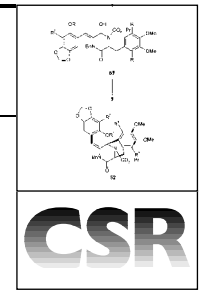
3-Ylidenepiperazine-2,5-diones as versatile organic substrates



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3-Ylidenepiperazine-2,5-diones and 3,6-diylidenepiperazine-2,5-diones are cyclic dipeptides consisting of one or two didehydroamino acid moieties, respectively. Some compounds of this series occur in nature. They can easily be synthesised by several methods also in optically active form and are prone to addition reactions to the C–C double bond by electrophiles (enamine reactivity), nucleophiles (Michael reactivity), radicals, oxidising reagents or 1,3-dipoles, usually in a stereoselective manner. The resulting adducts can further be transformed to natural products and analogues or serve as precursors for interesting α-amino or α-keto acid derivatives by cleavage of the diketopiperazine ring.

1 Introduction

3-Ylidenepiperazine-2,5-diones **1** (hereafter piperazine-2,5-dione is abbreviated as PDO, some authors prefer the term 2,5-diketopiperazine, abbreviated as DKP) and 3,6-diylidene-PDOs **5** have important functions in biochemistry and synthetic chemistry. Such compounds are cyclic dipeptides composed of a didehydroamino acid and an α-amino acid, or of two didehydroamino acids, respectively. 3-Ylidene-PDOs and 3,6-diylidene-PDOs were found as natural products[1] often produced by fungi such as *Actinomyces* strains and *Penicillium* species. Some of these compounds exhibit antibacterial activity and inhibit tumour growth in mice. Their biochemical origin is obviously from peptides and proteins.

From the synthetic point of view 3-ylidene-PDOs **1** and 3,6-diylidene-PDOs **5** have gained wide interest because of their various reactive functional groups allowing reactions at different positions of the ring and at the exocyclic carbon atom of the C–C double bond (Scheme 1). Nucleophilic attack at the carbonyl carbon atoms could be used for hydrolytic cleavage of the piperazine ring. If the ring nitrogen atoms are unsubstituted or are substituted by alkyl groups they can be attacked by electrophiles allowing the introduction of substituents at these positions. The carbon atom α to the carbonyl group at position 6 can be acidic. The C–C double bonds have been found to be particularly synthetically useful because they allow addition reactions affording saturated products **2** or **7** or partially unsaturated products **6**. Since chirality can be created at position 6 of 3-ylidene-PDOs **1** such additions can also be carried out in a stereoselective manner. After further hydrolytic cleavage of the PDO-ring of **2** interesting α-amino acids **3** could be synthesised. This hydrolytic cleavage is possible under acidic conditions without racemisation[2,3] and the resulting amino acids can be esterified for better separation.[3] Since the C–C double bonds of 3-ylidene-PDOs **1** or **5** are part of a didehydroamino acid, addition reactions can follow a different mechanism. Thus the exocyclic position of the C–C double bond can be attacked by nucleophiles (Michael acceptor reactivity, formation of enolates **8** and products **9**) or by electrophiles (enamine reactivity, formation of N-acyliminium

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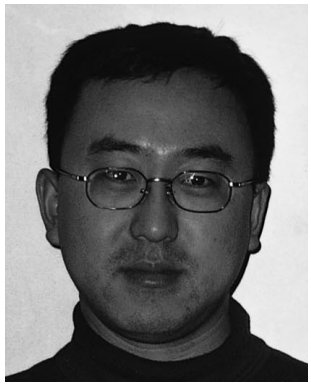

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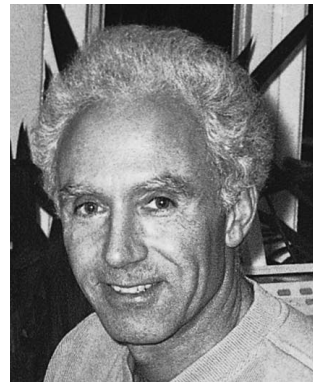

