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Ex-Chiral Pool Enaminones in the Synthesis of Functionalised Heterocycles†

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Summary. Various chiral enaminones and hydrazones, derived from chiral pool starting materials, such as *L*-aspartic acid, *L*-3-phenylalanine, (+)-camphor, and *D*-aldoses were employed as key-intermediates in the synthesis of functionalised heterocycles, such as aminomethylidene substituted tetramic acids, heteroaryl substituted phenethylamines and terpenes, and *C*-nucleosides.

Keywords. Enaminones; Amino acids; Terpenes; Cyclisations; Nucleosides.

Introduction

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 functionalised heterocyclic compounds, such as heteroarylalanines [1], peptidomimetics [2], and *C*-nucleosides [3]. The aim of our work in the field of functionalised heterocycles was to study synthetic methodologies for the preparation of heterocycles with an amino acid, hydroxy acid, amino alcohol, polyol, terpene, and related types of structural elements. Since our research interest is oriented towards various synthetic aspects of heterocyclic chemistry, we studied methodologies, which include formation of the heterocyclic part of the product as the key-step. Within our synthetic approaches towards functionalised heterocycles, enaminones, synthetic equivalents of 1,3-dicarbonyl compounds, represent the most frequently employed and versatile group of reagents [4]. In this connection, we have previously shown, that 2-substituted alkyl 3-(dimethylamino)propenoates **1** and related enaminones, including chiral cyclic analogs **2**–**5**, can serve as easily available and versatile reagents for the preparation of various heterocyclic systems and functionalised

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† Dedicated to Professor *Branko Stanovnik* on the occasion of his 65th anniversary

heterocyclic compounds [5]. For example, 3-heteroarylalanine derivatives were prepared by one step 'ring switching' transformations of pyroglutamates **2a**, **2b** with ambident nucleophiles [6–8]. In the same manner, some other related types of functionalised heterocycles, such as 3-heteroarylalaninol [9], 3-heteroaryllactic acid [10, 11], and 3-heteroarylpropane-1,2-diol derivatives [12] were obtained from the pyrrolidinone **3** and tetrahydrofuranones **4**, **5**. Chiral enaminones **2** and **4** were also used in the synthesis of heterocyclic analogs of dipeptides [4, 5, 13–16] (Fig. 1).

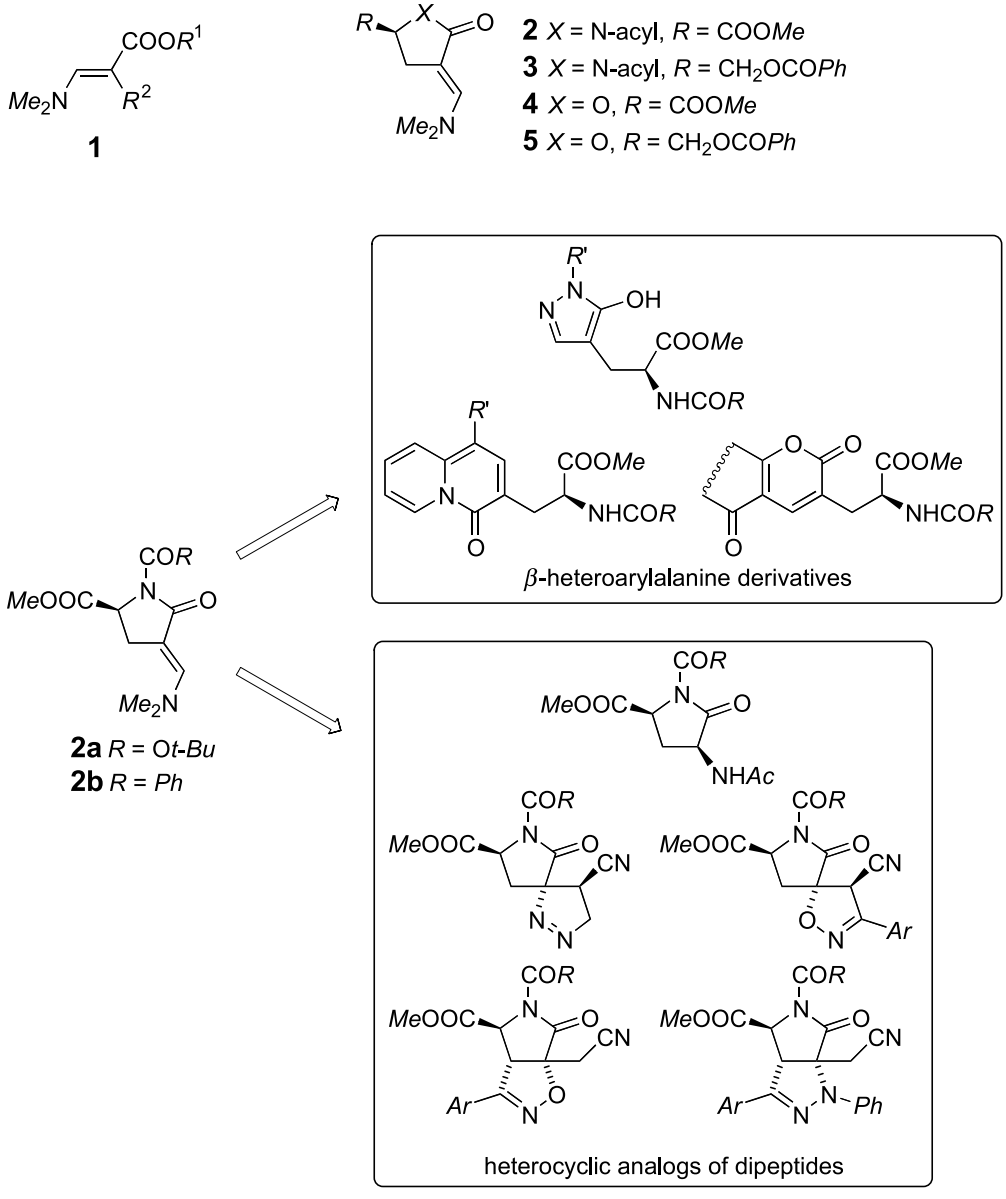


Fig. 1. Previous synthetic studies on chiral enaminones [4–16]

