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REACTIONS OF 5-SUBSTITUTED (*S*)-1-ACYL-3-[(*E*)-(DIMETHYLAMINO)-METHYLIDENE]PYRROLIDINE-2-ONES AND (*S*)-3-[(*E*)-(DIMETHYL-AMINO)METHYLIDENE]TETRAHYDROFURAN-2-ONES WITH AMINES. PREPARATION OF INTERMEDIATES IN THE 'RING SWITCHING' SYNTHESIS OF HETEROARYLALANINE- AND HETEROARYLLACTIC ACID DERIVATIVES AND THEIR ANALOGS

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Abstract. – 5-Substituted (*S*)-1-acyl-3-[(*E*)-(dimethylamino)methylidene]pyrrolidin-2-ones **1–3** and (*S*)-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one **4**, chiral cyclic analogs of 2-substituted alkyl 3-(dimethylamino)propenoates, were treated with alkyl, aryl, and heteroarylamines **6–25** under mild conditions to give 5-substituted (*S*)-3-[(substituted amino)methylidene]pyrrolidin-2-ones **26–47** and (*S*)-3-[(*E*)-(substituted amino)methylidene]-tetrahydrofuran-2-ones **48–52** as intermediates in a 'ring switcing' synthesis of 3-heteroarylalanine- and 3-heteroaryllactic acid derivatives and their analogs.

Introduction. – In the last few decades, several synthetic method for the preparation of 3-heteroarylalanines have been developed due to their occurrence in nature, biological activity, and synthetic aplicability [1]. Among various synthetic approaches, transformations of commercially available α-amino acids, such as serine,

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Dedicated to Prof. Dr. Drago Leskovšek on the occasion of his 80th birthday

aspartic acid, and glutamic acid, found a wide applicability in the preparation of 3-heteroarylalanines [2]. Recently, Young and coworkers reported the synthesis of 3-pyrazolyl-, 3-isoxazolyl-, and 3-pyrimidinyl-alanines from (*S*)-3-formylpyroglutamic acid derivatives, using a 'ring switching' strategy [3]. On the other hand, our previous study on the chemisty of polyfunctional alkyl 2-substituted 3-(dimethylamino)propenoates showed, that this type of compounds can serve as versatile, simple, and efficient synthetic tool for the preparation of a variety of heterocyclic systems, α,β-dehydro-α-amino acid derivatives and peptides, as well as *N*-protecting reagents in the peptide synthesis [4, 5]. In this connection, we introduced 5-substituted (*S*)-1-acyl-3-[(*E*)-(dimethyl-amino)methylidene]-pyrrolidin-2-ones **5**–**7** and (*S*)-3-[(*E*)-(dimethylamino)-methylidene]tetrahydrofuran-2-ones **8** and **9** which can be prepared in 2–3 steps from commercially available precursors **1**–**4** (Figure 1). Compounds **5**–**9** are actually optically active cyclic analogs of alkyl 2-substituted 3-(dimethylamino)propenoates and were used as precursors for the preparation of optically active 3-heteroarylalanine-, 3-heteroarylalaninol-, and 3-heteroaryllactic acid derivatives and for a stereoselective preparation of heterocyclic systems with α-amino acid structural element [6–11]. In continuation of our work in this field, we now report the preparation of 5-substituted (*S*)-3-[(substituted amino)methylidene]pyrrolidin-2-ones **30**–**51** and (*S*)-3-[(*E*)-(substituted amino)methylidene]tetrahydrofuran-2-ones **52**–**56** as intermediates in a 'ring switching' synthesis of 3-heteroarylalanine-, 3-heteroarylalaninol-, and 3-heteroaryllactic acid derivatives [8–11].

Figure 1

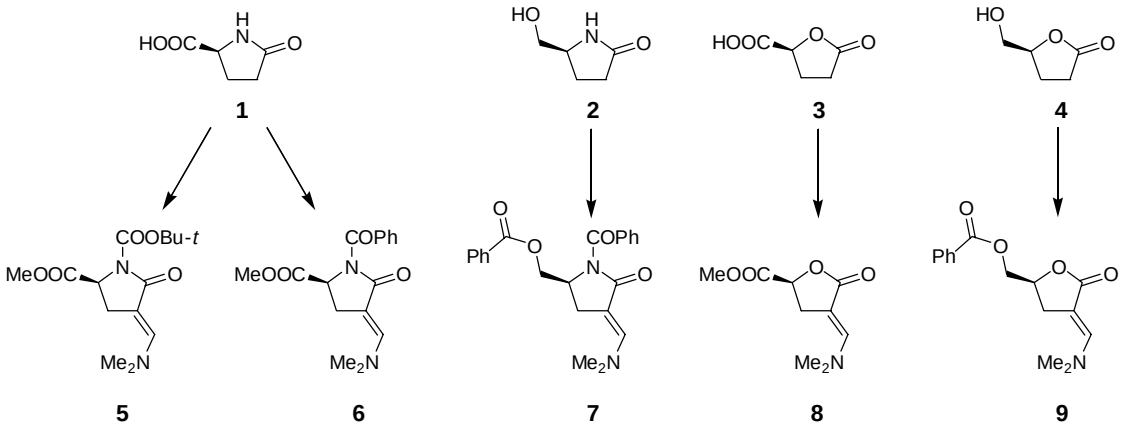
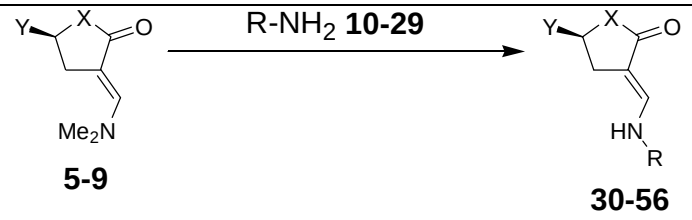


Table 1. List of Compounds **10**–**56**.



5-9 **30-56**

Compounds **10**–**56**

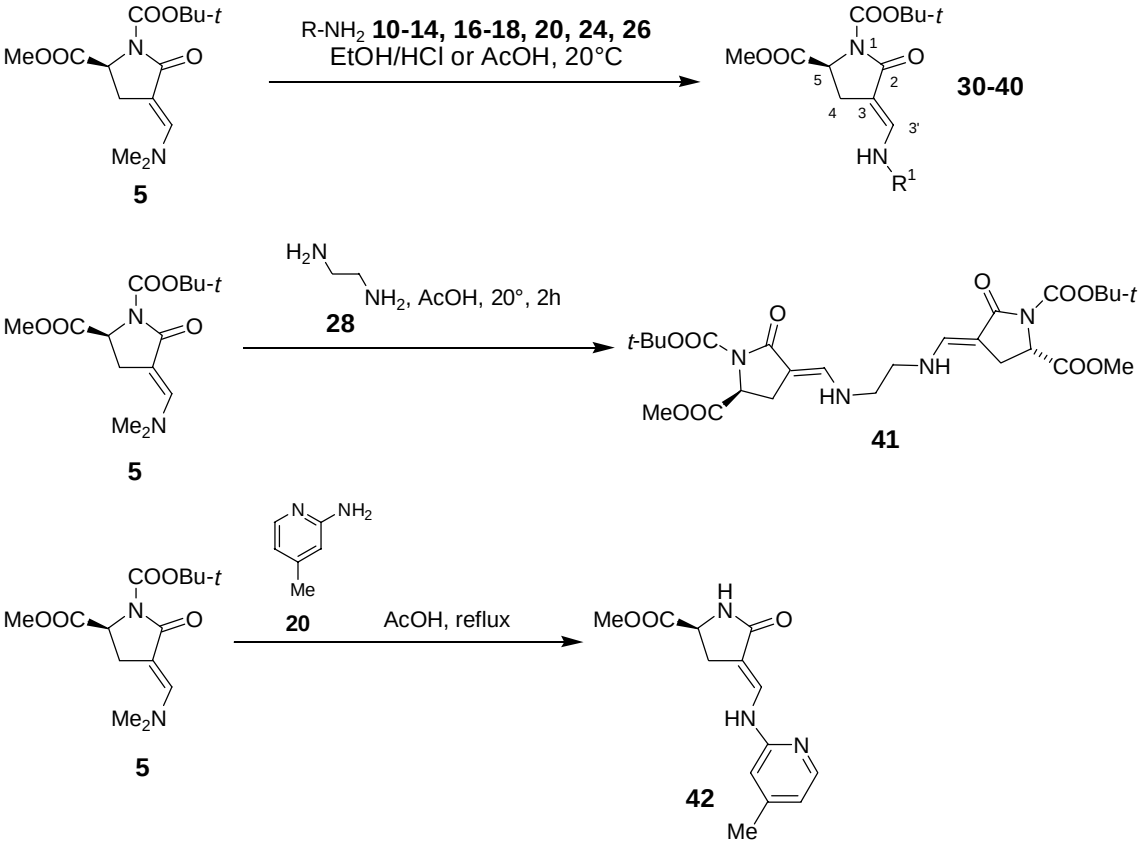
Amines **10**–**29** → Products **30**–**56** (Boc = COOBu-*t*, Bz = PhCO)

