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SYNTHESIS OF A *SECO* ANALOGUE OF ARDEEMIN

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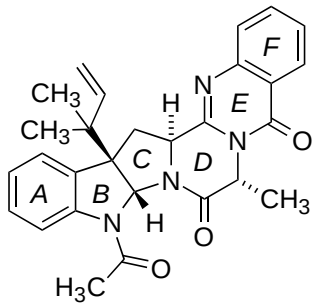
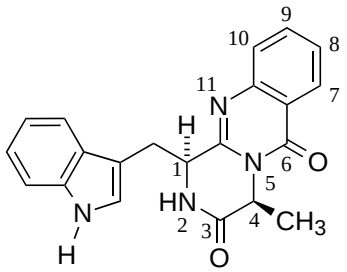
Abstract.- (1*S*,4*S*)-1-Indolylmethyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]-quinazaline-3,6-dione, a *seco* analogue of ardeemin, was synthesized in six steps from L-tryptophan methyl ester *via* an *N*-protected 2,5-piperazinedione and using an aza-Wittig reaction for the preparation of the quinazoline system. The final acid-promoted deprotection required tuning of the reaction conditions in order to minimize a side reaction involving loss of the indolylmethyl side chain.

INTRODUCTION

Multi-drug resistance to antitumour agents (MDR)[1] is a serious impediment in the use of drugs in the treatment of cancer, and therefore its inhibition is an important goal in cancer chemotherapy. *N*-Acetylardeemin (**1**)[2] is a potent MDR inhibitor,[3] and an interesting reference structure in the development of new compounds with biological activity in this area. As part of our current work on the synthesis of analogues of this natural product,[4,5] we became interested in the preparation of more flexible, *C*-ring *seco* analogues.[6] In this context, we report here the synthesis of compound (**2**), which is interesting as a potential precursor to the full ardeemin system and also to study its anti-MDR activity. The *DEF* fragment of ardeemin is responsible for its anti-MDR properties,[7] and can be found in several other natural products, such as glyantrypine,[8] fiscalin C[9] and fumiquinazolines F and G.[10]



N-Acetylardeemin **1**



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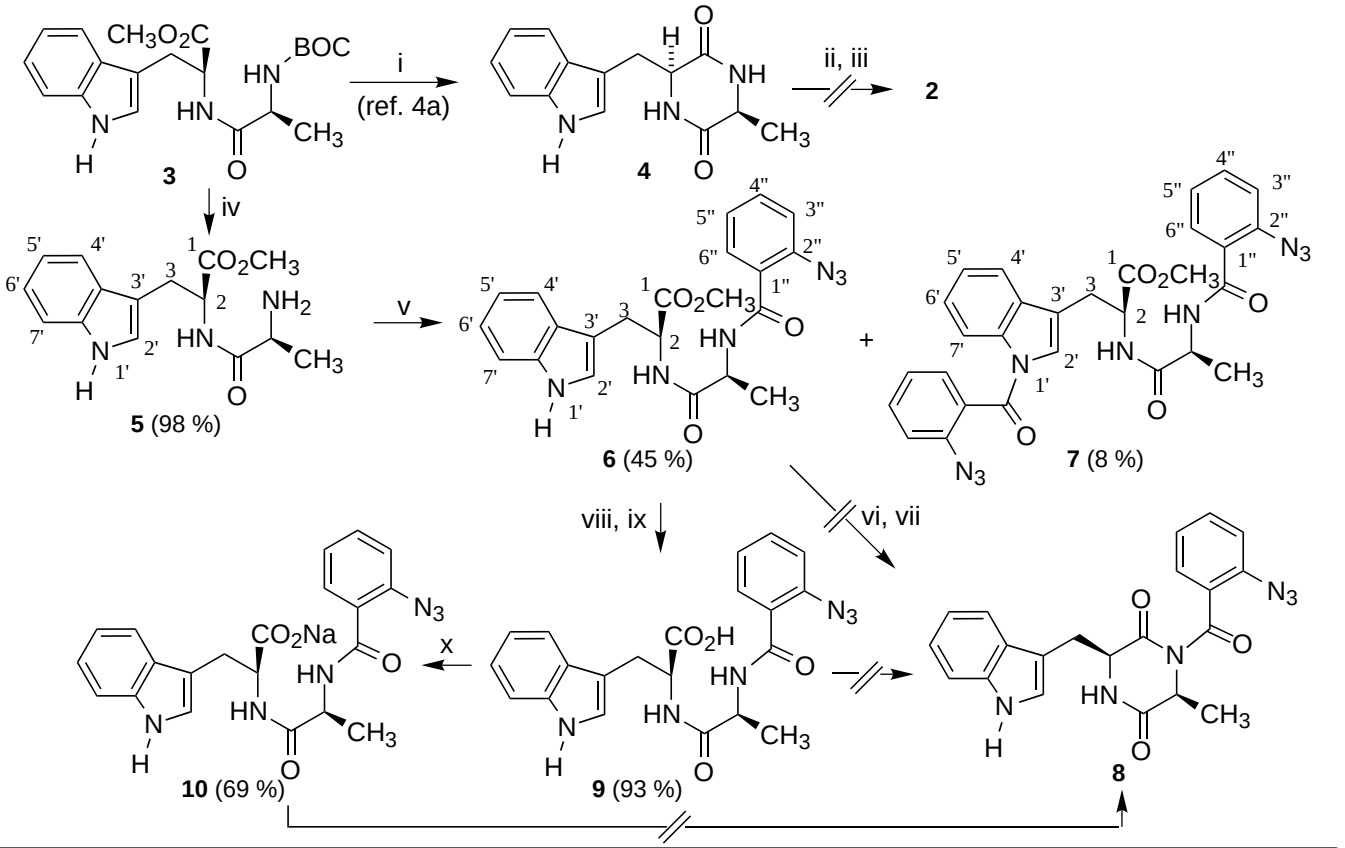
RESULTS AND DISCUSSION

The 2-methyl derivative of (**2**) has been prepared by alkylation[11] of the 2-methyl derivative of the *DEF* fragment,[12] but this method is not suitable for the unsubstituted compound (**2**). Cyclization of dipeptide (**3**)

to the known[13] diketopiperazine (**4**) followed by cyclocondensation of the latter with a suitable derivative of anthranilic acid would provide a very straightforward, although probably not regioselective, route to **2**. Unfortunately, all attempts to obtain **2** from **4** and anthranilic acid using several literature methods[14,15] were unsuccessful, owing to the poor solubility of the latter. We tried to resort to our recently described method[16] based on the double cyclization of *N*-(*o*-azidobenzoyl)aminoacylglycines; to this end, we prepared compound (**6**) by *N*-deprotection of **3** to give **5**, followed by acylation of the latter with *o*-azidobenzoyl chloride to **6**. Unfortunately, all our attempts to cyclize **6** to **8** under thermal conditions, with or without the presence of base, were unsuccessful. Hydrolysis of **6** gave **9**, but both this acid and its salt (**10**) must exist in a conformation unsuitable for cyclization,[17] and failed to react under several conditions designed to activate the carboxyl group for attack by an amide nitrogen[18] (Scheme 1).

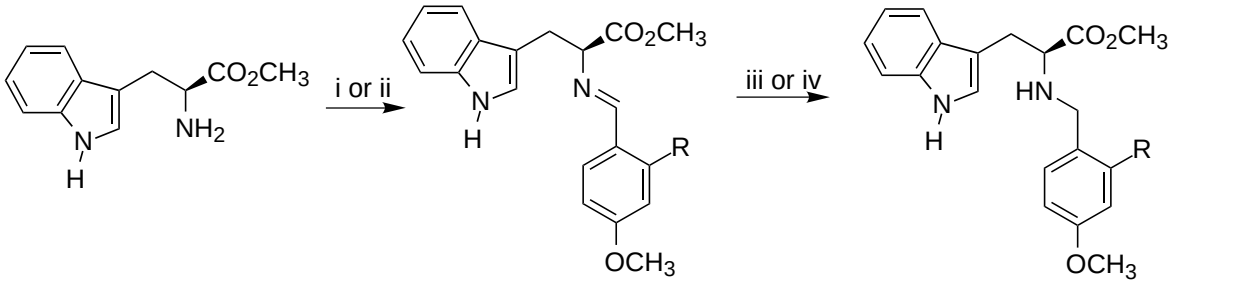


Reagents and conditions: i. 200 °C, 2 h. ii. 1. $SOCl_2$, benzene, 2 h, 80 °C. 2. Several solvents and temperatures. iii. 1. $Et_3O^+BF_4^-$, several solvents, rt [2. antranilic acid (neat), 140 °C]. iv. CF_3CO_2H, rt, 3 h. v. *o*-$N_3C_6H_4COCl$, Et_3N, DMAP, THF, rt, 10 min. vi. Et_3N, several solvents and temperatures. vii. 200 °C, 1 h. viii. NaOH, MeOH-H_2O, 50 °C, 2 h. ix. 2M HCl, rt, 5 min x. 0.5M NaOH, rt, 5 min

Scheme 1

In view of these results we decided to return to the initial approach, introducing a protecting group at the N-4 position of compound (**4**) in order to increase both its solubility and the regioselectivity of its reactions. Hoping to be able to achieve good regioselectivities regarding the indole nitrogen at later stages, we did not include a protecting group for this position. At the time, the literature contained little information on *N*-protecting groups for the 2,5-piperazinedione system[19] and therefore we decided to compare the 4-methoxy- and the 2,4-dimethoxybenzyl groups, two well-known protecting groups for amides. Preparation

of the tryptophan derivatives (**12**) required as starting materials proceeded uneventfully and in good yields, as shown in Scheme 2.



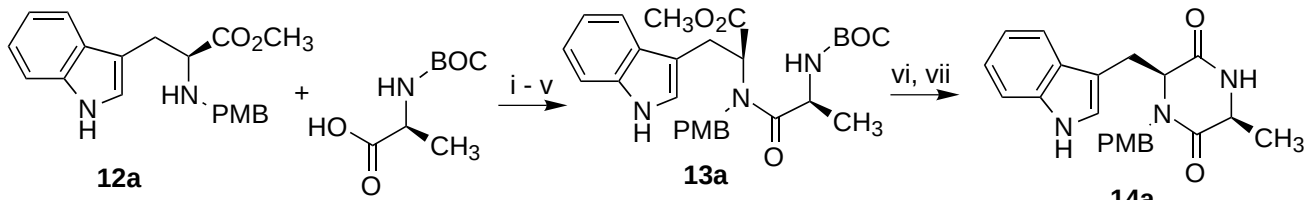
Comp.	R	Method	Yield, %
11a	H	i	---
11b	OCH_3	ii	83

Comp.	R	Method	Yield, %
12a	H	iii	61 (i + iii)
12b	OCH_3	iv	87

Reagents and conditions: i. 4-methoxybenzaldehyde, benzene, rt, 20 h. ii. 2,4-dimethoxybenzaldehyde, benzene, Na_2SO_4, rt, 15 h. iii. H_2, 10% Pd-C, MeOH, 42 psi, rt, 2 h. iv. $NaBH_4$, MeOH, rt, 15 h.

