

TRANSFORMATIONS OF (S)-1-ACYL-3-[(E)-(DIMETHYLAMINO)-METHYLIDENE]-5-(METHOXYCARBONYL)PYRROLIDIN-2-ONES. A ONE-STEP SYNTHESIS OF (S)-N-BENZOYL-3-(1-HETEROARYL-5-HYDROXY-1H-PYRAZOLYL-4)ALANINE ESTERS

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Abstract – (S)-1-Benzoyl-3-[(E)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**1**) and (S)-1-*tert*-butoxycarbonyl-3-[(E)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**2**) were transformed in one step with various hydrazines (**3-10**) into the corresponding (S)-3-(1-substituted 5-hydroxy-1*H*-pyrazolyl-4)alanine methyl esters (**11-19**).

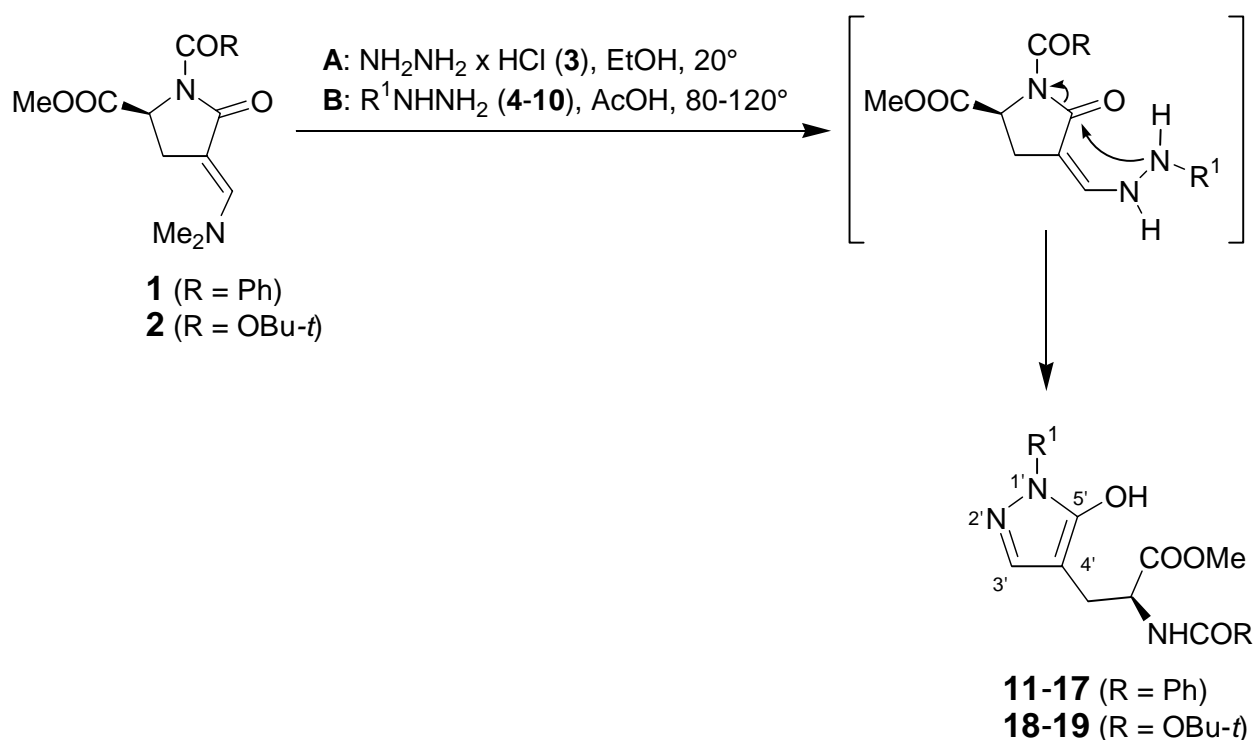
Since most of β -heteroarylalanines are non-proteinogenic amino acids widely found in nature, several synthetic methods for their preparation have been reported in last few decades.¹ Among them, the synthesis of 3-pyrazolylalanines has attracted considerable attention.² 3-(Pyrazolyl-1)alanine for example, was used as constituent of highly potent renine inhibitors.³ Due to their potential biological activity, Young and coworkers developed a ‘ring switching’ strategy to the synthesis of 3-(pyrazolyl-4)alanines from (S)-3-formylpyroglutamates and hydrazines.⁴

