Synthesis of Heteroaryl Substituted α-Amino Acid Derivatives, Polyols, and Related Compounds

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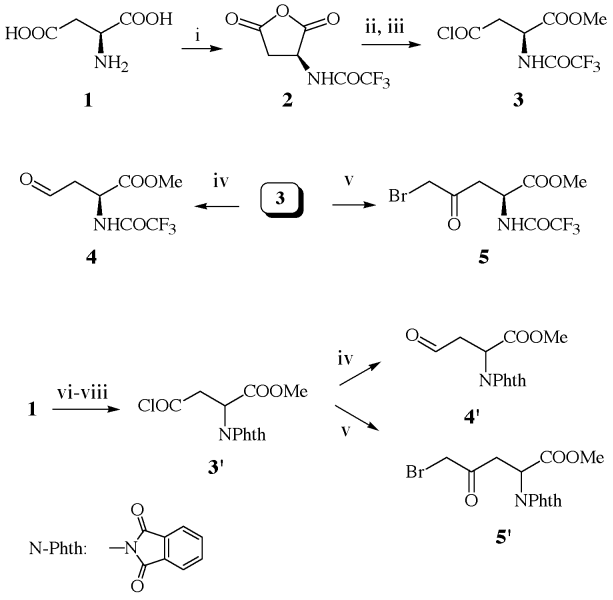
1. Introduction.

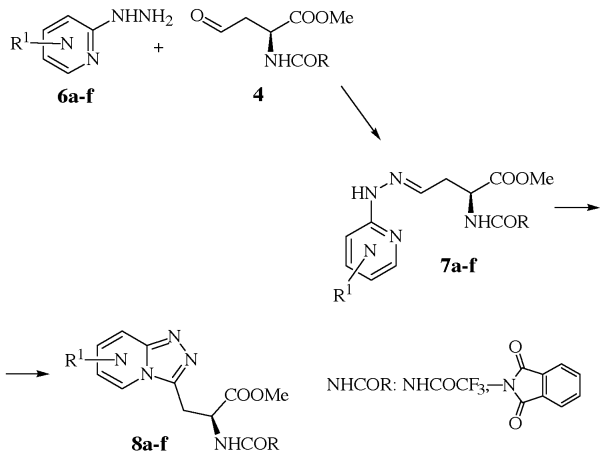
Heterocycles, amino acids, and polyols belong to the most representative groups of organic compounds. They are constituents of proteins, nucleic bases, and related types of compounds which play the essential role in cell metabolic processes. On the other hand, these types of compounds also found a wide applicability in organic synthesis, especially as starting materials, chiral building blocks, chiral auxiliaries, resolving agents, and ligands [1–3]. For this reason and due to their occurrence in nature, biological activity, and synthetic utility, there has been in the last few decades a significant interest for the synthesis of heterocyclic compounds containing an α-amino acid-, or/and polyol structural element [4–7]. The aim of our work was to study synthetic methodologies for the preparation of functionalized heterocycles such as heteroaryl substituted amino acids and polyols. Due to our primary interest in heterocyclic chemistry, we were focused on approaches which included formation of the heterocyclic part of the product as the key-step. Synthetic pathway should therefore consist of the preparation of a suitable precursor, which would then be, by a ring formation, transformed into a heterocyclic product. For this purpose, simple and commercially available α-amino

Scheme 1



i $(CF_3CO)_2O$, CF_3COOH, -15 to 20°; **ii** MeOH, reflux; **iii** $SOCl_2$, toluene, 70°, then crystallization; **iv** H_2, Pd-C, toluene, reflux; **v** CH_2N_2, Et_2O, 0°, then HBr, AcOH, 20°; **vi** phthalic acid anhydride, pyridine, reflux, then Ac_2O, 100°; **vii** MeOH, reflux, then crystallization; **viii** $SOCl_2$, toluene, reflux.

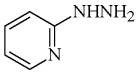
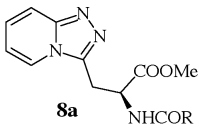
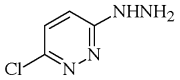
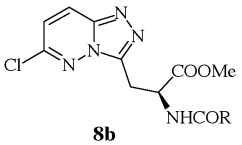
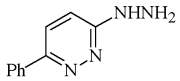
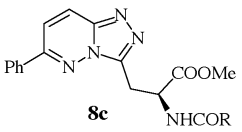
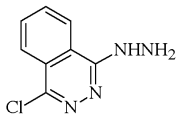
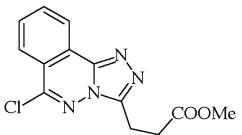
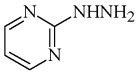
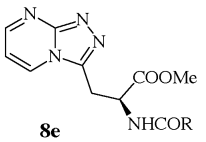
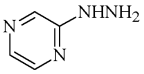
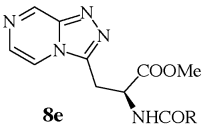
Scheme 2



i MeOH or EtOH, AcOH (cat.), 20°; **ii** MeOH, Br_2, AcONa, 20°.

Table 1

N-Acyl-3-(1,2,4-triazolo[4,3-*x*]azinyl-3)alanine Derivatives (**8a-f**)

Hydrazinoazine ⟶	3-Heteroarylalanine Derivative	Yield (%)
 **6a**	 **8a**	81, (S), $NHCOCF_3$ 57, (RS), $NHCOCF_3$ 33, (RS), *N*-Phthaloyl
 **6b**	 **8b**	77, (R), $NHCOCF_3$ 81, (S), $NHCOCF_3$ 75, (RS), $NHCOCF_3$ 75, (RS), *N*-Phthaloyl
 **6c**	 **8c**	86, (S), $NHCOCF_3$ 73, (RS), $NHCOCF_3$ 75, (RS), *N*-Phthaloyl
 **6d**	 **8d**	58, (RS), $NHCOCF_3$
 **6e**	 **8e**	55, (RS), *N*-Phthaloyl
 **6f**	 **8e**	42, (RS), *N*-Phthaloyl

acids and sugars are excellent starting materials since they offer an easy access to suitable precursors of functionalized heterocyclic compounds [5–8].

2. Synthesis of Azatryptophane Derivatives and Analogs from Aspartic Acid.

Since aspartic acid (**1**) can be regarded as 3-carboxy-alanine, a formal incorporation of its β-carboxy group into a newly formed heterocyclic ring system would lead to 3-heteroarylalanines. In order to achieve a selective transformation of the β-carboxy group of aspartic acid (**1**), the α-amino acid part of **1** has to be protected and the β-carboxy group has to be activated for the cyclization reaction. This activation can be achieved by transformation into another functional group which is a better building block for the formation of a heterocyclic ring. Such versatile and useful building blocks in heterocyclic chemistry are α-halo ketones and aldehydes since they enable the formation of various heterocyclic systems such as thiazoles [9], indolizines [10], imidazo[1,2–*x*]azines [11, 12], and 1,2,4-triazolo[4,3–*x*]azines [13, 14]. Transformations of (*S*)-aspartic acid (**1**) into (*S*)-3-formyl-alanine- and (*S*)-5-bromo-4-oxonorvaline derivatives have been described previously [15–19]. Upon slight modifications of the known procedures, (*S*)-aspartic acid (**1**) was first transformed in formally 3 steps, but actually in one pot transformation, into (*S*)-*N*-trifluoroacetylaspartic acid-4-chloride-1-methyl ester (**3**) in 76% overall yield. Rosenmund reduction of the acid chloride **3** afforded (*S*)-*N*-trifluoroacetyl-3-formyl alanine methyl ester (**4**) in 86%

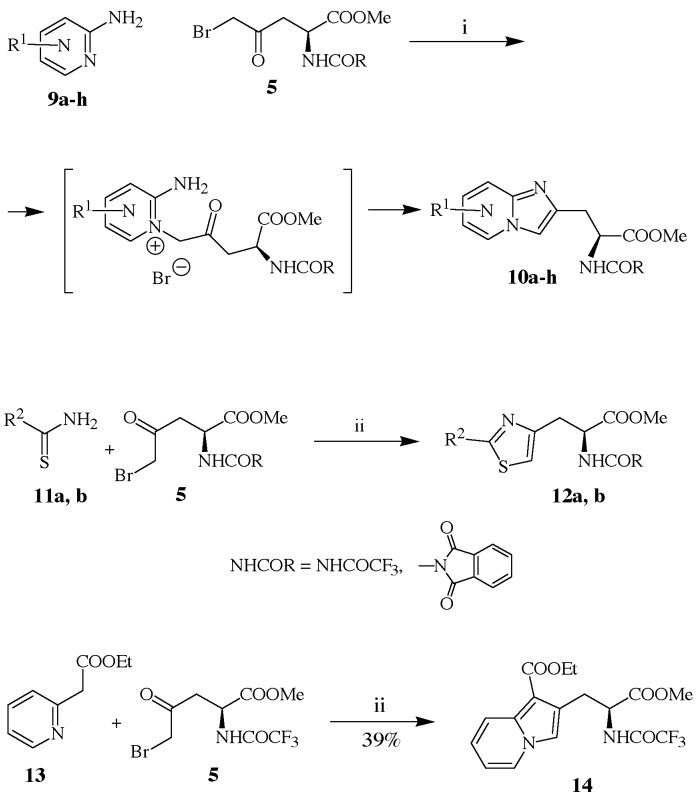
yield. On the other hand, treatment of the chloride **3** with excess diazomethane followed by treatment with hydrogen bromide gave (*S*)-*N*-trifluoroacetyl-5-bromo-4-oxonorvaline ester (**5**) in 85% yield. Starting from (*R*)- and (*RS*)-aspartic acid (**1**), the corresponding (*R*)- and (*RS*)-isomers of **4** and **5** were prepared [20]. Similarly, racemic *N*-phthaloyl protected precursors **4'** and **5'** were also prepared by the same procedure and in almost the same yields [21] (Scheme 1).

