Synthesis of Functionalized Compounds Containing Pyridazine and Related Moieties.

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3-Aminopyridazines **17** and 3-hydrazinopyridazines **18** were used as building blocks for the preparation of various types of functionalized, pyridazine ring containing compounds. 3-Aminopyridazines were employed in the synthesis of 3-(6-chloroimidazo[1,2–*b*]pyridazin-2-yl)alanines **26**, **27** and for the preparation of 3-amino-4*H*-pyrimido[1,2–*b*]pyridazin-4-ones **103**, intermediates in the 'ring switching' synthesis of alkyl 1-pyridazin-3-yl-1,2,3-triazole-4-carboxylates **106**. On the other hand, hydrazinopyridazines **18** were employed in a two-step preparation of 3-functionalized 1,2,4-triazolo[4,3–*b*]pyridazines *via* condensation with functionalized aldehydes and their enamino analogs followed by oxidative cyclization of the intermediate hydrazones. In this manner, 1,2,4-triazolo[4,3–*b*]pyridazin-3-yl substituted alanines **29**, **30**, polyols **33**, **39–48**, *C*-nucleosides **49**, **50**, and terpenes **58**, **62**, **64–69** were prepared. In another general approach, 3-hydrazinopyridazines **18** were treated with functionalized enaminones as 1,3-dielectrophiles to give the 1-(substituted pyridazin-3-yl)-1*H*-pyrazole derivatives containing an ester **72**, **73**, **75**, **76**, alanine **79**, **84**, **85**, **87**, 2-phenylethylamine **97**, **99**, and β-amino alcohol functional element **98**, **100**. In the reaction of 4-oxohomoglutamate **82** with hydrazine hydrate and methyl hydrazine, chiral functionalized tetrahydropyridazinones **88a,b** were obtained.

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1. Introduction.

Pyridazines belong among the most significant heterocyclic rings, which are frequently employed for the preparation of a variety of important products. Pyridazine derivatives have only recently been discovered among the natural products, such as pyridazinomycin (**1**), antifungal antibiotic isolated from *Streptomyces violacoeniger*, and tetrahydropyridazine- and hexahydropyridazine-6-carboxylic acid structural element containing peptides **2–6**, exhibiting antibiotic, antitumor, and collagenase inhibition activity [1] (Figure 1). On the other hand, a variety of synthetic pyridazine derivatives found use in agrochemical, pharmaceutical, and other applications. Examples of important synthetic pyridazine derivatives are Minaprine (**7**), Sulfomethoxypyridazine (**8**), Hydralazine (**9**), Azalestine (**10**), Endixaprine (**11**), Chlordiazone (**12**), Pyridate (**13**), and azolo fused pyridazines **14–16** [1, 2] (Figure 2).

Our studies in the field of the synthesis of functionalized heterocycles were oriented towards development of synthetic methodologies for the preparation of various types of functionalized heterocyclic compounds, *e.g.* heteroaryl substituted α-amino and α-hydroxy acids, β-amino alcohols, phenethylamines, diols, polyols, terpenes, and heterocyclic analogs of amino acids and dipeptides. Since numerous synthetic pyridazine derivatives found use in

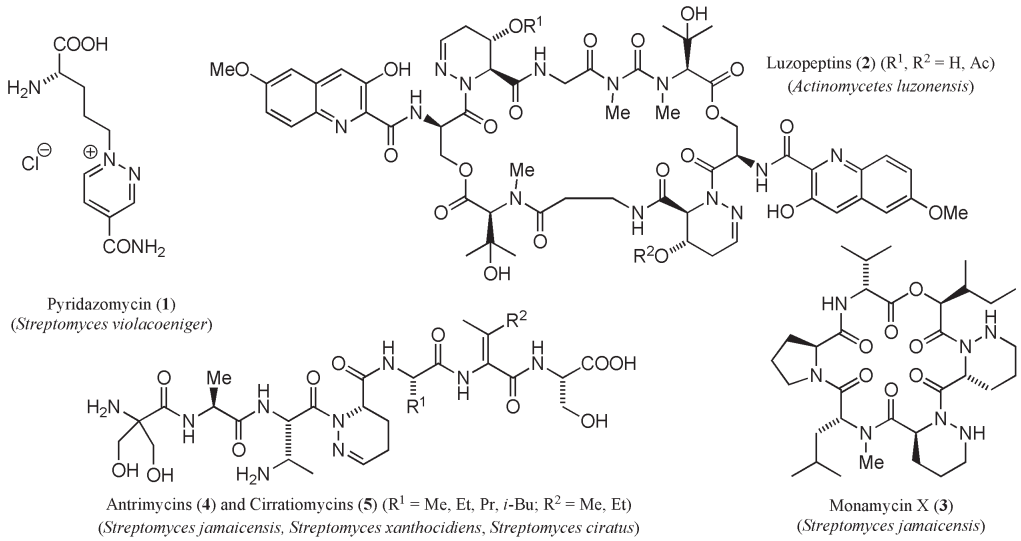


Figure 1

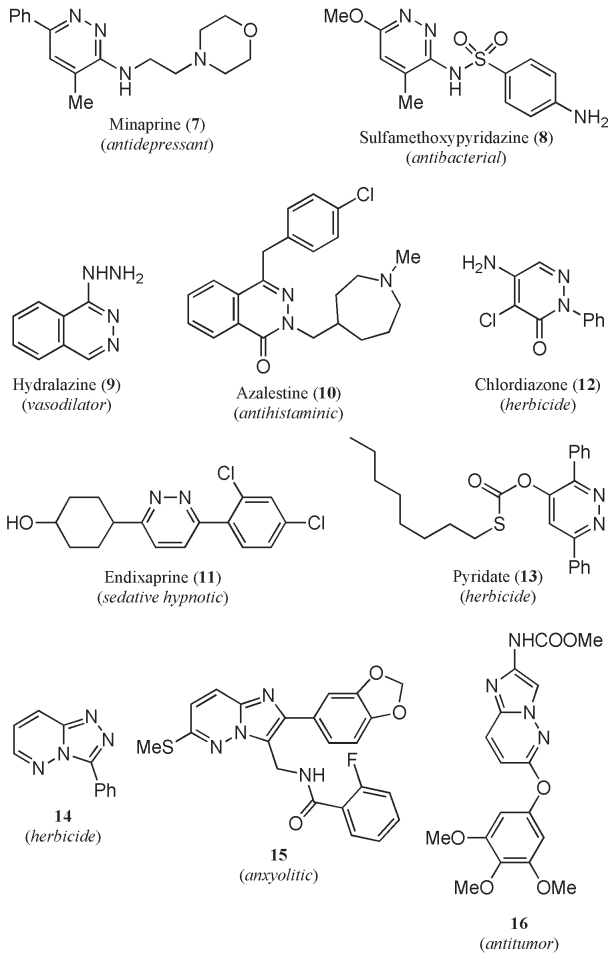


Figure 2

pharmaceutical and agrochemical applications, our attention was also focused on utilization 3-aminopyridazines **17** and 3-hydrazinopyridazines **18** in the synthesis of pyridazine containing functionalized heterocycles. Synthetic approaches were based on cyclocondensation of 3-aminopyridazines **17** and 3-hydrazinopyridazines **18** with functionalized electrophiles, such as α-bromo ketones, aldehydes, and enaminones. In the course of these studies, the following general types of functionalized pyridazines have been prepared: imidazo[1,2–*b*]pyridazines, 1,2,4-triazolo[4,3–*b*]pyridazines, 1-pyridazinyl-1*H*-pyrazoles, 4*H*-pyrimido[1,2–*b*]pyridazin-4-ones, and 1-pyridazinyl-1*H*-1,2,3-triazoles [3] (Figure 3).

2. Synthesis of Functionalized Imidazo[1,2–*b*]pyridazines and 1,2,4-Triazolo[4,3–*b*]pyridazines.

In the synthesis of 3-(imidazo[1,2–*b*]pyridazin-2-yl)- and 3-(1,2,4-triazolo[4,3–*b*]pyridazin-3-yl)alanine derivatives, functionalized α-bromo ketone **24** and aldehyde **25** were first prepared according to slightly modified procedures, described in the literature [4–6]. Thus, (*S*)-aspartic acid (**19**) was transformed in three steps into the acid chloride **22**. Treatment of **22** with excess diazomethane at 0° afforded diazoketone **23**, which was then transformed with hydrogen bromide into the functionalized α-bromo ketone **24**. On the other hand, Rosenmund reduction of acid chloride **22** furnished (*S*)-*N*-acyl-3-formylalanine methyl ester (**25**). Similarly, the (*R*)- and (*RS*)-isomers of **24** and **25** were prepared from (*R*)- and (*RS*)-aspartic acid (**19**), respectively [7, 8] (Scheme 1).