Previously, we have shown that 3-dimethylamino- and 3-cyanopropenoates can serve as versatile reagents for the preparation of a variety of heterocyclic systems.^{5,6} On the other hand, we recently reported a ‘ring switching’ synthesis of 3-phenyl-3-(pyrazolyl-1)alanine esters with known relative configuration starting from *rel*-(4*R*,5*R*)-4-benzoylamino-5-phenyl-3-pyrazolidinone.⁷ In this connection, we have recently reported the utilization of 5-substituted (S)-1-acyl-3-[(E)-(dimethylamino)methylidene]pyrrolidin-2-ones, (S)-3-[(E)-(dimethylamino)methylidene]pyrrolidin-2-ones, and their 3-(E)-cyanomethylidene analogs for the preparation of heteroarylalanine and heteroaryllactic acid derivatives and their analogs.⁸⁻¹⁰

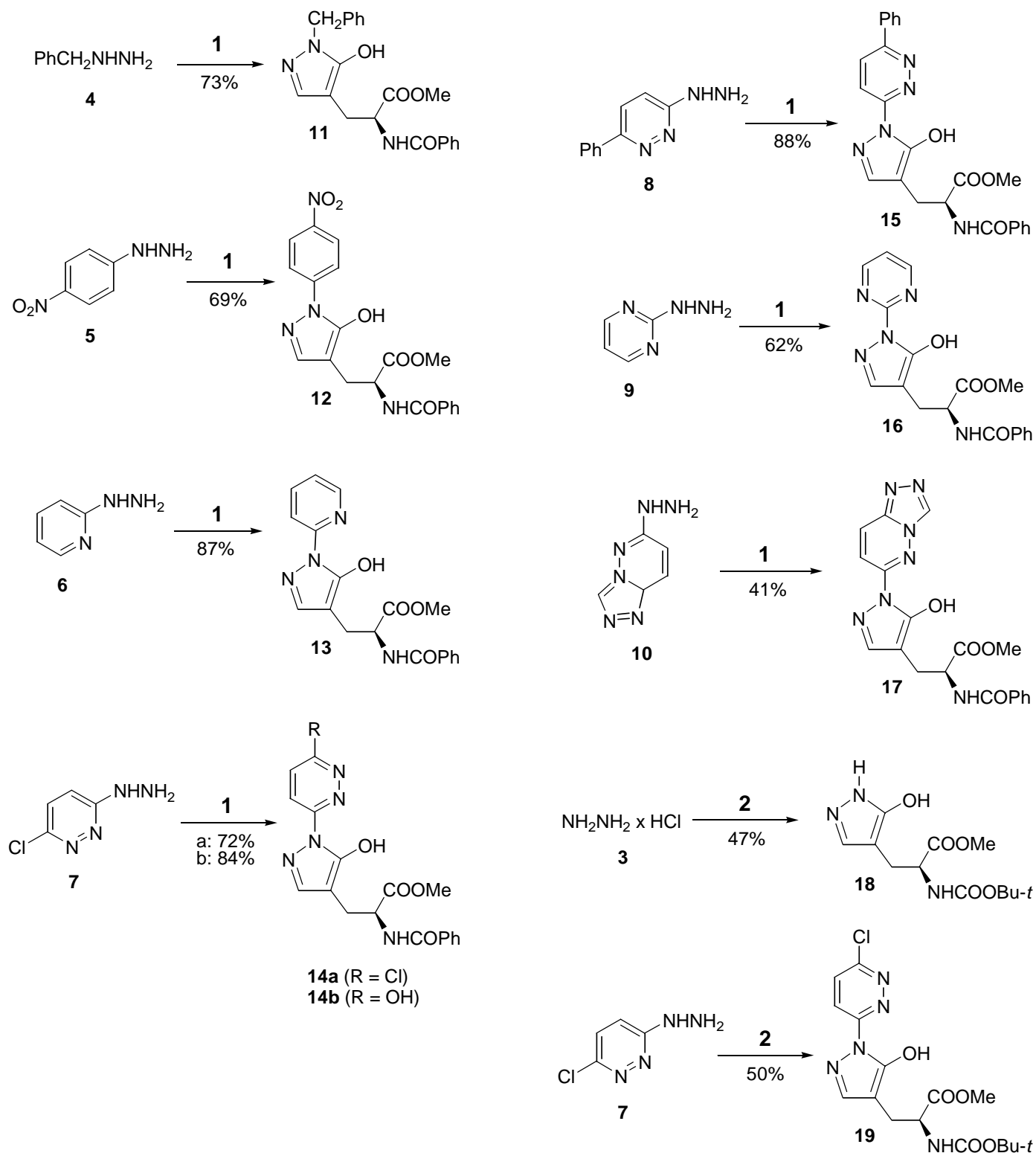
In continuation of our work in this field, we report an improved ‘ring switching’ strategy for the synthesis of novel (S)-*N*-acyl-3-(1-heteroaryl-5-hydroxy-1*H*-pyrazolyl-4)alanine esters (**11-19**) from easily available (S)-1-acyl-3-[(E)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-ones (**1**) and (**2**). Starting compounds, (S)-1-benzoyl-3-[(E)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**1**) and (S)-1-*tert*-butoxycarbonyl-3-[(E)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one

