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MODELS OF FOLATE COFACTORS - 23.[1] A SYNTHETIC STRATEGY TO THE ASPIDOSPERMA SKELETON. SYNTHESIS OF THE 21-EPIMER OF 20-DEETHYL-3,17-DIOXO-16-ETHOXYCARBONYL-1-METHYLASPIDOSPERMIDINE.

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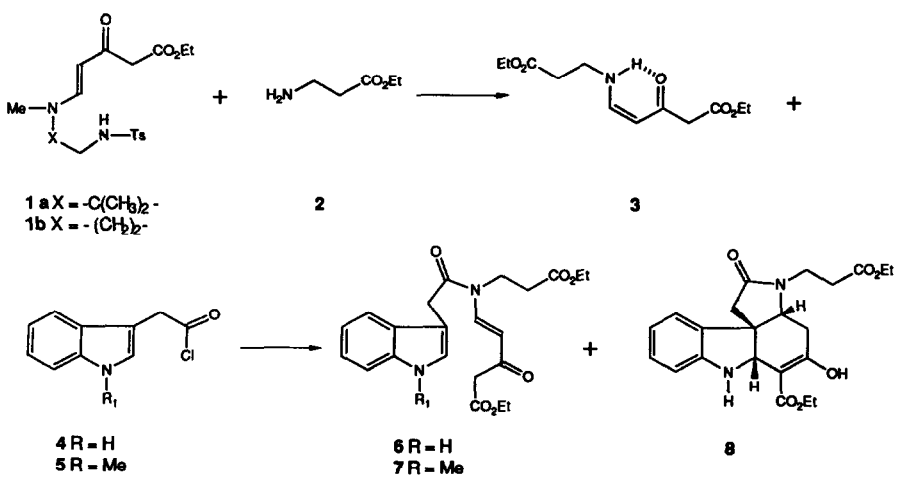
Abstract - The carbon-fragment transfer reactions between N(5),N(10)-methylenetetrahydrofolate models and amines furnish enaminones. The enaminones react with acid chlorides to give enamidones, which can be cyclized by Lewis acids to 2-oxopyrrolo[2,3-d]carbazoles or 1'-carbonyl-pyrrolo[2,3-d]carbazoles. The influence of both the location of the amide carbonyl (in the enamidone) and the Lewis acids on the stereochemical outcome of the cyclization reaction is discussed. The approach has been applied to the synthesis of the title compound.

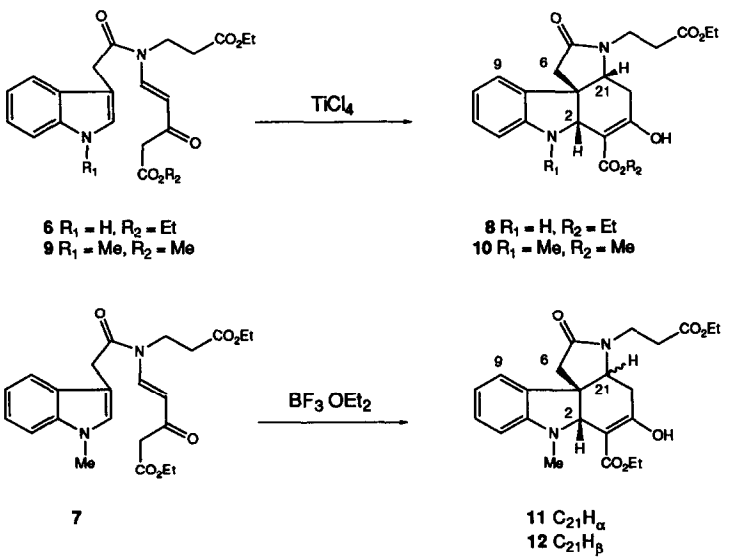
The substituted N(5),N(10)-methylenetetrahydrofolate models have demonstrated their synthetic utility in the approach to a variety of natural products and their analogues.[3] In our studies toward the synthesis of Aspidosperma alkaloids, special effort has been directed to the introduction of the alkoxycarbonyl group at C(16), which is present in several members of the Aspidosperma alkaloid family.[4,10] The strategy to the Aspidosperma alkaloids using this methodology has already been reported from this laboratory.[5] We now report its application to the synthesis of the 21-epi-Aspidosperma skeleton.

The transfer of the carbon-fragment of the acyclic tautomers of the models, i.e. **1a** and **1b** to ethyl β-alanate (**2**) furnished enaminone **3** in moderate yields (31 % and 34 %, respectively) (Scheme 1). Variation of the model/amine ratio and the reaction conditions did not improve the yield of this reaction. The Z-configuration of



Scheme 1

the enamine double bond in compound **3** was attested by a coupling constant of 7.3 Hz between the vinylic protons. The reaction between enamine **3** and the acid chloride of 3-indoloacetic acid (**4**) or its N-methyl analogue **5** resulted in the formation of enamides **6** and **7** in yields of 30 % and 37 %, respectively. The reaction between **3** and **4** however, also furnished the tetracyclic system **8** in 40 % yield. This compound resulted from the unexpected spontaneous cyclization of **6**. The double bond of the enamides **6** and **7** possessed the E-configuration. This was concluded from the observed coupling constant of 13.7 Hz between the two vinylic protons in both compounds. The cyclization of **6** and **9** induced by $TiCl_4$ proceeded smoothly and the pyrrolo[2,3-d]carbazoles **8** and **10** were isolated in 75 % and 57 % yield, respectively (Scheme 2).[6] Only products with the indicated stereochemistry were isolated.

