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First Total Synthesis of (-)-Fumitremorgin C[1]

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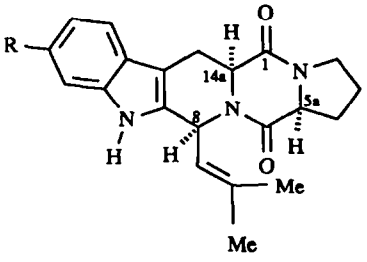
Abstract: The first total synthesis of the tremorgic mycotoxin fumitremorgin C (**1a**) employing 6-methoxy-N-hydroxytryptophan (**5a**) is presented. Our approach features formation of the nitrone (**6a**), stereoselective cycloaddition to yield **7a**, ring opening and coupling with an L-proline derivative to form **14**. Base-catalysed epimerisation gave **16**, which was converted into the title compound by deprotection of the amine function, dioxopiperazine formation and dehydration.

Recently, we reported the first stereoselective approach to tetrahydro-β-carbolines (c.f. **7**) having a masked C(1) 2-hydroxy-2-methylpropyl side chain moiety.[3] Subsequent to the development of this efficient, N-hydroxytryptophan mediated synthesis of these tetrahydro-β-carbolines, one of our goals has been the synthesis of the skeleton of fumitremorgins.[2] Through the synthesis of the fumitremorgin C analog **2b**, we became evidence -though inconclusive- that this compound is not the skeleton of fumitremorgin C (**1a**) but a C(14a) epimer. It should be born in mind that at that time the stereochemistry at C(14a) of the natural product was unknown.[4]



1a Fumitremorgin C
1b
2a,b (C(14a)-epimer)
3a,b (C(8)-epimer)
4a,b (C(8) and C(14a)-epimer)

a: R=OMe
b: R=H

Unfortunately, our approach to **2b** employing the cycloadduct **7b** invariably led to compounds having a *trans*-relationship between the tetrahydro-β-carbolines C(1) and C(3) substituents (Scheme I). So the problem we faced was a selective epimerisation at the carbon atom C(3) of **7** or one of its successors. The second challenge to address was the introduction of the methoxy substituent at the 6-position of the indole nucleus.

Reported here are solutions to both of these problems. The result is an efficient synthesis of the

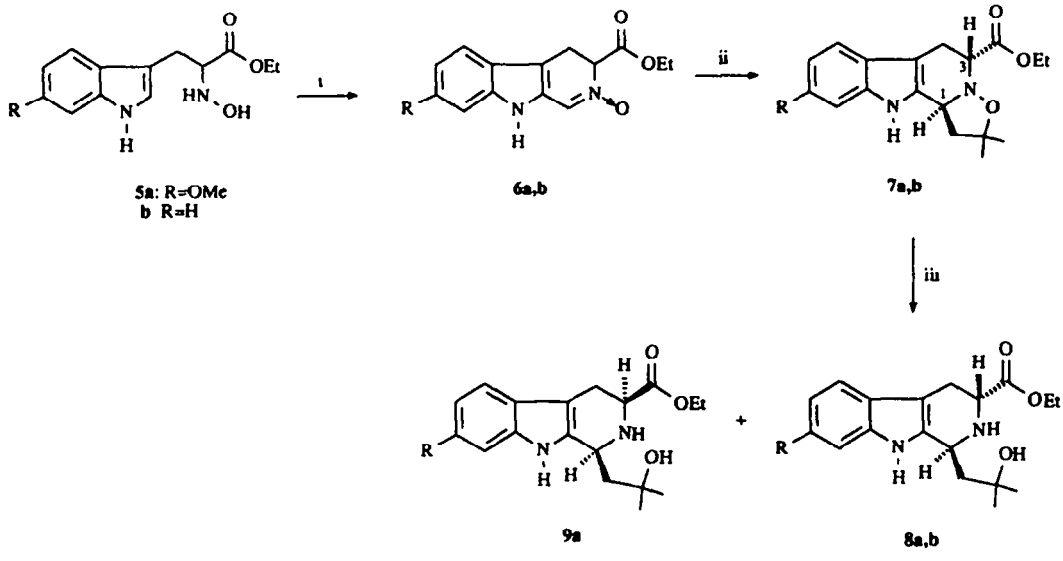
optically pure tremogenic mycotoxin fumitremorgin C (**1a**) and it isomers **2a-4a**.

Over the last years other members of the fumitremorgin-verruculogen class of mycotoxins have been targets for total synthesis.[5]

Results

Nitrone **6a** (Scheme I) was prepared by a known procedure[2,3,6] from **5a**. 1,3-Dipolar cycloaddition of isobutene with **6a** proceeded regio- and stereoselectively to give quantitatively the *trans*-adduct **7a**. The desired cleavage of the isoxazolidine N-O bond was accomplished by treatment of **7a** with zinc dust at 40°C in an argon atmosphere.[7]

Scheme I



i) $HC(OMe)_3$ / H^+ ii) isobutene in toluene (120°C, 8 bar) iii) Zn / HOAc

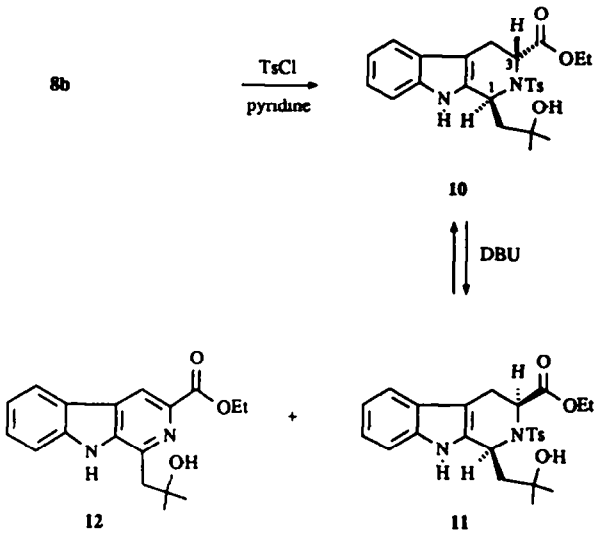
Surprisingly[8], this procedure gave a diastereomeric mixture of **8a** (*trans*) and **9a** (*cis*) in 98% yield. The ratio **8a/9a** varied from 12.5/1 to 25/1. We have not established unambiguously whether this epimerisation at C(3) occurs with **7a** or with **8a**, mainly because the efficiency of this process was too low to be of synthetic value. We rather preferred to study the epimerisation of **8a** and its progeners.

Epimerisation

First we established that isoxazolidin tetrahydro-β-carbolines, **7** cannot be epimerised. Treatment with base (NaH or tBuOK in dimethoxyethane) gave **12** in 75% yield. (Scheme II) Therefore we selected the N(2) amides as target molecules for epimerisation studies. As a model compound we selected the N(2) sulfonamide derivative **10**, which was prepared in 82% yield by treatment of **8b**[2] with TosCl in pyridine.

