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Diastereocontrolled multicomponent pathway to 3,4-heterocycle-annulated tetrahydro-β-carbolines

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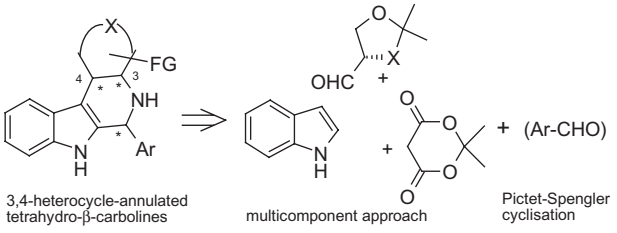
Abstract—A diastereoselective synthesis, using the Yonemitsu-type trimolecular condensation as the key step, has been used for the preparation of 3,4-heterocycle(furanone-, pyrrolidinone- and pyranone-) annulated tetrahydro-β-carbolines. The chirality of D-glyceraldehyde or that of the Garner's aldehyde ensured a high and predictable diastereocontrol of the additional newly created stereocentres.

1. Introduction

The tetrahydro-β-carboline core is a commonly occurring structural feature of numerous *Vinca*-, *Harman*-, *Rauwolfia*-type alkaloids and related synthetic compounds with valuable biological properties.[1] 3,4-Annulated (tetrahydro)-β-carboline derivatives[2] were reported to be benzodiazepine,[3] tyrosine-kinase[4] or glucagon-like peptide (GLP-1) receptor inhibitors.[5] Such a family of tetrahydro-β-carbolines is accessible from heterocycle-fused tryptamines via the well-established Pictet–Spengler[6] and Bischler–Napieralski[7] cyclisation reactions. Furthermore, heterocycle-fused tryptamines are considered as intermediates for the preparation of conformationally congested serotonin and melatonin analogues.[8]

As part of our ongoing programme on the synthetic application of the Yonemitsu multicomponent reaction,[9] we have recently proposed an alternative pathway[10] using a masked nucleophile function containing chiral aldehydes as electrophile partners for the preparation of such 3,4-heterocycle annulated tetrahydro-β-carbolines.

Our synthetic approach is based on a diastereoselective trimolecular condensation between indole, Meldrum's acid and orthogonally protected[11] polyfunctional aldehydes.



Chemoselective deprotection, followed by internal nucleophilic attack on the Meldrum's acid moiety afforded functionalised indolylpropionic acid derivatives in a diastereoselective manner. The carboxylic acid function of the latter was relayed towards heterocycle-fused tryptamines.

Herein, we report in full detail an efficient access for the synthesis of new, chiral, nonracemic 3,4-furane-, pyrane- and pyrrolidine-ring annulated 1-aryl-substituted tetrahydro-β-carboline derivatives.

2. Results and discussion

2.1. Synthesis of 3,4-furane-annulated tetrahydro-β-carbolines

Chiral indolyl lactone-acid **5** was obtained in two steps via **4**, from indole **1**, 2,3-*O*-isopropylidene-D-glyceraldehyde **2**[12] and Meldrum's acid **3** with high

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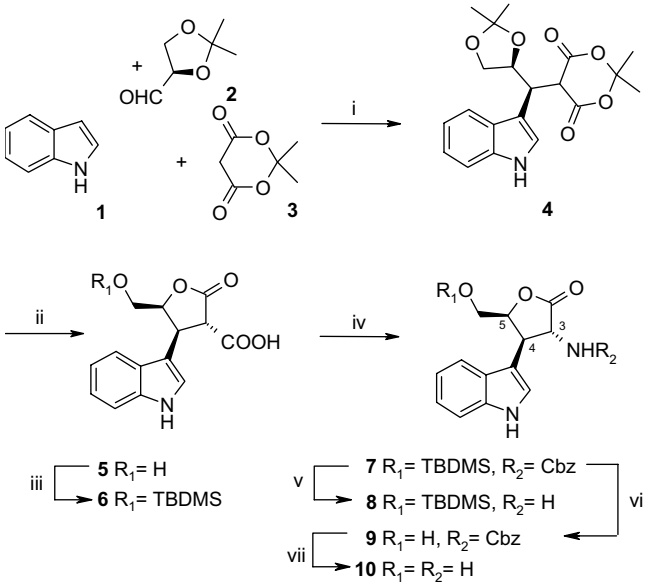
diastereocontrol, as described previously.[13] The primary hydroxyl group of **5** was protected and the carboxylic acid → amine (carbamate) interconversion[14] was achieved by means of three consecutive functional group transformations (Scheme 1): treatment of **6** with diphenylphosphorylazide (DPPA) in the presence of triethylamine, followed by a thermally induced Curtius rearrangement provided the appropriate isocyanate species, which was trapped by benzyl alcohol furnishing the corresponding benzyl carbamate **7** in acceptable yield (63% from **6**).

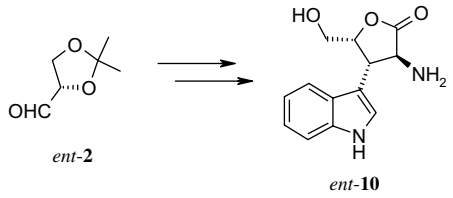


Scheme 1. Reagents and conditions: (i) cat. D,L-proline, CH_3CN, 76%; (ii) 10% HCl, THF, 92%; (iii) TBDMSCl, imidazole, CH_2Cl_2, DMF, 90%; (iv) (a) DPPA, Et_3N, CH_3CN, 0 °C, (b) Δ, toluene, (c) BnOH, toluene, Δ, 63%; (v) Pd–C, H_2, EtOAc, 80%; (vi) AcOH–H_2O–THF, 60 °C, 97%; (vii) Pd–C, H_2, MeOH, 80%.

Acyl azide formation via a mixed anhydride[15] failed. It is important to note that acid **6** was very sensitive to decarboxylation; therefore unreacted starting material, reagents and eventually formed by-products had to be removed by rapid flash chromatography on a short column. Without this purification, the overall yield dropped to 30–35%. Debenzylation of carbamate **7** gave the corresponding amine **8** in 80% yield. To obtain chiral furane-annulated tryptamine **10**, acid catalysed desilylation, followed by debenzylation of **9** was proposed. As Curtius rearrangements are known to proceed with retention, the absolute configuration of tryptamine **10** remained unchanged [(3*R*,4*R*,5*S*)], as supported by detailed NMR experiments. Enantiomeric tryptamine *ent*-**10** was prepared starting from 2,3-*O*-isopropylidene-L-glyceraldehyde *ent*-**2**[16] via the same manipulations (Scheme 2).

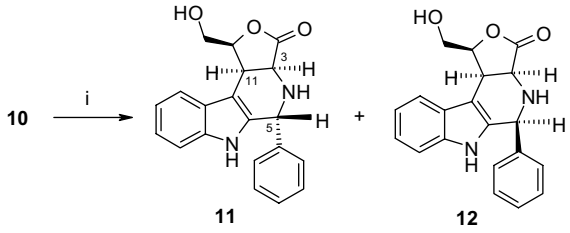
It is important to note that the 5-epimer of *ent*-**10** has been described by Dodd and co-workers by using a Lewis acid catalysed regio- and stereoselective ring opening of chiral aziridino-furasonide as key step.[17]

Pictet–Spengler cyclisation of *trans* furane-fused tryptamine **10** proved to be troublesome. Previously we



Scheme 2. Reagents and conditions: see Scheme 1.

found that cyclisation of the related tryptamines with a *trans* relative stereochemistry failed under kinetic control.[18] As for **10** condensation with benzaldehyde smoothly occurred although the intermediate Schiff-base did not cyclise even in the presence of acid promoter. However, when Pictet–Spengler condensation was conducted in refluxing benzene–TFA mixture, the corresponding diastereomeric tetrahydro-β-carbolines **11** (24%) and **12** (31%) were isolated after chromatography (Scheme 3).



Scheme 3. Reagents and conditions: (i) (a) PhCHO, MeOH, Δ; (b) TFA, benzene, Δ, 55%.

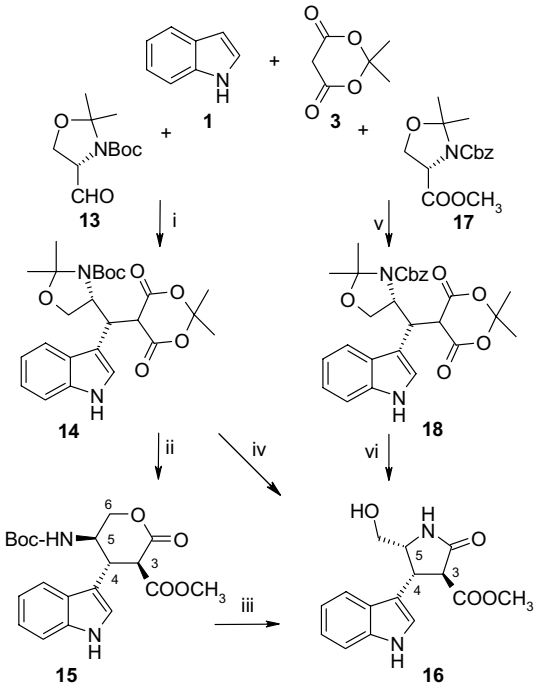
The absolute configuration of the newly created stereocentre (C-5) in **12** could not be determined by using NOE methods because of overlapping of the appropriate signals. Nevertheless, the observed long-range coupling (^5J = 1.4 Hz) between H-5 (δ = 5.30 ppm) and H-11 (δ = 4.19 ppm) suggested a relative *cis*-position for these protons. Conversely, no H-5/H-11 long-range coupling was observed in the more polar diastereomer **11**. From these observations we concluded the less polar diastereomer **12** to have a (5*S*)-configuration and consequently **11** to be its epimer (5*R*). Additionally, C-3 and C-5 carbons of diastereomer **12** shifted downfield (δ = 54.8 and 57.6 ppm in acetone-d_6, respectively) relative to those of the more polar diastereomer **11** (δ = 53.1 and 55.2 ppm, respectively). It is known that these carbon atoms in *trans*-1,3-disubstituted (numbering: β-carboline skeleton) tetrahydro-β-carbolines are consistently upfielded to those of the *cis*-isomer.[19] From this knowledge we concluded a *cis* relative stereochemistry for the H-5 and H-3 protons in **12** and *trans* in **11**. Such a stereochemical arrangement supported the epimerisation of the C-3 carbon via imine–iminium species during the Pictet–Spengler cyclisation.[20]

This poor C-5 diastereoselectivity could be slightly improved to the detriment of the total yield by using a higher excess of benzaldehyde and decreased quantity of TFA. Silylether containing amine **8** gave the same tetrahydro-β-carbolines in lower yield along with trifluoroacetamido by-products.