Scheme 2

Compound (**12a**) was used for studying the conditions for coupling with *N*-BOC-L-Ala (Scheme 3). After discarding ethyl chloroformate as a coupling reagent because of the poor yield obtained, we verified that DCC and EDC gave identical results, and therefore we continued our study with the experimentally more convenient EDC. Finally, we settled on the use of 4 equivalents of the alanine derivative and the coupling reagent, which led to dipeptide (**13a**) in 79 % yield. This compound was quantitatively transformed into the piperazinedione derivative (**14a**), either in the presence of acid or under thermal conditions.



Method	Eqs. BOC-Ala	Yield, %
i	1	15
ii	2	30
iii	2	30
iv	3	37
v	4	79

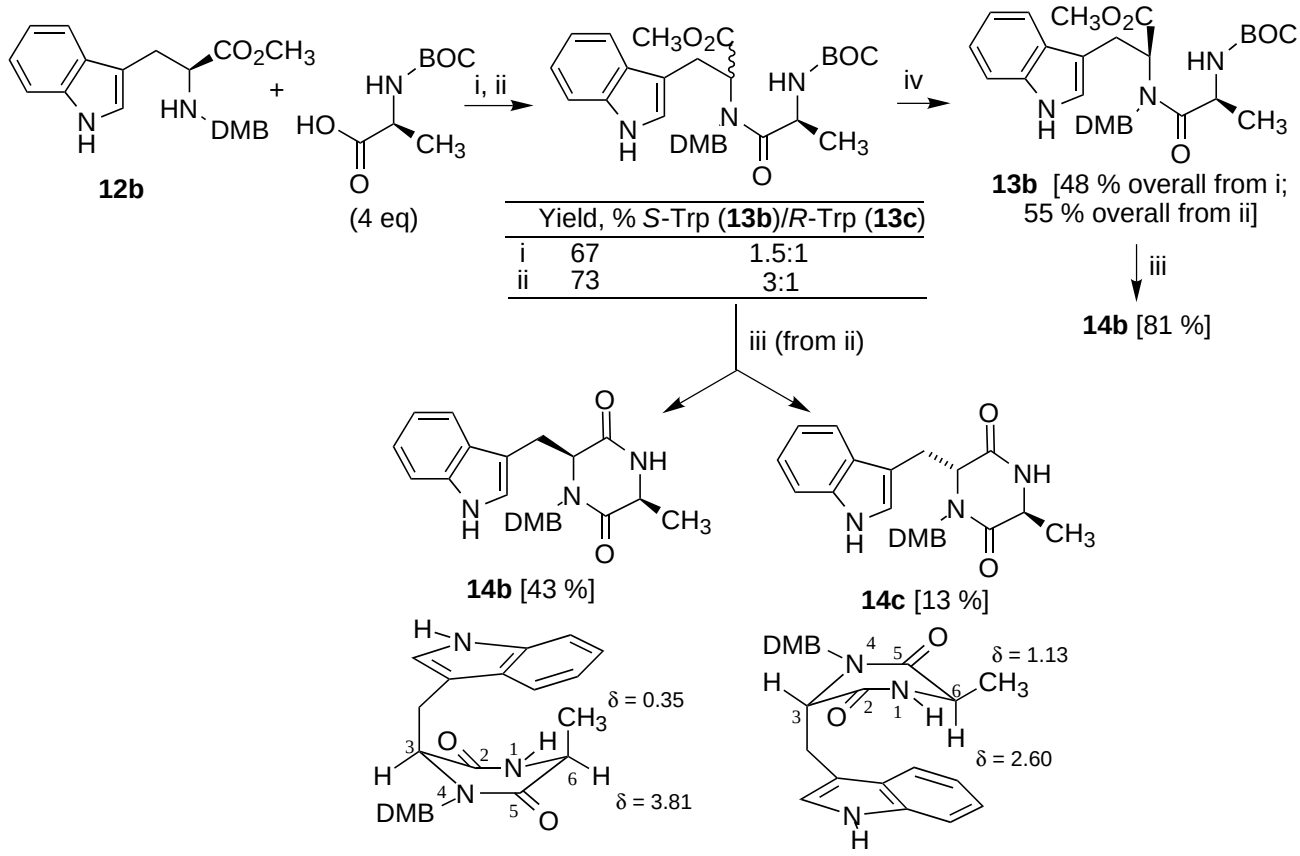
Method	Yield, %
vi	95
vii	100

Reagents and conditions: i. $ClCO_2Et$, Et_3N, THF, 80 °C, 23 h. ii. DCC (2 eq), THF, 80 °C, 54 h. iii. EDC (1 eq), THF, rt, 93 h, then EDC (2 eq), 80 °C, 21 h. iv. DCC (2 eq), 80 °C, 46 h, then DCC (3 eq), 80 °C, 48 h. v. DCC (3 eq), 80 °C, 24 h, then DCC (1 eq), rt, 48 h. vi. CH_2Cl_2, CF_3CO_2H (1:1), 0°C, 30 min. vii. 200 °C, 2 h.

Scheme 3

Application of the optimal conditions determined above to the dimethoxybenzyl derivative (**12b**) led to epimerization of the tryptophan stereocenter. The higher conformational rigidity expected for dipeptides derived from **12b** can explain their tendency to epimerization, particularly in the presence of the basic EDC for long periods of time. Indeed, replacement of EDC for DCC led to an improved ratio (3:1) of the desired

dipeptide (**13b**). Cyclization of the dipeptide mixture under thermal conditions gave a mixture of piperazinediones (**14b**) and (**14c**), which were easily separated by chromatography. The values for the isolated overall yields of **14b** (43 %) and **14c** (13 %) suggested that this last step proceeded without epimerization, which was confirmed in a separate experiment starting from pure **13b** (Scheme 4). Stereochemical assignments of compounds (**14b**) and (**14c**) (and hence of **13b**) were based on the well-known[20] upfield shift of the signals of any pseudoaxial groups in the C-6 position of a 2,5-piperazinedione that are *cis* with respect to an arylmethyl substituent at C-3.



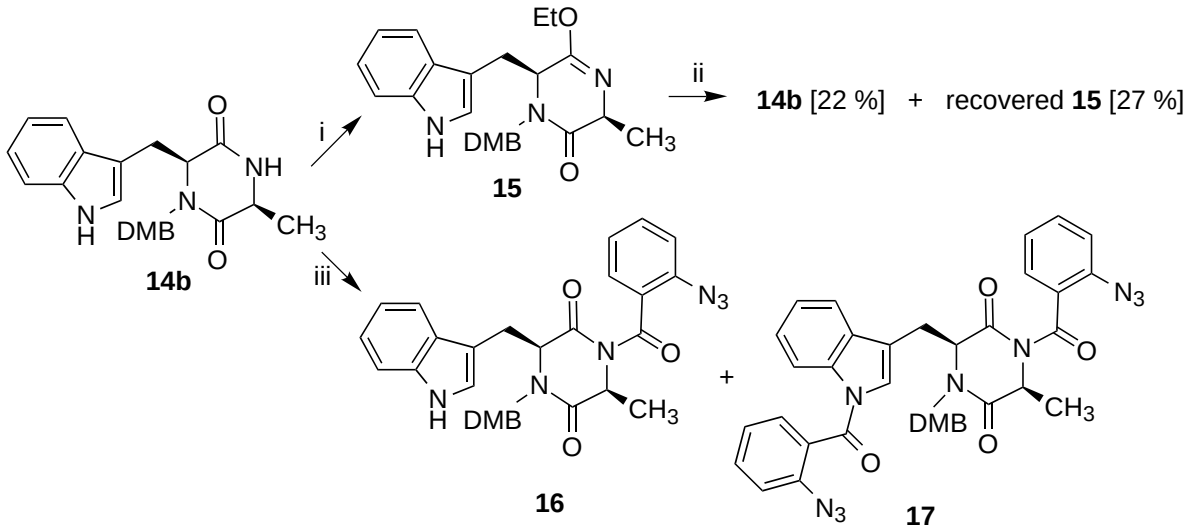
	Yield, % *S*-Trp (**13b**)	*/R*-Trp (**13c**)
i	67	1.5:1
ii	73	3:1

Reagents and conditions: i. EDC (4 eq.), CH_2Cl_2, rt, 22 h. ii. DCC (4 eq), THF, rt, 44 h. iii. 200 °C, 5 h. iv. recrystallization from Et_2O.

Scheme 4

While the work described in Schemes 3 and 4 was in progress, other members of our group found difficulties in the deprotection of a *N*-(4-methoxybenzyl)-2,5-piperazinedione derivative.[21] This prompted us to choose compound (**14b**) as the starting material for the last steps of our synthesis. As shown in Scheme 5, **14b** was easily transformed into iminoether (**15**) but the attempted cyclocondensation of this compound with anthranilic acid was unsuccessful and led to a mixture of recovered starting material (**15**) and some **14b**, from its hydrolysis. With a subsequent aza-Wittig cyclization[22] in mind, we studied the acylation of **14b** with *o*-azidobenzoyl chloride in the presence of potassium hexamethyldisilazide, and obtained the results shown in Scheme 5. We found that the best selectivity in favor of the acylation of the amide nitrogen to give the desired compound (**16**) was achieved by using deficiency of the base in order to stop the reaction at a low conversion.

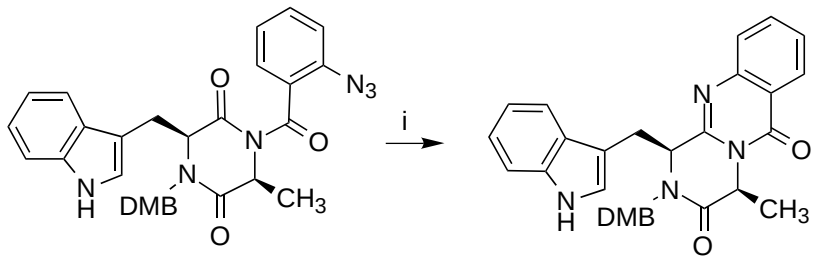
As shown in Scheme 6, treatment of **16** with tributylphosphine led to its aza-Wittig cyclization to **18** in 75 % yield. The final deprotection step was initially carried out by treatment with neat trifluoroacetic acid at



Eq *o*-$N_3C_6H_4Cl$	Eq KHMDS	Temperature, time	% **16**	% **17**	%Conversion
2.5	1.5	- 78 °C, 2 h → rt, 13 h	20	43	100
1.5	1.2	- 78 °C, 3 h → rt, 17 h	27	26	85
1.1	0.7	- 78 °C, 3 h → rt, 14 h	66	9	41

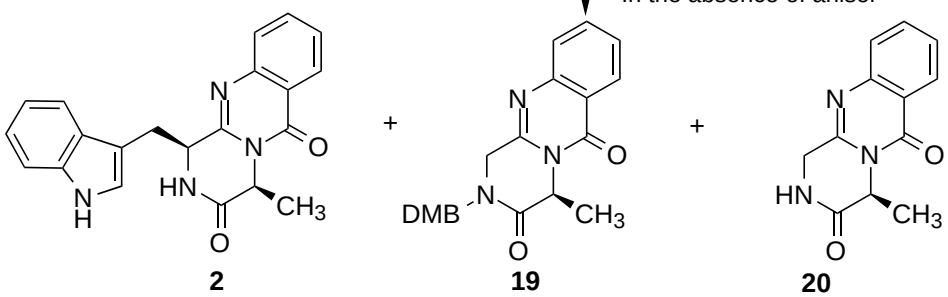
Reagents and conditions: i. Et_3O^+ BF_4^-, Na_2CO_3, CH_2Cl_2, rt, 18 h. ii. anthranilic acid, 140 °C, 4.5 h. iii. *o*-$N_3C_6H_4Cl$, KHMDS, THF.