An efficient method for epimerisation of **10** was only found after several unsuccesful attempts. No isomerisation occured when **10** was treated with Et_3N in dichloromethane. Employment of the stronger base NaOEt in ethanol, led to the undesired β-carboline **12** as the main product.[9]The method of choice for the anticipated epimerisation appeared to be treatment of **10** with DBU in CH_2Cl_2 at room temperature. The *cis/trans* equilibrium ratio of this reaction was estimated as **11/10**=8.5/1.0. Minute quantities (5%) of **12** as side product were observed.[10]

Scheme II



That epimerisation occured selectively at the C(3) carbon was secured by the following experiment. Reaction of **10** with DBU in a mixture of CD_3OD and dichloromethane led to deuterium incorporation exclusively at the C(3) carbon; in addition the side product **12** was detected again.

Encouraged by these results we selected the diastereomeric amides **14** and **15** (Scheme III) as targets for epimerisation. These compounds were prepared in the following manner. Treatment of the racemic amine **8a** with the acid chloride of TrOC-L-proline (**13**) at -20°C[11] provided in 77% yield the amides **14** and **15** (diastereomeric ratio 1/1.5),[12] which were separated by column chromatography. Isomerisation of the key intermediate **14** into its epimer **16** was achieved now as follows. When **14** was treated with DBU in chloroform for 2 days at 45°C an equilibrium ratio of **14/16**=1/1 was observed. Fortunately, this procedure afforded no oxidized β-carbolines. Subsequently, **15** was treated in the same manner to give an equilibrium ratio of **15/17**=2/3. These diastereomeric mixtures could easily be separated by column chromatography where upon the *trans* compounds were subjected again to this epimerisation proces. This way the *trans* compounds **14** and **15** could be converted nearly completely into the corresponding *cis* compounds **16** and **17**, respectively.

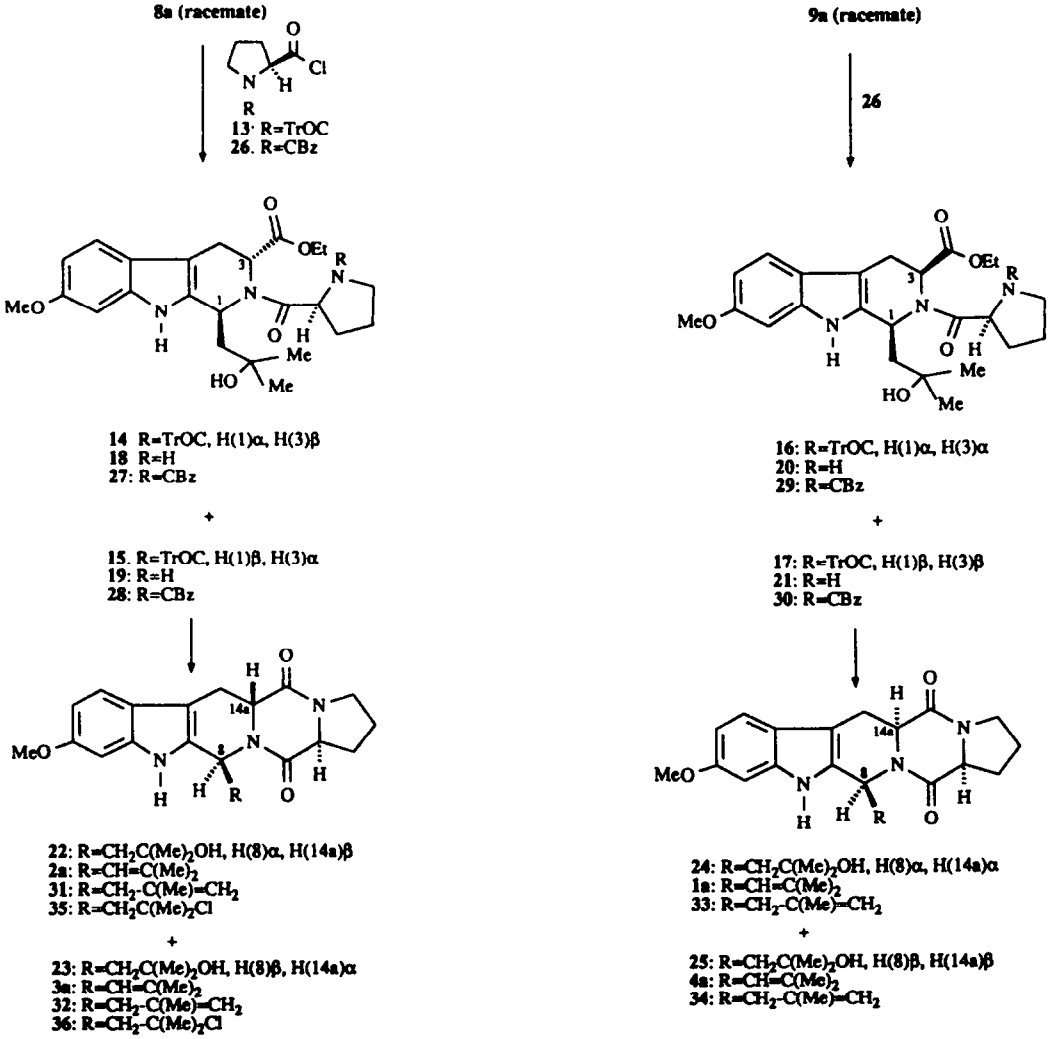
The proline amine functions of the compounds **14-17** were deprotected by means of zinc dust in refluxing methanol to give the amines **18-21** which -under these conditions- cyclized to give the pentacyclic compounds **22-25**. We noticed that the *trans* compounds **22** and **23** were obtained quantitatively within 10 minutes, whereas the *cis* compounds **24** and **25** were obtained in 63% and

45% yield, respectively only after prolonged reaction of 3 days.

Comparison of CPK models revealed that in **24** and **25** there is considerable steric hindrance between the side-chain and the proline moiety. This observation might rationalise the rather sluggish dioxopiperazine formation in the *cis*-series.

Alternatively, the four pentacycles **22-25** could be prepared -though less efficiently for **24** and **25**- from the isomers **8a** and **9a** (*vide-supra*). Thus coupling of **8a** and **9a** with CBz-L-proline acid chloride (**26**) (Scheme III) provided the amides **27** and **28** (ratio 1/1.25) in 79% and **29** and **30** (ratio 1/1.15) in 71% yield, respectively. Again kinetic resolution was observed.[2] Chromatographic separation of the diastereomers, followed by deprotection by catalytic hydrogenation and subsequent ring closure of the intermediates **18-21** afforded again the pentacyclic dioxopiperazines **22** (100%), **23** (100%), **24** (10%) and **25** (10%), respectively. The yields again are indicating that ring closure of the *cis* compounds is unfavourable.