2.2. Synthesis of 3,4-pyrane- and pyrrolidine-annulated tetrahydro-β-carbolines

Continuing our studies on the synthesis of chiral 3,4-heterocycle fused tetrahydro-β-carbolines, it was interesting to examine the diastereocontrol of newly formed stereocentres by using an orthogonally protected bifunctional chiral aldehyde such as the Garner's aldehyde **13**.[21]

To this end, a three-component condensation of Garner's aldehyde **13** with indole **1**, and Meldrum's acid **3** provided the unstable corresponding adduct **14** (90%) in good (de >90%) diastereoselectivity.[10] Depending on the solvolysis conditions, chemoselective internal *O*- or *N*-nucleophilic ring closures were envisaged (Scheme 4).



Scheme 4. Reagents and conditions: (i) cat. D,L-proline, CH_3CN, 90%; (ii) (a) *p*-TsOH, MeOH, (b) CH_2N_2, 86%; (iii) TFA, CH_2Cl_2, 95%; (iv) HCl–MeOH, 71% (v) (a) DIBAL-H, toluene −78 °C, then **1** and **3**, (b) cat. D,L-proline, CH_3CN, 57%; (vi) (a) Pd–C, H_2, EtOH, (b) CH_2N_2, 63%.

Mild isopropylidene deprotection of **14** in methanol containing a catalytic amount of *p*-TsOH, smoothly afforded the appropriate, very unstable δ-lactone-acid, which was immediately subjected to diazomethane-assisted methylation. The absolute configuration of the two newly created stereocentres of **15** was determined by detailed NMR experiences. The large coupling constant between H-3 and H-4 protons ($^3J = 11.6$ Hz) is in accordance with their *trans* relative stereochemistry, while strong NOE interactions between the irradiated NH and H-4 and H-6 protons evidenced equatorial position for the substituents and (*R*) absolute configuration for C-4 carbon (Fig. 1).

Further hydrolysis of **15** with TFA removed the Boc protecting group allowing ring contractile lactamisation affording **16**. This deprotection enabled us to set up stereochemical correlation between the pyrano **15** and pyrrolidino **16** series.

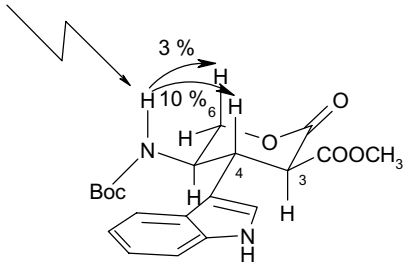
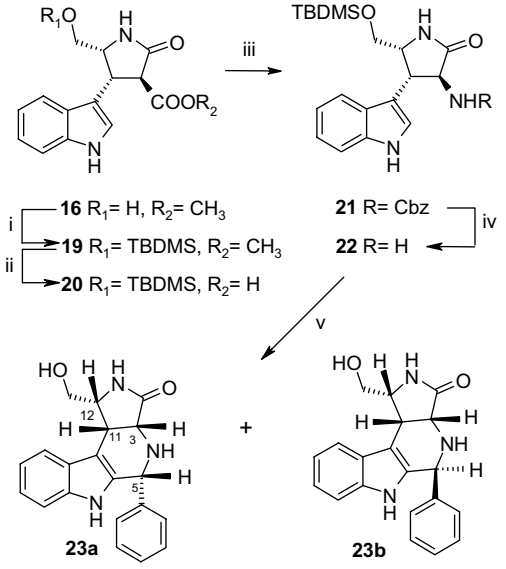


Figure 1. NOE interactions in compound **15**.

Pyrrolidine ester **16** could also be prepared from trimolecular adduct **14** in a one-pot reaction (Scheme 4). A third route to the key intermediate **16** has also been developed: the DIBAL-H mediated reduction of the *N*-benzyloxycarbonyl L-serinate derivative **17**[22] led to the corresponding crude aldehyde, which was condensed with indole **1** and Meldrum's acid **3**, as usual, to yield trimolecular derivative **18**. Hydrogenolytic removal of the Cbz-group with Pd–C failed in aprotic solvents (ethyl acetate, THF, acetone) even at medium pressure of hydrogen (10 bar). In contrast, debenzylation smoothly took place in ethanol at normal pressure with simultaneous solvolysis of the isopropylidene protecting group. Treatment of the intermediate with an excess of diazomethane provided **16**, identical in all respects to that obtained by the two previously mentioned methods.

Before conversion of the carboxylic acid into the carbamate, functional group transformations, for example, protection of the primary alcohol to give **19**, followed by hydrolysis of the ester function, were realised (Scheme 5). Acid **20** was transformed into carbamate

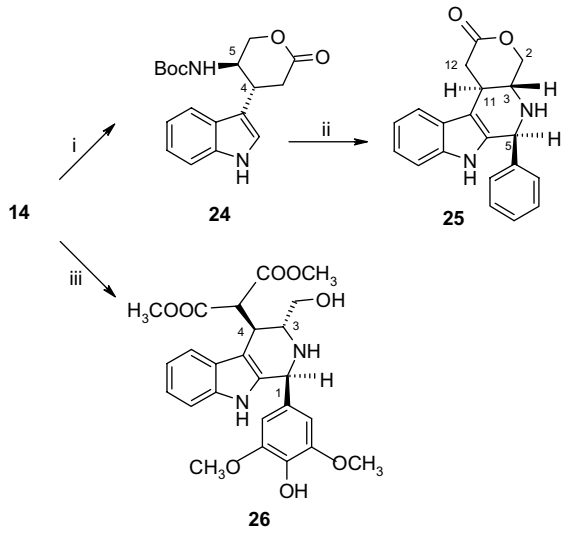


Scheme 5. Reagents and conditions: (i) TBDMSCl, imidazole, DMF, 80%; (ii) KOH aq, 87%; (iii) (a) DPPA, Et_3N, CH_3CN, 0 °C, (b) Δ, THF, (c) BnOH, THF, Δ, 80%; (iv) Pd–C, H_2, EtOAc, 97%; (v) (a) PhCHO, dry $MgSO_4$, (b) TFA, toluene, Δ, 67% (**23a**), 17% (**23b**).

21 by diphenylphosphoryl azide assisted acyl azide formation, followed by a Curtius rearrangement in the presence of benzyl alcohol. Deprotection of **21** by hydrogenolysis led almost quantitatively to pyrrolidinone tryptamine **22**.

Pictet–Spengler cyclisation of **22** with benzaldehyde under thermodynamic conditions provided 1,3,4-trisubstituted tetrahydro-β-carboline **23a** in 67% yield, along with some C-5 epimer **23b** (17%). Investigation of the stereochemical outcome by detailed NMR experiments (e.g., $J_{\text{H-3/H-11}} = 6.5$ and 7.0 Hz for **23a** and **23b**, respectively) confirmed the supposed C-3 epimerisation during the thermally induced Pictet–Spengler cyclisation.[20] Thus, the all-*cis* nature of H-5, H-3, H-11 and H-12 protons in **23a** was established by long-range COSY and NOESY experiments. In **23b** the absence of a correlation between H-5 and H-3, H-11 indicated that the minor compound **23b** had an opposite C-5 absolute configuration. Additionally, Bailey and Cook's empirical observations[19] were in accordance with the relative *cis* in **23a** and *trans* in **23b**, configurations concerning the H-5 and H-3 protons.

Treatment of trimolecular condensation product **14** with 70% aqueous acetic acid at room temperature provided pyrane-fused tryptamine **24** (82%), as a result of selective isopropylidene deprotection, followed by internal ring opening of the Meldrum's acid appendage and decarboxylation (Scheme 6). The *trans* relative configuration of H-4 ($\delta = 3.63$ ppm) and H-5 ($\delta = 4.27$ ppm) protons (pyranone numbering) in **24** was supported by the observed large coupling constant ($J = 8.9$ Hz). Pyranone-annulated tetrahydro-β-carboline **25** was prepared in 49% yield by stirring a solution of **24** with benzaldehyde in the presence of the desiccating agent ($MgSO_4$) and TFA at room temperature. The stereochemistry of **25** was determined by combined NMR methods. NOESY experiments showed correlation between H-5 and H-11 protons in accord with their *cis* relative configuration. No correlation was observed between H-5 and H-3.



Scheme 6. Reagents and conditions: (i) AcOH aq, rt, 82%; (ii) (a) PhCHO, CH_2Cl_2, dry $MgSO_4$, (b) TFA, rt, 49%; (iii) (a) HCl–MeOH, CH_2Cl_2, rt, (b) syringaldehyde, CH_2Cl_2, Δ, 65%.

Owing to the overlapping of angular protons ($\delta = 3.91$ ppm) the *trans* C/D ring junction was determined by couplings measured between H-3 and H-11, and neighbouring methylene protons H-2 and H-12, respectively. Geminal protons H-2 were observed as two doublets at $\delta = 4.51$ and 4.73 ppm, the upfield one with two large coupling constants ($J_{\text{H-2a/H-2b}} = 10.9$ Hz and $J_{\text{H-2b/H-3}} = 10.9$ Hz), supporting H-3/H-2a *trans* diaxial position. Similarly, *trans* diaxial arrangement was observed between H-11 and H-12a ($\delta = 2.61$ ppm, $J_{\text{H-12a/H-11}} = 12.9$ Hz) protons. Equatorial position of H-12b was evidenced by a smaller $J_{\text{H-12b/H-11}} = 5.3$ Hz coupling constant.

