Enaminone-Based Synthesis of Dipodazine Derivatives

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A series of racemic dipodazine analogues **9** were prepared in 22–80% yield from (3*Z*,6*RS*)-3-[(dimethylamino)methylidene]-6-methyl-1-(phenylmethyl)piperazine-2,5-dione (**7**) (*Scheme 1*), which was prepared in four steps from (*RS*)-alanine methyl ester hydrochloride. The preparation of nonracemic **7** from (*S*)-alanine methyl ester hydrochloride failed, since the introduction of the enamino functionality at position 3 of the precursor **6** was accompanied by almost complete racemization.

Introduction. – Many marine natural products with potent pharmacological activities contain an indole nucleus [1]. Such indole derivatives are, *e.g.*, aplysinopsins (**1**; *Fig. 1*), which have attracted considerable interest due to their cytotoxicity towards cancer cells and their ability to affect neurotransmitters [2]. Recently, the nortopsentins and meridianins (**2**), another series of indole alkaloids with interesting antitumor properties, have been isolated from the sponge *Spongosorites ruetzleri*, and from tunicate *Aplidium meridianum* [3]. Structurally, the meridianins comprise a brominated and/or hydroxylated indole nucleus bearing a 2-aminopyrimidine substituent at the 3-position [4], and they are potent inhibitors of several protein kinases [5]. Other interesting biologically active indole alkaloids are *1*) tryptophan-dehydrobutyrine diketopiperazine (TDD; **3**) [6], a fungal metabolite isolated from *Streptomyces spectabilis* and *Streptomyces* sp. M1513-bF5; *2*) barettin (**4**) [7], isolated from the marine sponge *Geodia barretti*, a diketopiperazine condensation product of 6-bromodehydrotryptophan and arginine; as well as *3*) dipodazine (**5**) [8], a diketopiperazine derivative composed of dehydrotryptophan and glycine, which has been isolated from *Penicillium dipodomyis* and meat-associated *P. nalgiovese*. The syntheses of compounds **3**–**5** and their analogues include condensation of 1*H*-indole-3-carbaldehyde with piperazine-2,5-dione derivatives as the key-step [6–8].

Alkyl 3-(dimethylamino)propenoates and related enaminones have been recently used as building blocks for the preparation of dehydro-alanine derivatives and many heterocyclic systems such as fused pyridines, pyrimidines, pyranones, and other compounds, including some natural products (*e.g.*, indole alkaloids) and their synthetic analogues [9]. Various chiral analogues of 3-(dimethylamino)propenoates have also been prepared from commercially available, enantiomerically pure starting materials such as α-amino acids and (+)-camphor, and were employed as key intermediates and reagents in the synthesis of *1*) functionalized heterocycles, *e.g.*, 3-heteroarylalanine derivatives and related compounds, *2*) heterocyclic analogues of dipeptides, and *3*) terpene-func-