Scheme 5



Conditions	%**2**	%**19**	%**20**	% Rec. **18**
80 °C, 3 h 30 min	44	22	13	20
80 °C, 7 h 15 min	0	40	57	0
80 °C, 3 h*	16	12	13	31

*In the absence of anisol

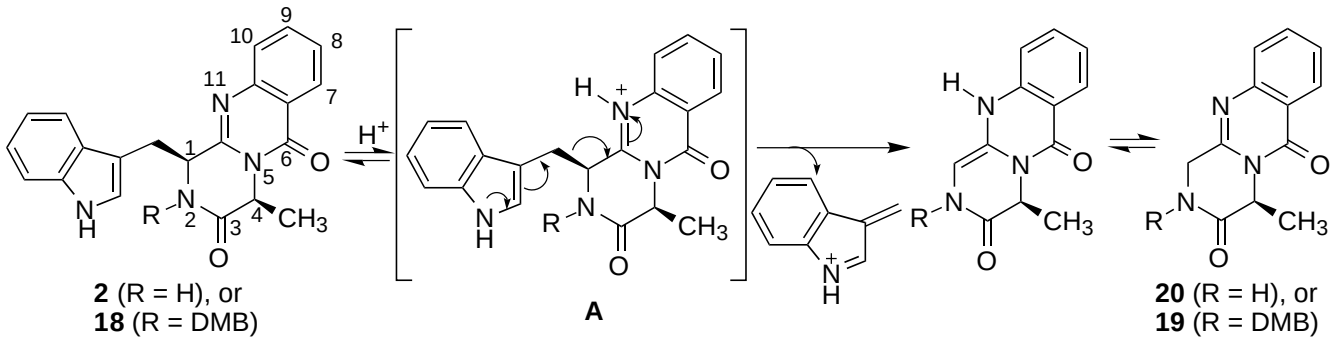


Reagents and conditions: i. Bu_3P, toluene, 80 °C, 2.5 h. ii. CF_3CO_2H, anisol

Scheme 6

80 °C for 3 h and led to a mixture of the desired final product (**2**) and compounds (**19**) and (**20**), arising from loss of the indolylmethyl side chain. The yield of **2** was greatly increased by carrying out the deprotection in the presence of anisol[17] (44 % isolated, 55 % based on unrecovered starting material). However, an attempt to complete the reaction by using a longer reaction time led only to a mixture of **19** and **20**.

Loss of the indolylmethyl group can be explained by taking into account that the N-11 position of compounds (**2**) and (**18**) belongs to an amidine-like substructure and should be easily protonated to give an intermediate **A**, which could lose a 3-methyleneindole unit to give **20** or **19**, respectively (Scheme 7).



Scheme 7

The participation of the N-11 group in this mechanism was proved by the fact that piperazinedione (**14b**) was deprotected to **4** in 80 % yield under very similar conditions (CF_3CO_2H, anisol, 80 °C, 3 h) without detectable loss of the indolylmenthyl unit. Several attempts to use cerium ammonium nitrate[19,23] for the deprotection of **18** led to complex mixtures.

In conclusion, we have developed a six-step sequence to the target (1*S*,4*S*)-1-indolylmethyl-4-methyl-2,4-dihydro-1*H*-pyrazino[2,1-*b*]quinazaline-3,6-dione. Our work has also uncovered some useful results concerning protection and deprotection of 2,5-piperazinedione nitrogens.

EXPERIMENTAL

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (SDS) were dried and purified using standard techniques. Petroleum ether refers to the fraction boiling at 40-60 °C. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Macherey-Nagel Alugram Sil G/UV_{254}). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230-400 mesh). Melting points were measured in open capillary tubes using a Reichert 723 hot stage microsope, and are uncorrected. IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrophotometer, with compounds examined as KBr pellets or as films on a NaCl disk. NMR spectra were obtained on a Bruker AC-250 spectrometer (250 MHz for ^1H, 63 MHz for ^{13}C), with $CDCl_3$ as solvent (Servicio de Espectroscopía, Universidad Complutense). When necessary, assignments were aided by HOMO decoupling, DEPT and COSY experiments. MS spectra were obtained by the Servicio de Espectroscopía, Universidad Complutense, on a Hewlett-Packard 5989A spectrometer using the electron impact mode, with the exception of compound

(**14**), for which chemical ionization with methane was also employed. High resolution MS measurements were obtained by the Servicio Central de Soporte a la Investigación Experimental (Universidad de Valencia) on a UG Autospec spectrometer. Optical rotations were determined at 25 °C on a 1 mL cell, using a Perkin Elmer 240 polarimeter operating at the emission wavelength of a sodium lamp; concentrations are given in g/100 mL. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin Elmer 2400 CHN microanalyzer.

Methyl (*S*)-Alanyl-(*S*)-tryptophanate (5)

A solution of the *N*-protected dipeptide (**3**)[4a] (500 mg, 1.29 mmol) in neat trifluoroacetic acid (8.5 mL) was stirred at rt for 30 min. The reaction mixture was poured onto a vigorously stirred biphasic system formed by 20 % aqueous Na_2CO_3 (50 mL) and CH_2Cl_2 (25 mL), cooled in an ice bath. The aqueous layer was extracted with CH_2Cl_2 (15 x 10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated, yielding 364 mg (98 %) of compound (**5**) as a pale yellow solid. Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.17; H, 6.36; N, 14.27; mp 272-274 °C (acetone); $[\alpha]_D^{25}$ - 12.1° (*c* 0.52, $CHCl_3$); ν_{max} (NaCl) 3242 (NH_2); 1738 (CO_2CH_3); 1673 (CO-N) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.26 (br s, 1H, NH^i), 7.69 (d, 1H, *J* 8.2 Hz, NH-Trp), 7.54 (d, 1H, *J* 7.6 Hz, H-4'), 7.34 (d, 1H, *J* 7.7 Hz, H-7'), 7.10 (m, 2H, H-5' and H-6'), 7.00 (d, 1H, *J* 2.2 Hz, H-2'), 4.91 (m, 1H, H–2), 3.68 (s, 3H, CO_2CH_3), 3.47 (q, 1H, *J* 6.9 Hz, Hα-Ala), 3.31 (d, 2H, *J* 6.1 Hz, H-3), 2.27 (br s, 2H, NH_2), 1.25 (d, 3H, *J* 6.9 Hz, CH_3-Ala); δ_C (63 MHz, $CDCl_3$) 175.55 and 172.76 (*C*O-Ala and CO_2CH_3), 136.26 (C-7'a), 127.71 (C-3'a), 123.11 (C-2'), 122.07 (C-5'), 119.41 (C-4'), 118.67 (C-6'), 111.52 (C-7'), 109.87 (C-3'), 52.71 (C-2), 52.47 (CO_2CH_3), 50.68 (Cα-Ala), 27.85 (C-3), 21.42 (CH_3-Ala).

Acylation of 5 with *o*-Azidobenzoyl Chloride

A solution of *o*-azidobenzoyl chloride,[24] prepared from 338 mg, 2.08 mmol of the corresponding acid in dry THF (5 mL) was added to a solution of compound (**5**) (300 mg, 1.04 mmol), triethylamine (0.9 mL, 6.23 mmol) and DMAP (12.7 mg, 0.10 mmol) in dry THF (20 mL). The reaction mixture was stirred at rt for 10 min. A white precipitate was filtered off, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (25 mL), and the solution was washed with saturated aqueous NH_4Cl (10 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel, eluting with petroleum ether-ethyl acetate (2.5:1), affording 165 mg (45 %) of methyl *N*-(*o*-azidobenzoyl)-(*S*)-alanyl-(*S*)-tryptophanate (**6**), as a colourless oil, and 48 mg (8 %) of methyl 1',*N*-di(*o*-azidobenzoyl)-(*S*)-alanyl-(*S*)-tryptophanate (**7**), as white crystals.

Data for **6**: Anal. Calcd for $C_{22}H_{22}N_6O_4$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.78; H, 5.27; N, 19.12; $[\alpha]_D^{25}$ + 47.5° (*c* 0.34, $CHCl_3$); ν_{max} (NaCl) 3334 (NH), 2131 (N_3), 1741 (CO_2CH_3), 1636 (CO-N) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 8.31 (br s, 1H, NH^i), 7.96 (dd, 1H, *J* 7.9 Hz and *J* 1.5 Hz, H-6''), 7.89 (d, 1H, *J* 7.3 Hz, NH-Ala), 7.44 (m, 2H, H-5'' and H-4'), 7.00 (m, 6H, H-5', H-6', H-7', H-3'', H-4'' and NH-Trp), 6.89 (d, 1H, *J* 2.2 Hz, H-2'), 4.89 (q, 1H, *J* 6.1 Hz, H-2), 4.74 (quint, 1H, *J* 7.0 Hz, Hα-Ala), 3.67 (s, 3H, CO_2CH_3), 3.30 (dd, 1H, *J* 14.9 Hz and *J* 5.1 Hz, H-3), 3.21 (dd, 1H, *J* 14.9 Hz and *J* 6.2 Hz, H-3), 1.44 (d, 3H, *J* 7.0 Hz, CH_3-Ala); δ_C (63 MHz, $CDCl_3$) 172.25 and 172.18 (*C*O-

Ala and *C*O_2CH_3), 164.52 (*C*O-ArN_3), 137.46 (C-7'a), 136.19 (C-1''), 132.65 (C-4''), 132.06 (C-6''), 127.50 (C-3'a), 125.10 (C-5''), 124.44 (C-2''), 123.20 (C-2'), 122.14 (C-5'), 119.57 (C-4'), 118.46 and 118.47 (C-6' and C-3''), 111.34 (C-7'), 109.75 (C-3'), 53.16 (C-2), 52.52 (CO_2CH_3), 49.52 (Cα-Ala), 27.55 (C-3), 18.40 (CH_3-Ala).