Scheme III



That no racemisation had taken place in the proline moiety during the coupling procedure was secured with the chiral shift reagens tris[3-((heptafluoropropyl)hydroxymethylene)camphorato]-europium (III) as described earlier.[2] Stereochemical structure assignments are made by extending our previous results[2] assuming that no deviant behaviour is caused by the methoxy moiety on the indole nucleus.

For obvious reasons we finally subjected the pentacyclic compounds **22** and **23** to DBU in $CHCl_3$ at 60°C (*vide supra)* as well as to NaOEt in ethanol at 60°C. However no epimerisation was observed.

Finally, transformation of the alcohol functions of **22-25** into the alkene functions of **1a-4a** was accomplished by means of $SOCl_2$ in pyridine at -40°C.[2] The desired alkenes **1a-4a** were accompanied by products due to Hofmann eliminations and -in some cases- by the corresponding chlorides. Thus **24** gave **1a** (4%) and **33** (44%) and **22** gave **2a** (65%), **31** (11%) and **35** (7%) and **23** gave **3a** (28%), **32** (13%) and **36** (12%) and **25** gave **4a** (5%) and **34** (16%). It was discouraging to observe that in the *cis* series the dehydration afforded mainly the undesired products of Hofmann elimination. A tentative rationale comes from studying the CPK models; the proton participating in the Saytzeff elimination is sterically more hindered than the corresponding proton in the *trans* series. Attempts to isomerize the olefins **31-34** into **1a-4a** by means of catalytic amounts of acid or a metal complex failed.

Of the four pentacycles **1a-4a** only the product **1a** possessed spectral characteristics identical to those reported for fumitremorgin C.[4]

Discussion

From this result we concluded that the product **2b** we reported earlier[2] is indeed the C(14a) epimeric analog of the natural product.

The synthesis of fumitremorgin C (**1a**) as well as the developed method to achieve the desired tetrahydro-β-carboline having a *cis* relationship of the C(1), C(3) substituents demonstrates the utility of N-hydroxytryptophan in the synthesis of indole alkaloids.

Epimerisation at the C(3) carbon in 1,3-disubstituted-tetrahydro-β-carbolines was accomplished only when N(2) amides were used and steric interactions absent.

The methodology used is sufficiently flexible to be adapted to the preparation of other members of the fumitremorgin - verruculogen group. This will be demonstrated in future reports.

Experimental Section

Melting points were taken on Koefler hot stage (Leitz-Wetzlar) and are uncorrected. Ultraviolet spectra were measured with a LKB spectrophotometer, Model 4050. Proton magnetic resonance spectra were measured on a Bruker WH-90 spectrometer. Chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane as an internal standard. As a chiral reagent we used tris[3-((heptafluoropropyl) hydroxy-methylene)-*d*-camphorato]europium(III) (Janssen Chimica, Belgium). Mass spectra were obtained with a double focusing VG 7070E spectrometer. Thin layer chromatography (TLC) was carried out by using Merck precoated silicagel F-254 plates (thickness, 0.25 mm). Spots were visualized with a UV hand lamp, iodine vapor, Cl_2-TDM.[13] For column chromatography Merk silicagel 60H was used. Solvent systems used were as follows: system A: $CHCl_3$/MeOH,93/7,v/v; system B: $CHCl_3$/MeOH,97/3, v/v; system C:EtOAc; system D:$CHCl_3$/MeOH,99/1,v/v.

2,2-Dimethyl-5-(ethoxycarbonyl)-9-methoxy-4,5,6,11b-tetrahydro-isoxazolidin[2,3-a]-β--carboline (7a)

Thermal reaction conditions: A stirred solution of **6a**[6] (2.04 g, 7.06 mmol) in dry toluene (75 mL) and isobutene (50 mL) was heated for 4h at 120°C in a 250 mL pressure vessel. The pressure increased up to 9 bar. Filtration of the mixture gave 1.99 g (82%) product. Evaporation of the filtrate and recrystallisation of the residue (CH_2Cl_2) gave additional 0.3 g (12%) of **7a**. Total yield (94%); mp 263-265°C ; R_f 0.57 (solvent system A); UV (methanol) λmax 226,265, 269, 297 nm, λmin 250, 280 nm; EIMS (70 eV) m/z (relative intensity), 344 (M^+, 73%), 271 ($[C_{16}H_{19}N_2O_2]^+$, 100%), 198 ($[C_{12}H_{10}N_2O]^+$, 55%), exact mass for $C_{19}H_{24}N_2O_4$ calcd. 344.1736, found 344.1731; ^1H NMR δ 7.89 (br s, 1H, NH), 7.37-6.70 (m, 2H, C(7)-C(8)H), 6.81 (s, 1H, C(10)H), 4.85 (X part of ABX spectrum, 1H, C(11b)H), 4.29 and 4.24 (2 q from diastereotopic protons, 2H, OCH_2CH_3), 4.09 (t, 1H, ^3J=7.0 Hz, C(5)H), 3.78 (s, 3H, OCH_3), 3.02 (d, 2H, ^3J=7.0 Hz, C(6)H), 2.42 and 2.23 (AB part of ABX spectrum, 2H, ^2J=12.3 Hz, ^3J=6.7 Hz, ^3J=11.1 Hz, $C(1)H_2$), 1.42 and 1.31 (2xs, 6H, 2x CH_3), 1.28 (t, 3H, OCH_2CH_3); Anal. Calcd. for $C_{19}H_{24}N_2O_4$ (MW 344.412) : C, 66.26; H, 7.02; N, 8.13. Found: C, 66.11; H, 7.02; N, 8.12.

High-Pressure reaction conditions: The nitrone **6a** (288 mg, 1 mmol) and isobutene (3 mL) were dissolved in 4 mL DMF and brought into a teflon high-pressure vessel, which was placed in a high-pressure apparatus. After 20h at 12 kbar the reaction was completed as monitored by TLC. Filtration of the mixture gave 255 mg (75%) product. Evaporation of the filtrate and recrystallisation of the residue gave additional 40 mg (11%) of **7a**. Total yield 86%.

1-(2'-Hydroxy-methylpropyl)-3-(ethoxycarbonyl)-7-methoxy-1,2,3,4-tetrahydro-β-carboline (*trans* 8a, *cis* 9a)

Activated zinc dust was added portionwise to a stirred solution of **7a** (750 mg, 2.2 mmol) in 100 mL glacial acetic acid. The reaction mixture was kept at 40°C for 7 h and during that time argon was bubbled through the solution. The reaction was monitored by TLC (solvent system A). The reaction mixture was filtered and washed with CH_2Cl_2, the filtrate concentrated to dryness and the residue dissolved in CH_2Cl_2. This solution was washed successively with saturated $NaHCO_3$, brine, and dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue subjected to flash chromatography ($CHCl_3$/MeOH, 98/2. v/v) to yield 32 mg (4%) of **9a** and 706 mg (94%) of **8a**. These products resisted crystallisation attempts.