3-(Imidazo[1,2–*b*]pyridazin-2-yl)alanine derivatives **26a,b** were synthesized according to general synthetic methodology for the preparation of 2-substituted imidazo[1,2–*b*]pyridazines from 3-aminopyridazines and α-halo carbonyl compounds [9]. (*S*)-*N*-Acyl-5-bromo-4-oxonorvaline methyl ester (**24**) and its (*R*)- and (*RS*)-isomers were treated with 3-aminopyridazine (**17a**) and 3-amino-6-chloropyridazine (**17b**) in methanol under reflux to afford (*S*)-*N*-acyl-3-(imidazo[1,2–*b*]pyridazin-2-yl)alanine esters **26a,b** and their (*R*)- and (*RS*)-isomers in

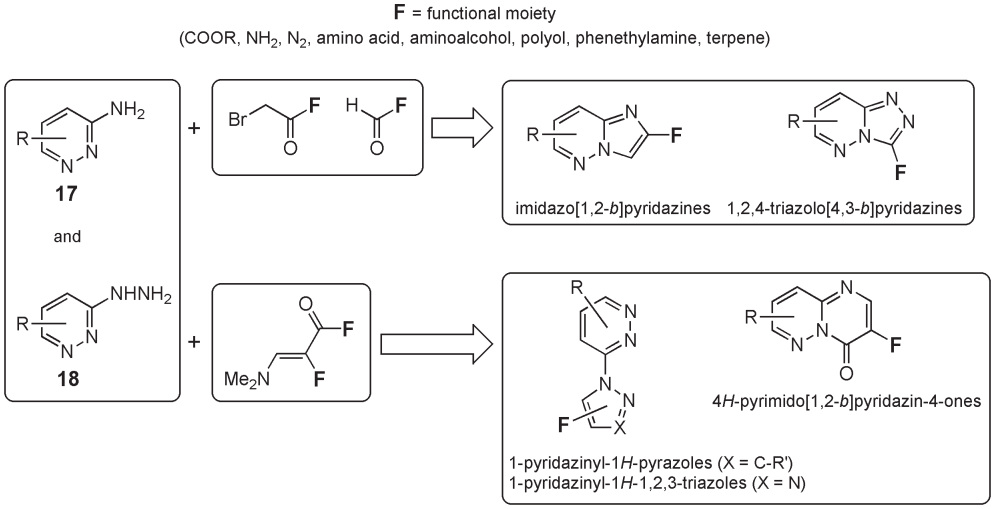
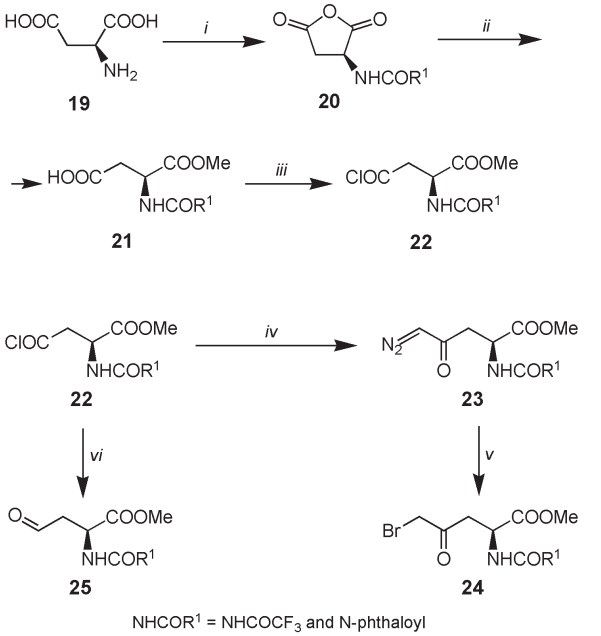


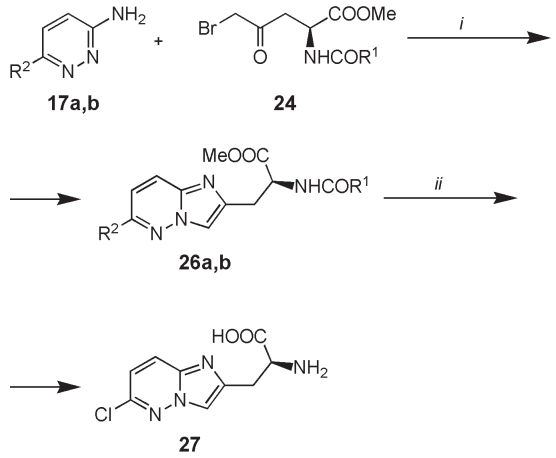
Figure 3

Scheme 1



Reagents and Conditions. (i) $(CF_3CO)_2O$, CF_3COOH, –15°_20° ($NHCOR^1$ = $NHCOCF_3$) or phthalic anhydride, pyridine reflux, then Ac_2O, 50° ($NHCOR^1$ = N-phthaloyl); (ii) MeOH, reflux; (iii) $SOCl_2$, toluene, 70°, then crystallization; (iv) CH_2N_2, Et_2O, 0°; (v) HBr, AcOH, 0°; (vi) H_2, Pd–C, toluene, reflux.

Scheme 2



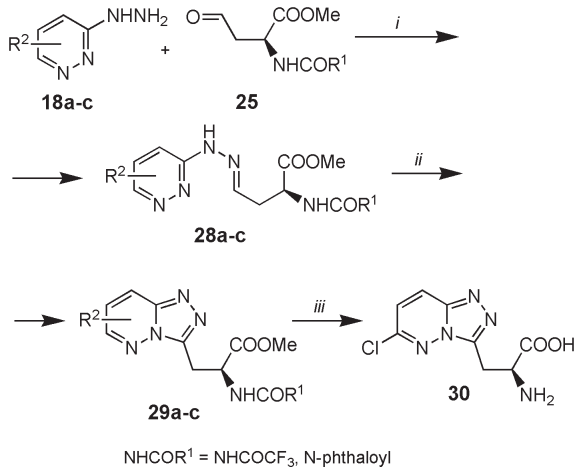
Compound	$NHCOR^1$	R^2	Configuration	Yield (%)	Ref.
26a	$NHCOCF_3$	H	*RS*	16	
26b	$NHCOCF_3$	Cl	*R*	74	
26b	$NHCOCF_3$	Cl	*S*	46	
26b	$NHCOCF_3$	Cl	*RS*	74	
26b	N-Phthaloyl	Cl	*RS*	36	
27		Cl	*R*	65	
27		Cl	*S*	70	
27		Cl	*RS*	69	

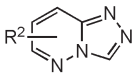
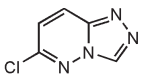
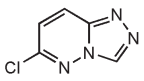
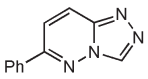
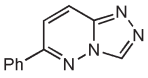
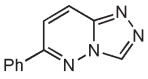
Reagents and Conditions. (i) MeOH, reflux; (ii) 5 *N* HCl (aq.), reflux.

16–74% yields. Deprotection of **26b** in 5 *N* hydrochloric acid under reflux afforded the free amino acid **27** [7, 8] (Scheme 2).