As a preliminary result, a new type of tetrahydro-β-carboline derivative **26** was obtained (65%) when the trimolecular adduct **14** was treated with a saturated HCl–MeOH solution at room temperature and the intermediate subsequently refluxed with syringaldehyde. The formation of **26** can be explained by a multistep process involving complete deprotection, methanolysis of the Meldrum's acid moiety and final Pictet–Spengler cyclisation. In fact, the 3,5-dimethoxy-4-hydroxyphenyl appendage is commonly found in polycyclic compounds of biological interest and chiral 1,2-aminoalcohol moiety with neighbouring malonester function could be considered as anchoring points for further heterocyclisation. The stereochemistry of the C-1 carbon of **26** was established to be (*S*) owing to the correlation between the H-1 and H-4 protons in the COSY and NOESY spectra.

3. Conclusion

In summary, a diastereoselective synthesis using the Yonemitsu-type trimolecular condensation as key step has been developed for the preparation of 3,4-furanone-, pyrrolidinone- and pyranone-annulated tetrahydro-β-carbolines of biological interest. We have shown that the chirality of D-glyceraldehyde or that of the Garner's aldehyde ensured a high and predictable enantiocontrol of the additional newly created stereocentres. Application of this strategy using multifunctional chiral aldehydes to the synthesis of polycyclic compounds is in progress.

4. Experimental

General: Melting points were determined on a Reichert Thermovar hot-stage apparatus and are uncorrected. IR spectra were measured with a BOMEM FTIR instrument. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker AC 300 spectrometer using TMS as internal standard. All mass spectrometric measurements were run on VG Autospec apparatus. Optical rotations were measured in a 10 cm pathlength cell at 21 °C using a Perkin–Elmer 241 polarimeter. Reactions were monitored using Merck precoated plates (Kieselgel 60 F_{254}). Column chromatography was

performed on SDS Chromagel (silica gel 35–70 or 70–200 μm) support.

4.1. (*S*,*S*)-5-[(2,2-Dimethyl-1,3-dioxolan-4-yl)-(1*H*-indol-3-yl)-methyl]-2,2-dimethyl-1,3-dioxan-4,6-dione, 4

To a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde **2** (502 mg, 3.86 mmol) in acetonitrile (50 mL) were added successively indole **1** (226 mg, 1.93 mmol), Meldrum's acid **3** (278 mg, 1.93 mmol) and D,L-proline (11 mg, 0.096 mmol). The reaction mixture was stirred at room temperature under N_2 for 36 h, the solvent was evaporated and the residue was purified by column chromatography (hexane–ethyl acetate 8:2) to afford **4** (550 mg, 76%), as a yellowish solid. Mp: 65 °C (hexane); $[\alpha]_D = -33.2$ (*c* 1.22, $CHCl_3$); IR (KBr) $\nu = 3408$, 2988, 1773 and 1740 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.09$ (s, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.61 (s, 3H), 3.68 (d, 1H, $J = 2.8$ Hz), 3.99 (dd, 1H, $J = 8.1$, 7.0 Hz), 4.26 (dd, 1H, $J = 8.1$, 5.9 Hz), 4.35 (dd, 1H, $J = 9.0$, 2.8 Hz), 5.08 (ddd, 1H, $J = 9.0$, 7.0, 5.9 Hz), 7.11–7.16 (m, 3H), 7.25 (d, 1H, $J = 6.0$ Hz), 7.66 (d, 1H, $J = 6.0$ Hz), 8.32 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 25.7$, 26.8, 27.9, 28.2, 40.1, 48.9, 68.0, 77.1, 105.6, 109.7, 111.1, 111.8, 119.1, 120.0, 122.3, 123.8, 127.0, 135.5, 165.4, 165.5 ppm; MS (EI) *m*/*z* (%) = 373 ($M^{+\cdot}$, 12), 300 (4), 273 (8), 272 (7), 258 (7), 196 (6), 187 (8), 170 (100); HREIMS for $C_{20}H_{23}NO_6$ calcd: 373.1525. Found: 373.1549.

4.2. (*R*,*R*)-5-[(2,2-Dimethyl-1,3-dioxolan-4-yl)-(1*H*-indol-3-yl)-methyl]-2,2-dimethyl-1,3-dioxan-4,6-dione, *ent*-4

Yield: 66%. Mp: 65 °C (hexane); $[\alpha]_D = +34.8$ (*c* 1.27, $CHCl_3$); HREIMS for $C_{20}H_{23}NO_6$ calcd: 373.1525. Found: 373.1541.

4.3. (3*S*,4*S*,5*S*)-5-Hydroxymethyl-4-(1*H*-indol-3-yl)-2-oxotetrahydrofuran-3-carboxylic acid, 5

To a solution of **4** (767 mg, 2.06 mmol) in THF (12.5 mL), 10% HCl solution (7 mL) was added dropwise and the reaction mixture stirred at room temperature for 30 min. After evaporation of THF, the residue was partitioned between satd Na_2CO_3 solution (20 mL) and ethyl acetate (20 mL). The organic phase was extracted with satd $NaHCO_3$ solution (2×10 mL), the combined aqueous layers acidified with solid citric acid to pH = 5 and this acidic solution further extracted with ethyl acetate (3×15 mL). The combined organic layers were dried over Na_2SO_4, filtered, evaporated and the residue purified by column chromatography (hexane–ethyl acetate 1:1 with 0.5% acetic acid) and then crystallised in anhydrous diethyl ether to give acid **5** (520 mg, 92%). Mp: 87–88 °C (ether); $[\alpha]_D = +138.6$ (*c* 0.82, MeOH); IR (KBr) $\nu = 3410$, 2924, 1769, 1736 cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 3.49$ (dd, 1H, $J = 12.3$, 3.1 Hz), 3.70 (dd, 1H, $J = 12.3$, 2.6 Hz), 4.43 (d, 1H, $J = 12.2$ Hz), 4.71 (dd, 1H, $J = 12.2$, 8.1 Hz), 5.16 (m, 1H), 7.13 (m, 1H), 7.19 (m, 1H), 7.47 (s, 1H), 7.49 (d, 1H, $J = 7.8$ Hz), 7.75 (d, 1H, $J = 7.8$ Hz), 10.34 (br s, 1H) ppm; ^{13}C NMR (acetone-d_6): $\delta = 40.3$, 51.8, 61.3, 81.8, 109.8, 111.7, 118.6, 119.4, 122.0, 123.0, 127.6, 137.0, 169.4, 172.4 ppm; MS (FAB, magic bullet) *m*/*z* (%) = 298 ($M+Na^+$, 55), 276 ($M+H^+$, 100), 275 ($M^{+\cdot}$, 70); HRMS (FAB, magic bullet) for $C_{14}H_{13}NO_5$ calcd: 275.0794. Found: 275.0800.

4.4. (3*R*,4*R*,5*R*)-5-Hydroxymethyl-4-(1*H*-indol-3-yl)-2-oxotetrahydrofuran-3-carboxylic acid, *ent*-5

Yield: 91%. Mp: 86–87 °C (ether); $[\alpha]_D = -137.1$ (*c* 0.84, MeOH); HRMS (FAB, magic bullet) for $C_{14}H_{13}NO_5$ calcd: 275.0794. Found: 275.0781.

4.5. (3*S*,4*S*,5*S*)-5-(*tert*-Butyldimethylsilanyloxymethyl)-4-(1*H*-indol-3-yl)-2-oxotetrahydrofuran-3-carboxylic acid, 6

To an ice-cooled solution of acid **5** (697 mg, 2.53 mmol) in dry DMF (2 mL) and dry CH_2Cl_2 (13 mL), imidazole (431 mg, 6.33 mmol) and *tert*-butyldimethylsilyl chloride (TBDMSCl) (955 mg, 6.34 mmol) were added and the reaction mixture stirred at room temperature under N_2 for 20 h. After quenching with methanol (1 mL), the solution was diluted with CH_2Cl_2 and washed with 10% HCl solution. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL); the combined organic phases were washed with water, dried over Na_2SO_4, evaporated and the residue was purified by column chromatography (heptane–ethyl acetate 7:3→1:1, 0.5% acetic acid) to provide **6** (886 mg, 90%) as a white amorphous solid. Mp: 63–64 °C (hexane); $[\alpha]_D = +115.9$ (*c* 0.96, $CHCl_3$); IR (film) $\nu = 3410$, 2955, 2930, 2859, 1771, 1723 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = -0.10$ (s, 3H), -0.04 (s, 3H), 0.85 (s, 9H), 3.43 (d, 1H, $J = 11.3$ Hz), 3.74 (dd, 1H, $J = 11.3$, 2.2 Hz), 4.34 (d, 1H, $J = 12.8$ Hz), 4.60 (dd, 1H, $J = 12.8$, 8.0 Hz), 4.98 (dd, 1H, $J = 8.0$, 2.2 Hz), 7.13–7.27 (m, 3H), 7.40 (d, 1H, $J = 8.0$ Hz), 7.52 (d, 1H, $J = 8.0$ Hz), 8.22 (br s, 1H), 9.37 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = -6.2$, -6.1, 17.9, 25.5, 39.9, 51.2, 62.0, 81.0, 109.3, 111.5, 118.0, 119.7, 122.2, 122.3, 126.4, 136.1, 172.1, 172.6 ppm; MS (FAB, magic bullet) *m*/*z* (%) = 412 ($M+Na^+$, 100); HRMS (FAB, magic bullet) for $C_{20}H_{27}NO_5NaSi$ $(M+Na)^+$ calcd: 412.1556. Found: 412.1565.