R	X = N–Boc Y = COOMe	X = N–COPh Y = COOMe	X = N–COPh Y = CH_2OBz	X = O Y = COOMe
CH_2COOMe (**10**)	**30**	**43**	-	-
benzyl (**11**)	**31**	-	-	-
phenyl (**12**)	**32**	-	-	-
3-bromophenyl (**13**)	**33**	-	-	-
3-methylphenyl (**14**)	**34**	-	-	-
4-methylphenyl (**15**)	-	-	-	**52**
3-nitrophenyl (**16**)	**35**	-	-	-
1-naphthyl (**17**)	**36**	-	-	-
pyridinyl-2 (**18**)	**37**	-	-	-
5-chloropyridinyl-2 (**19**)	-	**44**	**50**	-
4-methylpyridinyl-2 (**20**)	**38**, (**42**, X = NH)	**45**	-	**53**
6-chloropyridazinyl-3 (**21**)	-	-	-	**54**
4,6-dimethylpyrimidinyl-2 (**22**)	-	**46**	**51**	**55**
pyrazinyl-2 (**23**)	-	**47**	-	-
isoxazolyl-3 (**24**)	**39**	-	-	-
5-methylisoxazolyl-3 (**25**)	-	**48**	-	-
thiazolyl-2 (**26**)	**40**	-	-	-
1*H*-1,2,4-triazolyl-3 (**27**)	-	-	-	**56**
ethane-1,2-diyl (**28**)	**41**	-	-	-
piperazin-1,4-diyl (**29**)	-	**49**	-	-

Results and discussion. – Starting compounds **5**–**9** were prepared by treatment of the corresponding 5-substituted (*S*)-γ-butyrolactams and (*S*)-γ-butyrolactones, prepared

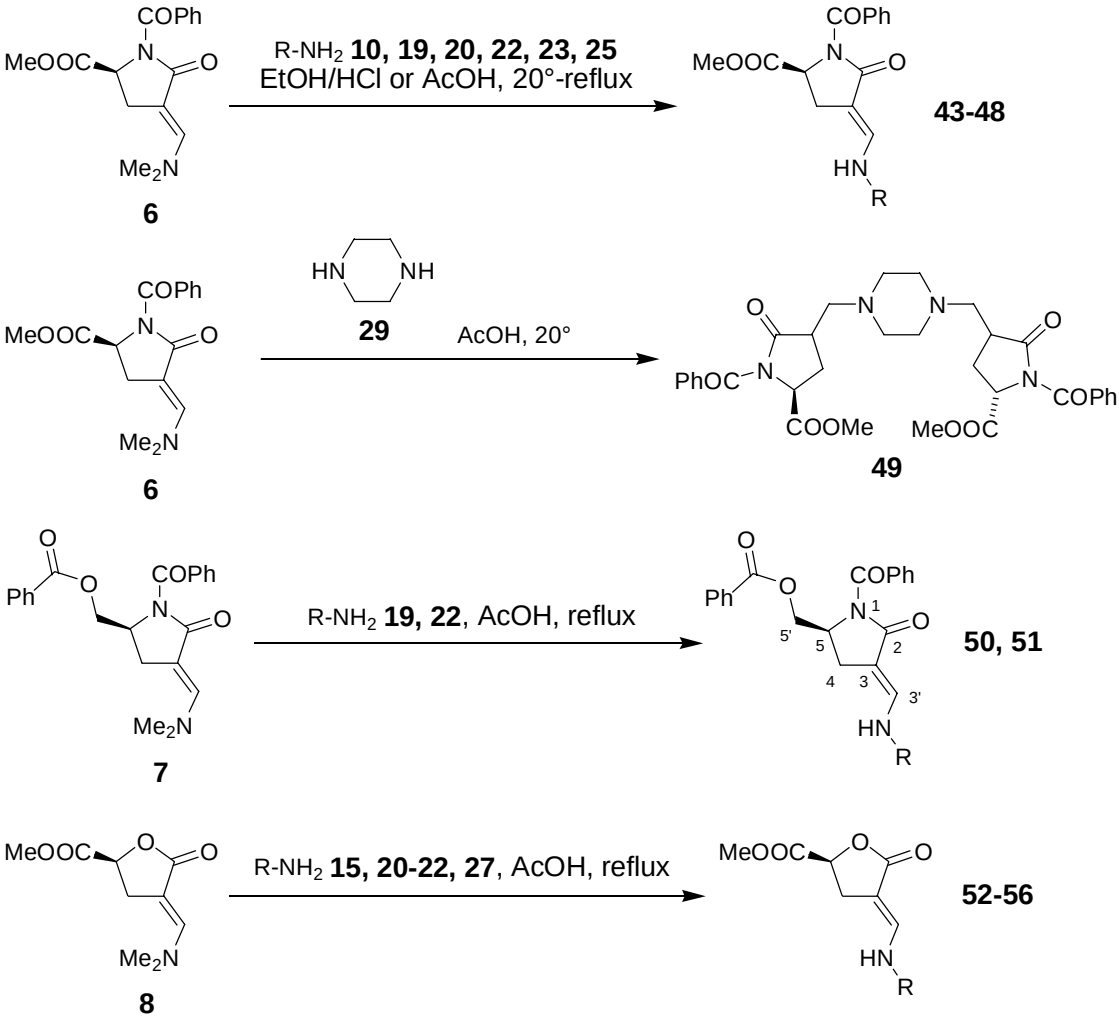
from compounds **1**–**4**, with bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) according to the procedures described previously [6, 7, 11]. Compounds **5**–**9** were then treated with the following alkyl-, aryl-, and heteroarylamines: glycine methyl ester hydrochloride (**10**), benzylamine hydrochloride (**11**), aniline (**12**), 3-bromoaniline (**13**), 3-methylaniline (**14**), 4-methylaniline (**15**), 3-nitroaniline (**16**), 1-naphthylamine (**17**), 2-aminopyridine (**18**), 2-amino-5-chloropyridine (**19**), 2-amino-4-methylpyridine (**20**), 3-amino-6-chloropyridazine (**21**), 2-amino-4,6-dimethylpyrimidine (**22**), aminopyrazine (**23**), 3-aminoisoxazole (**24**), 3-amino-5-methylisoxazole (**25**), 2-aminothiazole (**26**), 3-amino-*1H*-1,2,4-triazole (**27**), 1,2-diaminoethane (**28**), and piperazine (**29**) to give the corresponding 5-substituted (*S*)-3-[(substituted amino)-methylidene]pyrrolidin-2-ones **30**–**51** and (*S*)-3-[(substituted amino)methylidene]-pyrrolidin-2-ones **52**–**56** (Table 1).