The 3-(1,2,4-triazolo[4,3–*b*]pyridazin-3-yl)alanine derivatives **29a–c** were also prepared according to previously established general methodology for the synthesis of 3-substituted 1,2,4-triazolo[4,3–*b*]pyridazines, which includes treatment of hydrazinopyridazine with an aldehyde followed by oxidative cyclization of the intermediate hydrazone with bromine or lead tetraacetate [9]. Thus, (*S*)-*N*-acyl-3-formylalanine methyl ester (**25**) was treated with 3-hydrazinopyridazines **18a–c** to give the corresponding hydrazones **28a–c**. Upon oxidative cyclization of **28a–c** with methanolic bromine, (*S*)-*N*-acyl-3-(1,2,4-tria-

Scheme 3



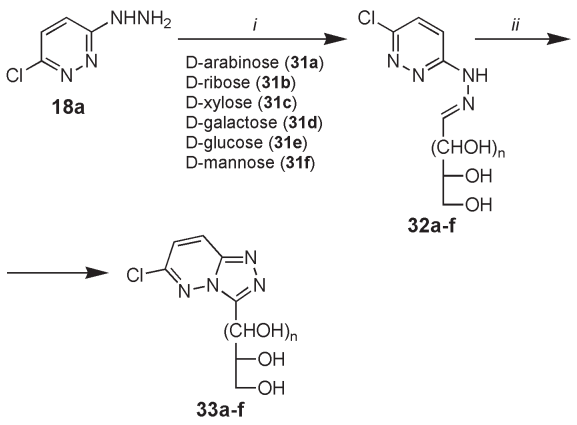
Compound		$NHCOR^1$	Configuration	Yield (%)	Ref.
29a		$NHCOCF_3$	*R*	77	
			S	81	
			RS	75	
29a		N-Phthaloyl	*RS*	75	
29b		$NHCOCF_3$	*S*	86	
			RS	73	
29b		N-Phthaloyl	*RS*	75	
29c		$NHCOCF_3$	*RS*	58	
30			*R*	65	
			S	81	
			RS	78	

Reagents and Conditions. (i) MeOH or EtOH, AcOH (cat.), 20°; (ii) Br_2, MeOH, AcONa, 20°; (iii) 5 *N* HCl, reflux.

zolo[4,3–*b*]pyridazin-3-yl)alanine esters **29a–c** and their (*R*)- and (*RS*)-isomers were obtained in 58–86% yields. Deprotection of **29a** in 5 *N* hydrochloric acid under reflux afforded the free amino acid **30** [7, 8] (Scheme 3).

In another synthetic application, 6-chloro-3-hydrazinopyridazine (**18a**) was used for the preparation of 6-chloro-1,2,4-triazolo[4,3–*b*]pyridazin-3-yl substituted polyols, *C*-nucleosides, and their analogs. Treatment of **18a** with commercially available unprotected aldoses **31a–f** resulted in the formation of hydrazones **32a–f**, which were oxidatively cyclized with methanolic bromine into the corresponding 6-chloro-1,2,4-triazolo[4,3–*b*]pyridazin-3-yl substituted polyols **33a–f** in 44–81% yields [10] (Scheme 4).

Scheme 4



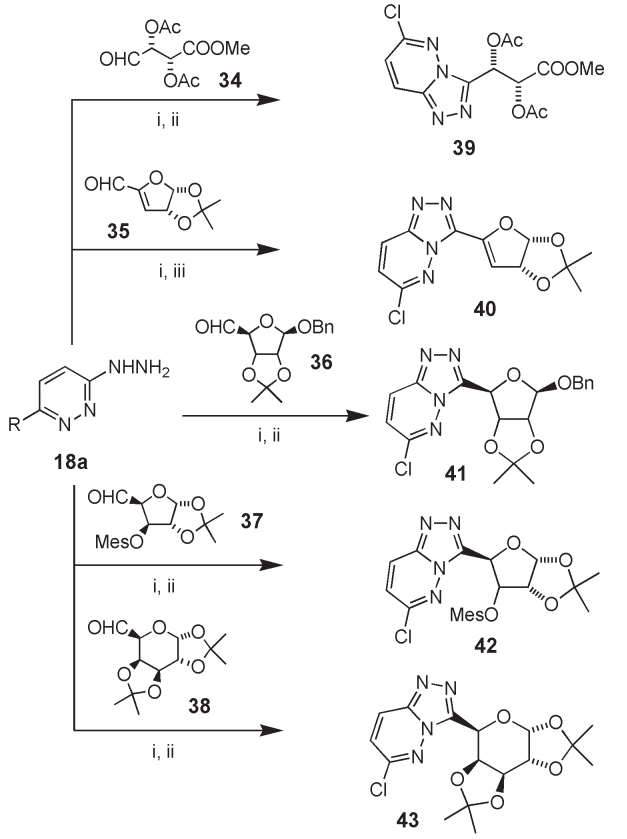
Compound	Configuration	Yield (%)	
		32	**33**
31a–33a	D-*arabino*	84	51
31b–33b	D-*ribo*	84	44
31c–33c	D-*xylo*	85	60 [a]
31d–33d	D-*galacto*	73	58
31e–33e	D-*gluco*	87	79
31f–33f	D-*manno*	87	81

[a] Isolated and characterized as 5-*O*-trityl derivative. Reagents and Conditions. (i) D-aldose (**31a–f**), MeOH, HCl (cat.), reflux; (ii) Br_2, MeOH, 20°.

In the same manner, aldehydo sugars **34–38**, prepared according to the literature procedures, were transformed into the protected cyclic polyols **39–43** as *C*-nucleoside analogs in 44–65% yields. In the reaction of **18a** with the unsaturated aldehyde **35**, lead tetraacetate was employed as the oxidizing agent [10, 11] (Scheme 5).

Acetonisation of D-glucose derived (1*S*)-1-*C*-(6-chloro-1,2,4-triazolo[4,3–*b*]pyridazin-3-yl)-D-arabinitol (**33e**) led to a mixture of two regioisomeric bis-ketals **44** and **45**, which were separated by MPLC or crystallization. Acetonisation of D-mannose derived (1*R*)-1-*C*-(6-chloro-1,2,4-triazolo[4,3–*b*]pyridazin-3-yl)-D-arabinitol (**33f**)

Scheme 5

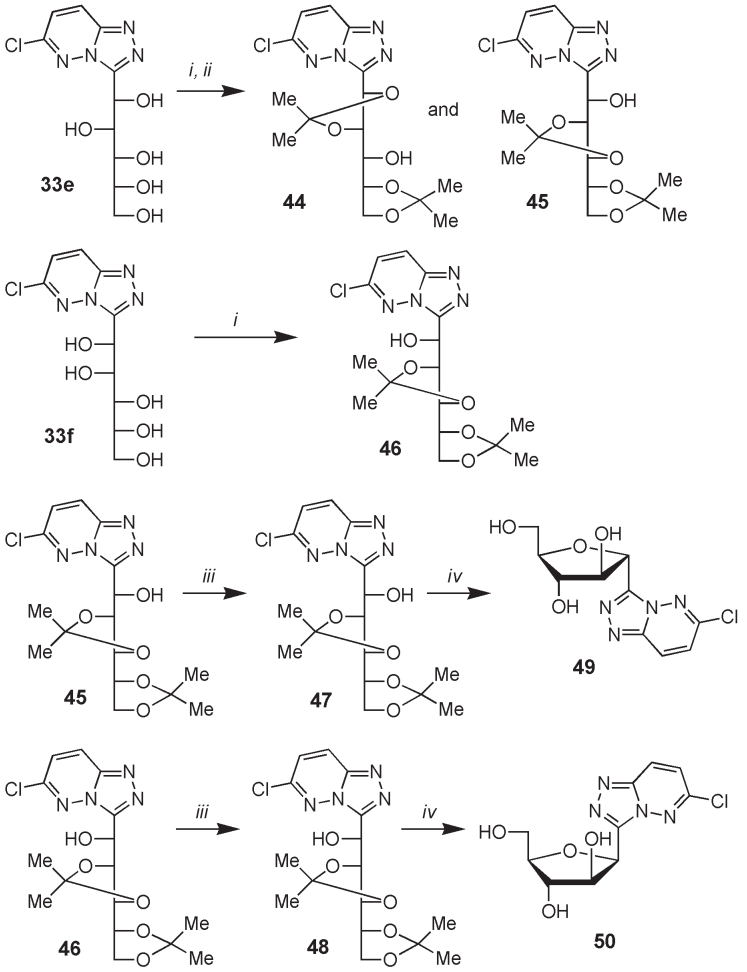


Reagents and Conditions. (i) MeOH, HCl (cat.), 20°; (ii) Br_2, MeOH, 20°; (iii) $Pb(OAc)_4$, CH_2Cl_2, 20°.

led, regioselectively, to (1*R*)-1-*C*-(6-chloro-1,2,4-triazolo[4,3–*b*]pyridazin-3-yl)-2,3:5,6-di-*O*-isopropylidene-D-arabinitol (**46**). In order to carry out transformation of bis-ketals **45**, **46** into *C*-nucleosides **49**, **50**, a slightly modified synthetic protocol, reported previously by Buchanan and co-workers [12], was employed. Thus, compounds **45** and **46** were mesylated and then, the mesylates **47** and **48** were heated in 1,2-dimethoxyethane in the presence of 1 equivalent of 4% hydrochloric acid to afford 3-(α-D-arabinofuranosyl)-6-chloro-1,2,4-triazolo[4,3–*b*]pyridazine (**49**) and its β-anomer **50** in 81% and 54% yield, respectively. The β-anomer **50** was obtained in the form of its HCl salt and its structure was determined by X-Ray diffraction [13] (Scheme 6).