(**2**) were prepared according to the procedures described previously.^{9,10} These were treated with hydrazine hydrochloride (**3**) and substituted hydrazines (**4–10**) to give the corresponding (*S*)-*N*-benzoyl- and (*S*)-*N*-*tert*-butoxycarbonyl-3-(1-substituted 5-hydroxy-1*H*-pyrazolyl-4)alanine methyl esters (**11–19**) (Scheme 1). Reactions of (*S*)-1-benzoyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**1**) with benzyl- (**4**), 4-nitrophenyl- (**5**), pyridinyl-2- (**6**), 6-chloropyridazinyl-3- (**7**), 6-phenylpyridazinyl-3- (**8**), pyrimidinyl-2- (**9**), and (1,2,4-triazolo[4,3-*b*]pyridazinyl-6)hydrazine (**10**) proceeded in refluxing acetic acid to give good yields of (*S*)-*N*-benzoyl-3-(5-hydroxy-1*H*-pyrazolyl-4)alanine methyl esters (**11–17**) with the corresponding substituents at the position 1 in the pyrazole ring. Reaction of **1** with (6-chloropyridazinyl-3)hydrazine (**7**) was found to be temperature dependent. The corresponding (*S*)-*N*-benzoyl-3-[1-(6-chloropyridazinyl-3)]alanine methyl ester (**14a**) was formed in acetic acid at 80°C. However, when the same reaction was carried out in refluxing acetic acid, also the substitution of chloro by a hydroxy group took place to give (*S*)-*N*-benzoyl-3-[1-(6-hydroxypyridazinyl-3)]alanine methyl ester (**14b**). On the other hand, treatment of (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**2**) under acidic conditions resulted in decomposition of the reagent **2** rather than in the formation of pyrazolyalanine esters. However, reaction of **2** with hydrazine hydrochloride (**3**) in ethanol at room temperature, as well as reaction with (6-chloropyridazinyl-3)hydrazine (**7**) in acetic acid at 80°C, gave the corresponding *N*-*tert*-butoxycarbonyl-3-(5-hydroxy-1*H*-pyrazolyl-4)- (**18**) and *N*-*tert*-butoxycarbonyl-3-[1-(1,2,4-triazolo[4,3-*b*]pyridazinyl-3)-5-hydroxy-1*H*-pyrazolyl-4)alanine methyl ester (**19**), respectively. (Scheme 2).