Scheme 1



Reactions of (*S*)-*tert*-butoxycarbonyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**5**) with amines **10**–**14**, **16**–**18**, **20**, **24**, **26** and **28** were carried out in ethanol or acetic acid at room temperature in order to avoid the removal of acid-labile *tert*-butoxycarbonyl group to give substitution products **30**–**40**. However, with 1,2-diaminoethane (**41**) 2 equivalents of starting compound **5** were employed to afford bis-substitution product **41**. Treatment of **5** with 2-amino-4-methylpyridine (**20**) in refluxing acetic acid furnished (*S*)-3-[(4-methyl-2-pyridinylamino)methylidene]-5-(methoxycarbonyl)-pyrrolidin-2-one (**42**), unsubstituted at the position 1 in the pyrrolidine ring. (Scheme 1).

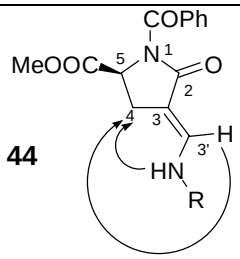
Scheme 2



On the other hand, (*S*)-1-benzoyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**6**), (*S*)-1-benzoyl-5-benzoyloxymethyl-3-[(*E*)-(dimethyamino)methylidene]pyrrolidin-2-one (**7**), and (*S*)-3-[(*E*)-(dimethylamino)-methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**8**), which are more stable under acidic conditions, were treated with amines **10**, **15**, **19**–**23**, **25**, **27**, and **29** at 20–120°C to give mono-substitution products **43**–**56**. Again, treatment of piperazine (**29**) with 2 equivalents of (*S*)-1-benzoyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxy-carbonyl)pyrrolidin-2-one (**6**) afforded a bis-substitution product **56** (Scheme 2).

Structures of products **30**–**56** were determined by NMR and elemental analyses. The (*E*)-orientation around the exocyclic C=C duoble in compound **44**, determined by NMR (NOESY) experiments, is in accordance with the orientation in acyclic 3-(substituted amino)propenoates since the 3-amino group is always *trans*-oriented with respect to the ester group [4–6] (Scheme 3).

Scheme 3. NMR (NOESY) determination of orientation around C=C double bond in compound **44** (R = 5-chloropyrimidinyl-2).

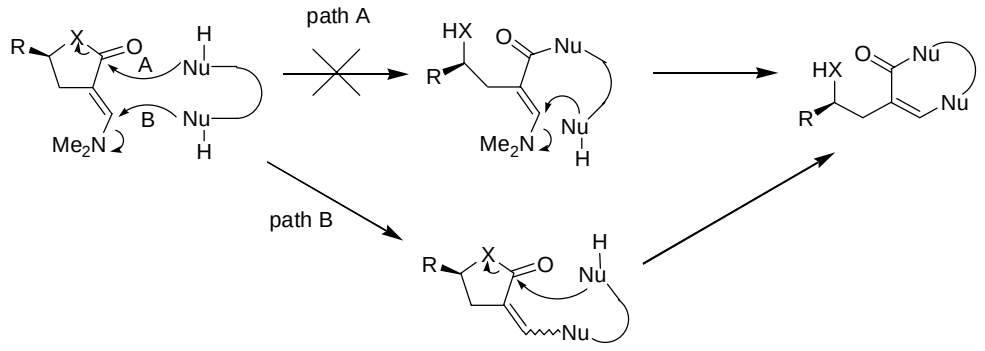


44

$d_{H3'–H4}$ (nm)		$d_{NH–H4}$ (nm)	
Calculated	Found	Calculated	Found
0.39 (*E*)	0.33	0.27 (*E*)	0.27
0.28 (*Z*)		0.46 (*Z*)	

Preparation and isolation of compounds **30**–**56** suggests, that the ‘ring switching’ transformation of 3-[(dimethylamino)methylidene]pyrrolidin-2-ones and 3-[(dimethylamino)methylidene]tetrahydrofuran-2-ones into 3-heteroaryl substituted α-amino- and α-hydroxy acids and α-amino alcohols proceeds predominantly *via* initial substitution of the dimethylamino group, followed by substitution at the ring carbonyl group (path B). This observation is also in accordance with the results of Young and coworkers and with our previous results in acyclic 3-(dimethylamino)propenoate series [3–5] (Figure 2).

Figure 2. Proposed mechanism for 'ring switching' transformation of **5**–**9** with dinucleophiles.



Experimental

General. All starting materials were commercially available (in most cases from Fluka) and purified following the standard techniques. The following compounds were prepared according to the procedures described in the literature: *(S)-1-tert-butoxycarbonyl-3-[(E)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one* **5** [7], *(S)-1-benzoyl-3-[(E)-(dimethylamino)methylidene]-5-(methoxycarbonyl)-pyrrolidin-2-one* **6** [6], *(S)-1-benzoyl-5-benzoyloxymethyl-3-[(E)-(dimethylamino)-methylidene]pyrrolidin-2-one* **7** [11], and *(S)-3-[(E)-(dimethylamino)methylidene]-tetrahydrofuran-2-one* **8** [7]. Column chromatography: *silica gel, Fluka, Kieselgel 60*. TLC: *Merck, Alufolien Kieselgel 60 F 254, 0.2mm*. M.p.: *Kofler* micro hot stage. Optical rotations: *Perkin-Elmer 241 MC* polarimeter. ^{1}H-NMR and ^{13}C-NMR: *Bruker Avance DPX 300* spectrometer. Elemental analyses: *Perkin-Elmer CHN Analyser 2400*.

Preparation of (S)-1-tert-butoxycarbonyl-3-[(E)-(substituted amino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-ones **30**–**40**. *General procedure.* A mixture of (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)-pyrrolidin-2-one **5** (298 mg,1 mmol), substituted amine **10**–**14**, **16**–**18**, **20**, **24**, or **26** (1 mmol), ethanol or acetic acid (100%, 5 ml), and hydrochloric acid (36%, 0.1 ml, 1 mmol) [12] was stirred at room temperature for several hours. Volatile components were evaporated *in vacuo*, the residue was triturated with an appropriate solvent, and the

precipitate was collected by filtration to give compounds **30**–**40**. In this manner, the following compounds were prepared:

(S)-1-tert-Butoxycarbonyl-3-[(methoxycarbonylmethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**30**). This compound was prepared from glycine methyl ester hydrochloride (**10**) and **5** in ethanol, stirring for 2 h, trituration with water. Yield: 77% (0.265 g). M.p. 144–146°C (EtOH/H_2O). $[\alpha]_D^{23}$ –10.4° (*c* = 0.72, CH_2Cl_2). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.38 (9H, s, CMe_3); 2.34 (1H, br d, *J* = 15.7 Hz, 4–Ha); 2.82 (1H, dd, *J* = 11.3, 15.1 Hz, 4–Hb); 3.66 (3H, s, OMe); 3.69 (3H, s, OMe); 4.03 (2H, d, *J* = 5.8 Hz, C*H*$_2$NH); 4.59 (1H, dd, *J* = 3.3, 10.7 Hz, 5–H); 6.90–6.97 (1H, m, NH); 7.07 (1H, br d, *J* = 13.1 Hz, 3'–H). Anal. calc. for $C_{15}H_{22}N_2O_7$ (342.34): C, 52.63; H, 6.48; N, 8.18; found: C, 52.62; H, 6.56; N, 8.14.