In continuation, our work was extended also on the synthesis of (+)-camphor (**51**) functionalized 1,2,4-triazolo[4,3–*b*]pyridazines. In this series, two reagents were prepared, (1*R*,4*R*)-3-[(*E*)-(dimethylamino)methylidene]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**52**) and (1*R*,5*R*)-4-[(*E*)-(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (**54**), which are both synthetic equivalents of the corresponding α-formyl substituted com-

Scheme 6

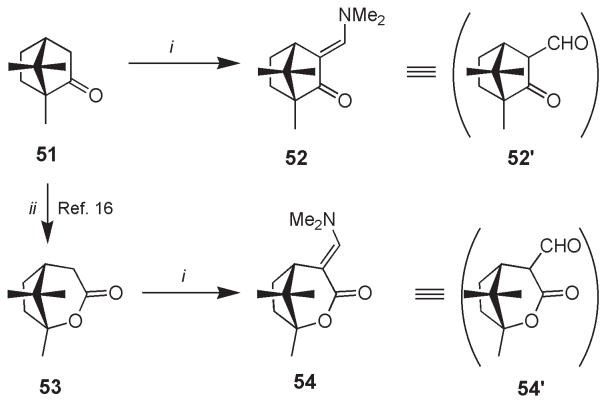


Reagents and conditions: (i) acetone, 97% H_2SO_4, r.t.; (ii) chromatographic separation (mplc) or crystallization; (iii) $MeSO_2Cl$, pyridine, 0°; (iv) 1,2-dimethoxyethane, 4% HCl (aq., 1 equiv.), reflux.

pounds **52'** and **54'**. Compound **52** has been first prepared almost hundred years ago by Staudinger and Kon in 2 steps *via* formylation of (+)-camphor (**51**) followed by condensation of **52'** with dimethylamine [14]. However, we prepared the enaminone **52** in one step from (+)-camphor (**51**) and bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent) [15]. The lactone reagent **54** was prepared in 2 steps. First, (+)-camphor (**51**) was transformed into the lactone analog **53** by Baeyer-Williger oxidation according to the literature procedure [16], followed by treatment with Bredereck's reagent to give the enamino lactone **54** [17] (Scheme 7).

(1*R*,4*R*)-3-[(*E*)-(Dimethylamino)methylidene]-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-one (**52**) was also employed in one-pot stereoselective synthesis of (1*R*,3*R*,4*R*)-3-(1,2,4-triazolo[4,3–*b*]pyridazin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ones **58a–c**. Treatment of **52** with hydrazinopyridazines **18a,b,d** followed by oxidative cyclization of the intermediate hydrazones with methanolic bromine and

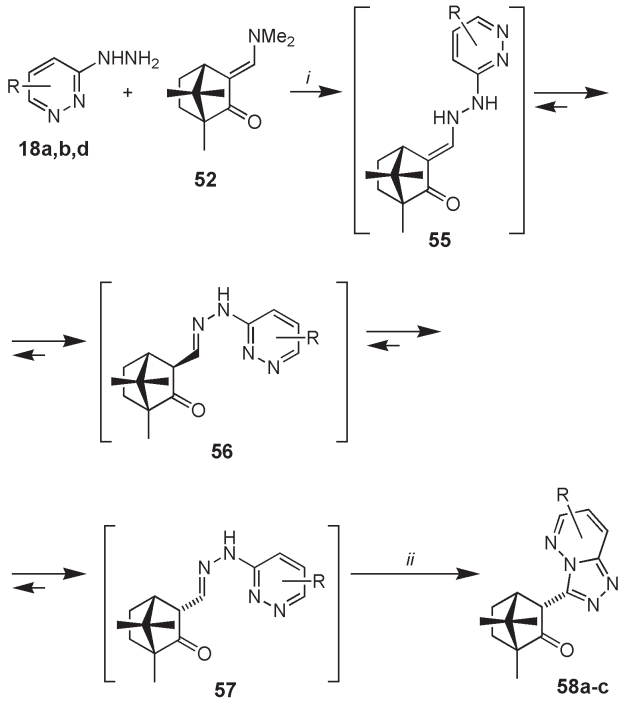
Scheme 7

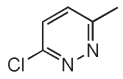
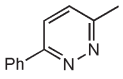
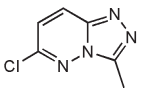
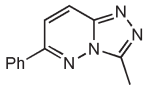
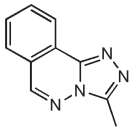


Reagents and conditions: (i) *t*-$BuOCH(NMe_2)_2$, DMF, reflux; (ii) AcOH, AcOOH, AcONa, 20°; (iii) *t*-$BuOCH(NMe_2)_2$, decaline, reflux.

chromatographic purification afforded, stereoselectively, the *endo*-isomers of 3-(1,2,4-triazolo[4,3–*b*]pyridazin-3-yl)camphors **58a–c** in 61–79% yields and in 84–94% d.e.. This one-pot transformation proceeds by initial substitution of the dimethylamino group to give the enehydrazines **55** which tautomerize into the hydrazono forms **56** and **57**. The major *endo*-hydrazones **57a** and **57b** have also been isolated in pure form. Further oxidative cyclization of hydrazones **56** and **57** leads to (1*R*,3*R*,4*R*)-3-(1,2,4-triazolo[4,3–*x*]azin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones **58a–c** [15] (Scheme 8).

Scheme 8

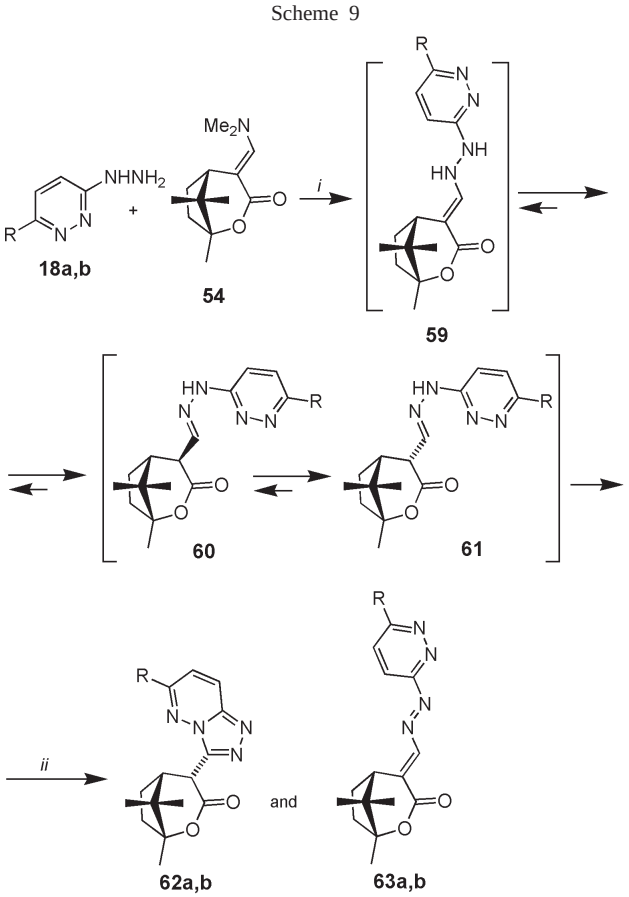


Compound	Pyridazine Moiety	Yield (%)	D.e. (%)
57a		48	22
57b		51	78
58a		71	94
58b		79	84
58c		61	92

Reagents and conditions: (i) MeOH, 37% HCl (1 equiv.), 20°; (ii) Br_2, MeOH, AcONa, 20°, then chromatographic purification (cc, mplc).

Similar treatment of (1*R*,5*R*)-4-[(*E*)-(dimethylamino)-methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (**54**) with 6-chloro-3-hydrazinopyridazine (**18a**) and 3-hydrazino-6-phenylpyridazine (**18b**) followed by oxidative cyclization with lead tetraacetate led to two types of products. (1*R*,4*R*,5*R*)-4-(1,2,4-Triazolo[4,3–*b*]pyridazin-3-yl)-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-ones **62a** and **62b** were obtained as the major products in 46% and 52% yields and in 90% and 94% d.e., respectively. As the minor products, 1,8,8-trimethyl-4-{[(*E*)-pyridazinyl-2-yldiazenyl]methylidene}-2-oxabicyclo[3.2.1]octan-3-ones **63a** and **63b** were obtained in 29% and 10% yield (Scheme 9). However, with other α-hydrazinoazines as starting compounds, such as 2-hydrazinopyridine, 2-hydrazinopyrimidine, and hydrazinopyrazine, predominant formation of diazenes **63** took place [18].