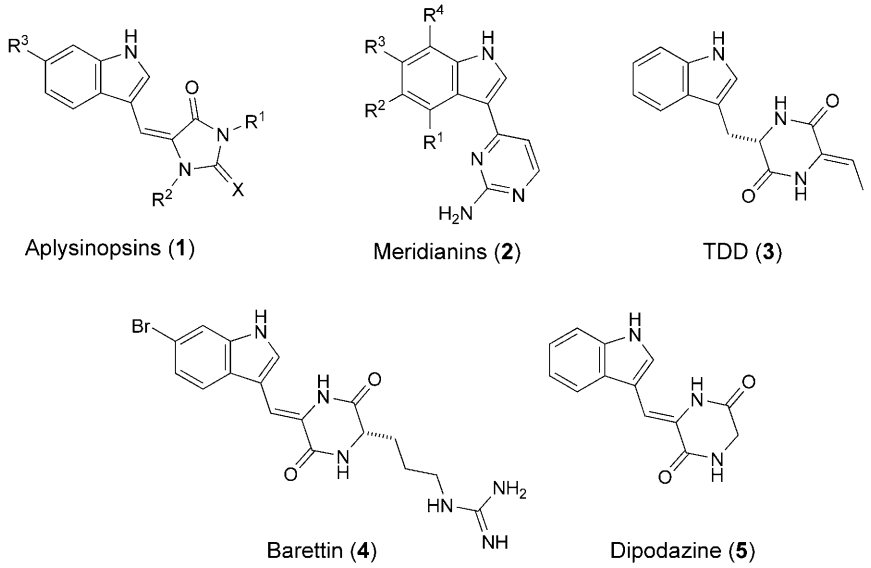


Fig. 1. *A selection of pharmaceutically relevant diketopiperazine derivatives*

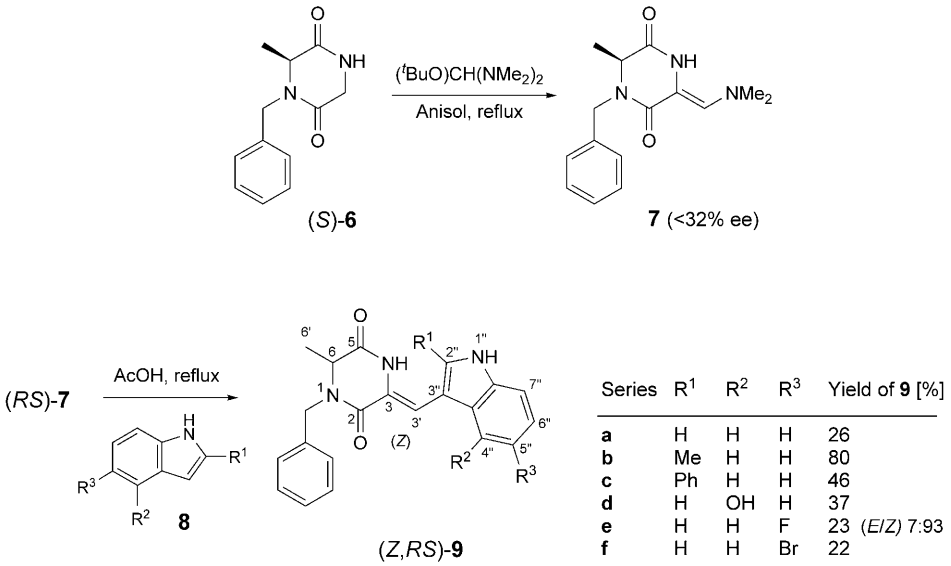
tionalized heterocycles [9–11]. Recently, utilization of 3-(dimethylamino)propenoates in combinatorial synthesis of dehydro-alanines and of fused heterocycles has also been reported [12].

In the context of the enaminone-based synthesis of natural products and their analogues, we already reported the application of 3-(dimethylamino)-2-(vinylamino)propenoates and dimethylaminomethylidene-substituted heterocycles as intermediates for the preparation of *1*) various aplysinopsins (**1**) and their analogues [13], *2*) 3-heteroarylindoles (including polycyclic meridianin (**2**) analogues with an uracil structural unit), and *3*) condensed 3-(1*H*-indol-3-yl)-2*H*-pyran-2-ones as chromene derivatives [14]. In continuation of our work on the synthesis of indole alkaloids, we now report an alternative approach towards the preparation of racemic dipodazine (**5**) analogues.

Results and Discussion. – 1. *Synthesis.* The starting compound (*S*)-6-methyl-1-(phenylmethyl)piperazine-2,5-dione (**6**) was prepared according to the literature in three steps from commercially available (*S*)-alanine methyl ester hydrochloride *via* reductive benzylation [15], followed by *N*-chloroacetylation [16] and cyclization [17]. The optical rotation data of **6** were in complete agreement with those reported [17]. As shown in *Scheme 1*, treatment of (*S*)-**6** with 1.5 equiv. of '*tert*-butoxy-bis(dimethylamino)methane' (*Bredereck*'s reagent)[1] in refluxing anisole afforded the desired (3*Z*,6*S*)-3-[(dimethylamino)methylidene]-6-methyl-1-(phenylmethyl)piperazine-2,5-dione (**7**) in 75% yield, but only with an enantiomeric excess (ee) of 32%. Attempts to avoid racemization by modification of the reaction conditions were unsuccessful. In some cases,

[1]) Systematic name: 1-(*tert*-butoxy)-*N*,*N*,*N*′,*N*′-tetramethylmethanediamine.