(S)-1-tert-Butoxycarbonyl-3-[(benzylamino)methylidene]-5-(methoxycarbonyl)-pyrrolidin-2-one (**31**). This compound was prepared from benzylamine hydrochloride (**11**) and **5** in ethanol, stirring for 2 h, trituration with water. Yield: 71% (0.256 g). M.p. 154–156°C (EtOH/H_2O). $[\alpha]_D^{23}$ +1.6° (*c* = 1.12, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.37 (9H, s, CMe_3); 2.34 (1H, dd, *J* = 2.1, 16.1 Hz, 4–Ha); 2.83 (1H, dd, *J* = 11.3, 16.1 Hz, 4–Hb); 3.67 (3H, s, OMe); 4.36 (2H, d, *J* = 5.3 Hz, C*H*$_2$NH); 4.57 (1H, dd, *J* = 3.6, 10.8 Hz, 5–H); 7.15–7.35 (7H, m, Ph, 3'–H, and NH). Anal. calc. for $C_{19}H_{24}N_2O_5$ (360.40): C, 63.32; H, 6.71; N, 7.77; found: C, 63.22; H, 6.96; N, 7.74.

(S)-1-tert-Butoxycarbonyl-3-[(anilino)methylidene]-5-(methoxycarbonyl)-pyrrolidin-2-one (**32**). This compound was prepared from aniline (**12**) and **5** in ethanol, stirring for 2 h, trituration with ethanol. Yield: 86% (0.298 g). M.p. 186–188°C (EtOH/H_2O). $[\alpha]_D^{23}$ –9.9° (*c* = 0.85, CH_2Cl_2). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.44 (9H, s, CMe_3); 2.63 (1H, ddd, *J* = 1.9, 2.9, 16.6 Hz, 4–Ha); 3.07 (1H, ddd, *J* = 2.2, 10.8, 16.9 Hz, 4–Hb); 3.74 (3H, s, OMe); 4.72 (1H, dd, *J* = 3.3, 10.7 Hz, 5–H); 6.95–7.01 (1H, m, 1H–Ph); 7.15 (2H, d, *J* = 7.8 Hz, 2H–Ph); 7.29–7.35 (2H, m, 2H–Ph); 7.64 (1H,

d, *J* = 13.1 Hz, 3'–H); 9.01 (1H, d, *J* = 13.1 Hz, NH). Anal. calc. for $C_{18}H_{22}N_2O_5$ (346.38): C, 62.42; H, 6.40; N, 8.09; found: C, 62.05; H, 6.43; N, 7.94.

(S)-1-tert-Butoxycarbonyl-3-[(3-bromoanilino)methylidene]-5-(methoxy-carbonyl)pyrrolidin-2-one (**33**). This compound was prepared from 3-bromoaniline (**13**) and **5** in ethanol, stirring for 2 h, trituration with water. Yield: 88% (0.374 g). M.p. 170–172°C (EtOH/H_2O). $[\alpha]_D^{23}$ +3.1° (*c* = 1.01, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.41 (9H, s, CMe_3); 2.60 (1H, deg dt, *J* = 2.5, 16.6 Hz, 4–Ha); 3.03 (1H, ddd, *J* = 2.1, 10.7, 16.6 Hz, 4–Hb); 3.71 (3H, s, OMe); 4.70 (1H, dd, *J* = 3.2, 10.7 Hz, 5–H); 7.09–7.29 (3H, m, 3H–Ar); 7.33 (1H, s, 1H–Ar); 7.61 (1H, d, *J* = 12.8 Hz, 3'–H); 9.04 (1H, d, *J* = 12.8 Hz, NH). Anal. calc. for $C_{18}H_{21}BrN_2O_5$ (425.27): C, 50.84; H, 4.98; N, 6.59; found: C, 51.09; H, 5.09; N, 6.55.

(S)-1-tert-Butoxycarbonyl-3-[(3-methylanilino)methylidene]-5-(methoxy-carbonyl)pyrrolidin-2-one (**34**). This compound was prepared from 3-methylaniline (**14**) and **5** in acetic acid, stirring for 2 h at 20°, trituration with acetic acid. Yield: 66% (0.238 g). M.p. 195–197°C (EtOH/H_2O). $[\alpha]_D^{23}$ +2.8° (*c* = 1.01, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.41 (9H, s, CMe_3); 2.28 (3H, s, Ar–Me); 2.58 (1H, deg dt, *J* = 2.8, 16.7 Hz, 4–Ha); 3.02 (1H, ddd, *J* = 2.2, 10.7, 16.7 Hz, 4–Hb); 3.71 (3H, s, OMe); 4.68 (1H, dd, *J* = 3.3, 10.7 Hz, 5–H); 6.77 (1H, d, *J* = 7.4 Hz, 1H–Ar); 6.91 (1H, d, *J* = 7.4 Hz, 1H–Ar); 6.96 (1H, s, 1H–Ar); 7.16 (1H, deg t, *J* = 7.4 Hz, 1H–Ar); 7.61 (1H, d, *J* = 13.1 Hz, 3'–H); 8.92 (1H, d, *J* = 13.1 Hz, NH). Anal. calc. for $C_{19}H_{24}N_2O_5$ (360.40): C, 63.32; H, 6.71; N, 7.77; found: C, 63.06; H, 6.97; N, 7.73.

(S)-1-tert-Butoxycarbonyl-3-[(3-nitroanilino)methylidene]-5-(methoxycarbonyl)-pyrrolidin-2-one (**35**). This compound was prepared from 3-nitroaniline (**16**) and **5** in ethanol, stirring for 2 h, trituration with ethanol. Yield: 95% (0.372 g). M.p. 194–196°C (EtOH). $[\alpha]_D^{23}$ –7.6° (*c* = 1.04, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.42 (9H, s, CMe_3); 2.69 (1H, m, 4–Ha); 3.06 (1H, m, 4–Hb); 3.72 (3H, s, OMe); 4.72 (1H, dd, *J* = 3.3, 10.6 Hz, 5–H); 7.55–7.73 (4H, m, 4H–Ar); 7.94 (1H, br s, 3'–H); 9.32 (1H, d, *J* =

11.7 Hz, NH). Anal. calc. for $C_{18}H_{21}N_3O_7$ (391.38): C, 55.24; H, 5.41; N, 10.74; found: C, 55.59; H, 5.47; N, 10.91.

(S)-1-tert-Butoxycarbonyl-3-[(1-naphthylamino)methylidene]-5-(methoxy-carbonyl)pyrrolidin-2-one (**36**). This compound was prepared from 1-naphthylamine (**17**) and **5** in acetic acid, stirring for 6 h, trituration with water. Yield: 93% (0.368 g). M.p. 95–98°C (H_2O). $[\alpha]_D^{23}$ +27.3° (*c* = 0.86, CH_2Cl_2). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.42 (9H, s, CMe_3); 2.78 (1H, ddd, *J* = 2.1, 3.0, 16.9 Hz, 4–Ha); 3.15 (1H, ddd, *J* = 2.2, 10.7, 16.8 Hz, 4–Hb); 3.73 (3H, s, OMe); 4.72 (1H, dd, *J* = 3.4, 10.7 Hz, 5–H); 7.23 (1H, d, *J* = 13.1 Hz, 1H–Ar); 7.37–7.69 (5H, m, 4H–Ar and 3'–H); 7.90–7.97 (1H, m, 1H–Ar); 8.23–8.28 (1H, m, 1H–Ar); 9.03 (1H, d, *J* = 12.4 Hz, NH). Anal. calc. for $C_{22}H_{24}N_2O_5$ (396.44): C, 66.65; H, 6.10; N, 7.07; found: C, 66.44; H, 6.22; N, 7.06.