Scheme 9



Reagents and conditions: (i) MeOH, 97% H_2SO_4 (1 equiv.), 20°; (ii) $Pb(OAc)_4$, CH_2Cl_2, 20°, then chromatographic separation (cc, mplc).

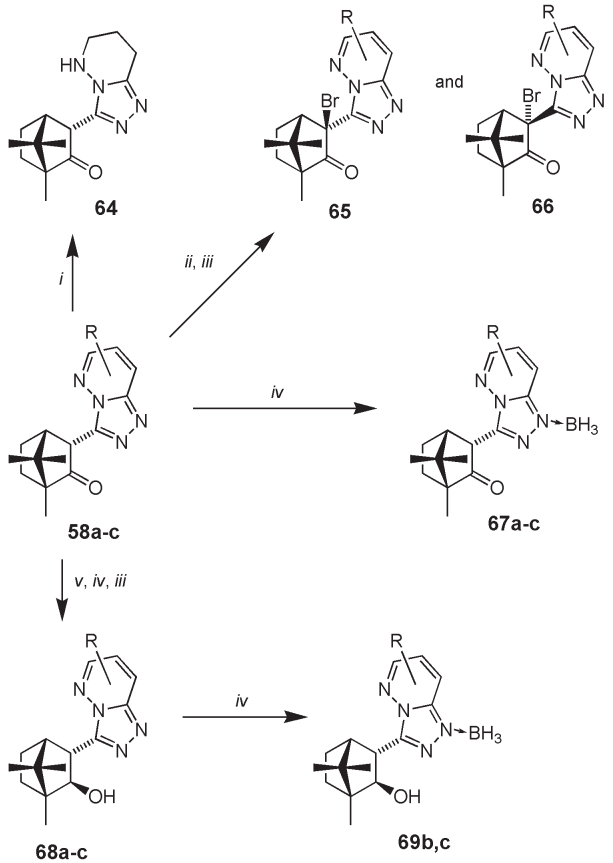
Further transformations of (1*R*,3*R*,4*R*)-3-(1,2,4-triazolo[4,3–*x*]azin-3-yl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones **58a–c** were also studied. Catalytic hydrogenation of **58a** under 50 bars of hydrogen resulted in satura-

tion of the pyridazine ring to give compound **64**. α-Bromination of **58b** in dichloromethane afforded both epimers, **65** and **66**, in a ratio of 1:1. Isomers **65** and **66** were separated by medium pressure liquid chromatography (mplc) and the structures were confirmed by X-ray diffraction. Upon treatment of compounds **58a–c** with borane–methyl sulfide in dichloromethane under reflux, stable complexes with borane **67a–c** were obtained in 29–58% yields. X–Ray diffraction analysis of **67b** showed, that complexation of borane occurs at the N-1 in the 1,2,4-triazolo[4,3–*x*]azinyl residue. On the other hand, activation of **58a–c** with 1 equivalent of boron trifluoride etherate followed by treatment with borane–methyl sulfide and thorough chromatographic purification furnished the corresponding isoborneols **68a–c** in 34–62% yields. Stable complexes **69b** and **69c** were also obtained from isoborneols **68b,c** and borane–methyl sulfide in refluxing dichloromethane [18] (Scheme 10).

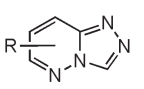
3.Synthesis of Functionalized 1-Pyridazinyl-1*H*-pyrazoles, 4*H*-Pyrimidino[1,2–*b*]pyridazin-4-ones, and 1-Pyridazinyl-1*H*-1,2,3-triazoles.

For the preparation of functionalized 1-pyridazinyl-1*H*-pyrazoles, 4*H*-pyrimidino[1,2–*b*]pyridazin-4-ones, and

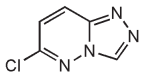
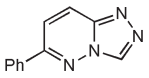
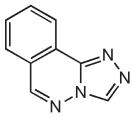
Scheme 10



Scheme 10 (Continued).



Yield (%)

	64	65	66	67	68	69
 **64a**, **67a**, **68a**	73			29	57	
 **65b–69b**		44	43	58	62	23
 **67c–69c**				39	34	10

Reagents and conditions: (i) H_2 (50 bar), Pd–C, EtOH, 50°; (ii) Br_2, CH_2Cl_2, 20°; (iii) chromatographic separation (cc, mplc); (iv) BH_3–Me_2S, CH_2Cl_2, reflux; (v) BF_3–Et_2O, CH_2Cl_2, 0°.

1-pyridazinyl-1*H*-1,2,3-triazoles, cyclocondensation reactions between amino- and hydrazinopyridazines and functionalized enaminones were employed in the key-step. Recently, a series of alkyl 2-substituted 3-(dimethylamino)propenoates and related enaminones, synthetic equivalents of 1,3-dicarbonyl compounds, have been prepared and used for the preparation of dehydroalanine esters and various heterocyclic systems. Chiral analogs of 3-(dimethylamino)propenoates were also prepared from commercially available enantiopure starting materials, such as α-amino acids and (+)-camphor (**51**). The α-amino acid derived chiral enaminones were employed as the key-intermediates and reagents in the synthesis of functionalized heterocycles, *e.g.* in the 'ring switching' synthesis of 3-heteroarylalanine derivatives and related compounds and in the synthesis of heterocyclic analogs of dipeptides [3]. Recently, utilization of 3-(dimethylamino)propenoates in combinatorial synthesis has also been reported [19, 20]. In most cases, 2-substituted 3-(dimethylamino)-propenoates are prepared by treatment of α-substituted acetic acid ester with a *N*,*N*-dimethylformamide acetal, such as *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) and bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent). Acid-catalyzed reactions with nucleophiles proceed by initial substitution of the dimethylamino group to give the substitution product. In the case of ambident nucleophiles, further condensation to the ester group can take place to afford five- and six-membered heterocycles. For example, 1-pyridazinyl-1*H*-pyrazoles are formed upon reaction of enaminones with hydrazino-

pyridazines, while reactions of enamino esters with 3-aminopyridazines lead to 4*H*-pyrimidino[1,2–*b*]pyridazin-4-ones [3] (Figure 4).

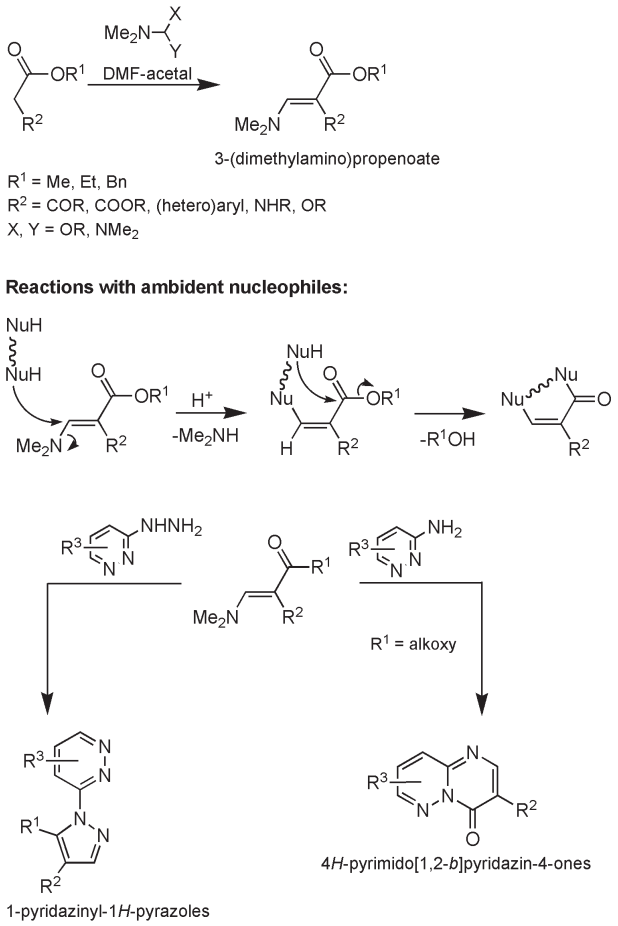
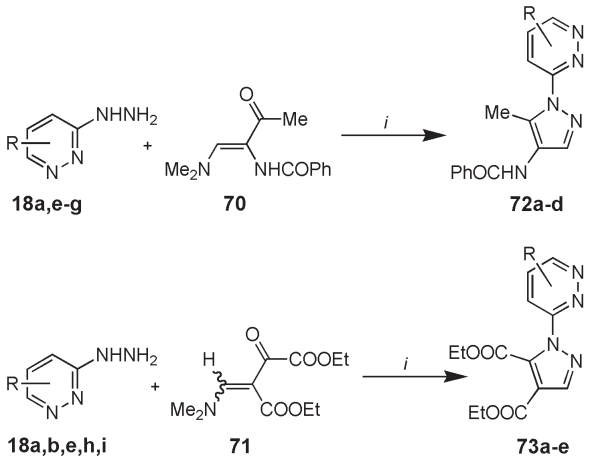


