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MODELS OF FOLATE COFACTORS - 22.[1] LEWIS ACID CATALYZED CYCLIZATION OF CARBON-FRAGMENT TRANSFER PRODUCTS OF FOLATE COFACTOR MODELS. SYNTHESIS OF ENANTIOMERICALLY PURE TETRACYCLIC (ABCE) RING SYSTEM OF ASPIDOSPERMA ALKALOIDS.

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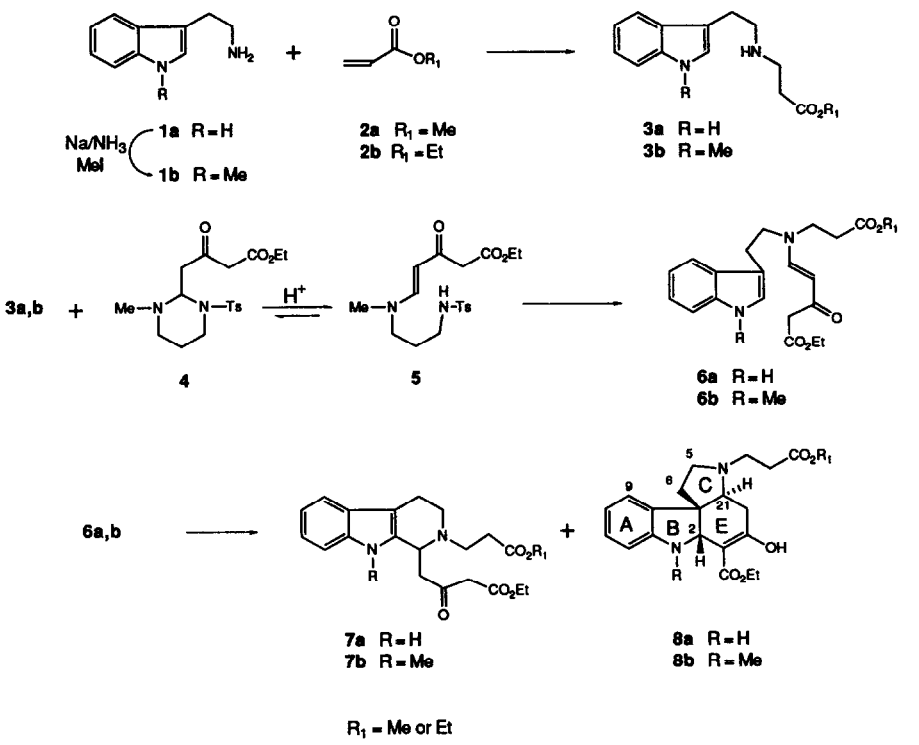
Abstract: Michael adducts of tryptamine, N(1)-methyltryptamine and tryptophane with acrylic esters react with substituted imidazolidines (N(5),N(10)-methylenetetrahydrofolate models) to give enaminones which cyclize under influence of Lewis acid, to give mixtures of tetrahydro-1*H*-pyrido[3,4-b]indoles and pyrrolo[2,3-d]carbazoles. The influence of the nature of Lewis acid on product formation is discussed. The synthesis of an enantiomerically pure pyrrolo[2,3-d]carbazole system is reported.

Work in our laboratory has demonstrated that suitable folate cofactor models can be employed as pivotal reagents in the synthetic approach to a variety of natural products and their analogues.[3] In our studies directed to the application of substitued N(5),N(10)-methylenetetrahydrofolate models in alkaloid synthesis, we have reported the preparation of heterocyclic systems representing the functionalized Aspidosperma skeleton.[1,4] In this study the folate cofactor models have been so chosen that the carbon-fragment transferred, contains the carbon atoms 16, 17, 20, and 21 of the final Aspidosperma skeleton as well as the alkoxycarbonyl group at C(16), which is present in several, pharmacological active, members of the Aspidosperma alkaloid family.[5] We emphasize our results on the Lewis acid induced cyclization of the enaminone intermediates derived from the reaction of tryptamine derivatives **3a,b** and tryptophanate ester **27**, with folate cofactor model **4**. In this cyclization reaction, which is analogous to that utilized in several synthetic strategies towards the Aspidosperma skeleton, the C(7)-C(21), and the C(2)-C(16) bonds are formed, presumably in a stepwise manner, to generate rings C and E of the alkaloid system.[6,7]

The starting substances **3a,b** were conveniently obtained by the Michael addition of tryptamines **1a,b** to acrylic esters (**2a,b**) (Scheme 1). The carbon-fragment transfer from the folate model, employed in its ring-opened form **5**, to **3a,b**, furnished the crucial enaminone intermediates **6a,b**. These were subjected to cyclization reactions under influence of $BF_3{\cdot}OEt_2$ or $TiCl_4$, whereupon tetrahydro-β-carbolines **7a,b** and octahydro-1*H*-pyrrolo-[2,3-d]carbazoles **8a,b** were formed as the salient reaction products.[8] The reaction mixtures could be monitored and analyzed by HPLC and the results are presented in Table 1.

Table 1
Lewis acid catalyzed cyclization of **6a,b**

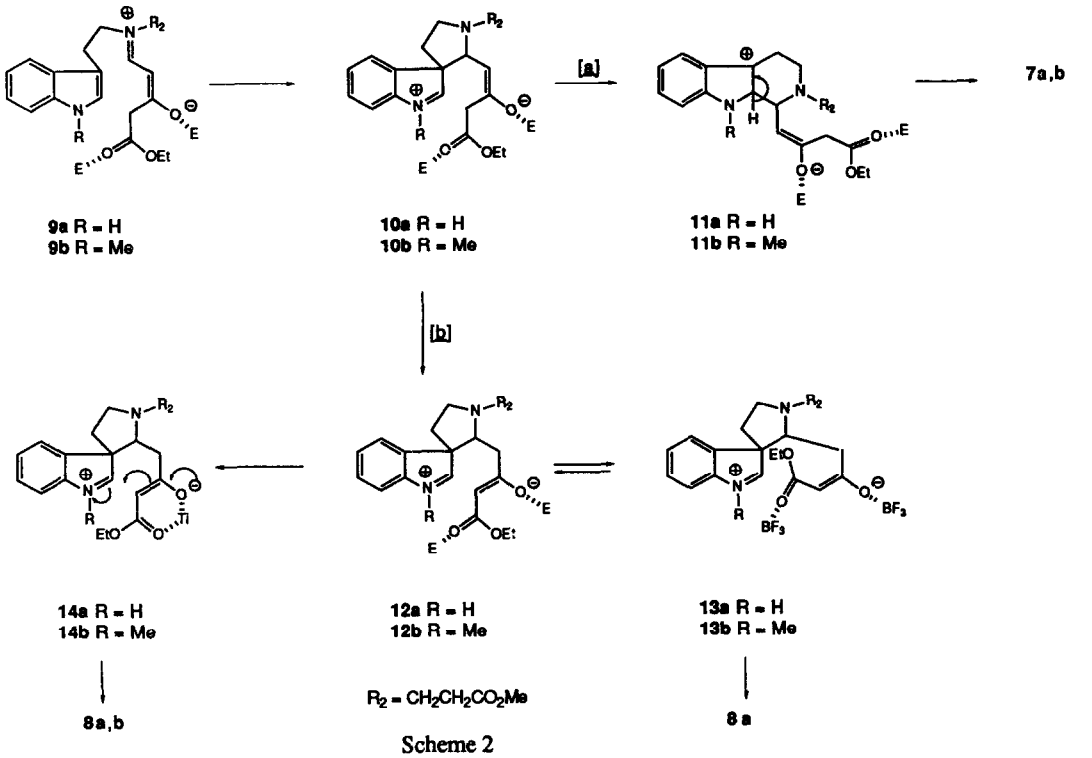
compound	Lewis acid	pyridoindole	pyrrolocarbazole
6a	$BF_3{\cdot}OEt_2$	**7a** 45 %	**8a** 19 %
6b	$BF_3{\cdot}OEt_2$	**7b** 49 %	-
6a	$TiCl_4$	-	**8a** 26 %
6b	$TiCl_4$	-	**8b** 55 %



