Pergamon

Tetrahedron 56 (2000) 2683–2692

TETRAHEDRON

Synthesis of Tetrahydro-β-carbolines and Studies of the Pictet–Spengler Reaction

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Received 11 October 1999; accepted 22 February 2000

Abstract—Tetrahydro-β-carbolines have been prepared in a diastereomerically pure form by a short, efficient synthetic sequence consisting of reaction of α-aminoaldehydes with tryptamine. A study was made of the major factors affecting the stereoselectivity of the Pictet–Spengler reaction. © 2000 Elsevier Science Ltd. All rights reserved.

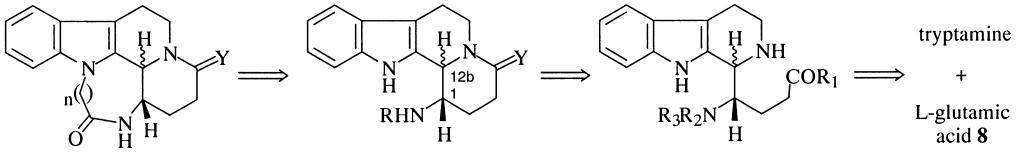
Introduction

In the course of our study of Tyrosine Hydroxylase (TH) gene inductors, we established the importance of the *cis*/*trans* relative stereochemistry of *E*-azaeburnane compounds of type **1**–**2** for biological activity.[1] We then reported a new diastereoselective synthesis of the racemic *cis* 1-aminoindolo[2,3-a]quinolizidine **5b**,[2] followed by an improved diastereoselective and enantioselective synthesis of (+)-(1*S*, 12b*R*) amine **5b**,[3] key precursors in the synthesis of the *E*-azaeburnanes **1**–**3** (Scheme 1).

As structure/activity relationship studies pointed out the biological interest of the *trans* series, it became important to either reverse the diastereoselectivity of the Pictet–Spengler reaction, or alternatively to seek a new route. Furthermore, pentacyclic compounds such as **3a** and **3b** are interesting in their own right as well as being key precursors for some new series. In spite of many attempts to reverse the diastereoselectivity of the reaction by modifying both reaction conditions and protecting groups, *trans* β-carbolines have never been obtained as unique diastereoisomers.[4] In previous work, we postulated a hydrogen-bonded intermediate state to explain the *cis* diastereoselectivity of the Pictet–Spengler reaction with *N*-protected α-aminoaldehydes.[3] In order to confirm this model and to access the *trans* series we varied the steric bulk of the carbamate and furthermore used pyrrole as the amine precursor and phthalimide as the amino-protecting group. Indeed, these two groups are bulkier than the carbamates and pyrrole cannot participate in hydrogen bonding.

We therefore report in the present paper a stereoselective route to tetrahydro-β-carbolines **6** and **7**, primary precursors of the 1-aminoindolo[2,3-a]quinolizidines **4** and **5**, together with our studies of the diastereoselectivity of the Pictet–Spengler reaction between tryptamine and variously protected α-aminoaldehydes derived from L-glutamic acid.

L-Glutamic acid was selectively protected as the oxazolidinone **9**, as described previously,[5] allowing selective



n	Y	$H_{12b}\alpha$	$H_{12b}\beta$
0	H_2	**1a**	**1b**
1	H_2	**2a**	**2b**
0	O	**3a**	**3b**

R	Y	$H_{12b}\alpha$	$H_{12b}\beta$
Cbz	O	**4a**	**4b**
H	H_2	**5a**	**5b**

6 Hα *trans*
7 Hβ *cis*

Scheme 1.

Keywords: Pictet–Spengler reaction; α-aminoaldehydes; tryptamine.
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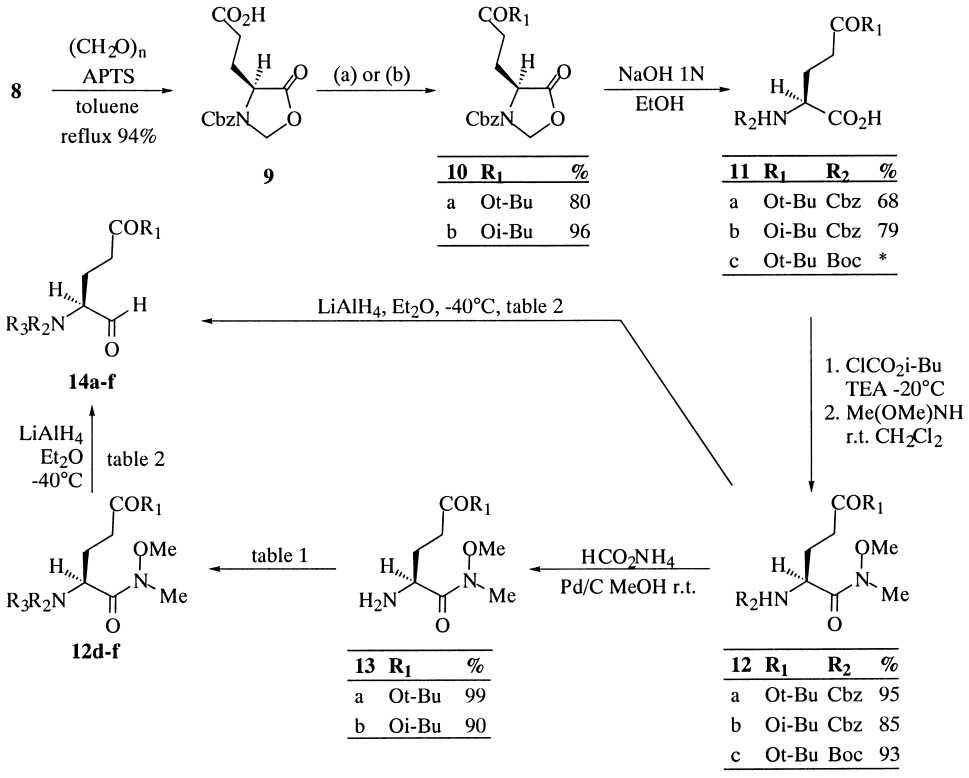
PII: S0040-4020(00)00165-4



(a) iso-butene/H_2SO_4, CH_2Cl_2, -50°C, 48h; *(b)* $ClCO_2$i-Bu/TEA, CH_2Cl_2, -20°C then *tert*-BuOH, r.t., 2h.
(*) commercially available.

Scheme 2.

esterification at the γ position. Whereas *iso*-butene in acidic media led to the desired *tert*-butyl ester **10a** with reasonable yields, attempts to improve this reaction by the addition of *tert*-butanol to the activated carboxylic acid function unfortunately led to the rearranged *iso*-butyl ester **10b**.[6,7] The oxazolidinones were hydrolysed using sodium hydroxide in ethanol to give **11a**,**b** in good yields. Both *tert*-butyl and *iso*-butyl esters were then used in the following steps to prepare hydroxamates **12a**–**c**, known to be good precursors of α-aminoaldehydes[8] (Scheme 2).

Hydroxamates **12a**–**c** were obtained in good yields by addition of *N*-methoxy-*N*-methyl amine to the activated carboxylic function. In order to allow introduction of different protecting groups on the amine, the benzyl carbamates of **12a**,**b** were then removed by hydrogenolysis in good yields. Protecting groups were attached to the amines **13a**,**b** thus obtained to form the corresponding hydroxamates **12d**–**f** (Table 1).

Reduction of hydroxamates **12a**–**f** with lithiumaluminium hydride, as previously described by Fehrentz et al.,[8] led to the corresponding aldehydes **14a**–**f** (Table 2), with good to excellent yields.

Since the phtalimide group is incompatible with hydride reduction, the *N*-phthaloyl derivative was prepared using a different approach in four steps starting from the commercially available *N*-phthaloyl-L-glutamic anhydride **15**. The latter was regioselectively opened with diethylamine[9] (Scheme 3) and the free acid was transformed into the mixed anhydride **17** which was then reduced quickly and selectively in situ with sodium borohydride.[10] The resulting alcohol **18** was readily oxidized with PCC to form the desired aldehyde **14g** in 60% overall yield from acid **16**.

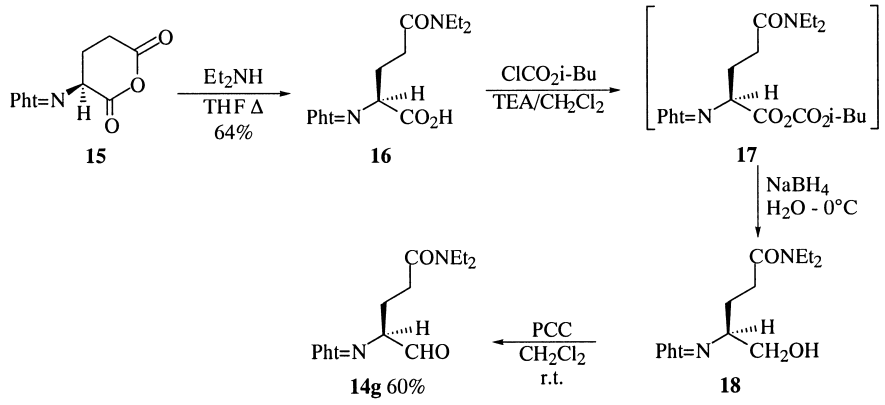
Aldehydes **14a**–**g** were then condensed with tryptamine under a variety of conditions in an attempt to form selectively *cis* and *trans* β-carbolines (Scheme 4, Table 3). Diastereomeric excesses of β-carbolines were measured using ^{1}H NMR and/or HPLC. Further cyclisation using NaOMe in methanol led to the corresponding lactams **20** and **21** in good yields (68–90%), except for the *N*-Troc and

Table 1.

#	R_1	R_2	R_3	Conditions	12	Yield (%)
i	O*t*-Bu	CO_2Me	H	$ClCO_2Me$/TEA	**d**	98
ii	O*i*-Bu	Troc	H	$ClCO_2CH_2CCl_3$ TEA	**e**	97
iii	O*t*-Bu	Pyrrole		2,5-di-OMe-furan AcOH/AcONa	**f**	79

Table 2.