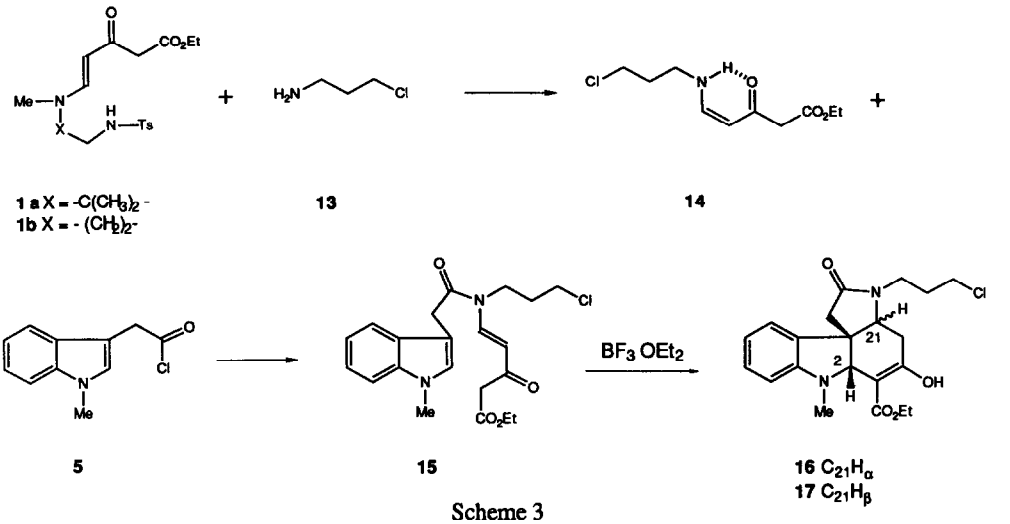


Scheme 2

Cyclization of **7** under the influence of $BF_3{\cdot}OEt_2$ resulted in a mixture of the diastereomers **11** and **12** in a total yield of 40 %. Although separation of the products proved laborious they could be identified. The stereochemistry of the tetracyclic systems **8, 10, 11, 12** was established by NMR techniques. All relevant signals in the ^{1}H-NMR spectrum could be assigned by COSY 2D NMR. The stereochemistry was attested by NOE experiments on compounds **10, 11** and **12**. Irradiation of C(2)Hβ resulted in nuclear Overhauser effects on the signals of C(6)Hβ and NCH_3 in all three products. The compounds **10** and **12** however, also showed an enhancement of the signal of C(21)H. Irradiation of C(9)H resulted in a nuclear Overhauser effect on the signal of C(21)H in compound **11**. The same experiments with **10** and **12** did not result in an analogous nuclear Overhauser effect. These results attest to the β orientation of C(21)H in the tetracyclic compounds **10** and **12**, and the α orientation of C(21)H in compound **11**. The stereochemistry of compound **8** was deduced from its ^{1}H-NMR spectrum, which is similar to that of compounds **10** and **12**.

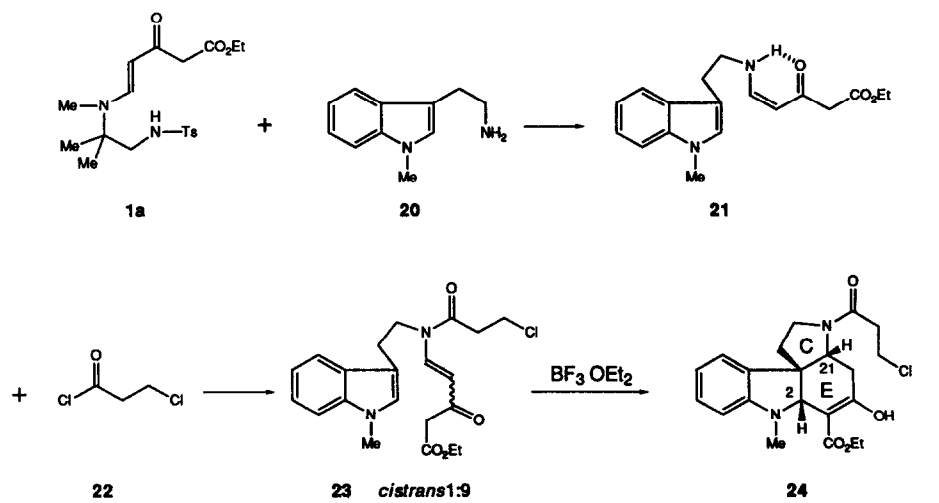
Enaminone **14** was formed in the transfer reaction between folate models **1a,1b** with 3-chloropropylamine (**13**) (Scheme 3). The yields in these reactions were moderate, the maximum yields being 28 % and 40 % for **1a** and **1b**, respectively. The acylation reaction of **14** with N-methylindoleacetyl chloride (**5**) resulted in the enamide **15** in 55 % yield. Upon treatment of **15** with $BF_3{\cdot}OEt_2$ the tetracyclic diastereomers **16** and **17** were formed in 25 % and 70 % yield, respectively. The stereochemistry was determined by NOE experiments. In compound **17** a

nuclear Overhauser effect was observed between C(2)Hβ and C(21)H, which attested to the β orientation of the latter proton in **17**. In compound **16** the C(21)H is assigned the α orientation on the basis of the absence of such nuclear Overhauser effect.



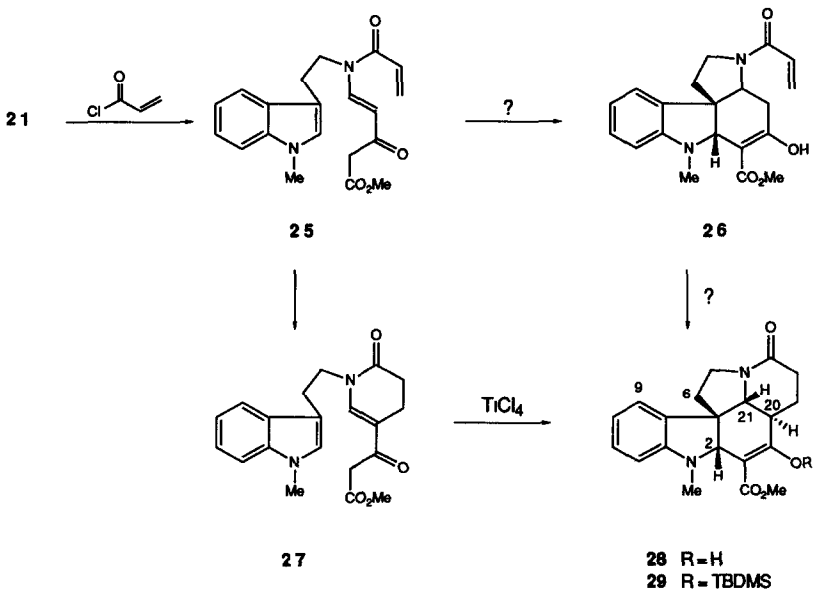
Scheme 3

The transformation of the synthesized tetracycles into the corresponding pentacyclic systems could not be achieved. To effect a nucleophilic attack of the anion at C(20), on the chloride or the carbonyl at C(15), in order to generate a pentacyclic system, a number of bases (2 eq. LDA (HMPT); NaH, BuLi; KOtBu, BuLi; 2 eq. BuLi) and a variety of reaction conditions were examined. However, none of these experiments resulted in the formation of a pentacyclic product.