Scheme 1

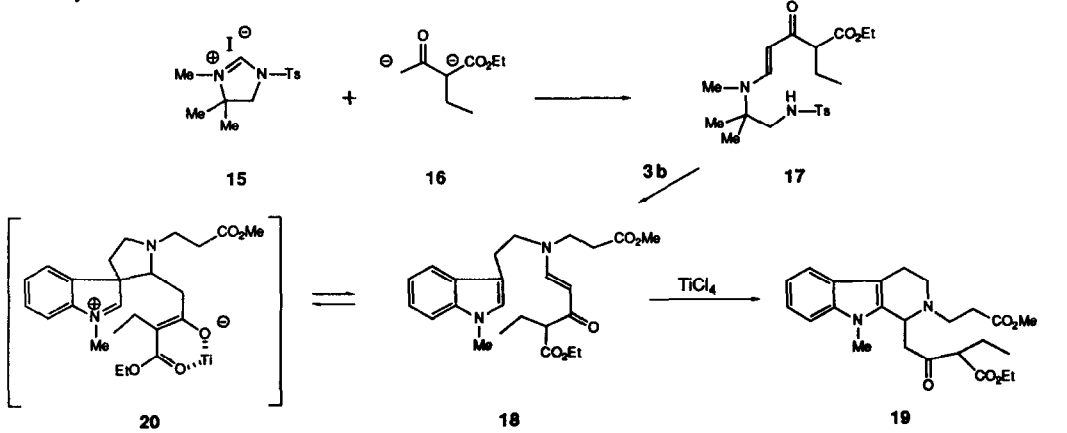
Inspection of Table 1 reveals that the BF_3·OEt_2 catalyzed cyclization results predominantly in the pyridoindole system, whereas the $TiCl_4$ mediated reaction leads exclusively to the tetracyclic pyrrolocarbazole product. The mechanism of formation of the two products can be explained by considering, in particular, the coordination of the Lewis acid with the two carbonyl groups of the β-keto ester moiety in the enaminone system **6** (**a**,**b**). The resulting iminium intermediate **9** (**a**,**b**) (Scheme 2), undergoes a cyclization step involving the indole nucleus as a nucleophile, whereupon intermediate **10** (**a**,**b**) is formed. This spiroindolenine system can undergo two different fates depending upon the nature of the Lewis acid. According to pathway [a], the intermediate **10** (**a**,**b**) undergoes a typical Wagner-Meerwein rearrangement, to result in the β-carboline cation **11** (**a**,**b**) which deprotonates to form **7** (**a**,**b**). In an alternate pathway [b], **10** (**a**,**b**) can isomerize to **12** (**a**,**b**), which subsequently cyclizes to tetracyclic pyrrolocarbazole **8** (**a**,**b**), via intermediate **14** (**a**,**b**).

In the BF_3·OEt_2 mediated reaction, processes [a] and [b] compete with each other, the product distribution depending upon the relative stabilities of systems **10** and **12**. It should be noted that in case of **12**, complexation with BF_3·OEt_2 will stereoelectronically favour a situation in which the two BF_3 coordinated sites are remote from each other (**E**-configuration; e.g. **13**). However, in **13**, the transition state of the cyclization step will encounter serious steric repulsion between the indole nucleus and the BF_3-complexed ester function. This factor will adversely affect the formation of the tetracyclic heterocyclic system **8** (**a**,**b**). This is in line with the observation that, whereas **6a** yields **8a** as the minor product, the introduction of the methyl substituent in the indole moiety (**6b**) presumably suppresses intermediates **12b** = **13b**, that is pathway [b], and thereby the formation of **8b**.



Scheme 2

The exclusive formation of tetracyclic products **8a** and **8b** in the $TiCl_4$ induced cyclization reactions is attributed to the ability of Ti(IV) to coordinate simultaneously with more than one electro-negative group. The same Ti(IV) cation will coordinate with both the oxygen of the enolate and the carbonyl group of the ester. This results in the formation of intermediate **14 (a,b)**, in which there is minimum steric hindrance to the cyclization reaction, leading to **8 (a,b)**. The importance of steric interactions in this cyclization step is emphasized by the $TiCl_4$ induced cyclization reaction of enaminone **18** (Scheme 3).

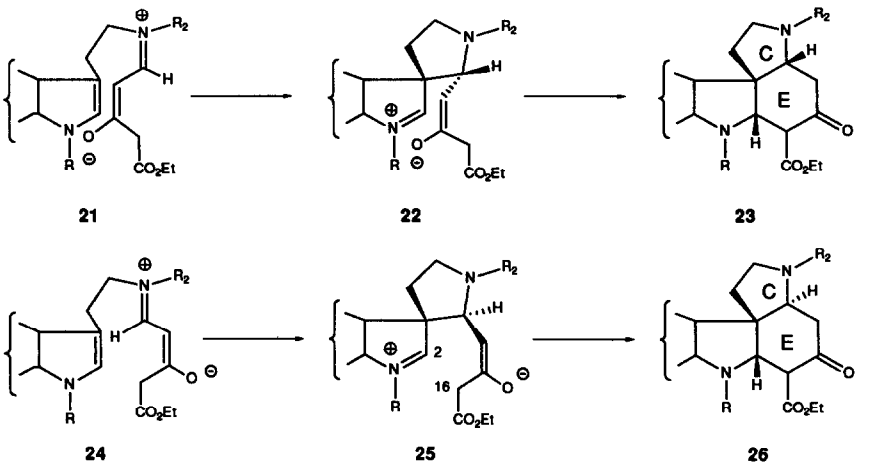


Scheme 3

Open form of the folate model i.e. **17** was formed upon addition of the imidazolidinium salt **15** to the dianion of β-keto ester (**16**). The carbon-fragment transfer reaction from **17** to tryptamine derivative **3b** furnished enaminone **18**, that bears an ethyl substituent on the α-carbon of the β-keto ester. Treatment of enaminone **18** with $TiCl_4$ led only to the isolation of the β-carboline **19**. This is clearly due to additional steric hindrance between the ethyl group and the indole nucleus in the spiroindolenine intermediate **20**; the attack of the enolate on the iminium ion being prevented, the intermediate reverts to the one corresponding to **10** (Scheme 1), which after a Wagner-Meerwein rearrangement leads to **19**.

