Acta Chemica Scandinavica, 1998: 52: 683–693
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ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

Cyclisations of Tryptophans. IV.† Cyclisation of N_b-Acyl-L-Tryptophanamides

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Dedicated to Professor Lennart Eberson on the occasion of his 65th birthday

Holst, P. B., Anthoni, U., Christophersen, C., Larsen, S., Nielsen, P. H. and Püschl, A., 1998. Cyclisations of Tryptophans. IV. Cyclisation of N_b-Acyl-L-tryptophanamides. – Acta Chem. Scand. 52: 683–693. © Acta Chemica Scandinavica 1998.

Three derivatives of tryptophanamide, N_b-methoxycarbonyl-L-tryptophanamide (**2a**), N_b-acetyl-L-tryptohanamide (**2b**), and N_b-trifluoroacetyl-L-tryptophanamide (**2c**), have been prepared and their reaction with trifluoroacetic acid investigated. The structure of the diastereomeric pyrroloindoles **6a** and **7a** formed from **2a** on cyclisation was established through crystal structure determination of **7a** and NMR experiments. In the case of **2b** two diastereomeric dimers **8a** and **9b** were isolated with smaller amounts of two related lactams **11** and **12**. From **2c** diastereomeric dimers **8c** and **9c** were found in addition to a small amount of an aromatic biindole **10c**. The change from cyclisation to dimerisation is correlated with the decrease in side chain nucleophilicity from **2a** to **2c**. The stereochemistry of the products was determined by NOE results in combination with CD spectra and Cotton effects.

Tryptophan derivatives on treatment with trifluoroacetic acid (TFA) are subject to competing dimerisation and cyclisation reactions as illustrated in Scheme 1 for tryptophanamides. Initial protonation of the indole ring of **2a–c** gives the electrophilic and diastereomeric 3-protonated indolenium ions **4** and **5**. The factors governing the relative ease of the ensuing reactions are only partly known.[2] The main condition for cyclisation to pyrroloindoles (**6** or **7**) seems to be that the side chain N_b nitrogen must retain its nucleophilicity as in the N_b-acyl derivatives **4a–c** or **5a–c** (Scheme 1).[3,4] Since tryptamines are more readily dimerised in an acid medium than are tryptophans, the formation of dimers (e.g., **8** or **9**) is assumed to be controlled partly by steric factors[2] in line with other evidence.[5,6] Prolonged acid treatment of acyltryptamines, which initially cyclise (e.g., N_b-methoxycarbonyltryptamine), leads to increasing amounts of dimerisation.[3] Since the acid-catalysed cyclisation is a fast[3,4] reversible process, this result suggests the dimer to be the stable product and/or formed in an irreversible reaction.

The influence of base strength and protonation of the side chain on competing dimerisation/cyclisation is well documented. Carbamic esters derived from tryptamine (N_b-methoxycarbonyl- or -benzyloxycarbonyltryptamine) give good yields of pyrroloindoles[3] while N_b-acetyltryptamine with diminished side chain nucleophilicity due to the increased amide resonance stabilisation fails to cyclise.[3] Alternatively, if tryptamine or N_b-alkyltryptamines are dissolved in acids such as TFA and 85% phosphoric acid, diprotonation at N_b and the indolic 3-position occurs. Since cyclisation is thus prevented 2,2′-dimers are formed.[3] While monoprotonated N_b-methoxycarbonyltryptophan and esters readily cyclise[3,4,7,8] the less nucleophilic side chain nitrogen in N_b-acetyltryptophan methyl ester favours dimerisation.[9] Tryptophan and esters which are not N_b-acylated are diprotonated in strong acids.[4,10]

The balance between cyclisation and dimerisation is, moreover, strongly dependent upon the medium and the structure of the reacting species and/or the product. In contrast with N_b-acetyltryptamine, indole-3-*N*-methylacetamide[11] (or the precursor 3-indolylacetonitrile[12]) cyclise in good yield on treatment with acids. When diastereomeric compounds are formed (e.g., **6** and **7**) on cyclisation of L-tryptophan derivatives (e.g., **2a–c**) their relative amounts depend on both ease of formation and

† Part III, see Ref. 1.
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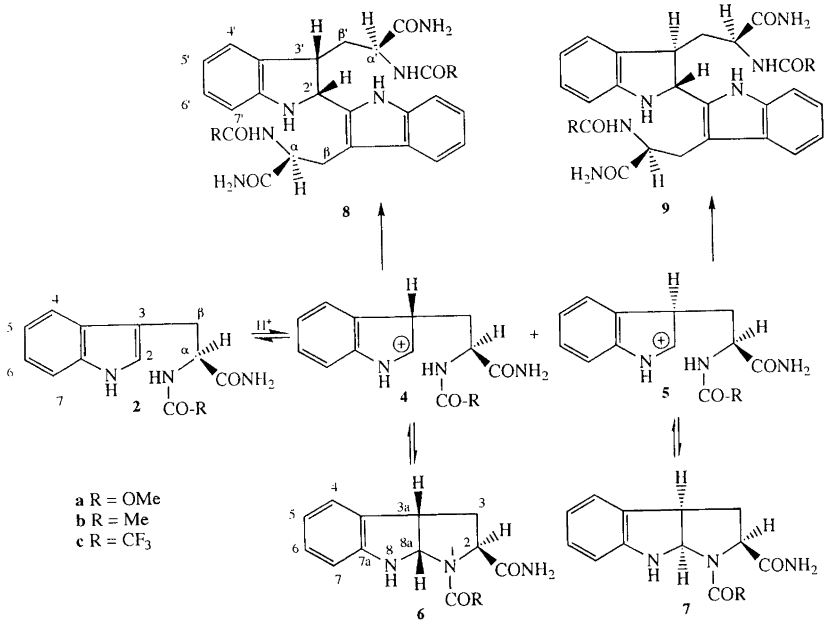


Scheme 1.

stability, i.e., different ratios are obtained under kinetic and thermodynamic control.[3,4] The mechanism controlling the ratios of diastereomeric dimers in TFA are not known, but conceivably involves migration of indolic substituents from the 3- to the 2-position, assumed to be general for substitution reactions and well investigated for, e.g., 3-benzylindoles.[13] During acid treatment substitution may occur, e.g., sulfonation may be prominent in concentrated sulfuric acid[4] and 3-trifluoroacetylation in TFA.[6]

By analogy to these and related cyclisations[14,15] the reaction sequence outlined in Scheme 1 is expected for derivatives **2a–c** of tryptophanamide (**1**) in TFA. Initial 3-protonation leads to a mixture of diastereomeric cations (**4/5**) which cyclise reversibly to diastereomeric **6/7** or are converted into diastereomeric dimers **8/9**. The present paper reports the cyclisation and/or dimerisation reactions observed with N_b-methoxycarbonyl-L-tryptophanamide (**2a**), N_b-acetyl-L-tryptophanamide (**2b**), and N_b-trifluoroacetyl-L-tryptophanamide (**2c**) in TFA.

Results and discussion

Nucleophilicity of acylated nitrogen in the tryptophanamides 2a–c in methanol and TFA. The dimerisation reaction (**4/5**⟶**8/9**) relies on the simultaneous occurrence of non-protonated and 3-protonated species in solution. Since the only difference between **2a–c** is located in the side chain and the steric effects are comparable, dimerisation is predicted to proceed with similar ease in these three compounds. On the other hand, the rate of the cyclisation reaction (**4/5**⟶**6/7**) depends on the nucleophilicity of the acylated nitrogen and is expected to increase relative to dimerisation in the sequence COOMe (**2a**) > COMe (**2b**) > $COCF_3$ (**2c**).

The ^1H and ^{13}C NMR data of **1** and **2a–c** in methanolic solution show that the positive charge of the acylated nitrogen increases, i.e., the nucleophilicity decreases with the electronegativity of the acyl substituent as predicted. The shifts for the α-protons progressively increase towards lower fields (δ = 3.64, 4.41, 4.68, 4.74, for **1**, **2a**, **2b**, and **2c**, respectively) and a similar trend even can be observed for each of the β-protons (δ = 3.20, 2.96, 3.27, 3.08 and 3.28, 3.09, 3.37, 3.18). In the ^{13}C NMR spectra the upfield shifts of C-β (δ = 30.5, 27.3, 27.1, 26.8, for **1**, **2a**, **2b**, and **2c**, respectively) and $CONH_2$ (δ = 178.3, 175.5, 174.9, 174.4) also correlate with the charge on the acylated nitrogen as expected for β-shifts.[16]

In equimolar amounts of TFA, associates are formed with structures ranging from hydrogen-bonded (e.g., amides[17–19] and esters[20]) to ion pairs (e.g., pyridine[21]). In excess TFA, 2:1 or 3:1 TFA–base complexes may be formed which are usually ion pairs,[21,22] although cyclic[23] or linear[24] hydrogen-bonded complexes may occur. Accordingly both the amide and ester groups present in **2a–c** are expected to occur preferentially as hydrogen-bonded ion-pairs with a protonated C=O group in TFA.[23] Since the strength of the hydrogen bond may vary it cannot *a priori* be predicted whether the order of nucleophilicity present in methanol (NHCOOMe > NHCOMe > $NHCOCF_3$) persists in TFA. However, the ^{13}C signals of the model compounds MeNHCOOEt, MeNHCOMe and $MeNHCOCF_3$ in TFA showed downfield shifts from those in MeOH of 4.5, 5.1 and 4.4 ppm (MeN) and 6.4, 7.5, and 5.0 ppm (C=O), respectively, similar to those reported for Me_2NCOMe of 3.6 (MeN) and 5.8 ppm (C=O).[22] In analogy to the thoroughly investigated Me_2NCOMe[22] this result demonstrates (i) that they are extensively C=O protonated and (ii) that the changes in chemical shift on addition of TFA are of