4.6. (3*R*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilanyloxymethyl)-4-(1*H*-indol-3-yl)-2-oxotetrahydrofuran-3-carboxylic acid, *ent*-6

Yield: 87%. Mp: 63–64 °C (hexane); $[\alpha]_D = -120.0$ (*c* 1.00, $CHCl_3$); HRMS (FAB, magic bullet) for $C_{20}H_{27}NO_5NaSi$ $(M+Na)^+$ calcd: 412.1556. Found: 412.1533.

4.7. (3*R*,4*R*,5*S*)-[5-(*tert*-Butyldimethylsilanyloxymethyl)-4-(1*H*-indol-3-yl)-2-oxotetrahydrofuran-3-yl]-carbamic acid benzyl ester, 7

To an ice-cooled solution of **6** (96 mg, 0.247 mmol) in acetonitrile (3 mL) were added triethylamine (52 μL, 0.371 mmol) and DPPA (108 μL, 0.499 mmol) under N_2 and the resulting mixture stirred for 3 h while being warmed to room temperature. After evaporation of the solvent the residue was purified by flash

chromatography (cyclohexane–ethyl acetate 1:1). The crude azide obtained was dissolved in dry toluene (3 mL) and the solution heated at 70 °C under N_2. After 1 h heating benzyl alcohol (31 μL, 0.300 mmol) was added via syringe and the heating prolonged for a further 20 h. After cooling the solvent was evaporated, and the residue purified by column chromatography (heptane–ethyl acetate 8:2→7:3) giving **7** as a white solid (77 mg, 63%). Mp: 78–79 °C (heptane); $[\alpha]_D = +96.2$ (*c* 0.68, $CHCl_3$); IR (film) $\nu = 3370, 2956, 2928, 2857, 1779, 1705, 1524\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = -0.04$ (s, 3H), −0.01 (s, 3H), 0.92 (s, 9H), 3.40 (d, 1H, $J = 11.4$ Hz), 3.73 (dd, 1H, $J = 11.4$, 1.6 Hz), 4.14 (dd, 1H, $J = 12.0$, 8.3 Hz), 4.93 (d, 1H, $J = 8.3$ Hz), 5.00 (AB system, 1H, $J = 12.4$ Hz), 5.05 (AB system, 1H, $J = 12.4$ Hz), 5.49 (dd, 1H, $J = 12.0$, 9.4 Hz), 5.67 (d, 1H, $J = 9.4$ Hz), 7.17–7.54 (m, 10H), 8.73 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = -6.0$, −5.9, 18.1, 25.7, 42.7, 53.8, 62.0, 67.2, 79.5, 109.2, 111.6, 118.0, 119.9, 122.4, 123.2, 127.1, 127.9, 128.1, 128.4, 135.9, 136.3, 156.4, 175.1 ppm; MS (EI) *m/z* (%) = 494 ($M^{+\cdot}$, 18), 437 (10), 409 (8), 393 (9), 319 (13), 286 (92), 275 (17), 156 (22), 130 (57), 117 (100); HREIMS for $C_{27}H_{34}N_2O_5Si$ calcd: 494.2237. Found: 494.2226.

4.8. (3*S*,4*S*,5*R*)-[5-(*tert*-Butyldimethylsilanyloxymethyl)-4-(1*H*-indol-3-yl)-2-oxotetrahydrofuran-3-yl]-carbamic acid benzyl ester, *ent*-7

Yield: 70%. Mp: 77–78 °C (heptane); $[\alpha]_D = -95.8$ (*c* 0.68, $CHCl_3$); HREIMS for $C_{27}H_{34}N_2O_5Si$ calcd: 494.2237. Found: 494.2195.

4.9. (3*R*,4*R*,5*S*)-(3-Amino-5-(*tert*-butyldimethylsilanyloxymethyl)-4-(1*H*-indol-3-yl))-dihydrofuran-2-one, 8

A solution of **7** (172 mg, 0.348 mmol) and triethylamine (three drops) in ethyl acetate (5 mL) was hydrogenated over 10% Pd–C (25 mg) for 24 h. The catalyst was removed by filtration, the filtrate evaporated and the residue purified by chromatography (ethyl acetate–heptane 1:1→6:4 with 0.5% Et_3N) to yield **8** (100 mg, 80%), as a white solid. Mp: 185–187 °C (heptane); $[\alpha]_D = +136.4$ (*c* 0.68, CH_2Cl_2); IR (film) $\nu = 3378, 2930, 2859, 1773, 1644\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = -0.08$ (s, 3H), −0.04 (s, 3H), 0.84 (s, 9H), 1.86 (br, 2H), 3.42 (dd, 1H, $J = 11.6$, 1.5 Hz), 3.71 (dd, 1H, $J = 11.6$, 2.7 Hz), 3.89 (dd, 1H, $J = 12.0$, 8.3 Hz), 4.38 (d, 1H, $J = 12.0$ Hz), 4.81 (m, 1H), 7.12–7.26 (m, 3H) 7.40 (d, 1H, $J = 7.9$ Hz), 7.53 (d, 1H, $J = 7.9$ Hz), 8.47 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = -5.9$, 18.1, 25.8, 44.7, 54.6, 61.9, 79.6, 110.2, 111.5, 118.1, 119.8, 122.0, 122.5, 127.3, 136.3, 178.7 ppm; MS (EI) *m/z* (%) = 360 ($M^{+\cdot}$, 1), 275 (56), 230 (12), 183 (18), 159 (42), 130 (38), 117 (100); HREIMS for $C_{19}H_{28}N_2O_3Si$ calcd: 360.1869. Found: 360.1889.

4.10. (3*R*,4*R*,5*S*)-(5-Hydroxymethyl-4-(1*H*-indol-3-yl)-2-oxotetrahydrofuran-3-yl)-carbamic acid benzylester, 9

A solution of **7** (111 mg, 0.225 mmol) in a mixture of acetic acid (4 mL), water (1.5 mL) and THF (1.5 mL) was heated to 60 °C for 20 h. After cooling, the solvents were evaporated and the residue purified by column chromatography (ethyl acetate–heptane 1:1→6:4) to afford **9** (83 mg, 97%), as a white solid. Mp: 87–88 °C (heptane); $[\alpha]_D = +86.3$ (*c* 0.76, CH_2Cl_2); IR (film) $\nu = 3434, 3368, 3320, 2926, 1775, 1701, 1528\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 2.95$ (br s, 1H) 3.33 (d, 1H, $J = 12.1$ Hz), 3.56 (d, 1H, $J = 12.1$ Hz), 4.26 (dd, 1H, $J = 12.4$, 8.3 Hz), 4.86 (d, 1H, $J = 8.3$ Hz), 4.93 (s, 2H), 5.26 (dd, 1H, $J = 12.4$, 9.1 Hz), 5.76 (d, 1H, $J = 9.1$ Hz), 7.06–7.44 (m, 10H), 8.62 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 41.1$, 54.1, 61.4, 67.4, 80.4, 108.9, 111.8, 118.0, 119.9, 122.5, 123.1, 127.1, 127.9, 128.1, 128.4, 135.7, 136.3, 156.5, 175.7 ppm; MS (EI) *m/z* (%) = 380 ($M^{+\cdot}$, 27), 272 (26), 229 (75), 198 (25), 184 (15), 173 (61), 156 (32), 144 (27), 130 (100), 117 (63); HREIMS for $C_{21}H_{20}N_2O_5$ calcd: 380.1372. Found: 380.1388.

4.11. (3*S*,4*S*,5*R*)-(5-Hydroxymethyl-4-(1*H*-indol-3-yl)-2-oxotetrahydrofuran-3-yl)-carbamic acid benzyl ester, *ent*-9

Yield: 97%. Mp: 86–87 °C (heptane); $[\alpha]_D = -88.6$ (*c* 0.77, CH_2Cl_2); HREIMS for $C_{21}H_{20}N_2O_5$ calcd: 380.1372. Found: 380.1361.

4.12. (3*R*,4*R*,5*S*)-(3-Amino-4-(1*H*-indol-3-yl)-5-hydroxymethyl)-dihydrofuran-2-one, 10

A solution of **9** (136 mg, 0.358 mmol) and triethylamine (three drops) in methanol (7 mL) was hydrogenated over 10% Pd–C (30 mg) for 2.5 h. The catalyst was filtered on a Celite pad and the filtrate purified by column chromatography (toluene–methanol 9:1→8:2 with 0.2% Et_3N) to give **10** (70 mg, 80%), as a white solid. Mp: 170–172 °C; $[\alpha]_D = +186.1$ (*c* 0.63, MeOH); IR (KBr) $\nu = 3431, 3397, 3368, 3053, 2928, 2866, 1769, 1622\ cm^{-1}$; ^1H NMR (CD_3OD): $\delta = 3.35$ (dd, 1H, $J = 12.1$, 3.4 Hz), 3.53 (dd, 1H, J = 12.1, 2.6 Hz), 4.06 (dd, 1H, $J = 12.4$, 8.4 Hz,), 4.51 (d, 1H, $J = 12.4$ Hz), 4.95 (m, 1H), 7.05 (dt, 1H, $J = 7.5$, 1.1 Hz), 7.14 (dt, 1H, $J = 7.5$, 1.1 Hz), 7.38 (s, 1H), 7.42 (d, 1H, $J = 8.0$ Hz), 7.58 (d, 1H, $J = 8.0$ Hz) ppm; ^{13}C NMR (CD_3OD) = 44.6, 54.7, 61.8, 82.4, 109.6, 112.6, 119.0, 120.3, 122.9, 123.9, 128.7, 138.2, 179.2 ppm; MS (EI) *m/z* (%) = 246 ($M^{+\cdot}$, 18), 173 (78), 158 (18), 144 (27), 130 (100), 117 (70); HREIMS for $C_{13}H_{14}N_2O_3$ calcd: 246.1004. Found: 246.0996.