(S)-1-tert-Butoxycarbonyl-3-[(2-pyridinylamino)methylidene]-5-(methoxy-carbonyl)pyrrolidin-2-one (**37**). This compound was prepared from 2-aminopyridine (**18**) and **5** in acetic acid, stirring for 2 h, trituration with water. Yield: 91% (0.316 g). M.p. 185–188°C (EtOH/H_2O). $[\alpha]_D^{23}$ –5.7° (*c* = 0.72, CH_2Cl_2). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.41 (9H, s, CMe_3); 2.63 (1H, ddd, *J* = 2.3, 3.4, 16.6 Hz, 4–Ha); 3.05 (1H, ddd, *J* = 2.4, 10.9, 16.6 Hz, 4–Hb); 3.71 (3H, s, OMe); 4.71 (1H, dd, *J* = 3.2, 10.7 Hz, 5–H); 6.91–6.95 (2H, m, 2H–pyridine); 7.64–7.94 (1H, m, 1H–pyridine); 8.21–8.25 (2H, m, 1H-pyridine and 3'–H); 9.56 (1H, d, *J* = 12.5 Hz, NH). Anal. calc. for $C_{17}H_{21}N_3O_5$ (347.37): C, 55.78; H, 6.09; N, 12.10; found: C, 58.68; H, 6.28; N, 12.03.

(S)-1-tert-Butoxycarbonyl-3-[(4-methyl-2-pyridinylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**38**). This compound was prepared from 2-amino-4-methylpyridine (**20**) and **5** in acetic acid, stirring for 1 h, trituration with water. Yield: 90% (0.326 g). M.p. 172–174°C (EtOH/H_2O). $[\alpha]_D^{23}$ +108.9° (*c* = 0.90, DMF). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.41 (9H, s, CMe_3); 2.26 (3H, s, Het–Me); 2.61 (1H, ddd, *J* = 2.2, 3.1, 16.8 Hz, 4–Ha); 3.04 (1H, ddd, *J* = 2.4, 10.7, 16.7 Hz, 4–Hb); 3.71

(3H, s, OMe); 4.70 (1H, dd. *J* = 3.3, 10.7 Hz, 5–H); 6.75 (1H, s, 1H–pyridine); 6.78 (1H, d, *J* = 5.3 Hz, 1H–pyridine); 8.09 (1H, d, *J* = 5.1 Hz, 1H–pyridine); 8.21 (1H, br d, *J* = 12.3 Hz, 3'–H); 9.47 (1H, d, *J* = 12.3 Hz, NH). Anal. calc. for $C_{18}H_{23}N_3O_5$ (361.39): C, 59.82; H, 6.41; N, 11.63; found: C, 60.10; H, 6.80; N, 11.71.

(S)-1-tert-Butoxycarbonyl-3-[(3-isoxazolylamino)methylidene]-5-(methoxy-carbonyl)pyrrolidin-2-one (**39**). This compound was prepared from 3-aminoisoxazole (**24**) and **5** in acetic acid, stirring for 2 h, trituration with water. Yield: 88% (0.296 g). M.p. 187–189°C (EtOH/H_2O). $[\alpha]_D^{23}$ +22.2° (*c* = 0.68, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.41 (9H, s, CMe_3); 2.59 (1H, deg dt, *J* = 2.6, 16.9 Hz, 4–Ha); 3.02 (1H, ddd, *J* = 2.5, 10.6, 16.9 Hz, 4–Hb); 3.71 (3H, s, OMe); 4.69 (1H, dd. *J* = 3.2, 10.6 Hz, 5–H); 6.45 (1H, d, *J* = 1.7 Hz, 1H-isoxazole); 7.50 (1H, d, *J* = 11.5 Hz, 3'–H); 8.70 (1H, d, *J* = 1.7 Hz, 1H–isoxazole); 9.65 (1H, d, *J* = 11.8 Hz, NH). Anal. calc. for $C_{15}H_{19}N_3O_6$ (337.33): C, 53.41; H, 5.68; N, 12.46; found: C, 53.53; H, 5.95; N, 12.35.

(S)-1-tert-Butoxycarbonyl-3-[(2-thiazolylamino)methylidene]-5-(methoxy-carbonyl)pyrrolidin-2-one (**40**). This compound was prepared from 2-aminothiazole (**26**) and **5** in acetic acid, stirring for 2 h, trituration with water. Yield: 72% (0.256 g). M.p. 173–175°C (EtOH/H_2O). $[\alpha]_D^{23}$ +76.3° (*c* = 0.56, DMF). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.41 (9H, s, CMe_3); 2.59 (1H, ddd, *J* = 2.3, 3.0, 17.0 Hz, 4–Ha); 3.03 (1H, ddd, *J* = 2.6, 10.6, 17.0 Hz, 4–Hb); 3.71 (3H, s, OMe); 4.70 (1H, dd. *J* = 3.2, 10.6 Hz, 5–H); 7.08 (1H, d, *J* = 3.5 Hz, 1H-thiazole); 7.31 (1H, d, *J* = 3.5 Hz, 1H-thiazole); 7.79 (1H, br s, 3'–H); 10.52 (1H, br s, NH). Anal. calc. for $C_{15}H_{19}N_3O_5S$ (353.39): C, 50.98; H, 5.42; N, 11.89; found: C, 50.88; H, 5.69; N, 11.77.

(S,S)-N,N'-bis-[(1-tert-Butoxycarbonyl-5-methoxycarbonyl-2-oxopyrrolidin-3-ylidene)methyl]-1,2-diaminoethane (**41**). A mixture of (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one **5** (596 mg, 2 mmol), 1,2-diaminoethane **28** (60 mg, 1 mmol), and acetic acid (100%, 5 ml) was stirred at room temperature for 2 hours. Volatile components were evaporated *in vacuo*, water (10 ml) and ethanol (1 ml) were added to the residue, and the precipitate was

collected by filtration to give **41**. Yield: 68% (0.386 g). M.p. 172–175°C (EtOH/H_2O). $[\alpha]_D^{23}$ +38.1° (*c* = 0.73, CH_2Cl_2). ^{1}H-NMR (300 MHz, (D_6)DMSO): 1.37 (18H, s, 2 x CMe_3); 2.29 (2H, br d, *J* = 15.0 Hz, 2 x 4'–Ha); 2.77 (2H, br deg t, *J* = 13.2 Hz, 2 x 4'–Hb); 3.31 (4H, s, 1–CH_2 and 2–CH_2); 3.68 (6H, s, 2 x OMe); 4.53 (2H, dd. *J* = 3.8, 10.8 Hz, 2 x 5'–H); 6.73 (2H, br d, *J* = 13.2 Hz, 2 x 3''–H); 7.05 (2H, d, *J* = 13.6 Hz, 2 x NH). Anal. calc. for $C_{26}H_{38}N_4O_{10}$ (566.60): C, 55.11; H, 6.76; N, 9.89; found: C, 54.80; H, 6.67; N, 9.91.

(S)-3-[(4-methyl-2-pyridinylamino)methylidene]-5-(methoxycarbonyl)-pyrrolidin-2-one (**42**). A mixture of (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-(dimethylamino)-methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one **5** (298 mg, 1 mmol), 2-amino-4-methylpyridine **20** (108 mg, 1 mmol), and acetic acid (100%, 5 ml) was stirred at reflux temperature for 2 hours. Volatile components were evaporated *in vacuo*, the residue was triturated with a mixture of water and methanol (1 : 1, 5 ml), and the precipitate was collected by filtration to give **42**. Yield: 61% (0.158 g). M.p. 202–205°C (MeOH/H_2O). $[\alpha]_D^{23}$ +111.1° (*c* = 0.65, DMF). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.24 (3H, s, Het–Me); 2.76 (1H, ddd, *J* = 2.4, 3.3, 16.9 Hz, 4–Ha); 3.07 (1H, ddd, *J* = 2.5, 9.8, 16.8 Hz, 4–Hb); 3.69 (3H, s, OMe); 4.29 (1H, dd. *J* = 3.6, 10.0 Hz, 5–H); 6.67–6.69 (2H, m, 2H–pyridine); 7.77 (1H, s, 1–H); 7.93 (1H, deg dt, *J* = 2.2, 12.0 Hz, 3'–H); 8.02 (1H, d, *J* = 5.7 Hz, 1H–pyridine); 9.01 (1H, d, *J* = 12.0 Hz, 3'–NH). Anal. calc. for $C_{13}H_{15}N_3O_3$ (261.28): C, 59.76; H, 5.79; N, 16.08; found: C, 59.52; H, 5.78; N, 15.92.