Scheme 1



Scheme 2



EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^1H NMR spectra was obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer with DMSO-d_6 as solvent and Me_4Si as internal standard. The

microanalyses for C, H, and N were obtained on a Perkin-Elmer CHN Analyser 2400. The optical rotations were measured on a Perkin-Elmer 241 MC Polarimeter. (*S*)-1-Benzoyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**1**) and (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**2**) were prepared according to the procedures described in the literature.^{9,10}

General Procedure for the Preparation of (*S*)-*N*-Benzoyl-3-(1-substituted 5-hydroxy-1*H*-pyrazolyl-4)alanine Methyl Esters (11–17**).** A mixture of (*S*)-1-benzoyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**1**) (302 mg, 1 mmol), hydrazine derivative (**4–10**) (1 mmol), and glacial acetic acid (4 mL) was heated at reflux temperature for 2–3 h.¹¹ Volatile components were evaporated *in vacuo*, the solid residue was crystallised from methanol, and the precipitate was collected by filtration to give (*S*)-*N*-benzoyl-3-(1-substituted 5-hydroxy-1*H*-pyrazolyl-4)alanine methyl esters (**11–17**).

(*S*)-*N*-Benzoyl-3-(1-benzyl-5-hydroxy-1*H*-pyrazolyl-4)alanine Methyl Ester (11**).** This compound was prepared from benzylhydrazine (**4**), 2 h of reflux, yield 73%; mp 170–172° (from methanol/water). $[\alpha]_{\text{D}}^{23} = -27.4^{\circ}$ ($c = 0.86$, DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 2.80 (1H, dd, $J = 8.0, 14.7$ Hz, 3-Ha), 2.89 (1H, dd, $J = 5.2, 14.7$ Hz, 3-Hb), 3.61 (3H, s, OMe), 4.56 (1H, ddd, $J = 5.2, 7.5, 8.3$ Hz, 2-H), 5.01 (2H, s, CH₂Ph), 7.08–7.11 (2H, m, 2H-Ph), 7.22–7.29 (4H, m, 3H-Ph and 3'-H), 7.45–7.58 (3H, m, 3H-Ph), 7.87–7.90 (2H, m, 2H-Ph), 9.29 (1H, br s, NH), 10.66 (1H, br s, 5'-OH). *Anal.* Calcd for C₂₁H₂₁ N₃O₄: C, 66.48; H, 5.58; N, 11.07. Found: C, 66.79; H, 5.55; N, 10.96.

(*S*)-*N*-Benzoyl-3-[1-(4-nitrophenyl)-5-hydroxy-1*H*-pyrazolyl-4]alanine Methyl Ester (12**).** This compound was prepared from 4-nitrophenylhydrazine (**5**), 3 h of reflux, yield 69%; mp 185–188° (from methanol); $[\alpha]_{\text{D}}^{23} = -91.8^{\circ}$ ($c = 0.74$, DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 2.85 (1H, dd, $J = 9.0, 14.7$ Hz, 3-Ha), 2.96 (1H, dd, $J = 5.3, 14.7$ Hz, 3-Hb), 3.66 (3H, s, OMe), 4.61 (1H, ddd, $J = 5.3, 7.6, 8.7$ Hz, 2-H), 7.45–7.55 (3H, m, 3H-Ph), 7.60 (1H, s, 3'-H), 7.88–7.90 (2H, m, 2H-Ph), 8.11 (2H, d, $J = 9.0$ Hz, 2H-Ar), 8.32 (2H, $J = 9.0$ Hz, 2H-Ar), 9.08 (1H, d, $J = 7.2$ Hz, NH), 11.82 (1H, br s, 5'-OH). *Anal.* Calcd for C₂₀H₁₈ N₄O₆: C, 58.53; H, 4.42; N, 13.65. Found: C, 58.41; H, 4.54; N, 13.58.

(*S*)-*N*-Benzoyl-3-[5-hydroxy-1-(pyridinyl-2)-1*H*-pyrazolyl-4]alanine Methyl Ester (13**).** This compound was prepared from 2-hydrazinopyridine (**6**), 2 h of reflux, yield 87%; mp 160–163° (from methanol/water); $[\alpha]_{\text{D}}^{23} = -66.3^{\circ}$ ($c = 1.0$, DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 2.82 (1H, dd, $J = 8.3, 14.7$ Hz, 3-Ha), 2.89 (1H, dd, $J = 4.8, 14.7$ Hz, 3-Hb), 3.65 (3H, s, OMe), 4.60 (1H, deg. dt, $J = 4.8, 8.1$ Hz, 2-H), 7.29 (1H,

