indole (8f): M.p. 250–252 °C; $[\alpha]_D^{22}$ = −205 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.23 (s, 1H, NH), 7.85–7.83 (m, 2H, aryl), 7.76–7.74 (m, 2H, aryl), 7.33 (d, ^3J(H,H) = 8.1 Hz, 1H, aryl), 7.28–7.24 (m, 5H, aryl), 7.13 (t, ^3J(H,H) = 7.4 Hz, 1H, aryl), 7.03 (s, 1H, CH), 7.01 (t, ^3J(H,H) = 7.5 Hz, 1H, aryl), 4.80 (s, 1H, α-CH), 3.77 (dd, ^2J(H,H) = 14.3 Hz, ^3J(H,H) = 4.5 Hz, 1H, NCH_2), 3.34–3.27 (m, 1H, NCH_2), 2.60 (dd, ^2J(H,H) = 15.4 Hz, ^3J(H,H) = 3.1 Hz, 1H, CH_2), 2.17–2.09 (m, 1H, CH_2), 1.17 (s, 9H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 167.75 (C=O), 166.06 (C=O), 138.73, 136.37, 134.47, 133.78, 131.37, 131.16, 130.12, 128.49, 126.30, 123.77, 121.95, 119.25, 117.88, 111.50, 109.07, 57.02 (CH), 51.68 (CH), 40.04 (CH_2), 37.22 (C), 27.82 (CH_3), 21.83 (CH_2); MS (70 eV, EI): *m/z* (%): 525.2 (27.7) [M^+], 281 (100) [$C_{17}H_{14}N_2Cl^+$]; IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3382 (NH), 1773 (C=O), 1720 (C=O), 1665 (C=O). $C_{31}H_{28}N_3O_3Cl$ (526.0): calcd C 70.78, H 5.37, N 7.99; found C 70.65, H 5.36, N 7.90.

1-(*R*)-Methyl-2-(phthaloylvalyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (8g): M.p. 300 °C; $[\alpha]_D^{22}$ = −154 (*c* = 0.9 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 10.91 (s, 1H, NH), 7.89–7.88 (m, 4H, aryl), 7.27 (d, ^3J(H,H) = 8.3 Hz, 1H, aryl), 7.24 (d, ^3J(H,H) = 8.5 Hz, 1H, aryl), 7.01 (t, ^3J(H,H) = 7.2 Hz, 1H, aryl), 6.89 (t, ^3J(H,H) = 7.3 Hz, 1H, aryl), 5.49 (q, ^3J(H,H) = 6.7 Hz, 1H, CH), 4.87 (d, ^3J(H,H) = 9.8 Hz, 1H, α-CH), 4.06 (dd, ^2J(H,H) = 14.8 Hz, ^3J(H,H) = 7.0 Hz, 1H, NCH_2), 3.41–3.36 (m, 1H, NCH_2), 2.98–2.89 (m, 1H, β-CH), 2.52–2.50 (m, 1H, CH_2), 2.28–2.15 (m, 1H, CH_2), 1.46 (d, 3H, CH_3) 1.07 (d, ^3J(H,H) = 6.6 Hz, 3H, CH_3), 0.87 (d, 3H, CH_3); ^{13}C NMR (62.9 MHz, [D_6]DMSO, 25 °C, TMS): δ = 167.16 (C=O), 165.96 (C=O), 135.76, 135.60, 134.84, 130.36, 125.79, 123.31, 120.64, 118.24, 117.40, 110.76, 105.52, 55.76 (CH), 45.62 (CH), 39.44 (CH_2), 27.25 (CH), 21.22 (CH_2), 19.94 (CH_3), 18.72 (CH_3), 18.29 (CH_3); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3285 (NH), 1770 (C=O), 1720 (C=O), 1641 (C=O); $C_{25}H_{25}N_3O_3$ (415.5): calcd C 72.27, H 6.06, N 10.11; found C 72.16, H 6.08, N 10.00.