Data for **7**: Anal. Calcd for $C_{29}H_{25}N_9O_5$: C, 60.10; H, 4.35; N, 21.75. Found: C, 60.42; H, 4.24; N, 21.67; mp 94-96 °C (chloroform-hexane); $[\alpha]_D^{25}$ + 44.1° (*c* 0.44, $CHCl_3$); ν_{max} (NaCl) 3344 (NH), 2131 (N_3), 1743 (CO_2CH_3), 1640 (CO-N) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.93 (dd, 1H, *J* 8.2 and 1.5 Hz, H-6''), 7.81 (d, 1H, *J* 7.0 Hz, NH-Ala), 7.51 (m, 4H, H-5'', H-5''', H-6''' and H-4'), 7.31 (m, 8H, H-5', H-6', H-7', H-3'', H-3''', H-4'', H-4''' and NH-Trp), 6.84 (s, 1H, H-2'), 4.87 (dd, 1H, *J* 17.0 and 5.9 Hz, H-2), 4.68 (quint, 1H, *J* 7.1 Hz, Hα-Ala), 3.62 (s, 3H, CO_2CH_3), 3.27 (dd, 1H, *J* 15.0 and 5.9 Hz, H-3), 3.16 (dd, 1H, *J* 14.8 and 5.9 Hz, H-3), 1.44 (d, 3H, *J* 7.0 Hz, CH_3-Ala); δ_C (63 MHz, $CDCl_3$) 172.25 and 171.73 (*C*O-Ala and *C*O_2CH_3), 165.89 and 164.44 (2 *C*O-Ar-N_3), 137.91 (C-7'a), 137.36 and 135.66 (C-1'' and C-1'''), 132.78, 132.67, 132.12 (C-4'', C-4''' and C-6''), 131.10 (C-2''), 129.22 (C-6'''), 127.02 (C-3'a), 125.20, 125.19 and 125.03 (C-5', C-5'' and C-5'''), 124.21 (C-2'), 118.96, 118.87 and 118.49 (C-4', C-3'', C-3''' and C-6'), 117.28 (C-2''), 116.63 (C-7'), 109.61 (C-3'), 52.71 (C-2), 52.54 (CO_2CH_3), 49.53 (Cα-Ala), 30.40 (C-3), 18.20 (CH_3-Ala).

_N_-(_o_-Azidobenzoyl)-(_S_)-alanyl-(_S_)-tryptophan (9)

To a solution of compound (**6**) (300 mg, 0.69 mmol) in methanol (4 mL) was added 0.5 M aqueous NaOH (2 mL, 1 mmol). The solution was heated at 50 °C for 2 h, and then cooled, poured onto 2 M aqueous HCl (3 mL) and extracted with CH_2Cl_2 (5 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, yielding 268 mg (93 %) of **9**, as a pale yellow solid. Anal. Calcd for $C_{21}H_{20}N_6O_4$: C, 59.99; H, 4.79; N, 19.99. Found: 59.93, H, 5.03, N, 19.87; mp 103-105 °C (ethanol); $[\alpha]_D^{25}$ + 54.7° (*c* 0,50, $CHCl_3$); ν_{max} (NaCl) 3348 (NH), 2132 (N_3), 1731 (CO_2H), 1637 (CO-N) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.31 (br s, 1H, NH^i), 7.94 (m, 2H, H-6'' and NH-Ala), 7.46 (m, 2H, H-5'' and H-4'), 7.05 (m, 6H, H-5', H-6', H-7', H-3'', H-4'' and NH-Trp), 6.87 (d, 1H, *J* 2.0 Hz, H-2'), 4.87 (dd, 1H, *J* 12.7 and 5.6 Hz, H-2), 4.67 (quint, 1H, *J* 7.2 Hz, Hα-Ala), 3.35 (dd, 1H, *J* 14,.9 Hz and *J* 5.2 Hz, H-3), 3.23 (dd, 1H, *J* 14.9 and 5.8 Hz, H-3), 1.39 (d, 3H, *J* 7.0 Hz, CH_3-Ala); δ_C ($CDCl_3$, 63 MHz) 173.66 (*C*O_2H), 171.72 (*C*O-Ala), 164.22 (*C*O-Ar-N_3), 136.86 (C-7'a), 135.32 (C-1''), 132.16 (C-4''), 131.27 (C-6''), 128.69 (C-3'a), 126.92 (C-2''), 124.39 (C-5''), 123.14 (C-2'), 122.86 (C-5'), 121.19 (C-4'), 118.67 (C-6'), 117.78 (C-3''), 110.63 (C-7'), 108.67 (C-3'), 52.62 (C-2), 48.88 (Cα-Ala), 26.36 (C-3), 17.46 (CH_3-Ala).

Sodium _N_-(_o_-Azidobenzoyl)-(_S_)-alanyl-(_S_)-tryptophanate (10)

To a solution of **9** (100 mg, 0.24 mmol) in methanol (2 mL) was added 0.5 M aqueous NaOH (0.5 mL, 0.25 mmol) and the solution was stirred at rt for 5 min and extracted with CH_2Cl_2 (10 x 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated, yielding 72 mg (69 %) of **10**, as a yellow solid. Anal. Calcd for $C_{21}H_{19}N_6O_4Na$: C, 57.01; H, 4.33; N, 19.00. Found: C, 56.93; H, 4.08; N, 19.28; mp (methanol) 150-152 °C; $[\alpha]_D^{25}$ + 26.7° (*c* 0.30, EtOH); ν_{max} (NaCl) 3362 (NH), 2131 (N_3), 1643 (CO), 1403 and 747 (CO_2^-) cm^{-1}; δ_H (CD_3OD, 250 MHz) 7.61 (m, 3H, H-6'', H-5'' and H-4'), 7.28 (m, 3H, H-7', H-3'', H-4''), 7.16 (s, 1H, H-2'), 6.97 (m, 2H, H-5' and H-6'), 4.59 (m, 2H, H-2 and Hα-Ala),

3.48 (dd, 1H, *J* 14.5 and 4.9 Hz, H-3), 3.27 (dd, 1H, *J* 14.5 and 6.1 Hz, H-3), 1.39 (d, 3H, *J* 7.1 Hz, C*H*$_3$-Ala); δ_C (CD$_3$OD, 63 MHz) 178.63 (*C*O$_2$Na), 173.80 (*C*O-Ala), 168.20 (*C*O-Ar-N$_3$), 139.25 (C-7'a), 138.06 (C-1''), 133.59 (C-4''), 131.75 (C-6''), 129.92 (C-3'a), 127.82 (C-2''), 126.18 (C-5''), 124.79 (C-2'), 122.27 (C-5'), 120.14, 119.96 and 119.74 (C-4', C-6' and C-3''), 112.29 (C-7'), 112.11 (C-3'), 57.49 (C-2), 51.38 (*C*α-Ala), 29.08 (C-3), 18.45 (*C*H$_3$-Ala).

Methyl (*S*)-*N'*-(*p*-Methoxybenzyl)tryptophanate (12a).

A solution of *S*-tryptophan methyl ester (1 g, 4.59 mmol) in dry benzene (20 mL) was cooled to 0 °C, and treated with *p*-methoxybenzaldehyde (625 mg, 4,59 mmol). The solution was stirred at 0 °C for 15 min and then at rt for 20 h. The reaction mixture was concentrated and residue was identified by IR and ^{1}H-NMR data as imine (**11a**). To a solution of the crude imine in methanol (12 mL) was added 10 % Pd-C (233 mg), and the suspension was hydrogenated at 45 psi for 2 h. The catalyst was filtered off through a layer of celite, and the filtrate was concentrated to dryness. The residue was recrystallized from CHCl$_3$-hexane, giving 948 mg (61 %) of compoud (**12a**) as white crystals.

When the same method was applied to tryptophan methyl ester hydrochloride, a 57 % yield of the hydrochloride of **12a** was obtained, as white crystals. This hydrochloride could be transformed into **12a**, as follows: To a suspension of **12a**.HCl (816 mg, 2.18 mmol) in CH$_2$Cl$_2$ (10 mL) was added triethylamine (0.3 mL, 2.18 mmol). Stirring at rt for 15 min led to a clear solution, which was washed with water (3 x 3 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated, yielding 682 mg (93 %) of **12a**.

Data for **11a** (oil): ν_{max} (NaCl): 1774 (CO$_2$CH$_3$), 1605 (C=N), 1257 (C-O) cm^{-1}; δ_H (CDCl$_3$, 250 MHz) 8.14 (br s, 1H, NH^i), 7.81 (s, 1H, H-α), 7.63 (m, 3H, H-4', H-2'' and H-6''), 7.31 (d, 1H, *J* 7.6 Hz, H-7'), 7.15 (m, 2H, H-5' and H-6'), 6.92 (d, 1H, *J* 2.2 Hz, H-2'), 6.87 (m, 2H, H-3'' and H-5''), 4.22 (dd, 1H, *J* 8.5 and 5.1 Hz, H-2), 3.81 (s, 3H, C4''-OC*H*$_3$), 3.74 (s, 3H, CO$_2$C*H*$_3$), 3.54 (dd, 1H, *J* 14.4 and 5.1 Hz, H-3), 3.23(dd, 1H, *J* 14.4 and 8.4 Hz, H-3).

Data for **12a**: Anal. Calcd for C$_{20}$H$_{22}$N$_2$O$_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 70.82; H, 6.32; N, 8.27; mp 101-103 °C (chloroform-hexane); $[\alpha]_D^{25}$ - 7.8° (*c* 0.41, CHCl$_3$); ν_{max} (NaCl) 3408 (NH), 1732 (CO$_2$CH$_3$), 1248 (C-O) cm^{-1}; δ_H (CDCl$_3$, 250 MHz) 8.12 (br s, 1H, NH^i), 7.57 (d, 1H, *J* 7.8 Hz, H-4'), 7.34 (d, 1H, *J* 7.8 Hz, H-7'), 7.15 (m, 4H, H-5', H-6', H-2'' and H-6''), 7.01 (d, 1H, *J* 2.3 Hz, H-2'), 6.78 (m, 2H, H-3'' and H-5''), 3.78 (m, 4H, C4''-OC*H*$_3$ and H-α), 3.63 (m, 5H, H-2, H-α and CO$_2$C*H*$_3$), 3.16 (m, 2H, H-3), 1.86 (br s, 1H, NH); δ_C (CDCl$_3$, 63 MHz) 175.51 (*C*O$_2$CH$_3$), 158.72 (C-4''), 136.25 (C-7'a), 131.83 (C-1''), 129.48 (C-2'' and C-6''), 127.56 (C-3'a), 122.92 (C-2'), 122.16 (C-5'), 119.51 (C-4'), 118.92 (C-6'), 113.80 (C-3'' and C-5''), 111.38 (C-7'), 111.23 (C-3'), 61.14 (C-2), 55.36 (C4''-OCH$_3$), 51.86 and 51.63 (C-α and CO$_2$*C*H$_3$); 29.40 (C-3).