The stereochemistry of **8a** and **8b** was established by NOE experiments. Irradiation of the signal of C(2)Hβ of **8a** resulted in an enhancement of the signal ascribed to C(6)Hβ, and irradiation of the signal of C(21)H resulted in an enhancement of a doublet at 6.7 ppm ascribed to C(9)H. In compound **8b** a nuclear Overhauser effect was observed for the protons at C(5) and C(21) upon irradiation of the signal of C(9)H. Irradiation of the signal of C(2)Hβ gave an enhancement of the signals of C(6)Hβ and NMe.

The tetracyclic ring systems have the same stereochemistry as the Aspidosperma alkaloids, viz. that the B/C and C/E ring junction possess the *cis* configuration. The stereochemistry of the reaction is determined during the formation of the spiro intermediate (e.g. **22** and **25** in Scheme 4). Two conformations of the iminium enolate (**21** and **24**) can be visualized, as is shown in Scheme 4. In intermediate **21** the indole nucleus lies above the iminium double bond. Formation of the spiro-intermediate **22**, followed by the second cyclization furnishes the indolenine **23** with the *trans* C/E ring junction. In intermediate **24** the iminium bond again lies under the indole moiety, but has a R_2,H *trans* configuration. Nucleophilic attack of the enamine double bond of the indole followed by the second cyclization step results in compound **26**, with the correct *cis* C/E geometry. It is evident that because of steric repulsion, the intermediate **24**, in which the enolate and indolylethyl substituent (of the iminium double bond) have a *trans*-configuration, is favoured over intermediate **21**. The selective formation of



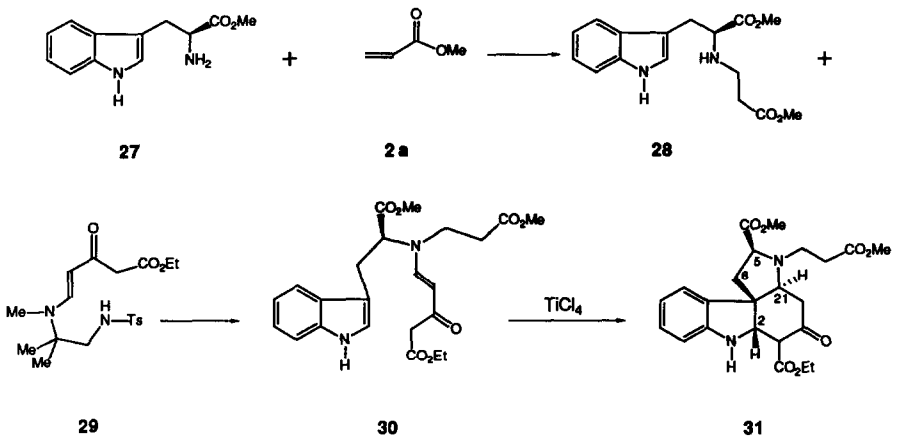
$R_2 = CH_2CH_2CO_2Me$

Scheme 4

the less strained tetracycles with the cis C/E ring junction can also be explained by assuming the reversability of the spiro intermediate formation.[9] The product formation can then be regarded to be thermodynamically controlled.

To see whether the asymmetric centre in L-(-)-tryptophane is capable of inducing stereospecificity in the $TiCl_4$ induced cyclization reaction, tryptamine was substituted by L-(-)-tryptophane methyl ester **27** in an analogous reaction scheme (Scheme 5). The Michael addition of **27** to methyl acrylate furnished compound **28**. Transfer of the carbon fragment of ring-opened model **29** to this compound resulted in enaminone **30**. This enaminone was optically active ($[\alpha]^{20}_D$ = -121° (c = 0.0102, $CHCl_3$)). The cyclization reaction of **30** with 2 eq $TiCl_4$ provided the tetracyclic ring system **31** ($[\alpha]^{20}_D$ = -50.3° (c = 0.0167, $CHCl_3$)). Only one product was isolated. Assuming that there had been no epimerization at C(5), it has the absolute stereochemistry shown in **31**; which is identical with the natural vindoline template. The ^{1}H-NMR spectrum of **31** was assigned unambiguously using the 2D-COSY technique. Furthermore, with NOE experiments the stereochemistry of the molecule was established. Irradiation of the signal of C(2)Hβ gave an enhancement of the signals of C(6)Hβ (dd, 2.08 ppm), the NH and C(16)H (m, 4.90 ppm). No interaction with C(21)H could be observed, which implies that C(21)H possesses the α orientation. The β orientation of the methoxycarbonyl group at C(5)H can be concluded from the nuclear Overhauser effect observed between C(5)H and C(21)Hα.

The enantiomeric purity of **31** was established by ^{1}H-NMR. Addition of the chiral shift reagent Eu(hfc)$_3$ to a solution of **31** did not result in splitting of signals in the ^{1}H-NMR spectrum. A complex was formed between Eu(hfc)$_3$ and **31**, as was attested by the shift of the signals in the spectrum of **31**.



Scheme 5

Experimental

Chromatographic separations were carried out by means of flash chromatography on freshly filled silica gel (230-400 mesh) columns, following literature procedure.[10] All m.ps are uncorrected. Infrared spectra were recorded on a Perkin Elmer 257 or 298 spectrometer. The absorbtions are given in cm^{-1}. ^{1}H-NMR measurements were performed on Varian A-60, HA-100 or XL-100 instruments or on Brucker WM-250 or AC-200 instruments. ^{13}C-NMR spectra were recorded on the Brucker WM-250 or AC-200 instruments. The chemical shifts are given in ppm downfield from tetramethylsilane. Unless stated otherwise IR and NMR spectra are taken in $CHCl_3$ and $CDCl_3$, respectively. Exact mass measurements were carried out using a Varian MAT 711 or a VG Micromass ZAB-2HF. The IUPAC nomenclature is used in naming the compounds. In the text and in the description of the NMR spectra a numbering method related to the Aspidosperma alkaloids is used (See note 7).