1-(*R*)-Methyl-2-(phthaloyl-*tert*-leucyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-b]indole (8h): M.p. 274 °C; $[\alpha]_D^{22}$ = −266.7 (*c* = 1 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.79 (s, 1H, NH), 7.88–7.81 (m, 2H, aryl), 7.75–7.70 (m, 2H, aryl), 7.38 (d, ^3J(H,H) = 8.0 Hz, 1H, aryl), 7.18 (d, ^3J(H,H) = 7.7 Hz, 1H, aryl), 7.07 (t, ^3J(H,H) = 7.2 Hz, 1H, aryl), 6.95 (t, ^3J(H,H) = 7.3 Hz, 1H, aryl), 5.81 (q, ^3J(H,H) = 6.7 Hz, 1H, CH), 4.89 (s, 1H, α-CH), 3.85 (dd, ^2J(H,H) = 13.7 Hz, ^3J(H,H) = 4.2 Hz, 1H, NCH_2), 3.48–3.39 (m, 1H, NCH_2), 2.55–2.49 (m, 1H, CH_2), 2.05–1.96 (m, 1H, CH_2), 1.61 (d, 3H, CH_3), 1.26 (s, 9H, CH_3); ^{13}C NMR

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(62.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 167.81 (C=O), 166.02 (C=O), 136.20, 135.62, 134.44, 131.19, 126.34, 123.76, 121.40, 118.99, 117.57, 111.40, 106.43, 57.09 (CH), 46.57 (CH), 40.28 (CH_2), 37.22 (C), 27.93 (CH_3), 21.81 (CH_2), 19.15 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = (NH), 1772 (C=O), 1719 (C=O), 1645 (C=O); $C_{26}H_{27}N_3O_3$ (429.5): calcd C 72.71, H 6.34, N 9.78; found C 72.61, H 6.31, N 9.70.

1-(*R*)-Ethyl-2-(phthaloylvalyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (8i): M.p. 228 °C; $[\alpha]_D^{22} = -131$ (c = 1.0 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 10.33 (s, 1H, NH), 7.85–7.80 (m, 2H, aryl), 7.79–7.74 (m, 2H, aryl), 7.28 (d, ^3J(H,H) = 8.3 Hz, 1H, aryl), 7.25 (d, ^3J(H,H) = 9.0 Hz, 1H, aryl), 7.05–6.99 (m, 1H, aryl), 6.95–6.86 (m, 1H, aryl), 5.75–5.70 (m, 1H, CH), 4.86 (d, ^3J(H,H) = 10.4 Hz, 1H, α-CH), 4.25–4.19 (m, 1H, NCH_2), 3.54–3.41 (m, 1H, NCH_2), 3.13–2.98 (m, 1H, β-CH), 2.61–2.52 (m, 1H, CH_2), 2.49–2.20 (m, 1H, CH_2), 2.01–1.92 (m, 1H, CH_2), 1.86–1.73 (m, 1H, CH_2), 1.14 (d, ^3J(H,H) = 6.6 Hz, 3H, CH_3), 1.05 (t, ^3J(H,H) = 7.4 Hz, 3H, CH_3), 0.91 (d, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 167.73 (C=O), 167.27 (C=O), 136.10, 134.70, 134.29, 131.29, 126.42, 123.62, 121.47, 119.13, 117.68, 111.36, 106.86, 56.79 (CH), 51.21 (CH), 40.44 (CH_2), 27.63 (CH), 27.57 (CH_2), 22.23 (CH_2), 20.50 (CH_3), 19.15 (CH_3), 10.89 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3341 (NH), 1771 (C=O), 1720 (C=O), 1650 (C=O); $C_{26}H_{27}N_3O_3$ (429.5): calcd C 72.71, H 6.34, N 9.78; found C 72.64, H 6.31, N 9.68.