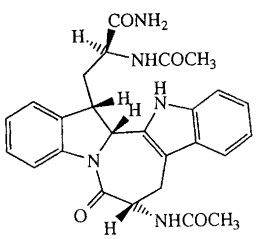
comparable magnitude in all three compounds. We may therefore assume that the order of side chain nucleophilicity in **2a–c** are also unchanged (i.e., the stability decreases in the sequence NHCOOMe > NHCOMe > $NHCOCF_3$) from MeOH to TFA. Owing to association the ^1H NMR shifts of the model compounds are irregular and do not correlate with the ^{13}C shifts.[23,25]

Structure of the protonated indole ring in TFA. Acid-catalysed exchange of hydrogen in the 3-position of indoles apparently always proceed by the A-S_E2 mechanism via the 3*H*-indolium salt even for weak acids such as acetic acid.[26–28] However, a series of ^1H NMR investigations by Jackson *et al.*[13,29–31] indicate the amount of 3*H*-indolium salt in equilibrium with unprotonated indole to be strongly dependent upon the strength of the acid. In summary, the available evidence suggests that while 3-alkylindoles (and 3-benzylindole) are only partly protonated in TFA, the increased basicity of 2-alkylindoles (including 2,3-dialkylindoles and tetrahydrocarbazole) effects complete conversion into 3*H*-indolium salts. Since this conclusion is important and many results are only incompletely reported we have reinvestigated the ^1H and ^{13}C NMR spectra of skatole and 2,3-dimethylindole in TFA. In our hands, even fresh solutions of skatole in TFA showed extensive dimerisation and the remaining amounts of indole and 3*H*-indolium forms in equilibrium were small. The spectra of 2,3-dimethylindole were consistent with complete conversion into the 3*H*-indolium ion.

It can therefore safely be assumed that, in TFA, the tryptophanamides **2a–c** occur in equilibrium with **4** and **5**.

Cyclisation and dimerisation reactions of ***2a–2c*** *in TFA.* In all cases an equilibrium between the pyrroloindoles **6**/**7** appears to develop although the formation of the corresponding pyridoindoles cannot be excluded for **2b**/**2c**. When **2a** is cyclised, **6a** is the kinetically favoured product while **7a** is the thermodynamically stable isomer. Although it has not been possible to isolate the pyrroloindoles **6b**/**7b** and **6c**/**7c** there is ample experimental evidence that their formation is similarly controlled.

While dimers have not been observed for **2a**, these are the main products in the case of **2b** and **2c**. In the case of **2b** we have been able to isolate two diastereomeric dimers **8b** and **9b**, and the corresponding lactams **11** and **12**. The lactams are formally derived from **8b** and **9b** by elimination of ammonia from the side chain amide and the indoline NH with formation of the pentacyclic derivative. The structures of **11** and **12** followed from their FAB-MS and ^1H NMR spectra in DMSO-d_6. These were very similar to **8b** and **9b** apart from the missing signals from the indoline NH and amide NH_2. From **2c** in TFA the dimers **8c** and **9c** were isolated. The NMR spectra indicated the additional presence of at least one cyclic dimer (doublet of doublets at 6.10 ppm). A small amount of the 2,2′-biindole **10c** was identified from the molecular weight (MS) and a ^1H NMR spectrum similar to that of **2c** except for lack of the H2′ signal.



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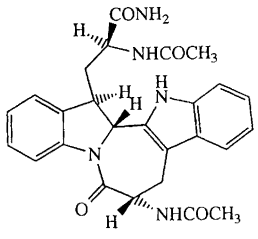

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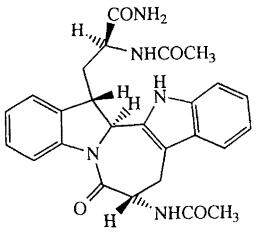

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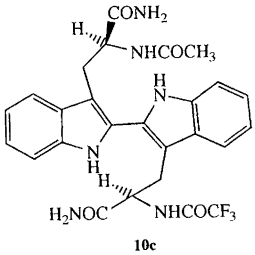

10c

From these results we may conclude that cyclisation occurs whether the side chain nucleophilicity is high (**2a**) or small (**2c**), but that the pyrroloindoles formed survive chromatographic separation only in the former case. Unstable pyrroloindoles (**6**/**7b** and **c**) form open or cyclised dimers but even on prolonged heating to 60 °C in TFA pyrroloindoles persist in the solution.

Stereochemistry of cyclisation. The ^1H and ^{13}C NMR spectra of **6a** and **7a** were assigned (COSY, HETCOR) as given in the Experimental section. As for the corresponding cyclised tryptophan esters[3] doubling of several signals due to *cis–trans* isomerism around the *N*-COOMe bonds was apparent from the merging of signals at 50 °C in $CDCl_3$. Since the spectra of the diastereomers are very similar the stereochemistry of **7a** was assigned based on NOE enhancement of the H2 signal (1%) on saturation of the signal originating from the *cis* H8a (no such enhancement was observed in **6a**).

The CD spectra of **6a** and **7a** both showed a negative Cotton effect around 240 nm. This contrasts with the findings of Taniguchi *et al.*[3,14] for diastereomeric pyrroloindoles derived from other tryptophan derivatives, all displaying opposite Cotton effects in the range below 280 nm. However, the ellipticity centred around 293 nm shows a positive Cotton effect for **6a** and a negative for **7a**. Unfortunately, Taniguchi only gives data below 280 nm and a comparison cannot be made with our findings. Nevertheless, these results clearly warn that CD data should be used with caution when assigning stereochemistry of pyrroloindoles.

Stereochemistry of dimerisation. Dimerisation of **2b** and **2c** gives rise to formation of mixtures of diastereomeric dimers **8b**/**9b** and **8c**/**9c**. Chemical shifts and coupling constants in the ^1H and ^{13}C NMR spectra do not

distinguish unambiguously between these isomers. Inspection of molecular models indicated that the H2′ proton could be brought into the immediate vicinity of the protons Hα′ and Hβ′ in the *trans*-isomer but not in the *cis*-isomer. Accordingly, NOE experiments for samples in DMSO-d_6 with irradiation of the H2′ resonance resulted in a 1–2% enhancement of the Hα′ and one of the Hβ′ signals in the *trans*-dimers **9b** and **9c** which was absent in the corresponding *cis*-dimers.

Analogous NOE experiments of **11** and **12** in DMSO-d_6 showed that the H2′ resonance undergoes large enhancements relative to **8b**, **9b**, **8c** and **9c** in accordance with the more strained structures. **11** showed NOE enhancements to Hα (11%), Hα′ (5%), and to H3′ (1%). The H2′ resonance for **12** showed an NOE enhancement only to Hα (10%). From molecular models it can be concluded that **11** must have a *cis* and **12** a *trans* configuration. Because of the small amounts available of **13**, the NOE experiment was inconclusive.

The CD spectra of **8b**/**9b**, **8c**/**9c**, and **11**/**13** are two by two identical, but show opposite Cotton effects in agreement with the assignment of diastereomeric structures. In support of the NOE results, the couples **8b**/**8c** and **9b**/**9c** have identical CD spectra and show identical Cotton effects. These results show that CD spectra are useful for distinguishing *cis* and *trans* isomers of dimeric couples. The CD spectrum and Cotton effects of **12**/**13** are identical, indicating that **13** has a *trans* configuration. The H2′ proton in **13** is in a *trans* position to both H3′ and Hα.

*Crystal structure of (2*S*,3a*R*,8a*R*)-1,2,3,3a,8,8a-hexahydro-1-methoxycarbonylpyrrolo[2,3-*b*]indole-2-carboxamide (**7a**).* The results of the structure determination from single-crystal X-ray diffraction data of **7a** (Table 1 and 2) confirm the structure assigned above from NMR data, indicating that the observed solid-state conformation persists in solution. The crystal packing and molecular structure are illustrated in Fig. 1 and the bond lengths, bond angles and torsion angles in Tables 3, 4 and 5, respectively. All distances and angles agree with commonly accepted values.