Treatment of (*R*)-, (*S*)- and (*RS*)-isomers of 3-formylalanine derivatives **4** with hydrazinoazines **6a–f**, having the hydrazino group attached at the *ortho*-position with respect to the ring nitrogen atom, furnished the corresponding hydrazones **7a–f**. These were then oxidatively cyclized with methanolic bromine at room temperature into (*S*)-*N*-acyl-3-(1,2,4-triazolo[4,3–*x*]azinyl-3)alanine methyl esters **8a–f** and their (*R*)- and (*RS*)-isomers. Various hydrazinoazines **6** were employed, such as 2-hydrazinopyridine (**6a**), hydrazinopyridazines **6b–d**, 2-hydrazinopyrimidine (**6e**), and hydrazinopyrazine (**6f**) [20, 21] (Scheme 2, Table 1).

Imidazo[1,2–*x*]azinyl- (**10a**, **b**), thiazolyl- (**12a**, **b**), and indolizinyl substituted (*S*)-alanine derivatives (**14**) and their (*R*)- and (*RS*)-isomers were prepared by treatment of the corresponding isomer of *N*-acyl-5-bromo-4-oxo-norvaline ester **5** with ambident 1,3-nucleophiles such as *ortho*-amino azines **9a–h**, thioamides **11a**, **b** and ethyl 2-pyridineacetate (**13**), respectively. *N*-Acyl-3-(imidazo[1,2–*x*]azinyl-2)-alanine esters **10a–h** were prepared in one step from *N*-acyl-5-bromo-4-oxonorvaline esters **5** and aminoazines **9a–h**. This transformation, which proceeds by initial quarternization followed by condenzation into imidazo-[1,2–*x*]azinil-2)alanine derivative **10** [11], proved to be useful for the preparation 3-(imidazo[1,2–*a*]pyridinyl-2)-(**10a–e**), 3-(imidazo [1,2–*b*]pyridazinyl-2)- (**10f, g**), and 3-(imidazo [1,2–*a*]pyrimidinyl-2)alanine derivatives (**10h**). Similarly, treatment of **5** with thiobenzamide **11a** and thiourea **11b** gave the corresponding *N*-acyl-3-(2-substituted thiazolyl-4)alanine esters **12a**, **b** in 63–81% yields [20, 21]. With ethyl 2-pyridineacetate (**13**), *N*-trifluoroacetyl-3-(1-ethoxycarbonylindolizinyl-2)alanine methyl ester (**14**) was obtained [22] (Scheme 3, Table 2).

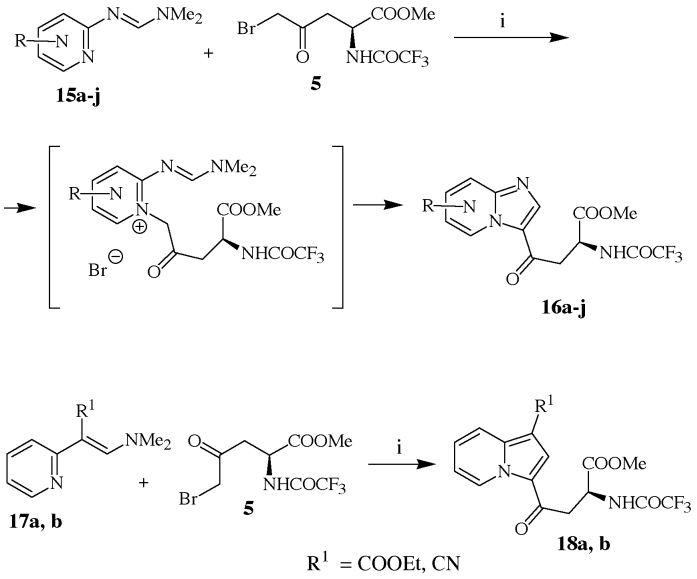
Reaction of (*S*)-*N*-trifluoroacetyl-5-bromo-4-oxonorvaline ester **5** and its (*R*)- and (*RS*)-isomer with *N*,*N*-dimethyl-*N*'-heteroarylformamidines **15a–j** furnished (*S*)-*N*-trifluoroacetyl-4-(imidazo[1,2–*x*]azinyl-3)-4-oxo-homoalanine methyl esters **16a–j** and their (*R*)- and

Scheme 3



i MeOH reflux; **ii** EtOH, 20–80°.

Scheme 4



i CH_2Cl_2 or $CHCl_3$ or EtOH, 20°-80°.

(*RS*)-isomers in 12–62% yields. The scope of this reaction was somehow limited, since only pyridinyl and pyrimidinyl substituted formamidines **15** gave the reaction

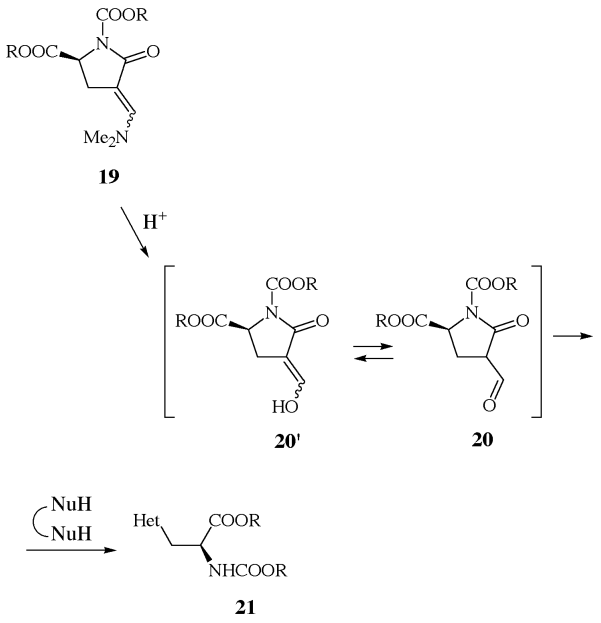


Figure 1

[23]. Analogously, indolizinyl substituted homoalanine esters **18a**, **b** were prapared in low yields upon treatment of the bromo ketone **5** with ethyl 2-[(dimethylamino)-methylene]-2-pyridineacetate (**17a**) and 2-[(dimethyl-amino)methylene]-2-pyridineacetonitrile (**17b**) [22]. The formation of imidazo[1,2–*x*]azine- and indolizine ring system can be explained in the following manner: quarternization of a ring nitrogen in a molecule of a formamidine activates the adjacent methylene group, which then undergoes cyclization by substitution of the dimethylamino group [22–24] (Scheme 4, Table 3).

3. Synthesis of 3-Heteroarylalanine-, 3-Heteroarylalaninol, and 3-Heteroaryllactic Acid Derivatives from (Dimethyl-amino)methylidene and Cyanomethylidene Substituted γ-Lactones and γ-Lactams.

Recently, Young and coworkers reported a 'ring switching' transformation of 3-formylpyroglutamic acid derivatives into various 3-heteroarylalanine derivatives. By this method, a 3-[(dimethylamino)methylidene] substituted pyrrolidinone derivative **19** was first hydrolysed *in situ* into a formyl substituted pyroglutamic acid derivative **20** which was then treated with ambident nucleophiles to afford 3-heteroarylalanine derivatives **21** [25–27] (Figure 1).

On the other hand, we have previously shown that alkyl 2-substituted 3-(dimethylamino)propenoates **22** can serve as easily available and versatile reagents for the preparation of a variety of heterocyclic systems [28–30]. Reactions with ambident nucleophiles, probably the most typical reactions of 3-(dimethylamino)propenoates **22**,

proceed by substitution of the dimethylamino group followed by cyclization to the ester group to give five and six membered heterocyclic systems. γ-Substituted α-[(dimethylamino)methylidene]-γ-lactams **23** and γ-lactones **24** are chiral cyclic analogs of 2-substituted alkyl 3-(dimethylamino)propenoates **22**, since they actually contain a 3-(dimethylamino)propenoate structural element partially incorporated in the lactam or lactone ring. Compounds **23** and **24** react in the same manner as acyclic 3-(dimethylamino)propenoates **22** giving 'ring switched' products with an amino acid, amino alcohol, hydroxy acid or a diol moiety containing side chain attached to the heterocyclic ring [31–36] (Figure 2).