Scheme 1



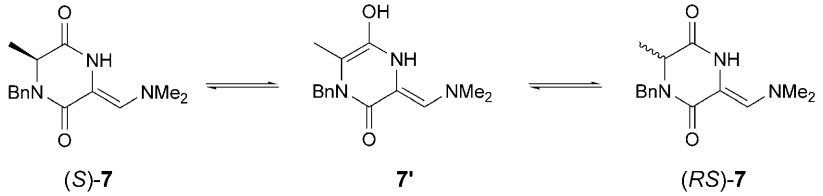
Series	R^1	R^2	R^3	Yield of **9** [%]
a	H	H	H	26
b	Me	H	H	80
c	Ph	H	H	46
d	H	OH	H	37
e	H	H	F	23 (*E*/*Z*) 7:93
f	H	H	Br	22

even complete racemization took place. Therefore, we decided to start from racemic (*RS*)-**6**, prepared from (*RS*)-alanine methyl ester hydrochloride [18], rather than from the optically pure compound. Upon applying the same methodology, we thus obtained (*RS*)-**7**. The latter was then treated with different indoles **8** in AcOH under reflux to afford the corresponding dipodazine analogues (3*Z*,6*RS*)-**9** in yields of 22–80%.

Until now, racemization has not been observed in the formation of chiral enaminones from active methylene precursors in the presence of *Bredereck*'s reagent at *ca.* 100° [9–11][12a]. However, the observed racemization of **7** is not very surprising: many α-amino acid derivatives readily racemize, usually under basic conditions [19]. In the case of (*S*)-**7**, isomerization can be rationalized by involvement of the tautomeric structure **7′** (*Scheme 2*). Racemization was probably facilitated by the required elevated temperature (*ca.* 150°), which is considerably higher than the usual temperature (100°) for the preparation of related enaminones. Furthermore, both *Bredereck*'s reagent and dimethylamine (formed during the condensation) can act as base promoters in the isomerization at C(6). A similar racemization was recently reported by *Avendaño* and coworkers in the synthesis of TDD (**3**) [6c].

2. *Structure Determination*. The structures of the new compounds **7** and **9a**–**f** were corroborated spectroscopically (IR, NMR), by MS and/or elemental analysis. Their spectroscopic data were in agreement with the data reported for related compounds [6–8][13]. All compounds **9**, except for **9e**, were isolated as the (*Z*)-isomers. In the case of **9e**, a (*Z*/*E*) mixture of 93:7 was obtained. The configuration of the exocyclic C=C bond in compound **9b** was established by HMBC spectroscopy on the basis of the ^3J(C,H) long-range coupling constant between the methylidene H-atom (H–

Scheme 2



C(3′))[2]) and the C(2) carbonyl atom, as determined from the antiphase splitting of the pertinent cross-peaks (*Fig. 2*). Generally, the magnitude of ^3J(C,H) for (*Z*)-configured nuclei are smaller (2–6 Hz) than for the (*E*)-configured *isomers* (8–12 Hz) [9d–f][11–14][20]. Thus, the observed ^3J(C,H) value of 6.0 Hz indicated (*Z*)-configuration.

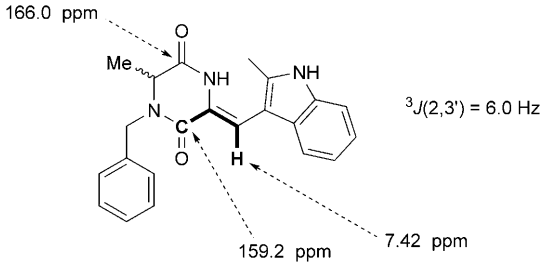


Fig. 2. *Key HMBC interaction indicating (Z)-configuration in* **9b**

The structure of racemic (3*Z*,6*RS*)-**7** was determined by X-ray diffraction (*Fig. 3*). The optical purity of (3*Z*,6*S*)-**7** was determined by ^{1}H-NMR ($CDCl_3$) with the aid of europium(III) tris[3-(heptafluoropropyl(hydroxy)methylene)-*d*-camphorate] as a shift reagent. The ^{1}H-NMR spectrum of racemic (*RS*)-**7** exhibited a sharp *singlet* at δ(H) 2.97 for the Me_2N group, which also corroborated that no (*Z*/*E*)-isomerization took place in solution. Then, upon addition of the shift reagent, the Me_2N resonance was split into two *singlet*s at δ(H) 2.96 and 3.01 in a ratio of 49 : 51. Under the same conditions, the Me_2N group of the optically enriched material resonated as two *singlet*s at δ(H) 2.86 and 2.89 in a ratio of 66 : 34, which corresponds to 32% ee (data not shown).

