1,3-Dipolar Cycloadditions of Diazoalkanes to Pyridazines. Asymmetric 1,3-Dipolar Cycloadditon of Azomethine Imines Derived from Diazoalkane-Pyridazine Cycloadducts

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Contents:

i) Introduction.

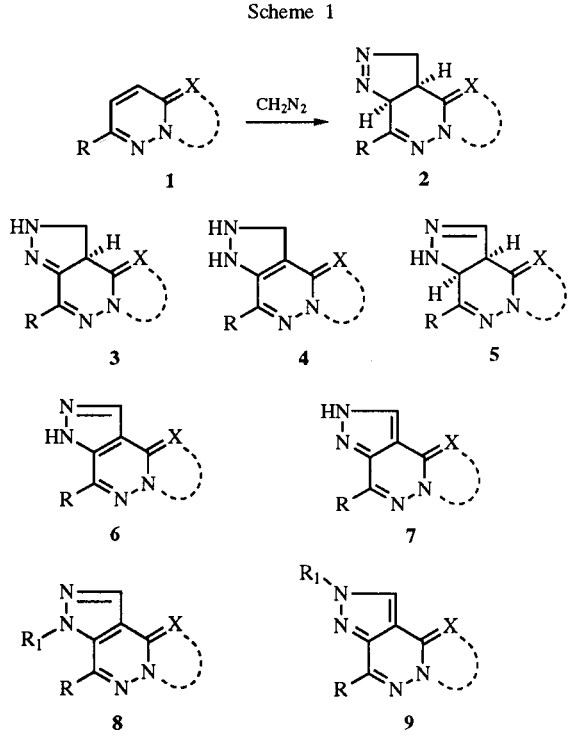
Since the discovery of aliphatic diazo compounds towards the end of the previous century [1-4], they have played an important role in 1,3-dipolar cycloaddition reactions [5] to the systems with double and triple bonds, heteromultiple bonds and heterocumulenes to form five-membered rings [6]. In aromatic and heteroaromatic series, there are only sporadic examples of cycloadditions to five- and six-membered rings reported in the literature, since these systems are less reactive and therefore the diazoalkanes have been frequently used as a source for carbenes in cyclopropanation reactions to produce norcaradienes and cycloheptatrienes and their aza-analogs [6].

In heterocycles a regiospecific cycloadditions to some highly substituted nitrogen-containing systems, such as imidazoles [7], pyridinones [8], diazepines [9] and oxygen-containing heterocycles, such as furanones [10-13] have been reported. In azolo[1,5-*a*]pyridine series the formation of bis-cycloadducts has been observed [14] and in the pyrrolo[1,2-*a*]pyrimidine series three cycloadducts have been isolated [15].

ii) Cycloadditions of Diazoalkanes to Pyridazines.

Cycloaddition of diazomethane to monocyclic pyridazine derivatives and bicyclic azolo- and azinopyridazines with a bridgehead nitrogen atom, of general formula **1** produces CH,CH-dihydro cycloadducts **2**, which can be transformed by sigmatropic rearrangements into CH,NH- and NH,NH-dihydro cycloadducts **3-5**. The reaction proceeds regiospecifically to the partially localized and polarized C_4-C_5 double bond in monocyclic pyridazines or to C_7-C_8 double bond in azolopyridazines [16,17]. With less reactive diazoalkanes, such as 2-diazobutane, phenyldiazomethane, 1-diazo-1-phenylethane the corresponding primary CH,CH-dihydro products of the type **2**, and the rearranged NH,CH-dihydro cycloadducts of the types **3** and **4** have been isolated [18]. By cycloaddition of diazomethane the formation of the primary CH,CH-dihydro cycloadduct is followed by dehydrogenation and sigmatropic rearrangement giving the tautomeric intermediates **6** and **7**. *N*-Methylation of these tautomers with an excess of diazomethane yields mixtures of the corresponding isomeric pairs **8** (R_1 = Me) and **9** (R_1 = Me) [19-21] (Scheme 1).

Scheme 1



Due to this additional tautomerization and further methylation, systematic studies of 1,3-dipolar cycloadditions to pyridazines and fused pyridazines have been carried out with 2-diazopropane in order to avoid further transformations.

It has been reported that regiospecific 1,3-dipolar cycloaddition of 2-diazopropane to 2-methyl-6-phenylpyridazin-3(2*H*)-one (**10**) in diethyl ether gives a mixture of three products: 1,2-diazepine derivative **13**, 4-isopropyl derivative **14** and diazabicyclo[4.1.0]heptanone derivative **15**, presumably formed from the primary cycloadduct **11** [22]. When this reaction was reinvestigated, it turned out, that it is strongly dependent upon the solvent and temperature. The cycloadduct **11** could be isolated in pure form at temperatures below 0°, due to its low solubility in diethyl ether. At room temperature, the secondary reactions were observed, in which the intermediate **11** is transformed in three different ways. In the presence of an acid, the isomerization into NH,NH-dihydro intermediate **12** takes place. In the presence of oxygen from the air dehydrogenation is the main process producing pyrazolo[3,4-*d*]-pyridazine derivative **16**, while elimination of a molecule of nitrogen from the pyrazole part of the bicyclic system followed by rearrangement, gives a mixture of **13-15**. The relative proportion of the products formed according to these three pathways is strongly dependent upon the solvent used in the reaction. In polar solvents, such as dimethylformamide, methanol and ethanol, in the presence of air, **11** is quantitatively dehydrogenated affording **16**, while in less polar solvents, in which oxygen is less soluble, such as acetonitrile, dioxane, ethyl acetate, benzene, and other compounds, **13-15** are formed [23] (Scheme 2).

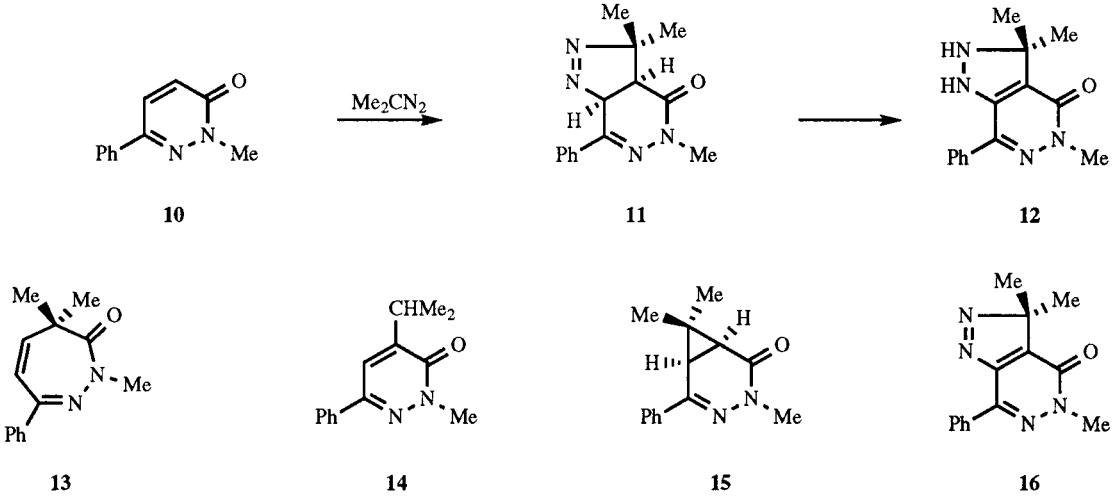
Oxidation of **11** and **12** could be achieved with a variety of oxidizing agents, such as oxygen and bromine. The simplest method is oxidation by air in the presence of a base. The transformation is practically quantitative to give **16** as the only product. Catalytic hydrogenation of **16** over Pd/C produces **11** as the only product [23].

iii) Directed Regiospecificity.

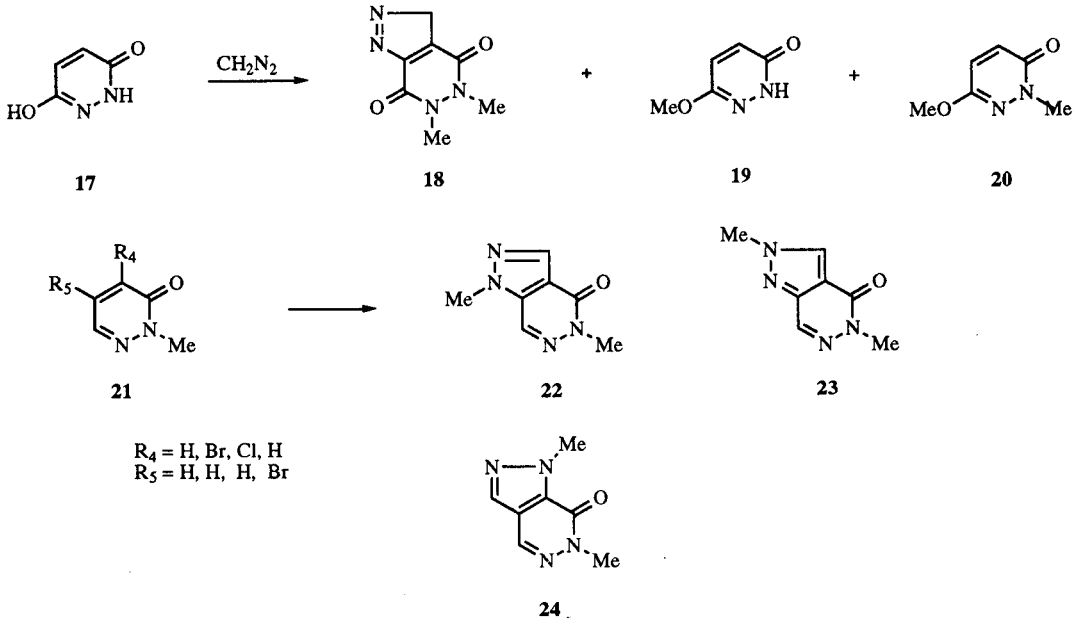
The cycloaddition of diazomethane to pyridazine derivatives has been first observed as a side reaction by methylation of 6-hydroxypyridazin-3(2*H*)-one **17** in which besides *O*-methyl- **19** and (*O*,*N*)-dimethyl- **20** also the corresponding pyrazolo[3,4-*d*]pyridazine derivative **18** was formed in 9% yield [24,25] (Scheme 3). *N*-Methylpyridazin-3(2*H*)-ones **21** give with diazomethane *N*-methylpyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones **22** and **23** as the major products and isomeric -7(6*H*)-one derivatives **24**, as the minor product [26] (Scheme 3).