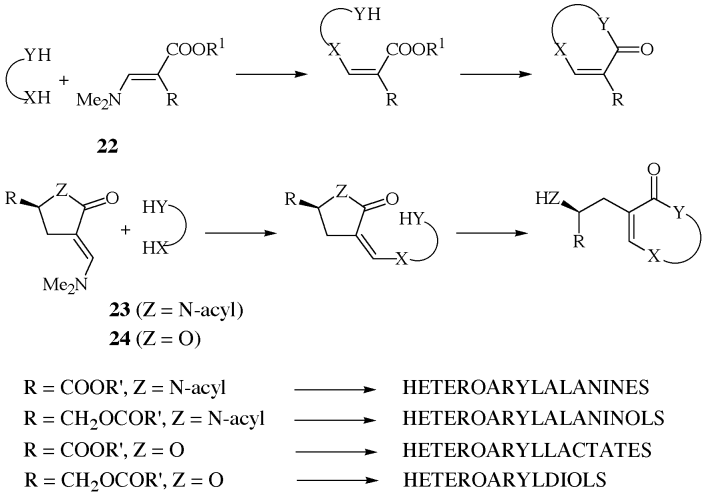
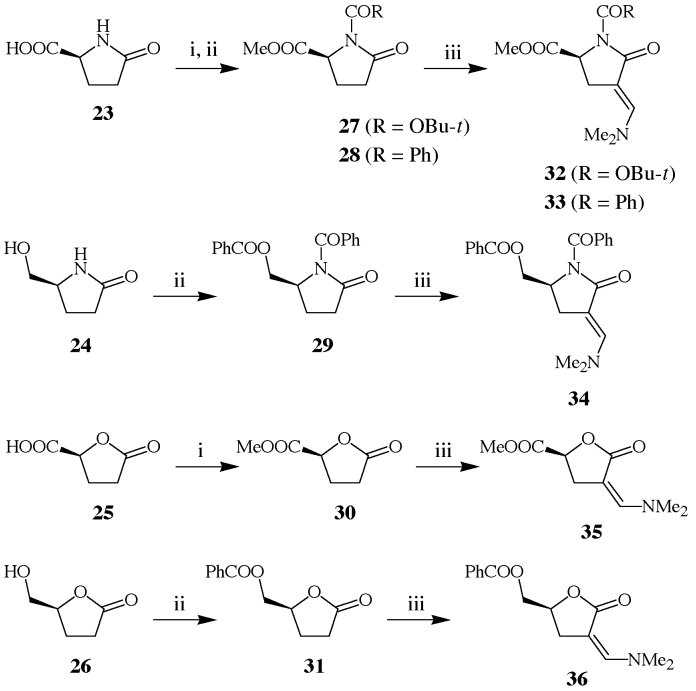


Figure 2

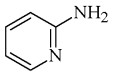
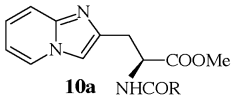
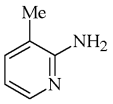
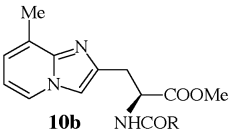
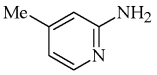
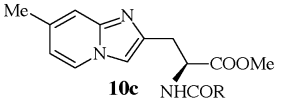
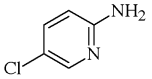
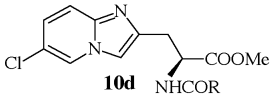
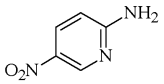
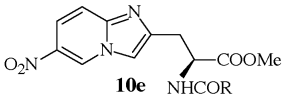
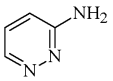
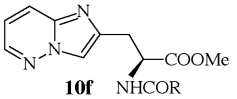
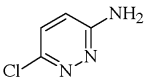
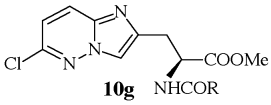
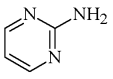
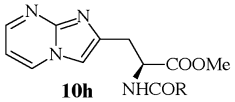
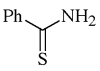
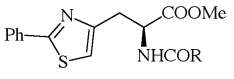
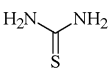
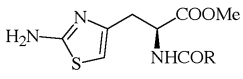
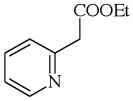
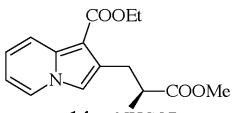
Scheme 5



i MeOH, $SOCl_2$, 0–20°; **ii** PhCOCl, pyridine, 20°or Boc_2O, Et_3N, MeCN, 20°; **iii** *t*-BuOCH$(NMe_2)_2$, toluene, 90–100°.

Table 2

N-Acyl-3-(imidazo[1,2–*x*]azinyl-2)alanine- (**10a–h**), *N*-Acyl-3-(thiazolyl-4)alanine- (**12a, b**), and *N*-Acyl-3-(indolizinyl-2)alanine Derivatives (**14**).

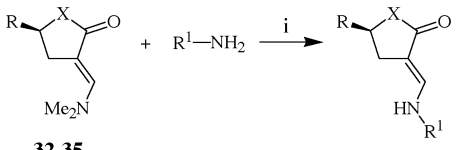
1,3-Dinucleophile →	Heteroarylalanine Derivative	Yield (%)
 **9a**	 **10a**	57, (*S*), $NHCOCF_3$ 58, (*RS*), $NHCOCF_3$ 24, (*RS*), *N*–Phthaloyl
 **9b**	 **10b**	41, (*RS*), $NHCOCF_3$ 75, (*RS*), *N*–Phthaloyl
 **9c**	 **10c**	55, (*RS*), $NHCOCF_3$ 30, (*RS*), *N*–Phthaloyl
 **9d**	 **10d**	30, (*RS*), *N*–Phthaloyl
 **9e**	 **10e**	67, (*R*), $NHCOCF_3$ 63, (*S*), $NHCOCF_3$ 53, (*RS*), $NHCOCF_3$ 84, (*RS*), *N*–Phthaloyl
 **9f**	 **10f**	16, (*RS*), $NHCOCF_3$
 **9g**	 **10g**	74, (*R*), $NHCOCF_3$ 46, (*S*), $NHCOCF_3$ 74, (*RS*), $NHCOCF_3$ 36, (*RS*), *N*–Phthaloyl
 **9h**	 **10h**	16, (*S*), $NHCOCF_3$ 25, (*RS*), $NHCOCF_3$
 **11a**	 **12a**	63, (*S*), $NHCOCF_3$ 78, (*RS*), *N*–Phthaloyl
 **11b**	 **12b**	81, (*S*), $NHCOCF_3$ 80, (*RS*), *N*–Phthaloyl
 **13**	 **14**	39, (*S*), $NHCOCF_3$ 36, (*RS*), $NHCOCF_3$

Supported by our results in acyclic 3-(dimethylamino)propenoate series [28–30] and by the results of Young and coworkers [25–27], we studied the extentions of 'ring switching' transformations of 5-substituted (*S*)-1-acyl-3-[(dimethylamino)methylidene]pyrrolidin-2-ones **32–34** and (*S*)-3-[(dimethylamino)methylidene]tetra-

hydrofuran-2-ones **35**, **36** towards the preparation of other types of heteroarylalanine derivatives, heteroarylalaninols, and heteroaryllactates. The following lactones and lactams were chosen: (*S*)-1-*tert*-butoxycarbonyl-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**32**), (*S*)-1-benzoyl-3-[(dimethylamino)methylidene]-5-(methoxy-carbonyl)pyrrolidin-2-one (**33**), (*S*)-1-benzoyl-5-benzoyloxymethyl-3-[(dimethylamino)-methylidene]pyrrolidin-2-one (**34**), (*S*)-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**35**), and (*S*)-5-benzoyloxymethyl-3-[(dimethylamino)methylidene]tetrahydrofuran-2-one (**36**). They were prepared in 2 steps from commercially available starting materials such as pyroglutamic acid (**23**), 5-hydroxymethyl-2-pyrrolidinone (**24**), 2-tetrahydrofuranone-5-carboxylic acid (**25**), and 5-hydroxymethyl-2-tetrahydrofuranone (**26**). Compounds **23–26** were first suitably protected followed by introduction of the (dimethylamino)methylidene group by reaction with bis dimethylamino-*tert*-butoxymethane (Bredereck's reagent) [37, 38] (Scheme 5).

Treatment of compounds **32–35** with various alkyl-, aryl-, and heteroarylamines resulted in substitution of the dimethylamino group thus, furnishing the corresponding substitution products **37–40** in 66–99% yields [32]. It turned out, that 3-(dimethylamino)methylidene lactams and lactones exhibit the reactivity which is in accordance with our previous results in acyclic 3-(dimethylamino)propenoate series. Therefore, the hydrolysis of the (dimethylamino)methylidene group into a formyl group can be avoided for further transformations, since (dimethylamino)methylidene group itself already acts as a masked formyl group [28–30, 32] (Scheme 6).

Scheme 6



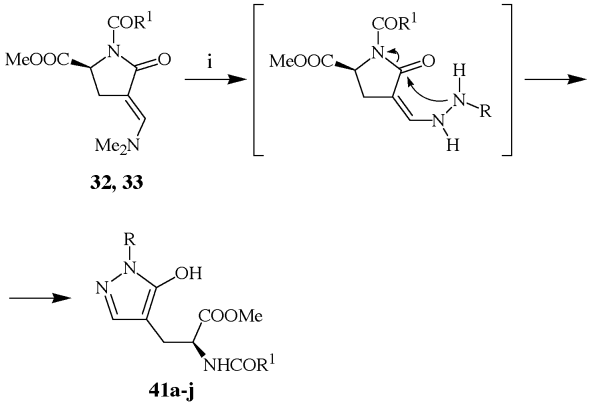
32-35 **37-40**

Compound	X	R
32, 37	N-Boc	COOMe
33, 38	N-COPh	COOMe
34, 39	N-COPh	CH_2OCOPh
35, 40	O	COOMe

R1 = CH_2COOMe, benzyl, phenyl, 3-bromophenyl, 3-methylphenyl, 4-methylphenyl, 3-nitrophenyl, 1-naphthyl, pyridinyl-2, 5-chloropyridinyl-2, 4-methylpyridinyl-2, 6-chloropyridazinyl-3, 4,6-dimethylpyrimidinyl-2, pyrazinyl-2, isoxazolyl-3, 5-methylisoxazolyl-3, thiazolyl-2, 1*H*-1,2,4-triazolyl-3, ethane-1,2-diyl, piperazin-1,4-diyl; **i** EtOH, HCl (1 equiv.), 20–80° or AcOH, 20–120°; 66–99% yields.