Data for **12a**.HCl: Anal. Calcd for C$_{20}$H$_{23}$N$_2$O$_3$Cl: C, 64.08; H, 6.18; N, 7.47. Found: C, 64.37; H, 6.32; N, 7.27; mp > 300 °C (ethanol); ν_{max} (KBr): 2840-2605 (NH$_2^+$), 1726 (CO$_2$CH$_3$), 1249 (C-O) cm^{-1}; δ_H (CDCl$_3$, 250 MHz) 11.53 (br s, 1H, NH^i), 7.48 (m, 3H, H-4', H-2'' and H-6''), 7.36 (d, 1H, *J* 7.9 Hz, H-7'), 7.23 (d, 1H, *J* 2.1 Hz, H-2'), 6.97 (m, 4H, H-5', H-6', H-3'' and H-5''), 4.10 (d, 2H, *J* 4.8 Hz, H-α), 4.03 (m, 1H, H-2), 3.76 (s, 3H, C4''-OC*H*$_3$), 3.50 (m, 4H, H-3 and CO$_2$C*H*$_3$), 3.26 (m, 1H, H-3); δ_C (CDCl$_3$, 63 MHz) 168.99 (*C*O$_2$CH$_3$), 159.67 (C-4''), 136.07 (C-7'a), 131.96 (C-2'' and

C-6''), 127.86 (C-1''), 126.74 (C-3'a), 124.59 (C-2'), 121.08 (C-5'), 118.48 (C-4'), 118.01 (C-6'), 113.81 (C-3'' and C-5''), 111.52 (C-7'), 106.48 (C-3'), 58.97 (C-2), 55.14 (C4''-O*C*H_3), 52.47 ($CO_2C H_3$), 48.64 (C-α), 25.58 (C-3).

Methyl (*S*)-*N'*-(2'',4''-Dimethoxybenzyliden)tryptophanate (11b)

A suspension of *S*-tryptophan methyl ester (2 g, 9.2 mmol) and 2,4-dimethoxybenzaldehyde (1.98 g, 11.9 mmol) in dry benzene (30 mL) was stirred at rt for 1 h. Finely powdered anhydrous Na_2SO_4 (10 g) was added, and the suspension was vigorously stirred at rt for 14 h. The solvent was concentrated and the residue was suspended in CH_2Cl_2 (50 mL) and stirred at rt for 5 min. Na_2SO_4 was filtered off and washed with CH_2Cl_2 (2 x 50 mL); the combined filtrates were concentrated. The residue was recrystallized from $CHCl_3$-petroleum ether, yielding 2.787 g (83 %) of **11b**, as white crystals. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.64; H, 6.12; N, 7.41; mp 125-127 °C (chloroform-petroleum ether); $[\alpha]_D^{25}$ + 1.4° (*c* 0.50, $CHCl_3$); ν_{max} (KBr) 1736 (CO_2CH_3), 1605 (C=N), 1273 and 1208 (C-O) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.35 (s, 1H, H-α), 8.25 (br s, 1H, NH[i]), 7.99 (d, 1H, *J* 8.6 Hz, H-6''), 7.67 (dd, 1H, *J* 8.4 and 1.4 Hz, H-4'), 7.30 (dd, 1H, *J* 6.7 and 1.3 Hz, H-7'), 7.15 (m, 2H, H-5' and H-6'), 6.94 (d, 1H, *J* 2.2 Hz, H-2'), 6.49 (dd, 1H, *J* 8.6 and 2.2 Hz, H-5''), 6.37 (d, 1H, *J* 2.2 Hz, H-3''), 4.29 (dd, 1H, *J* 8.0 and 5.7 Hz, H-2), 3.81 (s, 3H, C4''-OC*H*$_3$), 3,71 (s, 6H, C2''-OC*H*$_3$ and $CO_2C H_3$), 3.55 (dd, 1H, *J* 14.4 and 5.6 Hz, H-3), 3,24 (dd, 1H, *J* 14.4 and 8.1 Hz, H-3), δ_C ($CDCl_3$, 63 MHz) 173.19 (*C*O_2CH_3), 163.52 (*C*=N), 160.43 (C-2''), 159.36 (C-4''), 136.24 (C-7'a), 129.17 (C-6''), 127.56 (C-3'a), 123.57 (C-2'), 121.88 (C-5'), 119.32 (C-4'), 118.94 (C-6'), 117.52 (C-1''), 111.25 (C-7'), 110.93 (C-3'), 105.41 (C-5''), 98.02 (C-3''), 74.37 (C-2), 55.49 (C2''-O*C*H_3 and C4'-O*C*H_3), 52.26 ($CO_2C H_3$), 29.93 (C-3).

Methyl (*S*)-*N'*-(*2,4*-Dimethoxybenzyl)tryptophanate (12b)

Sodium borohydride (273 mg, 7.2 mmol) was added in small portions to a solution of imine (**11b**) (2.200 g, 6.01 mmol) in methanol (20 mL). The reaction mixture was stirred at rt under an argon atmosphere for 15 h. The solvent was concentrated, and the residue was suspended in water (10 mL), which was extracted with ethyl acetate (4 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated, and the residue was chromatographed on silica gel, eluting with 1:1 petroleum ether-ethyl acetate, yielding 1.92 g (87 %) of **12b** as a yellow oil. Anal. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.36; H, 6.33; N, 7.43; $[\alpha]_D^{25}$ - 1.4° (*c* 2.91, $CHCl_3$); ν_{max} (KBr) 3405 (NH), 1735 (CO_2CH_3), 1288 and 1207 (C-O) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.78 (br s, 1H, NH[i]), 7.51 (d, 1H, *J* 7.8 Hz, H-4'), 7.30 (d, 1H, *J* 8.0 Hz, H-7'), 7.16 (td, 1H, *J* 7.7 and 0.8 Hz, H-6'), 7.06 (m, 2H, H-5' and H-6''), 6.92 (d, 1H, *J* 2.1 Hz, H-2'), 6.35 (dd, 1H, *J* 8.2 and 2.3 Hz, H-5''), 6.26 (d, 1H, *J* 2.3 Hz, H-3''), 3.81 (d, 1H, *J* 13.3 Hz, H-α), 3.76 (s, 3H, $C_{4''}$-OC*H*$_3$), 3.68 (m, 4H, H-α, H-2 and $CO_2C H_3$), 3.40 (s, 3H, $C_{2''}$-OC*H*$_3$), 3.23 (dd, 1H, *J* 14.3 and 5.6 Hz, H-3), 3.08 (dd, 1H, *J* 14.3 and 8.3 Hz, H-3), 2.27 (br s, 1H, NH); δ_C ($CDCl_3$, 63 MHz) 175.43 (*C*O_2CH_3), 160.25 (C-2''), 158.64 (C-4''), 136.48 (C-7'a), 130.61 (C-6''), 127.55 (C-3'a), 123.45 (C-2'), 122.06 (C-5'), 119.43 (C-1''), 119.32 (C-4'), 118.81 (C-6'), 111.35 (C-7'), 110.65 (C-3'), 103.60 (C-5''), 98.38 (C-3''), 60.78 (C-2), 55.43 ($C_{4'}$-O*C*H_3), 54.82 ($C_{2''}$-O*C*H_3), 51.92 (COO*C*H_3), 47.59 (C-α), 29.50 (C-3).

Methyl *N*-*tert*-Butyloxycarbonyl-*N'*-(*p*-methoxybenzyl)-(*S*)-alanyl-(*S*)-tryptophanate (13a)

Method A. To an ice-cooled, stirred solution of *N-tert*butyloxycarbonyl-L-alanine (567 mg, 3 mmol) and triethylamine (0.42 mL, 3 mmol) in dry THF (20 mL) was slowly added ethyl chloroformate (0.3 mL, 3 mmol). The suspension thus obtained was stirred at 0 °C for 15 min and a solution of compound **12a** (500 mg, 1.5 mmol) in dry THF (2 mL) was added. The suspension was stirred at 80 °C for 23 h, then cooled, concentrated and suspended in CH_2Cl_2 (50 mL), which was washed with water (3 x 5 mL), dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel, eluting with 1:1 hexane-ethyl acetate, yielding 107 mg (15 %) of dipeptide (**13a**) and 184 mg (37 %) of recovered (**12a)**.

Method B. A solution of **12a** (114 mg, 0.34 mmol), *N-tert*-butyloxycarbonyl-L-alanine (64 mg, 0.34 mmol) and EDC (65 mg, 0.34 mmol) in dry dioxane (20 mL) was stirred at rt for 93 h and then refluxed for 21 h. *N-tert*-Butyloxycarbonyl-L-alanine (64 mg, 0.34 mmol) and EDC (65 mg, 0.34 mmol) were added and the reaction was refluxed for further 21 h, cooled and concentrated. The residue was dissolved in CH_2Cl_2 (50 mL) and washed sequentially with 1M HCl (10 mL), 9 % aqueous $NaHCO_3$ (10 mL) and water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated and the residue was chromatographed on silica gel, eluting with 2:1 hexane-ethyl acetate, yielding 51 mg (30 %) of **13a** and 20 mg (18 %) of recovered **12a**.

Method C. A solution of **12a** (224 mg, 0.67 mmol), *N-tert*-butyloxycarbonyl-L-alanine (375 mg, 2.01 mmol) and DCC (411 mg, 2.01 mmol) in dry THF (20 mL) was stirred at 80 °C for 24 h. Further amounts of *N-tert*-butyloxycarbonyl-L-alanine (125 mg, 0.67 mmol) and DCC (137 mg, 0.67 mmol) were added, and the reaction mixture was stirred at rt for 48 h. A precipitate of dicyclohexylurea was filtered off, and the filtrate was dissolved in CH_2Cl_2 (50 mL), washed with water (3 x 10 mL), dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel eluting with 1.5:1 hexane-ethyl acetate (1.5:1), yielding 265 mg (79 %) of **13a**.