#	R_1	R_2	R_3	14	Yield (%)
i	O*t*-Bu	Cbz	H	**a**	99
ii	O*i*-Bu	Cbz	H	**b**	91
iii	O*t*-Bu	Boc	H	**c**	93
iv	O*t*-Bu	CO_2Me	H	**d**	70
v	O*i*-Bu	Troc	H	**e**	86
vi	O*t*-Bu	Pyrrole		**f**	95



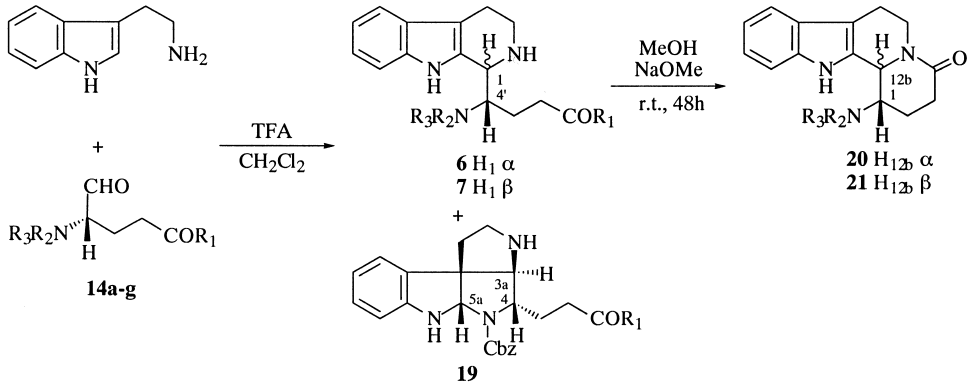
Scheme 3.

N-phthaloyl derivative **7e** and **6g**, respectively, which did not cyclise. Diastereomeric excesses of the lactams confirmed those of the corresponding β-carbolines.

In the carbamate series (*entries i–v*), the *cis* β-carboline was always the major diastereoisomer formed, the size of the carbamate group providing little influence on the course of the reaction's diastereoselectivity. The best diastereoselectivity was observed with the benzyl carbamate, with no influence of the R_1 ester group. Conversely, with either pyrrole or phthalimide groups, the diastereoselectivity was reversed (*entries vi and vii*).

In the *N*-Cbz series, low temperatures (below −20°C, *entry i, ii, viii, and ix*) led exclusively to the *cis* tetrahydro-β-carboline.[11] A temperature increase produced the diastereomeric *trans*-product and tetracyclic compound **19** (*entries x–xiii*). Formation of the latter was favoured by a short reaction time at 40°C (*entry xii*), whereas a higher temperature (*entry xiii*) led to degradation of starting materials. The relative stereochemistry of compound **19** (assigned using ^{1}H NMR) thus shows that it is formed *via* the same intermediate as the *trans* tetrahydro-β-carboline.

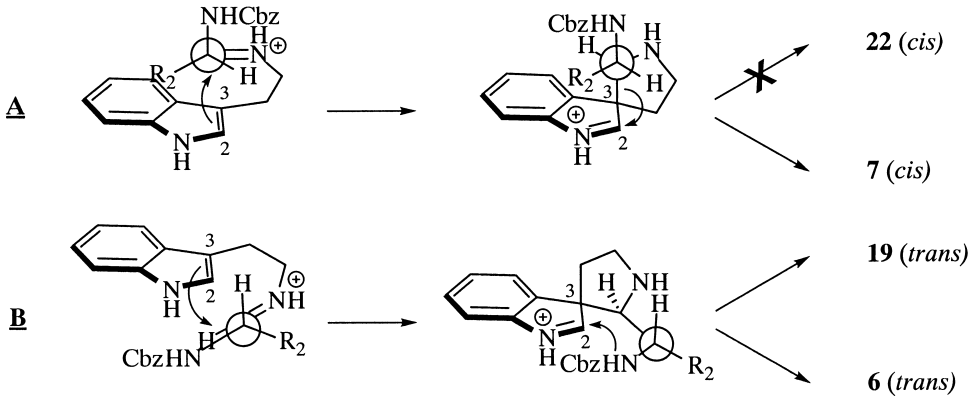
Acidity had no effect on the diastereoselectivity of the



Scheme 4.

Table 3.

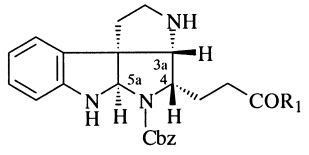
Entry	14	R_2	R_3	R_1	Solvent	*T* (°C)	Time	TFA (equiv.)	6+7 (%)	6	7	19 (%)
i	**a**	Cbz	H	O*t*-Bu	CH_2Cl_2	−40	2 h	2	81	0	100	0
ii	**b**	Cbz	H	O*i*-Bu	CH_2Cl_2	−40	2 h	2	77	0	100	0
iii	**c**	Boc	H	Ot-Bu	CH_2Cl_2	−40	2 h	2	71	10	90	0
iv	**d**	CO_2Me	H	O*t*-Bu	CH_2Cl_2	−40	2 h	2	73	9	91	0
v	**e**	Troc	H	O*i*-Bu	CH_2Cl_2	−40	2 h	2	74	14	86	0
vi	**f**	pyrrole		O*t*-Bu	CH_2Cl_2	−50	2 h	2	62	100	0	0
vii	**g**	phth		NEt_2	CH_2Cl_2	rt	2 h	2	68	93	7	0
viii	**a**	Cbz	H	O*t*-Bu	CH_2Cl_2	−65	2 4h	2	68	0	100	0
ix	**a**	Cbz	H	O*t*-Bu	CH_2Cl_2	−20	2 h	2	69	0	100	0
x	**a**	Cbz	H	O*t*-Bu	CH_2Cl_2	0	1 h	2	66	10	90	5
xi	**a**	Cbz	H	O*t*-Bu	CH_2Cl_2	rt	35 min	2	61	25	75	9
xii	**a**	Cbz	H	O*t*-Bu	CH_2Cl_2	40	15 min	2	54	28	72	30
xiii	**a**	Cbz	H	O*t*-Bu	$(CH_2Cl)_2$	60	7 min	2	51	23	77	5
xiv	**a**	Cbz	H	O*t*-Bu	CH_2Cl_2	rt	1 h	5	61	25	75	8
xv	**a**	Cbz	H	O*t*-Bu	CH_2Cl_2	rt	1 h	15	51	25	75	<5



Scheme 5.

reaction (*entry xi, xiv, and xv*). Compound **19** results from the attack of the nitrogen of the carbamate on the indolenininium intermediate, and provides a direct proof of the formation of a spiro intermediate in the Pictet–Spengler reaction.[4]

On the other hand, it should be stated at this point that we never observed the presence of a *cis* tetracyclic compound **22**. This can be explained by the Felkin–Anh model since under kinetic conditions, C_3 attack only occurs on the less hindered face of the iminium (model A). In this case the geometry of the spiroindoleninium intermediate formed is not favourable for nucleophilic attack by the carbamate's nitrogen, and therefore a Wagner–Meerwein rearrangement takes place, which leads to the *cis* β-carboline (Scheme 5). Conversely, under thermodynamic conditions, C_3 attack leads to spiro intermediates in which the nucleophilic attack is possible (model B).



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As previously mentioned, the longer the reaction time, the lower was the yield of tetracyclic derivative **19**. To verify whether formation of the latter is reversible or not and to investigate what stereochemistry the corresponding rearranged β-carboline would have, we applied the Pictet–Spengler reaction conditions to the isolated compound **19** (Table 4).

We thus observed a total conversion to the *trans* β-carboline **6a** at rt within two to four days, depending on the acidity of the reaction. Conversely, below 0°C, the formation of the *cis* β-carboline **7a** was not observed.

Table 4.

Entry	TFA	*T* (°C)	Time	**6a/7a**	Yield
i	5	rt	80 h	100/0	Quantitative
ii	10	rt	60 h	100/0	Quantitative
iii	15	rt	48 h	100/0	Quantitative
iv	5	0	2 weeks		Partial
v	10	−20	4 weeks		No
vi	15	−40	4 weeks		No

These results are direct proof that a) formation of the tetracyclic compound **19** is reversible and b) formation of the spiroindoleninium intermediate is either irreversible or considerably slower than the Wagner–Meerwein rearrangement, otherwise we would have observed *cis* β-carboline.

Conclusion

We have achieved an improved and highly stereoselective synthesis of protected 1-aminoindolo- [2,3-a]quinolizidin-4-ones, key intermediates in the synthesis of 1-aminoindolo[2,3-a]quinolizidines and *E*-azaeburnane compounds.

The use of bulky amino-protecting groups led to the *trans* system, whereas smaller protecting groups led to the *cis* series in accord with our previously published hypothesized hydrogen-bonded intermediate.[3]

Under kinetic conditions the *cis* compound was formed exclusively and, consequently under thermodynamic conditions we were able to slightly reverse the diastereoselectivity and increase the proportion of the *trans* compound generated. For these reactions, however, yields were lower due to the formation of a new tetracyclic compound, which is a direct proof of the spiroindoleninium intermediate formation.

Experimental

Flash chromatography was performed using silica gel (Merck, 230–400 Mesh). IR spectra were recorded on a Nicolet 250 FT-IR instrument. UV spectra were recorded on a Perkin–Elmer lambda 5 instrument. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Mass spectral measurements were obtained using an AEI MS50 (EI), or Kratos MS-80 (CI, HRMS) spectrometer. ^{1}H and ^{13}C NMR spectra were determined on Bruker AC-200, 250, 300 or 400 instruments. Chemical shifts are given as δ values with reference to $Si(CH_3)_4$ as internal standard, and coupling constants are given in Hz. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

4(*S*)-(2-Carboxyethyl)-5-*oxo*-oxazolidine 3-carboxylic acid benzyl ester 9. See Ref. 5. α_D=+73 (24°C, MeOH, *c*=2.3). IR ($CHCl_3$): ν=3520 (OH); 3030; 1800 (CO); 1710 (CO); 1715 (CO); 1410. MS (EI) *m/z*=293 (M+); 275 (M−H_2O); 249 (M−CO_2); 204; 158; 140; 107; 91. HRMS ($C_{14}H_{15}NO_6$) calcd 293.0899, obs. 293.0898. ^{1}H NMR (CDCl3, 200 MHz): 8.90 (1H, bs, ex., CO_2H); 7.70–7.20 (5H, m, Ph); 5.50–5.30 (4H, m, H_2, CH_2Ph); 4.30 (1H, t, H_4, $J_{4\text{-}1'}$=6 Hz); 2.60–2.10 (4H, m, $H_{1'}$, $H_{2'}$). ^{13}C NMR (CD_3OD, 50.3 MHz): 175.8 (CO_2H); 173.8 (C_5); 154.7 (CO Cbz); 137.1 (C_ϕ); 129.6 (CH_o); 129.3 (CH_p); 129.2 (CH_m); 79.1 (C_2); 68.8 (CH_2Ph); 55.3 (C_4); 30.0 ($C_{2'}$); 27.0 ($C_{1'}$).