Methyl 3-(2-(3-indolyl)ethyl)aminopropionate (**2a** R_1 = Me).
A solution of methyl acrylate (25 mmol, 2.1 g) in 20 ml abs. ethanol was added dropwise to a solution of 25 mmol (4.0 g) tryptamine in 50 ml of ethanol. The mixture was stirred for 2 h at room temperature and heated to 75 °C for 0.5 h. The mixture was concentrated under vacuum and purified by flash chromatography (ethyl acetate → ethyl acetate/ethanol 1:1). 5.98 g (93 %) of the product was isolated as a dark oil. **^{1}H-NMR** (250 MHz): 1.78 (br.s, 1H, CH_2NHCH_2), 2.50 (t, 2H, J = 6.6 Hz, CH_2CO_2), 2.92 (t, 2H, J = 6.6 Hz, $NCH_2CH_2CO_2$), 2.96 (br.s, 4H, indole-CH_2CH_2NH), 3.60 (s, 3H, OCH_3), 6.98 (d, 1H, J = 2.3 Hz, C(2)H indole), 7.07-7.21 (m, 2H, C(5)H and C(6)H indole), 7.31 (d, 1H, J = 7.7 Hz, C(7)H indole), 7.61 (d, 1H, J = 7.7 Hz, C(4)H indole), 8.43 (br.s, 1H, NH indole). **IR**: 3480 (sh.s), 3300 (br.w), 1730 (s).

Ethyl 3-(2-(3-indolyl)ethyl)aminopropionate (**2b** R_1 = Et).
Ethyl acrylate (15 mmol, 1.59 g) was added dropwise to a solution of 15 mmol tryptamine in 25 ml of abs. ethanol at 0 °C. After stirring for 24 h the reaction mixture was concentrated under vacuum and purified by flash chromatography (ethyl acetate → ethyl acetate-ethanol 1:1). The product was obtained as a red brown gum 83 % yield (3.25 g). Crystallization from ethyl acetate furnished yellow crystals (mpt. 71-72.5 °C). **^{1}H-NMR** (250 MHz): 1.13 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 2.00 (br.s, 1H, CH_2NHCH_2), 2.28-2.40 (m, 2H, CH_2CO_2), 2.80-3.05 (m, 6H, $CH_2CH_2NCH_2CH_2CO_2$), 4.05 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 6.90-7.70 (m, 5H, indole), 8.80 (br.s, 1H, NH indole). **^{13}C-NMR** (50 MHz, APT): 13.9 (OCH_2CH_3), 25.4 (indole-CH_2CH_2), 34.4 (CH_2CO_2), 44.7 and 49.5 (CH_2NHCH_2), 60.2 (OCH_2CH_3), 111.0 (C(7) indole), 113.0 (C(3) indole), 118.5 and 118.8 (C(4) and C(6) indole), 121.6 and 122.0 (C(5) and C(2) indole), 127.1 (C(3a) indole), 136.2 (C(7a) indole), 172.6 (CO_2Et). **IR**: 3480 (sh.s), 3300 (br.w), 1725 (s).

Ethyl 3-(2-(3-(N-methyl)indolyl)ethyl)aminopropionate (**3b** R_1 = Et).
A solution of 6.0 mmol (603 mg) ethyl acrylate in ethanol was added dropwise to a solution of 6.0 mmol N(1)-methyltryptamine in 10 ml abs. ethanol at room temperature under a nitrogen atmosphere. The solution was heated to reflux and after 3 h concentrated under vacuum and purified by flash chromatography (ethyl acetate → ethyl acetate/ethanol 9:1). 1.413 g (85 %) of the product was isolated as a dark oil. **^{1}H-NMR** (200 MHz): 1.26 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.49-2.52 (m, 2H, CH_2CO_2), 2.85-3.05 (m, 6H, $CH_2CH_2NHCH_2$), 3.76 (s, 3H, OCH_3), 4.12 (s, 3H, NCH_3), 6.89 (s, 1H, C(2)H indole), 7.10-7.35 (m, 3H, C(5)H, C(6)H and C(7)H indole), 7.63 (d, 1H, J = 7.6 Hz, C(4)H indole). **^{13}C-NMR** (50 MHz, APT): 14.0 (OCH_2CH_3), 25.4 (indole-CH_2CH_2NH), 32.3 (NCH_3), 34.6 (CH_2CO_2), 44.8 and 49.8 (CH_2NHCH_2), 61.1 (OCH_2CH_3), 109.0 (C(7) indole), 112.2 (C(3) indole), 118.5 and 118 7 (C(4) and C(6) indole), 121.4 (C(5) indole), 126.5 (C(2) indole), 127.7 (C(3a) indole), 136.9 (C(7a) indole), 172.4 (CO_2Et). **IR**: 1730 (s). **MS** (FD 10 mA): 274.

Methyl 3-(2-(3-(N-methyl)indolyl)ethyl)aminopropionate (**3b** R_1 = Me).
A solution of 2.61 g (28.7 mmol) methyl acrylate in 20 ml of ethanol was slowly added to a solution of 5.0 g (28.7 mmol) N(1)-methyltryptamine. The mixture was stirred for another 2 h at room temperature and heated for 0.5 h to 60 °C. After concentration of the mixture under vacuum it was purified by flash chromatography (ethyl acetate → ethyl acetate/ethanol 7:3) and 5.92 g (79 %) product was obtained as a brown oil. **^{1}H-NMR** (250 MHz): 2.06 (s, 1H, NH), 2.51 (t, 2H, J = 6.7 Hz, CH_2CO_2), 2.92 (t, 2H, J = 6.7 Hz, $NHCH_2$), 2.95 (s, 4H, indole-$CH_2CH_2NHCH_2$), 3.62 (s, 3H, OCH_3), 3.72 (s, 3H, NCH_3), 6.88 (s, 1H, C(2)H indole), 7.07-7.33 (m, 3H, C(5)H, C(6)H and C(7)H indole), 7.61 (d, 1H, J = 7.8 Hz, C(4)H indole). **^{13}C-NMR** (50 MHz, APT): 25.4 (indole-CH_2CH_2NH), 32.4 (NCH_3), 34.4 (CH_2CO_2), 44.8 and 49.8 (CH_2NHCH_2), 51.4 (OCH_3), 109.1 (C(7) indole), 112.1 (C(3) indole), 118.6 and 118.8 (C(4) and C(6) indole), 121.4 (C(5) indole), 126.6 (C(2) indole), 127.7 (C(3a) indole), 136.9 (C(7a) indole), 173.0 (CO_2Me). **IR**: 1725 (s).

Ethyl 5-[ethoxycarbonylethyl-(3-indolyl)ethyl]amino-3-oxo-4-pentenoate (**6a** R_1=Et).
A mixture of tryptamine derivative **3a** (2600 mg, 10 mmol) and folate model **5** (750 mg, 2 mmol) were refluxed in 16.5 ml of acetonitrile/acetic acid (10:1) under a nitrogen atmosphere for 6.5 h. The reaction mixture was concentrated under vacuum and the residue was dissolved in ethyl acetate. After addition of some silica gel the solvent was removed under reduced pressure and the powder was brought on top of a silica gel column for flash chromatography (eluent ethyl acetate/petroleum ether 60-80 1:1 → ethyl acetate) The product was isolated as a yellow oil in 63 % yield (496 mg). **^{1}H-NMR** (250 MHz) broad signals due to hindered rotation: 1.21-1.27 (m, 6H, 2 x $O_2CH_2CH_3$), 2.02-2 03 (m, 2H, $NCH_2CH_2O_2$), 2.40-2.51 (m, 2H, indole-CH_2), 2.81-3.45 (m, 6H, CH_2NCH_2 and $C(=O)CH_2CO_2$), 3 98-4.15 (m, 4H, 2 x OCH_2CH_3) 5.05-5 12 (m, 1H, NCH=CHC(=O)), 6.69-7.50 m, 6H, C(2)H, C(4)H,

C(5)H, C(6)H, C(7)H indole and NCH=CH-C(=O)), 8.73 (br.s, 1H, NH indole). **IR**: 3480 (sh.s), 1730 (s), 1650 (m), 1600 (m), 1560 (s). **MS** exact mass: found 400.1982 (calculated for $C_{22}H_{28}N_2O_5$: 400.199).