Data for **13a**: Anal. Calcd for $C_{28}H_{35}N_3O_6$: C, 65.99; H, 6.92; N, 8.25. Found: C, 66.17; H, 6.97; N, 8.09; mp 68-70 °C ($CHCl_3$-hexane); $[\alpha]_D^{25}$ - 7.6° (*c* 0.21, $CHCl_3$); ν_{max} (NaCl) 1738 and 1710 (CO_2R), 1643 (CO-N), 1247 (C-O) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.17 (br s, 1H, NH^i), 7.44 (d, 1H, *J* 7.9 Hz, H-4'), 7.38 (d, 1H, *J* 8.1 Hz, H-7'), 7.21 (t, 1H, *J* 8.0 Hz, H-6'), 7.10 (t, 1H, *J* 7.8 Hz, H-5'), 6.96 (s, 1H, H-2'), 6.87 (d, 2H, *J* 8.6 Hz, H-2'' and H-6''), 6.71 (d, 2H, *J* 8.7 Hz, H-3'' and H-5''), 5.48 (d, 1H, *J* 8.1 Hz, NH-Ala), 4.64 (quint, 1H, *J* 7.0 Hz, H-Ala), 4.40 (d, 1H, *J* 15.7 Hz, H-α), 4.24 (dd, 1H, *J* 9.0 and 5.7 Hz, H-2), 3.75 (s, 3H, $C_{4''}$-OCH_3), 3.64 (s, 3H, CO_2CH_3), 3.45 (m, 2H, H-α and H-3), 1.43 (s, 3H, $CO_2C(CH_3)_3$), 1.28 (d, 3H, *J* 6.9 Hz, CH_3-Ala); δ_C ($CDCl_3$, 63 MHz) 172.92 (CO_2CH_3), 170.88 (CO-Ala), 159.27 (C-4''), 151.29 ($CO_2C(CH_3)_3$), 136.35 (C-7'a), 129.57 (C-2'' and C-6''), 127.31 (C-3'a), 126.94 (C-1''), 123.28 (C-2'), 122.33 (C-5'), 119.64 (C-4'), 118.75 (C-6'), 113.78 (C-3'' and C-5''), 111.83 (C-3'), 111.44 (C-7'), 79.68 ($CO_2C(CH_3)_3$), 59.07 (C-2), 55.36 ($C_{4''}$-OCH_3), 52.17 (CO_2CH_3), 51.89 (C-α), 46.87 (Cα-Ala), 28.44 ($CO_2C(CH_3)_3$), 24.65 (C-3), 19.43 (CH_3-Ala).

Methyl *N*-*tert*-butyloxycarbonyl-*N'*-(2'',4''-dimethoxybenzyl)-(*S*)-alanyl-(*S*)-tryptophanate (13b)

Method A. A solution of **12b** (1.18 g, 3.2 mmol), *N*-*tert*-butyloxycarbonyl-L-alanine (2.43 g, 12.8 mmol) and EDC (2.45 g, 12.8 mmol) in dry CH_2Cl_2 (50 mL) was stirred at rt under an argon atmosphere for 22 h. The solution was sequentially washed with 1 M aqueous HCl (10 mL), 9 % aqueous $NaHCO_3$ (10 mL) and water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated and the residue was chromatographed on silica gel eluting with 1:1 petroleum ether-ethyl acetate, yielding 1.129 g (67 %) of a *ca.* 1.5:1 mixture of the dipeptides (**13b**) and (**13c**). Recrystallization of this mixture from ethyl ether gave 827 mg (48 %) of **13b**, as white crystals.

Method B. A solution of **12b** (2.186 g, 5.94 mmol), *N*-*tert*-butyloxycarbonyl-L-alanine (4.5 g, 23.8 mmol) and DCC (4.91 g, 23.8 mmol) in dry THF (50 mL) was stirred at rt for 44 h, under an argon atmosphere. A precipitate of dicyclohexylurea was filtered off, and the filtrate was concentrated to dryness. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (3 x 10 mL). The CH_2Cl_2 layer was dried (Na_2SO_4) and concentrated, and the residue was chromatographed on silica gel eluting with 1:1 petroleum ether-ethyl acetate, yielding 2.337 g (73 %) of a *ca.* 3:1 mixture of the dipeptides (**13b**) and (**13c**). Recrystallization of this mixture from ethyl ether gave 1.761 g (55 %) of **13b**, as white crystals.

Data for **13b**. Anal. Calcd for $C_{29}H_{37}N_3O_7$: C, 64.55; H, 6.91; N, 7.79. Found: C, 64.36; H, 6.83; N, 7.70; mp 172-173 °C (ether); $[\alpha]_D^{25}$ - 93.8° (*c* 0.56, $CHCl_3$); ν_{max} (NaCl) 1736 and 1708 (CO_2R), 1643 (CO-N), 1213 (C-O) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.12 (br s, 1H, NH^i), 7.53 (d, 1H, *J* 7.6 Hz, H-4'), 7.38 (d, 1H, *J* 7.8 Hz, H-7'), 7.16 (m, 2H, H-5' and H-6'), 6.96 (d, 1H, *J* 1.8 Hz, H-2'), 6.62 (d, 1H, *J* 8.2 Hz, H-6''), 6.31 (d, 1H, *J* 2.2 Hz, H-3''), 6.25 (dd, 1H, *J* 8.2 and 2.3 Hz, H-5''), 5.64 (d, 1H, *J* 7.8 Hz, NH-Ala), 4.95 (quint, 1H, *J* 7.2 Hz, H-Ala), 4.37 (d, 1H, *J* 15.1 Hz, H-α), 4.13 (m, 1H, H-2), 3.75 (s, 3H, $C_{4''}$-OCH_3), 3.64 (s, 3H, CO_2CH_3), 3.55 (s, 3H, $C_{2''}$-OCH_3), 3.46 (m, 2H, H-α and H-3), 1.45 (s, 3H, $CO_2C(CH_3)_3$), 1.29 (d, 3H, *J* 6.9 Hz, CH_3-Ala); δ_C ($CDCl_3$, 63 MHz) 172.63 (CO_2CH_3), 171.06 (CO-Ala), 161.07 (C-2''), 159.41 (C-4''), 155.10 ($CO_2C(CH_3)_3$), 136.43 (C-7'a), 131.11 (C-6''), 127.24 (C-3'a), 123.44 (C-2'), 122.21 (C-5'), 119.52 (C-4'), 118.70 (C-6'), 115.53 (C-1''), 111.91 (C-3'), 111.52 (C-7'), 103.27 (C-5''), 98.37 (C-3''), 79.38 ($CO_2C(CH_3)_3$), 58.43 (C-2), 55.37 (C4''-OCH_3), 54.99 ($C_{2''}$-OCH_3), 52.05 (CO_2CH_3), 48.60 (C-α), 46.79 (C-Ala), 28.48 ($CO_2C(CH_3)_3$), 24.47 (C-3), 20.19 (CH_3-Ala).

(3*S*,6*S*)-6-(3'-Indolylmethyl)-3-methyl-1-(*p*-methoxybenzyl)-2,5-piperazinedione (14a)

Method A. Trifluoroacetic acid (1 mL) was added dropwise to a solution of **13a** (100 mg, 0.2 mmol) in CH_2Cl_2 (1 mL), previuosly cooled in an ice bath. The solution was stirred at 0 °C for 30 min, neutralized with 13 % aqueous ammonium hydroxide and extracted with $CHCl_3$ (10 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, yielding 74 mg (95 %) of piperazinedione (**14a**).

Method B. Compound (**13a**) (20 mg, 0.04 mmol) was placed in a 50 mL round-bottomed flask, which was submitted to an argon stream for at least 10 min. The flask was then heated neat at 200 °C for 2 h, under an argon atmosphere. The remaining white solid (15 mg, 100 %) was identified as analytically pure compound (**14a**).

Data for **14a**: Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 70.23; H, 5.89; N, 10.99; mp 110-113 °C (ethanol); $[\alpha]_D^{25}$ - 26.5° (*c* 0.16, $CHCl_3$); ν_{max} (NaCl) 1643 (CO-N), 1248 (C-O) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.17 (br s, 1H, NH^i), 7.63 (d, 1H, *J* 7.6 Hz, H-4'), 7.35 (d, 1H, *J* 7.8 Hz, H-7'), 7.15 (m, 4H, H-5', H-6', H-2'' and H-6''), 6.98 (d, 1H, *J* 2.3 Hz, H-2'), 6.86 (d, 2H, *J* 8.6 Hz, H-3'' and H-5''), 5.71 (br s, 1H, N_4-H), 5.54 (d, 1H, *J* 14.5 Hz, H-α), 4.17 (t, 1H, *J* 4.2 Hz, H-6), 3.88 (m, 2H, H-3 and H-α), 3.80 (s, 3H, C4''-OC*H*$_3$), 3.54 (dd, 1H, *J* 15.0 and 3.7 Hz, H-Trp), 3.37 (dd, 1H, *J* 15.0 and 4.5 Hz, H-Trp), 0.43 (d, 3H, *J* 7.1 Hz, C_3-C*H*$_3$); δ_C ($CDCl_3$, 63 MHz) 167.50 (C-5), 167.01 (C-2), 159.57 (C-4''), 135.91 (C-7'a), 130.12 (C-2'' and C-6''), 127.79 (C-3'a), 127.39 (C-1''), 123.94 (C-2'), 122.52 (C-4'), 120.19 (C-5'), 119.16 (C-6'), 114.43 (C-3'' and C-5''), 111.27 (C-7'), 109.09 (C-3'), 58.86 (C-6), 55.44 ($C_{4''}$-O*C*H$_3$), 51.46 (C-3), 46.33 (C-α), 25.05 (C-Trp), 20.57 (C_3-*C*H$_3$).

Thermal Cyclization of Compounds (13b) and (13c)

The 3:1 mixture of **13b** and **13c** obtained above (2.337 g, 4.34 mmol) was heated at 200 °C for 5 h, under an argon atmosphere. The white residue was chromatographed on silica gel eluting with ethyl acetate, yielding 759 mg (43 %) of (3*S*,6*S*)-6-(3'-indolylmethyl)-3-methyl-1-(2,4-dimethoxybenzyl)-2,5-piperazinedione (**14b**) and 229 mg (13 %) of (3*S*,6*R*)-6-(3'-indolylmethyl)-3-methyl-1-(2,4-dimethoxybenzyl)-2,5-piperazinedione (**14c**), both as off-white solids.

Application of the same conditions to pure compound (**13b**) (250 mg, 0.37 mmol) gave 153 mg (81 %) of **14b**.