Conclusions. – (3*Z*,6*RS*)-3-[(dimethylamino)methylidene]-6-methyl-1-(phenylmethyl)piperazine-2,5-dione (**7**), prepared in three steps from (*RS*)-alanine methyl ester, was used for the one-step preparation of a series of dipodazine analogues of type **9**. While the previously described syntheses of dipodazines (**5**) [6] are based on the condensation of 1*H*-indole-3-carbaldehyde and piperazine-2,5-dione derivatives, our *alternative* approach consists of coupling of an 1*H*-indole derivative with **7** as an enamino-masked formylpiperazine-2,5-dione.

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[2]) Arbitrary C-atom numbering. For systematic names, see *Exper. Part.*

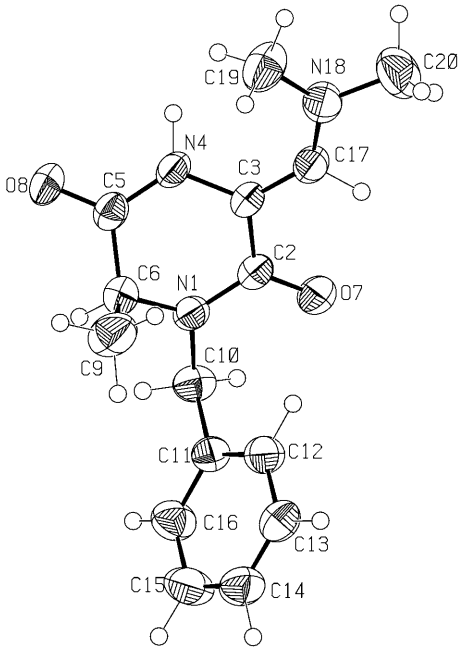

Fig. 3. *X-Ray crystal structure of* (*RS*)-**7** (ORTEP plot). Ellipsoids are shown at the 50% probability level.

Experimental Part

General. *tert*-Butoxy-bis(dimethylamino)methane[1]) and the indole derivatives **8a**–**f** were purchased from *Fluka*. (*S*)-**6** was prepared according to the literature [15–17] from commercially available substances (*Fluka*); and (*RS*)-**6** was prepared analogously (see text). Column chromatography (CC): silica gel *60* (0.04–0.06 mm; *Fluka*). Melting points (m.p.): *Koffler* micro hot stage; uncorrected. IR Spectra: *Perkin-Elmer Spectrum BX FT-IR* spectrophotometer; in cm^{-1}. NMR Spectra: *Bruker Avance DPX-300*, at 300 or 75 MHz for ^1H and ^{13}C-NMR, resp., in (D_6)DMSO or $CDCl_3$ soln.; δ in ppm rel. to Me_4Si, J in Hz. MS: *AutoSpecQ* spectrometer, in *m*/*z*. Elemental anal.: *Perkin-Elmer CHN Analyser 2400 II*.