Ethyl 5-[ethoxycarbonylethyl-(3-(N-methyl)indolyl)ethyl]amino-3-oxo-4-pentenoate (**7** R_1=Et).
Folate model **5** (750 mg, 2 mmol) and tryptamine derivative **3b** (1410 mg, 5 mmol) were dissolved in a mixture of acetonitrile/acetic acid (16.5 ml, 10:1) and the mixture was refluxed for 30 h under a nitrogen atmosphere. The mixture was concentrated under vacuum and the residue was taken up in ethyl acetate and the solution was washed with sat. $NaHCO_3$, brine and dried over $MgSO_4$. After filtration silica was added and the solvent was carefully removed under reduced pressure. The remaining powder was brought on top of a silica gel column for flash chromatography (eluent ethyl acetate → ethyl acetate/ethanol 1:1) and beside the product (433 mg, 52 %) also some starting material (**5**) was isolated (98 mg, 13 %). **^{1}H-NMR** (200 MHz) broad signals due to hindered rotation: 0.91 and 0.97 (2 x t, 2 x 3H, J = 7.1 Hz, 2 x OCH_2CH_3), 1.85-2.10 (m, 2H, $NCH_2CH_2CO_2$), 2.60-3.40 (m, 11H, indole-CH_2-CH_2NCH_2, NCH_3 and $C(=O)CH_2CO_2$), 3.85 and 4.00 (2 x q, 2 x 2H, J = 7.1 Hz, 2 x OCH_2CH_3) 5.23 (br.d, 1H, NCH=CHC(=O)), 6.69-7.50 m, 6H, C(2)H, C(4)H, C(5)H, C(6)H, C(7)H indole and NCH=CHC(=O)). **IR**: 1730 (s), 1650 (m), 1600 (m), 1560 (s). **MS** exact mass: found 414.2140 (calculated for $C_{23}H_{30}N_2O_5$: 414.2154).

BF_3·OEt_2 induced cyclization of enaminone **6a**.
A mixture of 77 mg of **6a** and 1 ml of freshly distilled BF_3·OEt_2 was stirred overnight at room temperature under a nitrogen atmosphere. After careful addition of sat. $NaHCO_3$, the water layer was extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The products were separated by chromatography on a silica plate (ethyl acetate) and 35 mg of the β-carboline **7a** (45 %) and 15 mg of **8a** (19 %) were isolated, both as a yellow oil.
2-Ethoxycarbonylethyl-1-(3-ethoxycarbonyl-2-oxo)propyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**7a** R_1=Et).
^{1}H-NMR (200 MHz): 1.21-1.29 (m, 3H, CH_2CH_3), 2.49-2.59 (m, 4H, $CH_2CH_2CO_2$ and $C(1)HCH_2C(=O)$), 2.89-3.25 (m, 6H, 2 x C(3)H, 2 x C(4)H and $CH_2C(=O)CH_2$), 3.49 (s, 2H, $C(=O)CH_2CO_2$), 4.08-4.26 (m, 3H, C(1)H and OCH_2CH_3), 7.07-7.18 (m, 2H, C(6)H and C(7)H), 7.30 (d, 1H, J = 7.3 Hz, C(8)H), 7.47 (d, 1H, J = 8.2 Hz, C(5)H), 8.35 (br.s, 1H, NH). **^{13}C-NMR** (50 MHz, APT): 14.0 and 14.2 (2 x OCH_2CH_3), 17.9 (C(4)), 34.0 ($CH_2CH_2CO_2$), 45.2 ($C(1)CH_2C(=O)CH_2$), 49.0, 49.2 and 49.8 (C(3), $C(=O)CH_2CO_2$ and $NCH_2CH_2CO_2$), 52.6 (C(1)), 60.3 and 61.5 (2 x OCH_2CH_3), 107.7 (C(4a)), 110.9 (C(8)), 118.0 (C(5)), 119.2 (C(6)), 121.7 (C(7)), 126.8 (C(4b)), 134.0 and 135.7 (C(8a) and C(9a)), 116.8 ($C(=O)CH_2CO_2$), 172.4 ($CH_2CH_2CO_2Et$), 203.9 ($CH_2C(=O)CH_2CO_2$). **IR**: 3469 (sh.s), 1725 (s). **MS** exact mass: found 400.1993 (calculated for $C_{22}H_{28}N_2O_5$ 400.1998).
rel-(3aS,6aR,11bS)-2,3,3a,4,6a,7-Hexahydro-5-hydroxy-6-methoxycarbonyl-3-(methoxy-carbonylethyl)-1H-pyrrolo[2,3-d]carbazole (**8a** R_1=Et).
^{1}H-NMR (200 MHz): 1.26 and 1.34 (2 x t, 2 x 3H, J = 7.1 Hz, 2 x OCH_2CH_3), 1.93 (dt, 1H, J = 9.1 and 13.5 Hz, C(6)Hβ), 2.08-2.63 (m, 8H, C(3)H, $C(5)H_\alpha$, $C(6)H_\alpha$, 2 x C(14)H, 2 x C(20)H, C(21)H), 3.06 (dt, 1H, J = 8.1 and 11.8 Hz, C(3)H), 3.38-3.46 (m, 1H, C(5)Hβ), 3.92-4.37 (m, 6H, 2 x OCH_2CH_3, C(16)H and C(2)H), 4.78 (d, 1H, J = 3.3 Hz, NH), 6.62 (d, 1H, J = 7.7 Hz, C(12)H), 6.78 (t, 1H, J = 7.4 Hz, C(11)H), 7.04-7.13 (m, 2H, C(9) and C(10)H). **^{13}C-NMR** (50 MHz, APT): 14.16 and 14.19 (2 x OCH_2CH_3), 34.0 (C(6)), 37.2 and 37.6 (C(20) and C(14)), 48.2 (C(3)), 52.9 (C(7)), 53.2 (C(5)), 54.4 (C(16)), 60.6 and 61.3 (OCH_2CH_3), 67.5 and 71.2 (C(2) and C(21)), 109.5 (C(12)), 119.2 (C(10)), 123.0 (C(9)), 128.5 (C(11)), 133.2 (C(8)), 150.0 (C(13)), 170.4 and 172.0 (2 x CO_2), 202.9 (C(17)). **^{1}H-NMR** (C_6D_6, 250 MHz): 1.02 and 1.13 (2 x t, 2 x 3H, J = 7.1 Hz, 2 x OCH_2CH_3), 1.27 (dt, 1H, J = 9.1 and 13.7 Hz, C(6)Hβ), 1.61-1.70 (m, 1H, C(14)H), 1.76 (dd, 1H, J = 9.1 and 12.2 Hz, $C(6)H_\alpha$), 1.93-2.32 (m, 6H, C(3)H, $C(5)H_\alpha$, C(14)H, 2 x C(20)H, C(21)H), 2.70 (ddd, 1H, J = 6.6, 10.0 and 12.0 Hz, C(3)H), 2.95-3.02 (m, 1H, C(5)Hβ), 3.70-3.72 (dd, 1H, J = 1.8 and 3.3 Hz, C(2)H), 3.87-4.21 (m, 4H, 2 x OCH_2CH_3), 4.36 (d, 1H, J = 1.8 Hz, C(16)H), 4.79 (br.d, 1H, J = 3.3 Hz, NH), 6.25 (d, 1H, J = 7.0 Hz, C(12)H), 6.67-7.03 (m, 3H, C(9)H, C(10)H and C(11)H). **IR**: 3400 (sh.m), 2860 (m), 2810 (m), 1725 (s), 1710 (s), 1600 (m). **MS** exact mass: found 400.1997 (calculated for $C_{22}H_{28}N_2O_5$: 400.1998).