Scheme 4

The carbon transfer reaction between model **1a** and N(1)-methyltryptamine **20** furnished the enaminone **21** in 65 % yield (Scheme 4). The double bond in the enaminone ester possesses the Z-configuration, which is favoured due to the hydrogen bond between the NH and the C=O group. This was substantiated by the coupling constant (7.2 Hz) between the vinylic protons. The acylation reaction of enaminone **21** with 3-chloropropionyl chloride **22** resulted in enamide **23**, which was isolated as a *cis/trans* mixture (1:9), in 87 % yield. Upon stirring the enamide **23** mixture in $BF_3{\cdot}OEt_2$ (neat), for 1 h at room temperature, the tetracyclic compound **24** was formed in 45 % yield. NMR experiments showed a nuclear Overhauser effect between C(2)H and C(21)H, which established the β orientation of the hydrogen at the C(21) centre.



Scheme 5

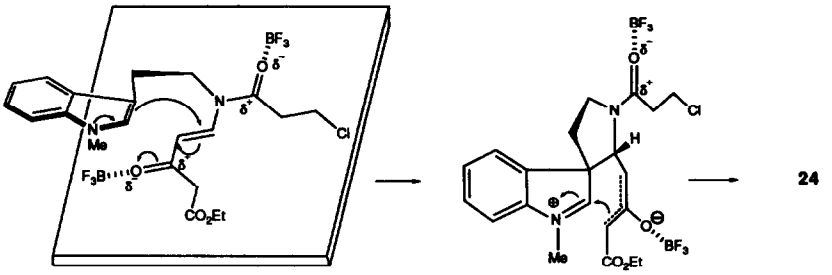
The enaminone **21** was acylated with acryloyl chloride (Scheme 5). It was expected that this reaction would give the acrylamide **25**, which could be cyclized to tetracyclic system **26**. An intramolecular Michael addition in **26** would lead to the pentacyclic skeleton **28**.[7] The reaction between the acid chloride and enaminone **21** furnished the expected product **26** directly, albeit in a low yield (2 %). The main product (42 %) of the reaction, however, consisted of compound **27**. This is probably formed from **25** via the enamine addition to the acrylamide moiety. System **27** seemed ideally suited for the synthesis of the pentacyclic Aspidosperma skeleton, since the D ring is already in place. The cyclization of **27** was affected by $TiCl_4$, whereupon the pentacyclic product **28** (keto-enol mixture), with the *trans* C/E ring junction, was formed in 63 % yield. Transformation of the keto enol mixture into the corresponding TBDMS enol ether furnished **29**.[4b]

The stereochemistry of **29** was determined by NMR experiments. The signals in the ^{1}H-NMR spectrum could be assigned by means of COSY 2D NMR. Irradiation of C(2)Hβ (s, 4.59 ppm) resulted in an enhancement of the signals of C(6)Hβ (m, 1.35-1.51 ppm), NCH_3 (s, 2.64 ppm) and C(21)Hβ (d, J = 10.5 Hz, 2.77 ppm). In a further experiment nuclear Overhauser effects between C(9)H (d, J = 7.2 Hz, 6.80 ppm) and C(20)Hα (m, 2.30-2.50 ppm) and C(5)Hα (m, 3.65-3.77 ppm) were observed upon irradiation of C(9)H. This allowed the assigment of the β orientation to C(21)H, and the α orientation to C(20)H. The proposed *trans* ring junction of

the D/E rings in **28** and **29**, is further substantiated by the coupling constant of 10.5 Hz between C(21)H and C(20)H.

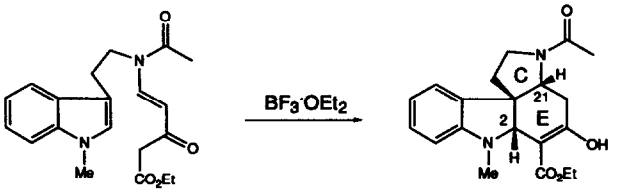
Discussion of the stereochemistry of the cyclization reaction.

The results of the Lewis acid induced cyclization reactions of enamidones differ markedly from the results of similar reactions with enaminones.[1] These differences are attributed to the amide functionality. The presence of an electron withdrawing carbonyl group next to the nitrogen stabilizes the spiro-intermediate (e.g. **31**, Scheme 6) and makes its formation irreversible. This explains the formation of the strained end products with the *trans* C/E ring junction and the absence of products, which result from a Wagner-Meerwein rearrangement of the spiro-intermediate, such are observed in the reaction of compounds without the amide function.



30 **31**

Scheme 6



32 **33**

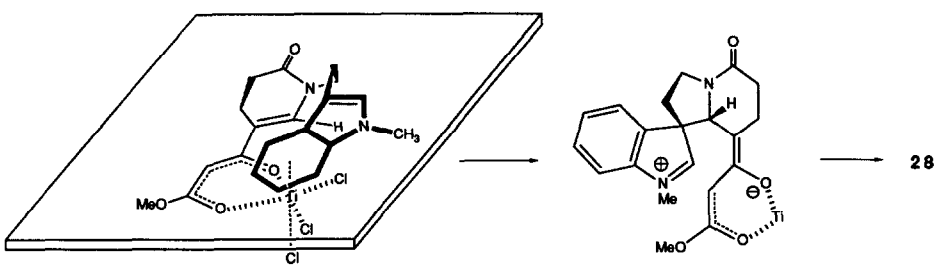
Scheme 7

The formation of **24** with the *trans* C/E ring junction (Scheme 4), is in agreement with the results obtained by Hiemstra [8] in the BF_3·OEt_2 catalyzed cyclization of enamide **32** (Scheme 7), whereby the tetracyclic compound **33** is obtained in 89 % yield. In this system the C(21)H also has the β orientation (*trans* C/E ring junction).

Inspection of Dreiding models shows that the products **24** and **33**, formed in these reactions are more strained than the isomers with the C/E *cis* ring junction (C(21)H α orientation). They are, therefore, considered to be the kinetically controlled products of these reactions. Their selective formation may be rationalized as follows. Both of the carbonyl groups of the amide and the enone are complexed by BF_3·OEt_2, as in **30** (Scheme 6). This results in the development of positive charges on the carbonyl carbon atoms. Due to electrostatic repulsion the system assumes the all *trans* conformation (of the conjugated system); something which is further favoured by the overlap of the amide π-orbital with the enone π-system. Attack of the enamine double bond of the indole nucleus, (situated above the plane of the paper) on the double bond of the enone, results in spiro intermediate **31**. In this reaction step the stereochemistry of the final product is irreversibly established. After equilibration of the enolate **31**, the C(16)-C(2) bond is formed by attack of the enolate on the iminium bond; to result in the formation of the final product **24**.