The pyrrolidine ring (B) adjacent to the benzene ring (A) is envelope-shaped with the atom C(8a) twisted out of the otherwise planar moiety as shown by the torsional angle C(7a)–C(4a)–C(3a)–C(8a) of −11.6(0.1)°. The other pyrrolidine ring (C) is *cis* fused with a torsional angle C(4)–C(4a)–C(3a)–C(3) of 53.2(0.2)° defining the relative position of the B and C rings. The C ring also adopts the envelope-configuration with C(2) with the attached amide group bending over the *endo* surface of the ring system. This leaves the C(2)–H and C(8a)–H protons in a *cis* position as used diagnostically in interpretation of the NOE enhancements of **7a** in solution. The presence of an amide functionality directed *endo* to the ring system has also been found in related acid-[32] or photo-catalysed[1,33] cyclisations of indole amides to pyrroloindolines and such compounds may exhibit exceptional stability.[34] Only in one instance of acid-catalysed cyclisation[35] was the opposite conformation adopted, possibly as a result of an ion-pair or concerted mechanism.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded at ambient temperatures on a Bruker 250 AM or on a Varian XL-400 spectrometer, operating at 250 or 400 MHz for protons and at 62.9 or 100.6 MHz for carbon, respectively. Me_4Si was used as an internal standard. The assignment of all spectra listed were confirmed by standard procedures (COSY, HETCOR). Mass spectra were obtained on a Masslab VG20–250 quadrupole or a JEOL JMS-HX/HX110A spectrometer using the direct inlet system. FT-IR spectra were recorded on a Perkin Elmer 1760X FT-IR or 580 IR spectrophotometer for samples as KBr discs. UV spectra were recorded on a Hewlett Packard 8452 A diode array instrument with a Vectra ES/12 hard disk or on a Perkin Elmer Lambda 2 (or 17) spectrometer. Melting points were determined on a Büchi 535 or on a hot-stage melting point apparatus and are uncorrected. Circular dichroism was determined with a JASCO J-710 spectropolarimeter and optical rotation by use of a Perkin Elmer model 141 polarimeter. TLC experiments were performed on Silica gel 60 F_{254} Merck, alumina Woelm, neutral, type E, and RP-18 F_{254}s plates. Unless otherwise stated UV detection (270 nm) was used during column purification. L-Tryptophan was from Fluka and used without further purification. TFA and TFAA were from Sigma.

*L-Tryptophanamide **1*** was prepared from L-tryptophan methyl ester hydrochloride[36] according to the directions given for the DL-derivative.[37] Trituration with $CHCl_3$ gave samples (m.p. 133–135 °C) containing small amounts of water, but analytically pure anhydrous **1** (C, H, N), m.p. 138–140 °C, could be obtained by recrystallisation from EtOH (the melting point given earlier,[38] 167–170 °C is apparently wrong). MS *m/z* (% rel. int.) 203 (M^+, 12), 186 ($M^+ - NH_3$, 13), 130 (3-methyleneindolium, 100). ^{1}H NMR (CD_3OD): δ 7.63 (dd, 1 H, H-4, $J_{4,5}$ 8 Hz, $J_{4,6}$ 1 Hz), 7.33 (dd, 1 H, H-7, $J_{6,7}$ 8 Hz, $J_{5,7}$ 1 Hz), 7.10 (s, 1 H, H-2), 7.09 (td, 1 H, H-6, $J_{5,6}$ = $J_{6,7}$ 8 Hz, $J_{4,6}$ 1 Hz), 7.00 (td, 1 H, H-5, $J_{4,5} = J_{5,6}$ 8 Hz, $J_{5,7}$ 1 Hz), 3.64 (dd, 1 H, H_α, $J_{\alpha,\beta}$ 5.5, 7.7 Hz), 3.20 (dd, 1 H, H_β, $J_{\alpha,\beta}$ 5.5 Hz, $J_{\beta,\beta}$ 14.3 Hz), 2.96 (dd, 1 H, H_β, $J_{\alpha,\beta}$ 7.9 Hz, $J_{\beta,\beta}$ 14.3 Hz). ^{13}C NMR (CD_3OD): δ 178.3 (C=O), 136.0 (C–7a), 126.9 (C–3a), 122.8 (C–2), 120.5 (C–6), 117.9 (C–5), 117.5 (C–4), 110.4 (C–7), 109.4 (C–3), 54.6 (C_α), 30.5 (C_β). IR (KBr, cm^{-1}), 3477vs (νNH, indole), 3410m, 3354s, 3322s and 3290s (νNH, amide), 1669vs,br (νCO). UV (abs EtOH), λ_{max} (log ε) = 221 (4.47), 281 (3.79), 290 (3.73). $[\alpha]_D^{23}$ −6.9° (*c* 0.34, EtOH); Baugess and Berg reported $[\alpha]_D^{20}$ −7.9° (*c* 2, EtOH). If the latter rotation represents the optically

Table 1. Crystal data and structure refinement for **7a**.

Empirical formula	$C_{13}H_{15}N_3O_3$
Formula weight	261.28 g mol^{-1}
Temperature	122(2) K
Wavelength	Cu Kα
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a=8.554(4) Å
	b=10.499(2) Å
	c=13.389(4) Å
Volume	1202.5(7) Å^3
Z	4
Density (calculated)	1.443 Mg m^{-3}
Absorption coefficient	0.868 mm^{-1}
F(000)	552
Crystal size	0.08 × 0.07 × 0.40 mm
Theta range for data	5.35–74.92°
Index ranges	$0 \leqslant h \leqslant 10, 0 \leqslant k \leqslant 10, -16 \leqslant l \leqslant 16$
Reflections collected	5216
Independent reflections	2464 [R(int)=0.014]
Data/restraints/parameters	2464/0/217
Goodness-of-fit on F^2	1.053
Final R* indices [$R \leqslant 4\sigma(F)$, 2352 reflections][a]	$R1$=0.029
R indices (all data)[a]	$R1$=0.0304, $wR2$=0.0752
Absolute structure parameter	−0.1(2)
Largest diff. peak and hole in electron difference map	0.128 and −0.197 e Å^{-3}

[a] $R1$ is the residual based on F and $R2$ the residual based on F^2. The weights are given by $w=1/[\sigma_o^2(F^2)+(0.590P)^2+0.68P]$, where $P=[\max(F_o^2, 0)+2F_c^2]/3$.

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters. U_{eq} in units of 10^{-3} Å^2 for **7a**. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Atom	x	y	z	U_{eq}
C(2)	9475(2)	2854(1)	3195(1)	17(1)
C(3)	9434(2)	1396(1)	3144(1)	20(1)
C(3a)	7781(2)	1029(1)	3475(1)	19(1)
C(4)	6442(2)	622(1)	1736(1)	27(1)
C(4a)	6516(2)	1135(1)	2690(1)	20(1)
C(5)	5127(2)	880(2)	1146(1)	33(1)
C(6)	3935(2)	1636(2)	1518(1)	32(1)
C(7a)	5316(2)	1908(1)	3046(1)	21(1)
C(7)	4003(2)	2162(2)	2474(1)	28(1)
C(8a)	7290(2)	2078(1)	4224(1)	18(1)
C(11)	8449(2)	4136(1)	4620(1)	17(1)
C(12)	9867(2)	5979(1)	5058(1)	25(1)
C(20)	9148(2)	3476(1)	2183(1)	20(1)
N(1)	5640(1)	2315(1)	4026(1)	23(1)
N(2)	8328(1)	3152(1)	3972(1)	16(1)
N(3)	7822(2)	4137(1)	2084(1)	24(1)
O(11)	7563(1)	4287(1)	5322(1)	22(1)
O(12)	9618(1)	4931(1)	4375(1)	21(1)
O(20)	10113(1)	3342(1)	1512(1)	31(1)

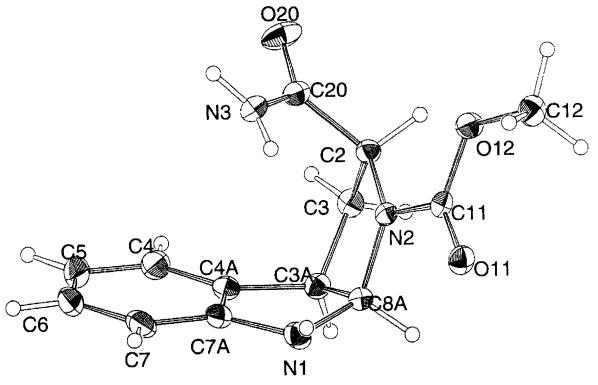

Fig. 1. ORTEPII drawing of **7a** showing the atomic numbering scheme. The thermal ellipsoids are drawn at the 50% probability level. The hydrogen atoms are drawn as spheres with a fixed radius.

pure compound the present derivative contains approximately 6% of the D-enantiomer.