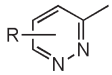
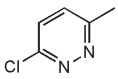
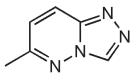
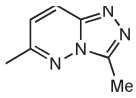
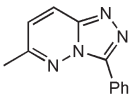
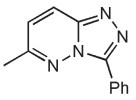
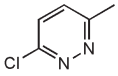
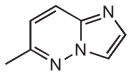
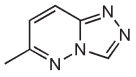
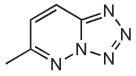
Figure 4

One of the most common methods for the preparation of pyrazoles is reaction of 1,3-dicarbonyl compounds and their analogs, including enaminones, with hydrazine derivatives [21]. Typical examples of utilization of enaminones in the pyrazole synthesis are preparation of 1-substituted 4-benzoylamino-5-methyl-1*H*-pyrazoles **72** from 4-dimethylamino-2-oxobut-3-ene (**70**) and preparation of 1-substituted diethyl 1*H*-pyrazole-dicarboxylates **73** from diethyl 3-dimethylaminomethylidene-2-oxosuccinate (**71**). In this connection, 4-benzoylamino-5-methyl-1-pyridazinyl-1*H*-pyrazoles **72a–d** and diethyl 1-pyridazinyl-1*H*-pyrazole-4,5-dicarboxylates **73a–e** were prepared in 20–70% yields by treatment of enaminones **70** and **71** with hydrazinopyridazines **18a,b,e–i**. [22, 23] (Scheme 11).

In reactions of hydrazines with closely related ethyl (*E*)-4-dimethylamino-2-oxobut-3-enoate (**74**), specific behavior of hydrazino-pyridazines **18a,b,e** was observed. Upon treatment of **74** with hydrazine hydrochloride (**18j**) and with arylhydrazines **18k,l** in ethanol at 20–60°, ethyl 1*H*-pyrazole-5-carboxylates **75a–c** were obtained. Under the same reaction conditions, treatment of **74** with pyridazinylhydrazines **18a,b,d** afforded ethyl 4,5-dihydro-5-

Scheme 11



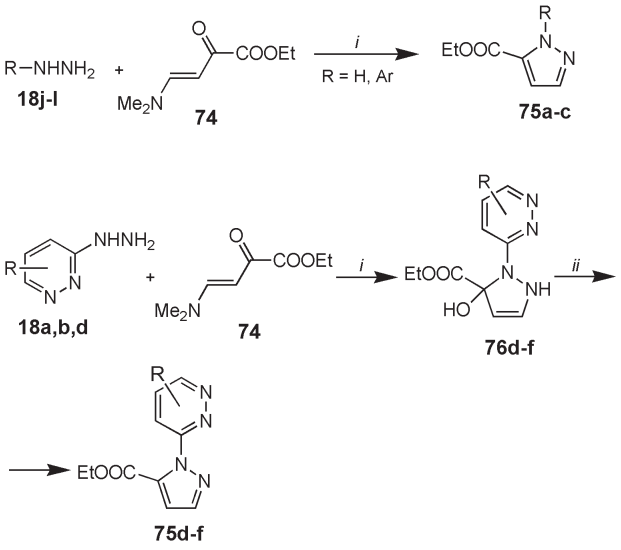
Reaction		Yield (%)	Ref.
18a→72a		20	22
18e→72b		20	22
18f→72c		59	22
18g→72d		36	22
18a→73a		29	23
18b→73b		37	23
18h→73c		48	23
18e→73d		44	23
18i→73e		70	23

Reagents and conditions: (i) R–$NHNH_2$, EtOH, 37% HCl (aq., 1 equiv.), 20–60°.

hydroxy-1*H*-pyrazole-5-carboxylates **76d–f** as stable intermediates in the pyrazole ring formation. Aromatization of dihydropyrazoles **76** was achieved in refluxing acetic acid to afford ethyl 1-pyridazinyl-1*H*-pyrazole-5-carboxylates **75d–f** [23] (Scheme 12).

Hydrazinopyridazines were also employed in the 'ring switching' synthesis of (*S*)-*N*-acyl-3-(5-hydroxy-1-pyridazinyl-1*H*-pyrazol-4-yl)alanine esters **79a–e**. Treatment of methyl (*S*)-*N*-acyl-3-[(*E*)-(dimethylamino)methylidene]-2-oxopyrrolidine-5-carboxylates **77a,b** with hydrazinopyridazines **18a,b,e** in acetic acid at 80–120° afforded the corresponding 3-(1-pyridazinyl-1*H*-pyrazol-4-yl)alanine derivatives **79a–e** in 41–88% yields. Reactions proceed by initial dimethylamine substitution to give the enehydrazine intermediate **78**, followed by condensation to the lactam carbonyl group with simultaneous formation of the pyrazole ring and opening of the pyrrolidinone ring taking place to give the 'ring switched' products **79** [24, 25] (Scheme 13).

Scheme 12



Compound	R	Yield (%)
76a	H	76
76b	Ph	9
76c	4-nitrophenyl	72
75d	-	78
75e	-	95
75f		47

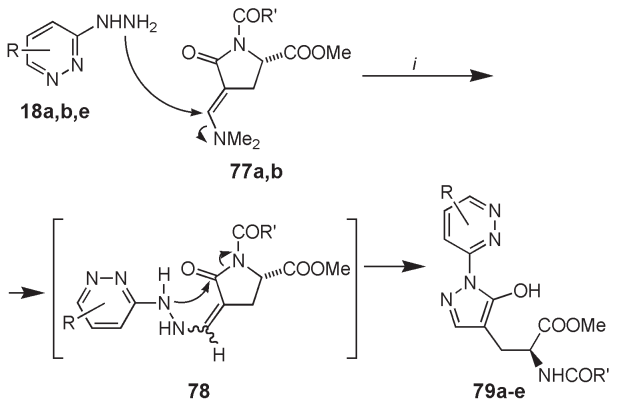
Scheme 12 (continued)

Compound	R	Yield (%)
76d	-	75
76e		88
76f		69

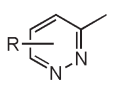
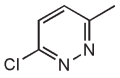
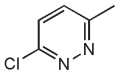
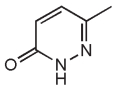
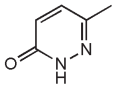
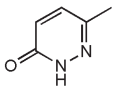
Reagents and conditions: (i) R–NHNH$_2$, EtOH, 37% HCl (aq., 1 equiv.), 20–60°; (ii) AcOH, reflux.