4(*S*)-(2-*tert*-Butoxycarbonylethyl)-5-*oxo*-oxazolidine 3-carboxylic acid benzyl ester 10a. See Ref. 5. α_D(=+27.9 (22°C, EtOH, *c*=1.58). IR ($CHCl_3$): ν=3030–2970; 1802 (CO); 1720 (CO); 1417. MS (CI^+): *m/z*=350 ($[M+H]^+$); 294 (M−=<; 100%); 250 (M−*t*-BuO_2C); 107 ($PhCH_2O$); 91 ($PhCH_2$, 100%); 77. Analysis ($C_{18}H_{23}NO_6$): calcd C: 61.88; H: 6.64; O: 27.48; N: 4.01; obs: C: 62.16; H: 6.83; O: 24.55; N: 3.51 ^{1}H NMR ($CDCl_3$, 200 MHz): 7.40 (5H, s, Ph); 5.55 (1H, dl, H_2); 5.20 (1H, d, H_2); 5.15 (2H, s, CH_2Ph); 4.40 (1H, t, H_4); 2.50–2.10 (4H, m, $H_{2'}$, $H_{1'}$); 1.45 (9H, s, $C(CH_3)_3$). ^{13}C NMR (CD_3OD, 50.3 MHz): 171.9 ($C_{3'}$); 171.3 (C_5); 158.0 (*C*O Cbz); 135.3 (C_ϕ); 128.8 (CH_o); 128.7 (CH_p); 128.4 (CH_m); 80.9 ($OC(CH_3)_3$); 77.8 (C_2); 68.1 (CH_2Ph); 54.2 (C_4); 30.6 ($C_{2'}$); 28.1 ($C_{1'}$); 26.0 ($C(CH_3)_3$).

4(*S*)-(2-Isobutoxycarbonylethyl)-5-*oxo*-oxazolidine 3-carboxylic acid benzyl ester 10b. To a stirred solution of **9** (2.6 g, 8.90 mmol) in 30 ml CH_2Cl_2 at −15°C were added successively 1.50 ml (10.7 mmol) of triethylamine then dropwise 1.20 ml (10.7 mmol) of *iso*-butyl chloroformate. After stirring for 15 min, 1.25 ml (13.3 mmol) of *tert*-butanol were added, and the temperature was allowed to increase to rt over 2 h. The reaction mixture was extracted with a saturated solution of sodium carbonate, washed with brine and dried over sodium sulfate. The combined organic layers were then concentrated under reduced pressure, and purified by chromatography (CH_2Cl_2 97/CH_3OH 3) to yield 3.0 g (96%) of a colorless oil. α_D=+35° (22°C, MeOH, *c*=1.4). IR ($CHCl_3$): ν=3030–2970; 1800 (CO); 1780 (CO); 1410. MS (EI): *m/z*=349 (M^+); 305 (M−CO_2); 293 (M−=<; 100%); 276 (M−*i*-BuO); 107 ($PhCH_2O$); 91 (100%); 77. HRMS ($C_{18}H_{23}NO_6$): calcd 349.1525; obs. 349.1528. Analysis: calcd C: 61.88; H: 6.64; O: 27.48; N: 4.01; obs. C: 62.36; H: 6.66; O: 24.86; N: 3.46. ^{1}H NMR ($CDCl_3$, 200 MHz): 7.60–7.20 (5H; m, Ph); 5.55 (1H, bd, H_2); 5.25 (1H, d, H_2); 5.20 (2H, s, CH_2Ph); 5.05 (1H, d, $CH(CH_3)_2$); 4.40 (1H, t, H_4); 2.75 (2H, t, $H_{2'}$); 2.30 (2H, m, CH_2 (*i*-Bu)); 2.00 (2H, m, $H_{1'}$); 1.00 (6H, d, CH_3 (*i*-Bu)); ^{13}C NMR (CD_3OD, 50.3 MHz): 173.0 ($C_{3'}$); 172.6 (C_5); 157.3 (*C*O Cbz); 136.9 (C_ϕ); 129.9 (CH_o); 129.7 (CH_p); 129.4 (CH_m); 79.3 (OCH_2. *i*-Bu); 72.0 (C_2); 68.9 (CH_2Ph); 54.9 (C_4); 30.0 ($C_{2'}$); 28.7 (*C*H, *i*-Bu); 26.9 ($C_{1'}$); 20.3 (CH_3 (*i*-Bu)).

2(*S*)-Benzyloxycarbonylaminopentanedioic acid 5-*tert*-butyl ester 11a. See Ref. 5. α_D=−12 (24°C, MeOH, *c*=1.6). IR ($CHCl_3$): ν=3435; 3050–2940; 1715 (CO). MS; (EI): *m/z*=337 (M^+); 292 (M−CO_2H); 264; 91 (100%, CH_2Ph). Analysis ($C_{17}H_{23}NO_6$+3.7% silica gel): calcd C: 60.52; H: 6.87; O: 28.45; N: 4.15; obs. C: 59.28; H: 6.79; O: 26.44; N: 3.82. ^{1}H NMR ($CDCl_3$, 200 MHz): 9.75 (1H, bs, CO_2H); 7.35 (5H, s, Ph); 5.70 (1H, d, NH-Cbz, $J_{NH\text{-}4}$=8 Hz); 5.10 (2H, s, CH_2Ph); 4.40 (1H, m, H_2); 2.40 (2H, t, H_4, $J_{2\text{-}3}$=7 MHz); 2.30–1.90 (2H, m, H_3); 1.45 (9H, s, CH_3 (*t*-Bu)). ^{13}C NMR (CD_3OD, 50.3 MHz): 175.5 (C_1); 173.8 (C_5); 154.0 (*C*ONH); 138.3 (C_ϕ); 129.4 (CH_o); 129.0 (CH_p); 128.8 (CH_m); 81.8 ($OC(CH_3)_3$); 67.6 (CH_2Ph); 54.5 (C_2); 32.6 (C_4); 28.3 ($C(CH_3)_3$); 28.0 (C_3).

2(*S*)-Benzyloxycarbonylaminopentanedioic acid 5-*iso*-butyl ester 11b. See Ref. 5. IR ($CHCl_3$): ν=3435; 3050–2940; 1725 (CO). MS; (EI): *m/z*=337 ($M^{+\cdot}$; 292 (M−CO_2H); 264; 230 (M−OBn); 107 (OBn, 100%); 91 (CH_2Ph). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.35 (5H, s, Ph); 5.80 (1H, d, NH-Cbz, $J_{NH\text{-}4}$=8 MHz); 5.10 (2H, s, CH_2Ph); 4.30 (1H, m, H_2); 3.95 (2H, d, CH_2 *i*-Bu, *J*=7.6 MHz); 2.50 (2H, m, H_4); 2.20 (1H, m, CH *i*-Bu); 1.95 (2H, m, H_3); 0.95 (6H, d, CH_3 *i*-Bu). ^{13}C NMR (CD_3OD, 50.3 MHz): 180.6 (C_1); 173.6 (C_5); 154.9 (*C*ONH); 133.3 (C_ϕ); 128.7 (CH_o); 128.2 (CH_p); 127.7 (CH_m); 70.1 (CH_2Ph); 66.8 (OCH_2 *i*-Bu); 53.6 (C_2); 30.5 (C_4); 27.8 (C_3); 27.1 (*C*H *i*-Bu); 18.8 (CH_3).

General procedure for hydroxamate formation

To a stirred solution of 12.8 g (37.9 mmol) of acid **11** and 8.2 ml (74.6 mmol) of *N*-methylmorpholine in 160 ml CH_2Cl_2 at −15°C were added dropwise 4.9 ml (37.9 mmol) of *iso*-butyl chloroformate. After stirring for 30 min at the same temperature, 3.7 g (37.9 mmol) of N.O-dimethylhydroxylamine hydrochloride were added. After a further hour at −15°C, the reaction mixture was allowed to warm to rt over 1 h. 150 ml of water was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were then washed with brine, dried over sodium sulfate, concentrated under reduced pressure and purified by chromatography (CH_2Cl_2 95/CH_3OH 5) to yield 11 g (78%) of a colorless oil.

4(*S*)-Benzyloxycarbonylamino-4-(methoxymethylcarbamoyl) butyric acid *tert*-butyl ester 12a. α_D=−12.9 (24°C, MeOH, *c*=0.6). IR ($CHCl_3$): ν=3015 (NH); 1720 (CO); 1510; 1370. MS (CI^+) *m/z*=381 ($[M+H]^+$, 100%); 325 (381−>=); 217; 91. Analysis ($C_{19}H_{28}N_2O_6$): calcd C: 59.99; H: 7.42; O: 25.23; N: 7.36; obs. C: 60.24; H: 7.24; O: 25.05; N: 7.31. ^{1}H NMR ($CDCl_3$, 200 MHz): 7.50–7.20 (5H, m, Ph); 5.90 (1H, d ex., NH-Cbz, $J_{NH\text{-}4}$=8 Hz); 5.10 (2H, s, CH_2Ph); 4.80–4.70 (1H, m, H_4); 3.80 (3H, s, OCH_3); 3.20 (3H, s, NCH_3); 2.20 (2H, t, H_2, $J_{2\text{-}3}$=7 Hz); 2.10–1.70 (2H, m, H_3); 1.30 (9H, s, CH_3 (*t*-Bu)). ^{13}C NMR (CD_3OD, 50.3 MHz): 172.0 (C_1); 168.3 (C_5); 156.3 (*C*O Cbz); 136.5 (C_ϕ); 126.0 (CH_o, CH_m, CH_p); 80.5 ($OC(CH_3)_3$); 66.8 (CH_2Ph); 61.6 (OCH_3); 50.6 (C_4); 32.2 (NCH_3); 31.3 (C_2); 28.1 (CH_3 *t*-Bu); 27.8 (C_3).

4(*S*)-Benzyloxycarbonylamino-4-(methoxymethylcarbamoyl) butyric acid isobutyl ester 12b. IR ($CHCl_3$): ν=3015 (NH); 1720 (CO); 1510; 1370. MS (CI^+): *m/z*=381 ($[M+H]^+$, 100%); 325 (381−>=); 217; 91; 57. Analysis ($C_{19}H_{28}N_2O_6$): calcd C: 59.99; H: 7.42; O: 25.23; N: 7.36; obs. C: 59.63; H: 7.31; O: 24.54; N: 7.38. ^{1}H NMR

($CDCl_3$, 200 MHz): 7.30 (5H, bs, Ph); 5.80 (1H, d ex., NH-Cbz, J_{NH-4}=8 Hz); 5.10 (2H, s, CH_2Ph); 4.80 (1H, m, H_4); 3.80 (2H, d, CH_2 (*i*-Bu), *J*=8 Hz); 3.75 (3H, s, OCH_3); 3.20 (3H, s, NCH_3); 2.40 (2H, t, H_2, J_{2-3}=7 Hz); 2.10 (1H, m, CH (*i*-Bu)); 1.90 (2H, m, H_3); 0.95 (6H, d, CH_3 (*i*-Bu), *J*=8 Hz). ^{13}C NMR (CD_3OD, 50.3 MHz): 172.5 (C_1); 169.1 (C_5); 156.4 (*C*O); 137.3 (C_ϕ); 126.2 (CH_o, CH_m); 126.1 (CH_p); 72.4 (OCH_2 *i*-Bu); 67.1 (CH_2Ph); 61.3 (OCH_3); 50.9 (C_4); 32.8 (NCH_3); 31.4 (C_2); 27.8 (C_3); 27.2 (*C*H *i*-Bu); 19.2 (CH_3 *i*-Bu).