If an all *trans* intermediate, such as **30**, would play an imperative role in the $BF_3{\cdot}OEt_2$ induced cyclization of compounds **7** and **15**, only products with the *cis* C/E ring junction would be formed. A study of Dreiding models of **7** and **15**, however, shows that the indole nucleus and the enamide double bond are forced away from each other. The resulting lack of conformational integrity of the conjugated system like **30** will prevent the exclusive formation of an intermediate with the stereochemistry of **31**. As a consequence, the reaction will lead to a mixture of isomeric products.

In comparison with the $BF_3{\cdot}OEt_2$ induced reaction, the $TiCl_4$ induced cyclization resulted, in the selective formation of products with a *trans* C/E ring junction. Only the compounds **8**, **10** and **28**, in which C(21)H has the β orientation, were isolated. In this context the formation of **28** is considered remarkable because this product possesses severe steric strain compared to its diastereomer, with the *cis* C/E ring junction. However, inspection of molecular models demonstrated that the selective formation of the obligatory spiro intermediate **35**, could not be attributed to steric factors alone. A possible explanation of the results may lie in the formation of complex **34** (Scheme 8), in which the hexa-coordinated titanium ion is complexed with the β-keto ester and with the electron rich indole nucleus. This complex can only cyclize to form **35**, which will lead to the isolated product **28**.



34 **35**

Scheme 8

Experimental

Chromatographic separations were carried out by means of flash chromatography on freshly filled silica gel (230-400 mesh) columns, following literature procedure.[9] 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.[10]

Ethyl 5-(ethoxycarbonylethyl)amino-3-oxo-4-pentenoate (**3**).

A solution of folate model **1b** (1mmol) and ß-alanine ethyl ester **2** (2 mmol) in 11 ml of acetonitrile/acetic acid 10:1 was refluxed for 4 h. The mixture was cooled to room temperature and concentrated under vacuum. The residue was dissolved in ethyl acetate and the solution was washed with sat. $NaHCO_3$ solution and with brine, dried over $MgSO_4$ and concentrated under vacuum. The product was isolated after flash chromatography (eluent ethyl acetate/hexanes 1:1 → 2:1) in 31 % yield as a yellow oil and also 6 % of the folate model **2b** was recovered. **^{1}H-NMR** (250 MHz): 1.23 (t, 6H, J = 7.1 Hz, 2 x $OCH_2\underline{CH_3}$), 2.53 (t, 2H, J = 6.4 Hz, $NH\text{-}CH_2\underline{CH_2}CO_2$), 3.29 (s, 2H, $C(=O)\underline{CH_2}CO_2$), 3.46 (dt, 2H, J = 6.4 and 12.8 Hz, $NHC\underline{H_2}$), 4.12 and 4.14 (2 x q, 4H, 2 x $CO_2\underline{CH_2}CH_3$), 5.00 (d, 1H, J = 7.3 Hz, $NHCH{=}C\underline{H}C(=O)$), 6.75 (dd, 1H, J = 7.3 and 12.8 Hz, $NHC\underline{H}{=}CHC(=O)$), 9.81 (br.s, 1H, NH). **IR**: 3430 (br.w), 1720 (s), 1635 (s), 1565 (s), 1480 (m).

Ethyl 5-[(ethoxycarbonylethyl)(2-(3-indolyl)]-1-oxoethyl)amino-3-oxo-4-pentenoate (**6**).
To a solution of 0.31 mmol enamine (**3**) and 0.6 mmol pyridine in 3 ml of acetonitrile the acid chloride **4** (0.45 mmol) was added under a nitrogen atmosphere at 0 °C. The clear yellow solution was stirred overnight at room temperature and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and the solution was washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated under vacuum. The enaminone amide **6** was isolated in 30 % yield as a brown oil and the tetracyclic compound **8** in 43 % yield after flash chromatography (eluent ethyl acetate/hexanes 1:2 → ethyl acetate). **^{1}H-NMR** (200 MHz): 1.16-1.27 (m, 6H, 2 x OCH_2CH_3) 2.43-2.50 (m, 2H, NCH_2CH_2), 3.42 (s, 2 H, $C(=O)CH_2CO_2$), 3.81-4.33 (m, 8H, 2 x OCH_2CH_3, indolyl-CH_2, NCH_2CH_2), 5.68 (d, 1H, J = 13.7 Hz, NCH=CHCO), 7.09-7.20 (m, 3H, C(2)H, C(5)H and C(6)H indole), 7.31 (d, 1H, J = 7.8 Hz, C(7)H indole), 7.58 (d, 1H, J = 7.5 Hz, C(4)H indole) 8.26 (d, 1H, J = 13.7 Hz, NCH=CHCO), 8.41 (br.s, 1H, NH). **IR**: 3480 (sh,m), 1730 (s), 1680 (m), 1615 (m), 1580 (s). **MS** (FD 10 mA): 414.
A similar experiment with indole acetic acid anhydride (2 eq) Et_3N (2 eq) furnished the enaminone amide in 19 % yield and the starting enaminone was recycled in 80 %.

Methyl 5-[(ethoxycarbonylethyl)(2-(3-(N-methyl)indolyl)]-1-oxoethyl)amino-3-oxo-4-pentenoate (**7**).
To a cooled solution (-40 °C) of enaminone **3** (142 mg, 0.58 mmol) and pyridine (1.2 eq) in CH_3CN a solution of 147 mg (1.2 eq) N-methyl indolyl acetic acid chloride (**5**) in acetonitrile was added via a syringe under a nitrogen atmosphere. The solution was slowly warmed to room temperature (1 h), stirred for another 4 h and poured out into a sat. NaCl solution. The mixture was extracted with ethyl acetate and the combined organic layers were washed once with brine, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography (eluent ethyl acetate/petroleum ether 60-80 1:3 → ethyl acetate) of the residue gave 90 mg of **7** (37 % yield) as a yellow oil. **^{1}H-NMR** (250 MHz): 1.22 (t, 3H, J = 7.3 Hz, OCH_2CH_3), 2.49 (t, 2H, J = 7.7 Hz, $NCH_2CH_2CO_2$), 3.45 (s, 2H, $COCH_2CO_2$), 3.71 and 3.74 (2 x s, 2 x 3H, N-CH_3 and OCH_3), 3.92 (t, 2H, J = 7.7 Hz, $NCH_2CH_2CO_2$), 4.10 (q, 2H, J = 7.3 Hz, OCH_2CH_3), 4.10 (s, 2H, CH_2CON), 5.70 (d, 1H, J = 13.7 Hz, NCH=CHCO), 7.04 (s, 1H, C(2)H indole), 7.08-7.30 (m, 3H, C(4)H, C(5)H, C(6)H indole), 8.27 (d, 1H, J = 13.7 Hz, NCH=CHCO). **IR**: 1730 (s), 1685 (s), 1650 (s), 1615 (s), 1580 (s).