4.13. (3*S*,4*S*,5*R*)-(3-Amino-4-(1*H*-indol-3-yl)-5-hydroxymethyl)-dihydrofuran-2-one, *ent*-10

Yield: 65%. Mp: 168–170 °C (heptane); $[\alpha]_D = -185.5$ (*c* 0.59, MeOH); HREIMS for $C_{13}H_{14}N_2O_3$ calcd: 246.1004. Found: 246.0981.

4.14. (3*S*,5*R*,11*R*,12*S*)-12-Hydroxymethyl-5-phenyl-3,4,5,11-tetrahydrofuro[3,4-*c*]-β-carboline-2(12*H*)-one, 11, and (3*S*,5*S*,11*R*,12*S*)-12-hydroxymethyl-5-phenyl-3,4,5,11-tetrahydrofuro[3,4-*c*]-β-carboline-2(12*H*)-one, 12

A solution of **10** (31.0 mg, 0.126 mmol) and benzaldehyde (19 μL, 0.188 mmol) in methanol (3 mL) was

heated to reflux under N_2 for 1.5 h. After cooling, the solvent was evaporated and the residue co-evaporated with dry benzene. The resulting yellow solid was dissolved in dry benzene (7 mL) and to this solution, molecular sieves (4 Å) and TFA (19 μL, 0.245 mmol) added and the mixture stirred and heated to reflux under N_2 for 3 h. The cooled solution was washed with satd K_2CO_3 solution (10 mL). The aqueous phase was extracted with ethyl acetate (7 mL) and the combined organic layers dried over Na_2SO_4, filtered and purified by column chromatography (toluene–ethyl acetate 8:2→7:3 with 0.5% of Et_3N) to afford the (5*S*)-isomer **12** (13.2 mg, 31%), as a white solid. Mp: 250–252 °C (hexane–CH_2Cl_2); $[\alpha]_D = +105.3$ (*c* 0.26, acetone); IR (KBr) $\nu = 3449$, 3416, 3391, 3312, 3265, 2861, 1780, 1456 cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 2.85$ (s, 1H), 3.61 (m, 2H), 4.02 (d, 1H, $J = 7.3$ Hz), 4.19 (ddd, 1H, $J = 8.6$, 7.3, 1.4 Hz), 5.30 (d, 1H, $J = 1.4$ Hz), 5.36 (dt, 1H, $J = 8.6$, 3.4 Hz), 7.07 (m, 2H), 7.29–7.45 (m, 6H) 7.57 (dd, 1H, $J = 6.8$, 2.0 Hz), 9.76 (br s, 1H) ppm; ^{13}C NMR (acetone-d_6): $\delta = 36.2$, 54.8, 57.6, 60.8, 82.4, 103.8, 111.3, 117.8, 119.3, 121.4, 126.5, 128.1, 128.4, 128.8, 136.1, 136.6, 140.0, 174.4 ppm; MS (EI) *m*/*z* (%) = 335 ($(M+1)^+$, 23), 334 ($M^{+\cdot}$, 100), 333 (35), 259 (32), 257 (45), 245 (44), 220 (39), 219 (60), 169 (77); HREIMS for $C_{20}H_{18}N_2O_3$ calcd: 334.1317. Found: 334.1289.

Continuing the chromatography with toluene–ethyl acetate 1:1 then heptane–acetone 1:1 (both containing 0.5% Et_3N) the more polar isomer **11** [(5*R*)-isomer] (10.2 mg, 24%) was collected. Mp: 111–112 °C (hexane–CH_2Cl_2); $[\alpha]_D = +98.0$ (*c* 0.20, acetone); IR (KBr) $\nu = 3433$, 3389, 3319, 3281, 2924, 2854, 1768, 1454 cm^{-1}; ^1H NMR (acetone-d_6) $\delta = 2.88$ (br s, 1H), 3.48 (dd, 1H, $J = 12.1$, 4.4 Hz), 3.80 (dd, 1H, $J = 12.1$, 3.7 Hz), 3.95 (d, 1H, $J = 7.1$ Hz), 4.23 (dd, 1H, $J = 7.1$, 7.0 Hz), 5.18 (ddd, 1H, $J = 7.0$, 4.4, 3.4 Hz), 5.33 (s, 1H), 7.09 (m, 2H), 7.25–7.37 (m, 6H), 7.68 (dd, 1H, $J = 6.7$, 1.6 Hz), 9.97 (br s, 1H) ppm; ^{13}C NMR (acetone-d_6): $\delta = 37.1$, 53.1, 55.2, 62.2, 83.5, 105.2, 112.3, 119.5, 120.2, 122.5, 127.8, 128.8, 129.3, 136.8, 137.5, 141.7, 176.3 ppm; MS (EI) *m*/*z* (%) = 335 ($(M+1)^+$, 17), 334 ($M^{+\cdot}$, 68), 333 (15), 316 (52), 257 (36), 245 (100), 244 (90), 243 (50), 219 (47), 218 (45), 169 (77), 168 (57), 149 (67); HREIMS for $C_{20}H_{18}N_2O_3$ calcd: 334.1317. Found: 334.1348.

4.15. (*R*,*R*)-4-[(2,2-Dimethyl-4,6-dioxo-1,3-dioxane-5-yl)-(1*H*-indol-3-yl)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester, 14

Meldrum's acid **3** (524 mg, 3.64 mmol) and a catalytic amount of D,L-proline were added to a solution of Garner's aldehyde **13** (1.00 g, 4.37 mmol) in acetonitrile (15 mL) with molecular sieves (4 Å). After 30 min stirring, indole **1** (426 mg, 3.64 mmol) was added to the reaction mixture and stirring continued overnight. After removal of the solvent under reduced pressure the residue was purified by chromatography (CH_2Cl_2 then cyclohexane–ethyl acetate 6:4) to give **14** (1.55 g, 90%), a quite unstable foam. $[\alpha]_D = -1.31$ (*c* 3.66, CH_2Cl_2); IR (film) $\nu = 3400$, 3358, 2982, 1745, 1682, 1458 cm^{-1}; ^1H NMR (C_6D_6, 343 K): $\delta = 1.20$ (s, 3H), 1.47 (s, 3H), 1.71 (s, 9H), 1.83 (s, 3H), 2.05 (s, 3H), 4.17 (dd, 1H, $J = 9.3$, 6.3 Hz), 4.46 (s, 1H), 4.98 (br s, 1H), 5.12 (br s, 1H), 5.34 (br d, 1H, $J = 4.0$ Hz), 7.38–7.52 (m, 4H), 7.86 (br s, 1H), 8.32 (d, 1H, $J = 5.2$ Hz) ppm; ^{13}C NMR (C_6D_6, 343 K): $\delta = 27.3$, 28.0, 28.2, 28.3, 28.5, 39.6, 48.7, 61.0, 66.2, 80.2, 94.5, 104.6, 111.3, 112.3, 119.7, 120.2, 122.4, 125.3, 128.6, 135.9, 153.2, 165.4, 166.3 ppm; MS (FAB, gly) *m*/*z* (%) = 474 ($(M+H)^+$, 6), 473 ($M^{+\cdot}$, 21), 472 (7), 414 (9), 359 (30), 301 (43), 273 (27), 245 (35), 200 (29), 187 (32), 185 (24), 170 (100).

4.16. (3*R*,4*R*,5*R*)-5-*tert*-Butoxycarbonylamino-4-(1*H*-indol-3-yl)-2-oxo-tetrahydropyran-3-carboxylic acid methyl ester, 15

A solution of **14** (404 mg, 0.85 mmol) and *p*-TsOH (10 mg, 0.05 mmol) in methanol (10 mL) was stirred at room temperature for 1 h 15 min. Then freshly prepared ethereal diazomethane solution was added to the reaction mixture and allowed to stand at 0–5 °C for 30 min. The solvents were removed under reduced pressure and the residue heated under reflux in CH_2Cl_2 (10 mL) in the presence of *p*-TsOH (10 mg) for 6 h. The solvent was evaporated and the crude product purified by chromatography (cyclohexane–ethyl acetate 1:1), crystallised in hexane–CH_2Cl_2 to give **15** (283 mg, 86%), as white crystals. Mp: 147–149 °C (hexane–CH_2Cl_2); $[\alpha]_D = -18.6$ (*c* 1.00, $CHCl_3$); IR (film) $\nu = 3397$, 2928, 1753–1697, 1520, 1460 cm^{-1}; ^1H NMR (acetone-d_6): $\delta = 1.26$ (s, 9H), 3.51 (s, 3H), 3.95 (dd, 1H, $J = 11.6$, 8.6 Hz), 4.22 (d, 1H, $J = 11.6$ Hz), 4.30–4.38 (m, 2H), 4.63 (dd, 1H, $J = 10.8$, 3.8 Hz), 6.46 (d, 1H, $J = 7.2$ Hz), 7.03 (t, 1H, $J = 7.9$ Hz), 7.11 (t, 1H, $J = 7.9$ Hz), 7.31 (d, 1H, $J = 2.3$ Hz), 7.39 (d, 1H, $J = 7.9$ Hz), 7.70 (d, 1H, $J = 7.9$ Hz), 10.23 (br s, 1H) ppm; ^{13}C NMR (acetone-d_6): $\delta = 27.7$, 38.4, 50.5, 51.9, 53.8, 70.6, 78.6, 111.8, 113.6, 119.1, 119.2, 121.8, 123.0, 126.7, 137.1, 155.5, 167.4, 168.7 ppm; MS (EI) *m*/*z* (%) = 388 ($M^{+\cdot}$, 5), 332 (12), 271 (63), 213 (45), 212 (100), 201 (46), 170 (81); HREIMS for $C_{20}H_{24}N_2O_6$ calcd: 388.1634. Found: 388.1627.