cis-product 9a: R_f 0.30 (solvent system B); EIMS (70 eV) m/z (relative intensity) 346 (M^+, 20%), 273 ($[C_{16}H_{21}N_2O_2]^+$, 100%), 199 ($[C_{12}H_{11}N_2O]^+$, 25%); exact mass for $C_{19}H_{26}N_2O_4$ calcd. 346.1893, found 346.1892; ^1H NMR δ 8.86 (br s, 1H, N(9)H), 7.38-6.72 (m, 2H, C(5)-C(6)H), 6.81 (s, 1H, C(8)H), 4.44-4.08 (X part of ABX spectrum, 1H, C(1)H), 4.26 (q, 2H, OCH_2CH_3), 3.83 (s, 3H. OCH_3), 3.78 (X part of ABX spectrum, 1H, C(3)H), 3.04 and 2.77 (AB part of ABX spectrum, 2H, ^2J=15.3 Hz, ^3J=4.0 Hz, ^3J=11.5 Hz, $C(4)H_2$), 2.29 (br s, 2H, N(2)H and OH), 2.11 and 1.84 (AB part of ABX spectrum, 2H, ^2J=14.7 Hz, ^3J=6.0 Hz, ^3J=6.0 Hz, C(1)-CH_2), 1.39 (s, 6H, 2xCH_3), 1.33 (t, 3H, OCH_2CH_3).

trans-product 8a: R_f 0.27 (solvent system B); EIMS (70 eV) m/z (relative intensity) 346 (M^+, 39%), 273 (100%), 199 (40%); exact mass for $C_{19}H_{26}N_2O_4$ calcd. 346.1893, found 346.1889; ^1H NMR δ 7.83 (br s, 1H, N(9)H), 7.40-6.73 (m, 2H, C(5)-C(6)H), 6.82 (s, 1H, C(8)H), 4.51 (X part of ABX spectrum, 1H, C(1)H), 4.23 (q, 2H, OCH_2CH_3), 3.93 (X part of ABX spectrum, 1H, C(3)H), 3.83 (s, 3H, OCH_3), 3.10 and 2.74 (AB part of ABX spectrum, 2H, ^2J=15.6 Hz, ^3J=4.8 Hz, ^3J=10.0 Hz, $C(4)H_2$), 1.95 and 1.72 (AB part of ABX spectrum, 2H, ^2J=14.5 Hz, ^3J=5.1 Hz, ^3J=12.3 Hz, C(1)-CH_2), 1.40 and 1.25 (2xs, 6H, 2xCH_3), 1.31 (t, 3H, OCH_2CH_3).

1-(2'-Hydroxy-methylpropyl)-2-(tosyl)-3-(ethoxycarbonyl)-7-methoxy-1,2,3,4-tetrahydro--β-carboline (10)

To a stirring solution of **8b**[2] (1.24 g, 4 mmol) in dry pyridine (10 mL) at 0°C in an argon atmosphere was added dropwise tosyl chloride (840 mg, 4.4 mmol) in dry pyridine (5 mL). The solution was allowed to warm to room temperature. The reaction was completed within one hour. After dilution with CH_2Cl_2 (100 mL) the solution was succesively washed with, 2N aqueous HCl, brine and dried with Na_2SO_4. Evaporation of the filtrate gave 1.52 g (82%) of **10**, which was crystallized from CCl_4/Et_2O; mp 165-168°C; R_f 0.75 (solvent system A); UV (methanol) λmax 220, 264, 269, 275, 281, 287 nm, λmin 257 nm; CIMS (100 eV) m/z (relative intensity) 471 ($[M+1]^+$, 14%), 453 ($[C_{25}H_{29}N_2O_4S]^+$, 60%), 413 ($[C_{22}H_{25}N_2O_4S]^+$, 100%), 397 ($[C_{22}H_{25}N_2O_3S]^+$, 51%), 315 ($[C_{18}H_{23}N_2O_3]^+$, 35%); exact mass for $C_{25}H_{31}N_2O_5S$ calcd. 471.195, found 471.193; ^1H NMR δ 8.54 (br s, 1H, N(9)H), 7.80-7.00 (m, 8H, C(5)-C(8)H and C_6H_4), 5.20 (t, 1H, ^3J=6.1 Hz, C(1)H), 4.40 (q, 2H, OCH_2CH_3), 4.33 (X part of ABX spectrum, 1H, C(3)H), 3.20 and 2.97 (AB part of ABX spectrum, 2H, ^2J=16.2 Hz, ^3J=12.0 Hz, ^3J=4.4 Hz, $C(4)H_2$), 2.58 (br s, 1H, OH), 2.22 (s, 3H, p-CH_3), 2.08 (d, 2H, ^3J=6.1 Hz, C(1)-CH_2), 1.42 (t, 3H,

OCH_2CH_3), 1.26 (s, 6H, 2xCH_3); Anal. Calcd. for $C_{25}H_{30}N_2O_5S$ (MW 470.589): C, 63.81; H, 6.43; N, 5.95. Found: C, 63.19; H, 6.52; N, 5.99.

Epimerisation of N(2)-sulfonamide 10

A solution of sulfonamide **10** (108 mg, 0.23 mmol) and DBU (35 mg, 0.23 mmol) in dry CH_2Cl_2 (10 mL) was stirred at room temperature in an argon atmosphere for 24 h. The reaction mixture was washed with 0.1N aqueous HCl and brine, and dried with Na_2SO_4. Evaporation of the solvent and subsequent flash chromatography (n-hexane/EtOAc, 75/25, v/v) of the residue gave the epimerized product **11** (85%), starting material (10%) and aromatised product **12** (5%).[2]

Compound 11: This product resisted crystallisation attempts.R_f 0.90 (solvent system A); EIMS (70 eV) m/z (relative intensity) 470 (M^+, 35%), 397 (100%), 169 (90%); exact mass for $C_{25}H_{30}N_2O_5S$ calcd. 470.1875, found 470.1878; ^1H NMR δ 9.98 (br s, 1H, N(9)H), 7.78-7.00 (m, 8H, C(5)-C(8)H and C_6H_4), 5.22 (br d, 2H, C(1)H and C(3)H), 4.05 and 4.03 (2q from diastereotopic protons, 2H, OCH_2CH_3), 3.44-3.28 (A part of ABX spectrum, 1H, C(4)Ha), 2.73-2.18 (m, 3H, C(4)Hb and C(1)-CH_2), 2.33 (s, 3H, p-CH_3), 2.09 (br s, 1H, OH), 1.61 and 1.36 (2xs, 6H, 2xCH_3), 1.16 (t, 3H, OCH_2CH_3).

Deuterium incorporation at C(3)-position of 10.