rel-(3aS,6aS)-6-Ethoxycarbonyl-3-ethoxycarbonylethyl-2,3,3a,4,6a,7-hexahydro-5-hydroxy-2-oxo-1H-pyrrolo[2,3-d]carbazole (**8**).
Enaminone **6** (40 mg, 0.097 mmol) was dissolved in 5 ml of dry dichloromethane and 150 µl of a 1M $TiCl_4$ solution in CH_2Cl_2 was added via a syringe under a nitrogen atmosphere at room temperature. The troubled, brown mixture was stirred for 2 h and poured out into a sat. $NaHCO_3$ solution. The water layer was extracted with ethyl acetate and the combined organic layers were washed with brine. The residue was purified on a silica gel plate (eluent ethyl acetate) and 20 mg of **8** was isolated as a yellow oil (yield 50 %). **^{1}H-NMR** (200 MHz): 1.27 (t, 3H, J = 7.1 Hz, $C(15)O_2CH_2CH_3$), 1.39 (t, 3H, J = 7.1 Hz, $C(16)CO_2CH_2CH_3$), 2.41-2.75 (m, 6H, 2 x C(6)H, 2 x C(14)H, 2 x C(20)H), 3.43-3.58 (m, 1H, C(3)H), 3.76-3.94 (m, 2H, C(3)H and C(21)H$_\beta$), 4.05-4.48 (m, 4H, 2 x OCH_2CH_3), 4.46 (s, 1H, C(2)H$_\beta$), 6.60-6.71 (m, 2H, C(10)H and C(12)H), 6.99-7.10 (m, 2H, C(9)H and C(10)H), 12.34 (s, 1H, OH). **IR**: 3400 (br.w), 1720 (s), 1685 (s), 1640 (m), 1600 (m).

rel-(3aS,6aS)-3-Ethoxycarbonylethyl-2,3,3a,4,6a,7-hexahydro-5-hydroxy-6-methoxycarbonyl-7-methyl-2-oxo-1H-pyrrolo[2,3-d]–carbazole (**10**).
Enaminone **9** (21 mg, 0.05 mmol) was dissolved in 15 ml CH_2Cl_2 and 150 µl of a 1M $TiCl_4$ in CH_2Cl_2 was added via a syringe under a nitrogen atmosphere at room temperature. The brown troubled mixture was stirred overnight and poured out into sat. $NaHCO_3$. The water layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography (eluent ethyl acetate/petroleum ether 60-80 1:2 → ethyl acetate) of the residue furnished 12 mg of **10** as a colourless oil (yield 57 %). **^{1}H-NMR** (250 MHz): 1.26 (t, 3H, J = 7.1 Hz, OCH_2CH_3) 2.44 (d, 1H, J = 15.5 Hz, C(6)H$_\alpha$), 2.57-2.75 (m, 5H, C(6)H$_\beta$, 2 x C(14)H and 2 x C(20)H), 2.82 (s, 3H, NCH_3), 3.42-3.53 (m, 1H, C(3)H), 3.77-3.88 (m, 2H, C(3)H and C(21)H$_\beta$), 3.83 (s, 3H, OCH_3), 4.13 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 4.51 (s, 1H, C(2)H$_\beta$), 6.42 (d, 1H, J = 7.6 Hz, C(12)H), 6.57-6.63 (m, 1H, C(10)H), 6.93 (d, 1H, J = 7.3 Hz, C(9)H), 7.06-7.12 (m, 1H, C(11)H), 12.19 (s, 1H, OH). **IR**: 1725 (s), 1690 (s), 1645 (s), 1600 (s), 1485 (m), 1440 (m).

Cyclization of compound **7** with $BF_3{\cdot}OEt_2$. Synthesis of **11** and **12**.
To a solution of **7** (49 mg, 0.11 mmol) in CH_2Cl_2 50 µl of $BF_3{\cdot}OEt_2$ (3.5 eq) was added via a syringe under a nitrogen atmosphere at room temperature. The mixture was stirred at room temperature and after 1 h a sat. $NaHCO_3$ solution was added. The water layer was extracted with dichloromethane and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography of the residue furnished 19 mg of a brown oil, that was a mixture of diastereomers. Further purification on a silica gel plate (eluent ethyl acetate/petroleum ether 60-80 1:1) furnished 4 mg of **11** and 10 mg of **12**.

rel-(3aS,6aR)-*6-Ethoxycarbonyl-3-ethoxycarbonylethyl-2,3,3a,4,6a,7-hexahydro-5-hydroxy-7-methyl-2-oxo-1H-pyrrolo[2,3-d]carbazole* (**11**). **^{1}H-NMR** (200 MHz): 1.25 (t, 3H, J = 7.1 Hz, C(15)$O_2CH_2C\underline{H}_3$), 1.32 (t, 3H, J = 7.1 Hz, C(16)$CO_2CH_2C\underline{H}_3$), 2.39-2.61 (m, 3H, C(6)Hβ, 2 x C(14)H), 2.60 (s, 3H, NCH_3), 2.67-2.85 (m, 2H, C(20)H_2), 3.10 (d, 1H, J = 18.1 Hz, C(6)Hα), 3.27-3.38 (m, 1H, C(3)H), 3.70-3.84 (m, 2H, C(3)H), 3.86-3.89 (m, 1H, C(21)Hα), 4.07-4.35 (m, 5H, C(2)Hβ and 2 x $OC\underline{H}_2CH_3$), 6.49 (d, 1H, J = 7.9 Hz, C(12)H), 6.75-6.83 (m, 1H, C(10)H), 7.09-7.16 (m, 2H, C(9)H and C(11)H), 12.59 (s, 1H, OH).