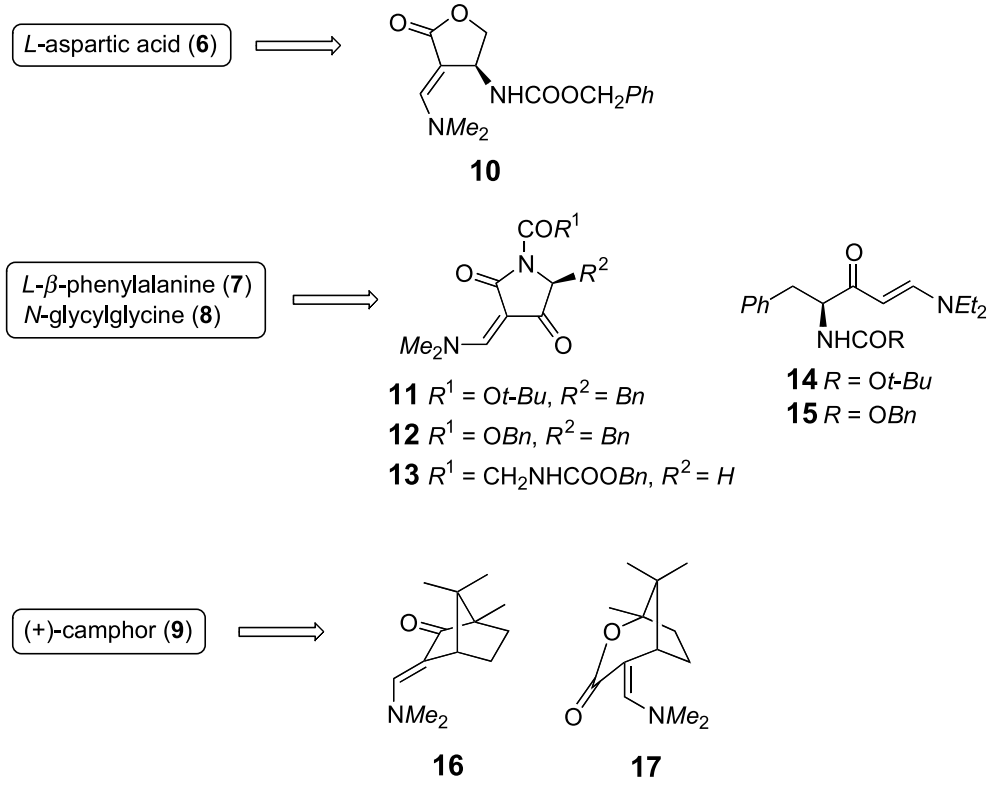


Fig. 2. Recent synthetic studies on chiral enaminones

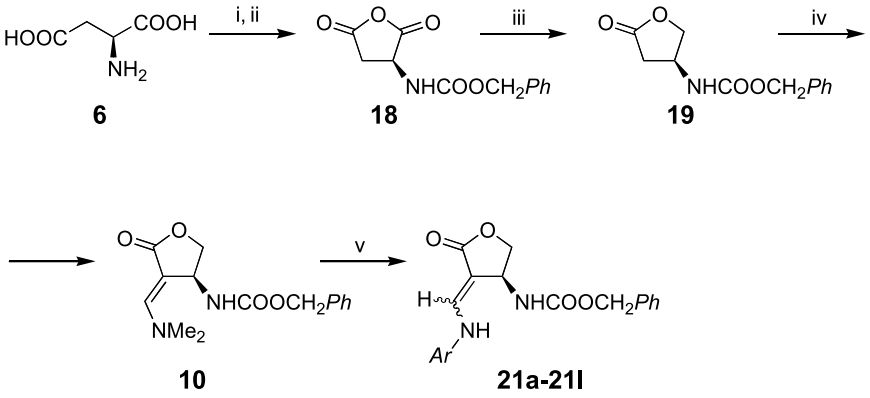
In continuation of our research in this field, we have recently studied synthetic applications of enaminones **10**–**17**, which were prepared from *L*-aspartic acid (**6**), *L*-3-phenylalanine (**7**), *N*-glycylglycine (**8**), and (+)-camphor (**9**) (Fig. 2).

Studies on synthetic applicability of reagents **10**–**17** for the preparation of functionalised heterocycles are presented as the first two topics of this review. As the third topic, utilisation of *D*-aldose derived *N*-(heteroaryl)hydrazones in the synthesis of *C*-nucleosides is described.

Syntheses with α-Amino Acid Derived Enaminones

Preparation and Transformations of Benzyl (3S,4E)-4-[(Dimethylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamate

Benzyl (3*S*,4*E*)-4-[(dimethylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamate (**10**) was synthesised in 4 steps from *L*-aspartic acid (**6**). First, tetrahydrofuranone **19** was prepared *via* transformation of **6** into the *N*-protected anhydride **18** followed by reduction and subsequent lactonisation according to literature procedures [17–19]. Lactone **19** was then treated with bis(dimethylamino)-*tert*-butoxymethane (*Bredereck*'s reagent) to give **10** in 89% yield. Compound **10** was used in the parallel solution-phase synthesis of a library of twelve benzyl (3*S*,4*E*)-4-[(arylamino)methylidene]-5-oxotetrahydrofuran-3-ylcarbamates **21a**–**21l**. Upon



Scheme 1. Reagents and conditions: i) ClCOO*Bn*, NaOH, H_2O, 0°C; ii) Ac_2O, 100°C; iii) $NaBH_4$, *THF*, 0–20°C, then benzene, *p-Ts*OH (cat.), reflux (*Dean-Stark* apparatus); iv) *t-Bu*OCH(NMe_2)$_2$, toluene, 100°C; v) *Ar*NH_2 × HCl (**20a**–**20l**), 50% *Et*OH (aq.), rt

Table 1. Arylaminomethylidene substituted lactones **21a**–**21l**

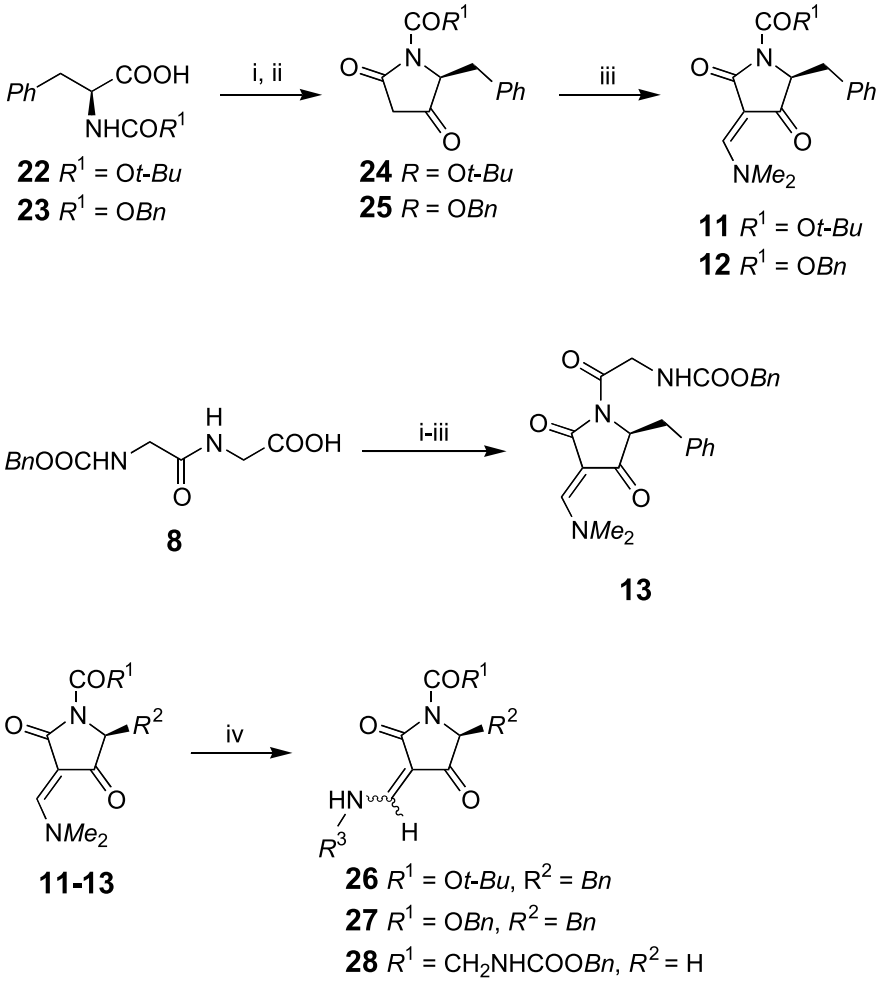
Compound	*Ar*	Yield/%	*E*:*Z*
21a	phenyl	89	93:7
21b	2-methylphenyl	45	81:19
21c	3-methylphenyl	76	96:4
21d	4-methylphenyl	88	93:7
21e	2-methoxyphenyl	77	81:19
21f	3-methoxyphenyl	62	87:13
21g	4-methoxyphenyl	73	99:1
21h	2-bromophenyl	71	77:23
21i	3-bromophenyl	70	94:6
21j	4-bromophenyl	74	90:10
21k	3-hydroxyphenyl	94	90:10
21l	4-hydroxyphenyl	46	100:0

addition of aqueous solutions of aniline hydrochlorides **20a**–**20l** to an ethanolic solution of reagent **10**, stirring at room temperature, filtration of the precipitated products, washing, and thorough drying, the corresponding dimethylamine substitution products **21a**–**21l** were obtained in 45–94% yields, in most cases in analytically pure form. Compounds **21a**–**21k** were isolated as mixtures of the major (*E*)-isomers and the minor (*Z*)-isomers, while compound **21l** was isolated as pure (*E*)-isomer [20] (Scheme 1, Table 1).