1,3-Dipolar cycloadditions of diazoakanes 4- and 5-unsubstituted pyridazin-3(2*H*)-ones is regiospecific producing in most cases pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones as the major products and in some instances the corresponding -7(6*H*)-ones as the minor products. However, the cycloadditions are regiospecifically controlled by the position of substituents. When 4-substituted 6-methoxy-2-methylpyridazin-3(2*H*)-ones **26** are treated with 2-diazopropane in a mixture of chloroform and diethyl ether in the presence of triethylamine the corresponding 3*H*-pyrazolo[3,4-*d*]-pyridazin-7(6*H*)-one **28** is formed as the only product after elimination of a molecule of HX from the primary cycloadducts **27**. On the other hand, 5-substituted derivatives **29** afford the isomeric -4(5*H*)-ones **31** as the only product, while 6-methoxy-2-methylpyridazin-3(2*H*)-one (**25**) gives a mixture of **28** (5%) and **31** (82%) [27,28] (Scheme 4).

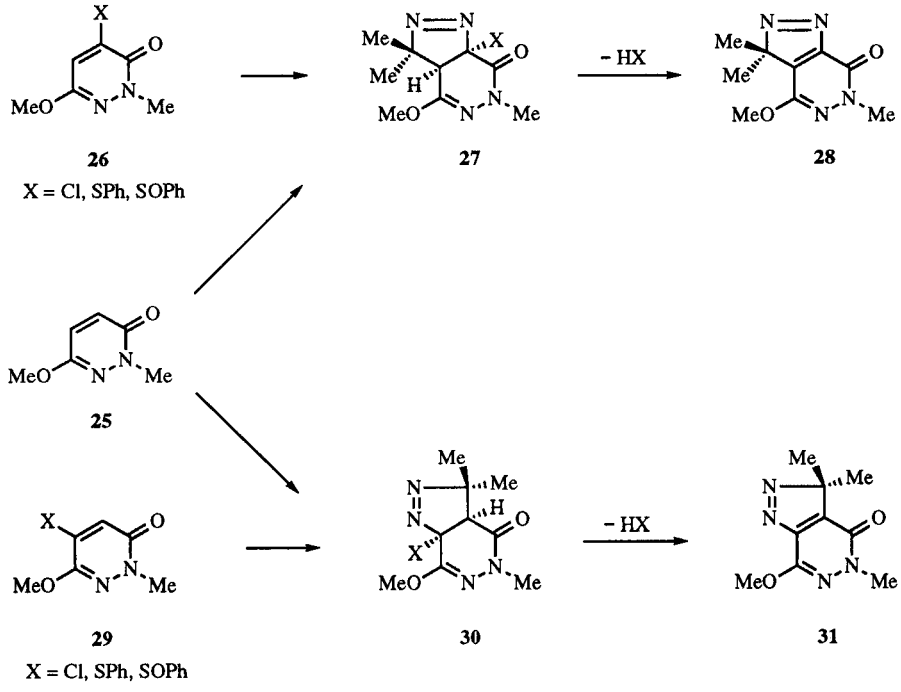
Scheme 2



Scheme 3

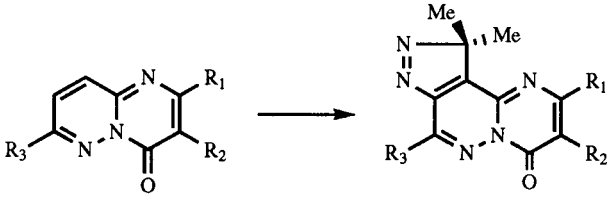


Scheme 4



Cycloadditions of diazoalkanes to bicyclic heteroaromatic 10π-electron systems with a bridgehead nitrogen atom, such as imidazo[1,2-*b*]pyridazine, *s*-triazolo[4,3-*b*]-pyridazine, *s*-triazolo[1,5-*b*]pyridazine, and tetrazolo[1,5-*b*]-pyridazine proceed as a regiospecific cycloaddition to partially localized and polarized double bond C_7-C_8 followed by loss of a molecule of hydrogen from the primary or rearranged cycloadducts affording stable pyrazoloazolopyridazines. In this manner derivatives of the following systems were prepared: 9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine [29-31], 9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine [32], 9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[1,5-*b*]pyridazine [32] and 9*H*-pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine [33]. Similarly, cycloaddition takes place to the C_8-C_9 double bond in pyrimido[1,2-*b*]pyridazin-4(10*H*)-one **32** giving 10*H*-pyrazolo[4,3-*d*]pyrimido-[1,2-*b*]pyridazin-4(10*H*)-one derivatives **33** [34] (Scheme 5).

Scheme 5



32 **33**

iv) The Synthesis of Isomeric Pyrazolo[3,4-*d*]azolopyridazines.

Derivatives of pyrazolo[3,4-*d*]azolopyridazine fused systems can be prepared by azido-tetrazolo valence isomerization, observed earlier in tetrazolo[1,5-*b*]pyridazine system [35-39], from the corresponding pyrazolo[4,3-*d*]-tetrazolo[1,5-*b*]pyridazine systems. For example, the compound **34** gives with 2-diazopropane the corresponding 6-chloropyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine **35**. This was transformed by heating with hydrazine into hydrazino compound **36** and further transformed with nitrous acid into azido derivative **37**. When this is heated in dimethyl sulfoxide solution at 110°, the azido-tetrazolo isomerization produces a mixture of **37** and isomeric 7*H*-pyrazolo[3,4-*d*]tetrazolo[1,5-*b*]pyridazine derivative **38** in a ratio 4:1. In the reaction of **36** with a mixture of triethyl orthoformate and acetic anhydride 7*H*-pyrazolo[3,4-*d*]-*s*-triazolo[4,3-*b*]pyridazine derivative **39** was obtained. Similarly, derivatives of imidazo[1,2-*b*]pyrazolo[3,4-*d*]-pyridazine **41** were prepared [20,21] (Scheme 6).

Cycloaddition of 2-diazopropane to tricyclic systems, such as **42** occurs across C_4-C_5 double bond producing a mixture of the isomeric derivatives of **43** and **44** of the tetracyclic system 11*H*-pyrazolo[3,4-*d*]-bis-*s*-triazolo-[4,3-*b*:3',4'-*f*]pyridazine. The structure of both isomers were proven by independent syntheses starting from **45** and **48** by the reaction sequences **45** → **46** → **47** → **43** and **48** → **49** → **50** → **51** → **44**, respectively [40]. Similarly, the tricyclic system **52** gives derivatives of two isomeric tetracyclic systems **53** and **54** [33] (Scheme 7).

v) Transformations of Cycloadducts.

a) Thermal Reactions.

3,3-Dimethyl-3*H*-pyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones **55**, when heated in polyphosphoric acid at 120° for 30 minutes, give the isomeric N_2 methylated products **56** and C_{3a}-methylated isomers **57**. The isomeric -7(6*H*)-one **58** affords only the N_2-methylated product **59** [41]. From the NH,NH-dihydro derivative **80** elimination of methane takes place by heating in an inert solvent giving 1*H*-pyrazolo[3,4-*d*]pyridazine derivative **61** [23] (Scheme 8).

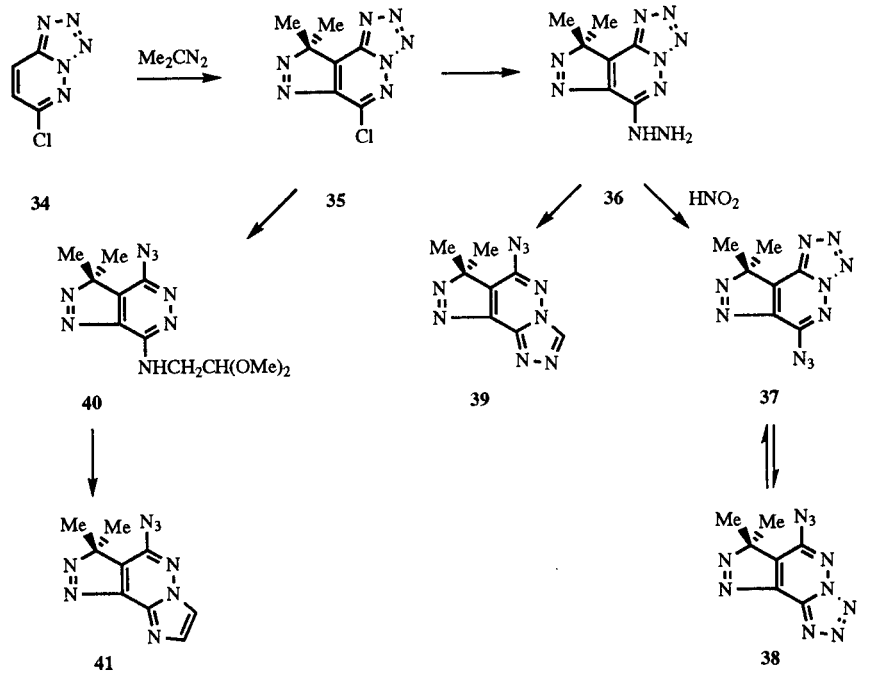
b) Photochemical Reactions.

