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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-1*H*-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]

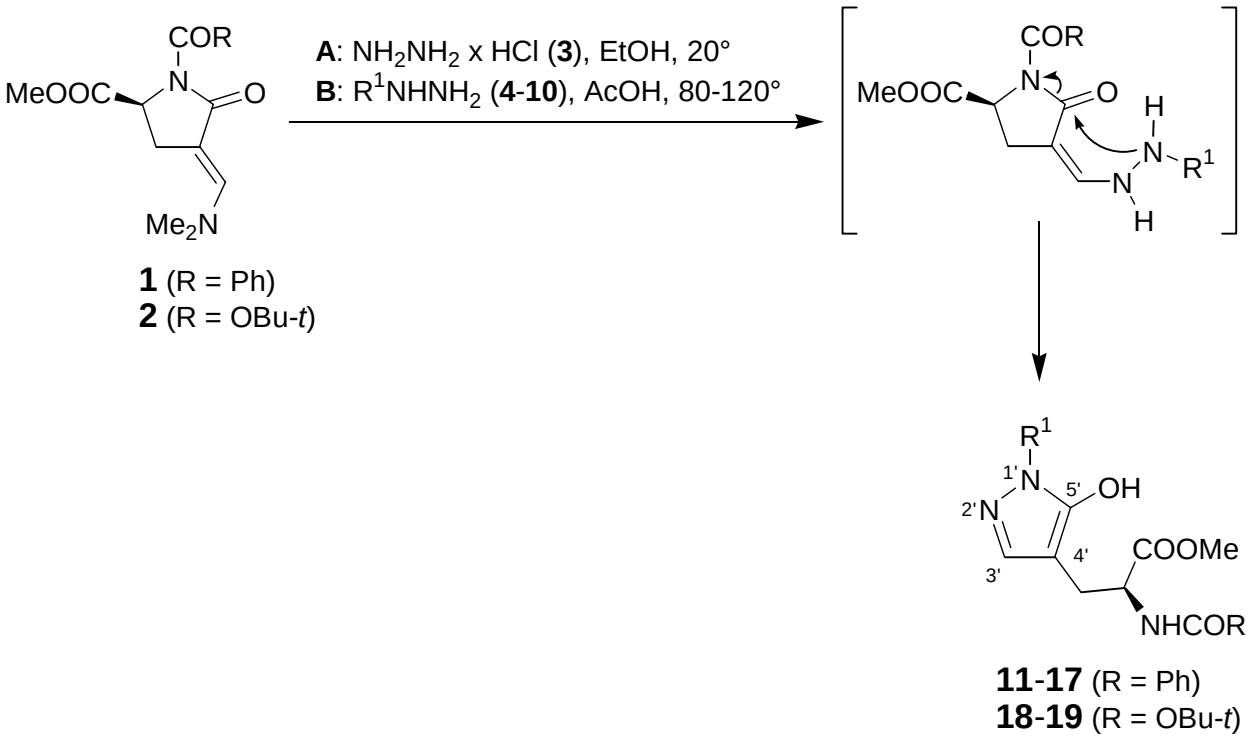
Previously, we have shown that 3-dimethylamino- and 3-cyanopropenoates can serve as versatile reagents for the preparation of a variety of heterocyclic systems.[5,6] On the other hand, we recently reported a 'ring switching' synthesis of 3-phenyl-3-(pyrazolyl-1)alanine esters with known relative configuration 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