1-(*R*)-Ethyl-2-(phthaloyl-*tert*-leucyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (8j): M.p. 262 °C; $[\alpha]_D^{22} = -194$ (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.72 (s, 1H, NH), 7.82–7.81 (m, 2H, aryl), 7.72–7.70 (m, 2H, aryl), 7.37 (d, ^3J(H,H) = 7.9 Hz, 1H, aryl), 7.14 (d, ^3J(H,H) = 7.8 Hz, 1H, aryl), 7.07–7.03 (m, 1H, aryl), 6.95–6.91 (m, 1H, aryl), 5.95 (dd, ^2J(H,H) = 9.1 Hz, ^3J(H,H) = 5.4 Hz, 1H, CH), 4.94 (s, 1H, α-CH), 3.90 (dd, ^2J(H,H) = 14.1 Hz, ^3J(H,H) = 4.8 Hz, 1H, NCH_2), 3.45 (m, 1H, NCH_2), 2.52 (dd, ^2J(H,H) = 15.2 Hz, ^3J(H,H) = 3.2 Hz, 1H, CH_2), 2.13–1.98 (m, 2H, CH_2), 1.88–1.78 (m, 1H, CH_2), 1.26 (s, 9H, CH_3), 1.07 (t, ^3J(H,H) = 7.5 Hz, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 167.74 (C=O), 165.97 (C=O), 136.15, 135.20, 134.36, 131.11, 126.32, 123.65, 121.06, 118.70, 117.30, 111.60, 105.95, 57.16 (CH), 50.67 (CH), 40.13 (CH_2), 37.11 (C), 27.84 (CH_3), 27.48 (CH_2), 21.92 (CH_2), 10.61 (CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3381 (NH), 1773 (C=O), 1719 (C=O), 1649 (C=O); $C_{27}H_{29}N_3O_3$ (443.5): calcd C 73.11, H 6.59, N 9.47; found C 72.91, H 6.50, N 9.52.

1-(*R*)-Isopropyl-2-(phthaloylvalyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (8k): M.p. 254 °C; $[\alpha]_D^{22} = -111$ (c = 1.0 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.27 (s, 1H, NH), 7.89–7.75 (m, 2H, aryl), 7.74–7.67 (m, 2H, aryl), 7.38 (d, ^3J(H,H) = 8.0 Hz, 1H, aryl), 7.28 (d, ^3J(H,H) = 9.3 Hz, 1H, aryl), 7.13–7.06 (m, 1H, aryl), 7.02–6.96 (m, 1H, aryl), 5.67 (d, ^3J(H,H) = 8.4 Hz, 1H, CH), 4.89 (d, ^3J(H,H) = 10.7 Hz, 1H, α-CH), 4.34 (dd, ^2J(H,H) = 14.2 Hz, ^3J(H,H) = 5.4 Hz, 1H, NCH_2), 3.67–3.55 (m, 1H, NCH_2), 3.31–3.16 (m, 1H, β-CH), 2.70 (dd, ^2J(H,H) = 15.5 Hz, ^3J(H,H) = 3.8 Hz, 1H, CH_2), 2.51–2.38 (m, 1H, CH_2), 2.22–2.11 (m, 1H, CH), 1.20 (d, ^3J(H,H) = 6.7 Hz, 3H, CH_3), 1.16 (d, 3H, CH_3), 1.06 (d, ^3J(H,H) = 6.8 Hz, 3H, CH_3), 0.92 (d, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 167.61 (C=O), 166.96 (C=O), 135.85, 134.23, 133.96, 131.22, 126.38, 123.58, 121.48, 119.06, 117.67, 111.17, 107.35, 56.72 (CH), 55.17 (CH), 40.62 (CH_2), 33.14 (CH), 27.46 (CH), 22.18 (CH_2), 20.44 (CH_3), 20.06 (CH_3), 19.92 (CH_3), 19.01 (CH_3); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3356 (NH), 1770 (C=O), 1722 (C=O), 1646 (C=O); $C_{27}H_{29}N_3O_3$ (443.5): calcd C 73.11, H 6.59, N 9.47; found C 72.76, H 6.59, N 9.47.