A solution of **10** (106 mg, 0.2 mmol) and DBU in CH_2Cl_2/CD_3OD, 8/2, v/v (4 mL) was stirred at room temperature in an argon atmosphere for 24 h. The solvent was evaporated and the residue subjected to flash chromatography ($CHCl_3$) to yield 140 mg (80%) C(3)-deuterated **11**: EIMS (70 eV) m/z (relative intensity) 471 (M^+, 22%), 398 ($[C_{22}H_{24}DN_2O_3S]^+$, 100%), 170 ($[C_{11}H_8DN_2]^+$, 69%); ^1H NMR δ 9.96 (br s, 1H, N(9)H), 7.72-6.98 (m, 8H, C(5)-C(8)H and C_6H_4), 5.19 (br d, 1H, C(1)H), 4.05 (q, 2H, OCH_2CH_3), 3.44-3.24 (A part of AB spectrum, 1H, C(4)Ha), 2.71-1.90 (B part of AB spectrum, 1H, C(4)Hb and AB part of ABX spectrum, 2H, C(1)-CH_2), 2.33 (s, 3H, p-CH_3), 1.86 (br s, 1H, OH), 1.60 and 1.36 (2xs, 6H, 2xCH_3), 1.15 (t, 3H, OCH_2CH_3).

8-(2'-Hydroxy-2'-methylpropyl)-7,8,14,14a-tetrahydro-pyrrolidino-[1,2-c]-piperazino-[1',6'--2,3]-β-carboline-(5aHα, 8Hα, 14aHβ)-1,6-dione (22) and 8-(2'-Hydroxy-2'-methylpropyl)--7,8,14,14a-tetrahydro-pyrrolidino-[1,2-c]-piperazino-[1',6'-2,3]-β-carboline-(5aHα, 8Hβ, 14aHα)-1,6-dione (23)

Method a: A solution of **8a** (680 mg, 1.97 mmol) and Et_3N (200 mg, 1.98 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a cooled (-20°C) stirring solution of L-TrOC-Pro-Cl[14] (2.43 mmol) in dry CH_2Cl_2 (20 mL) in an argon atmosphere. The reaction mixture was allowed to warm to room temperature and was monitored by TLC (solvent system A; **15** R_f 0.53.; **14** R_f 0.49). After one hour the reaction was completed, and the reaction mixture was washed succesively with 0.1 N aqueous HCl, 0.1 N $NaHCO_3$ and brine and dried with Na_2SO_4. Evaporation of the solvent *in vacuo* gave a crystalline material, which was subjected to flash chromatography ($CHCl_3$/MeOH, 99.7/0.3, v/v) to yield 527 mg (43%) of **15** and 415 mg (34%) of **14**. Removal of the N-protecting group was accomplished quantitatively by refluxing the dipeptides in methanol (50 mL) with zinc dust for 10 minutes. Filtration and evaporation of the solvent gave 336 mg (43%) of **23** and 266 mg (34%) of **22**. Yields are based on **8a**.

Method b: Coupling of **8a** (840 mg, 2.43 mmol) with L-CBz-Pro-Cl[2] as described above and subsequently flash chromatography ($CHCl_3$/MeOH, 99.25/0.75, v/v) gave 610 mg (44%) of **28** (R_f 0.62, solvent system A) and 492 mg (35%) of **27** (R_f 0.53, solvent system A). Of these N-protected dipeptides the CBZ-group was removed by catalytic hydrogenation using Pd-C in ethanolic solution at atmospheric pressure. Filtration and evaporation of the solvent gave 403 mg (44%) of **23** and 320 mg (32%) of **22**.

Compound 22: R_f 0.26 (solvent system B); mp 270-271°C ($CHCl_3$/n-hexane); $[\alpha]_D^{22}$ +112 (c=1.25, methanol); UV (methanol) λmax 225, 267, 297 nm, λmin 251, 281 nm; EIMS (70 eV) m/z (relative intensity) 397 (M^+, 46%), 379 (8%), 324 (100%), 199 (42%); exact mass for $C_{22}H_{27}N_3O_4$ calcd. 397.2002, found 397.2003; ^1H NMR δ 8.69 (br s, 1H, NH), 7.33-6.68 (m, 2H, C(12)-C(13)H), 6.81 (s, 1H, C(10)H), 5.93 (t, 1H, ^3J=5.4 Hz, C(8)H), 4.36 (X part of ABX spectrum, 1H, C(14a)H), 4.24-3.97 (m, 1H, C(5a)H), 3.85-3.51 (m, 2H, C(3)H_2), 3.82 (s, 3H, OCH_3), 3.30 and 2.89 (AB part of ABX spectrum, 2H, ^2J=15.3 Hz, ^3J=3.9 Hz, ^3J=11.7 Hz, C(14)H_2), 2.60-1.68 (m, 7H, C(4)H_2-C(5)H_2, C(8)-C(1')H_2 and OH), 1.43 and 1.34 (2xs, 6H, 2xCH_3). Addition of the chiral shift reagent tris[3-((heptafluoropropyl)hydroxy-methylene)-*d*-camphorato]europium (III) to the $CDCl_3$ solution of **22** did not cause splitting of signals. Anal. Calcd. for $C_{22}H_{27}N_3O_4$. 0.4$CHCl_3$ (Mw 445.229): C, 60.43; H, 6.20; N, 9.44. Found: C, 60.28; H, 6.17; N, 9.43.

Compound 23: R_f 0.26 (solvent system B); mp 234-236°C ($CHCl_3$/n-hexane); $[\alpha]_D^{22}$ -159 (c=2.0, methanol); UV (methanol) λmax 225, 267, 297 nm, λmin 250, 278 nm; E_HIMS (70 eV) m/z (relative intensity) 397 (M^+, 36%), 379 ($[C_{22}H_{25}N_3O_3]^{+\cdot}$ 5%), 324 ($C_{18}H_{18}N_3O_3]^+$, 100%), 199 (38%); exact mass for $C_{22}H_{27}N_3O_4$, calcd. 397.2002, found 397.1996; ^1H NMR δ 9.09 (br s, 1H, NH), 7.40-6.71 (m, 2H, C(12)-C(13)H), 6.82 (s, 1H, C(10)H, 6.00-5.87 (X part of ABX spectrum, 1H, C(8)H), 4.40 (X part of ABX spectrum, 1H, C(14a)H), 4.23-3.33 (m, 3H, C(5a)H and $C(3)H_2$), 3.83 (s, 3H, OCH_3), 2.95-1.73 (m, 9H, 2x AB part of ABX spectrum $C(14)H_2$ and C(8)-$C(1')H_2$, $C(4)H_2$-$C(5)H_2$ and OH), 1.53 and 1.35 (2xs, 6H, $2xCH_3$). Addition of the chiral shift reagent tris[3-((heptafluoropropyl)hydroxymethylene)-*d*-camphorato]europium (III) to the $CDCl_3$ solution of **23** did not cause splitting of signals. Anal. Calcd. for $C_{22}H_{27}N_3O_4$. 0.8 $CHCl_3$ (Mw 492.981) : C, 55.55; H, 5.68; N, 8.52. Found: C, 55.28; H, 5.64; N, 8.48.