dd, $J = 4.9, 8.3$ Hz, 5''-H), 7.46–7.59 (3H, deg. dt, $J = 1.7, 8.3$ Hz, 3H-Ph), 7.66 (1H, s, 3'-H), 7.88–7.91 (2H, m, 2H-Ph), 7.96–8.02 (1H, m, 4''-H), 8.26–8.31 (1H, m, 3''-H), 8.43–8.46 (1H, ddd, $J = 1.1, 1.9, 5.1$ Hz, 6''-H), 9.13 (1H, d, $J = 7.2$ Hz, NH), 12.28 (1H, br s, 5'-OH). *Anal.* Calcd for C₁₉H₁₈N₄O₄: C, 62.29; H, 4.95; N, 15.29. Found: C, 62.32; H, 4.67; N, 15.31.

(S)-N-Benzoyl-3-[1-(6-chloropyridazinyl-3)-5-hydroxy-1H-pyrazolyl-4]alanine Methyl Ester (14a).

This compound was prepared from 6-chloro-3-hydrazinopyridazine (**7**), stirring at 80°C for 3 h, yield 72%; mp 223–225°C (from methanol); $[\alpha]_{\text{D}}^{23} = -70.7^\circ$ ($c = 0.71$, DMF). ¹H NMR (300 MHz, DMSO-d₆): δ 2.81 (1H, dd, $J = 8.3, 14.7$ Hz, 3-Ha), 2.89 (1H, dd, $J = 5.3, 14.7$ Hz, 3-Hb), 3.66 (3H, s, OMe), 4.60 (1H, deg. dt, $J = 4.9, 7.6$ Hz, 2-H), 7.46–7.60 (3H, m, 3H-Ph), 7.85 (1H, s, 3'-H), 7.88–7.92 (2H, m, 2H-Ph), 8.03 (1H, d, $J = 9.4$ Hz, 5''-H), 8.77 (1H, d, $J = 9.4$ Hz, 4''-H), 9.06 (1H, d, $J = 6.8$ Hz, NH), 12.30 (1H, br s, 5'-OH). *Anal.* Calcd for C₁₈H₁₆N₅O₄Cl: C, 53.81; H, 4.01; N, 17.43. Found: C, 54.08; H, 4.05; N, 17.37.

(S)-N-Benzoyl-3-[5-hydroxy-1-(6-hydroxypyridazinyl-3)-1H-pyrazolyl-4]alanine Methyl Ester (14b).

This compound was prepared from 6-chloro-3-hydrazinopyridazine (**7**), 3 h of reflux, yield 84%; mp 256–258°C (from methanol); $[\alpha]_{\text{D}}^{23} = -64.1^\circ$ ($c = 1.08$, DMF). ¹H NMR (300 MHz, DMSO-d₆): δ 2.79 (1H, dd, $J = 8.7, 14.7$ Hz, 3-Ha), 2.88 (1H, dd, $J = 5.3, 14.7$ Hz, 3-Hb), 3.65 (3H, s, OMe), 4.60 (1H, deg. dt, $J = 5.3, 8.3$ Hz, 2-H), 7.06 (1H, d, $J = 10.2$ Hz, 5''-H), 7.46–7.59 (3H, m, 3H-Ph), 7.66 (1H, s, 3'-H), 7.86–7.89 (2H, m, 2H-Ph), 8.24 (1H, br s, 4''-H), 9.01 (1H, d, $J = 6.7$ Hz, NH), 11.57 (1H, br s, 5'-OH), 12.95 (1H, s, 6''-OH). *Anal.* Calcd for C₁₈H₁₇N₅O₅: C, 56.40; H, 4.47; N, 18.27. Found: C, 56.19; H, 4.55; N, 18.16.

(S)-N-Benzoyl-3-[5-hydroxy-1-(6-phenylpyridazinyl-3)-1H-pyrazolyl-4]alanine Methyl Ester (15).