N$_b$-*Methoxycarbonyl-L-tryptophanamide* **2a**. Methyl chloroformate (1.5 ml, 19.4 mmol) dissolved in EtOAc (10 ml) was added dropwise with stirring to a solution of **1** (2.00 g hydrate, 9.6 mmol) in EtOAc (220 ml) cooled in an ice–salt bath. The precipitate (**2a**, hydrochloride) redissolved on addition of a slight excess of aqueous 2 M NaOH (10 ml, 20 mmol) at room temperature. The EtOAc phase was separated and washed with saturated aqueous NaCl. Drying ($MgSO_4$) of the combined organic layers and evaporation gave crude **2a** which was dried in a desiccator (conc. H_2SO_4) overnight. Recrystallization from aqueous MeOH or MeOH–ether and prolonged drying in desiccator as before gave partially hydrated **2a** (1.39 g, 55%) as colourless, somewhat hygroscopic crystals with m.p. 147–153 °C. Anal. $C_{13}H_{15}N_3O_3 \cdot 1/4\ H_2O$: C, H, N. MS m/z (% rel. int.) 261 (M^+, 2), 186 ($M^+ - CONH_2 - OCH_3$, 6), 130 (3-methyleneindolium, 100). ^{1}H NMR (CD_3OD): δ 7.61 (d, 1 H, H-4, $J_{4,5}$ 8 Hz), 7.32 (d, 1 H, H-7, $J_{6,7}$ 8 Hz), 7.10 (s, 1 H, H-2), 7.08 (td, 1 H, H-6, $J_{5,6}=J_{6,7}$ 8 Hz, $J_{4,6}$ 1 Hz),

7.01 (t, 1 H, H-5, $J_{4,5}=J_{5,6}$ 8 Hz), 4.41 (dd, 1 H, H_α, $J_{\alpha,\beta}$ 6.0, 8.1 Hz), 3.57 (s, 3 H, CH_3), 3.27 (dd, 1 H, H_β, $J_{\alpha,\beta}$ 6.0 Hz, $J_{\beta,\beta}$ 14.6 Hz), 3.08 (dd, 1 H, H_β, $J_{\alpha,\beta}$ 8.1 Hz, $J_{\beta,\beta}$ 14.6 Hz). ^{13}C NMR (CD_3OD): δ 175.5 ($CONH_2$), 157.0 (NC=O) 136.1 (C-7a), 126.8 (C-3a), 122.6 (C-2), 120.5 (C-6), 117.9 (C-5), 117.4 (C-4), 110.3 (C-7), 109.1 (C-3), 55.1 (CH_3), 50.7 (C_α), 27.3 (C_β). IR (KBr, cm^{-1}), 3449s (νNH, indole), 3407 m and 3308s (νNH, amide), 1714s (νCO, carbamate), 1669vs (νCO, amide). UV (abs EtOH), λ_{max} (log ε)=221 (4.56), 281 (3.76) 290 (3.70). $[\alpha]_D^{30}$ +6.8° (*c* 0.205, EtOH).

N_b-*Acetyl-L-tryptophanamide* ***2b***. This amide is usually prepared by treating N_b-acetyltryptophan methyl ester with ammonia[39–41] but has been reported once[42] in a low yield by acetylation of **2a**. However, in our hands the latter procedure proved highly satisfactory. The amide **2a** (2.0 g as hydrate, 9.6 mmol) was dissolved by prolonged reflux in dry EtOAc (250 ml). The solution was stirred at 30 °C and dropwise addition of acetic anhydride (2 ml, 21 mmol) resulted in the clean formation of **2b** [R_f=0.64, BuOH–AcOH–H_2O (4:1:1); R_f=0.29, $CHCl_3$–acetone–AcOH (5:4:1)]. The organic phase was repeatedly washed with 10% $NaHCO_3$ and water, dried ($MgSO_4$), and the solvent removed. Drying overnight in an desiccator (conc. H_2SO_4) left almost pure **2b** (2.26 g, m.p. 187–189 °C). Recrystallization from water raised the melting point of the colourless crystals to 190–191 °C in accordance with reported values (191.5–192.5 °C,[39] 192–193 °C;[40] the range 97–100 °C[42] is obviously due to a printing error since the R_f values correspond to that found for our preparation). Anal. $C_{13}H_{15}N_3O_2$: C, H, N. MS *m/z* (% rel. int) 245 (M^+, 5), 186 ($M^+-CONH_2-CH_3$, 29), 130 (3-methyleneindolium, 100). ^1H NMR (CD_3OD): δ 7.61 (d, 1 H, H-4, $J_{4,5}$ 8 Hz), 7.32 (d, 1 H, H-7, $J_{6,7}$ 8 Hz), 7.10 (s, 1 H, H-2), 7.08 (td, 1 H, H-6, $J_{5,6}=J_{6,7}$ 8 Hz, $J_{4,6}$ 1 Hz), 7.00 (t, 1 H, H-5, $J_{4,5}=J_{5,6}$ 8 Hz), 4.68 (dd, 1 H, H_α, $J_{\alpha,\beta}$ 6.5, 8.0 Hz), 3.28 (dd, 1 H, H_β, $J_{\alpha,\beta}$ 6.5 Hz, $J_{\beta,\beta}$ 14.7 Hz), 3.09 (dd, 1 H, H_β, $J_{\alpha,\beta}$ 8.0 Hz, $J_{\beta,\beta}$ 14.7 Hz), 1.89 (s, 3 H, CH_3). ^{13}C NMR (CD_3OD): δ 174.9 ($CONH_2$), 171.2 (NC=O) 136.1 (C-7a), 126.9 (C-3a), 122.4 (C-2), 120.5 (C-6), 117.8 (C-5), 117.4 (C-4), 110.3 (C-7), 109.2 (C-3), 53.4 (C_α), 27.1 (C_β), 20.6 (CH_3). IR (KBr, cm^{-1}), 3420s (νNH, indole), 3377s, 3301vs and 3210s (νNH, amide), 1641vs,br (νCO, amide). UV (MeOH), λ_{max} (log ε)=226 (4.16), 282 (3.74), 290 (3.67). $[\alpha]_D^{20}$ +19.4° (*c* 0.196, MeOH); (lit.[43] $[\alpha]_D^{20}$ +19.0° (*c* 0.5, MeOH).

Table 3. Bond lengths (Å) for **7a**.

O(12)–C(11)	1.343(2)
O(12)–C(12)	1.446(2)
O(11)–C(11)	1.218(2)
O(20)–O(20)	1.227(2)
N(2)–C(11)	1.354(2)
N(2)–C(2)	1.463(2)
N(2)–C(8a)	1.475(2)
N(3)–C(20)	1.336(2)
N(1)–C(7a)	1.408(2)
N(1)–C(8a)	1.458(2)
C(3a)–C(4a)	1.513(2)
C(3a)–C(3)	1.531(2)
C(3a)–C(8a)	1.547(2)
C(4)–C(4a)	1.388(2)
C(4)–C(5)	1.401(2)
C(7)–C(7a)	1.386(2)
C(7)–C(6)	1.394(2)
C(20)–C(2)	1.530(2)
C(4a)–C(7a)	1.392(2)
C(2)–C(3)	1.533(2)
C(6)–C(5)	1.386(3)

Table 5. Torsion angles (deg) for **7a**.

C(4)–C(4a)–C(3a)–C(3)	53.2(0.2)
C(7a)–C(4a)–C(3a)–C(3)	−125.1(0.1)
C(4a)–C(3a)–C(3)–C(2)	80.7(0.1)
C(4a)–C(3a)–C(8a)–N(2)	−100.2(0.1)
C(4)–C(4a)–C(7a)–N(1)	180.0(0.1)
C(7)–C(7a)–C(4a)–C(3a)	−179.8(0.1)
C(7a)–C(4a)–C(3a)–C(8a)	−11.6(0.1)
C(6)–C(7)–C(7a)–N(1)	−179.2(0.1)
H(3a)–C(3a)–C(8a)–H(8a)	23.0(2)
C(8a)–N(2)–C(11)–O(12)	169.6(0.1)
C(8a)–N(1)–C(2)–C(20)	171.7(0.1)

Table 4. Bond angles (deg) for **7a**.

C(11)–O(12)–C(12)	115.34(10)	C(11)–N(2)–C(2)	124.56(11)
C(11)–N(2)–C(8a)	118.88(11)	C(2)–N(2)–C(8a)	113.79(10)
O(11)–C(11)–O(12)	124.82(12)	O(11)–C(11)–N(2)	123.13(12)
O(12)–C(11)–N(2)	112.02(11)	C(7a)–N(1)–C(8a)	107.94(11)
C(4a)–C(3a)–C(3)	116.15(11)	C(4a)–C(3a)–C(8a)	101.78(10)
C(3)–C(3a)–C(8a)	105.06(10)	C(4a)–C(4)–C(5)	118.8(2)
C(7a)–C(7)–C(6)	117.7(2)	N(1)–C(8a)–N(2)	114.24(11)
N(1)–C(8a)–C(3a)	105.47(10)	N(2)–C(8a)–C(3a)	103.41(10)
O(20)–C(20)–N(3)	123.95(13)	O(20)–C(20)–C(2)	118.42(13)
N(3)–C(20)–C(2)	117.63(11)	C(4)–C(4a)–C(7a)	120.51(13)
C(4)–C(4a)–C(3a)	130.09(13)	C(7a)–C(4a)–C(3a)	109.38(12)
N(2)–C(2)–C(20)	114.58(11)	N(2)–C(2)–C(3)	103.28(10)
C(20)–C(2)–C(3)	112.45(10)	C(3a)–C(3)–C(2)	105.04(10)
C(7)–C(7a)–C(4a)	121.35(14)	C(7)–C(7a)–N(1)	128.05(14)
C(4a)–C(7a)–N(1)	110.57(12)	C(5)–C(6)–C(7)	121.76(14)
C(6)–C(5)–C(4)	119.91(14)		

N_b-Trifluoroacetyl-L-tryptophanamide **2c**, *and N_b-trifluoroacetyl-L-tryptophannitrile* **3c**. The D-form of amide **2c** was prepared by Huang and Niemann[44] (or essentially as **2b**) by treating **1** with trifluoroacetic anhydride in EtOAc, however, in only 30% yield. On reproducing their preparation, ^{1}H NMR spectra of the crude product showed that mixtures varying from 1:1 to 1:2.5 of **2c** and **3c** had been formed, thus explaining the low yield of **2c**. Obviously the acid anhydride not only gives rise to trifluoroacetylation of **1** but also to partial dehydration of the amide to nitrile.