(3Z,6S)-3-[(Dimethylamino)methylidene]-6-methyl-1-(phenylmethyl)piperazine-2,5-dione ((*S*)-**7**). A mixture of (*S*)-(**6**) (4.40 g, 20 mmol), anh. anisole (30 ml), and *Bredereck*'s *reagent*[1]) (6.27 ml, 30 mmol) was heated at reflux for 4.5 h. The volatile components were evaporated *in vacuo*. The brown, oily residue was dissolved in a minimum of CH_2Cl_2 (7–10 ml) and crystallized by slow addition of heptane and scratching with a glass stick. The precipitate was collected by filtration to give a first portion of **7**, which can be further purified by recrystallization from H_2O. The above org. filtrate was evaporated *in vacuo*, and the residue was purified by CC (SiO_2; AcOEt) to afford a second portion of the product. Total yield of **7**: 4.097 g (75%). Colorless solid. M.p. 166° (CH_2Cl_2/heptane). Optical purity: 32% ee. $[\alpha]_D^{23} = -12.4$ ($c = 2.9$, $CHCl_3$). IR (KBr): 3191, 3068, 2978, 2916, 1689 (C=O), 1665 (C=O), 1594, 1447, 1359, 1304, 1113, 746, 698 (Ph). ^{1}H-NMR ((D_6)DMSO): 1.20 (*d*, $J = 6.8$, Me); 2.93 (*s*, Me_2N); 3.69 (*q*, $J = 6.8$, H–C(6)); 4.13, 4.91 (2*d*, $J = 15.1$ each, PhCH_2); 6.63 (*s*, H–C(3′)); 7.20–7.40 (*m*, Ph); 9.28 (br. *s*, NH). ^{1}H-NMR ($CDCl_3$): 1.37 (*d*, $J = 6.9$, Me); 2.97 (*s*, Me_2N); 3.85 (*q*, $J = 6.9$, H–C(6)); 4.06, 5.20 (2*d*, $J = 15.0$ each, PhCH_2); 6.82 (*s*, H–C(3′)); 7.22–7.35 (*m*, Ph); 8.01 (br. *s*, NH). EI-MS: 273 (M^+). HR-EI-MS: 273.1485 (M^+, $C_{15}H_{19}N_3O_2^+$; calc. 273.1477). Anal. calc. for $C_{15}H_{19}N_3O_2$ (273.33): C 65.91, H 7.01, N 15.37; found: C 65.62, H 7.08, N 15.06.

(3Z,6RS)-3-[(Dimethylamino)methylidene]-6-methyl-1-(phenylmethyl)piperazine-2,5-dione ((*RS*)-**7**). This compound was prepared from (*RS*)-**6** in the same manner as (*S*)-**7**. Yield: 3.653 g (67%). Colorless solid. M.p. 163–166° (CH_2Cl_2/heptane). For spectroscopic data, see above.

General Procedure for the Preparation of Compounds **9**. A mixture of **7** (137 mg, 0.5 mmol), AcOH (2 ml), and one of the indole derivatives **8** (0.5 mmol) was heated at reflux for 1–6 h. The volatile components were evaporated *in vacuo*, and the crude product was either precipitated with anh. EtOH (2.5 ml; for **9a**, **9c**, **9e**, and **9f**) or purified by CC (for **9b** and **9e**).

*(3Z,6*RS*)-3-[(1*H*-Indol-3-yl)methylidene]-6-methyl-1-(phenylmethyl)piperazine-2,5-dione* (**9a**). Prepared from (*RS*)-**7** (137 mg, 0.5 mmol) and **8a** (59 mg, 0.5 mmol) under reflux for 5 h. Yield: 45 mg (26%). Brownish solid. M.p. 227–229° (EtOH). IR (KBr): 3398, 3058, 2980, 2930, 1699 (C=O), 1655 (C=O), 1606, 1443, 1358, 1264, 1130, 1107, 893, 747, 702. ^{1}H-NMR ($CDCl_3$): 1.57 (*d*, *J* = 6.8, Me); 4.04 (*q*, *J* = 7.2, H–C(6)); 4.16, 5.42 (2*d*, *J* = 15.1 each, PhCH_2); 7.20–7.46 (*m*, 10 arom. H, H–C(3′)); 7.68 (br. *s*, NH); 7.70–7.77 (*m*, H–C(2″)); 8.58 (br. *s*, NH). EI-MS: 346 ([*M* + H]$^+$). HR-EI-MS: 345.1485 (*M*$^+$, $C_{21}H_{19}N_3O_2^+$; calc. 345.1477). Anal. calc. for $C_{21}H_{19}N_3O_2$ (345.39): C 73.03, H 5.54, N 12.17; found: C 73.03, H 5.69, N 11.96.