The irradiation of compounds **62** leads to the loss of molecular nitrogen from the pyrazole part of the molecule in the first step to produce the diradical **63**. In the second step, when the reactions were carried out in a mixture of tetrahydrofuran and pentane 8-isopropenylazolopyridazines **65** are formed in 7-29% yield. Irradiation in methanol provides mixtures of products, from which **65** are isolated as the minor components (5-30%) and methyl ethers **66** as the major components (36-67%). Cyclopropa[*d*]pyridazine derivatives **64** were not isolated (Scheme 9). However, the 1,3-diradicals **63** react also with furan to form 1:1 adducts **67** in 56-70% yields, accompanied by small amounts of the alkenes **65** (8-12%). In the presence of buta-1,3-diene two types of addition products are formed. The major components are 7*H*-dihydrocyclohepta[*d*]pyridazine **68**, corresponding to 1,4-cycloaddition. The minor components correspond to 1,2-cycloaddition to form cyclopenta[*d*]pyridazines **69** [32,34,42,-43,44] (Scheme 9).

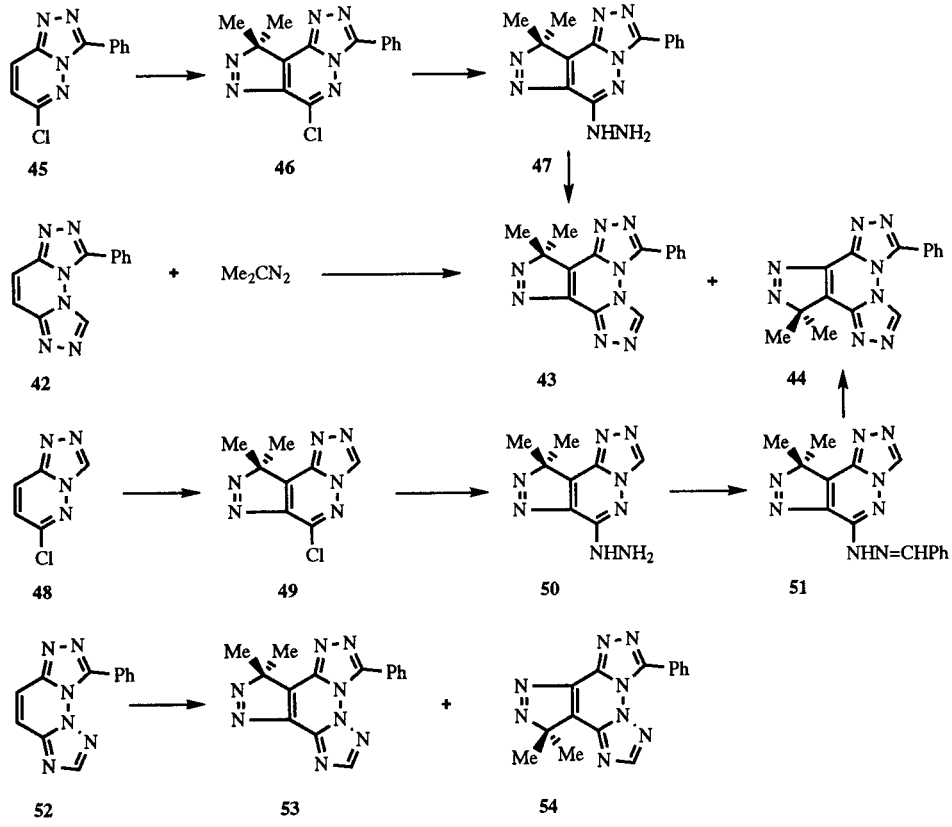
c) Ring Enlargements.

The cycloaddition of 2-diazopropane to 6-methoxy-2-methyl-5-phenylsulfonylpyridazin-3(2*H*)-one (**70**) produces the intermediate **71**, from which phenylsulfinic acid is not eliminated, contrary to the observation with other 5-substituted pyridazin-3(2*H*)-one derivatives. In this case, elimination of molecular nitrogen followed by rearrangement affords 1,2-diazepine derivative **72**. This reacts further, when an excess of 2-diazopropane is used, to give pyrazolo[3,4-*d*]-1,2-diazepine derivative **73** [27] (Scheme 10).

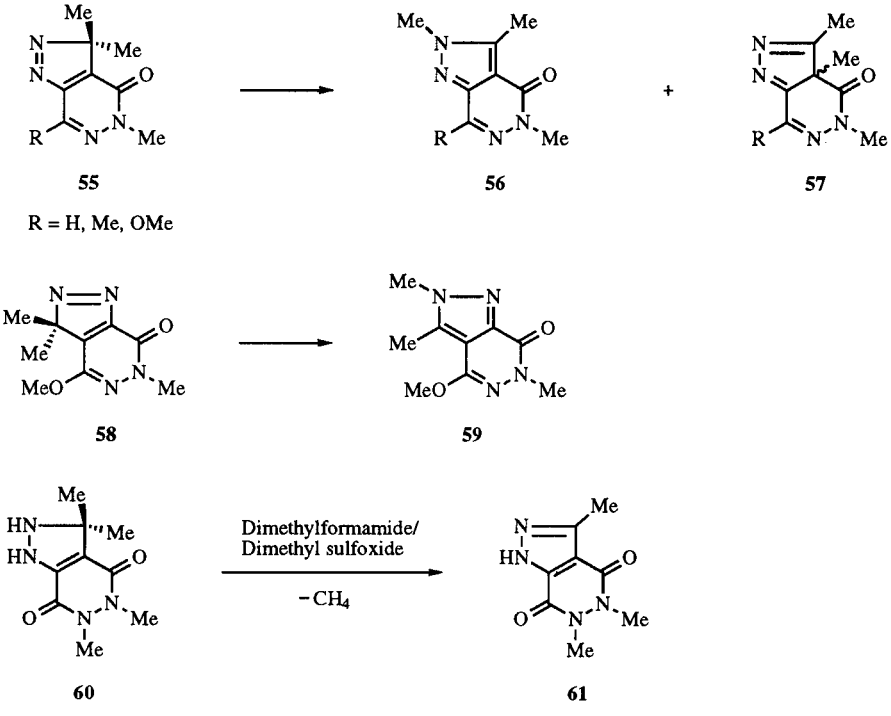
Scheme 6



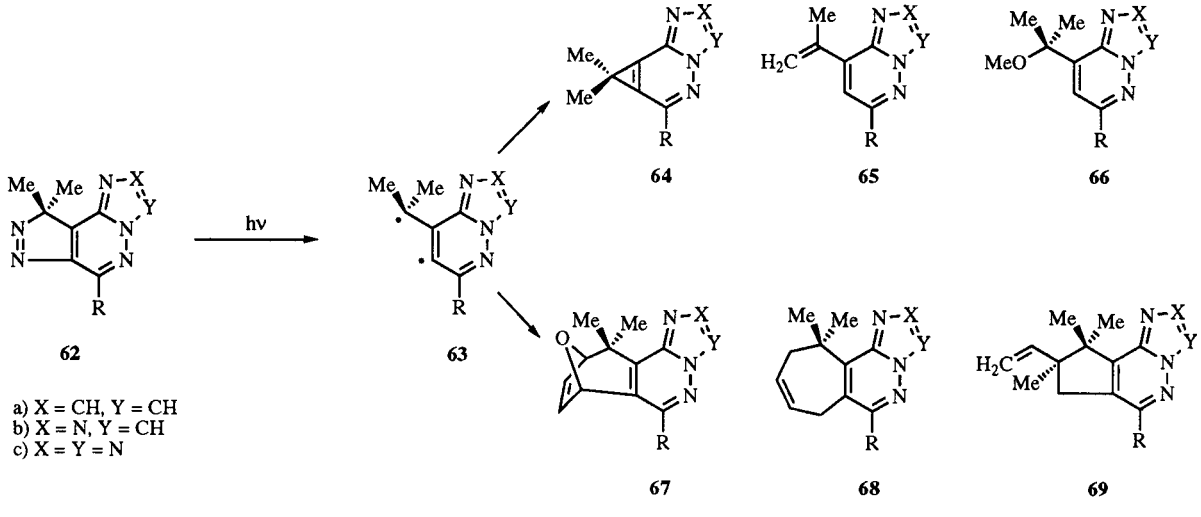
Scheme 7



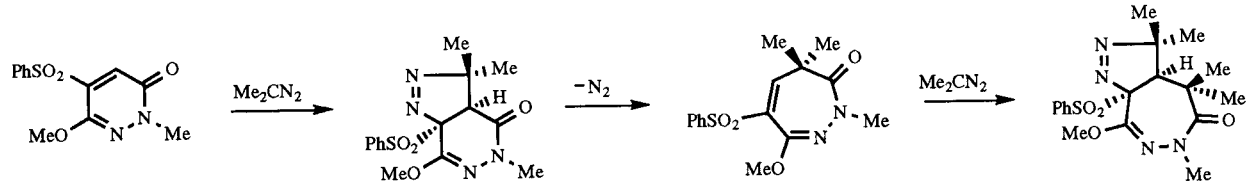
Scheme 8



Scheme 9



Scheme 10



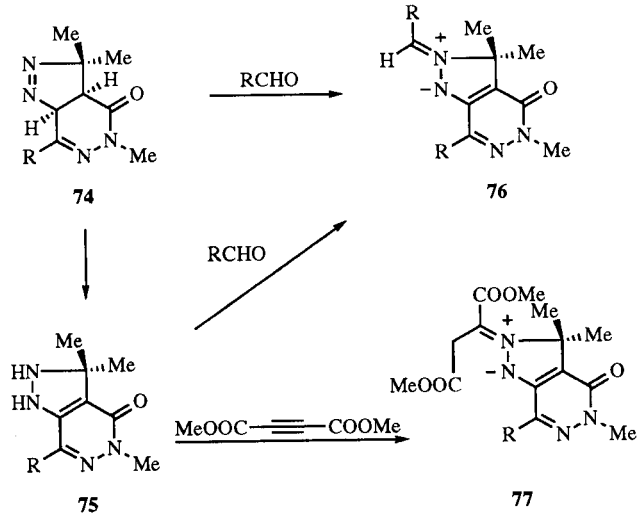
vi) Tranformations of Dihydrocycloadducts.

a) Formation of Azomethine Imines.