8-(2'-Hydroxy-2'-methylpropyl)-7,8,14,14a-tetrahydro-pyrrolidino-[1,2-c]-piperazino-[1',6'--2,3]-β-carboline-(5aHα, 8Hα, 14aHα)-1,6-dione (24) and 8-(2'-Hydroxy-2'-methylpropyl)--7,8,14,14a-tetrahydro-pyrrolidino-[1,2-c]-piperazino-[1',6'-2,3]-β-carboline-(5aHα, 8Hβ, 14aHβ)-1,6-dione (25)

Method a: Compound **9a** (155 mg, 0.45 mmol) was coupled with L-CBz-Pro-Cl (0.56 mmol) as described for the preparation of **22** abd **23**. This procedure gave 75 mg (29%) of **29** and 110 mg (42%) of **30**. The N-protecting group of these dipeptides was removed by catalytic hydrogenation using Pd-C in ethanolic solution at room temperature and atmospheric pressure to yield **20** and **21**, respectively. Cyclisation to the corresponding dioxopiperazines did not occur under these conditions. This was achieved by refluxing a solution of the amines **20** and **21** in ethanol to give 18 mg (10%) of **24** and 18 mg (10%) of **25**.

Method b (Epimerisation of N-protected dipeptides 14 and 15): A solution of **14** or **15** (325 mg, 0.53 mmol) and DBU (85 mg, 0.53 mmol) in dry $CHCl_3$ was stirred at 45°C in an argon atmosphere. Monitoring of the reaction by TLC showed that after 48 h. the equilibrium was reached. The reaction mixture was washed with 0.1 N aqueous HCl, brine and dried with Na_2SO_4. After evaporation of the solvent the residue was subjected to flash chromatography ($CHCl_3$/MeOH, 99.5/0.5, v/v) to yield 162 mg (50%) of **16** (R_f 0.42, solvent sytem B) and 162 mg starting material **14** (or 217 mg (67%) of **17** (R_f 0.40, solvent system B) and 108 mg starting material **15**). Removal of the N-protecting group and cyclisation to the diketopiperazines **24** and **25** was accomplished by refluxing a solution of **16** or **17** in a methanol (5 mL) with zinc dust for 3 days. After filtration and evaporation of the solvent, the residue was subjected to flash chromatography ($CHCl_3$/MeOH, 99.5/0.5, v/v) to yield 65 mg (63%) of **24** (or 63 mg (45%) of **25**).

Compound 24: Crystallisation attempts were unsuccesful. R_f 0.34 (solvent system B); $[\alpha]_D^{22}$ -62.5 (c=3.8, methanol); UV (methanol) λmax 226, 267, 297 nm, λmin 250, 280 nm; EIMS (70 eV) m/z (relative intensity) 397 (M^+, 42%), 279 (6%), 324 (100%), 199 (38%); exact mass for $C_{22}H_{27}N_3O_4$ calcd. 397.2002, found 397.1998; ^1H NMR δ 8.81 (br s, 1H, NH), 7.43-6.67 (m, 2H, C(12)-C(13)H), 6.85 (s, 1H, C(10)H), 5.67 (X part of ABX spectrum, 1H, C(8)H), 4.20-4.00 (m, 2H, C(5a)H and X part of ABX spectrum C(14a)H), 3.80 (s, 3H, OCH_3), 3.72-2.93 (m, 4H, $C(3)H_2$ and AB part of ABX spectrum $C(14)H_2$), 2.49-1.64 (m, 7H, $C(4)H_2$-$C(5)H_2$, AB part of ABX spectrum C(8)-$C(1')H_2$ and OH), 1.38 and 1.13 (2xs, 6H, $2XCH_3$).

Compound 25: Crystallisation attempts were unsuccesful. R_f 0.34 (solvent system B); $[\alpha]_D^{22}$ +30 (c=4.3, methanol); UV (methanol) λmax 225, 267, 297 nm, λmin 249, 281 nm; EIMS (70 eV) m/z (relative intensity) 397 (M^+, 40%), 479 (7%), 324 (100%), 199 (45%); exact mass for $C_{22}H_{27}N_3O_4$ calcd. 397.2002, found 397.2000; ^1H NMR δ 9.56 (br s, 1H, NH), 7.35-6.71 (m, 2H, C(12)-C(13)H), 6.81 (s, 1H, C(10)H), 4.94-4.73 (X part of ABX spectrum, 1H, C(8)H), 4.34-3.98 (m, 2H, C(5a)H and X part of ABX spectrum C(14a)H), 3.82 (s, 3H, OCH_3), 3.84-1.71 (m, 11H, $C(3)H_2$, AB part of ABX spectrum $C(14)H_2$, AB part of ABX spectrum C(8)-$C(1')H_2$, $C(4)H_2$-$C(5)H_2$ and OH), 1.45 and 1.41 (2xs, 6H, $2xCH_3$).

Dehydration of 22-25

General method: To a stirred and cooled (-40°C) solution of the alcohol in dry pyridine (1 mL per 0.1 mmol of alcohol) was added freshly distilled thionyl chloride (1.5 equivalents) in an argon atmosphere. The reaction was monitored by TLC (solvent system C). The solution was allowed to warm to room temperature. After dilution with CH_2Cl_2 the resulting mixture was washed with 2 N aqueous HCl, brine and dried with Na_2SO_4. Evaporation of the solvent gave a mixture of reaction products, which were separated by flash chromatography.

Reaction of 22 (100 mg, 0.25 mmol) with $SOCl_2$ (44mg, 0.375 mmol) gave after flash

chromatography (EtOAc/n-hexane, 60/40, v/v) 7 mg (7%) of **35**, 10 mg (11%) of **31** and 62 mg (65%) of **2a**.

8-(2'-methyl-1'-propenyl)-7,8,14,14a-tetrahydro-pyrrolidino-[1,2-c]-piperazino-[1',6'-2,3]-β-carboline-(5aHα, 8Hα, 14aHβ)-1,6-dione (2a): R_f 0.42 (solvent system C); mp 261-263°C (EtOAc/n-hexane); $[\alpha]^{22}_D$ +250 (c=0.9, methanol); UV (methanol) λmax 230, 268, 297 nm, λmin 255, 282 nm; EIMS (70 eV) m/z (relative intensity) 379 (M^+, 82%), 324 (37%), 281 (100%), 199 (20%); ^{1}H NMR δ 7.76 (br s ,1H, NH), 7.32 (br d, 1H, C(13)H), 6.82 (s, 1H, C(10)H), 6.76 (m, 1H, C(12)H), 6.44 (d, 1H, ^{3}J=9.3 Hz, C(8)H), 5.34 (d, 1H, ^{3}J=9.3 Hz, C(1')H), 4.40 (X part of ABX spectrum, 1H, C(14a)H), 4.27-3.98 (m, 1H, C(5a)H), 3.82 (s, 3H, OCH_3), 3.82-3.50 (m, 2H, C(3)H_2), 3.27 and 2.87 (AB part of ABX spectrum, 2H, ^{2}J=15.0 Hz, ^{3}J=3.9 Hz, ^{3}J=11.7 Hz, C(14)H_2), 2.51-1.98)m, 4H, C(4)H_2-C(5)H_2), 1.96 and 1.75 (2xs, 6H, 2xCH_3); Anal. Calcd. for $C_{22}H_{25}N_3O_3$ (Mw 379.463): C, 69.64; H, 6.64; N, 11.07. Found: C, 69.49; H, 6.69; N, 10.92.