*(3Z,6*RS*)-6-Methyl-3-[(2-methyl-1*H*-indol-3-yl)methylidene]-1-(phenylmethyl)piperazine-2,5-dione* (**9b**). Prepared from (*RS*)-**7** (137 mg, 0.5 mmol) and **8b** (59 mg, 0.5 mmol) under reflux for 1 h, followed by CC (SiO_2; AcOEt/petroleum ether 1:1). Yield: 144 mg (80%). Colorless solid. M.p. 187–188° (AcOEt/petroleum ether). IR (KBr): 3310, 3223, 2972, 2931, 1697 (C=O), 1663 (C=O), 1620, 1452, 1393, 1261, 742, 704. ^{1}H-NMR ($CDCl_3$): 1.59 (*d*, *J* = 6.9, Me); 2.45 (*s*, 2″-Me); 4.04 (*q*, *J* = 7.1, H–C(6)); 4.16, 5.44 (2*d*, *J* = 15.1 each, PhCH_2); 7.12–7.22 (*m*, H–C(5″), H–C(6″)); 7.42 (*s*, H–C(1′)); 7.29–7.43 (7 arom. H); 7.50, 8.33 (2 br. *s*, 2 NH). ^{13}C-NMR ($CDCl_3$): 12.6; 18.9; 47.5; 55.7; 105.5; 111.0; 111.6; 118.9; 121.0; 122.2; 123.5; 125.9; 128.0; 128.3; 128.9; 135.7; 135.2; 136.0; 159.2; 166.0. EI-MS: 359 (*M*$^+$). HR-EI-MS: 359.1642 (*M*$^+$, $C_{22}H_{21}N_3O_2^+$; calc. 359.1634). Anal calc. for $C_{22}H_{21}N_3O_2$ (359.42): C 73.52, H 5.89, N 11.69; found: C 73.78, H 6.05, N 11.78.

*(3Z,6*RS*)-6-Methyl-3-[(2-phenyl-1*H*-indol-3-yl)methylidene]-1-(phenylmethyl)piperazine-2,5-dione* (**9c**). Prepared from (*RS*)-**7** (137 mg, 0.5 mmol) and **8c** (97 mg, 0.5 mmol) under reflux for 3 h. Yield: 97 mg (46%). Yellowish solid. M.p. 241–243° (EtOH). IR (KBr): 3260, 3057, 1656 (C=O), 1642 (C=O), 1452, 1433, 1410, 1256, 883, 736, 699. ^{1}H-NMR ($CDCl_3$): 1.47 (*d*, *J* = 6.8, Me); 3.95 (*q*, *J* = 6.8, H–C(6)); 4.13, 5.41 (2*d*, *J* = 15.1 each, PhCH_2); 7.20–7.45 (*m*, 10 H of Ph, 4 H of indole, NH, H–C(1′)); 8.61 (*s*, NH). EI-MS: 421 (*M*$^+$). HR-EI-MS: 421.1790 (*M*$^+$, $C_{27}H_{23}N_3O_2^+$; calc. 421.1799). Anal. calc. for $C_{27}H_{23}N_3O_2$: C 76.67, H 5.66, N 9.91; found: C 76.94, H 5.50, N 9.97.

*(3Z,6*RS*)-3-[(4-Hydroxy-1*H*-indol-3-yl)methylidene]-6-methyl-1-(phenylmethyl)piperazine-2,5-dione* (**9d**). Prepared from (*RS*)-**7** (205 mg, 0.75 mmol) and **8d** (100 mg, 0.75 mmol) under reflux for 4 h, followed by CC (SiO_2; 1. AcOEt/petroleum ether 1:1, 2. AcOEt). Yield: 66 mg (37%). Yellow solid. M.p. 276° (AcOEt). IR (KBr): 3246, 1666 (C=O), 1651 (C=O), 1611, 1445, 1299, 1166, 1046, 736, 700, 611. ^{1}H-NMR ((D$_6$)DMSO): 1.32 (*d*, *J* = 6.8, Me); 3.91 (*q*, *J* = 6.8, H–C(6)); 4.28, 5.02 (2*d*, *J* = 14.9 each, PhCH_2); 6.47 (*d*, *J* = 7.6, H–C(5″)); 6.86 (*d*, *J* = 7.9, H–C(7″)); 6.91 (*dd*, *J* = 7.7, 7.5, H–C(6″)); 7.20–7.50 (*m*, Ph); 7.76 (*s*, H–C(3′), H–C(2″)); 9.64, 9.68, 11.51 (3*s*, 2 NH, OH). EI-MS: 361 (*M*$^+$). HR-EI-MS: 361.1432 (*M*$^+$, $C_{21}H_{19}N_3O_3^+$; calc. 361.1426). Anal. calc. for $C_{21}H_{19}N_3O_3$ (361.39): C 69.79, H 5.30, N 11.63; found: C 69.58, H 5.46, N 11.46.