Treatment of (*S*)-1-*tert*-butoxycarbonyl-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**32**) and (*S*)-1-benzoyl-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**33**) with substituted hydrazines gave the corresponding (*S*)-*N*-acyl-3-(1-substituted 5-hydroxy-1*H*-pyrazolyl-4)alanine methyl esters (**41a–j**) in 41–88% yields. Reaction of **33** with (6-chloropyridazinyl-3)hydrazine was found to be temperature dependent. 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 (**41g**) however, at 80°C (*S*)-*N*-benzoyl-3-[1-(6-chloropyridazinyl-3)]alanine methyl ester (**41f**) was formed. On the other hand, treatment of (*S*)-1-*tert*-butoxycarbonyl-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**32**) with hydrazines under acidic conditions resulted in decomposition of the reagent **32** rather than in the formation of pyrazolyalanine esters. However, reaction of **32** with hydrazine hydrochloride in ethanol at room temperature, as well as reaction with (6-chloropyridazinyl-3)hydrazine in acetic acid at 80°C, gave the corresponding *N*-*tert*-butoxycarbonyl-3-(5-hydroxy-1*H*-pyrazolyl-4)- (**41a**) and *N*-*tert*-butoxycarbonyl-3-[1-(6-chloropyridazinyl-3)-5-hydroxy-1*H*-pyrazolyl-4)alanine methyl ester (**41e**), respectively [34] (Scheme 7).

Scheme 7



32, 33 **41a-j**

Compound **41**	R	R^1	Method	Yield (%)
a	H	OBu-*t*	C	47
b	benzyl	Ph	A	73
c	4-nitrophenyl	Ph	A	69
d	pyridinyl-2	Ph	A	87
e	6-chloropyridazinyl-3	OBu-*t*	B	50
f	6-chloropyridazinyl-3	Ph	B	72
g	6-hydroxypyridazinyl-3	Ph	A	84
h	6-phenylpyridazinyl-3	Ph	A	88
i	pyrimidinyl-2	Ph	A	62
j	1,2,4-triazolo[4,3-*b*]pyridazinyl-6	Ph	A	41

i R–$NHNH_2$, AcOH, reflux (Method A); R-$NHNH_2$, AcOH, 80° (Method B); NH_2NH_3Cl, EtOH, 20° (Method C).

Table 3

N-Trifluoroacetyl-4-(imidazo[1,2–*x*]azinyl-2)-4-oxohomoalanine- (**16a–j**) and *N*-Trifluoroacetyl-4-(indolizinyl-3)-4-oxohomoalanine Derivatives (**18a, b**).

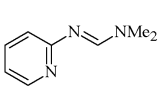
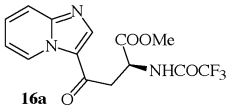
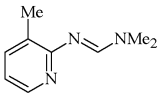
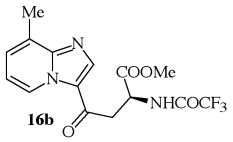
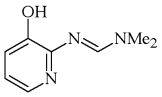
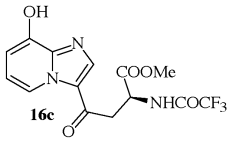
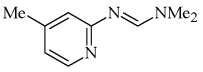
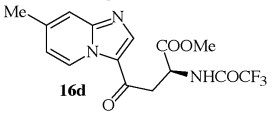
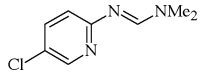
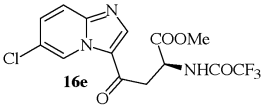
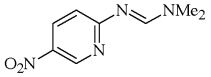
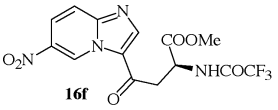
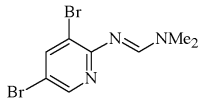
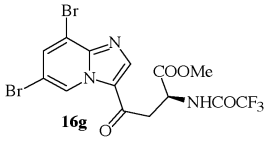
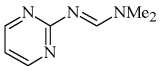
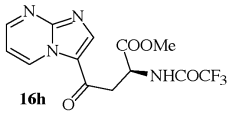
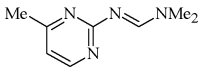
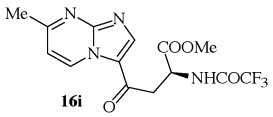
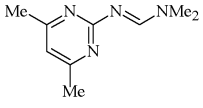
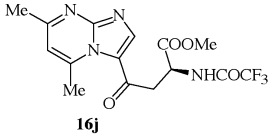
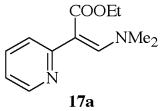
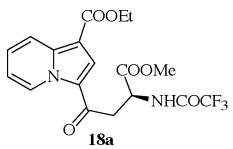
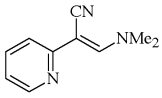
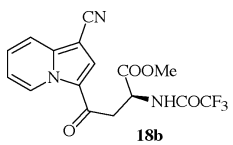
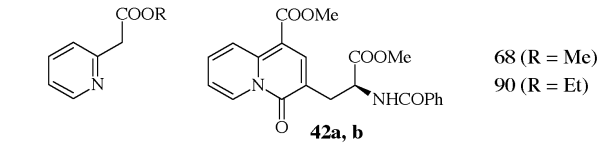
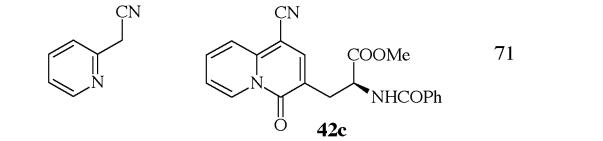
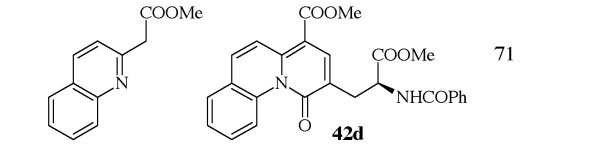
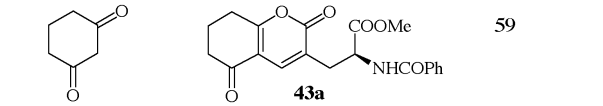
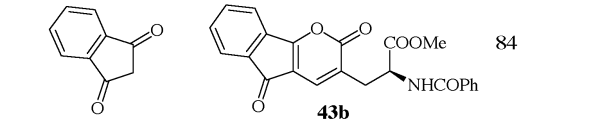
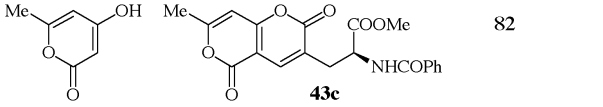
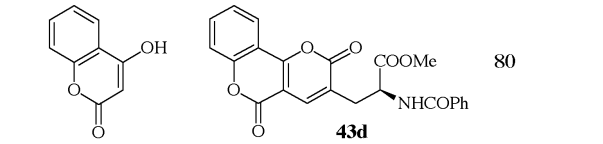
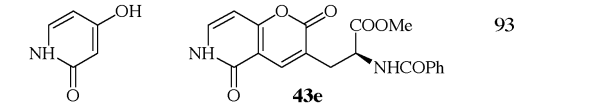
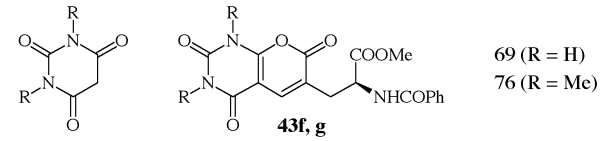
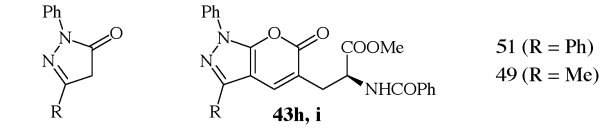
Formamidine or Enamine →	4-Heteroarylhomoalanine Derivative	Yield (%)
 **15a**	 **16a**	43, (*S*) 29, (*RS*)
 **15b**	 **16b**	26, (*RS*)
 **15c**	 **16c**	33, (*S*) 25, (*RS*)
 **15d**	 **16d**	43, (*S*) 25, (*RS*)
 **15e**	 **16e**	67, (*R*) 12, (*S*) 44, (*RS*)
 **15f**	 **16f**	21, (*RS*)
 **15g**	 **16g**	15, (*RS*)
 **15h**	 **16h**	62, (*R*) 41, (*S*) 26, (*RS*)
 **15i**	 **16i**	53, (*S*) 21, (*RS*)
 **15j**	 **16j**	46, (*S*) 35, (*RS*)
 **17a**	 **18a**	18, (*S*)
 **17b**	 **18b**	7, (*S*)

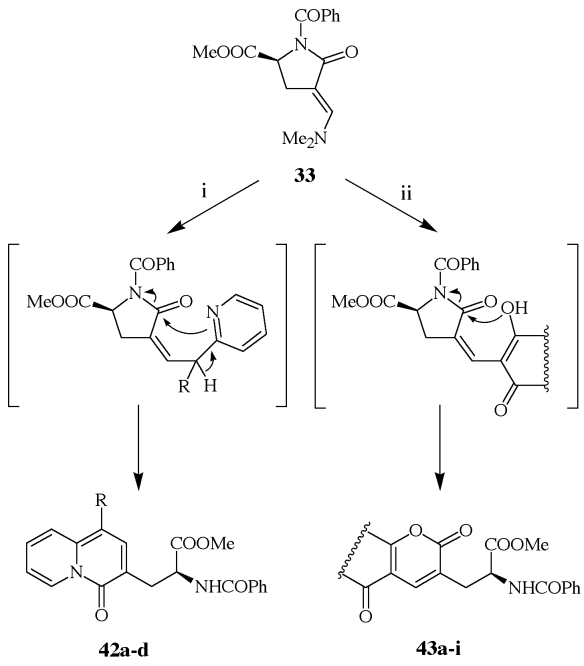
Table 4

(*S*)-*N*-Benzoyl-3-(quinolizinyl-3)- (**42a–d**) and (*S*)-*N*-Benzoyl-3-(2-oxo-2*H*-pyranyl-3)alanine Methyl Esters (**43a–i**).