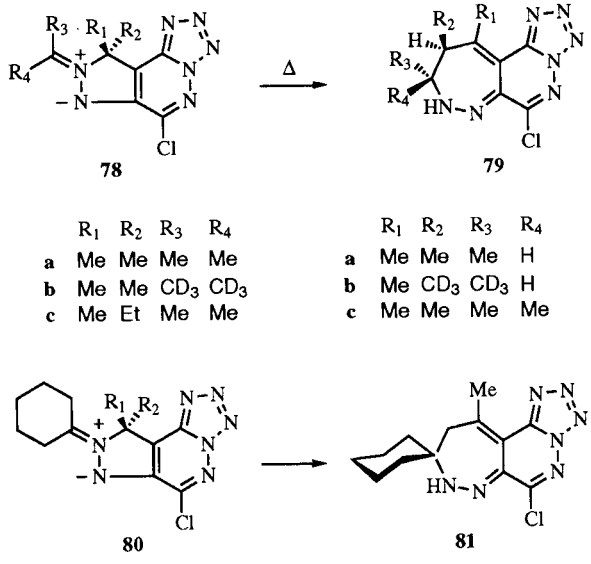
Azomethine imines are important intermediates as 1,3-dipoles in cycloadditions and electrocyclic reactions in which five-, six-, and seven-membered rings are formed [45].

The dihydro intermediates **74** and **75** react with aldehydes and masked aldehydes, such as *N,N*-dimethylformamide dimethyl acetal, and dimethyl acetylenedicarboxylate to give azomethine imines **76** and **77** [23] (Scheme 11).

Scheme 11



Scheme 12



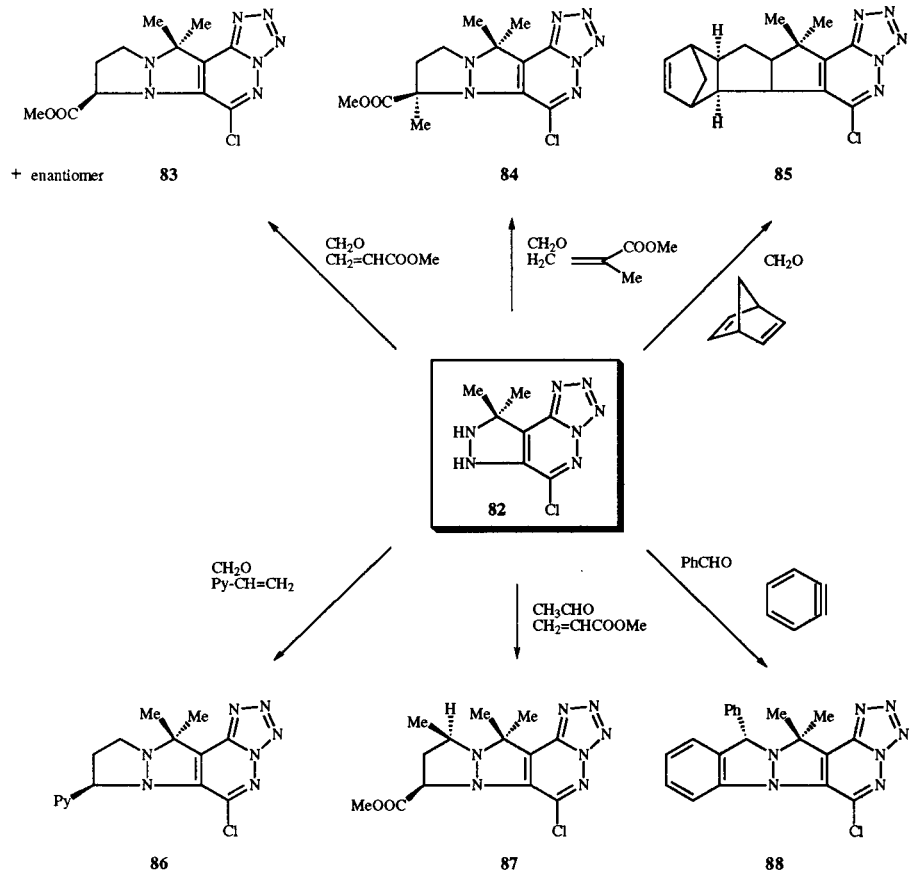
b) Thermal Rearrangements of Azomethine Imines.

An interesting thermal rearrangement was observed, when studying the chemical properties of these intermediates. Azomethine imines **78**, prepared from dihydro cycloadducts and ketones, are transformed by heating in xylene, into tetrazolopyridazinodiazepine derivatives **79** [46]. Similarly, the azomethine imine **80**, prepared from dihydro cycloadduct and cyclohexanone, gives the spiro compound **81** [47] (Scheme 12).

c) 1,3-Dipolar Cycloadditions of Azomethine Imines.

Azomethine imines react as 1,3-dipoles with unsaturated compounds, such as olefins, acetylenes and arynes. The azomethine imines can be prepared *in situ*. For example, compound **82** reacts with a mixture of formaldehyde and an unsaturated compound to give tetracyclic systems **83-87**, and with a mixture of benzaldehyde and benzyne to form the pentacyclic system **88** [47] (Scheme 13).

Scheme 13



This reaction sequence can be conveniently applied to the synthesis of γ-amino acid derivatives. For example, the NH,NH-dihydro cycloadduct **82** forms with the protected aminoacetaldehyde the corresponding azomethine imine **89**, which reacts with dimethyl acetylenedicarboxylate or dimethyl maleinate to give the corresponding pyrazolo[1',2':1,2]pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazine derivatives **90** and **91** [47], respectively. The structure of **91** was also confirmed by X-ray analysis [48] (Scheme 14).

d) Asymmetric 1,3-Dipolar Cycloadditions of Azomethine Imines.

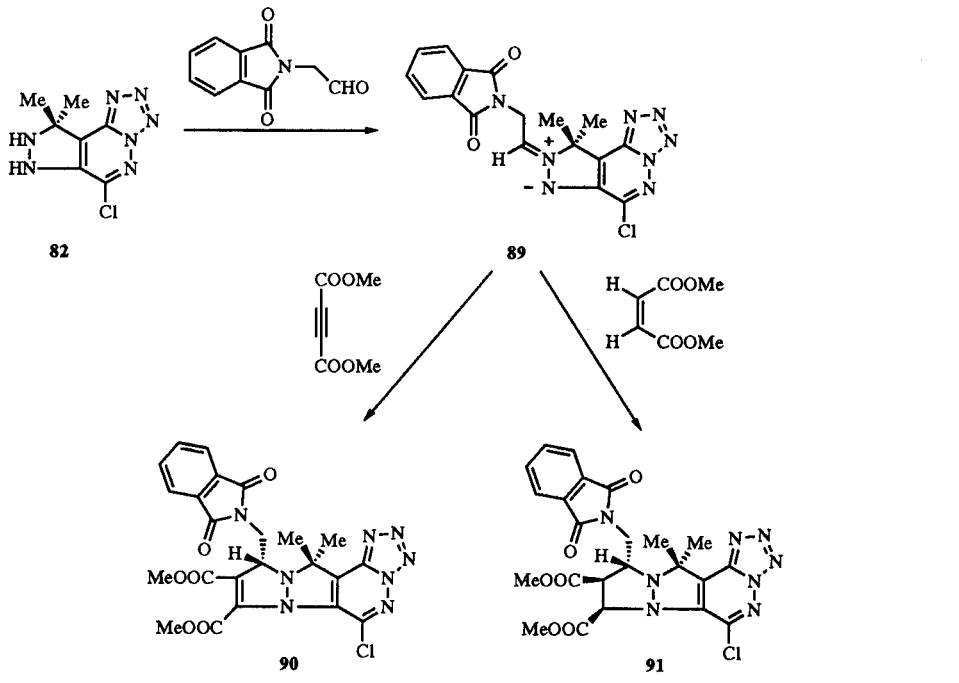
The development of asymmetric 1,3-dipolar cycloaddition reactions has in recent years entered a new stage. The selectivity challenge is to control regiodiastereo-, and enantioselectivity of this type of reactions.

There are four types of carbohydrate derivatives, which reacts as 1,3-dipoles in cycloaddition reactions, described in the literature. They are azides [49,50], nitrones [51-53], nitrile oxides [54], and diazo derivatives [55,56]. Only azides and acyclic diazo carbohydrates have been isolated in pure form, while the corresponding nitrones and nitrile oxides have been prepared *in situ* and used as such in further transformations.