Preparation of (S)-1-benzoyl-3-[(substituted amino)methylidene-]-5-(methoxycarbonyl)pyrrolidin-2-ones **43–48**. *General Procedure.* A mixture of (*S*)-1-benzoyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one **6** (302 mg,1 mmol), substituted amine **10**, **19**, **20**, **22**, **23**,or **25** (1 mmol), and ethanol or acetic acid (100%, 5 ml) was stirred at 20–120°C for several hours. Volatile components were evaporated *in vacuo*, the residue was triturated with an appropriate solvent, and the precipitate was collected by filtration to give compounds **43**–**48**. In this manner, the following compounds were prepared:

(S)-1-Benzoyl-3-[(methoxycarbonylmethylamino)methylidene]-5-(methoxy-carbonyl)pyrrolidin-2-one (**43**). This compound was prepared from glycine methyl ester hydrochloride (**10**) and **6** in ethanol, stirring at 20°C for 2 h, trituration with methanol. Yield: 90% (0.310 g). M.p. 157–160°C (MeOH). $[\alpha]_D^{23}$ +4.1° (*c* = 1.0, CH_2Cl_2). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.45–2.52 (1H, m, 4–Ha); 2.97 (1H, br dd, *J* = 11.5, 14.9 Hz, 4–Hb); 3.66 (3H, s, OMe); 3.70 (3H, s, OMe); 4.06 (2H, d, *J* = 5.7 Hz, C*H*$_2$NH); 4.83 (1H, dd, *J* = 3.8, 11.6 Hz, 5–H); 7.13 (1H, br d, *J* = 13.6 Hz, 3'–H); 7.22–7.31 (1H, m, NH); 7.36–7.43 (2H, m 2H–Ph); 7.47–7.52 (3H, m, 3H–Ph). Anal. calc. for $C_{17}H_{18}N_2O_6$ (346.33): C, 58.96; H, 5.24; N, 8.09; found: C, 58.73; H, 5.24; N, 7.81.

(S)-1-Benzoyl-3-[(E)-(5-chloro-2-pyridinylamino)methylidene]-5-(methoxy-carbonyl)pyrrolidin-2-one (**44**). This compound was prepared from 2-amino-5-chloropyridine (**19**) and **6** in acetic acid, reflux for 2 h, trituration with methanol. Yield: 87% (0.336 g). M.p. 231–233°C (MeOH). $[\alpha]_D^{23}$ +38.63° (*c* = 1.17, DMF). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.76 (1H, ddd, *J* = 2.3, 3.0, 16.6 Hz, 4–Ha); 3.19 (1H, ddd, *J* = 2.3, 10.2, 16.6 Hz, 4–Hb); 3.73 (3H, s, OMe); 4.94 (1H, dd, *J* = 3.4, 10.2 Hz, 5–H); 7.01 (1H, d, *J* = 9.0 Hz, 1H–pyridine); 7.41–7.46 (2H, m, 2H–Ph); 7.53–7.57 (3H, m, 3H–Ph); 7.78 (1H, dd, *J* = 2.6, 8.7 Hz, 1H–pyridine); 8.17 (1H, br d, *J* = 11.7 Hz, 3'–H); 8.27 (1H, d, *J* = 2.3 Hz, 1H-pyridine); 9.91 (1H, d, *J* = 11.7 Hz, NH). Anal. calc. for $C_{19}H_{16}ClN_3O_4$ (385.80): C, 59.15; H, 4.18; N, 10.89; found: C, 59.04; H, 4.06; N, 10.63.

(S)-1-Benzoyl-3-[(4-methyl-2-pyridinylamino)methylidene]-5-(methoxycarbonyl)-pyrrolidin-2-one (**45**). This compound was prepared from 2-amino-4-methylpyridine (**20**) and **6** in acetic acid, reflux for 2 h, trituration with methanol/water. Yield: 94% (0.342 g). M.p. 202–204°C (MeOH/H_2O). $[\alpha]_D^{23}$ +59.2° (*c* = 0.51, DMF). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.27 (3H, s, Het–Me); 2.72–2.77 (1H, m, 4–Ha); 3.18 (1H, dd, *J* = 10.9, 15.3 Hz, 4–Hb); 3.72 (3H, s, OMe); 4.93 (1H, dd. *J* = 2.7, 10.0 Hz, 5–H); 6.79

(2H, br s, 2H–pyridine); 7.41–7.55 (5H, m, Ph); 8.08 (1H, d, *J* = 5.0 Hz, 1H–pyridine); 8.26 (1H, br d, *J* = 12.0 Hz, 3'–H); 9.68 (1H, d, *J* = 12.4 Hz, NH). Anal. calc. for $C_{20}H_{19}N_3O_4$ (365.38): C, 65.74; H, 5.24; N, 11.50; found: C, 65.45; H, 5.49; N, 11.22.

(S)-1-Benzoyl-3-[(4,6-dimethyl-2-pyrimidinylamino)methylidene]-5-(methoxy-carbonyl)pyrrolidin-2-one (**46**). This compound was prepared from 2-amino-4,6-dimethylpyrimidine (**22**) and **6** in acetic acid, reflux for 2 h, trituration with methanol. Yield: 80% (0.296 g). M.p. 217–219°C (MeOH). $[\alpha]_D^{23}$ +26.0° (*c* = 1.02, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.33 (6H, s, 2Het–Me); 2.80 (1H, ddd, *J* = 2.1, 3.2, 17.0 Hz, 4–Ha); 3.17 (1H, ddd, *J* = 2.3, 10.2, 17.0 Hz, 4–Hb); 3.72 (3H, s, OMe); 4.90 (1H, dd, *J* = 3.4, 10.2 Hz, 5–H); 6.82 (1H, s, 1H–pyrimidine); 7.41–7.46 (2H, m, 2H–Ph); 7.53–7.57 (3H, m, 3H–Ph); 8.21 (1H, br d, *J* = 12.1 Hz, 3'–H); 10.27 (1H, d, *J* = 12.1 Hz, NH). Anal. calc. for $C_{20}H_{20}N_4O_4$ (380.40): C, 63.15; H, 5.30; N, 14.73; found: C, 63.07; H, 5.27; N, 15.06.

(S)-1-Benzoyl-3-[(2-pyrazinylamino)methylidene]-5-(methoxycarbonyl)-pyrrolidin-2-one (**47**). This compound was prepared from 2-aminopyrazine (**23**) and **6** in acetic acid, reflux for 2 h, trituration with methanol. Yield: 79% (0.268 g). M.p. 175–177°C (MeOH). $[\alpha]_D^{23}$ +45.2° (*c* = 0.95, DMF). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.81 (1H, ddd, *J* = 2.1, 3.2, 16.5 Hz, 4–Ha); 3.23 (1H, ddd, *J* = 2.6, 10.2, 16.6 Hz, 4–Hb); 3.73 (3H, s, OMe); 4.96 (1H, dd. *J* = 3.0, 10.2 Hz, 5–H); 7.41–7.46 (2H, m, 2H–Ph); 7.54–7.58 (3H, m, 3H–Ph); 8.12–8.14 (1H, m, 3'–H); 8.16 (1H, d, *J* = 2.6 Hz, 1H-pyrazine); 8.25 (1H, dd, *J* = 1.5, 2.6 Hz, 1H-pyrazine); 8.35 (1H, d, *J* = 1.5 Hz, 1H–pyrazine); 10.07 (1H, br d, *J* = 6.8 Hz, NH). Anal. calc. for $C_{18}H_{16}N_4O_4$ (352.34): C, 61.36; H, 4.58; N, 15.90; found: C, 61.34; H, 4.58; N, 15.77.