1-(*R*)-Isopropyl-2-(phthaloyl-*tert*-leucyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole (8l): M.p. 235 °C; $[\alpha]_D^{22} = -181$ (c = 1.1 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.66 (br, 1H, NH), 7.81–7.72 (m, 2H, aryl), 7.70–7.67 (m, 2H, aryl), 7.35 (d, ^3J(H,H) = 7.8 Hz, 1H, aryl), 7.13 (d, ^3J(H,H) = 7.7 Hz, 1H, aryl), 7.04 (t, ^3J(H,H) = 7.1 Hz, 1H, aryl), 6.92 (t, ^3J(H,H) = 7.2, 1H, aryl), 5.71 (d, ^3J(H,H) = 8.3 Hz, 1H, CH), 4.96 (s, 1H, α-CH), 3.94 (dd, ^2J(H,H) = 14.3 Hz, ^3J(H,H) = 5.4 Hz, 1H, NCH_2), 3.62–3.50 (m, 1H, NCH_2), 2.54 (dd, ^2J(H,H) = 15.4 Hz, ^3J(H,H) = 3.8 Hz, 1H, CH_2), 2.21–1.95 (m, 2H, CH_2 and CH), 1.25 (s, 9H, CH_3) 1.21 (d, ^3J(H,H) = 6.7 Hz, 3H, CH_3), 1.04 (d, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): δ = 167.73 (C=O), 165.73 (C=O), 135.97, 134.36, 131.17, 126.38, 123.68, 121.21, 119.22, 117.41, 111.45, 106.69, 57.25 (CH), 54.76 (CH), 40.53 (CH_2), 37.17 (C), 32.83 (CH), 27.89 (CH_3), 21.31 (CH_2) 19.97 (CH_3), 19.90 (CH_3); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3393 (NH), 1772 (C=O), 1716 (C=O), 1648 (C=O); $C_{28}H_{31}N_3O_3$ (457.6): calcd C 73.50, H 6.83, N 9.18; found C 73.31, H 6.88, N 9.12.

1-(*R*)-Phenyltetrahydro-β-carboline (15): To a stirred solution of **8c** (100 mg, 0.203 mmol) in refluxing THF (10 mL) a solution of $LiAlH_4$ (0.20 mL, 1 M solution in THF) was injected with a syringe. After 5 min an additional amount of the $LiAlH_4$ solution (0.1 mL) was added, and stirring was continued for 0.5 h at room temperature. The reaction mixture was quenched with a saturated ammonium chloride solution, diluted with dichloromethane (100 mL), acidified with aqueous HCl until the white precipitate dissolved, and the pH was then adjusted to 8–9 with saturated sodium hydrogen carbonate solution. The aqueous layer was extracted three times with dichloromethane, the combined organic layers were dried with magnesium sulfate, filtered, and concentrated in vacuo. The oily residue was purified by flash chromatography ($CHCl_3$/MeOH, 20:1 [v/v]) to yield 33.4 mg (66%) of tetrahydro-β-carboline **15**. M.p. 186 °C; ref. [5]: M.p. 167 °C; $[\alpha]_D^{22} = -4.5$ (c = 1.0, $CHCl_3$); ref. [5]: $[\alpha]_D^{22} = 4.5$ (c = 1.0, $CHCl_3$); $[\alpha]_D^{24} = 15.6$ (c = 0.38, EtOH); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.56–7.47 (m, 2H, aryl and NH), 7.40–7.31 (m, 5H, aryl), 7.22 (m, 1H, aryl), 7.18–7.11 (m, 2H, aryl), 5.20 (s, 1H, CH), 3.39–3.37 (m, 1H, NCH_2), 3.20–3.10 (m, 1H, NCH_2), 2.93–2.76 (m, 2H, CH_2), 1.82 (br, 1H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C, TMS): 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), 23.11 (CH_2). IR: $\tilde{\nu}$ = 3398 (NH), 3300 (NH), 2885 (C-H), 1454 cm^{-1}.

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[16] Further details of the crystal structure investigation may be obtained from the Fachinformationszentrum Karlsruhe, 76344 Eggenstein-Leopoldshafen (Germany) on quoting the depository number CSD-59081.