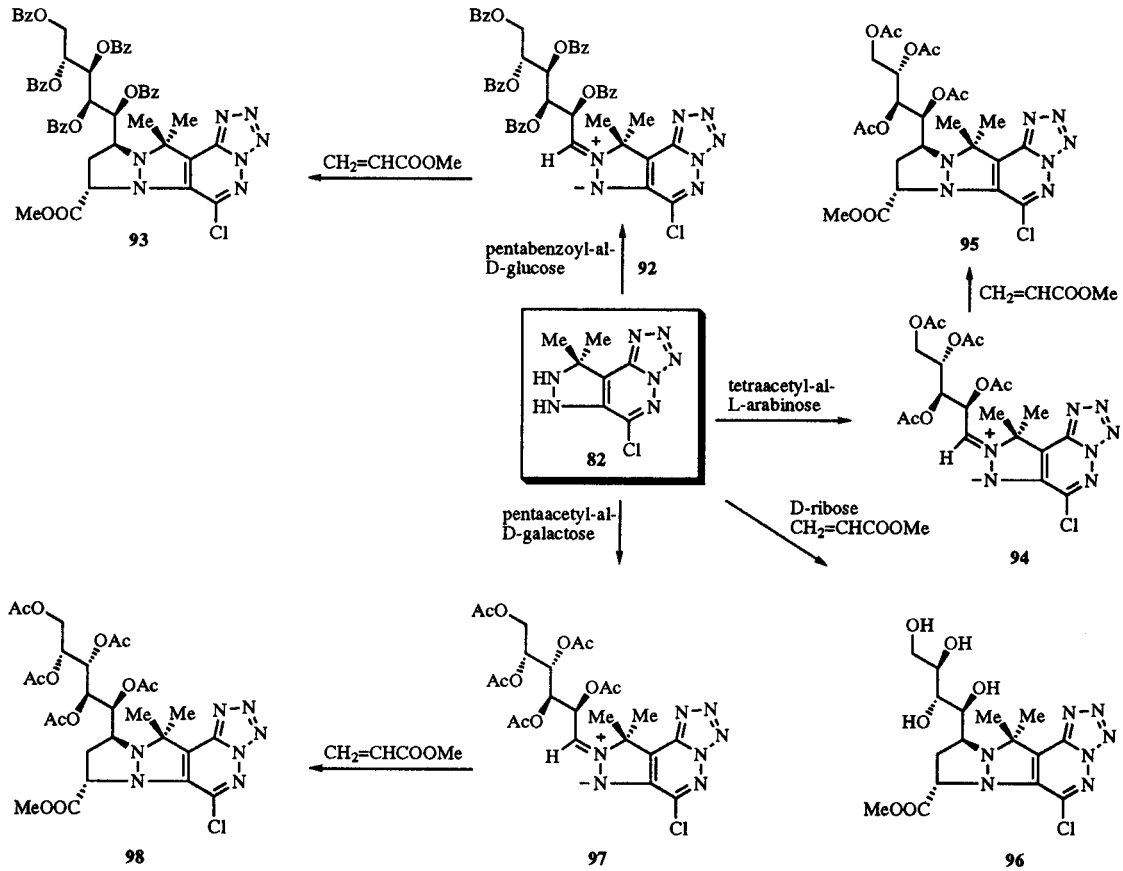
The use of azomethine imines in asymmetric 1,3-dipolar cycloadditions with alkenes is limited[57].

A new type of stable azomethine imines derived from 6-chloro-7,8-dihydro-9,9-dimethyl-9*H*-pyrazolo[4,3-*b*]tetrazolo[1,5-*b*]pyridazine (**82**) and carbohydrate derived aldehydes, such as tetra- and penta-*O*'-substituted aldehydo sugars: penta-benzoyl-al-D-glucose, tetraacetyl-al-L-arabinose and pentaacetyl-al-D-galactose to give the chiral azomethine imines **92**, **94**, and **97**, respectively. These, when heated with methyl acrylate as dipolarophile in acetonitrile produced the corresponding *O*'-acylated compounds **93**, **95**, and **98**, respectively. Compounds **95** and **98** were formed as pure (>95% d.e.) stereoisomers, while **93** contains around 10% of another isomer. The reaction can be carried out also as a one-pot synthesis. In this manner, the compound **82** was treated with D-ribose and methyl acrylate by heating in methanol in the presence of catalytic amounts of trifluoroacetic acid to give **96** [58,59] (Scheme 15). On the basis of this latter observation the reaction was extended to some other protected and unprotected sugars to give compounds **100-105** as pure (>95% d.e.) stereoisomers [60] (Scheme 16).

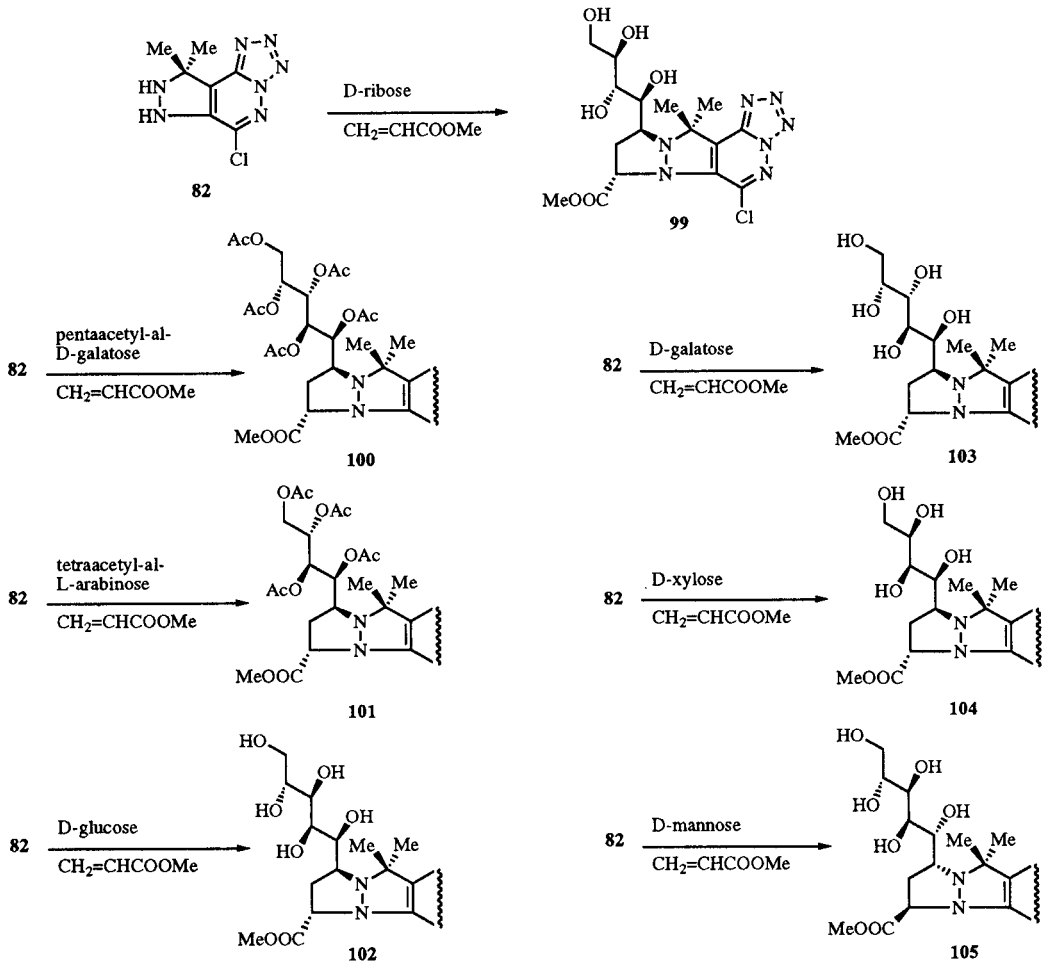
Scheme 14



Scheme 15



Scheme 16



In all these reactions two new chiral centers at C_8 and C_{10} are formed. Since the absolute configuration at $C_{1'}$ in the final product is given by the absolute configuration at C_2, *i.e.* at C atom α to the aldehydo group of the starting carbohydrate, the absolute configurations at C_8 and C_{10} can be determined by ^1H nmr data on the basis of the magnitude of coupling constants. It turned out, that compounds **106**, derived from 2'*R*-carbohydrates, *i.e.* carbohydrates with *R*-configuration at the C atom next to the aldehydo group, have the absolute configuration (1'*S*,8*S*,10*S*), while the compounds **107**, derived from 2'*S* carbohydrates, have the absolute configuration (1'*R*,8*R*,10*R*) [60]. The structure for compound **99** was confirmed by X-ray analysis [48] (Scheme 17).

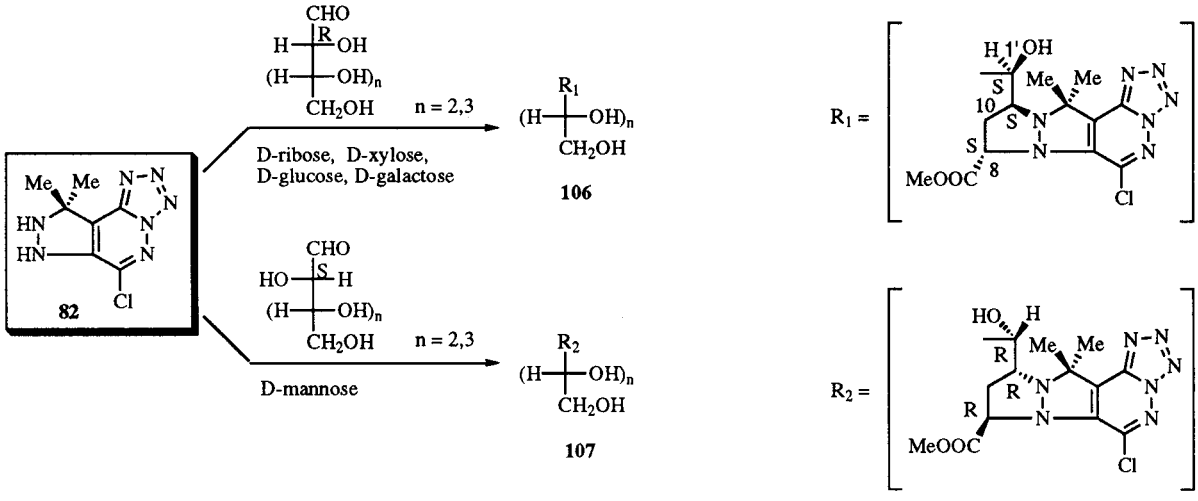
The reaction was extended to 1,2-dihydropyrazolo[3,4-*d*]-pyridazine derivatives **108**, which was transformed into azomethine imines **109**, **111**, **113**, and **115**, followed by treatment with methyl acrylate to give **110**, **112**, **114**, and **116**, respectively. However, in this case **116** was formed as pure (1'*S*,6*S*,8*S*) stereoisomer, **112** only in 70% de, **113** in 60% de, while **110** was obtained as a racemic mixture [61] (Scheme 18).