This compound was prepared from 6-phenyl-3-hydrazinopyridazine (**8**), 3 h of reflux, yield 88%; mp 198–200 °C (from methanol); $[\alpha]_{\text{D}}^{23} = -60.6^\circ$ ($c = 0.71$, CH₂Cl₂). ¹H NMR (300 MHz, DMSO-d₆): δ 2.83 (1H, dd, $J = 8.5, 14.9$ Hz, 3-Ha), 2.91 (1H, dd, $J = 5.3, 14.7$ Hz, 3-Hb), 3.66 (3H, s, OMe), 4.64 (1H, deg. dt, $J = 5.1, 8.1$ Hz, 2-H), 7.47–7.61 (6H, m, 6H-Ph), 7.86 (1H, s, 3'-H), 7.89–7.92 (2H, m, 2H-Ph), 8.12–8.16 (2H, m, 2H-Ph), 8.43 (1H, d, $J = 4.9$ Hz, 5''-H), 8.74 (1H, br s, 4''-H), 9.08 (1H, d, $J = 7.2$ Hz, NH), 12.67 (1H, br s, 5'-OH). *Anal.* Calcd for C₂₄H₂₁N₅O₄: C, 65.00; H, 4.77; N, 15.79. Found: C, 64.78; H, 4.63; N, 15.94.

(S)-N-Benzoyl-3-[5-hydroxy-1-(pyrimidinyl-2)-1H-pyrazolyl-4]alanine Methyl Ester (16).

This compound was prepared from 2-hydrazinopyrimidine (**9**), 3 h of reflux, yield 62%; mp 207–209 °C (from methanol); $[\alpha]_{\text{D}}^{23} = +82.3^\circ$ ($c = 0.70$, CH₂Cl₂). ¹H NMR (300 MHz, DMSO-d₆): δ 2.83 (1H, dd, $J = 8.7, 14.7$ Hz, 3-Ha), 2.91 (1H, dd, $J = 5.6, 14.7$ Hz, 3-Hb), 3.65 (3H, s, OMe), 4.61 (1H, ddd, $J = 5.5, 7.4, 8.3$ Hz,

2-H), 7.41 (1H, t, $J = 4.9$ Hz, 5''-H), 7.45–7.58 (3H, m, 3H-Ph), 7.61 (1H, s, 3'-H), 7.86–7.89 (2H, m, 2H-Ph), 8.84 (2H, d, $J = 4.9$ Hz, 4''-H and 6''-H), 9.00 (1H, d, $J = 6.8$ Hz, NH), 11.71 (1H, br s, 5'-OH). *Anal.* Calcd for C₁₈H₁₇N₅O₄: C, 58.85; H, 4.66; N, 19.06. Found: C, 58.79; H, 4.47; N, 18.95.

(S)-N-Benzoyl-3-[5-hydroxy-1-(1,2,4-triazolo[4,3-*b*]pyridazinyl-3)-1H-pyrazolyl-4]alanine Methyl Ester (17). This compound was prepared from 6-hydrazino-1,2,4-triazolo[4,3-*b*]pyridazine (**10**), 3 h of reflux, yield 41%; mp 210–212 °C (from methanol); $[\alpha]_{\text{D}}^{23} = -23.4^{\circ}$ ($c = 0.82$, DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 2.80 (1H, dd, $J = 8.7, 14.7$ Hz, 3-Ha), 2.89 (1H, dd, $J = 5.3, 15.1$ Hz, 3-Hb), 3.66 (3H, s, OMe), 4.62 (1H, ddd, $J = 5.4, 7.4, 8.3$ Hz, 2-H), 7.45–7.56 (3H, m, 3H-Ph), 7.84–7.89 (3H, m, 2H-Ph and 3'-H), 8.47–8.50 (2H, m, 7''-H and 8''-H), 8.97 (1H, d, $J = 7.1$ Hz, NH), 9.52 (1H, s, 3''-H), 12.08 (1H, br s, 5'-OH). *Anal.* Calcd for C₁₉H₁₇N₇O₄: C, 56.02; H, 4.21; N, 24.07. Found: C, 55.86; H, 4.25; N, 23.68.