Just recently, another method for the synthesis of 3-pyrazolylalanines was developed. (*S*)-*N*-benzyloxycarbonylaspartic acid-1-benzyl ester (**80**), available from L-aspartic acid (**19**) [26], was transformed in two steps into (*S*)-*N*-benzyloxycarbonyl-4-oxohomoglutamic acid-1-benzyl-4-methyl ester (**82**) in 66% yield. Treatment of **82** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) afforded the 5-dimethylaminomethylidene derivative **83** in almost quantitative yield. Acid catalyzed reactions of **83** with hydrazine derivatives led to (*S*)-*N*-benzyloxycarbonyl-3-(1-substituted 4-methoxycarbonyl-1*H*-pyrazol-5-yl)alanine benzyl esters. Upon deprotection by catalytic hydrogenation, the free amino acids were prepared. In this manner, also the 1'-(6-phenylpyridazin-3-yl) substituted pyrazolylalanine esters **84** and **85** were prepared in 53% and 27% yield, respectively, upon acid-catalyzed treatment of **83** with 3-hydrazino-6-phenylpyridazine (**18b**) in ethanol under reflux. Formation of the ethyl ester **85** can be explained by partial transesterification, which apparently took

Scheme 13

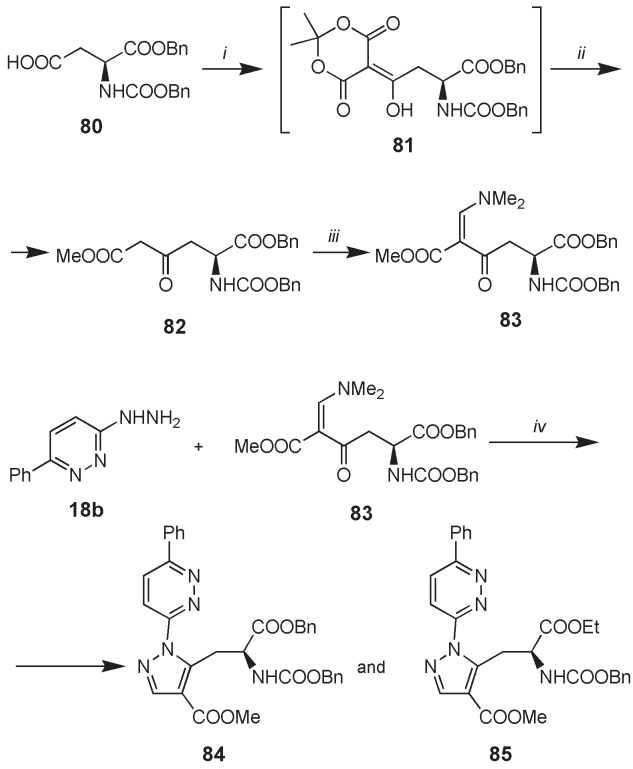


Scheme 13 (continued)

Compound		COR'	Yield (%)
			
18a, **79a**		Boc	50
18a, **79b**		COPh	72
18a, **79c**		COPh	84
18b, **79d**		COPh	88
18e, **79e**		COPh	41

Reagents and conditions: (i) AcOH, 80–110°.

Scheme 14

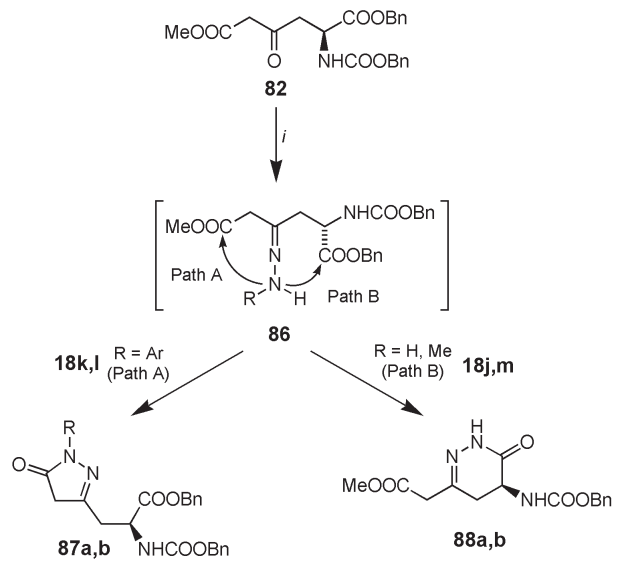


Reagents and conditions: (i) Meldrum's acid, DCC, CH_2Cl_2, –5°→20°C; (ii) MeOH, reflux; (iii) DMFDMA, CH_2Cl_2, 20°C; (iv) EtOH, 37% HCl (1 equiv.), reflux, then chromatographic separation (cc, mplc).

place in refluxing ethanol in the presence of hydrochloric acid [27] (Scheme 14).

Since (*S*)-*N*-benzyloxycarbonyl-4-oxohomoglutamic acid-1-benzyl-4-methyl ester (**82**) can also be regarded as alanine-functionalized *β*-keto ester, it could also serve as suitable reagent for the preparation of 3-pyrazolylalanines. Therefore, we carried out reactions with hydrazine hydrate (**18j**), methyl hydrazine (**18m**), phenylhydrazine (**18k**) and 4-nitrophenylhydrazine (**18l**). Treatment of **82** with arylhydrazines **18k,l** afforded the pyrazolylalanine esters **87a,b**, while treatment with hydrazine hydrate (**18j**) and methyl hydrazine (**18m**) gave functionalized tetrahydropyridazinones **88a,b** in moderate yields. Formation of two types of products, **87** and **88**, can be explained by initial condensation of the hydrazine derivative to the keto group to give the intermediate hydrazone **86**. From this point on, cyclization can take place, either to the COOMe group resulting in the formation of the pyrazolone **87** (Path A), or to the COOBn group to furnish the pyridazinone **88** (Path B) [27] (Scheme 15).

Scheme 15

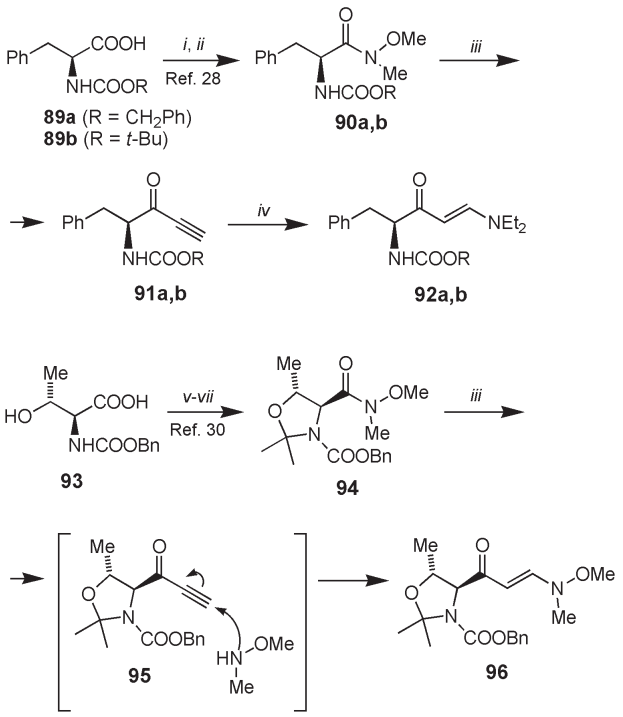


Reagents and conditions: (i) R–NHNH2 (**18j–m**), MeOH, 20°.

N-Protected L-3-phenylalanines **89a,b** and L-threonine **93** were also employed as chiral starting materials in the synthesis of phenylethylamine and *β*-amino alcohol functionalized 1*H*-pyrazoles **92a,b** and **96**. Thus, *N*-protected L-3-phenylalanines **89a,b** were transformed according to the literature procedures [28] into the corresponding Weinreb amides **90a,b**, which reacted with ethynylmagnesium bromide to give the acetylenic ketones **91a,b**. Michael addition of diethylamine to the triple bond afforded chiral enaminones **92a,b** [29]. Similarly, *N*-benzyloxycarbonyl-

L-threonine (**93**), was transformed in four steps into the enaminone **96** [29, 30]. In this case, treatment of Weinreb amide **94** with ethynylmagnesium bromide furnished the enaminone **96** directly, without isolation of the acetylenic ketone **95**. Most probably, Michael addition of *in situ* formed *N*,*O*-dimethylhydroxylamine to the intermediate ynone **95** occurred resulting in formation of compound **96** [29] (Scheme 16).

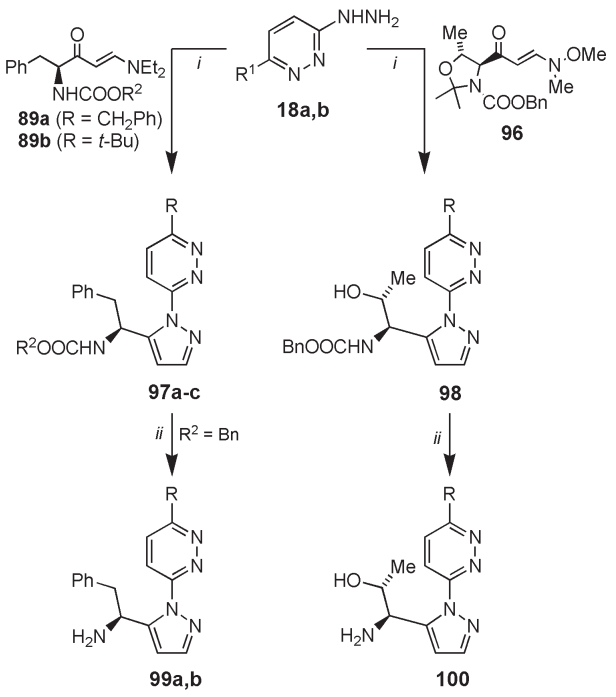
Scheme 16



Reagents and conditions: (i) ClCOOBu, CH_2Cl_2, 0°; (ii); MeNHOMe; (iii) HC≡CMgBr, THF, –78°→20°; (iv) Et_2NH, EtOH, 20°; (v) 2,2-dimethoxypropane, $BF_3{\times}Et_2O$, 20°; (vi) MeI, K_2CO_3; (vii) MeNHOMe, *i*-PrMgBr.