8-(2'-methyl-2'-propenyl)-7,8,14,14a-tetrahydro-pyrrolidino-[1,2-c]-piperazino-[1',6'-2,3]-β-carboline-(5aHα, 8Hα, 14aHβ)-1,6-dione (31): R_f 0.46 (solvent system C); oil; EIMS (70 eV) m/z (relative intensity) 379 (M^+, 13%), 324 (100%), 199 (29%); ^{1}H NMR δ 7.86 (br s, 1H, NH), 7.39-6.74 (m, 2H, C(12)-C(13)H), 6.83 (s, 1H, C(10)H), 5.90 (t, 1H, ^{3}J=7.2 Hz, C(8)H), 4.93 (br d, 2H, ^{2}J=7.8 Hz, C(3')H_2), 4,42 (X part of ABX spectrum, 1H, C(14a)H), 4.20-4.03 (m, 1H, C(5a)H), 3.83 (s, 3H, OCH_3), 3.83-3.53 (m, 2H, C(3)H_2), 3.32 and 2.88 (AB part of ABX spectrum, 2H, ^{2}J=15.3 Hz, ^{3}J=3.3 Hz, ^{3}J=12.0 Hz, C(14)H_2), 2.54 (d, 2H, ^{3}J=7.2 Hz, C(1')H_2), 2.54-1.68 (m, 4H, C(4)-C(5)H_2), 1.91 (s, 3H, CH_3).

8-(2'-chloro-2'-methylpropyl)-7,8,14,14a-tetrahydro-pyrrolidino-[1,2-c]-piperazino-[1',6'-2,3]-β-carboline-(5aHα, 8Hα, 14aHβ)-1,6-dione (35): R_f 0.52 (solvent system C); oil, FABMS (7 kV at 1.4 mA) m/z (relative intensity) 418 ($[M+3]^+$, 2.5%), 416 ($[M+1]^+$, 6.6%), 185 (100%); ^{1}H NMR δ 8.80 (br s, 1H, NH), 7.37-6.74 (m, 2H, C(12)-C(13)H), 6.83 (s, 1H, C(10)H), 6.09 (t, 1H, ^{3}J=4.5 Hz, C(8)H), 4.40 (X part of ABX spectrum, 1H, C(14a)H), 4.23-4.02 (m, 1H, C(5a)H), 3.87-3.57 (m, 2H, C(3)H_2), 3.83 (s, 3H, OCH_3), 3.27 and 2.87 (AB part of ABX spectrum, 2H, ^{2}J=15.0 Hz, ^{3}J=3.8 Hz, ^{3}J=11.4 Hz, C(14)H_2), 2.60-1.60 (m, 4H, C(4)-C(5)H_2), 2.60 (d, 2H, ^{3}J=4.5 Hz, C(1')H_2), 1.72 and 1.68 (2xs, 6H, 2xCH_3).

Reaction of 23 (100 mg, 0.25 mmol) and $SOCl_2$ (44 mg, 0.375 mmol) gave after flash chromatography (EtOAc/n-hexane, 55/45, v/v) 12 mg (12%) of **36**, 12 mg (13%) of **32** and 27 mg (28%) of **3a**.

8-(2'-methyl-1'-propenyl)-7,8,14,14a-tetrahydro-pyrrolidino-[1,2-c]-piperazino-[1',6'-2,3]-β-carboline-(5aHα, 8Hβ, 14aHα)-1,6-dione (3a): R_f 0.37 (solvent system C); mp 259-269°C (EtOAc/n-hexane); $[\alpha]^{22}_D$ -327 (c=0.8, methanol); UV (methanol) λmax, 225, 270, 297 nm, λmin 254, 281 nm; EIMS (70 eV) m/z (relative intensity) 379 (M^+, 98%), 324 (100%), 199 (46%); ^{1}H NMR δ 7.68 (br s, 1H, NH), 7.36 (br d, 1H, C(13)H), 6.83 (s, 1H, C(10)H), 6.83-6.73 (m, 1H, C(12)H), 6.38 (d, 1H, ^{3}J=9.8 Hz, C(8)H), 5.23 (2, 1H, ^{3}J=9.8 Hz, C(1')H), 4.44 (X part of ABX spectrum, 1H, C(14a)H), 4.22-4.00 (m, 1H, C(5a)H), 3.95-3.33 (m, 2H, C(3)H_2), 3.82 (s, 3H, OCH_3), 3.09-1.90 (m, 6H C(4)-C(5)H_2 and AB part of ABX spectrum C(14)H_2), 2.03 and 1.76 (2xs, 6H, 2xCH_3); Anal. Calcd. for $C_{22}H_{25}N_3O_3$ (Mw 379.463): C, 69.64; H, 6.64; N, 11.07. Found: C, 69.33; H, 6.68; N, 10.88.

8-(2'-methyl-2'-propenyl)-7,8,14,14a-tetrahydro-pyrrolidino-[1,2-c]-piperazino-[1',6'-2,3]-β-carboline-(5aHα, 8Hβ, 14aHα)-1,6-dione (32):R_f 0.42 (solvent system C); oil; EIMS (70 eV) m/z (relative intensity) 379 (M^+, 15%), 324 (100%), 199 (35%); ^{1}H NMR δ 7.96 (br s, 1H, NH), 7.42-6.75 (m, 2H, C(12)-C(13)H), 6.84 (s, 1H, C(10)H), 5.92 (t, 1H, ^{3}J=6.6 Hz, C(8)H), 4.91 (d, 2H, ^{2}J=7.5 Hz, C(3')H_2), 4.44 (X part of ABX spectrum, 1H, C(14a)H), 4.24-4.00 (m, 1H, C(5a)H), 3.94-3.33 (m, 2H, C(3)H_2), 3.84 (s, 3H, OCH_3), 3.04-1.62 (m, 6H, C(4)-C(5)H_2 and AB part of ABX spectrum C(14)H_2), 2.55 (d, 2H, ^{3}J=6.6 Hz, C(1')H_2), 1.89 (s, 3H, CH_3).