Preparation and Transformations of 2-Substituted 1-Acyl-4-[(E)-(dimethylamino)methylidene]pyrrolidin-3,5-diones and (S)-1-Acylamino-1-benzyl-4-diethylamino-2-oxobut-3-enes

The second type of chiral enaminones, which we used within our recent studies, are 4-(dimethylamino)methylidene substituted tetramic acids **11**–**13**. The first two

model reagents, **11** and **12**, were obtained from the *N*-protected *L*-3-phenylalanines **22** and **23**, which were first transformed into the corresponding (*S*)-1-acyl-2-benzyltetramic acids **24** and **25** according to literature procedures [21]. Treatment of compounds **24** and **25** with *N*,*N*-dimethylformamide dimethyl acetal (*DMFDMA*) gave the desired enaminones **11** and **12** in 91 and 89% yield, respectively. This method for preparation of enamino tetramic acids enables variation of substituents at positions 1 and 2 by suitable choice of *N*-protected α-amino acids and peptides as starting materials. In order to confirm these possible variations, 4-[(dimethylamino)methylidene]pyrrolidine-3,5-dione **13** with a glycine residue attached at the position 1 was prepared from *N*-(*N*-benzyloxycarbonylglycyl)glycine (**8**) in 65% overall yield according to the previously established procedure for the preparation of **11** and **12**. With all three enaminones **11**–**13** a series of dimethylamine substitution reactions was carried out with primary aliphatic amines and amino acid esters, as well as with aromatic and heteroaromatic amines. NMR structural studies



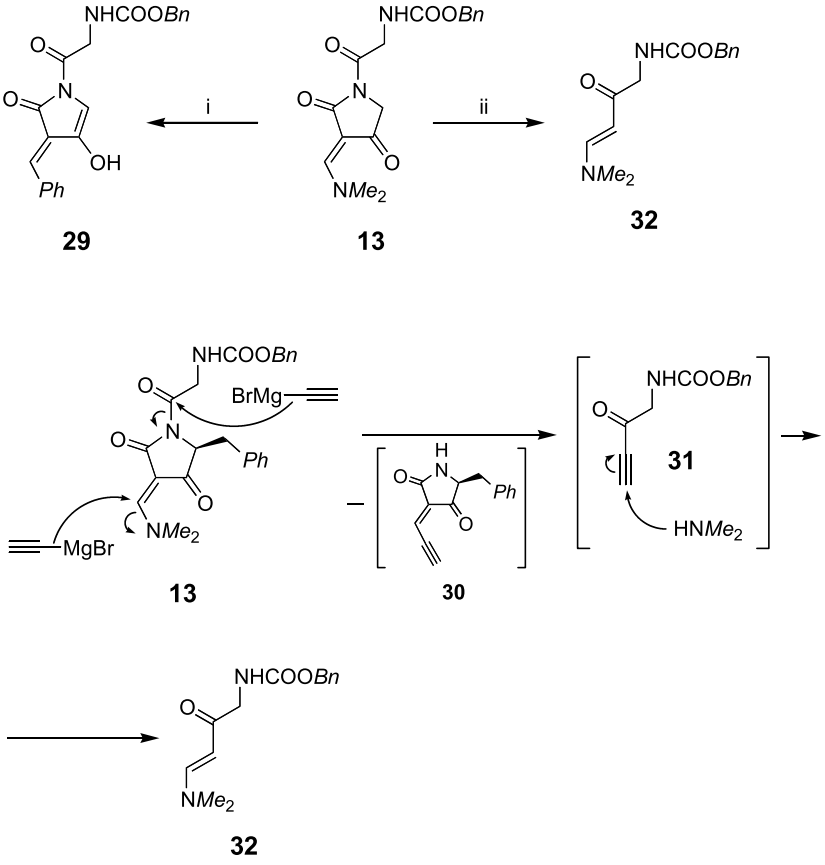
Scheme 2. Reagents and conditions: i) Meldrum's acid, *DCC*, *DMAP*, CH_2Cl_2, 0–20°C; ii) *Et*OA*c*, reflux; iii) *DMFDMA*, toluene or CH_2Cl_2, 45–80°C; iv) $R^3NH_2 \times HCl$, *Et*OH, 20–80°C

Table 2. 4-Aminomethylidene substituted tetramic acids **26–28**

Compound	R^3	Yield/%		
		26	**27**	**28**
26a–28a	CH_2COOMe	88	75	35
26b	$CH(Me)COOEt$ (*S*)	95		
26c, **27c**	$CH(i\text{-}Pr)COOMe$ (*S*)	89	93	
28d	$CH(CH_2Ph)COOMe$ (*S*)	88		
26e	$CH(CH_2CH_2COOEt)COOEt$ (*S*)	84		
26f, **27f**	$CH(CH_2SH)COOEt$ (*S*)	90	46	
26g	CH_2CH_2COOEt	95		
28h	1-adamantyl			51
26i–28i	*Ph*	87	83	92
28j	2-methoxyphenyl			84
28k	3-methoxyphenyl			86
28l	4-methoxyphenyl			83
28m	2-bromophenyl			83
28n	3-bromophenyl			86
28o	4-bromophenyl			90
26p–28p	4-nitrophenyl	68	79	83
28q	phenylene-1,4-diyl			95
28r	1-naphthyl			79
26s, **28s**	pyridin-2-yl	63		33
28t	quinolin-3-yl			89
26u	pyrimidin-2-yl	63		
26v–28v	pyrazinyl	76	94	25
28w	indazol-3-yl			89
26x	isoxazol-3-yl	63		
26y	5-methylisoxazol-3-yl	48		
27z	tetrazolyl		74	

showed, that the dimethylamine substitution products **26–28** exist in solution as the major (*Z*)-isomers and the minor (*E*)-isomers, while reagents **11–13** exist as single (*E*)-isomers. The structure of **11** was additionally confirmed by X-ray diffraction [22] (Scheme 2, Table 2).