4.17. (3*S*,4*R*,5*R*)-5-Hydroxymethyl-4-(1*H*-indol-3-yl)-2-oxo-pyrrolidine-3-carboxylic acid methyl ester, 16

From **14**: To a solution of HCl–MeOH (10 mL) was added dropwise at 0 °C a solution of **14** (200 mg, 0.47 mmol) in MeOH (4 mL). Stirring was continued at 0 °C for 1 h 30 min, then the solvent was evaporated. The residue was treated with triethylamine at 0 °C (pH >8) and evaporated again. The solid residue was purified by flash chromatography (toluene–ethyl acetate–methanol 6:3:1) affording **16** (96 mg, 71%), as white crystals.

From **15**: To a solution of **15** (126 mg, 0.325 mmol) in CH_2Cl_2 (5 mL) TFA (0.40 mL, 5.4 mmol) was added and the reaction mixture stirred at room temperature for 2.5 h. After evaporation to dryness, triethylamine (five drops) was added, evaporated again under reduced pressure and the residue purified by flash chromatography (toluene–ethyl acetate–methanol 6:3:1) to afford **16** (89 mg, 97%), as white crystals.

From **18**: A solution of **18** (1.04 g, 2.06 mmol) in ethanol (25 mL) and acetic acid (five drops) was hydrogenated over 10% Pd–C (100 mg) at room temperature for 20 h. The catalyst was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in methanol (12 mL), treated with an excess of freshly prepared ethereal diazomethane solution and allowed to stand at 0 °C for 30 min. After evaporation of the solvents, the residue was purified by chromatography giving **16** (375 mg, 63%), as a white solid. Mp: 206–207 °C (MeOH–ether); $[\alpha]_D = -226$ (*c* 0.60, MeOH); IR (KBr) $\nu = 3366, 1730, 1701, 1456, 1431\ cm^{-1}$; ^1H NMR (DMSO-d_6): $\delta = 3.05$ (m, 2H), 3.63 (s, 3H), 3.96 (m, 1H), 4.05 (d, 1H, $J = 12.0$ Hz), 4.30 (dd, 1H, $J = 12.0$, 7.9 Hz), 4.58 (t, 1H, $J = 4.7$ Hz), 7.01 (t, 1H, $J = 7.8$ Hz), 7.11 (t, 1H, $J = 7.8$ Hz), 7.23 (d, 1H, $J = 1.5$ Hz), 7.37 (d, 1H, $J = 7.8$ Hz), 7.63 (d, 1H, $J = 7.8$ Hz), 8.27 (s, 1H), 10.99 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 38.9, 52.1, 52.3, 56.3, 61.8, 110.3, 111.5, 118.5, 118.7, 121.3, 122.8, 126.9, 136.3, 170.9, 171.9$ ppm; MS (EI) *m*/*z* (%) = 289 ($(M+H)^+$, 12), 288 ($M^{+\cdot}$, 43), 257 (25), 229 (100), 201 (80), 197 (27), 170 (73); HREIMS for $C_{15}H_{16}N_2O_4$ calcd: 288.1110. Found: 288.1127.

4.18. (*R*,*R*)-4-[(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-(1*H*-indol-3-yl)-methyl]-2,2-dimethyl-oxazolidine-3-carboxylic acid benzyl ester, 18

To a −78 °C cooled solution of ester **17** (1.06 g, 3.60 mmol) in dry toluene (12 mL), a 1.5 M DIBAL solution in toluene (3.60 mL, 5.40 mmol) was added via syringe over a period of 50 min. Stirring continued at −78 °C for 30 min, after which the cold solution was quenched by the dropwise addition of methanol (1.60 mL). The resulting mixture was poured into an ice-cold 1 M HCl solution (20 mL). The two phases were separated, and the aqueous phase extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with satd $NaHCO_3$ solution and brine, dried (Na_2SO_4) and evaporated to afford the crude aldehyde (1.10 g).

To the solution of the latter in acetonitrile (20 mL) were added indole **1** (420 mg, 3.60 mmol), Meldrum's acid **3** (518 mg, 3.60 mmol) and D,L-proline (40 mg, 0.35 mmol) and the reaction mixture stirred at room temperature under N_2 for 15 h. After evaporation of the solvent the residue was purified by column chromatography (CH_2Cl_2 then cyclohexane–acetone 8:2→7:3) to give **18** (1.04 g, 57% for two steps), as an amorphous, unstable solid. Mp: 74–75 °C (ether); $[\alpha]_D = +11.0$ (*c* 3.14, CH_2Cl_2); IR (film) $\nu = 3412, 3344, 1774, 1741, 1695, 1458, 1404\ cm^{-1}$; ^1H NMR (C_6D_6, 343 K): $\delta = 1.13$ (s, 3H), 1.42 (s, 3H), 1.81 (s, 3H), 2.06 (s, 3H), 4.11 (dd, 1H, $J = 9.4$, 6.0 Hz), 4.34 (dd, 1H, $J = 2.3$ Hz), 4.93 (d, 1H, $J = 9.4$ Hz), 5.17 (m, 1H), 5.25 (AB system, 1H, $J = 12.3$ Hz), 5.31 (dd, 1H, $J = 6.4$, 2.3 Hz), 5.43 (AB system, 1H, $J = 12.3$ Hz), 7.31–7.55 (m, 10H), 8.16 (d, 1H, $J = 7.7$ Hz) ppm; MS (FAB, NBA) *m*/*z* (%) = 507 ($(M+H)^+$, 10), 506 ($M^{+\cdot}$, 9) 449 (8), 448 (5), 170 (100); HRMS (FAB, NBA) for $C_{28}H_{30}N_2O_7$ calcd: 506.2053. Found: 506.2075.

4.19. (3*S*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilanyloxymethyl)-4-(1*H*-indol-3-yl)-2-oxo-pyrrolidine-3-carboxylic acid methyl ester, 19

To an ice-cooled solution of **16** (474 mg, 1.65 mmol) in dry DMF (5 mL), imidazole (281 mg, 4.13 mmol) and TBDMSCl (298 mg, 1.98 mmol) were added. The reaction mixture was allowed to stir overnight and then a second batch of TBDMSCl (298 mg) was added. After 24 h the mixture was diluted with ethyl acetate (20 mL), extracted with water (10 mL) and satd NH_4Cl solution (3 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, evaporated and the crude product was purified by chromatography (cyclohexane–ethyl acetate 1:1) to give **19** (529 mg, 80%), as a white solid. Mp: 154 °C; $[\alpha]_D = -166.3$ (*c* 0.80, $CHCl_3$); IR (film) $\nu = 3375, 3340, 3279, 2920, 1740, 1698, 1468, 1435\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = -0.13$ (s, 3H), −0.10 (s, 3H), 0.81 (s, 9H), 3.26 (dd, 1H, $J = 10.6$, 5.8 Hz), 3.34 (dd, 1H, $J = 10.6$, 3.1 Hz), 3.74 (s, 3H), 3.97 (d, 1H, $J = 10.8$ Hz), 4.12 (m, 1H), 4.53 (dd, 1H, $J = 10.8$, 7.9 Hz), 6.16 (br s, 1H), 7.11–7.26 (m, 3H), 7.39 (d, 1H, $J = 8.0$ Hz), 7.57 (d, 1H, $J = 7.7$ Hz), 8.25 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = -5.7, 18.0, 25.8, 38.7, 52.6, 52.7, 57.0, 63.5, 111.4, 111.5, 118.6, 120.0, 121.9, 122.6, 126.9, 136.4, 170.1, 172.5$ ppm; MS (EI) *m*/*z* (%) = 403 ($(M+H)^+$, 8), 402 ($M^{+\cdot}$, 2), 388 (2), 372 (2), 346 (82), 313 (23), 283 (15), 202 (23), 197 (21), 196 (37), 170 (59), 144 (24), 130 (100); HREIMS for $C_{21}H_{30}N_2O_4Si$ calcd: 402.1975. Found: 402.1939.

4.20. (3*S*,4*R*,5*R*)-[5-(*tert*-Butyldimethylsilanyloxymethyl)-4-(1*H*-indol-3-yl)-2-oxo-pyrrolidin-3-yl]-carbamic acid benzyl ester, 21

To an ice-cooled solution of **19** (427 mg, 1.06 mmol) in THF (25 mL) were added 1.8 mL and 1 h later 1.8 mL 0.6 M KOH solution (2.16 mmol) and the reaction mixture stirred for 5 h. A third portion of 1.8 mL 0.6 M KOH (1.08 mmol) was added and the stirring continued at room temperature overnight. The mixture was treated with 5% citric acid solution (3 mL). The organic solvent was removed by evaporation, with the remaining aqueous solution acidified by the addition of 5% citric acid solution (10 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over Na_2SO_4, concentrated and the crude product purified by flash chromatography (ethyl acetate–acetic acid 98:2) to give acid **20** (350 mg, 87%), as a white foam. $[\alpha]_D = -201.9$ (*c* 0.52, $CHCl_3$); IR (film) $\nu = 3379, 2930, 2859, 1722, 1697, 1427\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = -0.17$ (s, 3H), −0.14 (s, 3H), 0.79 (s, 9H), 3.26 (dd, 1H, $J = 10.8$, 5.2 Hz), 3.33 (dd, 1H, $J = 10.8$, 3.0 Hz), 3.97 (d, 1H, $J = 11.2$ Hz), 4.12 (m, 1H), 4.42 (dd, 1H, $J = 11.2$, 8.0 Hz), 6.67 (br s, 1H), 7.08 (d, 1H $J = 2.0$ Hz), 7.13 (dt, 1H, $J = 7.8$, 1.0 Hz), 7.22 (dt, 1H, $J = 7.8$, 1.0 Hz), 7.38 (d, 1H, $J = 7.8$ Hz), 7.52 (d, 1H, $J = 7.8$ Hz), 8.20 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = -5.9, -5.8, 17.9, 25.7, 38.5, 52.0, 57.4, 63.1, 110.9, 111.6, 118.4, 119.6, 122.2, 122.4, 126.9, 136.4, 171.9, 174.7$ ppm.