2-Ethoxycarbonylethyl-1-(3-ethoxycarbonyl-2-oxo)propyl-9-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**7b** R_1=Et).
Compound **6b** (96 mg, 0.23 mmol) was dissolved in 2 ml of freshly distilled BF_3·OEt_2 and the mixture was heated to 60 °C. After refluxing for 5 h the reaction mixture was cooled on an ice-bath and sat. $NaHCO_3$ was added carefully. The water layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The product was obtained by chromatography on a silica plate and 47 mg of the β-carboline **7b** was isolated as a yellow oil (49 %). **^{1}H-NMR** (250 MHz): 1.25 and 1.28 (2 x t, 2 x 3H, J = 7.1 Hz, 2 x OCH_2CH_3), 2.50-2.58 (m, 4H, $CH_2CH_2CO_2$ and $CHCH_2C(=O)CH_2$), 2.65-3.19 (m, 6H, 2 x C(3)H, 2 x C(4)H, $NCH_2CH_2CO_2$, $COCH_2CO_2$), 3.60 (s, 3H, NCH_3), 4.06-4.23 (m, 4H, 2 x OCH_2CH_3), 4.32-4.37 (br.dd, 1H, C(1)H), 7.06-7.28 (m, 3H, C(6)H, C(7)H and C(8)H), 7.48 (d, 1H, J = 7.5 Hz, C(5)H).

^{13}C-NMR (50 MHz, APT): 14.1 and 14.2 (2 x $OCH_2\underline{C}H_3$), 16.8 (C(4)), 29.5 NCH_3), 33.8 ($NCH_2\underline{C}H_2CO_2$), 43.0 (C(1)$H\underline{C}H_2$-C(=O)$CH_2$), 47.0, 48.6 and 50.3 (C(3), C(=O)$\underline{C}H_2CO_2Et$ and $N\underline{C}H_2CH_2CO_2Et$), 53.1 (C(1)), 60.3 and 61.3 (2 x $O\underline{C}H_2CH_3$), 107.3 (C(4a)), 108.8 (C(8)), 118.1 (C(5)), 119.1 (C(6)), 121.5 (C(7)), 126.7 (C(4b)), 134.2 and 137.1 (C(8a) and C(9a)), 167.2 and 172.4 (2 x $\underline{C}O_2Et$), 201.1 ($CH_2\underline{C}$(=O)CH_2). **IR**: 1730 (br.s). **MS** exact mass: found 414.2160 (calculated for $C_{23}H_{30}N_2O_5$: 414.2155).

rel-(3aS,6aR,11bR)-2,3,3a,4,6a,7-Hexahydro-5-hydroxy-6-methoxycarbonyl-3-(methoxy-carbonylethyl)-7-methyl-1H-pyrrolo-[2,3-d]carbazole (**8b** R_1=Me).

Enaminone **6b** (165 mg, 0.43 mmol) was dissolved in 10 ml of dichloroethane and after addition of 1 ml of a 1.0 M $TiCl_4$ solution in dichloroethane the mixture was refluxed overnight. The mixture was cooled to room temperature and a sat. $NaHCO_3$ solution was added. The water layer was extracted with ethyl acetate and the combined organic layers were washed with brine and dried over $MgSO_4$. After flash chromatography 84 mg of **8b** was isolated as a yellow oil (51 %). **^{1}H-NMR** (200 MHz): 1.72-1.78 (m, 1H, C(6)Hβ), 2.10-2.60 (m, 11H, C(3)H, C(5)Hα, C(6)Hα, 2 x C(14)H, 2 x C(20)H, C(21)H, NCH_3), 3.02-3.23 (m, 2H, C(5)Hβ and C(3)H), 3.67 (s, 3H, C(15)O_2CH_3), 3.80 (s, 3H, C(16)CO_2CH_3), 4.07 (s, 1H, C(2)H), 6.48 (d, 1H, J = 7.8 Hz, C(12)H), 6.73 (t, 1H, J = 7.3 Hz, C(11)H), 7.04-7.14 (m, 2H, C(9) and C(10)H), 12.66 (s, 1H, OH). **^{13}C-NMR** (50 MHz, APT): 31.5 (C(14)), 33.5 (C(6)), 33.7 (NCH_3), 38.7 (C(20)), 48.8 (C(3)), 51.3 and 51.5 (2 x OCH_3), 53.1 and 53.9 (C(5) and C(7)), 69.6 and 73.5 (C(2) and C(21)), 93.9 (C(16)), 107.3 (C(12)), 118.6 (C(10)), 122.6 (C(9)), 127.8 (C(11)), 136.8 (C(8)), 152.2 (C(13)), 172.5 and 172.6 (2 x CO_2), 179.1 (C(17)). **IR**: 2860 (m), 2810 (m), 1730 (s), 1645 (s), 1605(s). **MS** exact mass: found 386.1851 (calculated for $C_{21}H_{26}N_2O_5$: 386.1841).

Ethyl 5-[(1,1-dimethyl-2-tosylamino)ethylmethyl]amino-2-ethyl-3-oxo-4-pentenoate (**17**).