Column chromatography of the mixture (1.6 g) on silica gel (AcOH–EtOH 94:6; TLC detection; pooling fractions 18–27 of a total of 56 fractions) gave pure nitrile **3c** (680 mg) as colourless crystals, m.p. 172–173 °C. Anal. $C_{13}H_{10}F_3N_3O$: C, H, N. MS *m/z* (% rel. int.) 281 (M^+, 8), 254 (M^+-HCN, 11), 130 (3-methyleneindolium, 100). ^{1}H NMR (CD_3OD): δ 7.59 (dd, 1 H, H-4, $J_{4,5}$ 8 Hz, $J_{4,6}$ 1 Hz), 7.36 (dd, 1 H, H-7, $J_{6,7}$ 8 Hz, $J_{5,7}$ 1 Hz), 7.20 (s, 1 H, H-2), 7.12 (td, 1 H, H-6, $J_{5,6}=J_{6,7}$ 8 Hz, $J_{4,6}$ 1 Hz), 7.04 (td, 1 H, H-5, $J_{4,5}=J_{5,6}$ 8 Hz, $J_{5,7}$ 1 Hz), 5.10 (t, 1 H, H_α, $J_{\alpha,\beta}$ 7.7 Hz), 3.39 (dd, 1 H, H_β, $J_{\alpha,\beta}$ 7.9 Hz, $J_{\beta,\beta}$ 14.3 Hz), 3.32 (dd, 1 H, H_β, $J_{\alpha,\beta}$ 7.5 Hz, $J_{\beta,\beta}$ 14.3 Hz). ^{13}C NMR (CD_3OD): δ 156.5 (NC=O) 136.1 (C-7a), 126.3 (C-3a), 123.2 (C-2), 120.8 (C-6), 118.3 (C-5), 117.0 (C-4), 116.8 (CN), 115.7 (CF_3), 110.6 (C-7), 106.8 (C-3), 41.5 (C_α), 27.7 (C_β). IR (KBr, cm^{-1}), 3415vs (νNH, indole), 3306s (νNH, amide), 2251w (νCN), 1703vs (νCO, amide), 1208vs and 1179vs (νCF). UV (MeOH), λ_{max} (log ε)=226 (3.78), 280 (3.57), 290 (3.49). $[\alpha]_D^{20}$ −27° (*c* 0.50, MeOH).

Fractions 33–50 gave pure amide **2c** (430 mg). M.p. 158–160 °C (lit.[44] 162 °C). This could be obtained in a much better yield (85% crude) by using DMAP for catalysis and to remove TFA, but purification proved to be extremely tedious with occasional formation of an oil. At present, chromatographic separation of the product obtained without addition of DMAP is therefore the recommended method for securing pure **2c**. MS *m/z* (% rel. int.) 299 (M^+, 7), 281 (M^+-H_2O, 3), 186 ($M^+-CONH_2-CF_3$, 13), 130 (3-methyleneindolium, 90), 18 (H_2O, 100). ^{1}H NMR (CD_3OD): δ 7.62 (dd, 1 H, H-4, $J_{4,5}$ 8 Hz, $J_{4,6}$ 1 Hz), 7.32 (dd, 1 H, H-7, $J_{6,7}$ 8 Hz, $J_{5,7}$ 1 Hz), 7.09 (s, 1 H, H-2), 7.09 (td, 1 H, H-6, $J_{5,6}=J_{6,7}$ 8 Hz, $J_{4,6}$ 1 Hz), 7.01 (td, 1 H, H-5, $J_{4,5}=J_{5,6}$ 8 Hz, $J_{5,7}$ 1 Hz), 4.74 (dd, 1 H, H_α, $J_{\alpha,\beta}$ 6.1, 8.2 Hz), 3.37 (dd, 1 H, H_β, $J_{\alpha,\beta}$ 6.1 Hz, $J_{\beta,\beta}$ 14.7 Hz), 3.18 (dd, 1 H, H_β, $J_{\alpha,\beta}$ 8.2 Hz, $J_{\beta,\beta}$ 14.7 Hz). ^{13}C NMR (CD_3OD): δ 174.4 ($CONH_2$), 156.5 (NC=O) 136.1 (C-7a), 126.7 (C-3a), 122.6 (C-2), 120.6 (C-6), 118.0 (C-5), 117.3 (C-4), 115.4 (CF_3), 110.3 (C-7), 108.6 (C-3), 53.7 (C_α), 26.8 (C_β). IR (KBr, cm^{-1}), 3418s (νNH, indole), 3370s,sh and 3300s,sh (νNH, amide), 1708vs and 1669vs (νCO, amide), 1217s and 1179vs (νCF). UV (MeOH), λ_{max} (log ε)=226 (3.51), 282 (3.10), 290 (3.03). $[\alpha]_D^{23.5}$ +12.0° (*c* 0.50, MeOH). Huang *et al.*[44] reported $[\alpha]_D^{23}$ −22° (*c* 0.5, MeOH) for the corresponding D-form.

Cyclisation of **2a** *in TFA*. Formation of **6a** and **7a** induced by dissolution of **2a** in TFA was monitored by ^{1}H NMR spectroscopy. The ratio **6a**/**7a** changed with time from 1.2 (5 min) to 0.1 (24 h) indicating the formation of **6a** to be kinetically slightly favoured while **7a** is the thermodynamically stable isomer. Dimerisation was not observed. Since our primary interest was to prepare pure samples of both diastereomers for comparison of physical and chemical properties, a reaction time of 5 min was chosen for preparative purposes.

A solution of **2a** (hydrate, 425 mg, 1.60 mmol) in TFA (10 ml) was left for 5 min and then poured into vigorously stirred aqueous sodium carbonate (150 ml, 10%) with cooling in an ice bath. Extraction with chloroform (3 × 50 ml), washing with aqueous NaCl, drying ($MgSO_4$) of the combined extracts and removal of the solvent gave a crude mixture of **2a**, **6a** and **7a** (363 mg, 85%). TLC on alumina (Woelm, neutral, type E) with $CHCl_3$–2-propanol–Et_3N 12:2:0.25 indicated an excellent separation (R_f=0.73, 0.52 and 0.23, for **7a**, **6a** and **2a**, respectively) and similar conditions were used for column chromatography. Using UV detection (270 nm) and a flow rate of 14 ml min^{-1} a total of eight fractions were collected and purified to give **6a** and **7a** as described below. Two further fractions were eluted with EtOH and **2a** (86 mg, 20%) was recovered from fraction 10.

(2S, 3aS, 8aS)-1,2,3,3a,8,8a-Hexahydro-1-methoxycarbonylpyrrolo[2,3-b]indole-2-carboxamide **6a**. Fractions 5–9 (96 mg) were pooled and recrystallized from heptane–EtOAc (1:1) with a few drops of Et_3N added to avoid reversal of the cyclisation. This gave **6a** as colourless needles (69 mg, 16% yield), m.p. 128–135 °C. Anal. $C_{13}H_{15}N_3O_3$: C, H, N. MS *m/z* (% rel. int.) 261 (M^+, 49), 217 (M^+-CONH_2, 51), 185 ($M^+-CONH_2-CH_3OH$, 38), 130 (3-methyleneindolium, 100). ^{1}H NMR (CD_3OD, mixture of *cis*- and *trans*-isomers): δ 7.10 and 7.08 (d, 1 H, H-4, $J_{4,5}$ 7.5 Hz), 7.01 (t, 1 H, H-6, $J_{5,6}=J_{6,7}$ 7.7 Hz), 6.70 and 6.68 (t, 1 H, H-5, $J_{4,5}=J_{5,6}$ 7.4 Hz), 6.61 and 6.60 (d, 1 H, H-7, $J_{6,7}$ 7.9 Hz), 5.71 (d, 1 H, H-8a, $J_{3a,8a}$ 7.3 Hz), 4.21 (dd, 0.5 H, H-2, $J_{2,3}$ 6.0 and 7.7 Hz), 4.15 (t, 0.5 H, H-2, $J_{2,3}$ 7.0 Hz), 3.92 and 3.86 (br t, 1 H, H-3a, $J_{3a,8a}$ 7.3), 3.80 and 3.60 (s, 3 H, CH_3), 2.40 and 2.35 (m, 1 H, H-2). ^{13}C NMR (CD_3OD, mixture of *cis*- and *trans*-isomers): δ 175.8 and 175.4 ($CONH_2$), 155.1 (NCO), 148.5 and 148.4 (C-7a), 128.8 and 128.7 (C-3b), 127.4 (C-6), 122.8 and 122.7 (C-4), 118.2 and 118.0 (C-5), 108.9 and 108.7 (C-7), 78.2 and 77.5 (C-8a), 60.0 and 59.7 (C-2), 51.4 and 51.1 (CH_3), 45.3 and 44.4 (C-3a), 35.6 and 35.2 (C-3). IR (KBr, cm^{-1}), 3400s (νNH, indoline), 3320s and 3200 m (νNH, amide), 1705vs (νCO, carbamate), 1660vs (νCO, amide). UV (abs. EtOH), λ_{max} (log ε)= 240.7 (3.92), 293.0 (3.47). $[\alpha]_D^{22}$ −292° (*c* 0.101, EtOH). CD [EtOH, *c*=0.044] nm (Δε) 242 (−0.83), 297 (0.23).