Data for **14b**: Anal. Calcd for $C_{23}H_{25}N_3O_4$: C, 67.80; H, 6.18; N, 10.31. Found: C, 67.72; H, 6.32; N, 10.04; mp 110-111 °C (ethanol); $[\alpha]_D^{25}$ - 45,4 ° (*c* 0.50, $CHCl_3$); ν_{max} (NaCl) 3277 (NH), 1644 (CO-N), 1215 (C-O) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.29 (br s, 1H, NH^i), 7.65 (d, 1H, *J* 7.7 Hz, H-4'), 7.35 (d, 1H, *J* 7.7 Hz, H-7'), 7.15 (m, 3H, H-5', H-6' and H-6''), 6.98 (d, 1H, *J* 2.3 Hz, H-2'), 6.44 (m, 2H, H-3'' and H-5''), 5.95 (br s, 1H, N_4-H), 5.30 (d, 1H, *J* 14.3 Hz, H-α), 4.29 (t, 1H, *J* 4.1 Hz, H-6), 4.22 (d, 1H, *J* 14.3 Hz, H-α), 3.81 (m, 7H, H-3, $C_{2''}$-OC*H*$_3$ and $C_{4''}$-OC*H*$_3$), 3.56 (dd, 1H, *J* 15.0 and 3.4 Hz, H-Trp), 3.44 (dd, 1H, *J* 15.1 and 4.3 Hz, H-Trp), 0.35 (d, 3H, *J* 7.1 Hz, C_3-C*H*$_3$); δ_C ($CDCl_3$, 63 MHz) 167.94 (C-5), 166.95 (C-2), 160.92 (C-2''), 158.92 (C-4''), 135.88 (C-7'a), 132.04 (C-6''), 127.93 (C-3'a), 124.10 (C-2'), 122.36 (C-4'), 120.08 (C-5'), 119.18 (C-6'), 116.19 (C-1''), 111.22 (C-7'), 109.22 (C-3'), 104.66 (C-5''), 98.54 (C-3''), 59.50 (C-6), 55.57 and 55.55 ($C_{2''}$-O*C*H$_3$ and $C_{4''}$-O*C*H$_3$), 51.33 (C-3), 41.30 (C-α), 26.99 (C-Trp), 20.37 (C_3-*C*H$_3$).

Data for **14c**: Anal. Calcd for $C_{23}H_{25}N_3O_4$: C, 67.80; H, 6.18; N, 10.31. Found: C, 67.92; H, 6.36; N, 9.99; mp 102-104 °C (ethanol); $[\alpha]_D^{25}$ - 13.7 ° (*c* 0.255, $CHCl_3$); ν_{max} (NaCl) 3273 (NH), 1678 (CO-N), 1211 (C-O) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.34 (br s, 1H, NH^i), 7.64 (d, 1H, *J* 7.8 Hz, H-4'), 7.34 (d, 1H, *J* 7.9 Hz, H-7'), 7.15 (m, 3H, H-5', H-6' and H-6''), 6.91 (d, 1H, *J* 2.3 Hz, H-2'), 6.44 (m, 2H, H-3'' and H-5''), 5.63 (br s, 1H, N_4-H), 5.20 (d, 1H, *J* 14.4 Hz, H-α), 4.25 (t, 1H, *J* 3.7 Hz, H-6), 4.19 (d, 1H, *J* 14.4 Hz, H-α), 3.82 and 3.80 (2 s, 6H, $C_{2''}$-OC*H*$_3$ and $C_{4''}$-OC*H*$_3$), 3.50 (dd, 1H, *J* 14.9 and 3.4 Hz, H-Trp), 3.33 (dd, 1H, *J* 14.9 and 4.8 Hz, H-Trp), 2.60 (q, 1H, *J* 6.8 Hz, H-3), 1.13 (d, 3H, *J* 6.8 Hz, C_3-C*H*$_3$); δ_C ($CDCl_3$, 63 MHz) 169.52 (C-5), 168.08 (C-2), 160.88 (C-2''), 158.85 (C-4''), 136.08 (C-7'a), 131.59 (C-6''), 127.44 (C-3'a), 124.39 (C-2'), 122.46 (C-4'), 120.00 (C-5'),

118.97 (C-6'), 116.37 (C-1''), 111.29 (C-7'), 109.12 (C-3'), 104.69 (C-5''), 98.59 (C-3''), 60.42 (C-6), 55.53 and 55.51 ($C_{2''}$-O*C*H_3 and $C_{4''}$-O*C*H_3), 49.39 (C-3), 41.71 (C-α), 26.95 (C-Trp), 19.03 (C_3-*C*H_3).

(3*S*,6*S*)-1-(2'',4''-Dimethoxybenzyl)-5-ethoxy-6-(3'-indolylmethyl)-3-methyl-2,5-piperazinedione (15)

A solution of **14b** (189 mg, 0.464 mmol) and triethyloxonium tetrafluoroborate (Meerwein salt) (279 mg, 1.39 mmol) in dry CH_2Cl_2 (20 mL), containing suspended Na_2CO_3 (246 mg, 2.32 mmol), was stirred at rt under an argon atmosphere for 18 h. The suspension was poured on ice (*ca*. 5 g) and extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated and the residue was chromatographed on silica gel eluting with ethyl acetate, yielding 154 mg (76 %) of **15**, as an off-white solid. Anal. Calcd for $C_{25}H_{29}N_3O_4$: C, 68.95; H, 6.71; N, 9.65. Found: C, 68.83; H, 6.52; N, 9.53; mp 70-72 °C (chlrorform-hexane); $[\alpha]_D^{25}$ - 5.7° (*c* 0.175, $CHCl_3$); ν_{max} (NaCl) 3267 (NH), 1697 (CO-N), 1634 (C=N), 1213 (C-O) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.55 (br s, 1H, NH^i), 7.38 (d, 1H, *J* 7.6 Hz, H-4'), 7.26 (m, 1H, H-7'), 7.15 (d, 1H, *J* 9.0 Hz, H-6''), 7.13 (m, 2H, H-5' and H-6'), 6.81 (d, 1H, *J* 1.4 Hz, H-2'), 6.35 (m, 2H, H-3'' and H-5''), 5.28 (d, 1H, *J* 14.5 Hz, H-α), 4.14 (d, 1H, *J* 14.5 Hz, H-α), 4.09 (m, 1H, H-6), 3.90 (m, 3H, H-3 and OC*H*$_2$CH$_3$), 3.72 and 3.71 (2 s, 6H, $C_{2''}$-OC*H*$_3$ and $C_{4''}$-OC*H*$_3$), 3.28 (m, 2H, H-Trp), 1.18 (t, 3H, *J* 7.1 Hz, OCH$_2$C*H*$_3$), 0.34 (d, 3H, *J* 7.2 Hz, C_3-C*H*$_3$); δ_C ($CDCl_3$, 63 MHz) 170.99 (C-2), 160.71 (C-2''), 158.95 (C-4''), 158.33 (C-1), 135.94 (C-7'a), 131.70 (C-6''), 128.04 (C-3'a), 123.78 (C-2'), 122.02 (C-4'), 119.48 (C-5'), 118.33 (C-6'), 116.63 (C-1''), 111.51 (C-7'), 109.04 (C-3'), 104.66 (C-5''), 98.55 (C-3''), 61.43 (O*C*H$_2$CH$_3$), 56.41 (C-6), 55.57 and 55.51 ($C_{2'',4''}$-O*C*H_3), 55.46 (C-3), 40,01 (C-α), 26.27 (C-Trp), 20.42 (C_3-*C*H_3), 14.6 (OCH$_2$*C*H$_3$).

Acylation of 14b with *o*-Azidobenzoyl Chloride

o-Azidobenzoyl chloride was prepared from *o*-azidobenzoic acid (66.2 mg, 0.41 mmol) as indicated for the synthesis of **6**. A solution of **14b** (150 mg, 0.37 mmol) in dry THF (20 mL), under an argon atmosphere, was cooled to -78 °C and treated dropwise with a 0.5 M solution of potassium hexamethyldisilazide in toluene (0.54 mL, 0.27 mmol). The solution was stirred at - 78 °C for 15 min, becoming deep yellow in colour. A solution of the crude *o*-azidobenzoyl chloride in dry THF (10 mL) was cooled to - 78 °C and added dropwise *via* cannula. The solution was left to reach rt over 19 h, while stirred. The solvent was concentrated and the residue was dissolved in CH_2Cl_2 (15 mL). This solution was washed with saturated aqueous NH_4Cl (10 mL), dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel eluting with 2:1 petroleum ether-ethyl acetate, yielding 89 mg (59 %) of recovered **14b**, 55 mg of (3*S*,6*S*)-1-(*o*-azidobenzoyl)-4-(2'',4''-dimethoxybenzyl)-3-(3'-indolylmethyl)-6-methyl-2,5-piperazine-dione (**16**) (27 % isolated, 68 % based on unrecovered **14b**) and 11 mg of (3*S*,6*S*)-1-(*o*-azidobenzoyl)-4-(2'',4''-dimethoxybenzyl)-3-[1'(*o*-azidobenzoyl)-3'-indolylmethyl]-6-methyl-2,5-piperazinedione (**17**) (4 % isolated, 10 % based on unrecovered **14b**).

Data for **16**: Anal. Calcd for $C_{30}H_{28}N_6O_5$: C, 65.21; H, 5.11; N, 15.21. Found: C, 65.12; H, 5.23; N, 15.39; mp 87-89 °C (chloroform-hexane); $[\alpha]_D^{25}$ - 65.2° (*c* 0.365, $CHCl_3$); ν_{max} (NaCl) 3249 (NH), 2127 (N_3), 1692 (CO-N), 1290 (C-O) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.16 (br s, 1H, NH^i), 7.54 (d,

1H, *J* 7.7 Hz, H-6’’’), 7.42 (td, 1H, *J* 8.0 and 1.6 Hz, H-5’’’), 7.34 (m, 2H, H-4’ and H-3’’’), 7.16 (m, 5H, H-5’, H-6’, H-7’, H-6’’ and H-4’’’), 7.03 (s, 1H, H-2’), 6.45 (m, 2H, H-3’’ and H-5’’), 5.35 (d, 1H, *J* 14.4 Hz, H-α), 4.82 (q, 1H, *J* 7.1 Hz, H-6), 4.51 (t, 1H, *J* 4.9 Hz, H-3), 4.07 (d, 1H, *J* 14.4 Hz, H-α), 3.78 and 3.75 (2 s, 6H, $C_{2''}$-OCH_3 and $C_{4''}$-OCH_3), 3.49 (m, 2H, H-Trp), 0.82 (d, 3H, *J* 7.1 Hz, C_6-CH_3); δ_C ($CDCl_3$, 63 MHz) 170.36 (C-2), 167.95 (C-5), 167.58 (*C*O-ArN_3), 160.97 (C-2’’), 158.91 (C-4’’), 136.11 and 136.02 (C-7’a and C-1’’’), 131.68 and 131.52 (C-6’’ and C-4’’’), 129.54 (C-6’’’), 128.41 (C-2’’’), 127.31 (C-3’a), 125.26 (C-5’’’), 124.01 (C-2’), 122.58 (C-4’), 120.15 (C-5’), 119.09 (C-3’’’), 117.94 (C-6’), 115.87 (C-1’’), 111.40 (C-7’), 109.67 (C-3’), 104.86 (C-5’’), 98.71 (C-3’’), 60.73 (C-3), 55.56 and 55.50 ($C_{2''}$-O*C*H_3 and $C_{4''}$-O*C*H_3), 54.24 (C-6), 41.26 (C-α), 27.55 (C-Trp), 19.41 (C_6-*C*H_3).