1,3-Nucleophile → 3-Heteroarylalanine Derivative	Yield (%)
 **42a, b**	68 (R = Me) 90 (R = Et)
 **42c**	71
 **42d**	71
 **43a**	59
 **43b**	84
 **43c**	82
 **43d**	80
 **43e**	93
 **43f, g**	69 (R = H) 76 (R = Me)
 **43h, i**	51 (R = Ph) 49 (R = Me)

Upon treatment of (*S*)-1-benzoyl-3-[(dimethylamino)-methylidene]-5-(methoxycarbonyl)pyrrolidin-2-one (**33**) with 2-pyridineacetic acid derivatives and 1,3-diacrbonyl compound analogs, the corresponding (*S*)-*N*-benzoyl-3-(4-oxo-4*H*-quinolizinyl-3)- (**42a–d**) and (*S*)-*N*-benzoyl-3-(2-oxo-2*H*-pyranyl-3)alanine esters (**43a–g**) were obtained in 49–93% yields [31] (Scheme 8, Table 4).

Scheme 8



Reagents and conditions: **i** 2-pyridineacetic acid derivative (R = COOMe, COOEt, CN), AcOH, reflux; **ii** 1,3-dicarbonyl compound analog, AcOH, reflux.

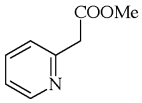
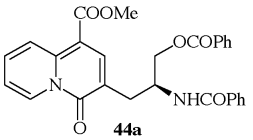
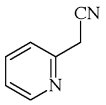
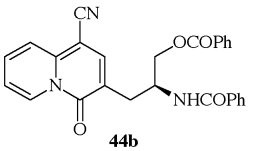
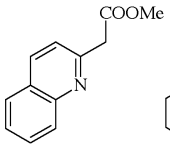
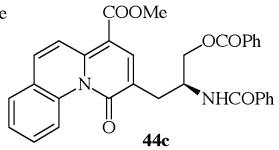
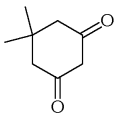
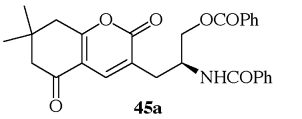
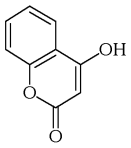
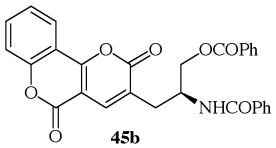
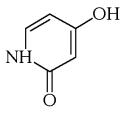
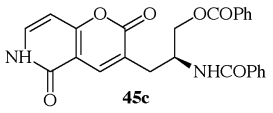
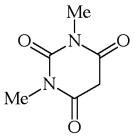
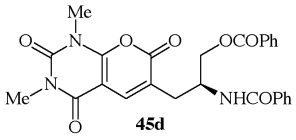
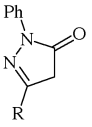
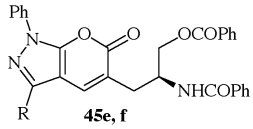
3-(Quinolizinyl-3)- **44a–c** and 3-(2-oxo-2*H*-pyranyl-3) substituted (*S*)-*O*-benzoyl-2-benzoylamino-1-propanols **45a–f** were prepared from (*S*)-1-benzoyl-5-benzoyl-oxymethyl-3-[(dimethylamino)methylidene]pyrrolidin-2-one (**34**) upon reaction with 2-pyridineacetic acid derivatives and 1,3-dicarbonyl compound analogs, respectively [35] (Scheme 9, Table 5).

Similarly, (*S*)-3-[(dimethylamino)methylidene]-5-(methoxycarbonyl)tetrahydrofuran-2-one (**35**) was employed for the preparation of (*S*)-3-(quinolizinyl-3)- (**46a–c**), (*S*)-3-(pyridino[1,2–*a*]pyrimidinyl-3)- (**47a, b**), and (*S*)-3-(2-oxo-2*H*-pyranyl-3)lactic acid esters (**48a–j**) [33, 36] (Scheme 10, Table 6).

Nitrosation of "active" methylene group followed by reduction of the resulting oxime is one of the most common methods for amination at the position adjacent to electron withdrawing group [39]. Unfortunetely, the scope

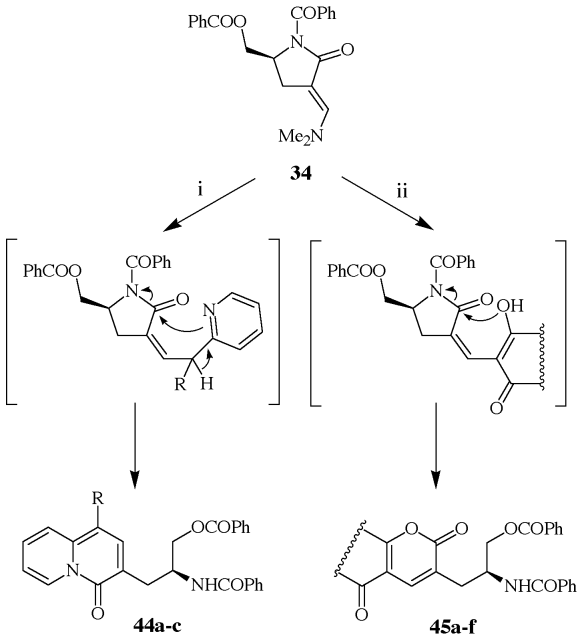
Table 5

(*S*)-*O*-Benzoyl-2-benzoylamino-3-heteroaryl-1-propanols.

1,3-Dinucleophile ⟶	3-Heteroarylalaninol Derivative	Yield (%)
	 **44a**	24
	 **44b**	23
	 **44c**	30
	 **45a**	27
	 **45b**	52
	 **45c**	37
	 **45d**	32
	 **45e, f**	22 (R = Ph) 24 (R = Me)

of this method is limited to methylene groups bearing strong electron withdrawing substituent, *e.g.*, nitroalkanes, ketones, 1,3-dicarbonyl compounds, and their analogs. On the other hand, we have previously shown, that nitrosation of alkyl 3-(dimethylamino)propenoates **22** leads to the formation of oximes [40, 41]. As an extension of this

Scheme 9

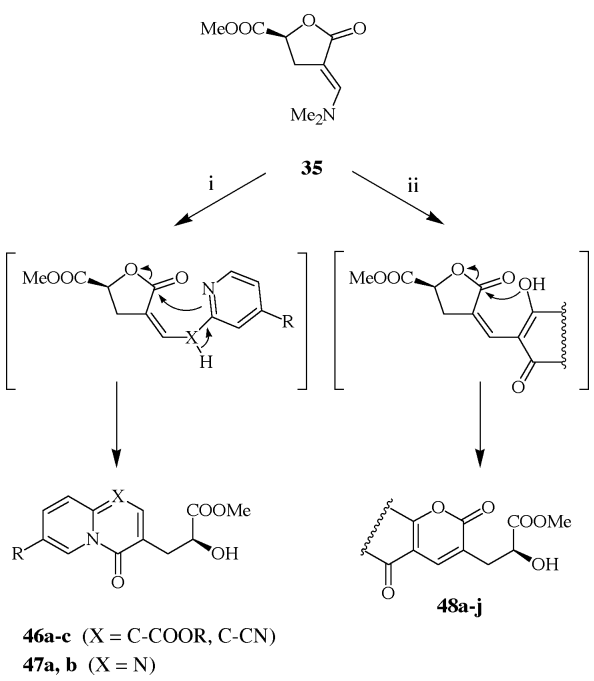


i 2-pyridineacetic acid derivative, AcOH, reflux; **ii** 1,3-dicarbonyl compound analog, AcOH, reflux.

useful reaction, a stereoselective amination of γ-lactones and γ-lactams *via* α-(dimethylamino)methylidene substituted lactones and lactams was developped [38]. (*S*)-3-[(Dimethylamino)methylidene]pyrrolidin-2-ones **32**, **33** and (*S*)-3-[(dimethylamino)methylidene]tetrahydrofuran-2-ones **35**, **36**, prepared from the corresponding 3-unsubstituted lactams **27**, **28** and lactones **30**, **31** and Bredereck's reagent, were treated with nitrous acid to afford the corresponding oximes **49–52**. These were then catalytically hydrogenated in a mixture of acetic acid and acetic anhydride to furnish 5-substituted (3*S*,5*S*)-3-(acetylamino)pyrrolidin-2-ones **53**, **54** and (3*S*,5*S*)-3-(acetylamino)tetrahydrofuran-2-ones **55**, **56** in 56–86% de. Since direct nitrosation of lactones and lactams is usually difficultly to achieve, these transformations represent a convenient method for stereoselective introduction of the amino group to the position adjacent to the ring carbonyl group in lactone and lactam moiety *via* 3-(dimethylaamino)methylene substituted lactones and lactams [38] (Scheme 11, see also Scheme 5).

Another type of precursors, which were employed for the preparation of cyclic analogs of heteroarylalanines or heteroarylglycines were 5-substituted (*S*)-1-acyl-3-[(*E*)-cyanomethylidene]pyrrolidin-2-ones **57**–**59**, prepared by treatment of the pyrrolidinones **32–34** with potassium cyanide in acetic acid. Cyano compounds **57–59** were used as chiral dipolarophiles in 1,3-dipolar cycloaddition

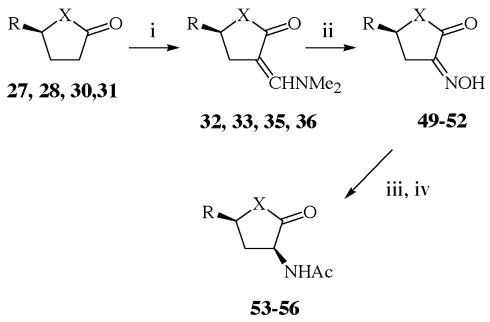
Scheme 10



46a-c (X = C-COOR, C-CN)
47a, b (X = N)

Reagents and conditions: **i** 2-pyridineacetic acid derivative (X = C–COOMe, C–COOEt, C–CN) or 2-aminopyridine derivative (X = N, R = H, Me), AcOH, reflux; **ii** 1,3-dicarbonyl compound analog, AcOH, reflux.