4(*S*)-*tert*-Butoxycarbonylamino-4-(methoxymethylcarbamoyl) butyric acid *tert*-butyl ester 12c. IR ($CHCl_3$): ν=3015 (NH); 1720 (CO); 1510; 1370. MS (SIMS): *m*/*z*=347 ($[M+H]^+$); 291 (M−>=); 235; 191; 173. HRMS ($C_{16}H_{30}N_2O_6$); calcd 347.2183; obs. 347.2191. ^1H NMR ($CDCl_3$, 250 MHz): 5.26 (1H, d ex, NH-Boc, J_{NH-4}=9.2 Hz); 4.80–4.60 (1H, m, H_4); 3.78 (3H, s, OCH_3); 3.21 (3H, s, NCH_3); 2.33 (2H, t, H_2, J_{2-3}=7.2 Hz); 2.10–1.6 (2H, m, H_3); 1.45 (18H, s, CH_3). ^{13}C NMR (CD_3OD, 50.3 MHz): 172.2 (C_1); 169.0 (C_5); 155.6 (*C*O Boc); 80.5 ($OC(CH_3)_3$); 79.9 ($C(CH_3)_3$); 61.3 (OCH_3); 50.0 (C_4); 32.2 (NCH_3); 31.5 (C_2); 28.4 ($C(CH_3)_3$); 28.1 ($C(CH_3)_3$); 27.9 (C_3).

General procedure for Cbz hydrogenolysis

To a stirred solution of 1.37 g (3.62 mmol) of hydroxamate **12a** in 30 ml of MeOH were added sucessively 46 mg of 10% palladium on charcoal, and 977 mg (18.1 mmol) of anhydrous ammonium formate. After stirring for 2 h at rt, the reaction mixture was filtered over celite. The organic layer was then concentrated under reduced pressure to yield 882 mg (99%) of an amorphous white solid, which was used without any further purification.

4(*S*)-Amino-4-(methoxymethylcarbamoyl)-butyric acid *tert*-butyl ester 13a. MS (SIMS): *m*/*z*=247 ($[M+H]^+$ 100%), 191 (M−>=), 173 (M−*t*-BuO), 102. RMN ^1H; $CDCl_3$; 200 MHz; 4.40; 1H; t; H_4; J_{4-3}=6 Hz 3.80; 3H; s; OCH_3; 3.25; 3H; s; NCH_3; 2.40; 2H; t; H_2; J_{2-3}=8 Hz 2.00; 2H; q; H_3; 1.45; 9H; s; CH_3 (*t*-Bu). ^{13}C NMR (CD_3OD; 75.5 MHz 172.1 (C_1), 169.6 (C_5), 97.8 ($OC(CH_3)$, 62.3 (OCH_3), 51.2 (C_4), 32.8 (NCH_3), 31.2 (C_2), 28.3 ($C(CH_3)$, 27.2 (C_3).

4(*S*)-Amino-4-(*N*-methoxy-*N*-methylcarbamoyl)-butyric acid isobutyl ester 13b. IR ($CHCl_3$): ν=3478; 3050; 1720 (CO); 1657 (CO); 1509; 1229; 1148. MS (SIMS): *m*/*z*=247 ($[M+H]^+$ 100%); 191; 173 (M−*i*-BuO). ^1H NMR ($CDCl_3$, 300 MHz): 4.50 (1H, t, H_4, J_{4-3}=6.0 Hz); 4.05 (2H, d, CH_2 (*i*-Bu), *J*=7.2 Hz); 3.95 (3H, s, OCH_3); 3.45 (3H, s, NCH_3); 2.70 (2H, t, H_2); 2.35 (2H, m, H_3); 2.10 (2H, m, $CH(CH_3)_2$); 0.95 (6H, d, CH_3 (*i*-Bu), *J*=7.5 Hz). ^{13}C NMR (CD_3OD, 75.5 MHz): 170.9 (C_1); 168.3 (C_5); 82.4 (OCH_2 *i*-Bu); 61.1 (OCH_3); 51.4 (C_4); 31.8 (NCH_3); 31.3 (C_2); 28.1 (*C*H *i*-Bu); 26.9 (C_3); 18.6 (CH_3 *i*-Bu).

4(*S*)-Methoxycarbonylamino-4-(methoxymethylcarbamoyl) butyric acid *tert*-butyl ester 12d. To a stirred solution of 402 mg (1.63 mmol) of hydroxamate **13a** in 20 ml of CH_2Cl_2 at rt, were successively added 140 μl (1.81 mmol) of methyl chloroformate and dropwise 254 μl (1.81 mmol) of triethylamine. After stirring for 2 h, the reaction mixture was hydrolysed by addition of 100 ml of a 1N hydrochloric acid solution, and extracted with CH_2Cl_2. The combined organic layers were then washed with brine, dried over sodium sulfate, filtered, concentrated under reduced pressure, and purified by chromatography AcOEt 70/heptane 30) to yield 490 mg (98%) of a colorless oil. IR ($CHCl_3$): ν=3423; 3027; 2981; 2941; 1721 (CO); 1686 (CO); 1659 (CO); 1509; 1478; 1424; 1369. MS (CI^+): *m*/*z*=305 ($[M+H]^+$, 100%); 275; 249 (M−=<); 98. HRMS ($C_{13}H_{24}N_2O_6$): calcd 305.1706, obs. 305.1702. ^1H NMR ($CDCl_3$, 250 MHz): 5.55 (1H, d, $NHCO_2$, J_{NH-4}=8.2 Hz); 4.70 (1H, m, H_4); 3.80 (3H, s, OCH_3); 3.70 (3H, s, OCH_3); 3.20 (3H, s, NCH_3); 2.30 (2H, t, H_2, J_{2-3}=8 Hz); 2.20–1.75 (2H, m, H_3); 1.40 (9H, s, CH_3 *t*-Bu). ^{13}C NMR (CD_3OD, 62.9 MHz): 171.7 (C_1); 170.9 (C_5); 160.4 (*C*ONH); 80.2 ($OC(CH_3)_3$); 61.2 (OCH_3); 51.9 (OCH_3); 50.2 (C_4); 46.9 (NCH_3); 30.9 (C_2); 27.7 ($C(CH_3)_3$); 27.3 (C_3).

4(*S*)-(Methoxymethylcarbamoyl)-4-(2,2,2-trichloroethoxycarbonylamino) butyric acid isobutyl ester 12e. To a stirred solution of 350 mg (1.42 mmol) of hydroxamate **13a** in 20 ml of CH_2Cl_2 at −40°C were added successively 240 μl (1.74 mmol) of 2,2,2-trichloroethyl chloroformate, and 243 μl (1.74 mmol) of triethylamine dropwise. After 1 h, the reaction mixture was hydrolysed by addition of 10 ml of 1N solution of hydrochloric acid, and extracted with CH_2Cl_2. The combined organic layers were then washed with brine, dried over sodium sulfate, filtered, concentrated under reduced pressure, and purified by chromatography (AcOEt 70/heptane 30) to yield 582 mg (97%) of a colorless oil. IR ($CHCl_3$): ν=1817; 1784; 1733; 1652; 1466; 1382; 710. MS (CI^+): *m*/*z*=421 ($[M+H]^+$ 100%); 365 (421−>=). ^1H NMR ($CDCl_3$, 250 MHz): 5.82 (1H, d. ech. $NHCO_2$, J_{NH-4}=8.8 Hz); 4.90–4.60 (3H, m, H_4, CO_2CH_2); 3.87 (2H, d, CH_2 (*i*-Bu), *J*=6.5 Hz); 3.80 (3H, s, OCH_3); 3.25 (3H, s, NCH_3); 2.45 (2H, t, H_2, J_{2-3}=7 Hz); 2.20 (1H, m, $CH(CH_3)_2$); 2.00 (2H, m, H_3); 1.00 (9H, d, CH_3 (*i*-Bu), *J*=6.5 Hz); ^{13}C NMR (CD_3OD, 62.9 MHz): 172.9 (C_1); 171.6 (C_5); 154.4 (*C*O Troc); 95.5 (CCl_3); 74.8 (CH_2 Troc); 70.9 (OCH_2 *i*-Bu); 61.8 (OCH_3); 50.9 (C_4); 32.3 (NCH_3); 31.2 (C_2); 29.9 (C_3); 27.8 (*C*H *i*-Bu); 19.2 (CH_3 *i*-Bu).

4(*S*)-(Methoxymethylcarbamoyl)-4-pyrrol-1-yl-butyric acid *tert*-butyl ester 12f. To a stirred solution of 720 mg (2.93 mmol) of hydroxamate **13a** in 20 ml of acetic acid was added 1.05 g (12.8 mmol) of sodum acetate. The reaction mixture was heated to reflux, and 380 μl (2.93 mmol) of 2,5-dimethoxytetrahydrofuran was added dropwise. After refluxing a further 10 min, the reaction mixture was cooled to rt, and hydrolysed by addition of 50 ml of water, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, concentrated under reduced pressure, and purified by chromatography (AcOEt 50/heptane 50) to yield 686 mg (79%) of a yellow oil. IR ($CHCl_3$): ν=3478; 3025; 2982; 2940; 1723 (CO); 1665 (CO); 1488; 1458; 1392; 1369. MS (EI): *m*/*z*=296 (M^+); 240 (M−=<; 100%); 208 (M−CON(Me)OMe). ^1H NMR ($CDCl_3$, 200 MHz): 6.80 (2H, t, $H_{2'}$, $J_{2'-3'}$=1.7 Hz); 6.10 (2H, t, $H_{3'}$, $J_{3'-2'}$=1.7 Hz); 5.20 (1H, t, H_4, J_{4-3}=7.6 Hz); 3.40 (3H, s, OCH_3); 3.20 (3H,

s, NCH_3); 2.30–2.00 (4H, m, H_2, H_3); 1.40 (9H, s, CH_3 (*t*-Bu). ^{13}C NMR (CD_3OD, 50.3 MHz): 171.8 (C_1); 169.9 (C_5); 119.8 ($C_{2'}$); 108.3 ($C_{3'}$); 80.2 ($C(CH_3)_3$); 61.1 (OCH_3); 56.3 (C_4); 32.0 (NCH_3); 30.8 (C_2); 27.9 (C_3); 27.8 ($C(CH_3)_3$).