(2S,3aR,8aR)-1,2,3,3a,8,8a-Hexahydro-1-methoxycarbonylpyrrolo[2,3-b]indole-2-carboxamide **7a**. Fractions 2–4

were pooled (94 mg, 23%) and recrystallized from heptane–EtOAc (1:1) with a few drops of Et_3N added to avoid reversal of the cyclisation. This gave **7a** as colourless needles (59 mg, 14% yield), m.p. 137–139 °C. Anal. $C_{13}H_{15}N_3O_3$: C, H, N. MS *m/z* (% rel. int.) 261 (M^+, 77), 217 ($M^+ - CONH_2$, 100), 185 ($M^+ - CONH_2 - CH_3OH$, 52), 130 (3-methyleneindolium, 80). ^{1}H NMR (CD_3OD, mixture of *cis*- and *trans*-isomers): δ 7.05 (d, 1 H, H-4, $J_{4,5}$ 7.5 Hz), 6.99 (t, 1 H, H-6, $J_{5,6}=J_{6,7}$ 7.5 Hz), 6.67 (t, 1 H, H-5, $J_{4,5}=J_{5,6}$ 7.3 Hz), 6.58 (d, 1 H, H-7, $J_{6,7}$ 7.7 Hz), 5.67 (d, 1 H, H-8a, $J_{3a,8a}$ 7.5 Hz), 4.40 (br d, 1 H, H-2, $J_{2,3}$ 7.5 Hz), 3.93 (br t, 1 H, H-3a, $J_{3a,8a}$ 7.3), 3.81 and 3.72 (s, 3 H, CH_3), 2.71 and 2.50 (m, 1 H, H-2, $J_{2,3}$ 13.2). ^{13}C NMR (CD_3OD, mixture of *cis*- and *trans*-isomer): δ 175.7 and 175.4 ($CONH_2$), 155.4 (NCO), 148.8 (C-7a), 128.6 (C-3b), 127.4 (C-6), 123.3 (C-4), 118.5 (C-5), 108.9 (C-7), 77.7 and 77.2 (C-8a), 60.6 and 60.3 (C-2), 51.7 and 51.6 (CH_3), 45.7 and 44.7 (C-3a), 34.2 and 33.3 (C-3). IR (KBr, cm^{-1}), 3430s (νNH, indoline), 3360s and 3200 m (νNH, amide), 1700vs (νCO, carbamate), 1670vs (νCO, amide). UV (abs. EtOH), λ_{max} (log ε)= 240 (3.85), 295 (3.38). $[\alpha]_D^{20}$ +197° (*c* 0.0706, EtOH). CD [EtOH, c=0.064] nm (Δε) 238 (−0.29), 299 (−0.26).

Dimerisation of ***2b*** *in TFA.* A solution of **2b** (83 mg) in TFA (0.6 ml) was monitored by ^{1}H NMR spectroscopy for 24 h. At room temperature initially eight compounds were formed, the pyrroloindoles **6b**/**7b**, the dimers **8b**/**9b** and the cyclised dimers **11**, **12** and **13**.

Three signals at 6.41, 6.17 and 6.06 ppm (TFA at 11.3 ppm as internal reference) were assigned to **6b**/**7b**. The relative intensity varied (kinetic/thermodynamic control as discussed for **6a**/**7a**) while the total intensity steadily decreased with time. The pyrroloindoles were inaccessible to chromatographic purification due to their instability. The appearance of three signals is attributed to *cis–trans* isomerism around the $CH_3CO-N<$ bond. The signals from H2′ at 5.48 and 5.52 ppm from the dimers **8b** and **9b**, respectively, were identified by comparison with the pure compounds. They became prominent after 2 h and constituted almost 80% of the mixture after 24 h. The H2′ protons of the cyclic dimers **11**–**13** gave rise to signals at 5.98, 5.59 and 4.96 ppm. The intensity of the first two compounds increased within the first 4 h while the last decreased indicating a reversible formation from the open dimers **8b**/**9b**. The cyclic dimers were easily recognized as doublets of doublets arising from coupling not only with H3′ as the dimers but also with one of the Hβ protons.

A solution of **2b** (60 mg, 0.25 mmol) in TFA (1.5 ml) was kept in the refrigerator at 10 °C for 4 h. This mixture was chosen for closer investigation since according to the NMR spectra abundant amounts of the pyrroloindoles were present. However, these proved to be unstable and could not be isolated. Evaporation by nitrogen followed by lyophilization furnished an oil, which was separated into four fractions by HPLC (RP-18, 250 × 25 mm, 7 μm; CH_3CN-H_2O 145:885). The first fraction was unchanged **2b** (29 mg, 47%) followed by **9b** (8.4 mg, 6.9%) and **8b** (8.3 mg, 6.8%). The last fraction (12.9 mg) was separated using MPLC [silica gel, Lobar Merck, size A; EtOAc–$CHCl_3$–EtOH (50:35:15)] giving **11** (1.7 mg, 1.4%), **12** (1.0 mg, 0.9%) and **13** (0.9 mg, 0.8%). Several other minor fractions were not purified.

*(2′*R*,3′*S*)-2′,3′-Dihydro-2,2′-bi(*N_b*-acetyl-*L*-tryptophanamide)* ***8b***. Yellowish crystals, m.p. 173–175 °C. MS *m/z* (% rel. int.) 490 (M^+, 2), 362 (M^+ − side chain $C_5H_8N_2O_2$, 5), 233 (100), 130 (3-methyleneindolium 36), 112 (27), 110 (25).

^{1}H NMR (CD_3OD): δ 10.70 (s, 1 H, indole NH), 7.97 and 7.87 (d, 2 H, $J_{NH,Ca}$ 9 and 8 Hz, respectively), 7.77–7.01 (8 H, aromatic protons), 7.37, 7.15, 7.01 and 6.95 (brs, 4 H, NH_2), 5.80 (d, 1 H, indoline NH, $J_{NH,2'}$ 3 Hz), 4.80 (dd, 1 H, H-2′, $J_{2',3'}$, in DMSO-d_6 3.6 and 9.2 Hz), 4.78 (dd, 1 H, H-α, $J_{\alpha,\beta}$ 7 Hz), 4.65 (dd, 1 H, H-α′, $J_{\alpha',\beta'}$ 5 and 10 Hz), 3.64 (ddd, 2 H, H-3′, $J_{3',\beta'}$ 5 and 8 Hz), 3.49 and 3.38 (dd, 2 H, H-β, $J_{\alpha,\beta}$ 7 Hz, $J_{\beta,\beta}$ 14 Hz), 2.48 (ddd, 1 H, H-β′, $J_{\alpha',\beta'}$ 5 Hz, $J_{\beta',3'}$ 8 Hz, $J_{\beta',\beta'}$ 14 Hz), 2.26 (ddd, 1 H, H-β′, $J_{\alpha',\beta'}$ 10 Hz, $J_{\beta',3'}$ 5 Hz, $J_{\beta',\beta'}$ 14 Hz), 2.08 (s, 3 H, CH_3), 2.01 (s, 3 H, CH_3). ^{13}C NMR (CD_3OD): δ 175.2, 174.8 ($NHCOCH_3$), 172.7, 172.4 ($CONH_2$), 149–110 (aromatic C), 127.0 (C-2), 105.9 (C-3), 59.9 (C-2′), 53.6 (C-α), 50.5 (C-α′), 45.0 (C-3′), 35.0 (C-β′), 25.5 (C-β), 20.8, 20.7 (CH_3). IR (KBr, cm^{-1}), 3383s–3195s (νNH, indole, indoline, amide), 1662s–1609s (νCO, amide). UV (MeOH), λ_{max} (log ε)=220 (4.55), 276 (3.96), 284 (3.99), 292 (3.95). $[\alpha]_D^{22}$ −54° (*c* 0.005, MeOH). CD [MeOH, c=0.003] nm (Δε) 224 (+13.7), 241 (−12.8), 277 (−4.2), 285 (−4.2), 294 (−3.5).