Scheme 11



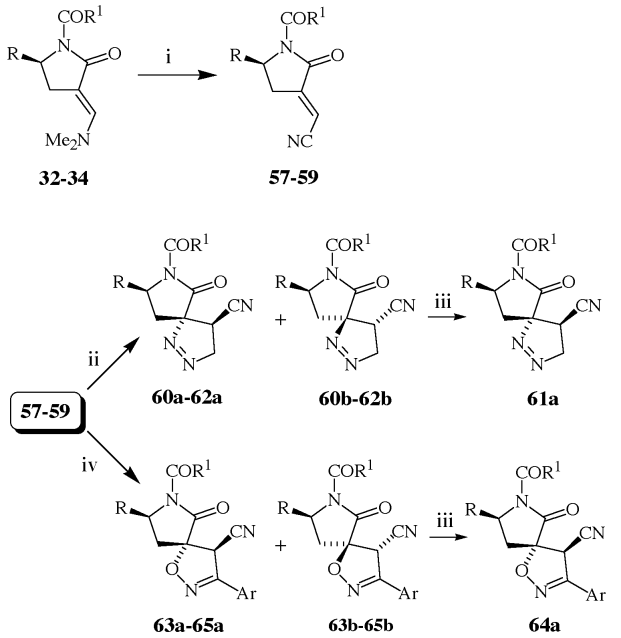
Compound	R	X	Yield (%)	49-52	53-56	d.e. (%)
27, 32, 49, 53	CO_2Me	N-COPh		79	45	50
28, 33, 50, 54	CO_2Me	N-Boc		79	44	86
30, 35, 51, 55	CO_2Me	O		78	58	82
31, 36, 52, 56	$PhCO_2CH_2$	O		81	56	86

Reagents and conditions: **i** bis-(dimethylamino)-*tert*-butoxymethane (*Bredereck's* reagent), toluene, 90–100°; **ii** HCl, $NaNO_2$, H_2O, 0°; **iii** H_2, Pd-C, AcOH-Ac_2O, 20-60°, 1 bar; **iv** crystallisation or chromatographic separation.

reactions. The (*E*)-orientation around the exocyclic C=C double bond was determined by NMR and by X–ray diffraction. Cycloaddition of diazomethane and 2,4,6-trimethoxybenzonitrile oxide to **57–59** afforded isomeric mixtures **60–62** and **63–65** with poor diastereoselectivity. Isomericaly pure major diastereoisomers **61a** and **64a** were isolated upon crystallization of the corresponding isomeric mixtures. The structure of cycloadduct **64a** was also confirmed by X–ray diffraction [37, 42] (Scheme 12).

On the other hand, cycloadditions of *N*-phenylbenzonitrile imines, generated *in situ* from the corresponding benzohydrazonoyl chlorides and triethylamine, afforded racemic pyrrolo[3,4–*c*]pyrazoles **67–70**. Since we

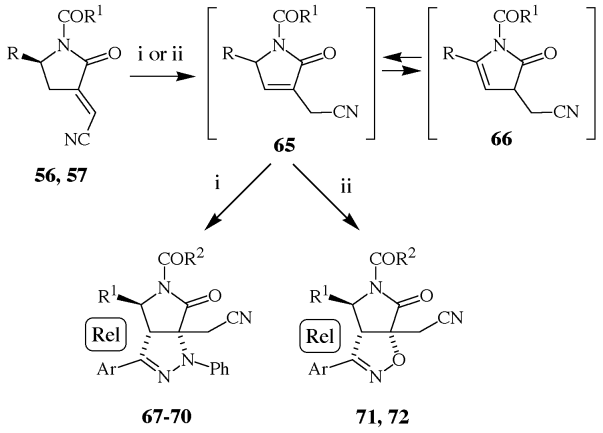
Scheme 12



Compound	R	R^1	Ar	Yield (%)	d.e. (%)
57	CO_2Me	OBu-*t*	-	63	
58	CO_2Me	Ph	-	73	
59	$PhCO_2CH_2$	Ph	-	80	
60a/60b	CO_2Me	OBu-*t*	-	96	0
61a/61b	CO_2Me	Ph	-	95 (42 [a])	38
62a/62b	$PhCO_2CH_2$	Ph	-	92	10
63a/63b	CO_2Me	OBu-*t*	2,4,6-tri-MeO-C_6H_2	80	22
64a/64b	CO_2Me	Ph	2,4,6-tri-MeO-C_6H_2	82 (44 [a])	20
65a/65b	$PhCO_2CH_2$	Ph	2,4,6-tri-MeO-C_6H_2	69	14

[a] Yield of isomerically pure compound; **i** KCN, AcOH, 20°C; **ii** CH_2N_2, Et_2O, -10°; **iii** crystallization; **iv** 2,4,6-trimethoxybenzonitrile oxide, $CHCl_3$, reflux.

Scheme 13



Compound	R^1	R^2	Ar	Yield (%)	d.e. (%)
67	CO_2Me	OBu-*t*	Ph		97
68	CO_2Me	OBu-*t*	4-Cl-C_6H_4		87
69	CO_2Me	Ph	Ph		61
70	CO_2Me	Ph	4-Cl-C_6H_4		56
71	CO_2Me	OBu-*t*	2,4,6-tri-MeO-C_6H_2		82
72	CO_2Me	Ph	2,4,6-tri-MeO-C_6H_2		86

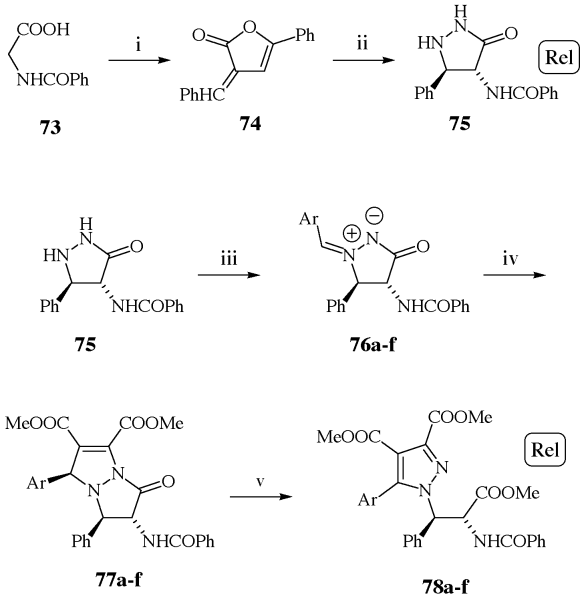
i N-phenylbenzohydrazonoyl chloride, Et_3N, CH_2Cl_2, reflux; **ii** 2,4,6-trimethoxybenzonitrile oxide, Et_3N, CH_2Cl_2.

suspected, that triethylamine could be responsible for this unusual reaction course, the cycloaddition of 2,4,6-trimethoxybenzonitrile oxide to **57** and **58** in the presence of triethylamine was performed. It turned out, that also in this case, racemic pyrrolo[3,4–*d*]isoxazoles **71** and **72** were formed. However, diastereoselectivity was much higher by this type of cycloadditions (56–97% de). The structure of cycloadduct **70** was confirmed by X–ray structural analysis. Formation of racemic compounds **67–72** could be explained by migration of the exocyclic double bond in dipolarophiles **56** and **57**. Apparently, 1,3-dipolar cycloaddition reaction proceeds *via* intermediate **65** and the racemization could be attributed to the intermediate **66** [37, 42] (Scheme 13).

4. Synthesis of *rel*-(2*R*,3*R*)-3-Phenyl-3-pyrazolylalanine Esters from *rel*-(4*R*,5*R*)-4-Benzoylamino-5-phenyl-3-pyrazolidinone.

rel-(4*R*,5*R*)-4-Benzoylamino-5-phenyl-3-pyrazolidinone (**75**), prepared in 2 steps from hippuric acid (**73**), was used as precursor for the preparation of *rel*-(2*R*,3*R*)-*N*-benzoyl-3-phenyl-3-(substituted pyrazolyl-1)alanine esters **78a–f** by oxidative ring opening of substituted pyrazolo[1,2–*a*]pyrazolones **77a–f**. The pyrazolidinone **75** was first transformed with aromatic aldehydes into its azomethine imines **76a–f**, which underwent 1,3-dipolar

Scheme 14



Compounds **76-78**	Ar	Yield (%)	**76**	**77**	**78**
a	phenyl		89	86	87
b	4-methylphenyl		90	85	94
c	4-methoxyphenyl		78	75	93
d	3-nitrophenyl		90	89	83
e	4-nitrophenyl		76	80	86
f	2,6-dichlorophenyl		88	77	89