*(6*RS*)-3-[(5-Fluoro-1*H*-indol-3-yl)methylidene]-6-methyl-1-(phenylmethyl)piperazine-2,5-dione* (**9e**). Prepared from (*RS*)-**7** (137 mg, 0.5 mmol) and **8e** (68 mg, 0.5 mmol) under reflux for 6 h. Yield: 42 mg (23%; (*E*/*Z*) 7:93). Colorless solid. M.p. 230–232° (EtOH). IR (KBr): 3235, 1687 (C=O), 1604, 1489, 1449, 1407, 1352, 1291, 1263, 1164, 941, 801, 746, 703, 631. ^{1}H-NMR ((D$_6$)DMSO; (*Z*)-isomer): 1.36 (*d*, *J* = 7.2, Me); 3.95 (*q*, *J* = 7.2, H–C(6)); 4.32, 5.03 (2*d*, *J* = 15.1 each; PhCH_2); 6.98–7.06 (*m*, H–C(6″)); 7.08 (*s*, H–C(3′)); 7.24–7.47 (*m*, 5 H of Ph, H–C(7″), H–C(4″)); 7.99 (*s*, H–C(2″)); 9.75, 11.77 (2*s*, 2 NH). ^{1}H-NMR ((D$_6$)DMSO; (*E*)-isomer, selected signals): 1.20 (*d*, *J* = 6.8, 6-Me); 4.13, 4.91 (*d*, *J* = 15.1 each; PhCH_2). EI-MS: 363 (*M*$^+$). HR-EI-MS: 363.1391 (*M*$^+$, $C_{21}H_{18}FN_3O_2^+$; calc. 363.1383). Anal. calc. for $C_{21}H_{18}FN_3O_2$ (363.38): C 69.41, H 4.99, N 11.56; found: C 69.29, H 5.11, N 11.64.

*(3Z,6*RS*)-3-[(5-Bromo-1*H*-indol-3-yl)methylidene]-6-methyl-1-(phenylmethyl)piperazine-2,5-dione* (**9f**). Prepared from (*RS*)-**7** (137 mg, 0.5 mmol) and **8f** (98 mg, 0.5 mmol) under reflux for 6 h. Yield: 46 mg (22%). Yellowish solid. M.p. 249–250° (EtOH). IR (KBr): 3225, 1680 (C=O), 1601, 1449, 1285, 1254,

882, 797, 743, 699. ^{1}H-NMR ((D$_6$)DMSO): 1.36 (*d*, *J* = 7.2, Me); 3.96 (*q*, *J* = 7.2, H–C(6)); 4.33, 5.03 (2*d*, *J* = 15.1 each, PhCH_2); 7.08 (*s*, H–C(3′)); 7.22–7.47 (*m*, 5 H of Ph, H–C(6″), H–C(7″)); 7.82 (*d*, *J* = 1.9, H–C(4″)); 7.97 (*d*, *J* = 1.9, H–C(2″)); 9.78, 11.85 (2*s*, 2 NH). EI-MS: 425 (M^+). HR-EI-MS: 423.0593 (M^+, $C_{21}H_{18}BrN_3O_2^+$; calc. 423.0582). Anal. calc. for $C_{21}H_{18}BrN_3O_2$ (424.29): C 59.45, H 4.28, N 9.90; found: C 59.45, H 4.32, N 9.84.

*X-Ray Crystal Structure of (*RS*)-***7***[3]*). Diffraction data were collected at r.t. on a *Nonius Kappa CCD* diffractometer, using the Nonius Collect software [21]. DENZO and SCALEPACK [22] were used for data indexing and scaling. The structure was solved by means of SIR97 [23], and refined with the Xtal3.4 [24] program package. The graphic representation (*Fig. 3*) was prepared by ORTEP III [25]. The crystal structure was refined on *F* by means of the full-matrix least-squares procedure. The non-H-atoms were refined anisotropically, their positions being calculated geometrically, without refinement of positional and isotropic atomic displacement parameters. Absorption correction was not necessary. The *Regina* [26] weighting scheme was used.

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