*(2′*S*,3′*R*)-2′,3′-Dihydro-2,2′-bi(*N_b*-acetyl-*L*-tryptophanamide)* ***9b***. Yellowish crystals, m.p. 170–171 °C. FAB-MS: *m/z*=491 ($M+H^+$). ^{1}H NMR (H_2O): δ 10.67 (s, 1 H, indole NH), 8.15 and 7.94 (d, 2 H, $J_{NH,C\alpha}$ 8 Hz), 7.57–6.80 (8 H, aromatic protons), 7.33, 7.31, 7.00 and 6.96 (br s, 4 H, NH_2), 5.80 (d, 1 H, indoline NH, $J_{NH,2'}$ 3 Hz), 4.83 (d, 1 H, H-2′, $J_{2',3'}$ 9.3 Hz), 4.47 (dd, 1 H, H-α, $J_{\alpha,\beta}$ 8 Hz), 4.02 (dd, 1 H, H-α′, $J_{\alpha',\beta'}$ 4 and 13 Hz), 3.76 (ddd, 2 H, H-3′, $J_{3',\beta'}$ 4 and 12 Hz, $J_{2',3'}$ 10 Hz), 3.25 and 3.16 (dd, 2 H, H-β, $J_{\alpha,\beta}$ 8 Hz, $J_{\beta,\beta}$ 15 Hz), 2.39 (ddd, 1 H, H-β′, $J_{\alpha',\beta'}$ 4 Hz, $J_{\beta',3'}$ 13 Hz, $J_{\beta',\beta'}$ 13 Hz), 2.14 (ddd, 1 H, H-β′, $J_{\alpha',\beta'}$ 4 Hz, $J_{\beta',3'}$ 13 Hz, $J_{\beta',\beta'}$ 13 Hz), 1.90 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3). ^{13}C NMR (H_2O): δ 176.9, 176.1 ($NHCOCH_3$), 173.9, 173.2 ($CONH_2$), 149–111 (aromatic C), 127.5 (C-2), 107.2 (C-3), 60.2 (C-2′), 54.6 (C-α), 51.3 (C-α′), 44.1 (C-3′), 34.8 (C-β′), 26.3 (C-β), 21.6, 20.6 (CH_3). IR (KBr, cm^{-1}), 3418s–3220s (νNH, indole, indoline, amide), 1680s (νCO, amide). UV (MeOH), λ_{max} (log ε)=222 (4.60), 276 (4.06), 283 (4.11), 290 (4.07). $[\alpha]_D^{22}$ +29° (*c* 0.005, H_2O). CD [H_2O, *c*=0.002] nm (Δε) 222 (−5.0), 238 (+28.3), 276 (+2.4), 284 (+3.4), 293 (+2.4).

*Pentacyclic lactam **11** derived from **8b***. Yellow oil. FAB-MS: $m/z = 474$ ($M^+ + H$). IR (KBr, cm^{-1}), 3521m–3136m (νNH, indole, amide), 1757s–1587s (νCO, amide, lactam). UV (MeOH), λ_{max} (log ε) = 220 (4.61), 253 (3.99), 280 (3.94), 290 (3.88). $[\alpha]_D^{22}$ −120° (*c* 0.056, MeOH). CD [MeOH, *c* = 0.002] nm (Δε) 221 (−15.8), 245 (−1.6), 261 (+4.0), 292 (−4.7). ^1H NMR (CD_3OD): δ 8.32–7.18 (8 H, aromatic protons), 6.28 (m, 1 H, H-2′), 5.72 (dd, 1 H, H-α, *J* 4.6, 12.8 Hz), 4.93 (dd, 1 H, H-α′, *J* 4.2, 10.6 Hz), 4.27 (m, 1 H, H-3′), 3.26 (ddd, 1 H, H-β, *J* 2.4, 4.4, 14.0 Hz), 2.45 (ddd, 1 H, H-β′, *J* 4.0, 9.6, 14.0 Hz), 2.31 and 2.25 (s, 3 H, CH_3), 2.25 (ddd, 1 H, H-β', *J* 4.0, 10.4, 14.0 Hz). The other Hβ is hidden under the solvent signal. The NH signals were observed in DMSO-d_6 as follows: δ 10.95 (s, 1 H, indolic NH), 8.36 (d, 1 H, N*H*COCH$_3$, *J* 7.0 Hz), 8.27 (d, 1 H, N*H*COCH$_3$, *J* 8.6 Hz), 7.53 (s, 1 H, CONH), 7.13 (s, 1 H, CONH). ^{13}C NMR (CD_3OD): δ 20.7 and 20.9 (CH_3), 27.1 (C-β), 39.4 (C-β′), 40.4 (C-3′), 50.2 (C-α′), 50.6 (C-α), 60.9 (C-2′), 110–141 (aromatic C), 170.4, 171.3 and 171.9 (4 partly superimposed CO).

*Pentacyclic lactam **12** derived from **9b***. Yellow oil. FAB-MS: $m/z = 474$ ($M^+ + H$). IR (KBr, cm^{-1}), 3642s–3144s (νNH, indole, amide), 1825s–1588s (νCO, amide, lactam). UV (MeOH), λ_{max} (log ε) = 220 (4.51), 251 (4.03), 280 (3.90), 289 (3.84). $[\alpha]_D^{22}$ −61° (*c* 0.026, MeOH). CD [MeOH, *c* = 0.002] nm (Δε) 223 (+14.1), 238 (−2.9), 259 (−3.7), 291 (+3.5). ^1H NMR (CD_3OD): δ 8.34–7.18 (8 H, aromatic protons), 6.22 (m, 1 H, H-2′), 5.63 (dd, 1 H, H-α, *J* 4.6, 13.2 Hz), 4.78 (dd, 1 H, H-α′, *J* 6.4, 8.4 Hz), 4.37 (m, 1 H, H-3′), 3.24 (ddd, 1 H, H-β, *J* 1.8, 12.8, 15.8 Hz), 2.50 (ddd, 1 H, Hβ′, *J* 6.4, 6.8, 14. Hz0), 2.36 (ddd, 1 H, H-β′, *J* 8.4, 8.8, 14.4 Hz), 2.30 and 2.15 (s, 3 H, CH_3). The NH signals were observed in DMSO-d_6 as follows: δ 11.12 (s, 1 H, indolic NH), 8.38 (d, 1 H, N*H*COCH$_3$, *J* 7.3 Hz), 8.32 (d, 1 H, N*H*COCH$_3$, *J* 8.2 Hz), 7.48 (s, 1 H, CONH), 7.16 (s, 1 H, CONH). ^{13}C NMR (CD_3OD): δ 20.7 (2CH_3), 27.0 (C-β), 38.2 (C-β′), 40.5 (C-3′), 50.7 (C-α′), 50.9 (C-α), 61.7 (C-2′), 110–141 (aromatic C), 170.3, 171.6 and 171.8 (4 partly superimposed CO).

*Pentacyclic lactam **13** derived from **9b***. Yellow oil. FAB-MS: $m/z = 496$ ($M^+ + H + Na$); with LiCl added 481 ($M^+ + H + Li$). IR (KBr, cm^{-1}), 3642s–3152s (νNH, indole, amide), 1802s–1576s (νCO, amide, lactam). UV (MeOH), λ_{max} (log ε) = 220 (4.18), 252 (3.69), 280 (3.54), 289 (3.47). $[\alpha]_D^{22}$ 0° (*c* 0.020, MeOH). CD [MeOH, *c* = 0.003] nm (Δε) 224 (+3.2), 240 (+0.4), 260 (−1.5), 292 (+1.1). ^1H NMR (CD_3OD): δ 8.42–7.22 (8 H, aromatic protons), 6.00 (m, 1 H, H-2′), 4.87 (dd, 1 H, H-α, *J* 3.6, 4.4 Hz), 4.70 (dd, 1 H, H-α′, *J* 6.2, 8.8 Hz), 4.50 (m, 1 H, H-3′), 3.57 (ddd, 1 H, H-β, *J* 2.0, 4.4, 12.0 Hz), the other H-β is hidden under the solvent signal, 2.54 (ddd, 1 H, H-β′, *J* 5.0, 8.8, 13.6 Hz), 2.21 (ddd, 1 H, H-β′, *J* 5.2, 9.2, 14.0), 2.19 and 2.15 (s, 3 H, CH_3). The NH signals were observed in DMSO-d_6 as follows: δ 11.32 (s, 1 H, indolic NH), 8.64 (d, 1 H, N*H*COCH$_3$, *J* 3.6 Hz), 8.22 (d, 1 H, N*H*COCH$_3$, *J* 8.4 Hz), 7.58 (br s, 1 H, CONH), 7.32 (br s, 1 H, CONH). Because of the small amount of **13**, a ^{13}C NMR spectrum was not obtained.

*Dimerisation of **2c** in TFA*. The reaction occurring in a solution of **2c** (100 mg) in TFA (0.6 ml) was followed by ^1H NMR spectroscopy for 24 h. Only five compounds were initially formed in contrast with the behaviour of **2b**. A signal at 6.40 ppm decreased with time and was ascribed to one of the pyrroloindoles **6c**/**7c**. At the same time, the intensity of the four signals at 6.10, 5.75, 5.70 and 5.60 ppm increased. Since only two pure dimers with H2′ protons, **8c** and **9c**, were isolated the distribution between dimers and cyclic dimers is not known.

A solution of **2c** (81 mg, 0.27 mmol) in TFA (1.8 ml) was kept in a refrigerator at 10 °C for 5 h 35 min. Evaporation by nitrogen followed by lyophilization furnished a red–brown oil which was separated into three fractions by HPLC (RP-18, 250 × 25 mm, 7 μm; CH_3CN–H_2O 37:63). The first fraction was unchanged **2c** (49 mg, 61%) followed by **9c** (8.4 mg, 5.2%). The remaining fraction (8.1 mg) was separated as before using CH_3CN–H_2O (35:65) resulting in **8c** (3.5 mg, 2.2%) followed by **10c** (2.5 mg, 1.6%).