rel-(3aS,6aS)-*6-Ethoxycarbonyl-3-ethoxycarbonylethyl-2,3,3a,4,6a,7-hexahydro-5-hydroxy-7-methyl-2-oxo-1H-pyrrolo[2,3-d]carbazole* (**12**). **^{1}H-NMR** ($CDCl_3$, 200 MHz): 1.28 (t, 3H, J = 7.1 Hz, C(15)$O_2CH_2C\underline{H}_3$), 1.40 (t, 3H, J = 7.1 Hz, C(16)$CO_2CH_2C\underline{H}_3$), 2.46 (d, 1H, J = 15.6 Hz, C(6)Hα), 2.53-2.80 (m, 5H, C(6)Hβ, 2 x C(14)H, 2 x C(20)H), 2.86 (s, 3H, NCH_3), 3.39-3.56 (m, 1H, C(3)H), 3.79-3.92 (m, 2H, C(3)H and C(21)Hβ), 4.16 (q, 2H, J = 7.1 Hz, C(15)$O_2C\underline{H}_2CH_3$), 4.31 (q, 2H, J = 7.1 Hz, C(16)$O_2C\underline{H}_2CH_3$), 4.53 (s. 1H, C(2)Hβ), 6.44 (d, 1H, J = 7.7 Hz, C(12)H), 6.58-6.65 (m, 1H, C(10)H), 6.95 (d, 1H, J = 7.4 Hz, C(9)H), 7.08-7.15 (m, 1H, C(11)H), 12.33 (s, 1H, OH).

Ethyl 5(2-chloropropyl)amino-3-oxo-4-pentenoate (**14**).

Folate model **1b** (0.6 mmol, 234 mg) and the HCl salt of 3-chloropropylamine (**13**, 0.7 mmol, 91 mg) were dissolved in a mixture of 5 ml of dry acetonitrile and 0.6 ml of acetic acid. The mixture was refluxed for 4 h, cooled to room temperature and concentrated under vacuum. Ethyl acetate and sat. $NaHCO_3$ were added, and the water layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. Flash chromatography (eluent ethyl acetate/petroleum ether 60-80 1:1 → ethyl acetate) of the residue afforded 56 mg the product as a yellow oil (40 % yield). **^{1}H-NMR** (100 MHz): 1.29 (t, 3H, J = 7 Hz, $OCH_2C\underline{H}_3$), 1.88-2.14 (m, 2H, NCH_2), 3.37 (s, 2H, C(=O)CH_2CO_2), 3.40-3.69 (m, 2H, CH_2Cl), 4.21 (q, 2H, J = 7 Hz, $OC\underline{H}_2CH_3$), 5.07 (d, 1H, J = 7 Hz, CH=C$\underline{H}$C(=O)), 6.80 (dd, 1H, J = 7 and 13 Hz, NHC$\underline{H}$=CH), 9.85 (br.s, 1H, NH). **IR**: 3440 (w), 1730 (s), 1640 (s), 1570 (s). **MS** exact mass: found 233.0807 (calculated for $C_{10}H_{16}NO_3Cl$ 233.0796).

Ethyl 5-[(2-(3'-N-methylindolyl)-1-oxoethyl)(2-chloropropyl)]amino-3-oxo-4-pentenoate (**15**).

Enaminone **14** (0.58 mmol, 135 mg) was dissolved in a mixture of 3.0 ml acetonitrile and 0.6 ml (0.7 mmol) pyridine and the acid chloride **5** (0.7 mmol, 145 mg) was added. The mixture was stirred overnight at room temperature under a nitrogen atmosphere and concentrated under vacuum. Ethyl acetate and sat. $NaHCO_3$ were added, and the water layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. Flash chromatography (ethyl acetate/hexanes 1:1) of the residue provided 130 mg of the product (55 % yield). **^{1}H-NMR** (100 MHz): 1.27 (t, 3H, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.78-2.05 (m, 2H, $CH_2C\underline{H}_2CH_2$), 3.43-4.31 (m, 8H, C(=O)$C\underline{H}_2CO_2$, indole-$C\underline{H}_2$ and $NC\underline{H}_2CH_2C\underline{H}_2Cl$), 3.78 (s, 3H, NCH_3), 5.78 (d, 1H, J = 14 Hz, NCH=C$\underline{H}$C(=O)), 7.07-7.33 (m, 4H, C(2)H, C(5)H, C(6)H and C(7)H indole), 7.58-7.67 (m, 1H, C(4)H indole), 8.34 (d, 1H, J = 14 Hz, NC$\underline{H}$=CHC(=O)).**IR**: 1730 (m), 1690 (s), 1625 (s), 1580 (s). **MS** (FD): 404/406 (3:1).

Cyclization of **15**. Synthesis of **16** and **17**.

Enamide **15** (2.29 mmol, 927 mg) was dissolved in 5 ml of BF_3·OEt_2, and stirred for 45 min at room temperature. The reaction was quenched by addition of an ice-cold $NaHCO_3$ solution and the water layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography over silica gel (eluent ethyl acetate/ hexanes 2:3 → 3:1). Compound **16** was isolated in 25 % yield (232 mg) as a colourless oil, and compound **17** could be isolated in 70 % yield (650 mg), also as a colourless oil.

rel-(3aR,6aS)-*3-(3-Chloropropyl)-6-ethoxycarbonyl-4-ethyl-2,3,3a,4,6a,7-hexahydro-5-hydroxy-7-methyl-2-oxo-1H-pyrrolo-[2,3-d]carbazole* (**16**). **^{1}H-NMR** (250 MHz): 1.30 (t, 3H, J = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.89-2.11 (m, 2H, $CH_2C\underline{H}_2CH_2Cl$), 2.49 (d, 1H, J = 18 Hz, C(6)Hβ), 2.60 (s, 3H, NCH_3), 2.65-2.84 (m, 2H, C(20)H_2), 3.10 (d, 1H, J = 18 Hz, C(6)Hα), 3.11-3.23 (m, 1H, 1 x C(3)H), 3.50-3.67 (m, 3H, 1 x C(3)H and CH_2Cl), 3.82-3.86 (m, 1H, C(21)Hα), 4.08-4.40 (m, 2H, $OC\underline{H}_2CH_3$), 4.21 (s, 1H, C(2)Hβ), 6.47 (d, 1H, J = 7 Hz, C(12)H), 6.78 (t, 1H, J = 7 Hz, C(10)H), 7.04-7.20 (m, 2H, C(9)H and C(11)H), 12.58 (br.s, 1H, OH). **IR**: 1670 (s), 1650 (s), 1605 (m). **MS** (FD): 404/406 (3:1). Exact mass: found 404.1484 (calculated for $C_{21}H_{25}N_2O_4Cl$ 404.1468).