The β-keto ester corresponding to **16** (1.58 g, 10 mmol) was added to a solution of 20 mmol of LDA in 80 ml of THF at 0 °C under a nitrogen atmosphere. The mixture was stirred for 30 min. and cooled to -78 °C and the imidazolidinium salt (3.94 g, 10 mmol) was added. The mixture was slowly warmed to 0 °C and after addition of 5 ml of sat. NH_4Cl solution the solvent was removed under vacuum. The residue was taken up in ethyl acetate and the organic layer was washed with sat. $NaHCO_3$, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography (eluent ethyl acetate/petroleum ether 60-80 2:1) and the product was isolated as a white foam (1.663 mg, 39 %). **^{1}H-NMR** (200 MHz): 0.93 (t, 3H, J = 7.1 Hz, $CHCH_2\underline{C}H_3$), 1.25 (t, 3H, J = 7.1 Hz, $OCH_2\underline{C}H_3$), 1.31 (s, 6H, $NC(\underline{C}H_3)_2CH_2$), 1.82-1.92 (m, 2H, $CH\underline{C}H_2CH_3$), 2.43 (s, 3H, $ArCH_3$), 2.71 (s, 3H, NCH_3), 2.95 (d, 2H, J = 6.8 Hz, $HN\underline{C}H_2C(CH_3)_2N$), 3.27 (t, 1H, J = 7.5 Hz, $CO\underline{C}HEtCO_2Et$), 4.16 (q, 2H, J = 7.1 Hz, $OCH_2\underline{C}H_3$), 5.15 (d, 1H, J = 12.3 Hz, NCH=C$\underline{H}$CO), 5.64 (t, 1H, J = 6.8 Hz, $CH_2\underline{N}HTs$), 7.30 (d, 2H, J = 8.2 Hz, C(3')H and C(5')H tosyl), 7.73 (d, 2H, J = 8.2 Hz, C(2')H and C(6')H tosyl), 7.86 (d, 1H, J = 12.3 Hz, NC$\underline{H}$=CHCO). **IR**: 1725 (s), 1640 (m), 1600 (m), 1550 (s), 1340 (m), 1160 (s), 1090 (m). **MS** (FI 90 °C): 424.

4-Ethoxycarbonyl-1-[methoxycarbonylethyl-(2(3-(N-methyl)indolyl)ethyl)]amino-3-oxo-1-hexene (**18**).

The folate model **17** (942 mg, 2.22 mmol) and tryptamine derivative **3b** (3.56 g) were dissolved in a mixture of 120 ml of acetonitrile/acetic acid (9:1) and the mixture was refluxed for 20 h under a nitrogen atmosphere. The solvent was removed under reduced pressure and the residue was taken up in ethyl acetate. The solution was washed with sat. $NaHCO_3$ solution to remove the acid and with sat. NaCl solution. The organic layer was dried over $MgSO_4$ and after concentration under vacuum the residue was purified by flash chromatography. 719 mg of the product was isolated as a yellow oil (75 % yield) and 2.600 g of the tryptamine derivative was recycled as its acetic acid salt (73 %). **^{1}H-NMR** (200 MHz): 0.93 (t, 3H, J = 7.3 Hz, $CHCH_2\underline{C}H_3$), 1.25 (t, 3H, J = 7,1 Hz, $OCH_2\underline{C}H_3$), 1.79-1.96 (m, 2H, $CHCH_2\underline{C}H_3$), 2.49-2.53 (br.m, 2H, $NCH_2\underline{C}H_2CO_2$), 2.93-3.01 (m, 2H, indole-$C\underline{H}_2CH_2N$), 3.25 (t, 1H, J = 7.3 Hz, $C\underline{H}CH_2CH_3$), 3.40-3.52 (m, 4H, $CH_2C\underline{H}_2NC\underline{H}_2CH_2$), 3.67 and 3.74 (2 x s, 2 x 3H, NCH_3 and OCH_3), 4.16 (q, 2H, J = 7.1 Hz, $OC\underline{H}_2CH_3$), 5.21 (m, 1H, NCCH=C$\underline{H}$CO), 6.85 (s, 1H, C(2)H indole), 7.10-7.30 (m, 3H, C(5)H, C(6)H and C(7)H indole), 7.50-7.60 (m, 2H, C(4)H indole and NC$\underline{H}$=CHCO). **IR**: 1730 (s), 1650 (m), 1600 (m), 1560 (s).

1-(3-Ethoxycarbonyl-2-oxo)pentyl-2-methoxycarbonylethyl-9-methyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (**19**).

To a solution of enaminone **18** (580 mg, 1.36 mmol) in 50 ml of dichloroethane, 2.7 ml of a 1.0 N $TiCl_4$ solution in CCl_4 was added and the solution was refluxed overnight. The mixture was cooled to room temperature and poured out in an ice cold sat. $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography (eluent ethyl acetate/petroleum ether 60-80 1:9 → 9:1) furnished the product in 30 % yield as a yellow oil (174 mg). **^{1}H-NMR** (200 MHz): 0.96 (t, 3H, J = 7.4 Hz, $CHCH_2\underline{C}H_3$), 1.25 (t, 3H, J = 7.1 Hz, $OCH_2\underline{C}H_3$), 1.83-1.98 (m, 2H, $CHC\underline{H}_2CH_3$), 2.49-2.60 (m, 4H, $CH_2C\underline{H}_2N$(R)$C\underline{H}_2CH_2CO_2Me$ and $CHC\underline{H}_2C$(=O)CH), 2.62-3.20 (m, 6H, $C\underline{H}_2C\underline{H}_2N$(R)-

CH_2CO_2Me), 3.38-3.46 (m, 1H, $CHCH_2CH_3$), 3.59 and 3.66 (2 x s, 2 x 3H, NCH_3 and OCH_3), 4.19 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 4.40 (m, 1H, CH_2CHN), 7.05-7.51 (m, 4H, C(4)H, C(5)H, C(6)H and C(7)H indole). **IR**: 1730 (s), 1705 (s), 1175 (m). **MS** exact mass: found 428.3213 (calculated for $C_{24}H_{32}N_2O_5$: 428.3231).

Methyl (1S)-3-(3-indolyl)-2-(2-methoxycarbonylethyl)aminopropanoate (**28**).
A solution of 3.18 g of the HCl-salt of the methyl ester of L-(-)-tryptophane **27** in chloroform was washed with a K_2CO_3 solution. The solution was dried over $MgSO_4$ and after concentration under vacuum the residue was dissolved in methanol. Methyl acrylate (1 eq) was added dropwise to the solution, which was stirred during 30 h at room temperature under a nitrogen atmosphere. After concentration under vacuum and flash chromatography (ethyl acetate/methanol) 2.35 g of the product was isolated as a yellow oil (62 %). **^{1}H-NMR** (250 MHz): 1.98 (br.s, 1H, NH), 2.45 (t, 2H, J = 6.6 Hz, $NCH_2CH_2CO_2Me$), 2.70-2.99 (m, 2H, $NCH_2CH_2CO_2Me$), 3.03-3.24 (m, 2H, indole-CH_2), 3.57 and 3.64 (2 x s, 2 x 3H, 2 x CO_2CH_3), 3.57-3.68 (m, 1H, indole-CH_2CH), 7.01 (d, 1H, J = 2.0 Hz, C(2)H indole), 7.07-7.20 (m, 2H, C(5)H and C(6)H indole), 7.31 (d, 1H, J = 7.4 Hz, C(7)H indole), 7.59 (d, 1H, J = 7.3 Hz, C(4)H indole), 8.34 (br.s, 1H, NH indole). **IR**: 3480 (s), 3320 (br.w), 1730 (s).