(2′R,3′S)-2′,3′-Dihydro-2,2′-bi(N_b*-trifluoroacetyl-L-tryptophanamide) **8c***. Yellow oil. MS *m/z* (% rel. int.) 598 (M^+, 26), 429 (M^+ − side chain fragment $C_4H_4F_3N_2O_2$, 11), 415 (M^+ − side chain $C_5H_6F_3N_2O_2$, 11), 271 (17), 259 (12), 245 (10), 130 (3-methyleneindolium, 100). ^1H NMR (CD_3OD, NH-signals from DMSO-d_6): δ 10.74 (s, 1 H, indole NH), 9.63 and 9.47 (br s, 2 H), 7.76–6.86 (8 H, aromatic protons), 7.58, 7.43, 7.17 and 7.14 (br s, 4 H, NH_2), 5.73 (d, 1 H, indoline NH, $J_{NH,2'}$ 3 Hz), 5.08 (d, 1 H, H-2′, $J_{2',3'}$ 7.5 Hz), 4.89 (dd, 1 H, H-α′, $J_{\alpha',\beta'}$ 6 and 9 Hz), 3.69 (ddd, 2 H, H-3′, $J_{3',\beta'}$ 6 and 8 Hz, $J_{2',3'}$ 7 Hz), 3.62 and 3.44 (dd, 2 H, H-β, $J_{\alpha,\beta}$ 7 Hz, $J_{\beta,\beta}$ 15 Hz), 2.60 (ddd, 1 H, H-β′, $J_{\alpha',\beta'}$ 6 Hz, $J_{\beta',3'}$ 8 Hz, $J_{\beta',\beta'}$ 14 Hz), 2.38 (ddd, 1 H, H-β′, $J_{\alpha',\beta'}$ 10 Hz, $J_{\beta',3'}$ 6 Hz, $J_{\beta',\beta'}$ 14 Hz). ^{13}C NMR (CD_3OD): δ 172.9, 172.7 ($CONH_2$), 156.7 (NHCO, $J_{C,F}$ 37 Hz), 150–109 (aromatic C), 127.6 (C-2), 115.4, 115.3 ($COCF_3$, $J_{C,F}$ 285 Hz), 106.0 (C-3), 60.5 (C-2′), 54.1 (C-α), 50.9 (C-α′), 45.2 (C-3′), 35.4 (C-β′), 26.1 (C-β). IR (KBr, cm^{-1}), 3533s–3121s (νNH, indole, indoline, amide), 1722s–1637 m (νCO, amide), 1208s, 1185s, and 1147s (νCF_3). UV (MeOH), λ_{max} (log ε) = 275 (2.58), 283 (2.61), 292 (2.57). $[\alpha]_D^{22}$ −38° (*c* 0.165, MeOH). CD [MeOH, *c* = 0.008] nm (Δε) 242 (−16.4), 275 (−4.4), 284 (−5.3), 293 (−4.9).

(2′S,3′R)-2′,3′-Dihydro-2,2′-bi(N_b*-trifluoroacetyl-L-tryptophanamide) **9c***. Yellowish crystals, m.p. 149–150 °C. MS *m/z* (% rel. int.) 598 (M^+, 100), 429 (M^+ − side chain fragment $C_4H_4F_3N_2O_2$, 85), 415 (M^+ − side chain $C_5H_6F_3N_2O_2$, 98), 271 (39), 259 (80), 245 (65), 130 (3-methyleneindolium, 73). ^1H NMR (CD_3OD,

NH-signals from DMSO-d_6): δ 10.79 (s, 1 H, indole NH), 9.61 and 9.33 (br s, 2 H), 7.74–6.85 (8 H, aromatic protons), 7.49, 7.41, 7.16 and 7.15 (br s, 4 H, NH_2), 5.76 (d, 1 H, indoline NH, $J_{NH,\,2'}$ 3 Hz), 5.11 (d, 1 H, H-2′, $J_{2',3'}$ 8.4 Hz), 4.87 (dd, 1 H, H-α′, $J_{\alpha,\beta}$ 6 and 9 Hz), 4.66 (dd, 1 H, H-α′, $J_{\alpha',\beta'}$ 4 and 11 Hz), 3.85 (ddd, 2 H, H-3′, $J_{3',\beta'}$ 4 and 10 Hz, $J_{2',3'}$ 9 Hz), 3.56 and 3.36 (dd, 2 H, H-β, $J_{\alpha,\beta}$ 6 and 9 Hz, $J_{\beta,\beta}$ 14 Hz), 2.65 (ddd, 1 H, H-β′, $J_{\alpha',\beta'}$ 4 Hz, $J_{\beta',3'}$ 10 Hz, $J_{\beta',\beta'}$ 15 Hz), 2.39 (ddd, 1 H, H-β′, $J_{\alpha',\beta'}$ 11 Hz, $J_{\beta',3'}$ 4 Hz, $J_{\beta',\beta'}$ 15 Hz). ^{13}C NMR (CD_3OD): δ 173.3, 173.0 ($CONH_2$), 156.8 (NHCO, $J_{C,F}$ 36 Hz), 150–109 (aromatic C), 127.5 (C-2), 115.4, 115.1 ($COCF_3$, $J_{C,F}$ 284 Hz), 105.9 (C-3), 60.8 (C-2′), 54.7 (C-α), 51.6 (C-α′), 45.1 (C-3′), 35.7 (C-β′), 26.2 (C-β). IR (KBr, cm^{-1}), 3386s–3197s (νNH, indole, indoline, amide), 1719s–1683s (νCO, amide), 1214s, 1186s, and 1159s (νCF_3). UV (MeOH), λ_{max} (log ε)=221 (4.59), 275 (4.02), 283 (4.04), 292 (4.01). $[\alpha]_D^{22}$ +88° (*c* 0.005, MeOH). CD [MeOH, *c*= 0.003] nm (Δε) 222 (−12.9), 241 (+17.6), 276 (+4.4), 284 (+4.4), 294 (+3.3).

2,2′-Bis(N_b*-trifluoroacetyl-L-tryptophanamide)* ***10c***. Yellow oil. MS *m/z* (% rel. int.) 596 (M^+, 48), 427 (M^+ − side chain fragment $C_4H_4F_3N_2O_2$, 100), 415 (20), 269 (69), 257 (427 − side chain fragment $C_4H_5F_3N_2O_2$, 56), 245 (24), 130 (3-methyleneindolium, 26). IR (KBr, cm^{-1}), 3602s–3164s (νNH, indole, amide), 1844s–1599s (νCO, amide), 1218s, 1176s, and 1144s (νCF). UV (MeOH), λ_{max} (log ε)=220 (4.18), 283 (3.85), 293 (3.88), 320 (3.91), 325 (3.92). $[\alpha]_D^{22}$ −28° (*c* 0.026, MeOH). CD [MeOH, *c*=0.005] nm (Δε) 228 (+4.5), 243 (−10.0), 274 (+0.9), 295 (−2.6), 327 (−2.3). ^{1}H NMR (CD_3OD): δ 7.93 (d, 2 H, H-4, *J* 8.0 Hz), 7.60 (d, 2 H, H-7, *J* 7.6 Hz), 7.34 (t, 2 H, H-6, *J* 7.6 Hz), 7.27 (t, 2 H, H-5, *J* 7.6 Hz), 5.20 (dd, 2 H, H-α, *J* 6.6, 9.0 Hz), 3.76 (dd, 2 H, H-β, *J* 9.0, 14.2 Hz), 3.42 (dd, 2 H, H-β, *J* 6.3, 13.4 Hz). Because of the small amount of **10c**, a ^{13}C NMR spectrum was not obtained.

Crystal structure determination. The experimental details in the crystallographic study of **7a** are presented in Table 1 and the final atomic coordinates in Table 2. The crystal was grown from a mixture of heptane and $CHCl_3$ with traces of triethylamine added to avoid ring opening. Low-temperature data were collected on an Enraf–Nonius CAD4 diffractometer with Cu Kα radiation using a graphite crystal as monochromator. The initial orientation matrix and cell parameters were determined from 20 reflections with θ in the range 37.84–38.01°. A total of 5436 reflections were measured on a needle-shaped crystal (dimensions 0.08 × 0.07 × 0.40 mm) with ω/2θ scans covering the octants *hkl*, *hk*−*l* from 5.35 to 74.92°.

The Blessing data reduction package DREADD[45] including corrections for Lorentz and polarisation terms was used for the data reduction and error analysis. The data were not corrected for absorption ($\mu = 0.868\ mm^{-1}$). The space group was uniquely determined from the systematically absent reflections as derived from the diffractometer list. The intensity-controlled reflections showed that no decay due to deterioration or misalignment occurred during data collection. The data were averaged with normal probability down-weighting of outliers. 1434 unique reflections with $R_{int}=0.0108$ were obtained. 1368 of these were observed with $F>4\sigma(F)$.

The direct method facility of SHELXS-86[46] was used for the structure solution. XMOL[47] was used as a graphic interface to a list of starting coordinates suggested by SHELXS-86. SHELXL-93[48] full matrix least-squares refinement on F^2 was used for the refinement process. The choice of stereoisomer was confirmed by the Flack[49] absolute structure parameter: Flack *x* parameter= −0.0534 (esd=0.1682) for the L-form versus 1.0538 (esd=0.1697) for the D-form.

Acknowledgements. We thank Flemming Hansen for assistance in the experimental crystallographic work. The Danish Natural Science Research Council supported this research by financing the X-ray diffractometer. We are indebted to Dr. S. E. Harnung for determination of CD data measured on a modifed Jasco 710 instrument financed by the Danish Natural Science Research Council, Grant No.//-0373-1.

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Received October 15, 1997.