General procedure for reduction of hydroxamates

To a stirred solution of 2.0 g (5.22 mmol) of hydroxamate in 50 ml Et_2O at −20°C were added portionwise 278 mg (7.31 mmol) of $LiAlH_4$. After 2 h 40 min the reaction mixture was slowly hydrolysed by addition of a 3% aqueous solution of sodium hydrogenosulfate, filtered and extracted with Et_2O. The combined organic layers were then washed successively with a solution of 1N hydrochloric acid, a saturated solution of sodium hydrogenocarbonate, and brine. The combined organic layers were then dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 1.66 g (99%) of a colorless oil which was used without further purification.

4(*S*)-Benzyloxycarbonylamino-5-*oxo*-pentanoic acid *tert*-butyl ester 14a. α_D=−23 (24°C, MeOH; *c*=0.9). IR ($CHCl_3$): ν=3430 (NH); 3025; 2965 (CH_3); 1700 (CO); 1710 (CO); 1510 (NH). MS (CI^+), *m*/*z*=322 ($[M+H]^+$, 100%); 304 (322−H_2O); 266 (322−>=; 100%); 107 ($PhCH_2O$); 91. HRMS ($C_{17}H_{23}NO_5$): calcd 322.1649, obs. 322.1672. ^1H NMR ($CDCl_3$, 200 MHz): 9.55 (1H, s, CHO); 7.30 (5H, s, Ph); 5.80 (1H, d ex. NHCO, $J_{NH\text{-}4}$=8 Hz); 5.05 (2H, s, CH_2Ph); 4.40–4.30 (1H, m, H_4); 2.30 (2H, t, H_2, $J_{2\text{-}3}$=7 Hz); 2.10–1.70 (2H, m, H_3); 1.40 (9H, s, CH_3 (*t*-Bu). ^{13}C NMR (CD_3OD, 50.3 MHz): 198.9 (C_5); 172.0 (C_1); 156.2 (*C*O Cbz); 136.2 (C_ϕ); 128.5 (CH_o); 128.2 (CH_p); 128.0 (CH_m); 80.9 ($OC(CH_3)_3$); 67.1 (CH_2Ph); 52.6 (C_4); 30.9 (C_2); 28.0 (CH_3 *t*-Bu); 24.1 (C_3).

4(*S*)-Benzyloxycarbonylamino-5-*oxo*-pentanoic acid isobutyl ester 14b. IR ($CHCl_3$): ν=3430 (NH); 3020; 1700 (CO); 1710 (CO); 1500 (NH). MS (CI^+), *m*/*z*=322 ($[M+H]^+$, 100%); 304 (322−H_2O); 266 (322−>=; 100%); 107 ($PhCH_2O$); 91. ^1H NMR ($CDCl_3$, 200 MHz): 9.60 (1H, s, CHO); 7.30 (5H, s, Ph); 5.70 (1H, d, ex., NHCO, $J_{NH\text{-}4}$=8 Hz); 5.10 (2H, s, CH_2Ph); 4.40–4.30 (1H, m, H_4); 3.90 (2H, d, CH_2 *i*-Bu, *J*=7.6 Hz); 2.35 (2H, t, H_2, $J_{2\text{-}3}$=7 Hz); 2.20 (1H, m, CH *i*-Bu); 2.00–1.85 (2H, m, H_3); 1.00 (6H, d, CH_3 *i*-Bu). ^{13}C NMR (CD_3OD, 50.3 MHz): 198.0 (C_5); 172.5 (C_1); 155.8 (*C*O Cbz); 136.1 (C_ϕ); 128.6 (CH_o); 128.3 (CH_p); 128.0 (CH_m); 68.3 (CH_2Ph); 66.7 ($OCCH_2$ *i*-Bu); 53.2 (C_4); 30.5 (C_2); 27.3 (*C*H *i*-Bu); 24.2 (C_3); 19.1 (CH_3 *i*-Bu).

4(*S*)-4-*tert*-Butoxycarbonylamino-5-*oxo*-pentanoic acid *tert*-butyl ester 14c. MS (CI^+): *m*/*z*=288 ($[M+H]^+$); 232 (M−==<); 176 (M−2x=<; 100%); 132. ^1H NMR ($CDCl_3$, 200 MHz): 9.50 (1H, s, CHO); 5.40 (1H, dl, NHCO); 4.00 (1H, m, H_4); 2.30 (2H, bt, H_2); 2.05 (2H, m, H_3); 1.40 (18H, bs, CH_3 (*t*-Bu)).

4(*S*)-4-(Methoxycarbonyl)amino-5-*oxo*-pentanoic acid *tert*-butyl ester 14d. ^1H NMR ($CDCl_3$, 200 MHz): 9.55 (1H, bs, CHO); 5.50 (1H, bd, $NHCO_2$); 3.60 (3H, s, OCH_3); 4.10 (1H, m, H_4); 2.25 (2H, t, H_2); 1.95 (2H, m, H_3); 1.35 (9H, s, CH_3 (*t*-Bu)).

5-*Oxo*-4(*S*)-(2,2,2-Trichloroethoxycarbonylamino) pentanoic acid isobutyl ester 14e. MS (CI^+): *m*/*z*=362 ($[M+H]^+$); 306 (M−==<). ^1H NMR ($CDCl_3$, 200 MHz): 9.60 (1H, s, CHO); 5.45 (1H, bd, $NHCO_2$); 4.70 (2H, m, CH_2CCl_3); 4.05 (1H, m, H_4); 3.80 (2H, d, OCH_2 (*i*-Bu)); 2.45 (2H, bt, H_2); 2.10 (1H, m, CH (*i*-Bu)); 2.05 (2H, m, H_3); 1.40 (6H, d, CH_3 (*i*-Bu), *J*=8 Hz).

5-*Oxo*-4(*S*)-Pyrrol-1-yl-pentanoic acid *tert*-butyl ester 14f. ^1H NMR ($CDCl_3$, 200 MHz): 9.60 (1H, s, CHO); 6.60 (2H, t, $H_{2'}$); 6.20 (2H, t, $H_{3'}$); 4.40 (1H, m, H_4); 2.40–1.80 (4H, m, H_2, H_3); 1.40 (9H, bs, CH_3 (*t*-Bu)).

4(*S*)-Diethylcarbamoyl-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl) butyric acid 16. To a stirred solution of 2.0 g (7.72 mmol) of *N*-phthaloyl glutamic anhydride in 10 ml of THF at rt was added dropwise a solution of 0.84 ml (8.13 mmol) of diethylamine in 5 ml of THF. After refluxing for 2 h, the reaction mixture was cooled to rt, and the resulting white precipitate was filtered and washed successively with 5 ml of THF, 10 ml of cooled (−20°C) Et_2O, and dried under reduced pressure to yield 1.64 g (64%) of a white amorphous solid. IR ($CHCl_3$): ν=3478; 3400–2450; 1751; 1625; 1467; 1385. MS (EI): *m*/*z*=332 (M^+); 287 (M−CO_2H); 259 (M−73); 232 (M−$CONEt_2$); (CI^+): *m*/*z*=333 ($[M+H]^+$ 100%); 315 (M−H_2O); 287 (M−CO_2H); 186. HRMS ($C_{17}H_{20}N_2O_5$): calcd 333.1443, obs. 333.1451. ^1H NMR ($CDCl_3$, 250 MHz): 10.80 (1H, bs, CO_2H); 7.85 (2H, m, $H_{4'}$ Pht); 7.70 (2H, m, $H_{5'}$ Pht); 4.90 (1H, m, H_4); 3.40–3.15 4H, m, CH_2 (Et)); 2.80–2.30 (4H, m, H_3, H_2); 1.10 (6H, m, CH_3 (Et)). ^{13}C NMR (CD_3OD, 50.3 MHz): 176.5 (C_5); 174.5 (C_1); 169.0 (*C*O Pht); 134.4 ($C_{5'}$); 132.5 ($C_{3'}$); 124.1 ($C_{4'}$); 54.3 (C_4); 42.2 (CH_3 Et); 32.6 (C_2); 25.6 (C_3); 11.2 (CH_3 Et).

4(*S*)-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-5-hydroxypentanoic acid diethylamide 18. To a stirred solution of 1.22 g (3.07 mmol) of **16** in 25 ml of THF at −15°C were successively added 338 μl (3.07 mmol) of *N*-methylmorpholine, and 399 μl (3.07 mmol) of *iso*-butyl chloroformate. After stirring for 1 min at −15°C, a solution of 350 mg (9.21 mmol) of sodium borohydride in 5 ml of water was added at once. The reaction mixture was stirred for 15 s then hydrolysed with 20 ml water, and extracted with AcOEt. The combined organic layers were then washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure to yield 1.02 g (88%) of a colorless oil which was used without further purification. IR ($CHCl_3$): ν=3627; 3602–3190; 3088; 2981; 2937; 2877; 2460; 1773 (CO); 1713; 1635; 1483; 1468; 1438. MS (EI): *m*/*z*=318 ($M^{+\cdot}$); 300 (M−18); 287 (M−CH_2OH); 246 (M−NEt_2); 186; 128. ^1H NMR ($CDCl_3$, 200 MHz): 7.80 (2H, m, $H_{4'}$ Pht); 7.75 (2H, m, $H_{5'}$ Pht); 4.40 (1H, m, H_4); 4.10–3.85 (2H, m, H_5); 3.25–3.05 (5H, m, CH_2 (Et), OH); 2.30–1.90 (4H, m, H_2, H_3); 1.00 (3H, t, CH_3 (Et)); 0.90 (3H, t, CH_3 (Et). ^{13}C NMR (CD_3OD, 50.3 MHz): 170.9 (*C*O); 168.9 (*C*O Pht); 133.9 (*C*H Pht); 131.7 (C_ϕ Pht); 123.1 (*C*H Pht); 62.6 (C_5); 53.7 (C_4); 41.9 (CH_2CH_3); 40.2 (CH_2CH_3); 29.6 (C_2); 24.1 (C_3); 14.0 (CH_2CH_3); 12.9 (CH_2CH_3).

4(*S*)-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-5-*oxo*-pentanoic acid diethylamide 14g. To a stirred solution of

41.8 mg (131 μmol) of alcohol **18** in 10 ml of CH_2Cl_2 at rt, were successively added 150 mg of 4Å molecular sieves, and 142 mg (655 μmol) of PCC. After 1 h of stirring at rt, the reaction mixture was filtered over Celite, concentrated under reduced pressure, and purified by chromatography (AcOEt 80/heptane 20) to yield 23 mg (68%) of a light yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): 9.70 (1H, s, CHO); 8.85 (2H, m, $H_{4'}$ Pht); 8.75 (2H, m, $H_{5'}$ Pht); 4.80 (1H, m, H_4); 3.40–3.10 (4H, m, CH_2 (Et)); 2.55–2.15 (4H, m, H_2, H_3); 1.05 (6H, m, CH_3 (Et)).