rel-(3aS,6aS)-*3-(3-Chloropropyl)-6-ethoxycarbonyl-4-ethyl-2,3,3a,4,6a,7-hexahydro-5-hydroxy-7-methyl-2-oxo-1H-pyrrolo-[2,3-d]carbazole* (**17**). **^{1}H-NMR** (250 MHz): 1.39 (t, 3H, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.97-2.18 (m, 2H, $CH_2C\underline{H}_2CH_2Cl$), 2.44-2.76 (m, 4H, C(6)H_2 and C(20)H_2), 2.85 (s, 3H, NCH_3), 3.29-3.73 (m, 4H, $C\underline{H}_2CH_2C\underline{H}_2Cl$), 3.80 (dd, 1H, J = 5 and 13 Hz, C(21)Hβ), 4 22-4.33 (m, 2H, $OC\underline{H}_2CH_3$), 4.52 (s, 1H, C(2)Hβ), 6.36-7.14 (m, 4H, C(12)H, C(10)H, C(9)H and C(11)H), 12.31 (s, 1H, OH). **IR**: 1690 (s), 1640 (s), 1605 (m). **MS** (FD): 404/406 (3:1). Exact mass: found 404.1484 (calculated for $C_{21}H_{25}N_2O_4Cl$ 404.1468).

Methyl 5-(3-N-methylindolyl)amino-3-oxo-4-pentenoate (**21**).

A solution of folate model **1a** (6.96 mmol, 2.66 g) and N(1)-methyltryptamine (**20**) in 55 ml of a mixture of dry acetonitril/acetic acid (10:1) was refluxed for 3 h. The mixture was concentrated under reduced pressure and the residue was taken up in $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography (eluent ethylacetate) of the residue gave 1.28 g of the product (65 %) as a yellow oil and 213 mg of **1a** (7 %). **^{1}H-NMR** (250 MHz): 2.98 (t, 2H, J = 6,9 Hz, indole-CH_2), 3.22 (s, 2H, C(=O)CH_2–CO_2), 3.41-3.51 (m, 2H, CH_2NH), 3.71 and 3.74 (2 x s, 2 x 3H, NCH_3 and OCH_3), 4.93 (d, 1H, J = 7.2 Hz, NHCH=CH), 6.60 (dd, 1H, J = 7.2 and 13.1 Hz, NHCH=CH), 6.86 (s, 1H, C(2)H indole), 7.05-7.30 (m, 3H, C(5)H, C(6)H and C(7)H indole), 7.52 (d, 1H, J = 7.8 Hz, C(4)H indole), 9.90 (br.s, 1H, NH). **IR**: 1725 (s), 1630 (s), 1560 (s).

Ethyl 5-[(3-chloro-1-oxopropyl)(2-(3'-N-methylindolyl))ethyl]amuno-3-oxo-4-pentenoate (**23**).

To a solution (cooled on an ice-bath) of enaminone **21** (0.77 mmol, 244 mg) and pyridine (0.9 mmol, 71 mg) in 5 ml of dry acetonitrile 3-chloropropionyl chloride (**22**, 0.9 mmol, 114 mg) was added. The solution was stirred for 45 min. at 0 °C, and for another 30 min. at room temperature. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. The solution was washed with $NaHCO_3$, with brine, dried over $MgSO_4$ and concentrated under vacuum. The product was isolated in 87 % yield (271 mg), after flash chromatography over silica gel (eluent ethyl acetate/petroleum ether 60-80 1:3 → 1:1), as a light brown oil. *cis /trans* = 1:9. **^{1}H-NMR** (200 MHz): 1.28 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.82-3.03 (m, 4H, C(=O)CH_2CH_2Cl and indole-CH_2), 3.46 (s, 2H, C(=O)CH_2CO_2), 3.66-3.96 (m, 7H, C(=O)CH_2CH_2Cl, NCH_3 and CH_2N), 4.21 (q, 2H, OCH_2CH_3), 5.46 (d, J = 8.3 Hz, NCH=CH, *cis*), 5.81 (d, J = 13.7 Hz, NCH=CH, *trans*), 6.54 (d, J = 8.3 Hz, NCH=CH, *cis*), 6.98 (s, 1H, C(2)H indole), 7.14-7.62 (m, 4H, 4 x CH indole and NCH=CH). **IR**: 1730 (s), 1680 (s), 1640 (m), 1615 (s), 1580 (s). **MS** exact mass found 404.1511 (calculated for $C_{21}H_{25}N_2O_4Cl$ 404.1503).

rel-(3aS,6aS)-3-(3-Chloro-1-oxopropyl)-6-ethoxycarbonyl-2,3,3a,4,6a,7-hexahydro-5-hydroxy-7-methyl-1H-pyrrolo[2,3-d]carbazole (**24**).

Enamide **23** (7.16 mmol, 2.90 g) was dissolved in 10 ml of $BF_3{\cdot}OEt_2$. The mixture was stirred for one hour at room temperature. After addition of ice and K_2CO_3 the residue was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, and concentrated under vacuum. The resulting oil was dissolved in ether and the solution was put overnight in the refrigerator. The product **24** could be isolated as white crystals (1.05 g, m. pt. 149-152 °C). Flash chromatography of the mother liquor furnished another 250 mg of the product. Total yield: 45 %. **^{1}H-NMR** 200 MHz): 1.39 (t, J = 7.2 Hz, OCH_2CH_3), 2.02-2.11 (m, 2H, C(6)H_2), 2.65 (dd, 1H, J = 11.8 and 17.1 Hz, C(20)H_α), 2.81-2.89 (t, 2H, J = 7.9 Hz, C(=O)CH_2CH_2Cl), 2.90 (s, 3H, NCH_3), 3.56 (dd, 1H, J = 4.2 and 17.1 Hz, C(20)H_β), 3.70-3.82 (m, 3H, C(21)H and C(5)H_2), 3.89 (t, 2H, J = 6.7 Hz, CH_2CH_2Cl), 4.29 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 4.48 (s, 1H, C(2)H), 6.47 (d, J = 7.7 Hz, C(12)H), 6.67 (t, 1H, J = 7.3 Hz, C(10)H), 6.93 (d, 1H, J = 6.9 Hz, C(9)H), 7.14 (t, 1H, J = 6.7 Hz, C(11)H), 12.21 (s, 1H, OH). **IR**: 1640 (s), 1600 (s). **MS** exact mass: found 404.1523 (calculated for $C_{21}H_{25}N_2O_4Cl$ 404.1503); EI: 404 (100), 368 (134), 358 (81), 275 (27), 267 (13), 224 (22), 157 (89), 144 (81).

Acylation of **21**. Synthesis of **25** and **27**.