1,3-Cycloaddition of chiral azomethine imines to heterocyclic dipolarophiles, such as substituted *p*-toluyl phthalimide, proceeds nonstereospecifically. For example, the compound **108** was transformed into azomethine imine *in situ* followed by treatment with *N*-(*p*-toluyl)-phthalimide to give *C*-nucleosides **117-120**, each of them as a mixture of two diastereoisomers [61] (Scheme 19).

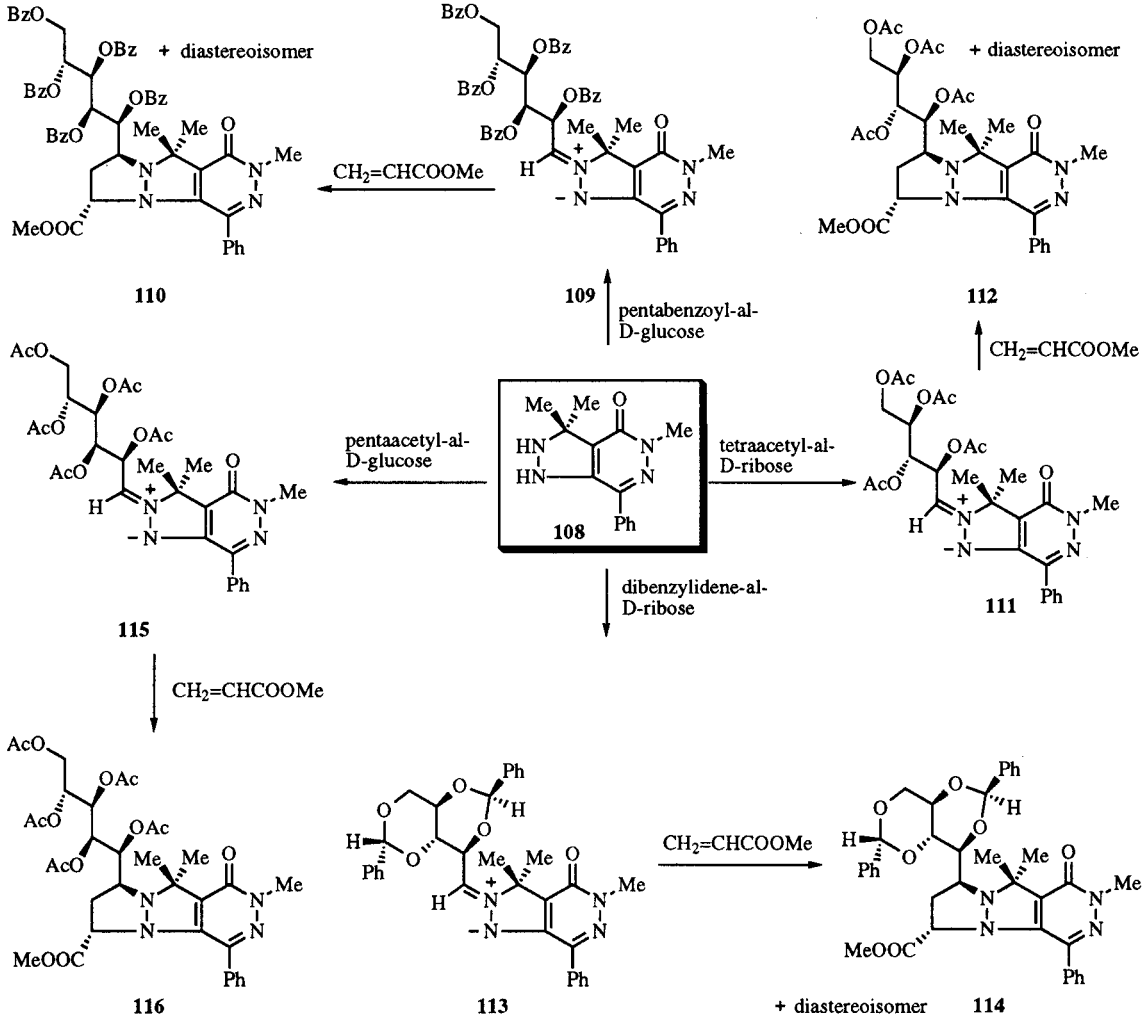
In order to test the generality of this stereochemical approach, compound **108** was treated with enantiomeric sugars, followed by addition of methyl acrylate. For example, D-glyceraldehyde and L-glyceraldehyde give enantiomers **121** and **122**, from D-arabinose and L-arabinose enantiomeric **123** and **126**, and **124** and **125** (Scheme 20), **127** and **128**, and **129** and **130** (Scheme 21) were obtained [62].

On the other hand, the cycloaddition of **108** to maleimide is non-stereospecific leading to formation of **131** and **132**, each of them being a mixture of diastereoisomers (Scheme 22). This can be explained by the tautomerization process **133** = **134** = **135** = **136** in which pyrrole ring is involved. (Scheme 23). On the other hand, when *N*-methylmaleimide is used, the enantiomeric pairs