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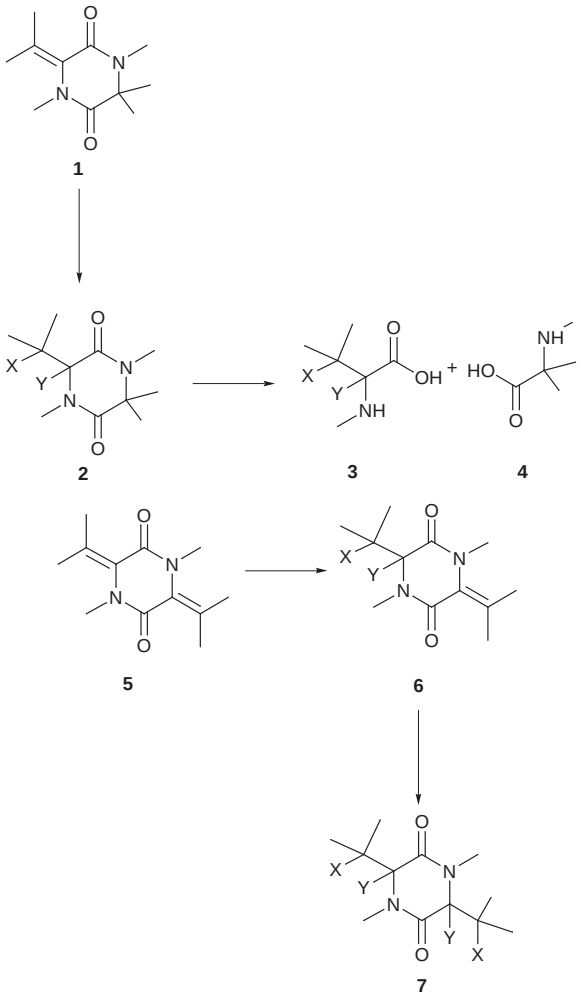


Scheme 1

structures **10** and products **11** Scheme 2). Furthermore radical attack is possible at this carbon since a radical intermediate **12** is formed which is stabilised by the capto-dative effect and cycloaddition reactions are also feasible. Semi-empirical calculations as well as the comparison of ^{13}C NMR chemical shifts revealed a good deal of enamine character for 3-ylidene-PDO **1**. Practical investigations however showed that the reaction behaviour, *i.e.* Michael system *versus* enamine system depends on several factors such as reaction conditions, substituents at the piperazine ring or the presence of a second ylidene group attached to the PDO ring such as in compounds **5**.

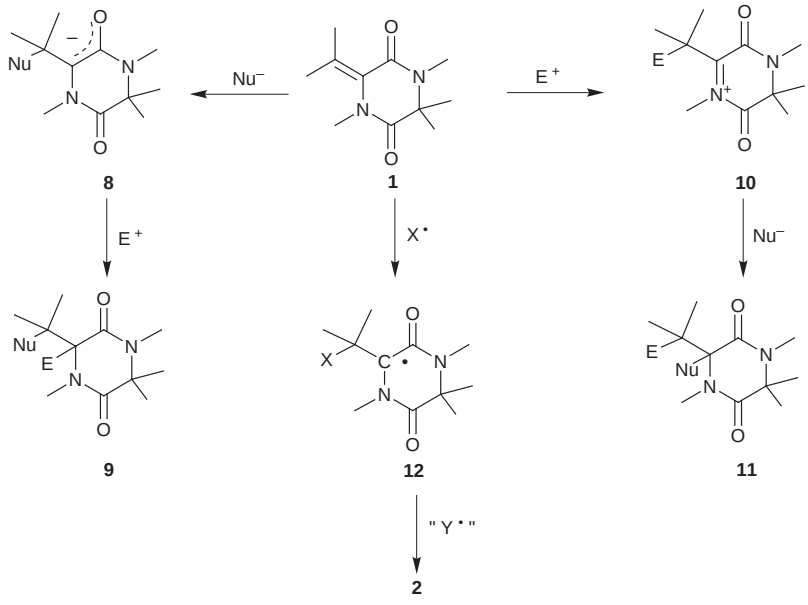
2 Synthesis of 3-ylidenepiperazine-2,5-diones

3-Ylidene-PDOs have been synthesised with various substituent patterns in the non-chiral, racemic and optically active series by different synthetic pathways. In the following just the basic principles will be addressed briefly. Syntheses of 3-ylidene-PDOs either established the piperazinedione ring from an open-chained didehydroamino acid precursor or started with a preformed PDO and introduced the ylidene group. Optically active 4-acyl-3-ylidene-PDOs **16** are conveniently available by an Erlenmeyer-type route by ring opening of 4-ylideneoxazolones **13** (Scheme 3) with α-amino carboxylates **14** and subsequent cyclisation of the resulting dipeptide **15**.[2] The *N*-acyl group of the 3-ylidene-PDO **16** could be removed by reaction with amino compounds (formation of **17**) and alkyl groups were introduced by further *N*-alkylation.