General procedure for the Pictet–Spengler reaction

To a stirred solution of 848 mg (2.64 mmol) of aldehyde and 465 mg (2.90 mmol) of tryptamine in 20 ml CH_2Cl_2 held at the desired temperature, was added dropwise a solution of 0.41 ml (5.80 mmol) of trifluoroacetic acid in 5 ml CH_2Cl_2. After 5 h, the reaction mixture was slowly hydrolysed by addition of a saturated solution of sodium carbonate. The reaction mixture was then extracted with CH_2Cl_2, and washed with brine. The combined organic layers were dried over sodium sulfate, filtered, concentrated under reduced pressure, and purified by chromatography (AcOEt 80/heptane 20, then AcOEt 100%, then AcOEt 90/MeOH 10) to yield 1.85 g (77%) of an amorphous beige solid.

1(*R*)-4′(*S*)-Benzyloxycarbonylamino-4′-(1,2,3,4-tetrahydro-1*H*-β-carbolin-1-yl) butyric acid *tert*-butyl ester 7a. α_D=+20 (25°C, MeOH, *c*=1.0). IR ($CHCl_3$): ν=3300 (NH); 3020–2980–2970; 1700 (CO); 1510. UV (EtOH): λ=225; 280. MS (EI): *m*/*z*=464 ($[M+H]^{+\cdot}$; 462 ($[M-H]^{+\cdot}$; 391 (M−O*t*-Bu); 171; 91; (CI^+): *m*/*z*=464 ($[M+H]^+$); 390 (M−O*t*-Bu); 298; 171 (100%); 143; 130; 117; 91. HRMS ($C_{27}H_{33}N_3O_4$): calcd 463.2463, obs. 463.2458. ^{1}H NMR ($CDCl_3$, 200 MHz): 8.55 (1H, bs, ex., H_9); 7.60–7.00 (9H, m, H arom.); 5.90–5.60 (1H, m, ex., H_2); 5.10 (2H, s, CH_2Ph); 4.95 (1H, d, H_1, $J_{1\text{-}4'}$=7 Hz); 4.60 (1H, d, ex., NH (Cbz), $J_{NH\text{-}4'}$=7 Hz); 4.40–4.10 (2H, m, H_3); 3.50–3.40 (1H, m, $H_{4'}$); 2.43 (2H, t, $H_{2'}$, $J_{2'\text{-}3'}$=7 Hz); 1.90–1.60 (4H, m, $H_{3'}$, H_4); 1.45 (9H, s, CH_3 (*t*-Bu)). ^{13}C NMR (CD_3OD, 50.3 MHz): 172.7 ($C_{1'}$); 156.9 (*C*O Cbz); 136.3 (C_{8a}); 136.6 (C_ϕ Cbz); 132.8 (C_{9a}); 128.2–127.2 (*C*H_o, *C*H_m, *C*H_p, C_{4b}); 121.3 (C_7); 118.9 (C_6); 117.7 (C_8); 110.5 (C_{4a}); 80.4 (O*C*$(CH_3)_3$); 66.2 (*C*H_2Ph); 56.1 (C_1); 52.6 ($C_{4'}$); 43.3 (C_3); 32.2 ($C_{2'}$); 27.9 (C(*C*$H_3)_3$); 27.2 (C_4); 22.5 ($C_{3'}$). Chiral HPLC (hexane 98 / ethanol 2): RT_1=42 min; RT_2=45 min; ee>99%.

1(*S*)-4′(*S*)-Benzyloxycarbonylamino-4′-(1,2,3,4-tetrahydro-1*H*-β-carbolin-1-yl) butyric acid *tert*-butyl ester 6a. α_D=−15 (24, MeOH, *c*=1.0). IR ($CHCl_3$): ν=3300 (NH); 3020–2980–2970; 1700 (CO); 1510. UV (EtOH): λ=225; 280. MS (EI): *m*/*z*=463 (M^+; 390 (M−O*t*-Bu); 288; 171 (100%); 144; 130; 91. HRMS ($C_{27}H_{33}N_3O_4$): calcd 463.2463, obs. 463.2444. Analysis: calcd C: 69.97, H: 7.17, O: 13.81, N: 9.06; obs., C: 69.69, H: 7.33, O: 13.98, N: 8.76. ^{1}H NMR ($CDCl_3$, 200 MHz): 8.85 (1H, bs, ex., H_9); 7.50 (1H, d, H_5, $J_{5\text{-}6}$=8 Hz); 7.40–6.90 (8H, m, H arom.); 5.70 (1H, m, ex., H_2); 4.90 (2H, s, CH_2Ph); 4.30 (1H, m, ex., $NHCO_2$); 4.20 (2H, m, H_1, H_3); 3.95 (1H, m, $H_{4'}$); 3.85–2.20 (4H, m, $H_{3'}$, $H_{2'}$); 2.10 (2H, m, H_4); 1.40 (9H, s, CH_3 (*t*-Bu)). ^{13}C NMR (CD_3OD, 50.3 MHz): 172.9 ($C_{1'}$); 157.1 (*C*O Cbz); 136.4 (C_{8a}); 132.6 (C_ϕ Cbz); 128.7 (C_{9a}); 128.5 (*C*H_o); 128.2 (C_{4b}); 127.9 (*C*H_p); 127.5 (*C*H_m); 121.8 (C_7); 119.4 (C_6); 118.1 (C_8); 111.4 (C_5); 110.9 (C_{4a}); 80.9 (O*C*$(CH_3)_3$); 66.6 (*C*H_2Ph); 56.2 (C_1); 52.6 ($C_{4'}$); 43.6 (C_3); 32.3 ($C_{2'}$); 28.2 (C(*C*$H_3)_3$); 27.3 (C_4); 21.9 ($C_{3'}$). Chiral HPLC (hexane 98/ethanol 2): RT_1=32 min; RT_2=40 min; ee=24%.

3a(*R*)-4(*S*)-5a(*S*)-1,2,3,3a,4,5-Hexahydro-4-(*tert*-butoxycarbonylpropyl)-5-(benzyloxycarbonyl)-pyrrolo[2′,3′:3,4]pyrrolo[2,3-b]indole 19. α_D=−40 (24°C, MeOH, *c*=1.0). IR ($CHCl_3$): ν=3437 (NH); 3028–2990–2975; 1710 (CO); 1520; 1426; 1216. UV (EtOH): λ=211; 242; 298. MS (CI^+): *m*/*z*=464 ($[M+H]^+$); 391 (M−O*t*-Bu); 301; 161. HRMS ($C_{27}H_{33}N_3O_4$): calcd 463.2463, 464.2542; obs. 463.2466, 464.2513. ^{1}H NMR ($CDCl_3$, 200 MHz): 7.50–7.30 (5H, m, H arom.); 7.20–7.00 (2H, m, H_8, H_{10}); 6.80 (1H, t, H_9, $J_{7\text{-}6}$=$J_{7\text{-}8}$=8 Hz); 6.60 (1H, d, H_7, $J_{5\text{-}6}$=8 Hz); 5.50 (1H, bs, ex., H_3); 5.41 (1H, bs, ex., H_6); 5.30–5.00 (3H, m, CH_2Ph, H_{5a}); 4.00 (1H, m, H_4); 3.60 (1H, bs, H_{3a}); 3.20 (2H, t, H_2, $J_{10\text{-}9}$=6 Hz); 2.30–2.00 (4H, m, $H_{2'}$, H_1); 1.80–1.50 (2H, m, $H_{3'}$); 1.30 (9H, s, CH_3 (*t*-Bu)). ^{13}C NMR (CD_3OD, 50.3 MHz): 172.4 (*C*O ester); 154.8 (*C*O Cbz); 136.6 (C_ϕ); 131.3 C_{6a}); 128.7 (*C*H_o, *C*H_p); 128.2 (*C*H_m); 128.0 (C_{10a}); 122.9 (C_8); 119.3 (C_9); 119.2 (C_{10}); 109.2 (C_7); 83.9 (C_{5a}); 80.3 (O*C*$(CH_3)_3$); 74.5 (C_{3a}); 67.3 (*C*H_2Ph); 65.4 (C_4); 47.2 (C_2); 32.6–29.4 ($C_{2'}$, $C_{3'}$, C_1); 29.7 (C_{10b}); 28.1 (C(*C*$H_3)_3$). Chiral HPLC (hexane 98/ethanol 2): RT_1=21 min; RT_2=29 min; ee=60%.

1(*R*)-4′(*S*)-Benzyloxycarbonylamino-4′-(1,2,3,4-tetrahydro-1*H*-β-carbolin-1-yl) butyric acid isobutyl ester 7b. IR ($CHCl_3$): ν=3300 (NH); 3020–2980–2970; 1700 (CO); 1510. MS (EI): *m*/*z*=463 ($M^{+\cdot}$; 390 (M−O*t*-Bu); 288; 171 (100%); 144; 130; 91. ^{1}H NMR ($CDCl_3$, 200 MHz): 8.85 (1H, bs, ex., H_9); 7.50 (1H, d, H_5, $J_{5\text{-}6}$=8 Hz); 7.40–6.90 (8H, m, H arom.); 5.70 (1H, m, ex., H_2); 4.90 (2H, s, CH_2Ph); 4.30 (1H, m, ex., $NHCO_2$); 4.20 (2H, m, H_1, H_3); 3.95 (1H, m, $H_{4'}$); 3.85 (2H, d, CH_2 (*i*-Bu), *J*=8 Hz); 3.75–2.15 (5H, m, $H_{3'}$, $H_{2'}$, CH (*i*-Bu)); 2.10 (2H, m, H_4); 0.95 (6H, d, CH_3 (*i*-Bu), *J*=8 Hz). ^{13}C NMR (CD_3OD, 50.3 MHz): 172.9 ($C_{1'}$); 157.1 (*C*O Cbz); 136.4 (C_{8a}); 132.6 (C_ϕ Cbz); 128.7 (C_{9a}); 128.5 (*C*H_o); 128.2 (C_{4b}); 127.9 (*C*H_p); 127.5 (*C*H_m); 121.8 (C_7); 119.4 (C_6); 118.1 (C_8); 111.4 (C_5); 110.9 (C_{4a}); 72.5 (O*C*H_2 *i*-Bu); 66.6 (*C*H_2Ph); 56.2 (C_1); 52.6 ($C_{4'}$); 43.6 (C_3); 32.3 ($C_{2'}$); 27.3 (C_4); 26.9 (*C*H *i*-Bu); 21.9 ($C_{3'}$); 19.4 (*C*H_3 *i*-Bu).