8-(2'-chloro-2'-methylpropyl)-7,8,14,14a-tetrahydro-pyrrolidino-[1,2-c]-piperazino-[1',6'-2,3]-β-carboline-(5aHα, 8Hβ, 14aHα)-1,6-dione (36): R_f 0.48 (solvent system C); oil; FABMS (7 kV at 1.4 mA) m/z (relative intensity) 418 ($[M+3]^+$, 2%), 416 ($[M+1]^+$, 5%), 185 (100%); ^{1}H NMR δ 8.23 (br s, 1H, NH), 7.37-6.74 (m, 2H, C(12)-C(13)H), 6.83 (s, 1H, C(10)H), 6.23 (t, 1H, ^{3}J=5.4 Hz, C(8)H), 4.49 (X part of ABX spectrum, 1H, C(14a)H), 4.28-4.00 (m, 1H, C(5a)H), 3.94-3.31 (m, 2H, C(3)H_2), 3.83 (s, 3H, OCH_3), 3.3-1.91 (m, 6H, C(4)-C(5)H_2 and AB part of ABX spectrum C(14)H_2), 2.31 (d, 2H, ^{3}J=5.4 Hz, C(1')H_2), 1.71 (s, 6H, 2xCH_3).

Reaction of 24 (50 mg, 0.12 mmol) and $SOCl_2$ (19 mg, 0.185 mmol) gave after flash chromatography (EtOAc/n-hexane, 50/50, v/v) 20 mg (44%) of **33** and 2 mg (4%) of **1a**.

Fumitremorgin C (1a). R_f 0.13 (solvent system D); oil; $[\alpha]^{22}_D$ -9 (methanol c=0.65); UV

(methanol) λmax 225, 270, 296 nm ,λmin 255, 280 nm; EIMS (70 eV) m/z (relative intensity) 379 (M^+, 72%), 324 (100%), 199 (52%);^{1}H NMR (200 MHz) δ 7.66 (br s, 1H, NH), 7.44 (d, 1H, C(13)H), 6.86-6.79 (m, 2H, C(10)H and C(12)H), 5.98 (d, 1H, ^{3}J=9.6 Hz, C(8)H), 4.91 (dt, 1H, ^{3}J=9.6 Hz, ^{4}J=1.5 Hz, C(1')H), 4.23-4.08 (m, 2H, C(14a)H and C(5a)H), 3.84 (s, 3H, OCH_3), 3.68-3.60 (m, 1H, C(3)H_2), 3.51 and 3.10 (AB part of ABX spectrum, 2H, ^{3}J=6.3 Hz, ^{3}J=12.3 Hz, ^{2}J=18.0 Hz, C(14)H_2), 2.46-1.91 (m, 4H, C(4)-C(5)H_2), 2.00 (d, 3H, ^{4}J=1.5 Hz, CH_3), 1.66 (d, 3H, ^{4}J=1.5 Hz, CH_3).

8-(2'-methyl-2'-propenyl)-7,8,14,14a-tetrahydro-pyrrolidino-[1,2-c]-piperazino-[1',6'-2,3]-β-carboline-(5aHα, 8Hα, 14aHα)-1,6-dione (**33**): R_f 0.14 (solvent system D);EIMS (70 eV) m/z (relative intensity) 379 (M^+, 14%), 324 (100%), 199 (42%); ^{1}H NMR δ 8.00 (br s, 1H, NH), 7.42 (d, 1H, C(13)H), 6.84 (s, 1H, C(10)H), 6.78 (d, 1H, C(12)H), 5.40 (X part of ABX spectrum, 1H, C(8)H), 4.64 (br d, 2H, ^{2}J=22.0 Hz, C(3')H_2), 4.20-3.97 (m, 2H, C(5a)H and C(14a)H), 3.84 (s, 3H, OCH_3), 3.67-1.73 (m, 10H, C(3)H_2, C(14)H_2, C(1')H_2 and C(4)-C(5)H_2), 1.64 (s, 3H, CH_3).

Reaction of 25 (40 mg, 0.1 mmol) and $SOCl_2$ (18 mg, 0.15 mmol) gave after flash chromatography (EtOAc/n-hexane, 60/40, v/v) 6 mg (16%) of **34** and 2 mg (5%) of **4a**.

8-(2'-methyl-1'-propenyl)-7,8,14,14a-tetrahydro-pyrrolidino-[1,2-c]-piperazino-[1',6'-2,3]-β-carboline-(5aHα, 8Hβ, 14aHβ)-1,6-dione (**4a**): R_f 0.13 (solvent system D); EIMS (70 eV) m/z (relative intensity) 379 (M^+, 83%), 324 (100%), 199 (35%); ^{1}H NMR δ 7.85 (br s, 1H, NH), 7.42 (d, 1H, C(13)H), 6.85 (s, 1H, C(10)H), 6.73 (d, 1H, C(12)H), 5.54 (d, 1H, ^{3}J=9.0 Hz, C(8)H), 4.95 (d, 1H,^{3}J=9.0 Hz, C(1')H), 4.31-4.01 (m, 2H, C(14a)H and C(5a)H), 3.85 (s, 3H, OCH_3), 3.84-2.74 (m, 4H, C(3)H_2 and C(14)H_2), 2.45-1.75 (m, 4H, C(4)-C(5)H_2), 1.92 and 1.82 (2xs, 6H, 2xCH_3).

8-(2'-methyl-2'-propenyl)-7,8,14,14a-tetrahydro-pyrrolidino-[1,2-c]-piperazino-[1',6'-2,3]-β-carboline-(5aHα, 8Hβ, 14aHβ)-1,6-dione (**34**): R_f 0.16 (solvent system D); EIMS (70 eV) m/z (relative intensity) 379 (M^+, 21%), 324 (100%), 199 (54%); ^{1}H NMR δ 8.26 (br s, 1H, NH), 7.37 (m, 1H, C(13)H), 6.83 (s, 1H, C(10)H), 6.77 (m, 1H, C(12)H), 5.10-4.85 (m, 1H, C(8)H), 4.96 (br d, 1H,^{2}J=8.1 Hz, C(3')H_2), 4.33-4.00 (m, 2H, C(14a)H and C(5a)H), 3.83 (s, 3H, OCH_3), 3.79-2.81 (m, 4H, C(3)H_2 and C(14)H_2), 2.53-1.67 (m, 6H, C(1')H_2 and C(4)-C(5)H_2), 1.80 (s, 3H, CH_3).

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7. Contrary to our earlier results, we were able to suppress the formation of β-carboline **12** by passing argon through the suspension.
8. Isomerisation of the compound **8b** under the same conditions was not observed.
9. Elimination and subsequent aromatisation of compounds related to **10** and **11** has been reported, see Harrison, D.M.; Sharma, R.B. *Tetrahedron Lett.* **1986**, *27* 521.
10. Elevated reaction temperatures led to considerable amounts of **12**.
11. In order to retain the homochirality of **13** during the coupling procedure, amine **8a** and triethylamine were added to a cooled (-20°C) solution of an excess of **13**.
12. Formation of **15** in a slight excess over **14** might be rationalised by kinetic resolution. When the experiment was carried out without triethylamine only diastereomer **15** was formed. When subsequently triethylamine was added **14** was formed from residual **8a** and **13**.
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14. We prepared N-(2,2,2-trichloroethyloxycarbonyl)-L-proline acid chloride (**13**) as described (see ref. 2) for N-(benzyloxycarbonyl)-L-proline acid chloride (**26**). During the course of our studies a related reaction involving **13** was reported.(see ref. 5a)