(S)-N-tert-Butoxycarbonyl-3-[3(5)-hydroxy-1H-pyrazolyl-4]alanine Methyl Ester (18). A mixture of (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**2**) (298 mg, 1 mmol), hydrazine hydrochloride (**3**) (69 mg, 1 mmol), and ethanol (5 mL) was stirred at rt for 2 h. Volatile components were evaporated *in vacuo*, water (10 mL) was added to residue and the product was extracted with chloroform (2×10 mL). Organic phases were combined, dried over sodium sulfate, filtered, and the filtrate was evaporated *in vacuo*. Water (5 mL) was added to the residue and the precipitate was collected by filtration to give compound (**18**) in 47% yield (0.135 g); mp 148–150 °C (from water); $[\alpha]_{\text{D}}^{23} = -25.7^{\circ}$ ($c = 0.7$, DMF). ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.35 (9H, s, Bu-*t*), 2.55 (1H, dd, $J = 8.9, 14.9$ Hz, 3-Ha), 2.67 (1H, dd, $J = 5.1, 14.3$ Hz, 3-Hb), 3.59 (3H, s, OMe), 4.03–4.06 (1H, m, 2-H), 7.04 (1H, d, $J = 7.4$ Hz, NH), 7.16 (1H, s, 3'-H), 9.71 (1H, br s, 1'-H), 11.31 (1H, br s, 5'-OH). *Anal.* Calcd for C₁₂H₁₉N₃O₅: C, 50.52; H, 6.71; N, 14.73. Found: C, 50.52; H, 6.69; N, 14.66.

(S)-N-tert-Butoxycarbonyl-3-[1-(6-chloropyridazinyl-3)-5-hydroxy-1H-pyrazolyl-4]alanine Methyl Ester (19). A mixture of (*S*)-1-*tert*-butoxycarbonyl-3-[(*E*)-(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**2**) (298 mg, 1 mmol), 6-chloro-3-hydrazinopyridazine (**7**) (145 mg, 1 mmol), and glacial acetic acid (4 mL) was heated at 80°C for 1 h. Volatile components were evaporated *in vacuo* and the residue was purified by column chromatography using chloroform/methanol (5:1) as eluant. Fractions containing the product were combined and were evaporated *in vacuo*. Water (5 mL) was added to the residue and the precipitate was collected by filtration to give compound (**19**) in 50% yield (0.200 g); mp 163–165 °C (from water); $[\alpha]_{\text{D}}^{23} = +28.3^{\circ}$ ($c = 0.6$, CH₂Cl₂). ¹H NMR (300 MHz, DMSO-*d*₆): δ 1.36 (9H, s, Bu-*t*), 2.56 (1H, dd, $J = 8.7, 14.3$ Hz, 3-Ha), 2.69 (1H, dd, $J = 5.1, 14.5$ Hz, 3-Hb), 3.62 (3H, s, OMe), 4.60