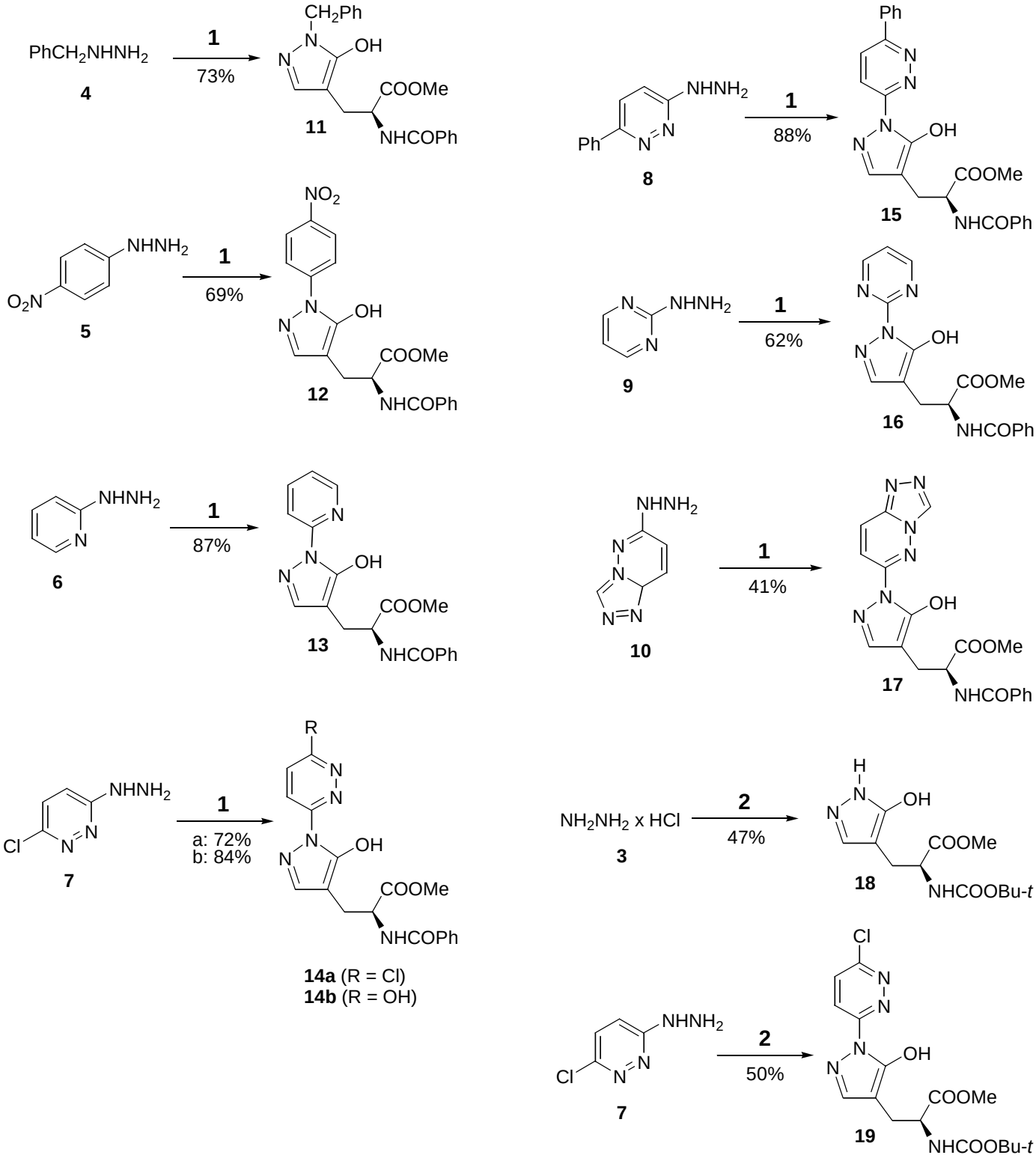
(**2**) were prepared according to the procedures described previously.[9,10] These were treated with hydrazine hydrochloride (**3**) and substituted hydrazines (**4**–**10**) to give the corresponding (*S*)-*N*-benzoyl- and (*S*)-*N*-*tert*-butoxycarbonyl-3-(1-substituted 5-hydroxy-1*H*-pyrazolyl-4)alanine 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 pyrazolylalanine 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).

Sheme 1



Sheme 2



EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H 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 *Anal*yser 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). $[\alpha]_D^{23}$ = –27.4° (*c* = 0.86, DMF). ^{1}H 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, C*H*$_2$Ph), 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 $C_{21}H_{21}N_3O_4$: 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); $[\alpha]_D^{23}$ = –91.8° (*c* = 0.74, DMF). ^{1}H 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 $C_{20}H_{18}N_4O_6$: 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); $[\alpha]_D^{23}$ = –66.3° (*c* =1.0, DMF). ^{1}H 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 $C_{19}H_{18}N_4O_4$: 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-1*H*-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); $[\alpha]_D^{23} = -70.7°$ (*c* = 0.71, DMF). ^{1}H NMR (300 MHz, DMSO-d_6): 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 $C_{18}H_{16}N_5O_4Cl$: 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)-1*H*-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° (from methanol); $[\alpha]_D^{23} = -64.1°$ (*c* = 1.08, DMF). ^{1}H NMR (300 MHz, DMSO-d_6): 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 $C_{18}H_{17}N_5O_5$: 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)-1*H*-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); $[\alpha]_D^{23} = -60.6°$ (*c* = 0.71, CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): 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 $C_{24}H_{21}N_5O_4$: 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)-1*H*-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); $[\alpha]_D^{23} = +82.3°$ (*c* = 0.70, CH_2Cl_2). ^{1}H NMR (300 MHz, DMSO-d_6): 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 $C_{18}H_{17}N_5O_4$: 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)-1*H*-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); $[\alpha]_D^{23} = -23.4°$ (*c* = 0.82, DMF). ^{1}H 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 $C_{19}H_{17}N_7O_4$: 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-1*H*-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); $[\alpha]_D^{23} = -25.7°$ (*c* = 0.7, DMF). ^{1}H 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 $C_{12}H_{19}N_3O_5$: 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-1*H*-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); $[\alpha]_D^{23} = +28.3°$ (*c* = 0.6, CH_2Cl_2). ^{1}H 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 $C_{16}H_{20}ClN_5O_5$: C, 48.31; H, 5.07; N, 17.60. Found: C, 48.32; H, 5.15; N, 17.62.

ACKNOWLEDGEMENT

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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**).