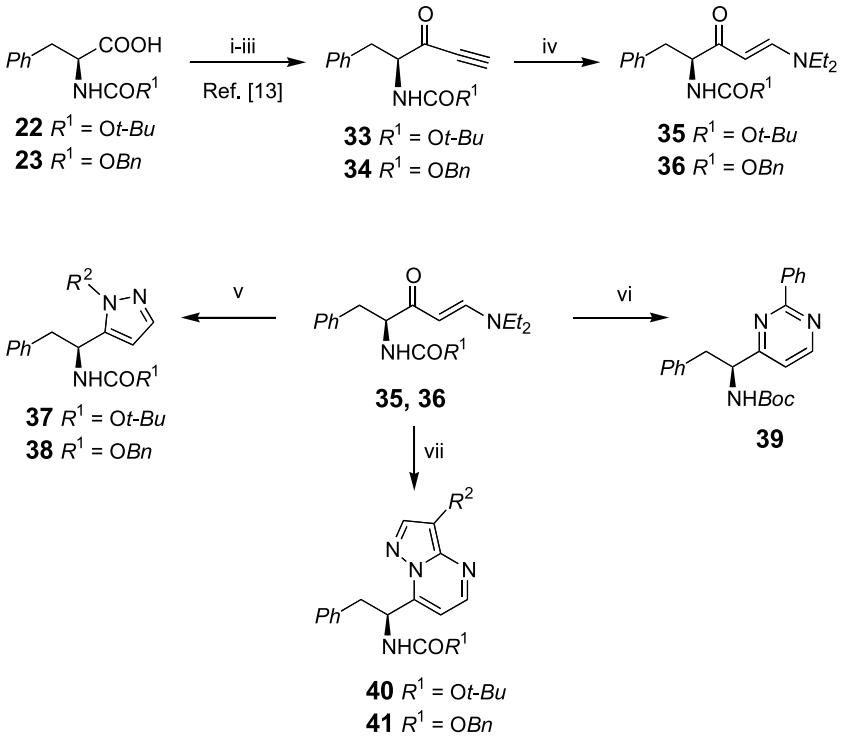
Further investigations were oriented towards the substitution of the dimethylamino group in the enaminones with *Grignard* reagents. The *N*-glycylglycine derived enaminone **13** was chosen for this purpose. In the first experiment, treatment of **13** with an excess of phenylmagnesium bromide afforded the expected substitution product **29** in 27% yield. On the other hand, upon treatment of enaminone **13** with an excess of ethynylmagnesium bromide, 1-benzyloxycarbonylamino-4-dimethylamino-2-oxobut-3-ene (**32**) was isolated in 50% yield. A possible explanation for formation of enaminone **32** could be, that ethynylmagnesium bromide apparently reacted at two sites: a) at the methylidene group leading to substitution of the dimethylamino group, releasing one equivalent of dimethylamine and b) at the carbonyl group of the glycine residue attached to position 1. The so formed acetylenic ketone **31** then reacts with dimethylamine



Scheme 3. Reagents and conditions: i) *Ph*MgBr (5 equiv), *THF*, $-78°C \rightarrow$ rt, then NH_4Cl (aq.); ii) HC≡CMgBr (5 equiv), *THF*, $-78°C \rightarrow$ rt, then NH_4Cl (aq.)

to give enamino ketone **32** [22]. This proposed way of formation of the enaminone **32** is supported also by analogous examples from the literature, *e.g.* synthesis of α-amino ketones from *N*-protected α-amino acids *via* transformation into the *Weinreb* amides followed by reaction with *Grignard* reagents including the acetylenic ones [23] (Scheme 3).

Since, to the best of our knowledge, there are no literature reports on utilization of acyclic chiral enamino ketones, such as enaminone **32**, in the synthesis of functionalised heterocycles, we decided to prepare two model reagents of this type in order to study their reactivity and possible synthetic applications. The *N*-protected *L*-3-phenylalanines **22** and **23** were transformed into the corresponding ketones **33** and **34** according to the literature procedure [24]. Addition of diethylamine to ethynyl ketones **33** and **34** gave enaminones **35** and **36**. It has to be mentioned, that compounds **35** and **36** are just the model reagents; the method for their preparation also enables the use of other *N*-protected α-amino acids as starting materials and, consequently, the introduction of other substituents of position 1. So far, only preliminary tests have been done in connection with synthetic applications of reagents **35** and **36**. Cyclocondensation reactions with hydrazines,



Scheme 4. Reagents and conditions: i) ClCOO*Bu*, CH_2Cl_2, −15°C; ii) NH*Me*O*Me* × HCl, Et_3N, CH_2Cl_2, 0–20°C; iii) HC≡CMgBr (5 equiv), *THF*, −78°C → rt, then NH_4Cl (aq.); iv) Et_2NH, *Et*OH, rt; v) R^2NHNH_2 × HCl, *Et*OH, reflux; vi) benzamidine hydrochloride, K_2CO_3, *Et*OH, reflux; vii) 3-aminopyrazole hydrochloride or 3-aminopyrazole-4-carbonitrile hydrochloride, *Et*OH, rt

Table 3. *N*-Acyl-1-heteroaryl-2-phenylethylamines **37**–**41**

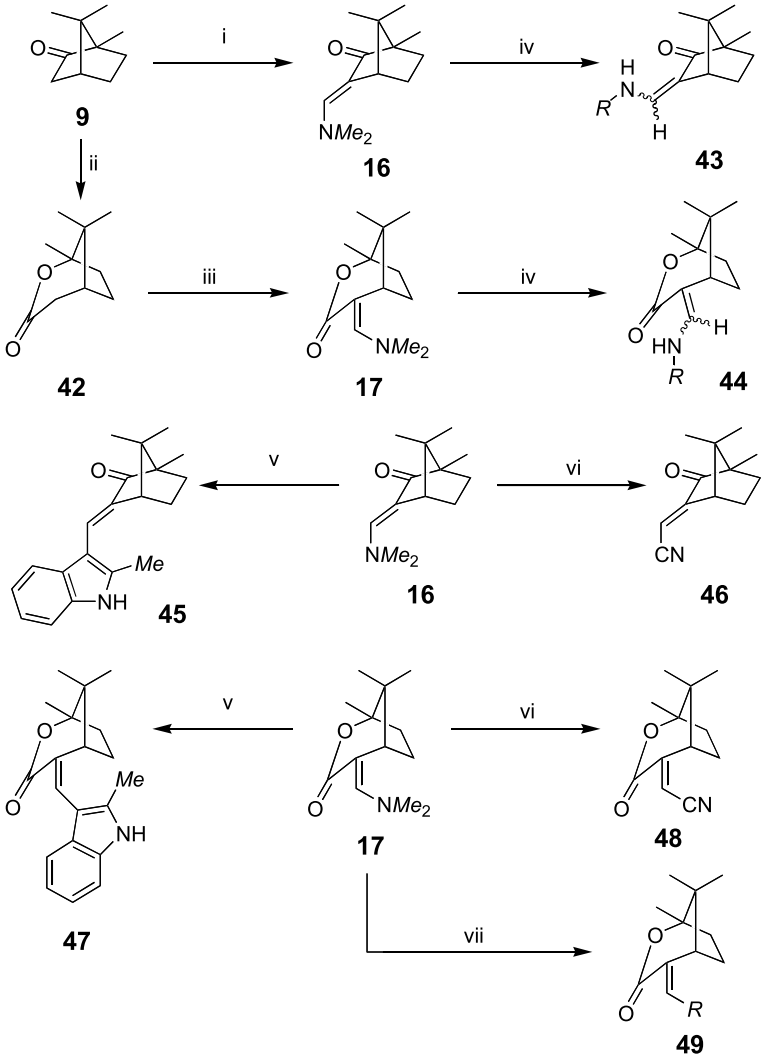
Compound	R^1	R^2	Yield/%
37a	O*t-Bu*	H	84
37b	O*t-Bu*	2-bromophenyl	85
37c	O*t-Bu*	6-chloropyridazin-3-yl	52
38c	O*Bn*	6-chloropyridazin-3-yl	91
39			27
40a	O*t-Bu*	H	44
40b	O*t-Bu*	CN	20
41a	O*Bn*	H	67

amidines, and aminoazoles as ambident nucleophiles furnished the corresponding 1-heteroaryl-2-phenylethylamines **37**–**41** [22] (Scheme 4, Table 3).