To a solution of **20** (150 mg, 0.387 mmol) in acetonitrile (10 mL) were added DPPA (0.17 mL, 0.78 mmol) and triethylamine (82 μL, 0.58 mmol) at 0 °C. The mixture was stirred and allowed to warm up to room temperature (2.5 h). The solvent was carefully evaporated and the residue was rapidly purified by flash chromatography (cyclohexane–ethyl acetate 1:1) providing acyl azide, which was dissolved in dry THF (5 mL) and refluxed under N_2 for 1 h. Benzyl alcohol (81 μL, 0.78 mmol) was added via syringe to the hot reaction mixture and the heating was continued under N_2 for 24 h. The solvents were then evaporated and the crude product was purified by chromatography (cyclohexane–ethyl acetate 1:1) and crystallised from ethyl acetate to give **21** (154 mg, 80%), as a white solid. Mp: 144–148 °C (ethyl acetate); $[\alpha]_D = -147.0$ (*c* 0.60, $CHCl_3$); IR (film) $\nu = 3285, 2928, 2856, 1705, 1530, 1460\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = -0.13$ (s, 3H), −0.11 (s, 3H), 0.82 (s, 9H), 3.29 (m, 2H), 3.91 (dd, 1H, $J = 9.9$, 9.6 Hz), 3.99 (m, 1H), 5.03 (s, 2H), 5.09 (m, 1H), 5.44 (d, 1H, $J = 9.9$ Hz), 6.62 (br s, 1H), 7.09–7.27 (m, 7H), 7.37–7.50 (m, 3H), 8.43 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = -5.8$, −5.7, 18.0, 25.7, 42.6, 54.4, 55.4, 63.0, 67.0, 110.1, 111.5, 118.2, 119.6, 122.2, 123.2, 127.3, 127.9, 128.0, 128.4, 136.0, 136.4, 156.8, 175.4 ppm; MS (EI) *m/z* (%) = 493 ($M^{+\cdot}$, 1), 436 (1), 402 (1), 329 (25), 328 (100), 286 (20), 285 (83), 211 (20), 184 (30), 170 (35); HREIMS for $C_{27}H_{35}N_3O_4Si$ calcd: 493.2397. Found: 493.2378.

4.21. (3*S*,4*S*,5*R*)-[3-Amino-5-(*tert*-butyldimethylsilanyloxymethyl)-4-(1*H*-indol-3-yl)]-pyrrolidin-2-one, 22

Carbamate **21** (120 mg, 0.243 mmol) dissolved in ethyl acetate (7 mL) was hydrogenated over 10% Pd–C (25 mg) catalyst at room temperature for 31 h. After filtration of the catalyst and evaporation of the solvent the residue was purified by chromatography (CH_2Cl_2–MeOH 9:1) to afford amine **22** (85 mg, 97%), as an amorphous solid. $[\alpha]_D = -211$ (*c* 0.89, $CHCl_3$); IR (film) $\nu = 3273, 2933, 2854, 1703, 1460\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = -0.13$ (s, 3H), −0.12 (s, 3H), 0.81 (s, 9H), 2.23 (br s, 2H), 3.26 (m, 2H), 3.70 (dd, 1H, $J = 11.1$, 8.0 Hz), 3.90 (m, 1H), 3.98 (d, 1H, $J = 11.1$ Hz), 6.58 (br s, 1H), 7.05–7.25 (m, 3H), 7.37 (d, 1H, $J = 7.9$ Hz), 7.51 (d, 1H, $J = 7.8$ Hz), 8.93 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = -5.7$, 17.8, 25.7, 43.9, 54.9, 55.8, 63.3, 110.6, 111.5, 118.2, 119.3, 122.0, 122.1, 127.3, 136.5, 178.3 ppm; MS (EI) *m/z* (%) = 360 ($(M+H)^+$, 10), 359 ($M^{+\cdot}$, 29), 303 (11), 302 (35), 287 (23), 285 (43), 257 (27), 230 (39), 227 (27), 170 (40); HREIMS for $C_{19}H_{29}N_3O_2Si$ calcd: 359.2029. Found: 359.2016.

4.22. (3*S*,5*R*,11*S*,12*R*)-12-Hydroxymethyl-5-phenyl-3,4,5,11-tetrahydropyrrolo[3,4-*c*]-β-carboline-2(12*H*)-one, 23a and (3*S*,5*S*,11*S*,12*R*)-12-hydroxymethyl-5-phenyl-3,4,5,11-tetrahydropyrrolo[3,4-*c*]-β-carboline-2(12*H*)-one, 23b

To a solution of **22** (75 mg, 0.228 mmol) in dry CH_2Cl_2 (4 mL) were added desiccated $MgSO_4$ (15 mg) and benzaldehyde (64 μL, 0.632 mmol) under N_2 and the reaction mixture stirred at room temperature for 1.5 h. Then dry toluene (4 mL) and TFA (33 μL, 0.430 mmol) were added and the reaction mixture heated under reflux for 19 h. The solvent was evaporated, the residue was dissolved in ethyl acetate (10 mL) and washed with satd $NaHCO_3$ solution. The aqueous phase was extracted with ethyl acetate (2 × 10 mL) and the combined organic layers dried over Na_2SO_4, filtered, evaporated and purified by flash chromatography (cyclohexane–ethyl acetate–methanol 5:4:1) to give **23a** (47 mg, 67%), as a white solid. Mp: 170–175 °C (ethyl acetate); $[\alpha]_D = -171.7$ (*c* 0.24, $CHCl_3$); IR (film) $\nu = 3249, 2910, 1692, 1455\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.85$ (br s, 1H), 3.46 (m, 2H), 3.77 (d, 1H, $J = 6.5$ Hz), 3.95 (br dd, 1H, $J = 6.7$, 6.5 Hz), 4.30 (br d, 1H, $J = 8.1$ Hz), 5.14 (d, 1H, $J = 1.4$ Hz), 6.59 (br s, 1H), 7.08–7.26 (m, 3H) 7.36 (s, 5H), 7.43 (d, 1H, $J = 6.6$ Hz), 7.69 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 36.6$, 56.7, 58.2, 58.3, 60.7, 105.4, 111.4, 118.1, 120.3, 122.4, 126.7, 128.7, 129.1, 129.3, 135.7, 136.1, 138.5, 175.6 ppm; MS (EI) *m/z* (%) = 334 ($(M+1)^+$, 9), 333 ($M^{+\cdot}$, 37), 332 (22), 315 (13), 303 (9), 256 (29), 245 (63), 244 (22), 243 (20), 231 (17), 220 (19), 219 (32), 169 (100); HREIMS for $C_{20}H_{19}N_3O_2$ calcd: 333.1477. Found: 333.1468.

Compound **23b**: Yield: 12 mg (17%). Mp: 161–163 °C (CH_2Cl_2); $[\alpha]_D = -155.6$ (*c* 0.22, MeOH); IR (film) $\nu = 3397, 2920, 1692, 1454\ cm^{-1}$; ^1H NMR ($CDCl_3$ + acetone-d_6): $\delta = 3.50$ (m, 2H), 3.79 (m, 1H), 3.95–4.05 (m, 1H), 4.40 (m, 1H), 5.21 (s, 1H), 6.85 (s, 1H), 7.05–7.21 (m, 2H), 7.25–7.55 (m, 7H), 8.85 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$ + acetone-d_6): $\delta = 36.3$, 56.5, 57.9, 58.0, 60.6, 104.9, 111.2, 117.7, 119.5, 121.7, 126.5, 128.5, 128.6, 128.7, 135.6, 136.1, 138.8, 175.1 ppm; MS (EI) *m/z* (%) = 334 (10), 333 ($M^{+\cdot}$, 45), 332 (10), 316 (14), 302 (15), 285 (12), 256 (16), 245 (100), 230 (14), 219 (25), 169 (92); HREIMS for $C_{20}H_{19}N_3O_2$ calcd: 333.1477. Found: 333.1425.

4.23. (4*R*,5*R*)-[4-(1*H*-Indol-3-yl)-2-oxo-tetrahydropyran-5-yl]-carbamic acid *tert*-butyl ester, 24

A solution of **14** (519 mg, 1.10 mmol) in 70% acetic acid (10 mL) was stirred at room temperature until the disappearance of the starting material (ca. 1.5 h). After evaporation of the solvent, the resulting brown syrup was dissolved in ethyl acetate (10 mL), heated under reflux for 2.5 h, evaporated to dryness and the residue was purified by column chromatography (cyclohexane–ethyl acetate 6:4) to yield **24** (298 mg, 82%), as a white solid. Mp: 177–178 °C (CH_2Cl_2); $[\alpha]_D = -15.6$ (*c* 0.64, $CHCl_3$); IR (film) $\nu = 3395, 3340, 1730, 1692, 1526\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 1.42$ (s, 9H), 2.87 (dd, 1H, $J = 17.8$, 6.9 Hz), 3.13 (dd, 1H, $J = 17.8$, 6.4 Hz), 3.63 (m, 1H), 4.18 (dd, 1H, $J = 11.4$, 5.2 Hz), 4.27 (dddd, 1H, $J = 8.9$, 6.1, 5.2, 3.7 Hz), 4.49 (dd, 1H, $J = 11.4$, 3.7 Hz), 4.87 (d, 1H, $J = 6.1$ Hz), 7.07 (d, 1H, $J = 2.2$ Hz), 7.17 (t, 1H, $J = 7.8$ Hz), 7.25 (t, 1H, $J = 8.1$ Hz), 7.40 (d, 1H, $J = 8.1$ Hz), 7.72 (d, 1H, $J = 7.8$ Hz), 8.22 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$ + CD_3OD): $\delta = 27.7$, 33.7, 33.8, 48.7, 70.2,

79.5, 111.3, 114.3, 118.3, 118.9, 121.2, 121.7, 125.7, 136.6, 155.9, 172.2 ppm; MS (EI) *m/z* (%) = 330 ($M^{+\cdot}$, 10), 274 (9), 257 (7), 229 (16), 213 (92), 188 (28), 170 (28); HREIMS for $C_{18}H_{22}N_2O_4$ calcd: 330.1580. Found: 330.1579.