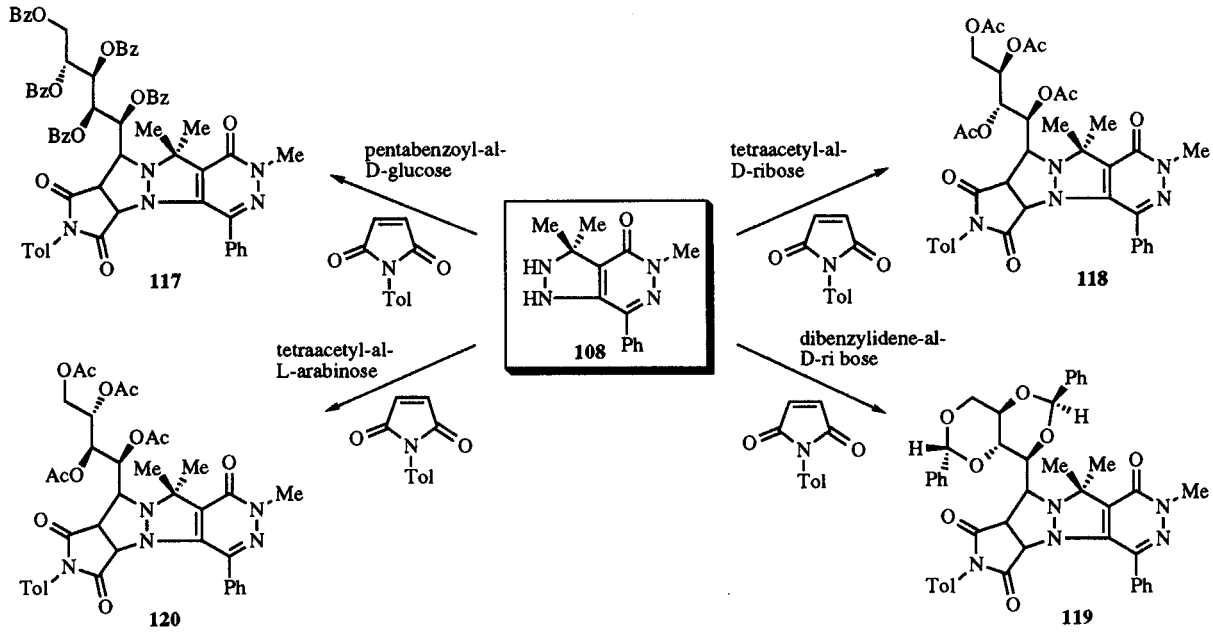
Scheme 17



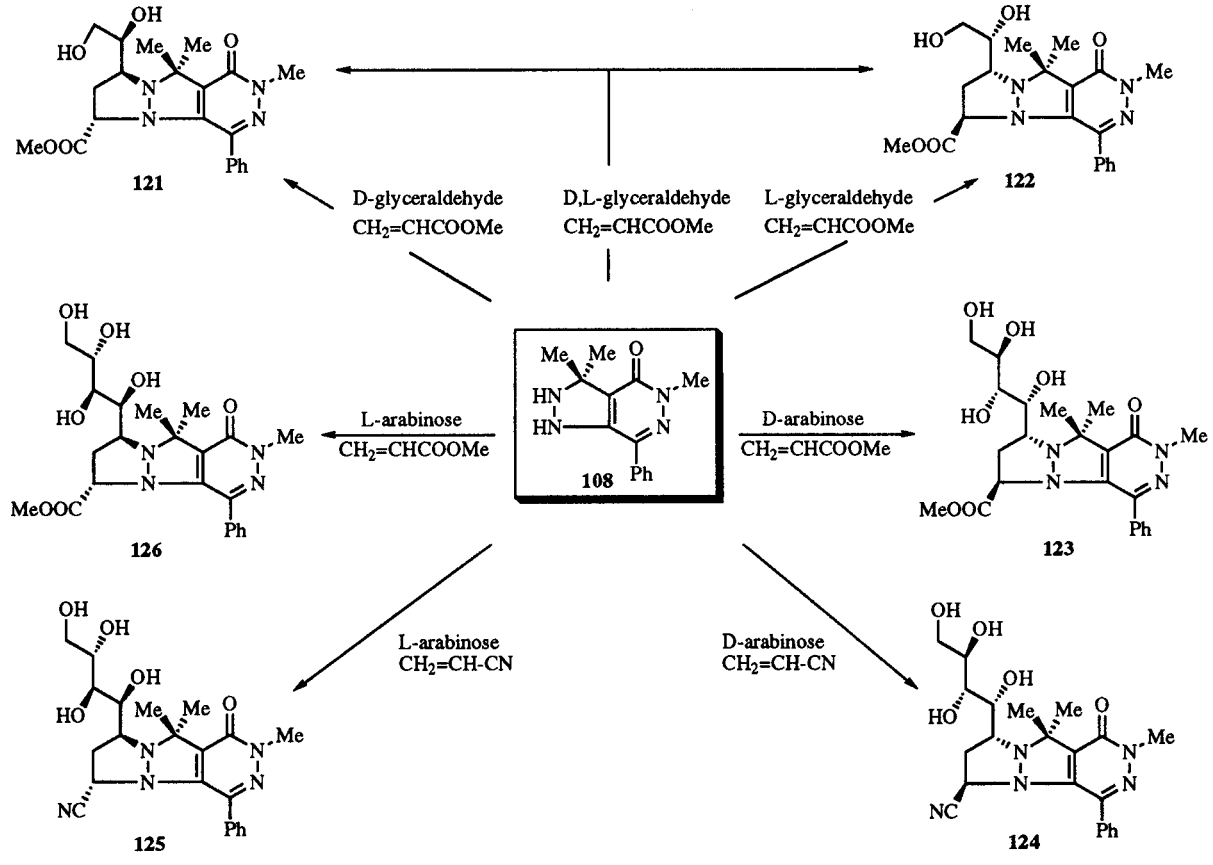
Scheme 18



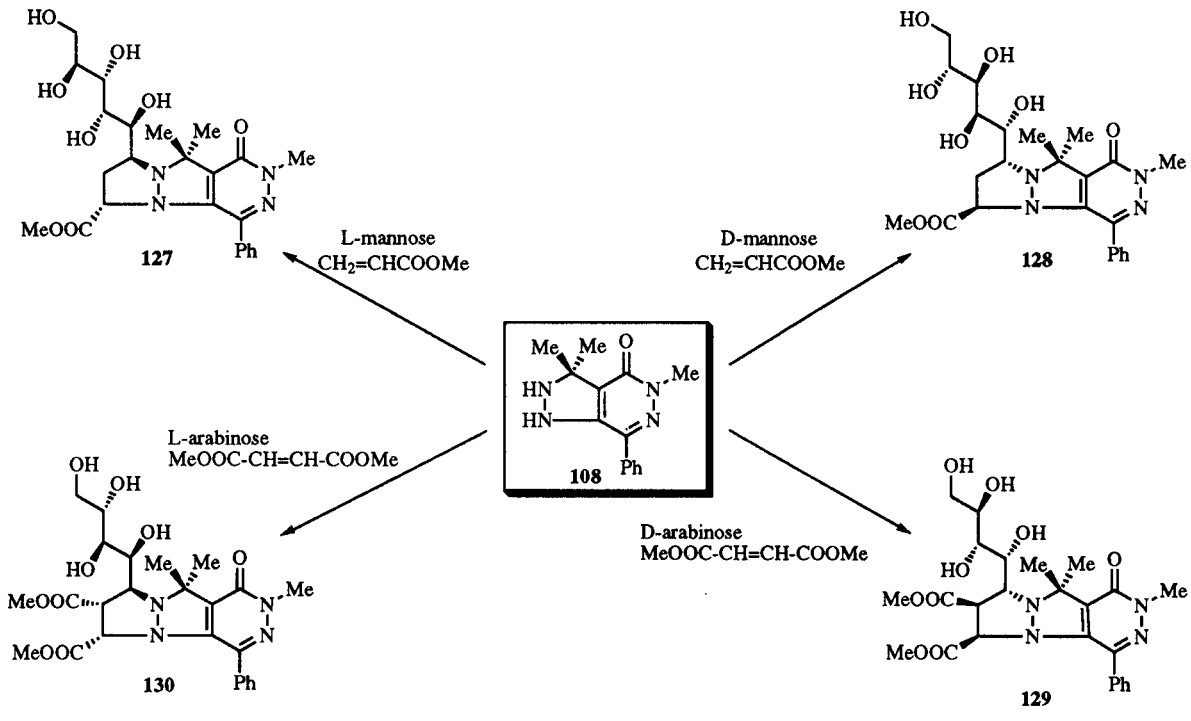
Scheme 19



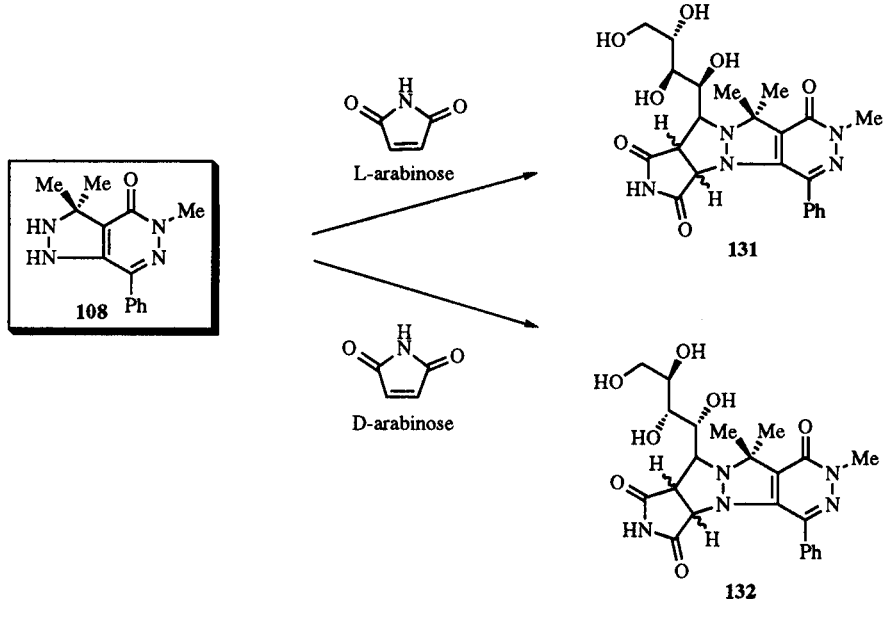
Scheme 20



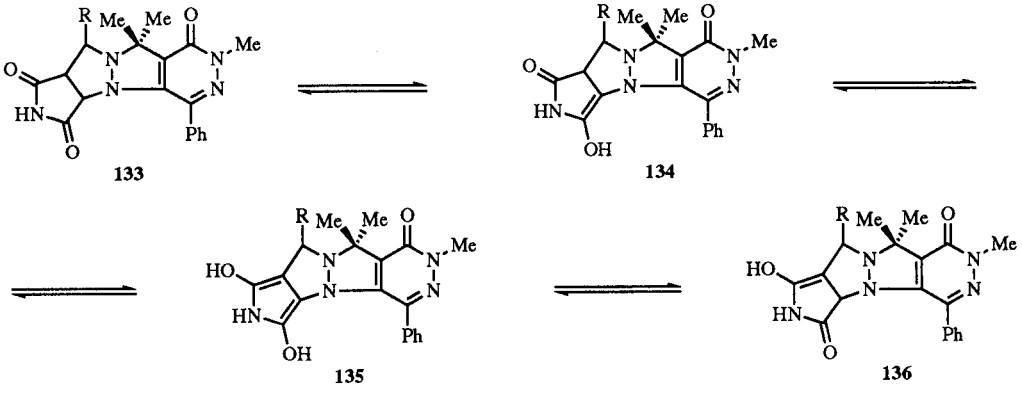
Scheme 21



Scheme 22



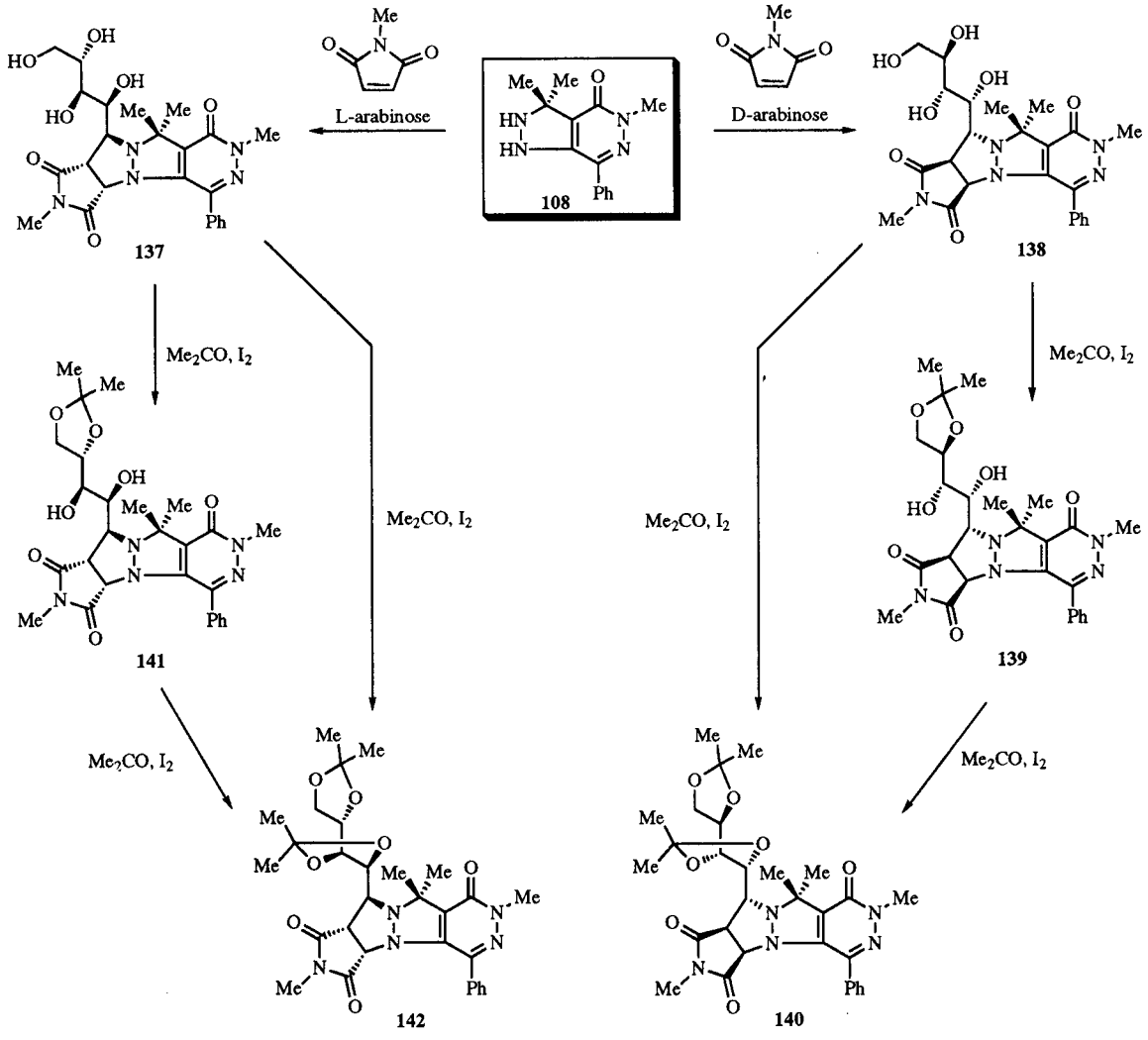
Scheme 23



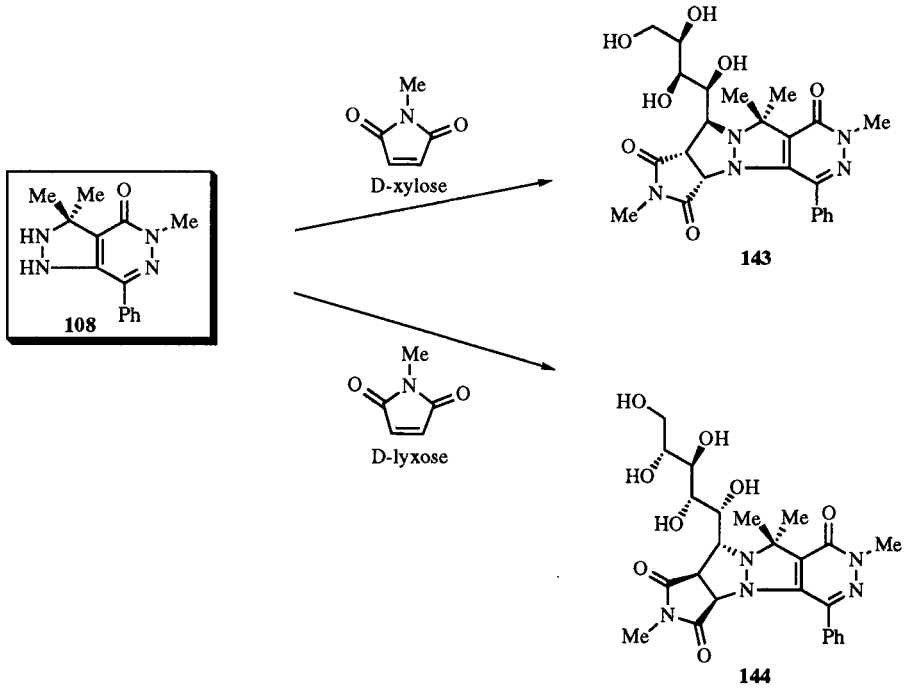
R = sugar chain

of sugars produce the enantiomeric pairs of *C*-nucleosides: **137** and **138**, **139** and **141**, **140** and **142** (Scheme 24). Also in these examples, the configuration is dependent upon the configuration at carbon atom next to the aldehydo group of sugar component. This is demonstrated by transformation of **108** with D-xylose and D-lyxose into **143** and **144** with opposite configurations on newly formed centers [62] (Scheme 25).