Synthesis with (+)-Camphor Derived Enaminones

In continuation, our work was extended also on (+)-camphor (**9**) derived enaminones. 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 (**16**) and (1*R*,5*S*)-4-[(*E*)-(dimethylamino)methylidene]-1,8,8-trimethyl-2-oxabicyclo[3.2.1]octan-3-one (**17**). Compound **16** has been prepared for the first time almost hundred years ago by *Staudinger* and *Kon* in 2 steps *via* the 3-formylcamphor followed by condensation with dimethylamine [25]. However, we prepared enaminone **16** in one step from (+)-camphor (**9**) and *Bredereck*'s reagent [26]. Reagent **17** was prepared in 2 steps. First, (+)-camphor (**9**) was transformed into the lactone **42** by *Baeyer-Williger* oxidation according to the literature procedure [27], followed by treatment with *Bredereck*'s reagent to give the enamino lactone **17** [28]. Also with enaminones **16** and **17** a series of substitution reactions was carried out with various primary amines including α-amino acid esters, as well as with *C*-nucleophiles, such as 2-methylindole, potassium



Scheme 5. Reagents and conditions: i) *t-Bu*OCH(N*Me*$_2$)$_2$, *DMF*, reflux; ii) *Ac*OOH, *Ac*OH, *Ac*ONa, rt; iii) *t-Bu*OCH(N*Me*$_2$)$_2$, decaline, reflux; iv) *R*NH$_2$ × HCl, *Et*OH, reflux; v) 2-methylindole, HCl, *Et*OH, reflux; vi) KCN, *Ac*OH, rt; vii) *R*MgBr (5 equiv), *THF*, −78°C → rt, then NH_4Cl (aq.)

cyanide, and *Grignard* reagents. Substitution products **43** and **44**, obtained upon reactions of **16** and **17** with primary amines, exist in solution as mixtures of the major (*Z*)-isomers and the minor (*E*)-isomers, whereas reagents **16** and **17** and substitution products **45**–**49**, obtained upon reactions with *C*-nucleophiles, exist as single (*E*)-isomers. In the case of both reagents, **16** and **17**, and several products obtained by substitution of the dimethylamino group, the configuration around the exocyclic C=C bond was determined by X-ray diffraction, as well as by NMR using N*O*ESY and HMBC techniques [26, 28] (Scheme 5, Table 4).

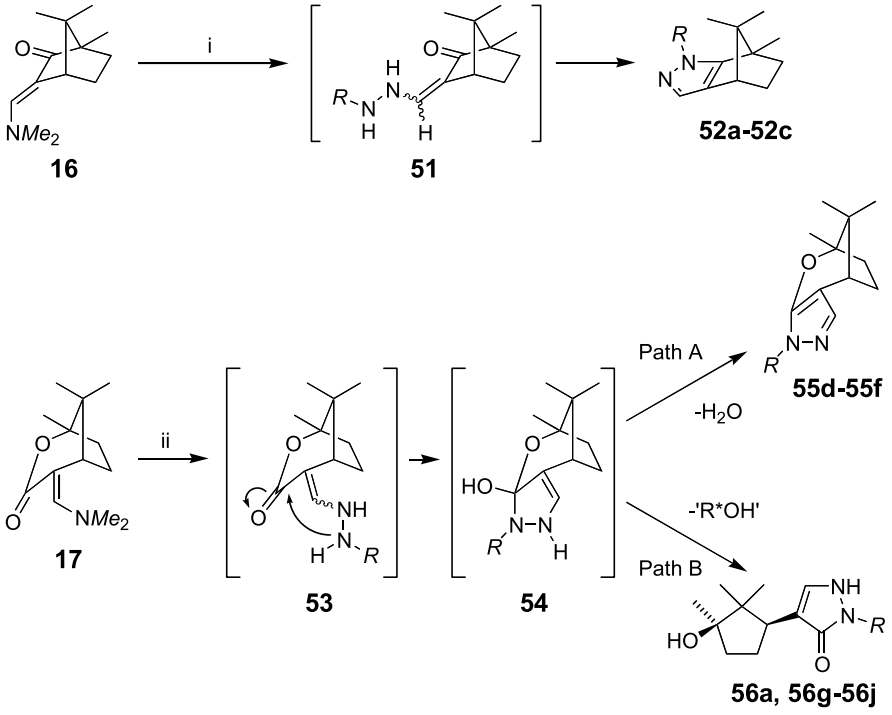
Cyclocondensation reactions were studied with various substituted hydrazines. Reactions of **16** with hydrazines **50a**–**50c** furnished 3,4-diazatricyclo[5.2.1.$0^{2,6}$]

Table 4. (+)-Camphor derived enaminones **16** and **17** and products obtained by substitution of the dimethylamino group **43**–**49**

Compound	*R*	Yield/%
16		43
17		44
43a, **44a**	CH_2CN	81, 34
43b, **44b**	CH_2COOMe	76, 40
43c, **44c**	CH_2CH_2COOEt	54, 30
43d, **44d**	$CH(CH_2CH_2COOEt)COOEt$ (*S*)	54, 41
44e	$CH(Me)COOEt$ (*S*)	36
44f	$CH[CH(OH)Me]COOEt$ (*S*)	55
44g	$CH(CH_2Ph)COOMe$ (*S*)	43
44h	$CH[CH_2(4\text{-}HO\text{-}C_6H_4]COOMe$ (*S*)	64
44i	CH(1*H*-indol-3-yl)COO*Me* (*S*)	36
44j	(1-adamantyl)methyl	43
44k	propargyl	68
44l	*Ph*	67
44m	4-methylphenyl	41
44n	4-methoxyphenyl	29
44o	4-nitrophenyl	44
44p	2-aminophenyl	63
44q	4-hydroxyphenyl	59
44r	quinolin-3-yl	69
44s	pyrazinyl	41
44t	indazol-3-yl	35
44u	[1,2,4]-1*H*-triazol-3-yl	52
45		84
46		14
47		31
48		49
49a	*Me*	71
49b	*Et*	83
49c	*n-Bu*	68
49d	benzyl	67
49e	*Ph*	89
49f	ethynyl	35

deca-2(6),4-dienes **52a**–**52c** in 63–83% yields. On the other hand, from lactone **17** and hydrazines **50a** and **50d**–**50j**, two types of products were formed, 7-oxa-4,5-diazatricyclo[6.2.1.$0^{2,6}$]undeca-2(6),3-dienes **55d**–**55f** and pyrazolones **56a** and **56g**–**56j**. Formation of both types of products can be explained by initial substitution of the dimethylamino group to give the enehydrazine **53** followed by addition of the second amino group to the lactone carbonyl group. From the intermediate **54**, elimination reaction can occur, either by elimination of water leading to pyrazolo fused lactones **55** (Path A), or by elimination of the alcohol moiety (opening of the lactone ring) leading to 'ring switched' pyrazolones **56** (Path B). This explanation is also in agreement with formation of hydroxy and alkoxy pyrazoles from hydrazines and β-keto esters [29]. Selectivity was dependent on the substituents attached to the hydrazino group. With *ortho*-unsubstituted phenylhydrazines **50d**–**50f** fused pyrazoles **55d**–**55f** were formed, whereas from hydrazine hydrochloride (**50a**) and *ortho*-substituted phenylhydrazines **50g**–**50j** the pyrazolones **56a** and **56g**–**56j** were obtained [28] (Scheme 6, Table 5).