To a solution of **21** (100 mg, 0.35 mmol) and 3 ml pyridine and a catalytic amount of DMAP in dry acetonitrile acryloyl chloride (75 µl, 0.92 mmol) was added at room temperature under a nitrogen atmosphere. The reaction mixture was refluxed overnight, cooled to room temperature and concentrated under vacuum. The residue was dissolved in dichloromethane and the organic layer was washed with 1M HCl, sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography over silica gel (eluent ethyl acetate/petroleum ether 60-80 1:1) gave 2.5 mg of **25** (2 %) and 52 mg of **27** (42 %), as brown oils.

Methyl 5-[2-(3-(N-methyl)indolyl)ethyl][1-oxo-2-propene]amino-3-oxo-4-pentenoate (**25**).

^{1}H-NMR (250 MHz): 3.02 (t, 2H, J = 7.7 Hz, CH_2CH_2N), 3.45 (s, 2H, $COCH_2CO_2$), 3.70 and 3.73 (2 x s, 2 x 3H, NCH_3 and OCH_3), 3.94 (t, 2H, J = 7.7 Hz, CH_2CH_2N), 5.77 (d, 1H, J = 13.9 Hz, NCHCHCO), 5 84 (dd, 1H, J = 1.5 and 10.4 Hz, CH=CH_2), 6.40 (dd, 1H, J = 1.5 and 16.7 Hz, CH=CH_2 *trans*), 6.63 (dd, 1H, J = 10.4 and 16 7 Hz, CH=CH_2 *cis*), 6.88 (s, 1H, C(2)H indole), 7.08-7.34 (m, 3H, C(5)H, C(6)H and C(7)H indole), 7.64 (d, 1H, J = 7.6 Hz, C(4)H indole), 8.20 (d, 1H, J = 13.9 Hz, NCH=CHCO). **IR**: 1735 (s), 1650 (s), 1610 (s), 1575 (s), 1405 (m), 1325 (m), 1150 (m).

4-(2-Methoxycarbonyl-1-oxo)ethyl-1-[2-(3-(N-methyl)indolyl)]ethyl-2-oxo-1,2,3,4-tetrahydro-pyridine (**27**).

^{1}H-NMR (200 MHz): 2.50 (m, 2H, $COCH_2CH_2$), 2.97 (s, 2H, $COCH_2CO_2$), 3.08 (t, 2H, J = 6.7 Hz, indolyl-CH_2CH_2N), 3.68 and 3.73 (2 x s, 2 x 3H, NCH_3 and OCH_3), 3.76 (m, 2H, $COCH_2CH_2$), 3.90 (t, 2H, J = 6.7 Hz, CH_2CH_2N), 6.62 (s, 1H, NCH=C), 6.83 (s, 1H, C(2)H indole), 7.10-7.33 (m, 3H, C(5)H, C(6)H and C(7)H indole), 7.60 (d, 1H, J = 7.5 Hz, C(4)H indole). **IR**: 1735 (s), 1685 (m), 1650 (m), 1625 (s), 1435 (m), 1370 (s), 1150 (s). **MS** (FI 70 eV): 354.

16,17-Dehydro-20-desethyl-21-epi-17-hydroxy-16-methoxycarbonyl-1-methyl-aspidospermidine (**28**).
To a solution of **27** (233.8 mg, 0.66 mmol) in 15 ml of dry dichloroethane a solution of $TiCl_4$ in tetra (2 eq) was added carefully, at room temperature under a nitrogen atmosphere. The troubled, brown reaction mixture was heated under reflux for 3 h until all starting material had disappeared (TLC). The mixture was poured into a sat. $NaHCO_3$ solution and extracted with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was chromatographed over silica gel (eluent ethyl acetate) and 147.3 mg of the product **28** was isolated as a yellow oil (63 % yield). 5 % of the starting material **27** could be recycled. **^{1}H-NMR** (C_6D_6, 200 MHz): a mixture of the keto- and enol. Characteristic signals are: 2.42 (s, NCH_3), 2.60 (s, NCH_3), 2.94 (d, J = 7.0 Hz, C(16)H (keto)), 3.30 (s, OCH_3), 3.43 (s, OCH_3), 4.04 (d, J = 7 0 Hz, C(2)H (keto)), 4.20 (s, C(2)H (enol)), 12.95 (s, enol-OH). **IR**: 2990 (m), 2950 (m), 2890 (w), 2810 (w), 1740 (s), 1720 (s), 1630 (vs), 1600 (s), 1260 (s). **MS** (FD 10 mA): 354.

16,17-Dehydro-20-desethyl-21-epi-17-tert-butyl-dimethyl-silyloxy-16-methoxycarbonyl-1-methyl-aspidospermidine (**29**).
To a solution of **28** (147.3 mg, 0.416 mmol) and 330 µl collidine (3 eq) in 10 ml of dry dichloromethane 480 µl of t-butyldimethylsilyl trifluoromethane-sulfonate (5 eq) was added carefully at 0 °C under a nitrogen atmosphere. The yellow solution turned orange and was stirred for 30 min at 0 °C and for another 2 h at room temperature. The reaction mixture was poured into a sat. $NaHCO_3$ solution and extracted with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography over (eluent ethyl acetate) The product was isolated as a yellow oil in 55 % yield (108 2 mg). **^{1}H-NMR** (C_6D_6, 250 MHz)· -0.18 and 0.12 (2 x s, 2 x 3H, 2 x $SiCH_3$), 0.85 (s, 9H, t-BuSi), 1.35-1 51 (m, 1H, C(6)Hβ),1.62-1.70 (m, 1H, C(6)H$_\alpha$), 2.04-2.12 (m, 1H, C(14)H), 2.30-2.50 (m, 2H, C(14)H, C(20)H), 2.64 (s, 3H, NCH_3), 2 77 (d, 1 H, J = 10 5 Hz, C(21)H), 3.38 (s, 3H, OCH_3), 3 43-3.52 (m, 1H, C(5)H), 3.65-3.77 (m, 1H, C(5)H), 4 59 (s, 1H, C(2)H), 6 30 (d, 1H, J = 7.8 Hz, C(12)H), 6.58 (t, 1H, J = 7.4 Hz, C(10)H), 6 80 (d, 1H, J = 7.2 Hz, C(9)H), 7.03 (dt, 1H, J = 1 0 and 7.6 Hz, C(11)H). **IR**: 1725 (s), 1630 (s), 1600 (m), 1260 (s), 840 (s).

References and notes

1 *for part 22 see* Huizenga, R.H.; Pandit, U.K. *Tetrahedron, see preceding paper.*

2 Taken in part from the doctorate dissertation of R.H. Huizenga, University of Amsterdam, **1990**.

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

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