(1H, deg. dt, $J = 5.3, 8.3$ Hz, 2-H), 7.29 (1H, d, $J = 7.5$ Hz, NH), 7.78 (1H, s, 3'-H), 8.02 (1H, d, $J = 9.4$ Hz, 5''-H), 8.74 (1H, d, $J = 9.0$ Hz, 4''-H), 12.40 (1H, br s, 5'-OH). *Anal.* Calcd for C₁₆H₂₀ClN₅O₅: C, 48.31; H, 5.07; N, 17.60. Found: C, 48.32; H, 5.15; N, 17.62.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. For a review see: P. Kolar, A. Petrič, and M. Tišler, *J. Heterocycl. Chem.*, 1997, **34**, 1067.
2. N. Sugimoto, H. Watanabe, and A. Ide, *Tetrahedron*, 1960, **11**, 231; I. L. Finar and K. Utting, *J. Chem. Soc.*, 1960, 5272; H. Reimlinger and J. F. M. Oth, *Chem. Ber.*, 1964, **97**, 331; L. D. Arnold, R. G. May, and J. C. Vederas, *J. Am. Chem. Soc.*, 1988, **110**, 2237; J. E. Baldwin, A. C. Spivey, and C. J. Schofield, *Tetrahedron Asymmetry*, 1990, **1**, 881; M. Perez and R. Pleixats, *Tetrahedron*, 1995, **51**, 8355.
3. S. H. Rosenberg, K. P. Spina, K. W. Woods, J. Polakowski, D. L. Martin, Z. Yao, H. H. Stein, J. Cohen, J. L. Barlow, D. A. Egan, K. A. Tricarico, W. R. Baker, and H. D. Kleinert, *J. Med. Chem.*, 1993, **36**, 449; S. H. Rosenberg, K. P. Spina, S. L. Condon, J. Polakowski, Z. Yao, P. Kovar, H. H. Stein, J. Cohen, J. L. Barlow, V. Klinghofer, D. A. Egan, K. A. Tricarico, T. J. Perun, W. R. Baker, and H. D. Kleinert, *J. Med. Chem.*, 1993, **36**, 460.
4. A. N. Bowler, P. M. Doyle, and D. W. Young, *J. Chem. Soc., Chem. Commun.*, 1991, 314; A. Dinsmore, P. M. Doyle, and D. W. Young, *Tetrahedron Lett.*, 1995, **36**, 7503; A. N. Bowler, A. Dinsmore, P. M. Doyle, and D. W. Young, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1297.
5. For short reviews see: B. Stanovnik, *Molecules*, 1996, **1**, 123; B. Stanovnik, "Methyl 2-Benzoylamino-3-dimethylaminopropenoate in the Synthesis of Heterocyclic Systems" in "Progress in Heterocyclic Chemistry", Vol 5, ed. by H. Suschitzky and E. F. V. Scriven, Pergamon Press, Oxford, 1993, pp. 34–53.
6. For recent publications see: L. Selič, S. Golič-Grdadolnik, and B. Stanovnik, *Helv. Chim. Acta*, 1997, **80**, 2418; J. Smodiš and B. Stanovnik, *Tetrahedron*, 1998, **54**, 9799; L. Selič and B. Stanovnik, *Helv. Chim. Acta*, 1998, **81**, 1634; L. Selič, S. Strah, R. Toplak, and B. Stanovnik, *Heterocycles*, 1998, **47**, 1017; L. Pizzioli, B. Ornik, J. Svete, and B. Stanovnik, *Helv. Chim. Acta*, 1998, **81**, 231; U. Bratušek, A. Hvala, and B. Stanovnik, *J. Heterocycl. Chem.*, 1998, **35**, 1281; G. Soršak, S. Golič-Grdadolnik,

- and B. Stanovnik, *J. Heterocycl. Chem.*, 1998, **35**, 1275; L. Selič and B. Stanovnik, *J. Heterocycl. Chem.*, 1998, **35**, 1527; L. Selič and B. Stanovnik, *Synthesis*, 1999, 479; R. Toplak, J. Svete, B. Stanovnik, and S. Golič-Grdadolnik, *J. Heterocycl. Chem.*, 1999, **35**, 225; R. Toplak, J. Svete, S. Golič-Grdadolnik, and B. Stanovnik, *Coll. Czech. Chem. Commun.*, 1999, **64**, 177.
7. A. Prešeren, J. Svete, and B. Stanovnik, *J. Heterocycl. Chem.*, 1999, **36**, 799. J. Svete and B. Stanovnik, *Heterocycles*, 1999, **51**, 2073.
 8. M. Škof, J. Svete, and B. Stanovnik, *Heterocycles*, 1999, **51**, 1051. M. Škof, J. Svete, and B. Stanovnik, *Heterocycles*, 2000, **52** (No. 2), in print. M. Škof, J. Svete, and B. Stanovnik, *J. Heterocycl. Chem.*, 1999, in print.
 9. M. Škof, J. Svete, B. Stanovnik, L. Golič, S. Golič-Grdadolnik, and L. Selič, *Helv. Chim. Acta*, 1998, **81**, 2332.
 10. M. Škof, J. Svete, M. Kmetič, B. Stanovnik, and S. Golič-Grdadolnik, *Eur. J. Org. Chem.*, 1999, 1581.
 11. Reaction of **1** with (6-chloropyridazinyl-3)hydrazine (**7**) in acetic acid was carried out at two temperatures: a) at 80°C to afford (*S*)-*N*-benzoyl-3-[1-(6-chloropyridazinyl-3)-5-hydroxy-1*H*-pyrazolyl-4]alanine methyl ester (**14a**); b) at reflux temperature (~120°C) to afford (*S*)-*N*-benzoyl-3-[1-(6-hydroxypyridazinyl-3)-5-hydroxy-1*H*-pyrazolyl-4]alanine methyl ester (**14b**).