1(*R*)-4′(*S*)-*tert*-Butoxycarbonylamino-4′-(1,2,3,4-tetrahydro-1*H*-β-carbolin-1-yl) butyric acid *tert*-butyl ester 7c. IR ($CHCl_3$): ν=3435 (NH); 3035–2850; 1764 (CO); 1704 (CO); 1499; 1456; 1368; 1151. MS (EI): *m*/*z*=429 ($M^{+\cdot}$; 355 (M−*t*-BuOH); 298; 282; 171 (100%). HRMS ($C_{24}H_{35}N_3O_4$): calcd 429.2627, obs. 429.2623. ^{1}H NMR ($CDCl_3$, 200 MHz): 8.70 (1H, s, H_9); 7.45 (1H, d, H_5, $J_{5\text{-}6}$=7.6 Hz); 7.25 (1H, d, H_8, $J_{8\text{-}7}$=7.6 Hz); 7.10 (2H, m, H_6, H_7); 5.25 (1H, bd, $NHCO_2$); 4.20 (1H, d, H_1, $J_{1\text{-}4'}$=8 Hz); 4.10 (1H, m, $H_{4'}$); 3.4 (1H, ddd, H_{3eq}, *J*=2.4 Hz, *J*=4.8 Hz, *J*=12 Hz); 3.05 (1H, ddd, H_{4ax}, *J*=4.9 Hz, *J*=9.6 Hz, *J*=9.6 Hz); 2.90–2.60 (2H, m, H_3, H_4); 2.40 (2H, t, $H_{2'}$); 2.10 (1H, bs, H_2); 1.90 (2H, m, $H_{3'}$); **6c**: 9.00 (1H, s, H_9); 7.30 (1H, d, H_8); 5.75 (1H, bd,

$NHCO_2$). ^{13}C NMR (CD_3OD, 50.3 MHz): 172.9 ($C_{1'}$); 156.6 (*C*O Boc); 136.3 (C_{8a}); 133.2 (C_{9a}); 127.4 (C_{4b}); 121.3 (C_7); 118.9 (C_6); 117.6 (C_8); 111.2 (C_5); 110.3 (C_{4a}); 80.6 ($C(CH_3)_3$); 79.4 ($C(CH_3)_3$); 56.6 (C_1); 51.2 ($C_{4'}$); 43.6 (C_3); 32.4 ($C_{2'}$); 28.1 (2 C(CH_3)$_3$); 27.1 (C_4); 22.0 ($C_{3'}$); **6c**: 173.1 ($C_{1'}$); 156.1 (*C*O Boc); 121.5 (C_7); 119.1 (C_6); 117.9 (C_8); 56.4 (C_1); 53.2 ($C_{4'}$); 43.0 (C_3).

1(*R*)-4′(*S*)-Methoxycarbonylamino-4′-(1,2,3,4-tetrahydro-1*H*-β-carbolin-1-yl) butyric acid *tert*-butyl ester 7d. IR ($CHCl_3$): ν=3423; 3027–2920; 1715 (CO); 1660; 1509; 1480; 1370; 1155. MS (CI^+): *m*/*z*=388 ($[M+H]^+$); 386 ($[M-H]^+$); 171; 161; 144. HRMS ($C_{21}H_{29}N_3O_4$): calcd 388.2229, obs. 388.2229. ^1H NMR ($CDCl_3$, 200 MHz): 8.65 (1H, bs, H_9); 7.45 (1H, d, H_5, $J_{5\text{-}6}$=8 Hz); 7.35 (1H, d, H_8, $J_{8\text{-}7}$=8 Hz); 7.20–6.95 (2H, m, H_6, H_7, 5.55 (1H, bd, ex., $NHCO_2$); 4.20 (3H, m, H_1, H_3); 3.45 (3H, s, OCH_3); 3.40 (1H, m, $H_{4'}$); 3.10–2.90 (1H, m, $H_{2'}$); 2.50–2.10 (3H, m, $H_{2'}$, $H_{3'}$); 2.00–1.90 (1H, m, H_4); 1.45 (9H, s, CH_3 (*t*-Bu)); **6d**: 9.05 (1H, bs, H_9); 5.80 (1H, bd, ex., $NHCO_2$). ^{13}C NMR (CD_3OD, 50.3 MHz): 172.9 ($C_{1'}$); 157.4 (*C*O); 136.2 (C_{8a}); 127.3 (C_{9a}); 117.9 (C_{4b}); 121.4 (C_7); 118.9 (C_6); 117.7 (C_8); 111.3 (C_5); 110.4 (C_{4a}); 80.7 (O*C*(CH_3)$_3$); 56.2 (O*C*H_3); 52.4 (C_1); 52.0 ($C_{4'}$); 43.5 (C_3); 32.3 ($C_{2'}$); 28.0 (C(*C*H_3)$_3$); 27.3 (C_4); 22.0 ($C_{3'}$); **6d**: 173.2 ($C_{1'}$); 156.2 (*C*O); 53.6 (C_1); 43.1 (C_3); 24.7 (C_4); 22.7 ($C_{2'}$).

1(*R*)-4′(*S*)-(1,2,3,4-Tetrahydro-1*H*-β-carbolin-1-yl)-4′-(2,2,2-trichloroethoxycarbonylamino) butyric acid isobutyl ester 7e. IR ($CHCl_3$): ν=3435 (NH); 3010–2970; 1722 (CO); 1735 (CO); 1510; 1136. MS (CI^+): *m*/*z*=504 ($[M+H]^+$); 421 (100%); 391; 319; 171. HRMS ($C_{22}H_{28}N_3O_4Cl_3$): calc 504.1224, obs. 504.1245. ^1H NMR ($CDCl_3$, 200 MHz): 8.60 (1H, s, H_9); 7.45 (1H, d, H_5, $J_{5\text{-}6}$=7.6 Hz); 7.20 (1H, d, H_8, $J_{8\text{-}7}$=7.6 Hz); 7.10 (2H, m, H_6, H_7); 5.90 (1H, d, H_1); 4.50 (2H, s, CH_2 (Troc)); 4.30 (1H, m, $H_{4'}$); 3.90 (2H, d, CH_2 (*i*-Bu)); 3.35 (1H, dd, H_{3eq}); 3.00 (1H, dd, H_{4ax}); 2.95–2.60 (2H, m, H_{3ax}, H_{4eq}); 2.55 (2H, t, $H_{2'}$); 2.25 (1H, m, CH (*i*-Bu)); 2.00 (2H, m, $H_{3'}$); 1.00 (6H, d, CH_3 (*i*-Bu)); **6e**: 8.95 (1H, s, H_9); 7.50 (1H, d, H_5); 7.35 (1H, d, H_8); 6.15 (1H, d, H_1). ^{13}C NMR (CD_3OD, 50.3 MHz): 173.6 ($C_{1'}$); 155.4 (*C*O Troc); 136.4 (C_{8a}); 132.2 (C_{9a}); 127.4 (C_{4b}); 122.0 (C_{4a}); 121.8 (C_7); 119.3 (C_6); 118.0 (C_8); 111.2 (C_5); 95.6 (*C*Cl_3); 74.2 (O*C*H_2 Troc); 71.0 (O*C*H_2 *i*-Bu); 56.2 (C_1); 52.9 ($C_{4'}$); 43.5 (C_3); 30.9 ($C_{2'}$); 27.8 (C_4); 27.5 (*C*H *i*-Bu); 22.0 ($C_{3'}$); 19.2 (*C*H_3 *i*-Bu); **6e**: 122.0 (C_7); 74.7 (O*C*H_2 Troc); 53.6 ($C_{4'}$); 43.1 (C_3); 30.6 ($C_{2'}$); 22.8 ($C_{3'}$).

1(*S*)-4′(*S*)-Pyrrol-1-yl-4′-(1,2,3,4-tetrahydro-1*H*-β-carbolin-1-yl) butyric acid *tert*-butyl ester 6f(IR ($CHCl_3$): ν=3410 (NH); 3025–2930; 1718 (CO); 1614; 1491; 1370; 1155; 1091. MS (EI): *m*/*z*=379 ($M^{+\cdot}$; 322 (M−*t*-Bu); 306; 287; 171 (100%). ^1H NMR ($CDCl_3$, 200 MHz): 7.45 (1H, d, H_5); 7.05 (3H, m, H_6, H_7, H_8); 6.60 (2H, t, $H_{2'}$); 6.40 (1H, s, H_9); 6.15 (2H, t, $H_{3'}$); 4.20 (1H, d, H_1, $J_{1\text{-}4'}$=8 Hz); 4.10 (1H, m, $H_{4'}$); 3.25–3.30 (2H, m, H_{3eq}. H_{4ax}); 2.80.2.60 (3H, m, H_{3ax}, H_{4eq}, $H_{3'}$); 2.20–1.90 (2H, m, $H_{2'}$, NH); 1.80 (1H, bs, $H_{3'}$); 1.40 (9H, s, CH_3 (*t*-Bu)); ^{13}C NMR (CD_3OD, 50.3 MHz): 167.3 (*C*O); 130.1 (C_{8a}); 129.5 (*C*$H_{2''}$); 128.6 (*C*$H_{3''}$); 121.3 (C_{9a}); 118.7 (C_7); 117.6 (C_{4b}); 110.4 (C_6); 108.7 (C_8); 108.3 (C_5); 106.5 (C_{4a}); 80.1 ($C(CH_3)_3$); 67.8 (C_1); 38.4 ($C_{4'}$); 30.0 (C_3); 28.5 ($C_{2'}$); 27.7 (C(*C*H_3)$_3$); 23.4 (C_4); 22.6 ($C_{3'}$).