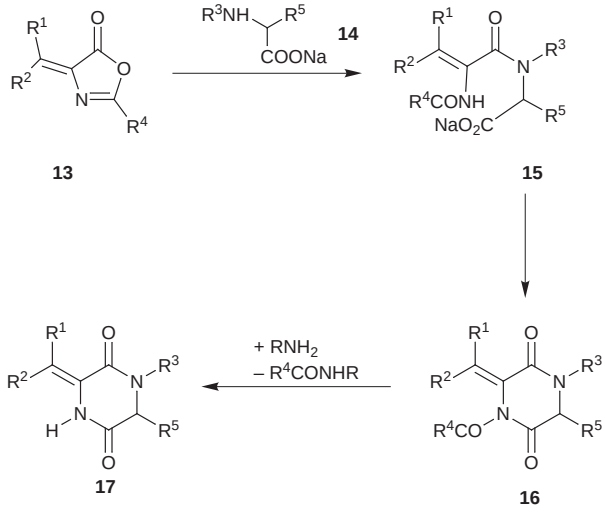
In an alternative route racemic or achiral 3-alkylidene-PDOs **21** could be synthesised by cyclisation of *N*-(α-aminoacyl)dehydroamino acid esters **20** obtained either from didehydroamino acid ester **18** and α-phthalimidoacyl chlorides **19** or by reaction of α-haloacetamides **23** with α-ketoesters **22**[4] (Scheme 4).

For establishing the ylidene group of PDOs **25**[5] and **27**[6] a Wittig or a Wittig–Horner reaction is suitable if either 2,3,5-triketopiperazines **24** (derived from an α-amino acid and oxalate) or PDO-3-phosphonate **26** are used as starting materials (Scheme 5). The latter method allowed optically active 3-ylidene-PDOs **27** to be obtained.

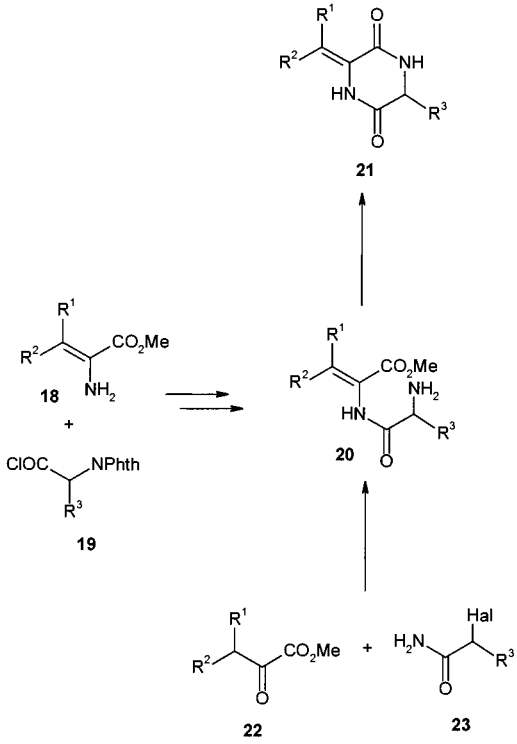
As an alternative to the Wittig reaction 3-ylidene groups could be introduced into PDOs by aldehydes using aldol reactions. Thus a one- or two-fold aldol condensation of **28** gave access to 3-ylidene-PDOs **29** and 3,6-diylidene-PDOs **30** (Scheme 6).[7] Often *N*,*N*′-diacetylated **28** (R^3 = R^4 = Ac) were used, losing the acetyl group attached to the N-atom at position 4 by an intramolecular acyl transfer thus affording 3-alkylidene-PDOs **31**.[7–10] While aldol condensations of PDOs were usually implemented as one-pot procedures in a basic medium[7–11] eventually under PTC conditions or accelerated by ultrasound or in the presence of AcONa–Ac_2O, sometimes intermediate