Scheme 24



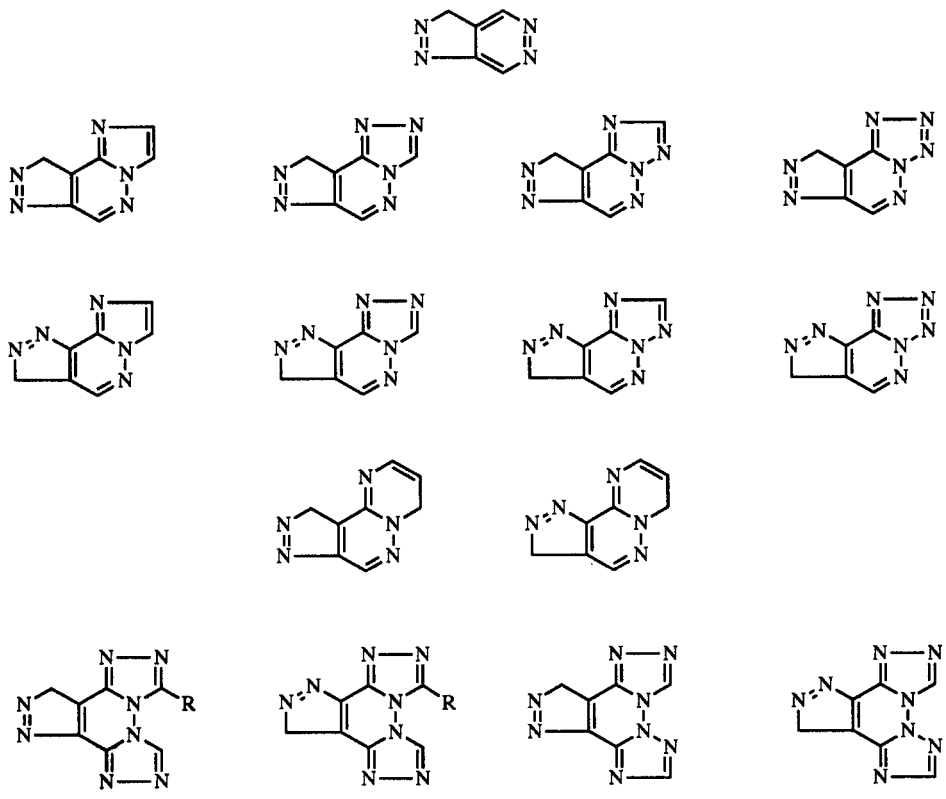
Scheme 25



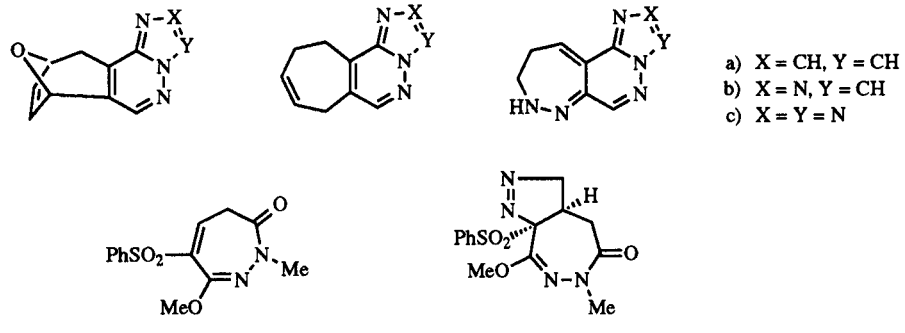
vii) Conclusion.

In conclusion, by 1,3-dipolar cycloadditions of diazoalkanes to pyridazine derivatives several bicyclic and polycyclic pyrazolopyridazine systems were obtained (Scheme 26). These systems can be transformed either thermally or photochemically into a series of systems shown on Sheme 27, and by asymmetric 1,3-dipolar cycloaddition of chiral azomethine imines two or three new chiral centers can be introduced with high degree of regio- and diastereoselectivity into heterocyclic systems (Scheme 28).

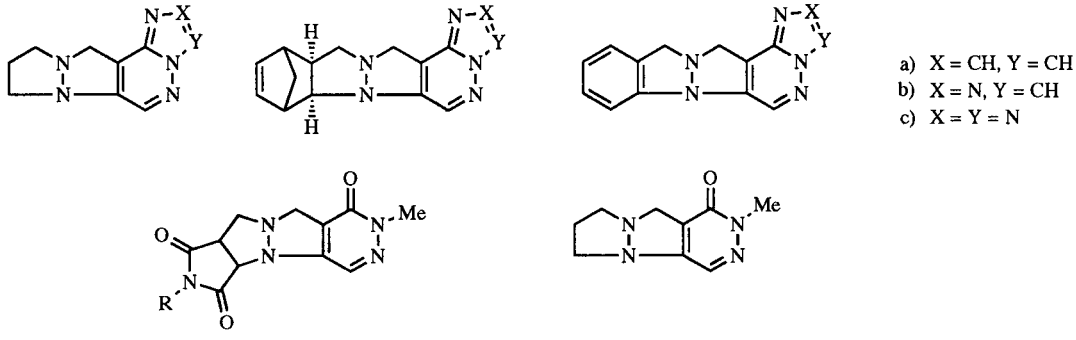
Scheme 26



Scheme 27



Scheme 28



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