4.24. (3*R*,5*S*,11*R*)-5-Phenyl-3,4,5,11-tetrahydropyrano[3,4-*c*]-β-carboline-13(2,12*H*)-one, 25

To a solution of **24** (137 mg, 0.415 mmol) in dry CH_2Cl_2 (10 mL) were added desiccated $MgSO_4$, benzaldehyde (128 μL, 1.26 mmol) and TFA (0.30 mL, 3.91 mmol) and the mixture stirred overnight at room temperature under N_2. After evaporation of the solvent the crude residue was purified by chromatography (ethyl acetate–cyclohexane 7:3) to give **25** (65 mg, 49%), as a white solid. Mp: 155–159 °C (ethyl acetate–cyclohexane); $[\alpha]_D$ = +128.7 (*c* 0.46, MeOH); IR (film) *v* = 3384, 2919, 2851, 1725, 1677, 1455 cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.71 (dd, 1H, *J* = 17.3, 12.0 Hz), 3.75 (dd, 1H, *J* = 17.3, 5.0 Hz), 3.91 (m, 2H), 4.48 (t, 1H, *J* = 10.3 Hz), 4.59 (dd, 1H, *J* = 10.3, 4.5 Hz), 6.04 (br s, 1H), 7.06 (t, 1H, *J* = 7.0 Hz), 7.14 (t, 1H, *J* = 7.0 Hz), 7.33 (d, 1H, *J* = 8.0 Hz), 7.44 (m, 2H), 7.55 (m, 3H), 7.68 (d, 1H, *J* = 8.0 Hz), 11.00 (br s, 1H) ppm; ^{13}C NMR (DMSO-d_6): δ = 30.7, 34.7, 53.0, 58.2, 60.5, 109.4, 109.5, 112.1, 119.6, 119.7, 122.1, 124.6, 127.6, 129.2, 130.1, 130.3, 137.0, 168.0 ppm; MS (EI) *m/z* (%) = 318 ($M^{+\cdot}$, 100), 271 (19), 259 (18), 241 (43), 230 (33); HREIMS for $C_{20}H_{18}N_2O_2$ calcd: 318.1368. Found: 318.1340.

4.25. 2-[(1*S*,3*R*,4*R*)-1-(4-Hydroxy-3,5-dimethoxyphenyl)-3-hydroxymethyl-2,3,4,9-tetrahydro-1*H*-β-carbolin-4-yl]-malonic acid dimethyl ester, 26

A solution of **14** (201 mg, 0.42 mmol) in toluene (2 mL) and CH_2Cl_2 (1 mL) was treated with HCl–MeOH (0.5 mL) at room temperature for 1 h and then syringaldehyde (200 mg, 1.1 mmol) dissolved in CH_2Cl_2 was added dropwise. The reaction mixture was heated under reflux for 4–5 h. After evaporation of the solvents the residue was dissolved in ethyl acetate (10 mL) and extracted with 5% citric acid (3 × 10 mL). The combined aqueous layers were alkalinised with solid K_2CO_3 and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, evaporated to dryness and the crude residue was purified by chromatography (CH_2Cl_2–MeOH 94:6) to give **26**, as a white solid (133 mg, 65%). Mp: 122–123 °C (ether); $[\alpha]_D$ = +65.8 (*c* 0.52, $CHCl_3$); IR (film) *v* = 3393, 2928, 1730, 1613, 1516 cm^{-1}; ^1H NMR (CD_3OD): δ = 3.27–3.32 (m, 4H), 3.51–3.71 (m 5H), 3.74–3.81 (m, 7H), 4.28 (d, 1H, *J* = 8.6 Hz), 5.06 (s, 1H), 6.73 (s, 2H), 6.92–7.03 (m, 2H), 7.20 (d, 1H, *J* = 7.7 Hz), 7.40 (d, 1H, *J* = 7.7 Hz) ppm; ^{13}C NMR (CD_3OD): δ = 35.2, 52.9, 54.6, 56.6, 57.5, 58.6, 62.5, 106.9, 107.4, 112.0, 119.3, 119.6, 122.3, 127.8, 134.2, 136.2, 136.4, 138.1, 149.2, 171.0, 171.3 ppm; MS (CI, NH_3 + isobutane) *m/z* (%) = 486 (M+1, 9), 335 (6), 316 (5), 288 (12), 172 (15), 155 (38), 154 (21), 150 (28), 134 (10), 133 (100).

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References

1. For a recent review, see: Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278–311.
2. (a) Mehta, A.; Dodd, R. H. *J. Org. Chem.* **1993**, *58*, 7587–7590; (b) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *Synthesis* **1995**, 1225–1227; (c) Batch, A.; Dodd, R. H. *Heterocycles* **1999**, *50*, 875–885.
3. Dubois, L.; Dorey, G.; Potier, P.; Dodd, R. H. *Tetrahedron: Asymmetry* **1995**, *6*, 455–462.
4. Teller, S.; Eluwa, S.; Koller, M.; Uecker, A.; Beckers, T.; Baasner, S.; Böhmer, F.-D.; Mahboobi, S. *Eur. J. Med. Chem.* **2000**, *35*, 413–427.
5. Truesdale, L. K.; Bychowski, R. A.; Gonzalez, J.; Kuki, A.; Rajapakse, R. J.; Teng, M.; Kiel, D.; Dhanoa, D. S.; Hong, Y.; Chou, T.-S.; Ling, A. L.; Johnson, M. D.; Gregor, V. E. (Agouron Pharm. Inc., USA) PCT Int. Appl. WO 2000033839, 2000; *Chem. Abstr.* **2000**, *133*, 43450.
6. For a review on Pictet–Spengler cyclisation, see: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842.
7. For a review on Bischler–Napieralski reaction, see: Whaley, M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74–150.
8. (a) Schlecht, M. F.; Giandinoto, S. *Heterocycles* **1987**, *25*, 485–491; (b) Macor, J. E.; Ryan, K. *Heterocycles* **1990**, *31*, 1497–1504; (c) Schlecht, M. F.; Tsaroushtsis, D.; Lipovac, M. N.; Debler, E. A. *J. Med. Chem.* **1990**, *33*, 386–394; (d) Ghosh, A.; Wang, W.; Freeman, J. P.; Althaus, J. S.; VonVoigtlander, P. F.; Scahill, T. A.; Mizsak, S. A.; Szmuszkovicz, J. *Tetrahedron* **1991**, *47*, 8653–8662; (e) Ezquerra, J.; Pedregal, C.; Lamas, C.; Pastor, A.; Alvarez, P.; Vaquero, J. J. *Tetrahedron Lett.* **1996**, *37*, 683–686.
9. (a) Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. *Tetrahedron Lett.* **1978**, *20*, 1759–1762; (b) Oikawa, Y.; Hirasawa, H.; Yonemitsu, O. *Chem. Pharm. Bull.* **1982**, *30*, 3092–3096.
10. Dardennes, E.; Kovács-Kulyassa, Á.; Renzetti, A.; Sapi, J.; Laronze, J.-Y. *Tetrahedron Lett.* **2003**, *44*, 221–223.
11. (a) Barany, G.; Merrifield, R. B. *J. Am. Chem. Soc.* **1977**, *99*, 7363–7365; (b) Barany, G.; Albericio, F. *J. Am. Chem. Soc.* **1985**, *107*, 4936–4942.
12. Hertel, L. W.; Grossman, C. S.; Kroin, J. S. *Synth. Commun.* **1991**, *21*, 151–154.
13. Boisbrun, M.; Kovács-Kulyassa, Á.; Jeannin, L.; Sapi, J.; Toupet, L.; Laronze, J.-Y. *Tetrahedron Lett.* **2000**, *41*, 9771–9775.
14. For experimental details, see: Nemes, C.; Jeannin, L.; Sapi, J.; Laronze, M.; Seghir, H.; Augé, F.; Laronze, J.-Y. *Tetrahedron* **2000**, *56*, 5479–5492.
15. Guanti, G.; Banfi, L.; Zanetti, M. T. *Gazz. Chim. Ital.* **1995**, *125*, 333–339.
16. Miller, D. B.; Raychaudhuri, S. R.; Avasthi, K.; Lal, K.; Levison, B.; Salomon, R. G. *J. Org. Chem.* **1990**, *55*, 3164–3175.

17. Hofmann, B.; Dauban, P.; Biron, J.-P.; Potier, P.; Dodd, R. H. *Heterocycles* **1997**, *46*, 473–488.
18. Boisbrun, M.; Jeannin, L.; Toupet, L.; Laronze, J.-Y. *Eur. J. Org. Chem.* **2000**, 3051–3057.
19. (a) Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M.; Silverton, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6976–6984; (b) Bailey, P. D.; Hollinshead, S. P. *J. Chem. Soc., Chem. Commun.* **1985**, 1575–1576.
20. For some references, see: (a) Harrison, D. M.; Sharma, R. B. *Tetrahedron Lett.* **1986**, *27*, 521–524; (b) Nakagawa, M.; Fukushima, H.; Kawate, T.; Hongu, M.; Kodato, S.; Une, T.; Taniguchi, M.; Hino, T. *Tetrahedron Lett.* **1986**, *27*, 3235–3238; (c) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R. *Tetrahedron Lett.* **1987**, *28*, 5177–5180; (d) Zhang, L.-H.; Bi, Y.-Z.; Yu, F.-X.; Menzia, G.; Cook, J. M. *Heterocycles* **1992**, *34*, 517–547.
21. (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361–2364; (b) Dondoni, A.; Perrone, D. *Org. Synth.* **1999**, *77*, 64–77.
22. Delle Monache, G.; Di Giovanni, M. C.; Maggio, F.; Misiti, D.; Zappia, G. *Synthesis* **1995**, 1155–1158.