Ethyl 5[(1,1-dimethyl-2-tosylamino)ethylmethyl]amino-3-oxo-4-pentenoate (**29**).
To a solution of diisopropylamine (3.050 g, 30.2 mmol) in 80 ml of dry THF at 0 °C under a nitrogen atmosphere was added 20 ml of 1.51 N BuLi solution in hexane. After addition of 15.6 mmol of ethyl acetoacetate the orange solution was cooled to -78 °C and the imidazolidinium salt **15** (6.107 g, 15.5 mmol) was added. The reaction mixture was allowed to warm up to 0 °C in 5 h upon which the mixture became clear. The reaction was quenched by addition of 2 ml sat. NH_4Cl solution and after stirring for 15 min the solvent was removed under reduced pressure, the residue was taken up in ethyl acetate, the layers were separated and the organic layer was washed with brine, dried over $MgSO_4$ and filtered. Silica gel was added and the solvent was removed carefully under vacuum. The powder was brought on top of a silica gel column for flash chromatography (eluent ethyl acetate/petroleum ether 60-80 1:1 → ethyl acetate). Only the ring-opened form of the product was isolated as a yellow foam in 90 % yield (5.43 g). **^{1}H-NMR** (250 MHz): 1.18 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.31 (s, 6H, $NC(CH_3)_2CH_2$), 2.30 (s, 3H, $ArCH_3$), 2.82 (s, 3H, NCH_3), 3.44 (s, 2H, $COCH_2EtCO_2Me$), 3.50-3.70 (m, 2H, CH_2NH), 4.03 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 5.16 (d, 1H, J = 11.9 Hz, NCH=CHCO), 6.78 (br.s, 1H, CH_2NHTs), 7.17 (d, 2H, J = 8.1 Hz, C(3')H and C(5')H tosyl), 7.75 (d, 2H, J = 8.1 Hz, C(2')H and C(6')H tosyl), 7.98 (d, 1H, J = 11.9 Hz, NCH=CHCO). **IR**: 1735 (s), 1635 (m), 1595 (m), 1550 (s), 1160 (s), 1090 (m).

Methyl (1S)-*3-(3-indolyl)-2-([1-(4-ethoxycarbonyl-3-oxo-1-butene)](2-methoxycarbonylethyl))aminopropanoate* (**30**).
Folate model **29** (1.4 mmol, 548 mg) and 1.1 eq tryptophane derivative **28** (480 mg) were refluxed overnight in a mixture of 10 ml of acetonitrile and 1 ml of acetic acid under a nitrogen atmosphere. After concentration under vacuum a solution of the residue in CH_2Cl_2 was washed with sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. After flash chromatography (ethanol/dichloromethane 1:19) 211 mg of the product was isolated (34 %) as a brown oil. 160 mg of the starting tryptophane derivative **28** (33 %) could be recycled. **^{1}H-NMR** (250 MHz): 1.27 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 2.38-2.50 (m, 2H, $NCH_2CH_2CO_2Me$), 3.17-3.53 (m, 6H, $NCH_2CH_2CO_2Me$, indole-CH_2, $COCH_2CO_2Et$), 3.58 and 3.74 (2 x s, 2 x 3H, 2 x CO_2CH_3), 4.18 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 4.35 (dd, 1H, J = 5.4 and 10.0 Hz, indole-CH_2CH), 5.16 (d, 1H, J = 13.1 Hz, NCH=CHCO), 6.97 (d, 1H, J = 2.3 Hz, C(2)H indole), 7.10-7.24 (m, 2H, C(5)H and C(6)H indole), 7.36 (d, 1H, J = 7.1 Hz, C(7)H indole), 7.56-7.64 (m, 2H, C(4)H indole and NCH=CHCO), 8.28 (br.s, 1H, NH indole). **IR**: 3480 (s), 3320 (br.w), 1730 (s), 1650 (m), 1600 (m), 1560 (s). **MS** (FD 10 mA): 444. $[\alpha]^{20}_D$ = -121° ($CHCl_3$, c = 0.0102 g/ml).

(2S,3aR,6aS,11bS)-*6-Ethoxycarbonyl-2,3,3a,4,6a,7-hexahydro-5-hydroxy-2-methoxycarbonyl-3(2-methoxycarbonyl)ethyl-1H-pyrrolo[2,3-d]carbazole* (**31**).
Compound **30** (146 mg) was dissolved in 15 ml of dichloroethane and 600 µl of a 1M solution of $TiCl_4$ in CCl_4 was added dropwise. After refluxing for 5 h and cooling to room temperature, the reaction mixture was added to a sat. $NaHCO_3$ solution. The mixture was extracted with dichloromethane. The organic layer was washed with brine and dried over $MgSO_4$. After concentration under vacuum the residue was chromatographed (ethyl acetate/petroleum ether 60-80 1:2) 69 mg of the product was isolated as a colourless oil (46 %). **^{1}H-NMR** (250 MHz): 1.34 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.08 (dd, 1H, J = 5.8 and 14.4 Hz, C(6)H$_\beta$), 2.34 (dd, 1H, J = 3.0 and 18.8 Hz, C(20)H), 2.40 (br.s, 2H, $NCH_2CH_2CO_2Me$), 2.54 (dd, 1H, J = 2.8 and 18.8 Hz, C(20)H), 2.66 (dt, 1H, J = 6.0 and 13.5 Hz, C(3)H), 2.85 (m, 1H, C(21)H), 2.90 (dd, 1H, J = 10.5 and 14.4 Hz, C(6)H$_\alpha$), 3.08 (dt, 1H, J = 7.8 and 13.5 Hz, C(3)H), 3.53 (dd, 1H, J = 5.8 and 10.5 Hz, C(5)H), 3.53 and 3.64 (2 x s, 2 x 3H, 2 x CO_2CH_3), 4.15-4.20 (m, 1H, C(2)H), 4.21-4.35 (m, 2H, OCH_2CH_3), 4.90-4.93 (m, 2H, NH and C(16)H), 6.59 (d, 1H, J = 7.7 Hz, C(12)H), 6.73 (t, 1H, J = 7.3

Hz, C(10)H), 7.04-7.09 (m, 2H, C(9)H and C(12)H). **IR**: 3320 (br.w), 1730 (br.s), 1600 (m). **MS** (FD 10 mA): 444. $[\alpha]^{20}_D$ = -50.3° ($CHCl_3$, c = 0.0167 g/ml).

References and notes

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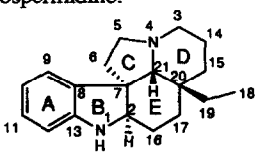

8 The tetracyclic products of the cyclization reactions were isolated as mixtures of keto-enol tautomers. The spectroscopic data of the predominant tautomer (more than 90 %) are given in the experimental section.

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