(S)-1-Benzoyl-3-[(5-methyl-3-isoxazolylamino)methylidene]-5-(methoxy-carbonyl)pyrrolidin-2-one (**48**). This compound was prepared from 3-amino-5-methylisoxazole (**25**) and **6** in acetic acid, reflux for 2 h, trituration with methanol. Yield: 83% (0.294 g). M.p. 209–210°C (MeOH). $[\alpha]_D^{23}$ +22.9° (*c* = 0.99, $CHCl_3$). ^{1}H-

NMR (300 MHz, (D_6)DMSO): 2.33 (3H, s, Het–Me); 2.72 (1H, ddd, *J* = 2.1, 3.3, 16.5 Hz, 4–Ha); 3.13 (1H, ddd, *J* = 2.3, 10.2, 16.6 Hz, 4–Hb); 3.74 (3H, s, OMe); 4.91 (1H, dd. *J* = 3.3, 10.2 Hz, 5–H); 6.13 (1H, s, 1H-isoxazole); 7.40–7.57 (6H, m, 5H–Ph and 3'–H); 9.74 (1H, br s, NH). Anal. calc. for $C_{18}H_{17}N_3O_5$ (355.34): C, 60.84; H, 4.82; N, 11.83; found: C, 60.50; H, 4.78; N, 11.63.

(S,S)-N,N'-bis-[(1-Benzoyl-5-methoxycarbonyl-2-oxopyrrolidin-3-ylidene)-methyl]piperazine monohydrate (**49**). A mixture of (*S*)-1-benzoyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one **6** (604 mg, 2 mmol), piperazine **29** (86 mg, 1 mmol), and acetic acid (100%, 5 ml) was stirred at reflux temperature for 1.5 hour. Volatile components were evaporated *in vacuo* and the residue was purified by column chromatography using a mixture of chloroform and methanol (5:1) as eluant. Fractions containing the product were combined, volatile components were evaporated *in vacuo*, methanol (3 ml) was added to the residue, and the precipitate was collected by filtration to give **49**. Yield: 71% (0.438 g). M.p. 291–293°C (MeOH). $[\alpha]_D^{23}$ +3.8° (*c* = 0.84, CH_2Cl_2). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.82 (2H, dd, *J* = 2.8, 15.0 Hz, 2 x 4'–Ha); 3.33 (2H, m, 2 x 4'–Hb); 3.35 (8H, s, 4 x CH_2–piperazine); 3.70 (6H, s, 2 x OMe); 4.79 (2H, dd. *J* = 4.0, 10.9 Hz, 2 x 5'–H); 7.07 (2H, br s, 2 x 3''–H); 7.36–7.41 (4H, m, 4H–Ph); 7.46–7.53 (6H, m, 6H–Ph). Anal. calc. for $C_{32}H_{32}N_4O_8$ x H_2O (618.64): C, 62.13; H, 5.54; N, 9.06; found: C, 61.93; H, 5.55; N, 9.09.

Preparation of (S)-1-Benzoyl-5-benzoyloxymethyl-3-[(substituted amino)-methylidene]pyrrolidin-2-ones **50**, **51**. *General procedure.* A mixture of (*S*)-1-benzoyl-5-benzoyloxymethyl-3-[(*E*)-(dimethylamino)methylidene]pyrrolidin-2-one **7** (378 mg,1 mmol), substituted amine **19** or **22** (1 mmol), and acetic acid (100%, 5 ml) was refluxed for several hours. Volatile components were evaporated *in vacuo*, the residue was triturated with an appropriate solvent, and the precipitate was collected by filtration to give compounds **50** and **51**, respectively. In this manner, the following compounds were prepared:

(S)-1-Benzoyl-5-benzoyloxymethyl-3-[(5-chloro-2-pyridinylamino)methylidene]-pyrrolidin-2-one (**50**). This compound was prepared from 2-amino-5-chloropyridine (**19**) and **7**, reflux for 3 h, trituration with methanol. Yield: 85% (0.391 g). M.p. 144–148°C (MeOH). $[\alpha]_D^{23}$ +203.6° (*c* = 0.62, CH_2Cl_2). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.71 (1H, ddd, *J* = 1.3, 2.8, 15.1 Hz, 4–Ha); 3.13 (1H, ddd, *J* = 1.9, 9.0, 15.4 Hz, 4–Hb); 4.50 (1H, dd, *J* = 2.8, 11.1 Hz, 5'–Ha); 4.77 (1H, dd, *J* = 3.6, 11.1 Hz, 5'–Hb); 4.80–4.85 (1H, m, 5–H); 7.24 (1H, d, *J* = 9.0 Hz, 1H–pyridine); 7.34–7.58 (8H, m, 8H–Ph); 7.73 (1H, dd, *J* = 2.6, 9.0 Hz, 1H–pyridine); 7.85–7.88 (2H, m, 2H–Ph); 7.91 (1H, br d, *J* = 11.7 Hz, 3'–H); 8.21 (1H, d, *J* = 2.4 Hz, 1H–pyridine); 9.94 (1H, d, *J* = 12.1 Hz, NH). Anal. calc. for $C_{25}H_{20}ClN_3O_4$ (461.90): C, 65.01; H, 4.36; N, 9.10; found: C, 64.80; H, 4.76; N, 9.02.

(S)-1-Benzoyl-5-benzoyloxymethyl-3-[(4,6-dimethyl-2-pyrimidinylamino)-methylidene]pyrrolidin-2-one (**51**). This compound was prepared from 2-amino-4,6-dimethylpyrimidine (**22**) and **7**, reflux for 2 h, trituration with methanol. Yield: 74% (0.336 g). M.p. 123–126°C (MeOH). $[\alpha]_D^{23}$ +12.8° (*c* = 0.72, CH_2Cl_2). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.33 (6H, s, 2Het–Me); 2.91 (1H, deg dt, *J* = 2.7, 16.6 Hz, 4–Ha); 3.02 (1H, ddd, *J* = 2.6, 9.0, 16.9 Hz, 4–Hb); 4.49 (1H, dd, *J* = 3.8, 11.3 Hz, 5'–Ha); 4.70 (1H, dd, *J* = 3.8, 11.3 Hz, 5'–Hb); 4.80–4.88 (1H, m, 5–H); 6.80 (1H, s, 1H–pyrimidine); 7.35–7.52 (7H, m, 7H–Ph); 7.58–7.63 (1H, m, 1H–Ph); 7.85–7.88 (2H, m, 2H–Ph); 8.18 (1H, br d, *J* = 12.1 Hz, 3'–H); 10.21 (1H, d, *J* = 12.1 Hz, NH). Anal. calc. for $C_{26}H_{24}N_4O_4$ (456.49): C, 68.41; H, 5.30; N, 12.27; found: C, 68.63; H, 5.28; N, 12.51.