Enaminone **16** was also employed in one-pot stereoselective syntheses 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 **60a**–**60g**. Treatment of **16** with α-hydrazinoazines **57a**–**57g** followed by oxidative cyclisation with methanolic bromine and chromatographic purification afforded, stereoselectively, the *endo*-isomers of 3-heteroarylcamphors **60a**–**60g** in 37–79% yields and in 68–94% d.e. Isomerically pure or isomerically enriched compounds **60a**–**60g** were obtained upon crystallisation. This one pot



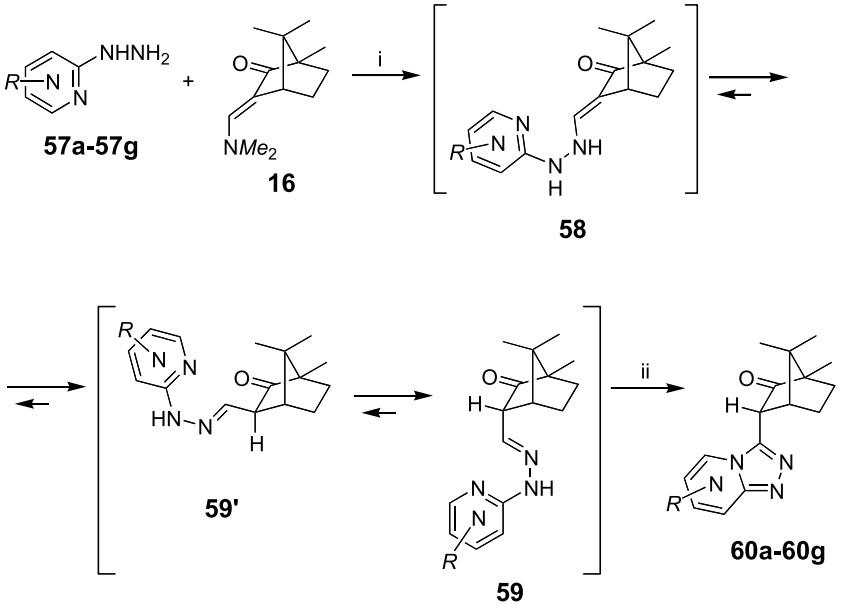
Scheme 6. Reagents and conditions: i) *R*NHNH$_2$ × HCl **50a**–**50c**, *Me*OH or *Ac*OH, reflux; ii) *R*NHNH$_2$ × HCl **50a**, **50d**–**50j**, *n-Pr*OH, reflux

Table 5. Cyclocondensation products **52**, **55**, and **56**

Compound	*R*	Yield/%		
		52	**55**	**56**
52a, **56a**	H	81		83
52b	benzyl	63		
52c	6-hydroxypyridazin-3-yl	83		
55d	*Ph*		91	
55e	3-methylphenyl		74	
55f	4-methylphenyl		85	
56g	2-methylphenyl			70
56h	2-chlorophenyl			61
56i	2-bromophenyl			63
56j	perfluorophenyl			56

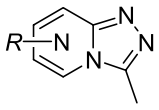
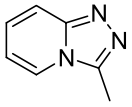
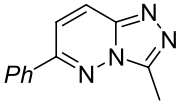
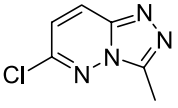
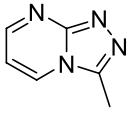
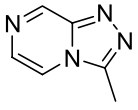
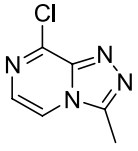
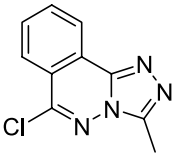
transformation proceeds by initial substitution of the dimethylamino group to give the enehydrazines **58** which tautomerise into the hydrazono forms **59** and **59′**. Further oxidative cyclisation of hydrazones **59**/**59′** leads to 1,2,4-triazolo[4,3-*x*]azine derivatives **60a**–**60g** [26] (Scheme 7, Table 6).

Similar treatment of **17** with α-hydrazinoazines **57a**–**57e** followed by oxidative cyclisation with lead tetraacetate led to two types of products, 1,2,4-triazolo[4,3-*x*]azine derivatives **63a**–**63e** and diazenes **64a**–**64e**. In the pyridazine series, 1,2,4-triazolo[4,3-*b*]pyridazines **63b** and **63c** were the major products, whereas



Scheme 7. Reagents and conditions: i) *Me*OH, 37% HCl (aq., 1 equiv), rt; ii) Br_2, *Me*OH, rt, then chromatographic purification

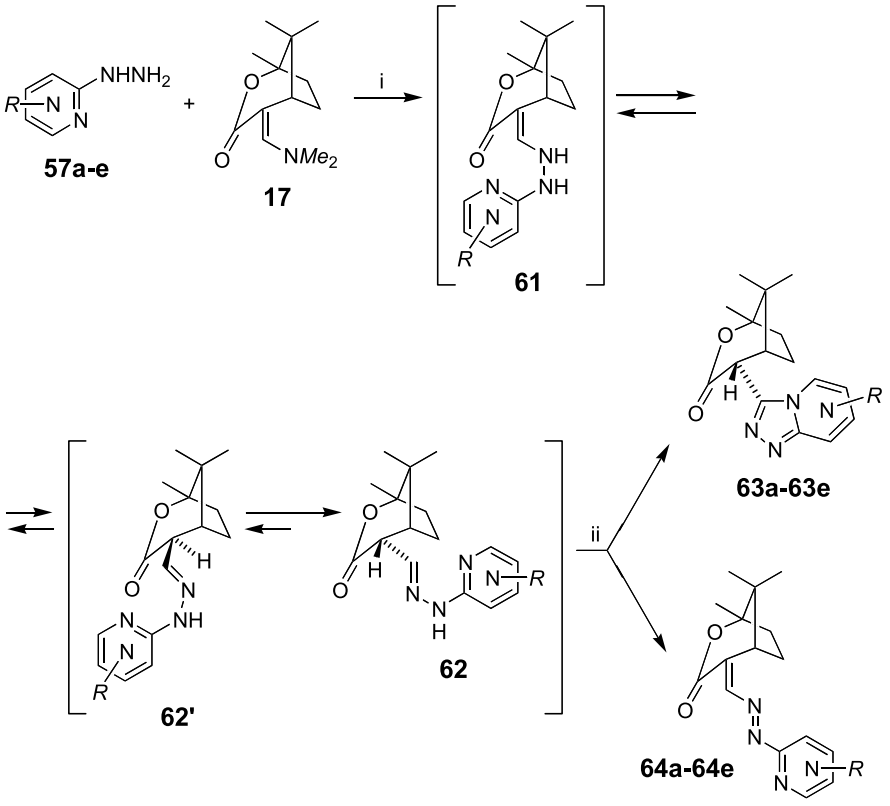
Table 6. 1,2,4-Triazolo[4,3-*x*]azines **60a–60g**

Compound		D.e./%	Yield/%
60a		68	37
60b		84	79
60c		94	71
60d		84	42
60e		72	59
60f		94	60
60g		92	61

predominant formation of diazenes **64a**, **64d**, and **64e** took place in the other three cases [28] (Scheme 8, Table 7).

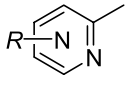
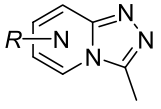
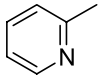
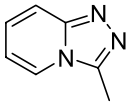
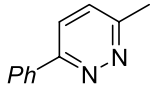
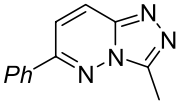
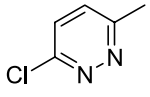
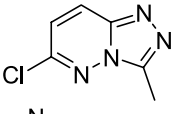
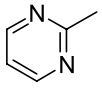
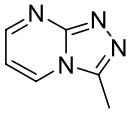
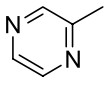
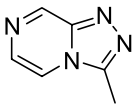
Further transformations of 3-heteroarylcamphors **60b–60e** were also studied. Catalytic hydrogenation of **60c–60e** under 50 bars of hydrogen resulted in saturation of the six-membered ring to give the tetrahydro analogues **65c–65e** in 73–93% yields. Bromination of **60b** in dichloromethane gave two isomeric α-bromination products **66** and **67** in 44 and 43% yield, respectively. Unfortunately, α-bromination was not stereoselective, since both isomers, **66** and **67**, were formed in 1:1 ratio. Isomers **66** and **67** were separated by medium pressure liquid chromatography (MPLC) and both structures were determined by X-ray analysis [28] (Scheme 9).