Data for **17**: Anal. Calcd for $C_{37}H_{31}N_9O_6$: C, 63.69; H, 4.48; N, 18.07. Found: C, 63.93; H, 4.73; N, 17.82; mp 89-91 °C (chloroform-hexane); $[\alpha]_D^{25}$ - 52.8° (*c* 0.265, $CHCl_3$); ν_{max} (NaCl) 2129 (N_3), 1671 (CO-N), 1295 (C-O) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.61 (td, 1H, *J* 6.4 and 1.5 Hz, H-5’’’), 7.35 (m, 11H, H-2’, H-4’, H-5’, H-6’, H-7’, H-3’’’, H-4’’’, H-6’’’, H-4^{iv},5^{iv},6^{iv}), 7.11 (d, 1H, *J* 9.0 Hz, H-6’’), 7.03 (d, 1H, *J* 8.0 Hz, H-3^{iv}), 6.38 (m, 2H, H-3’’ and H-5’’), 5.20 (d, 1H, *J* 14.4 Hz, H-α), 4.90 (q, 1H, *J* 7.1 Hz, H-6), 4.53 (t, 1H, *J* 5.4 Hz, H-3), 3.97 (d, 1H, *J* 14.4 Hz, H-α), 3.78 and 3.70 (2 s, 6H, $C_{2''}$-OCH_3 and $C_{4''}$-OCH_3), 3.39 (dd, 1H, *J* 14.8 Hz and *J* 4.8 Hz, H-Trp), 3.28 (dd, 1H, *J* 14.8 Hz and *J* 5.7 Hz, H-Trp), 1.20 (d, 3H, *J* 7.1 Hz, C_6-CH_3); δ_C ($CDCl_3$, 63 MHz) 169.56 (C-2), 167.72 (*C*O-ArN_3), 167.08 (C-5), 165.77 (*C*O-ArN_3), 160.75 (C-2’’), 158.53 (C-4’’), 137.82, 136.03 and 135.54 (C-7’a, C-1’’’ and C-1^{iv}), 132.14, 131.65 and 131.31 (C-6’’, C-4’’’ and C-4^{iv}), 130.28 (C-3’a), 129.38 and 129.21 (C-6’’’ and C-6^{iv}), 128.23, 128.00 and 126.54 (C-2’, C-2’’’ and C-2^{iv}), 125.75, 125.07 and 124.98 (C-4’, C-5’’’ and C-5^{iv}), 124.45 (C-5’), 119.09 and 118.79 (C-3’’’ and C-3^{iv}), 117.77 (C-6’), 116.94 (C-3’), 116.57 (C-7’), 115.45 (C-1’’), 104.63 (C-5’’), 98.42 (C-3’’), 59.94 (C-3), 55.46 ($C_{2''}$-O*C*H_3 and $C_{4''}$-O*C*H_3), 54.16 (C-6), 41.58 (C-α), 28.86 (*C*H_2-Trp), 20.03 (C_6-*C*H_3).

(1*S*,4*S*)-2-(2’’,4’’-Dimethoxybenzyl)-1-(3’-indolylmethyl)-4-methyl-2,3,4,6-tetrahydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (18)

A solution of **16** (220 mg, 0.40 mmol) and tributylphosphine (150 µl, 0.60 mmol) in toluene (5 mL) was stirred at 80 °C for 2.5 h under an argon atmosphere. The solvent was concentrated under reduced pressure and the residue was chromatographed on silica gel eluting with a gradient from 1:1 ethyl ether-petroleum ether to neat ethyl ether, yielding 152 mg (75 %) of **18** as an off-white solid. Anal. Calcd for $C_{30}H_{28}N_4O_4$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.79; H, 5.78; N, 11.20; mp 108-110 °C (chloroform-hexane); $[\alpha]_D^{25}$ - 24.5 (*c* 0.33, $CHCl_3$); ν_{max} (NaCl) 3311 (NH), 1660 (CO-N), 1213 (C-O) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.60 (br s, 1H, NH^i), 8.22 (d, 1H, *J* 7.7 Hz, H-7), 7.77 (t, 1H, *J* 7.2 Hz, H-9), 7.67 (d, 1H, *J* 7.2 Hz, H-10), 7.46 (t, 1H, *J* 7.7 Hz, H-8), 7.30 (m, 2H, H-4’ and H-7’), 7.10 (m, 2H, H-6’ and H-6’’), 6.98 (s, 1H, H-2’), 6.89 (t, 1H, *J* 7.7 Hz, H-5’), 6.37 (m, 2H, H-3’’ and H-5’’), 5.16 (m, 2H, H-4 and H-α), 5.02 (t, 1H, *J* 5.3 Hz, H-1), 4.01 (d, *J* 14.3 Hz, H-α), 3.74 and 3.70 (2 s, 6H, $C_{2'',4''}$-OCH_3), 3.62 (m, 2H, H-Trp), 1.07 (d, 3H, *J* 7.0 Hz, C_4-CH_3); δ_C ($CDCl_3$, 63 MHz) 167.40 (C-3), 160.87 and 160.54 (C-2’’ and C-6), 158.88 (C-4’’), 151.54 (C-11a), 147.48 (C-10a), 136.15 (C-7’a), 134.75 (C-9), 132.09 (C-6’’), 127.50 (C-3’a), 126.90, 126.86 and 126.79 (C-7, C-8 and C-10),

123.83 (C-2'), 122.47 (C-5'), 120.35 (C-6a), 120.00 (C-4'), 118.55 (C-6'), 116.16 (C-1''), 111.49 (C-7'), 109.74 (C-3'), 104.50 (C-5''), 98.59 (C-3''), 61.00 (C-1), 55.50 and 55.47 ($C_{2'',}$-O*C*H_3 and $C_{4'',}$-O*C*H_3), 52.46 (C-4), 42.87 (C-α), 31.48 (*C*H_2-Trp), 18.14 (C_4-*C*H_3).

Acid-promoted deprotection of 18

To a solution of **18** (24 mg, 0.047 mmol) in neat CF_3CO_2H (0.5 mL, 0.1 M solution) was added a drop of anisol and the solution was heated at 80 °C for 3.5 h under an argon atmosphere. After cooling, the reaction mixture was poured onto a cool (0 °C), stirred mixture of 20 % aqueous Na_2CO_3 (5 mL) and CH_2Cl_2 (5 mL). The mixture was extracted with CH_2Cl_2 (7 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel, eluting with 1:1 petroleum ether-ethyl acetate, yielding 7.5 mg (44 %) of (1*S*,4*S*)-1-(3'-indolylmethyl)-4-methyl-2,3,4,6-tetrahydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (**2**), 4 mg (22 %) of (4*S*)-2-(2",4"-dimethoxybenzyl)-4-methyl-2,3,4,6-tetrahydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (**19**), 1 mg (13 %) of (4*S*)-4-methyl-2,3,4,6-tetrahydro-1*H*-pyrazino[2,1-*b*]quinazoline-3,6-dione (**20**) and 5 mg (20 %) of recovered **18**. If heating was prolonged for 7 h 15 min, the isolated yields were: 40 % of **19** and 57 % of **20**. In the absence of anisol for 3 h, the yields obtained were: 16 % of **2**, 12 % of **19**, 13 % of **20** and 31 % of recovered **18**.

Data for **2**: mp 150-152 °C (chloroform-hexane); $[\alpha]_D^{25}$ + 50.4° (*c* 0.25, $CHCl_3$); ν_{max} (NaCl) 3284 (NH), 1678 (CO-N) cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.34 (br s, 1H, NH^i), 8.30 (d, 1H, *J* 7.8 Hz, H-7), 7.80 (m, 2H, H-9 and H-10), 7.60 (d, 1H, *J* 7.8 Hz, H-4'), 7.52 (td, 1H, *J* 7.8 and 1.5 Hz, H-8), 7.37 (d, 1H, *J* 7.1 Hz, H-7'), 7.19 (d, 1H, *J* 7.1 Hz, H-6'), 7.08 (m, 2H, H-2' and H-5'), 6.40 (br s, 1H, N_2-H), 5.23 (q, 1H, *J* 7.1 Hz, H-4), 4.85 (m, 1H, H-1), 3.54 (dd, 1H, *J* 14.3 and 3.4 Hz, H-Trp), 3.30 (dd, 1H, *J* 14.3 and 10.0 Hz, H-Trp), 1.53 (d, 3H, *J* 7.1 Hz, C_4-C*H*$_3$); δ_C ($CDCl_3$, 63 MHz) 168.63 (C-3), 160.41 (C-6), 150.09 (C-11a), 147.17 (C-10a), 136.18 (C-7'a), 134.74 (C-9), 127.17 (C-3'a), 127.00, 126.83 and 126.72 (C-7, C-8 and C-10), 123.67 (C-2'), 122.49 (C-5'), 120.12 (C-4'), 120.00 (C-6a), 118.41 (C-6'), 111.38 (C-7'), 109.28 (C-3'), 57.26 (C-1), 51.83 (C-4), 34.56 (C-Trp), 18.96 (C_4-*C*H_3); *m*/*z* (EI) 358 (7, M^+), 229 (44, M^+ - C_9H_7N); HRMS (EI): M^+, found 358.1433. $C_{21}H_{18}N_4O_2$ Anal. Calcd for 358.1430; M^+ - C_9H_7N, found 229.0850. $C_{12}H_{11}N_3O_2$ Anal. Calcd for 229.0851.

Data for **19** (oil) δ_H ($CDCl_3$, 250 MHz) 8.29 (d, 1H, *J* 6.8 Hz, H-7), 7.73 (m, 1H, H-9), 7.62 (d, 1H, *J* 7.6 Hz, H-10), 7.47 (m, 1H, H-8), 7.26 (m, 1H, H-6'), 6.47 (m, 2H, H-3' and H-5'), 5.51 (q, 1H, *J* 7.1 Hz, H-4), 4.85 (d, 1H, *J* 14.2 Hz, H-1), 4.51 (m, 2H, H-1 and H-α), 3.92 (d, 1H, *J* 13.7 Hz, H-α), 3.84 and 3.81 (2 s, 6H, $C_{2',4'}$-OC*H*$_3$), 1.58 (d, 3H, *J* 7.1 Hz, C_4-OC*H*$_3$).

Data for **20**: They were identical to those previously described.[16]

Acid-promoted deprotection of 14b

To a solution of **14b** (40 mg, 0.098 mmol) in neat CF_3CO_2H (1.0 mL, 0.1 M solution) was added a drop of anisol and the solution was heated at 80 °C for 3 h under an argon atmosphere. After cooling, the reaction mixture was poured onto a cool (0 °C), stirred mixture of 20 % aqueous Na_2CO_3 (7 mL) and CH_2Cl_2 (7 mL). The mixture was extracted with CH_2Cl_2 (7 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, yielding 20 mg (80 %) of (3*S*,6*S*)-3-(3'-indolylmethyl)-6-methyl-piperazine-2,5-dione (**4**).[13]

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