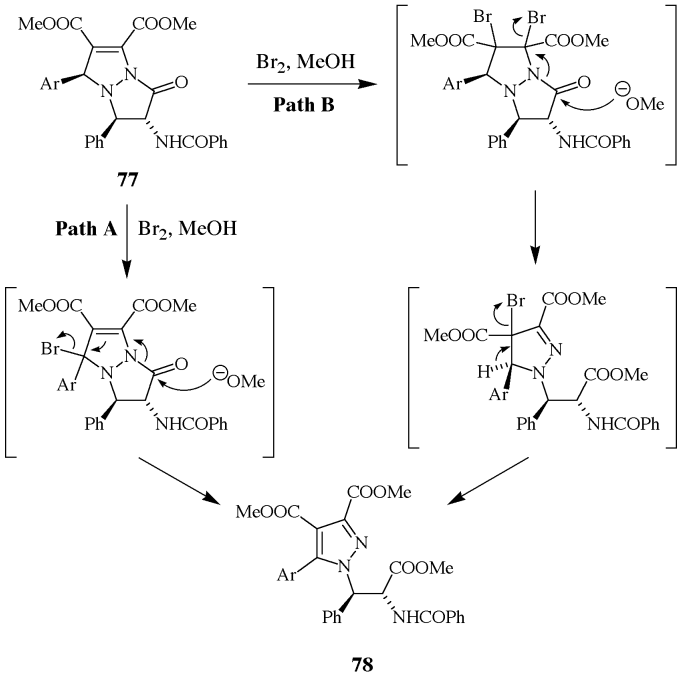
Reagents and conditions: **i** PhCHO, Ac_2O, AcONa, 100°; **ii** NH_2NH_2 x H_2O, 100°; **iii** ArCHO, ethanol, CF_3COOH (cat.), reflux, 2 h; **iv** dimethyl acetylenedicarboxylate, anisole, reflux; **v** Br_2, MeOH, 20°, then reflux.

cycloaddition reaction with dimethyl acetylenedicarboxylate to give cycloadducts **77a–f**. Treatment of pyrazolo-[1,2–*a*]pyrazolones **77a–f** with methanolic bromine afforded the corresponding *rel*-(2*R*,3*R*)-*N*-benzoyl-3-phenyl-3-[5-aryl-3,4-bis(methoxycarbonyl)pyrazolyl-1]alanine esters **78a–f** in high yields over 3 steps [43, 44] (Scheme 14).

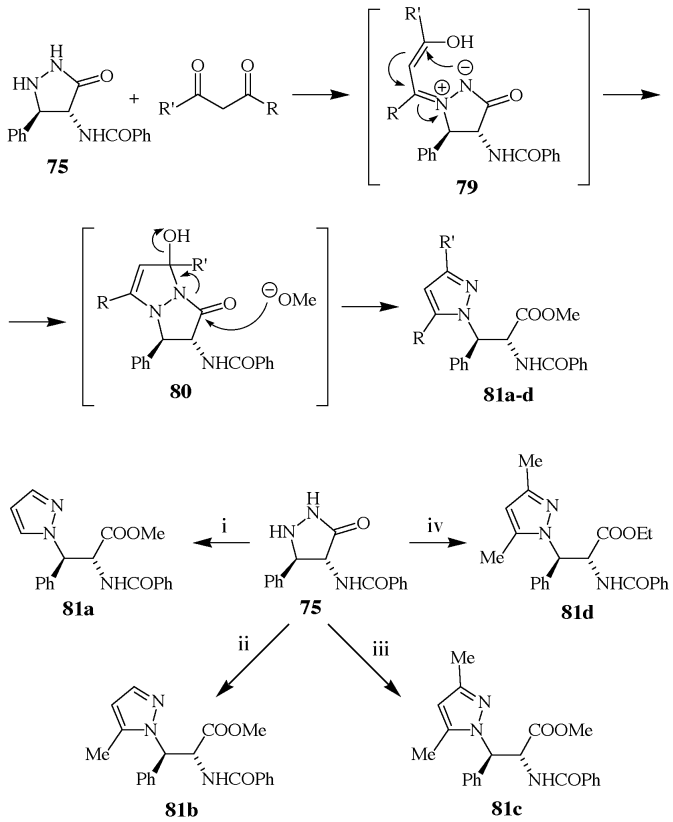
The following mechanism for oxidative ring-opening was proposed: A bicyclic cycloadduct **77** is first brominated, either at the allylic position (Path A) or at the double bond (Path B), followed by nucleophilic attack of methanol and ring-opening of the pyrazolidinone part of the bicyclic system which leads to the formation of 3-pyrazolylalanine ester **78** [44] (Scheme 15).

On the other hand, *rel*-(2*R*,3*R*)-*N*-benzoyl-3-phenyl-3-(pyrazolyl-1)alanine esters (**81a–d**) were also prepared in one step by 'ring switching' transformation of the pyrazolidinone **75** with aliphatic 1,3-diketones. Thus, reaction of **75** with 1,1,3,3-tetraethoxypropane, 3-oxobutyraldehyde dimethyl acetal, and pentane-2,4-dione in methanol in the presence of trifluoroacetic acid gave the corresponding

Scheme 15

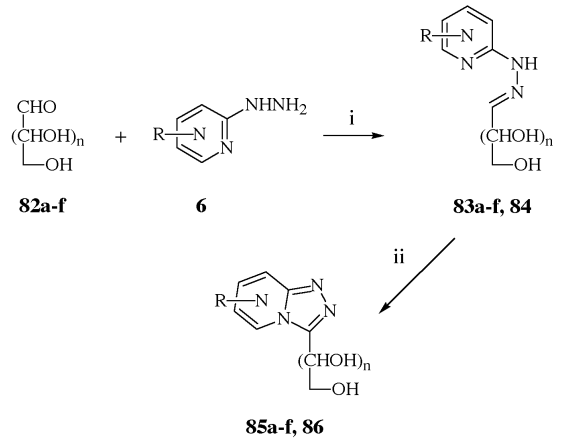


Scheme 16



Reagents and conditions: **i** 1,1,3,3-Tetraethoxypropane, MeOH, CF_3COOH, 20°; **ii** 3-oxobutyraldehyde dimethyl acetal, MeOH, CF_3COOH, 20°; **iii** pentane-2,4-dione, MeOH, CF_3COOH, 20°; iv pentane-2,4-dione, EtOH, CF_3COOH, reflux.

Scheme 17



82a-f **6** **83a-f, 84** **85a-f, 86**

From 6-Chloro-3-hydrazinopyridazine (**6b**) and Aldoses (**82a-f**):

Compound	Yield (%)	**83**	**85**	Configuration
82a, 83a, 85a		84	51	D-*arabino*
82b, 83b, 85b		84	44	D-*ribo*
82c, 83c, 85c		85	60 [a]	D-*xylo*
82d, 83d, 85d		73	58	D-*galacto*
82e, 83e, 85e		87	79	D-*gluco*
82f, 83f, 85f		87	81	D-*manno*

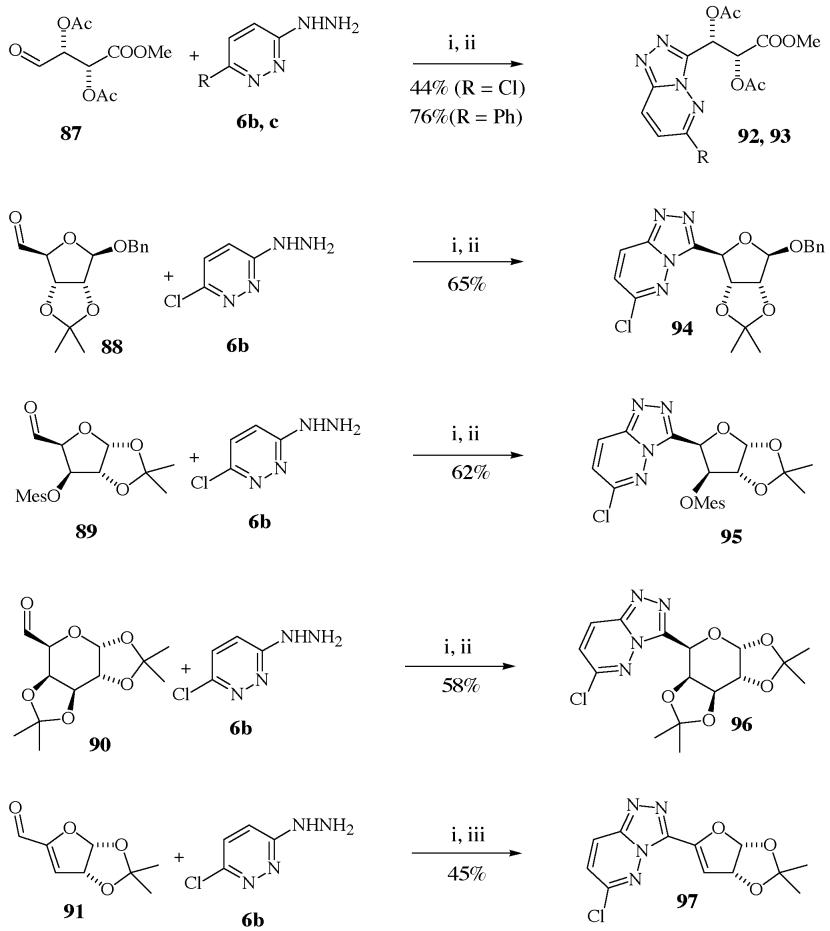
From 2-Hydrazinopyrimidine (**6e**) and D-Glucose (**82e**):

Compound	Yield (%)	**84**	**86**	Configuration
82e, 84, 86		75	60	D-*gluco*

[a] Isolated as its 5-*O*-(triphenyl)methyl derivative.

i MeOH or EtOH, 36 % HCl (cat.), reflux; **ii** Br_2, MeOH, 20°.