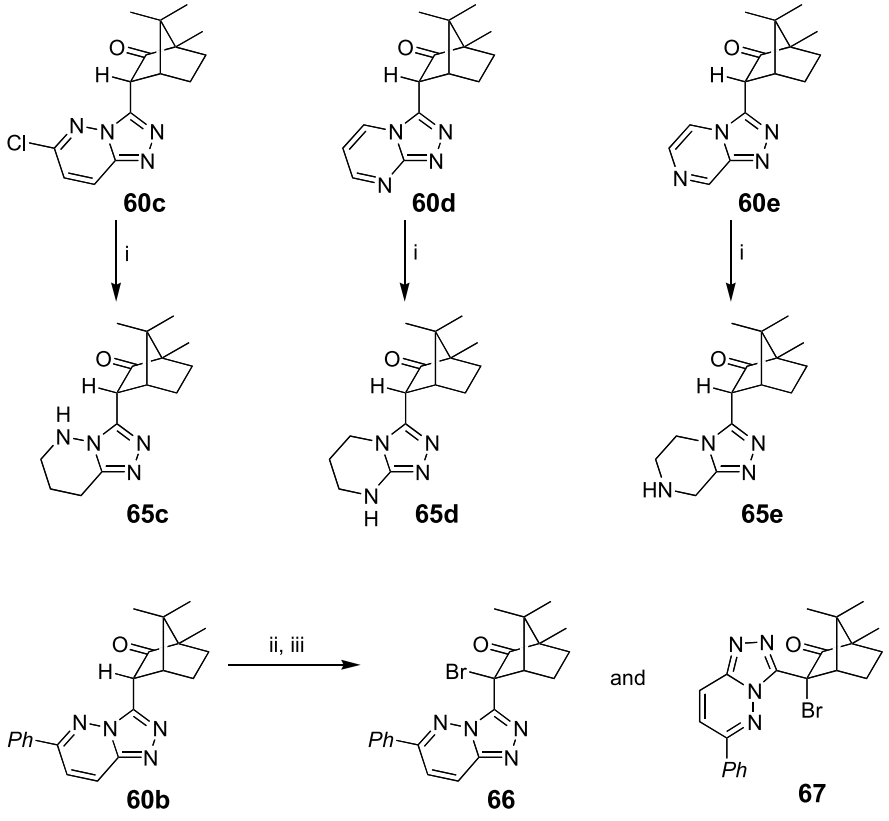
Upon treatment of compounds **60a–60c** and **60g** with borane–methylsulfide in dichloromethane under reflux, stable complexes with borane **68a–68c** and **68g** were obtained in 29–58% yields. X-Ray diffraction analysis of **68b** showed, that complexation of borane occurs at the N-1 in the 1,2,4-triazolo[4,3-*x*]azinyl residue.



Scheme 8. Reagents and conditions: i) *Me*OH, 97% H_2SO_4 (1 equiv), rt; ii) $Pb(OAc)_4$, CH_2Cl_2, rt, then chromatographic separation

Table 7. 1,2,4-Triazolo[4,3-*x*]azines **63a**–**63e** and diazenes **64a**–**64e**

Compound			D.e./%	Yield/%	
			63	**63**	**64**
63a, **64a**			66	11	50
63b, **64b**			94	52	10
63c, **64c**			90	46	29
63d, **64d**			54	4	54
63e, **64e**			70	6	42



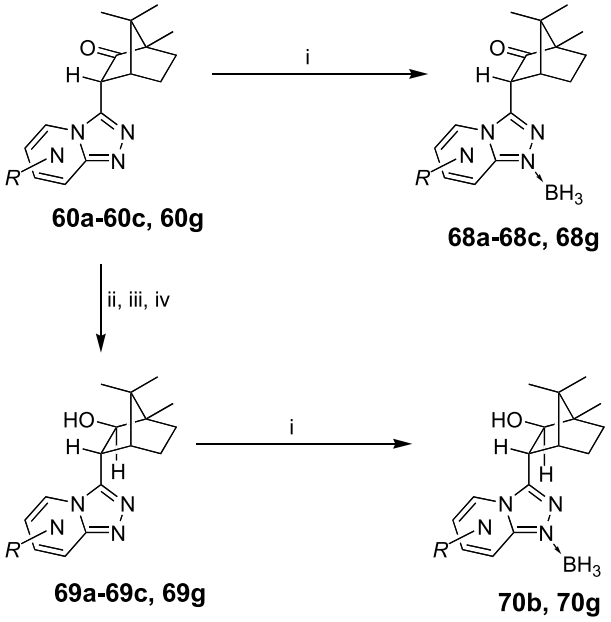
Scheme 9. Reagents and conditions: i) H_2 (50 bar), 10% Pd-C, *Et*OH, 50°C; ii) Br_2, CH_2Cl_2, rt; iii) chromatographic separation (MPLC)

On the other hand, activation of **60a–60c** and **60g** with 1 equivalent of boron trifluoride etherate followed by treatment with borane–methylsulfide and thorough chromatographic purification furnished the corresponding isoborneols **69a–69c** and **60g** in 39–62% yields. Upon treatment of isoborneols **69b** and **69g** with borane–methylsulfide in refluxing dichloromethane, complexes **70b** and **70g** were obtained in 23 and 10% yield, respectively [28] (Scheme 10, Table 8).

Synthesis of *C*-Nucleosides from *D*-Aldose Derived Hydrazones

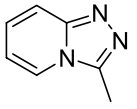
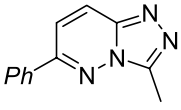
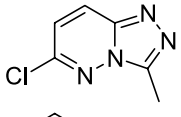
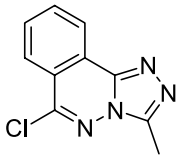
We have previously shown, that commercially available unprotected aldoses **71** can be transformed with α-hydrazinoazines **57** into the 1-(1,2,4-triazolo[4,3-*x*]azin-3-yl)polyols **73** using a 2 step one-pot protocol, which includes formation of aldose (*N*-azinyl)hydrazones **72** followed by oxidative cyclisation with methanolic bromine [30]. Similarly, cyclic *O*-protected analogs **79–83** were prepared from suitably protected aldehydo sugars **74–78** [30, 31] (Scheme 11).