1(*S*)-4′(*S*)-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-*N*,*N*-diethyl-4′-(1,2,3,4-tetrahydro-1*H*-β-carbolin-1-yl) butyramide 6g(IR ($CHCl_3$): ν=3470; 3050; 1708; 1629; 1394; 1365; 1270; 1142. MS (SIMS): *m*/*z*=459 ($[M+H]^+$, 100%); 442; 287; 171; 144. ^1H NMR ($CDCl_3$, 200 MHz): 9.4 (1H, s, ex., H_9); 7.80 (2H, m, $H_{4''}$ Pht); 7.70 (2H, m, $H_{5''}$ Pht); 7.45 (1H, d, H_5, $J_{5\text{-}6}$=8 Hz); 7.40 (1H, d, H_8, $J_{8\text{-}7}$=8 Hz); 7.15 (1H, t, H_7, $J_{7\text{-}6}$=$J_{7\text{-}8}$=8 Hz); 7.05 (1H, t, H_6, $J_{7\text{-}6}$=$J_{7\text{-}8}$= 8 Hz); 4.70 (1H, m, $H_{4'}$); 4.45 (1H, d, H_1, $J_{1\text{-}4'}$=9.6 Hz); 3.45–2.95 (6H, m, H_3 CH_2 (Et)); 2.85–2.60 (3H, m, H_4, $H_{3'}$); 2.55–2.20 (3H, m, $H_{2'}$, $H_{3'}$); 2.05 (bs, 1H, H_2); 1.15–0.95 (m, 6H, CH_3 (NEt_2)); **7g**: 8.95 (1H, s, ex., H_9); 4.95 (1H, m, $H_{4'}$); 4.55 (1H, d, H_1). ^{13}C NMR (CD_3OD, 50.3 MHz): 171.1 ($C_{1'}$); 169.3 (*C*O Pht); 136.2 (C_{8a}); 134.2 (*C*H Pht); 133.8 (C_ϕ Pht); 131.9 (C_{9a}); 127.3 (C_{4b}); 123.5 (*C*H Pht); 121.7 (C_7); 119.2 (C_6); 118.0 (C_5); 111.5 (C_8); 110.0 (C_{4a}); 54.6 (C_1); 53.9 ($C_{4'}$); 42.1 (*C*H_2 Et); 41.8 (C_3); 40.6 (*C*H_2 Et); 29.9 ($C_{2'}$); 25.4 ($C_{3'}$); 22.8 (C_4); 14.2 (*C*H_3 Et); 13.2 (*C*H_3 Et).

General procedure for lactam cyclisations

To a stirred solution of 345 mg (745 μmol) of β-carboline in 20 ml MeOH at rt were added 4 mg (814 μmol) of NaOMe. After 24 h, the reaction mixture was concentrated under reduced pressure, diluted in 50 ml AcOEt and washed successively with a solution of 1 N hydrochloric acid, 5% sodium hydrogenocarbonate solution, and brine. The combined organic layers were then dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by chromatography (AcOEt 90/heptane 10) to yield 261 mg (90%) of a beige amorphous solid.

1(*S*)-12b(*R*)-(4-*Oxo*-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-a]quinolizin-1-yl) carbamic acid benzyl ester 21a. α_D=+59 (24°C, MeOH, *c*=0.6). IR ($CHCl_3$): ν=3435 (NH); 3320 (NH); 3015–2980–2950; 1710 (CO); 1635 (C=N); 1510 (C=C); 1125 (C-O). UV (EtOH): λ=214; 242; 298. MS (EI): *m*/*z*=389 ($M^{+\cdot}$; 298 (M−$PhCH_2$); 281 (M−$PhCH_2OH$); 238 (M−NH_2Cbz; 100%); 171; 107 ($PhCH_2O$); 91; 77; (CI^+) *m*/*z*=390 ($[M+H]^+$); 312; 282; 256; 249; 212; 152; 147; 91. HRMS ($C_{23}H_{23}N_3O_3$): calcd 389.1734, obs. 389.1751. ^1H NMR ($CDCl_3$, 300 MHz): 9.54 (1H, s, ex., NH_{12}); 7.50–6.90 (9H, m, H arom.); 6.20 (1H, 02d, ex., $NHCO_2$, $J_{NH\text{-}1}$=6 Hz); 5.20 (2H, d, CH_2Ph); 4.45 (1H, bs, H_{12b}); 2.70 (5H, m, H_6, H_3, H_1); 2.40 (4H, m, H_7, H_2). ^{13}C NMR (CD_3OD, 50.3 MHz): 169.4 (C_4); 156.9 (*C*O Cbz); 136.9 (C_{11a}); 136.0 (C_ϕ); 130.0 (C_{12a}); 128.3 (*C*H_o); 127.7 (*C*H_p); 127.2 (*C*H_m); 126.6 (C_{7b}); 122.2 (C_{10}); 119.4 (C_9); 118.4 (C_8); 111.3 (C_{11}); 111.0 (C_{7a}); 66.5 (CH_2Ph); 58.2 (C_{12b}); 46.4 (C_1); 40.1 (C_6); 27.4 (C_3); 24.6 (C_2); 20.6 (C_7). Chiral HPLC (hexane 98/ethanol 2): RT_1=12 min; RT_2=16 min; ee>99%.

1(*S*)-12b(*S*)-(4-*Oxo*-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-a]quinolizin-1-yl)-carbamic acid benzyl ester 20a. IR ($CHCl_3$): ν=3422 (NH); 3070 (NH); 3007; 1687 (CO); 1645 (C=N); 1513 (C=C); 1135 (C–O). MS (EI): *m*/*z*=389 ($M^{+\cdot}$; 298 (M−CH_2Ph); 171; 91. HRMS ($C_{23}H_{23}N_3O_3$): calcd 389.1734, obs. 389.1735. ^1H NMR

($CDCl_3$, 200 MHz): 9.20 (1H, bs, ex., NH (Ind); 7.40 (1H, d, H_8, $J_{8\text{-}9}$=8 Hz); 7.30 (5H, bs, H Cbz); 7.25 (1H, d, H_{11}, $J_{11\text{-}10}$=8 Hz); 7.10 (1H, t, H_{10}); 7.05 (1H, t, H_9); 5.55 (1H, bs, ex., NH Cbz); 5.15 (2H, s, CH_2Ph); 4.95 (1H, m, H_{6eq}); 4.65 (1H, d, H_{12b}, $J_{12b\text{-}1}$=5.9 Hz); 4.15 (1H, m, H_1); 2.95–2.20 (5H, m, H_3, H_{6ax}, H_7); 2.05–1.70 (2H, m, H_2). ^{13}C NMR (CD_3OD, 50.3 MHz): 168.9 (C_4); 156.6 (*C*O Cbz); 136.2 (C_{11a}); 135.9 (C_ϕ); 131.7 (C_{12a}); 128.9 (*C*H_o); 128.7 (*C*H_p); 128.4 (*C*H_m); 124.6 (C_{7b}); 122.4 (C_{10}); 119.8 (C_9); 118.4 (C_8); 111.5 (C_{11}); 110.3 (C_{7a}); 67.8 (*C*H_2Ph); 60.1 (C_{12b}); 51.6 (C_1); 41.9 (C_6); 30.1 (C_3); 26.3 (C_2); 20.9 (C_7). Chiral HPLC (hexane 98 / ethanol 2): RT_1=18 min; RT_2=20 min; ee=46%.

1(*S*)-12b(*S*)-(4-*Oxo*-1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-a]quinolizin-1-yl)-carbamic acid *tert*-butyl ester 21c. IR ($CHCl_3$): ν=3439 (NH); 3015–2980–2950; 1795 (CO); 1641 (C=N); 1506 (C=C); 1157. MS (EI): *m*/*z*=355 ($M^{+\cdot}$; 298 (M−*t*-Bu); 281 (M−*t*-BuO); 238 (M−NH_2Boc, 100%); 107 ($PhCH_2O$); 91; 77. HRMS ($C_{20}H_{25}N_3O_3$): calc 355.1896, obs. 355.1887. ^1H NMR ($CDCl_3$, 200 MHz): 8.85 (1H, bs, ex., NH Ind); 7.45 (1H, d, H_8, $J_{8\text{-}9}$=8 Hz); 7.30 (1H, d, H_{11}, $J_{11\text{-}10}$=8 Hz); 7.20 (1H, t, H_{10}); 7.10 (1H, t, H_9); 5.30 (1H, d, ex., $NHCO_2$, $J_{NH\text{-}1}$=9.6 Hz); 5.15 (1H, dt, H_{6eq}, *J*=12 Hz, *J*=4 Hz); 4.95 (1H, d, H_{12b}, $J_{12b\text{-}1}$=5 Hz); 4.75 (1H, m, H_1); 2.85 (1H, m, H_{6ax}); 2.70 (2H, m, H_7); 2.65 (2H, m, H_3); 2.15 (2H, m, $H_{2)}$. ^{13}C NMR (CD_3OD, 50.3 MHz): 169.0 (C_4); 156.5 (*C*O Boc); 136.9 (C_{11a}); 130.1 (C_{7b}); 126.7 (C_{12a}); 123.6 (7_a); 122.3 (C_9); 119.5 (C_{10}); 118.4 (C_8); 111.4 (C_{11}); 80.6 (O*C*$(CH_3)_3$); 58.8 (C_{12b}); 45.5 (C_1); 40.2 (C_6); 28.2 (C(*C*$H_3)_3$); 27.5 (C_2); 24.7 (C_7); 20.7 (C_3).

1(*S*)-12b(*S*)-1-Pyrrol-1-yl-2,3,4,6,7,12,12b-hexahydro-1H-indolo[2,3-a]quinolizin-4-one 20f. IR ($CHCl_3$): ν=3423 (NH); 3050–2950; 2355; 1642 (CO). MS (CI^+): *m*/*z*=305 ($[M+H]^+$); 328; 170. HRMS ($C_{19}H_{19}N_3O$): calcd 305.1518, obs. 305.1521. ^1H NMR ($CDCl_3$, 200 MHz): 7.50 (1H, d, H_8, $J_{8\text{-}9}$=10.5 Hz); 7.10 (3H, m, H_9, H_{10}, H_{11}); 6.85 (2H, t, $H_{2'}$); 6.40 (2H, t, $H_{3'}$); 6.30 (1H, s, NH Ind); 5.20 (1H, m, H_{6eq}); 5.10 (1H, d, H_{12b}, $J_{12b\text{-}1}$=10.5 Hz); 4.15 (1H, ddd, H_1, $J_{1\text{-}12b}$=10.5 Hz, $J_{1\text{-}2}$=4 Hz); 3.95–2.55 (3H, m, H_{6ax}, H_3); 2.50–2.30 (4H, m, H_7, H_2). ^{13}C NMR (CD_3OD, 75.5 MHz): 167.9 (*C*O); 136.6 (C_{11a}); 130.2 (C_{7b}); 126.0 (C_{12a}); 125.7 (C_{11}); 122.3 (C_9); 119.7 (C_8); 118.3 ($C_{2'}$); 110.9 (C_{10}); 110.0 ($C_{3'}$); 60.1 (C_1); 58.8 (C_{12b}); 40.7 (C_6); 31.5 (C_3); 28.6 (C_2); 21.0 (C_7).

Acknowledgements

We wish to thank Professor P. Potier for his interest in this work and Dr R. Dodd for the very careful reading of the manuscript.

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11. Enantiomerically pure (ee >99%) as further proved by chiral HPLC of the 1-amino[2,3-a]quinolizidine, see Ref. 3.