Preparation of (S)-3-[(substituted amino)methylidene]-5-(methoxycarbonyl)-tetrahydrofuran-2-ones **52**–**56**. *General procedure.* A mixture of (*S*)-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one **8** (199 mg, 1 mmol), substituted amine **15**, **20**–**22** or **27** (1 mmol), and ethanol or acetic acid (100%, 5 ml) was stirred at 20–120°C for several hours. Volatile components were evaporated *in vacuo*, the residue was triturated with an appropriate solvent, and the precipitate was

collected by filtration to give compounds **52**–**56**. In this manner, the following compounds were prepared:

(S)-3-[(4-Methylanilino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**52**). This compound was prepared from 4-methylaniline hydrochloride (**15**) and **8** in ethanol, stirring at 20°C for 1 h, trituration with ethanol/water. Yield: 99% (0.258 g). M.p. 177–178°C (EtOH/H_2O). $[\alpha]_D^{23}$ +75.5° (*c* = 0.99, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.24 (3H, s, Ar–Me); 2.90 (1H, ddd, *J* = 2.0, 4.7, 16.2 Hz, 4–Ha); 3.21 (1H, ddd, *J* = 2.1, 10.1, 16.2 Hz, 4–Hb); 3.73 (3H, s, OMe); 5.11 (1H, dd, *J* = 4.7, 10.1 Hz, 5–H); 7.05–7.12 (4H, m, 4H–Ar); 7.66 (1H, dt, *J* = 1.9, 13.2 Hz, 3'–H); 9.97 (1H, d, *J* = 13.1 Hz, NH). Anal. calc. for $C_{14}H_{15}NO_4$ (261.27): C, 64.36; H, 5.79; N, 5.36; found: C, 64.16; H, 5.95; N, 5.34.

(S)-3-[(4-Methyl-2-pyridinylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**53**). This compound was prepared from 2-amino-4-methylpyridine (**20**) and **8** in acetic acid, reflux for 30 minutes, trituration with water. Yield: 70% (0.183 g). M.p. 151°C (EtOH/H_2O). $[\alpha]_D^{23}$ +0.8° (*c* = 1.01, $CHCl_3$). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.28 (3H, s, Het–Me); 2.93 (1H, ddd, *J* = 2.2, 4.7, 16.4 Hz, 4–Ha); 3.24 (1H, ddd, *J* = 2.2, 10.0, 16.4 Hz, 4–Hb); 3.74 (3H, s, OMe); 5.14 (1H, dd. *J* = 4.7, 10.0 Hz, 5–H); 6.79 (1H, s, 1H–pyridine); 6.81 (1H, d, *J* = 5.3 Hz, 1H-pyridine); 8.10 (1H, d, *J* = 5.1 Hz, 1H–pyridine); 8.29 (1H, dt, *J* = 2.3, 12.4 Hz, 3'–H); 9.67 (1H, d, *J* = 12.4 Hz, NH). Anal. calc. for $C_{13}H_{14}N_2O_4$ (262.26): C, 59.54; H, 5.38; N, 10.68; found: C, 59.28; H, 5.40; N, 10.67.

(S)-3-[(6-Chloro-3-pyridazinylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**54**). This compound was prepared from 3-amino-6-chloropyridazine (**21**) and **8** in acetic acid, reflux for 2 h, trituration with ethyl acetate. Yield: 96% (0.271 g). M.p. 221–223°C (ethyl acetate). $[\alpha]_D^{23}$ +3.1° (*c* = 0.42, DMF). ^{1}H-NMR (300 MHz, (D_6)DMSO): 3.00 (1H, ddd, *J* = 2.2, 4.5, 16.4 Hz, 4–Ha); 3.30 (1H, ddd, *J* = 2.6, 10.2, 16.5 Hz, 4–Hb); 3.74 (3H, s, OMe); 5.19 (1H, dd. *J* = 4.5, 9.8 Hz, 5–H); 7.37 (1H, d, *J*

= 9.0 Hz, 1H–pyridazine); 7.73 (1H, d, *J* = 9.0 Hz, 1H–pyridazine); 8.22 (1H, d, *J* = 12.0 Hz, 3'–H); 10.04 (1H, d, *J* = 12.0 Hz, NH). Anal. calc. for $C_{11}H_{10}ClN_3O_4$ (283.67): C, 46.57; H, 3.55; N, 14.81; found: C, 46.58; H, 3.53; N, 14.67.

(S)-3-[(4,6-Dimethyl-2-pyrimidinylamino)methylidene]-5-(methoxycarbonyl)-tetrahydrofuran-2-one (**55**). This compound was prepared from 2-amino-4,6-dimethylpyrimidine (**22**) and **8** in acetic acid, reflux for 2 h, trituration with ethyl acetate. Yield: 92% (0.254 g). M.p. 138–140°C (ethyl acetate). $[\alpha]_D^{23}$ +1.1° (*c* = 0.76, CH_2Cl_2). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.35 (6H, s, 2Het–Me); 2.94 (1H, ddd, *J* = 2.3, 4.5, 17.0 Hz, 4–Ha); 3.25 (1H, ddd, *J* = 2.6, 10.0, 16.0 Hz, 4–Hb); 3.72 (3H, s, OMe); 5.13 (1H, dd. *J* = 4.7, 10.0 Hz, 5–H); 6.84 (1H, s, 1H–pyrimidine); 8.22 (1H, br d, *J* = 12.4 Hz, 3'–H); 10.26 (1H, d, *J* = 12.1 Hz, NH). Anal. calc. for $C_{13}H_{15}N_3O_4$ (277.28): C, 56.31; H, 5.45; N, 15.15; found: C, 55.94; H, 5.28; N, 14.97.

(S)-3-[(1,2,4-Triazol-3-ylamino)methylidene]-5-(methoxycarbonyl)-tetrahydro-furan-2-one (**56**). This compound was prepared from 3-amino-1,2,4-triazole (**27**) and **8** in acetic acid, reflux for 2 h, trituration with ethyl acetate. Yield: 97% (0.231 g). M.p. 222–224°C (ethyl acetate). $[\alpha]_D^{23}$ –1.0° (*c* = 0.89, DMF). ^{1}H-NMR (300 MHz, (D_6)DMSO): 2.87 (1H, ddd, *J* = 2.1, 4.7, 16.7 Hz, 4–Ha); 3.19 (1H, ddd, *J* = 2.3, 10.2, 16.6 Hz, 4–Hb); 3.72 (3H, s, OMe); 5.10 (1H, dd. *J* = 4.5, 9.8 Hz, 5–H); 7.83 (1H, br d, *J* = 12.4 Hz, 3'–H); 8.34 (1H, s, 1H–triazole); 10.08 (1H, d, *J* = 11.3 Hz, NH); 11.96 (1H, br s, NH–triazole). Anal. calc. for $C_9H_{10}N_4O_4$ (238.20): C, 45.38; H, 4.23; N, 23.52; found: C, 45.37; H, 3.96; N, 23.19.

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[12] Reactions with methyl glycinate hydrochloride (**10**) or benzylamine hydrochloride (**11**) in ethanol were carried out without the addition of hydrochloric acid.

Povzetek. – 5-Substituirani (*S*)-1-acil-3-[(*E*)-(dimetilamino)metiliden]pirolidin-2-oni **5–7** in 3-[(*E*)-(dimetilamino)metiliden]-5-(metoksikarbonil)tetrahidrofuran-2-on **8**, kiralni ciklični analogi 2-substituiranih alkil 3-(dimetilamino)propenoatov, reagirajo z različnimi alkil-, aril-, and heteroarilamini **10–29** pod blagimi pogoji, pri čemer nastanejo 5-substituirani (*S*)-3-[(substituirani amino)metiliden]pirolidin-2-oni **30–51** in (*S*)-3-[(substituirani amino)metiliden]tetrahidrofuran-2-oni **52–56** kot intermediati v 'ring switching' sintezi derivatov 3-heteroarilalanina, 3-heteroarilmlečne kisline in njihovih analogov.