Functionalized enaminones **89a,b** and **96** were then transformed with monosubstituted hydrazines into the corresponding pyrazole derivatives. In the hydrazinopyridazine series, reaction of **89a,b** and **96** with 6-chloro-3-hydrazinopyridazine (**18a**) and 3-hydrazino-6-phenylpyridazine (**18b**) gave the *N*-protected (*S*)-1-[1-(6-substituted pyridazin-3-yl)-1*H*-pyrazol-5-yl]-2-phenylethylamines **97a–c** and (1*R*,2*S*)-1-amino-1-[1-(6-phenylpyridazin-3-yl)-1*H*-pyrazol-5-yl]propan-2-ol (**98**) in 52–91% yields. Finally, hydrogenolysis of the *N*-benzyloxycarbonyl protected compounds **97a,c** and **98** afforded the free phenylethylamines **99a,b** and *β*-amino alcohol **100** [29] (Scheme 17).

Scheme 17

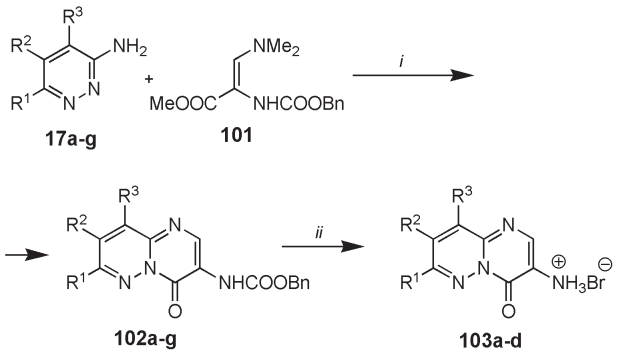


Compound	R1	R2	Yield (%)
97a	Cl	CH_2Ph	91
97b	Cl	*t*-Bu	52
97c	Ph	CH_2Ph	78
98	Ph	CH_2Ph	64
99a	H		99
99b	Ph		88
100	Ph		65

Reagents and conditions: (i) EtOH, 37% HCl (1 equiv.), reflux; (ii); H2, Pd–C, EtOH, 20°.

One of the general synthetic methods for the preparation of azino and azolo fused 3-amino-4*H*-pyrimidin-4-ones consists of treatment of *α*-aminoazoles and *α*-aminoazines with alkyl 3-dimethylamino-2-(substituted amino)propenoates. A series *N*-protected 3-amino-4*H*-azino[1,2–*x*]pyrimidin-4-ones and their azolo fused analogs have been prepared in this manner. For the preparation of the unprotected amines, the benzyloxycarbonyl *N*-protecting group was found to be the most suitable, since it is easily removable, either by transfer catalytic hydrogenation with cyclohexene in the presence of Pd–C, or by treatment with hydrogen bromide in acetic acid at slightly elevated temperature [3, 31, 32]. In this context, also a series of 3-benzyloxycarbonylamino-4*H*-pyrimido[1,2–*b*]pyridazin-4-ones **102a–g** were synthesized in 19–93% yields by heating of 3-aminopyridazines **17a–g** with methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)propenoate (**101**) in acetic acid in the presence of anhydrous sodium acetate. Deprotection of compounds **102a,b,e,g** with hydrogen bromide in acetic acid at 40–50° furnished 3-amino-4*H*-pyrimido[1,2–*b*]pyridazin-4-ones hydrobromides **103a–d** in

Scheme 18



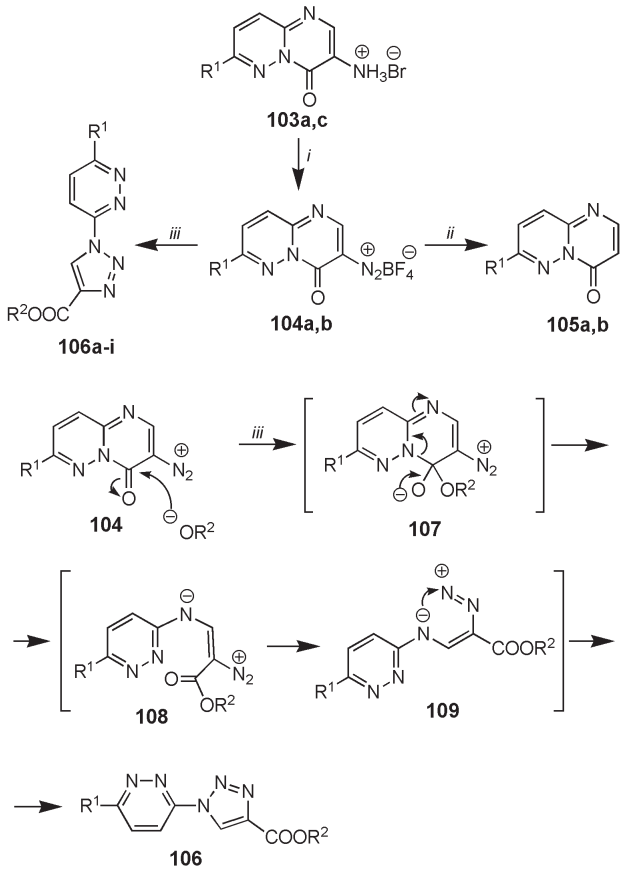
Compound	R1	R2	R3	Yield (%)	
				102	**103**
17a, **102a**, **103a**	H	H	H	79	88
17b, **102b**, **103b**	Cl	H	H	59	99
17c, **102c**	OH	H	H	19	
17d, **102d**	Cl	H	Me	72	
17e, **102e**, **103c**	Ph	H	H	93	98
17f, **102f**	Ph	Ph	CN	39	
17g, **102g**, **103d**	Me	H	H	69	92

Reagents and conditions: (i) AcOH, AcONa, reflux; (ii) HBr, AcOH, 40–50°.

88–99% yields [33] (Scheme 18).

According to methodology, previously established in 3-amino-4*H*-pyrido[1,2–*a*]pyrimidin-4-one series [34], the 3-amino-4*H*-pyrimido[1,2–*b*]pyridazin-4-ones hydrobromides **103a** and **103c** were transformed into the corresponding diazonium tetrafluoroborates **104a** and **104b** in 83% and 70% yield, respectively. Heating of diazonium salts **104a,b** in 2-propanol resulted in reduction to the 3-unsubstituted 4*H*-pyrimido[1,2–*b*]pyridazin-4-ones **105a,b**. On the other hand, heating of **104a,b** with primary alcohols at 60–80° afforded the 1-pyridazinyl substituted alkyl 1*H*-1,2,3-triazole-4-carboxylates **106a–i** in 23–66% yields [33]. Formation of triazoles **106** could be explained according to the 'ring switching' mechanism, proposed previously in the 4*H*-pyrido[1,2–*a*]pyrimidin-4-one series [34]. Primary alcohol undergoes covalent solvation with the diazonium salt **104**, followed by opening of the pyrimidone ring to give the intermediate **108**. Upon rotation around the C–N single bond intermediate **109** is formed, which then cyclizes into the triazole derivative **106** [33] (Scheme 19).

Scheme 19



Compound	R1	R2	Yield (%)		
			104	**105**	**106**
104a, 105a	H		70	80	
104b, 105b	Ph		83	75	
106a	H	Me			64
106b	H	Et			30
106c	H	*n*-Pr			33
106d	H	*n*-Bu			33
106e	Ph	Me			66
106f	Ph	Et			23
106g	Ph	*n*-Pr			31
106h	Ph	*n*-Bu			34
106i	Ph	*n*-Pe			34

Reagents and conditions: (i) $NaNO_2$, HCl, H_2O, 0°, then HBF_4, H_2O; (ii) *i*-PrOH, reflux; (iii) R2OH, 60–80°.

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