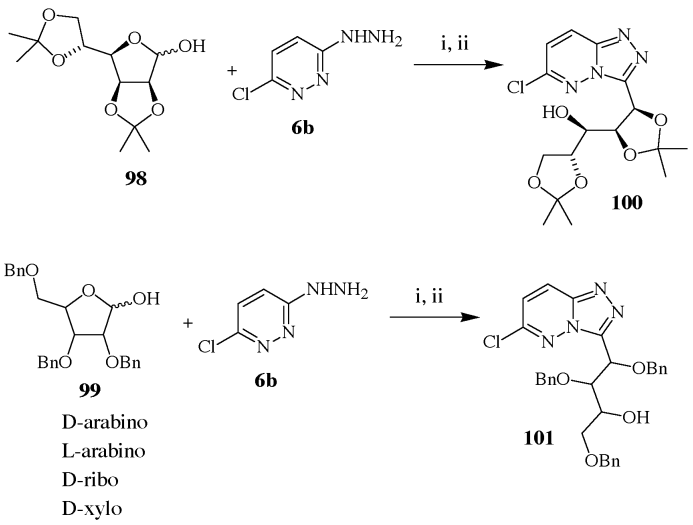
Scheme 18



87 **6b, c** **92, 93** **88** **6b** **94** **89** **6b** **95** **90** **6b** **96** **91** **6b** **97**

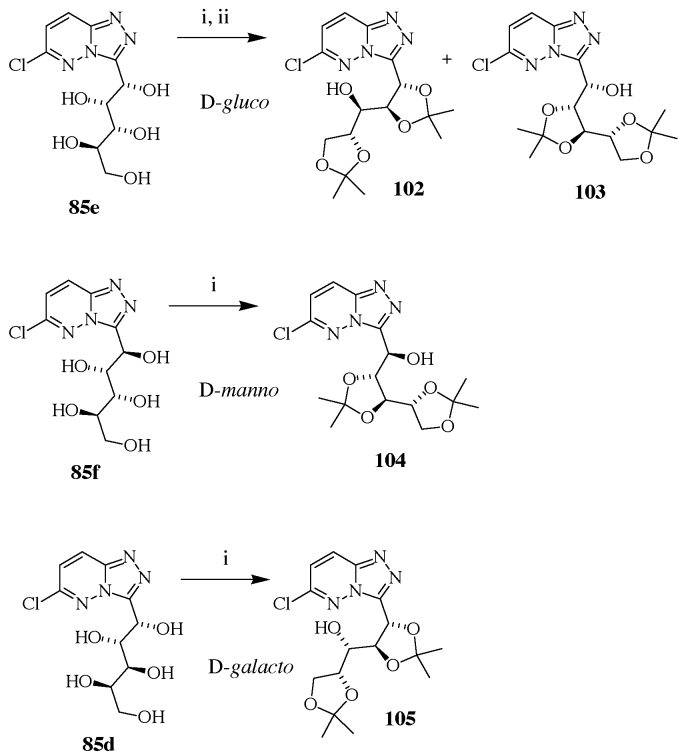
i MeOH, AcOH (cat.), 20°; **ii** Br_2, MeOH, AcONa, 20°; **iii** $Pb(OAc)_4$, CH_2Cl_2, 20°.

Scheme 19



i MeOH, AcOH (cat.), 20°; **ii** Br_2, MeOH, AcONa, 20°.

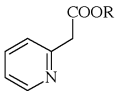
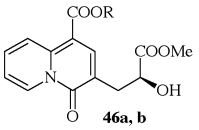
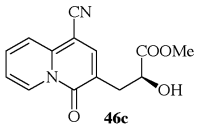
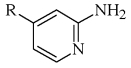
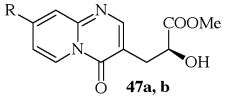
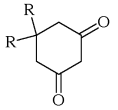
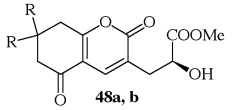
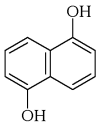
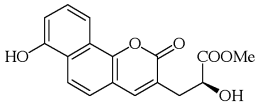
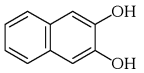
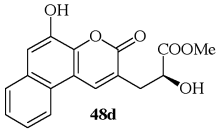
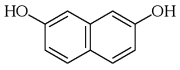
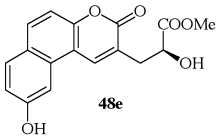
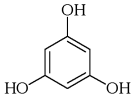
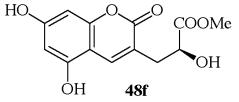
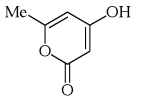
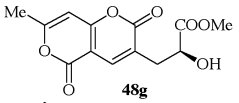
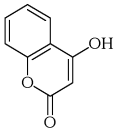
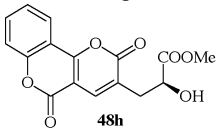
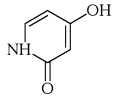
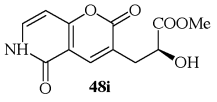
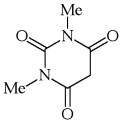
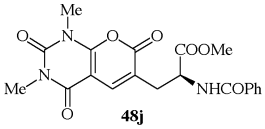
Scheme 20



i acetone, H_2SO_4 (cat.), 20°; **ii** crystallization (from EtOH) or MPLC separation (silicagel, 0.02-0.04 mm, EtOAc/EtOH, 95:5).

Table 6

Methyl (S)-3-(Quinolizinyl-3)- (**46a–c**), Methyl (*S*)-3-(Pyridino[1,2–*a*]pyrimidinyl-3)- (**47a, b**), and Methyl (*S*)-3-(2-Oxo-2*H*-pyranyl-3)lactates (**48a–j**).

1,3-Nucleophile ⟶	Methyl 3-Heteroaryllactate	Yield (%)
	 **46a, b**	43 (R = Me) 35 (R = Et)
	 **46c**	45
	 **47a, b**	19 (R = H) 15 (R = Me)
	 **48a, b**	20 (R = H) 64 (R = Me)
	 **48c**	27
	 **48d**	28
	 **48e**	13
	 **48f**	31
	 **48g**	65
	 **48h**	81
	 **48i**	64
	 **48j**	30

rel-(2*R*,3*R*)-*N*-benzoyl-3-phenyl-3-(pyrazolyl-1)alanine esters (**81a–c**). Similar treatment of **75** with pentane-2,4-dione in ethanol afforded the corresponding pyrazolylalanine ethyl ester **81d**. Reaction mechanism can be explained by initial formation of the corresponding azomethine imine **79** which is in equilibrium with non-dipolar bicyclic isomer **80**. Intermediate **80** then undergoes nucleophilic attack of alcohol followed by elimination of water giving a pyrazolylalanine derivative **81** as product. However, this proposed mechanism is only hypothetical, since we were so far are not able to isolate any of the intermediates [45] (Scheme 16).

5. Synthesis of 1,2,4-Triazolo[4,3-x]azinyl Substituted Polyols from Aldoses.

C-Glycoside analogs, 1-(1,2,4-triazolo[4,3–*x*]azinyl-3)-polyols can be conveniently prepared in two steps from commercially available unprotected aldoses **82** and hydrazinoazines **6**. Acid-catalyzed treatment of 6-chloro-3-hydrazinopyridazine (**6b**) with unprotected aldoses **82a–f** afforded the corresponding hydrazones **83a–f** in good yields. Oxidative cyclization of hydrazones **83a–f** with methanolic bromine furnished 1-(6-chloro-1,2,4-triazolo[4,3–*b*]pyridazinyl-3)polyols **85a–f**. Similarly, 1-(1,2,4-triazolo[4,3–*a*]pyrimidinyl-3)-D-*gluco*-pentitol (**86**) was prepared from 2-hydrazinopyrimidine (**6e**) and D-glucose (**82e**). Polyols **85a–f** and **86** can also be prepared in one-pot procedure [46] (Scheme 17).

This reaction was also applied to protected sugar analogs **87–91** with a free formyl group. It turned out that this methodology allowed utilization of various typical sugar *O*-protective groups such as acetyl-, isopropylidene-, and benzyl protective group. Sodium acetate was used to buffer the reaction mixture in order to avoid removal of acid-sensitive protective groups (*e. g.* isopropylidene group) by hydrogen bromide which was formed during oxidative cyclization. In the case of the unsaturated aldehyde **91**, the oxidation step had to be performed with lead tetraacetate. In this manner, the corresponding cyclic 1,2,4-triazolo[4,3–*b*]pyridazinyl substituted polyols **92–97** were obtained in 44–76% yields [46, 47] (Scheme 18).

Similarly, sugar derivatives with the unprotected anomeric hydroxy group such as 2,3;5,6-di-*O*-isopropylidene mannose (**98**) and 2,3,5-tri-*O*-benzylaldopentoses **99** were also used as starting compounds for the preparation of partially protected 1-(6-chloro-1,2,4-triazolo[4,3–*b*]-pyridazinyl-3)polyols **100** and **101** (Scheme 19).

Partially protected 1-(6-chloro-1,2,4-triazolo-[4,3–*b*]pyridazinyl-3)polyols **102**–**105** were also obtained by acetonization of the unprotected 1-(6-chloro-1,2,4-triazolo[4,3–*b*]azinyl-3)polyols **85d–f**. Acetonization of pentitols **85d–f** depended on the configuration of the pentitol moiety. Thus, D-*gluco*-pentitol **85e** gave a mixture of bis-acetonides **102** and **103** which were separated either by crystallization or by medium pressure liquid chromatography (MPLC). On the other hand, D-*manno*-pentitol

85f and D-*galacto*-isomer **85d** furnished isomerically pure bis-acetonides **104** and **105**, respectively. Synthesis of partially protected polyols might be of synthetic importance, since selective intramolecular cyclization of the polyol chain would lead to *C*-nucleoside analogs. On the other hand, the formation new fused ring by cyclization of the polyol chain to the pyridazine ring would furnish fused analogs of iminopolyols [46, 48] (Scheme 20).

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