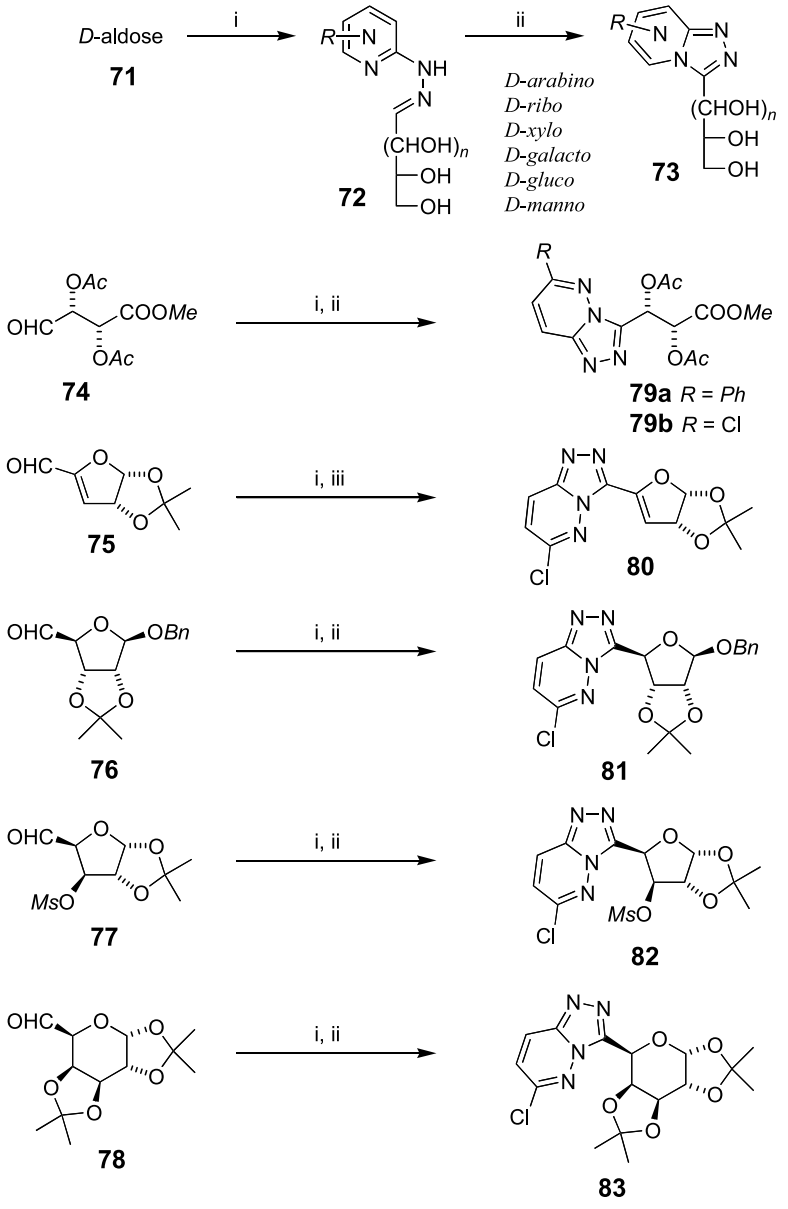
Acetonisation of *D*-glucose derived arabinitol **73a** led to a mixture of two regioisomeric bis-ketals **84** and **85**, which were separated by MPLC or crystallization. Acetonisation of *D*-mannose derived arabinitol **73b** led regioselectively to 2,3:5,6-di-*O*-isopropylidene-*D*-arabinitol **86**. In order to carry out transformation



Scheme 10. Reagents and conditions: i) $BH_3 \times Me_2S$, CH_2Cl_2, reflux; ii) $BF_3 \times Et_2O$, CH_2Cl_2, 0°C; iii) $BH_3 \times Me_2S$, CH_2Cl_2, 0–20°C; iv) chromatographic separation: first column chromatography followed by medium pressure liquid chromatography (MPLC)

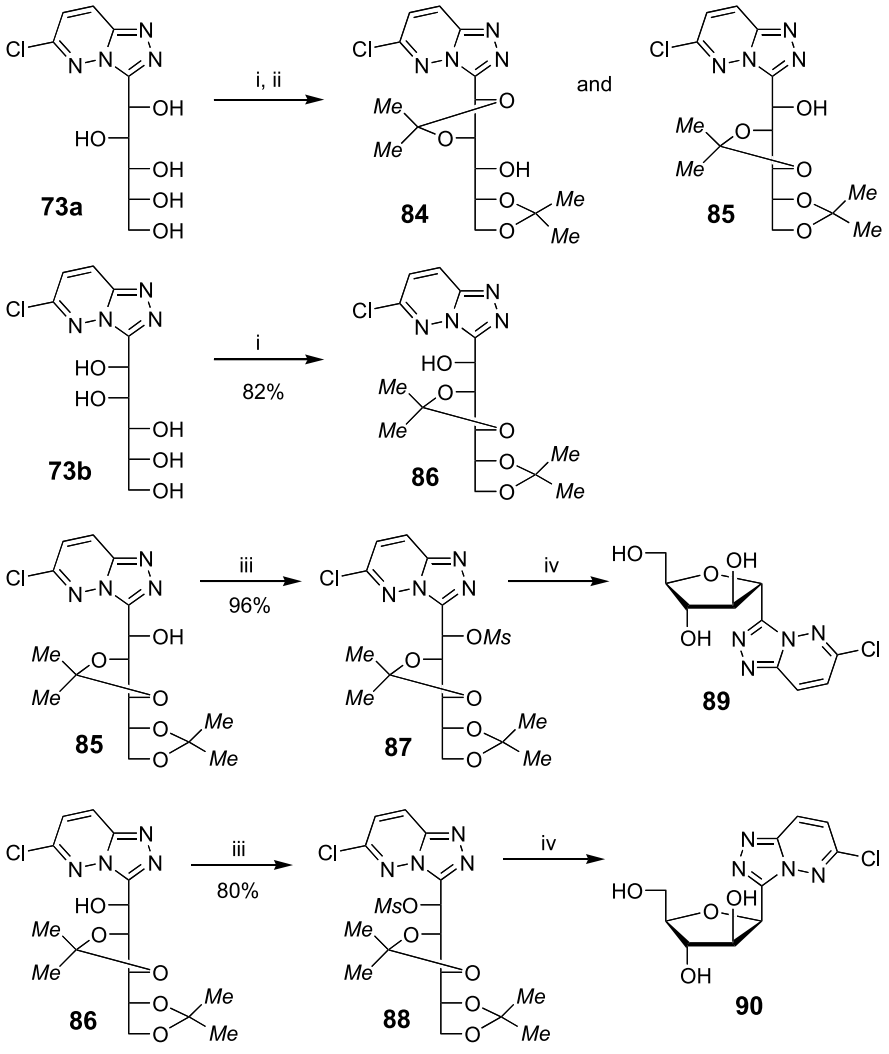
Table 8. Borane-1,2,4-triazolo[4,3-*x*]azines **68a**–**68c**, **68g**, **70b**, and **70g** and isoborneols **69a**–**69c**, and **69g**

Compound		Yield/%		
		68	**69**	**70**
68a, **69a**		58	58	
68b–**70b**		58	62	23
68c, **69c**		29	57	
68g–**70g**		34	39	10



Scheme 11. Reagents and conditions: i) α-hydrazinoazine **57**, *Me*OH, 37% HCl (aq., cat.), rt-reflux; ii) Br_2, *Me*OH, rt; iii) $Pb(OAc)_4$, CH_2Cl_2, rt

of bis-ketals **85** and **86** into *C*-nucleosides **89** and **90**, a slightly modified synthetic protocol, reported previously by *Buchanan et al.* [32], was employed. Thus, compounds **85** and **86** were mesylated and the mesylates **87** and **88** were then heated in 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 (**89**) and its β-anomer **90** in 81 and 54% yield, respectively. The β-anomer **90** was obtained in the form of its HCl salt and its structure was determined by X-ray diffraction [33] (Scheme 12).



Scheme 12. Reagents and conditions: i) acetone, 97% H_2SO_4, rt; ii) chromatographic separation or crystallisation; iii) *Me*SO_2Cl (*Ms*Cl), pyridine, 0°C; iv) 1,2-dimethoxyethane, 4% HCl (aq., 1 equiv), reflux

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