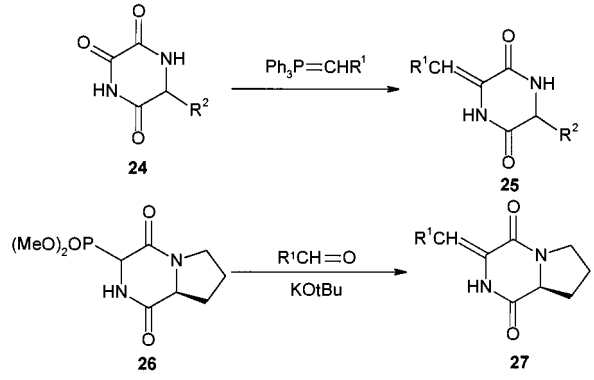
Scheme 2



Scheme 3



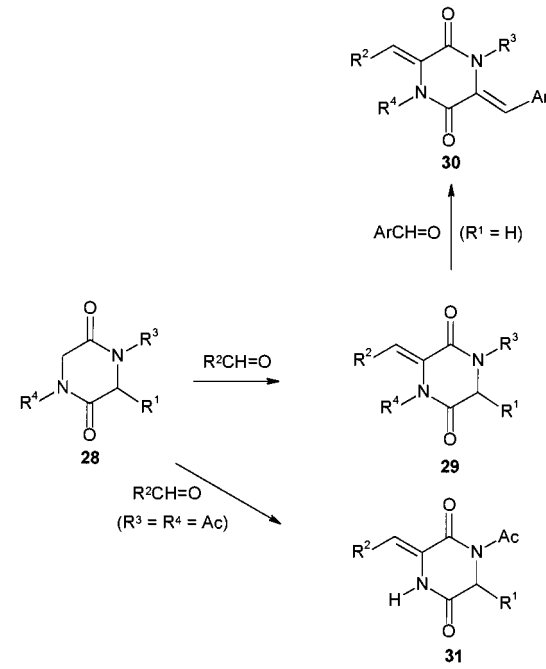
Scheme 4



Scheme 5

3-(α-hydroxyalkyl)-PDOs **32** (X = OH) were isolated and dehydrated in a separate step.

Similar 3-(α-hydroxyalkyl)-PDOs or derivatives **32** (X = OH, OSO_2Me, OAc) or corresponding sulfur analogues **32** (X = SR) could alternatively be obtained by cyclisation of dipeptides derived from serine or cysteine. β-Elimination of **32** gave access to optically active 3-ylidene-PDOs **33**, in particular to 3-methylidene derivatives (R^2 = H) and to 3,6-diylidene-PDOs **33** (R^1 represents =CHR) (Scheme 7).[12–15] Leaving groups for elimination to 3-ylidene-PDOs **33** and to corresponding 3,6-diylidene-PDOs can also be situated at the ring position (*e.g.* reactants **34**).[15] Such 3-alkyl-3-hydroxy-PDOs **34** (X = OH) acted as intermediates in the transformation of α-(α′-ketoacylamino)amides **35** into 3-methylidene-PDOs **33** (R^2 = H).[16–18] Finally the debromination and dehydrogenation of 3-alkyl-PDOs **36** (X = Br or H, respectively) are to be mentioned as entries to 3-alkylidene-PDOs **33** (see also Scheme 16).[19]



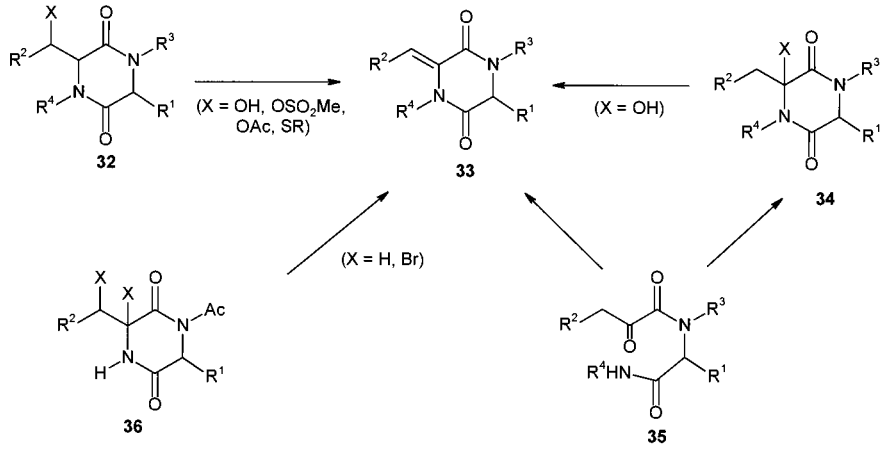
Scheme 6

3 Isomerisation of 3-ylidenepiperazine-2,5-diones

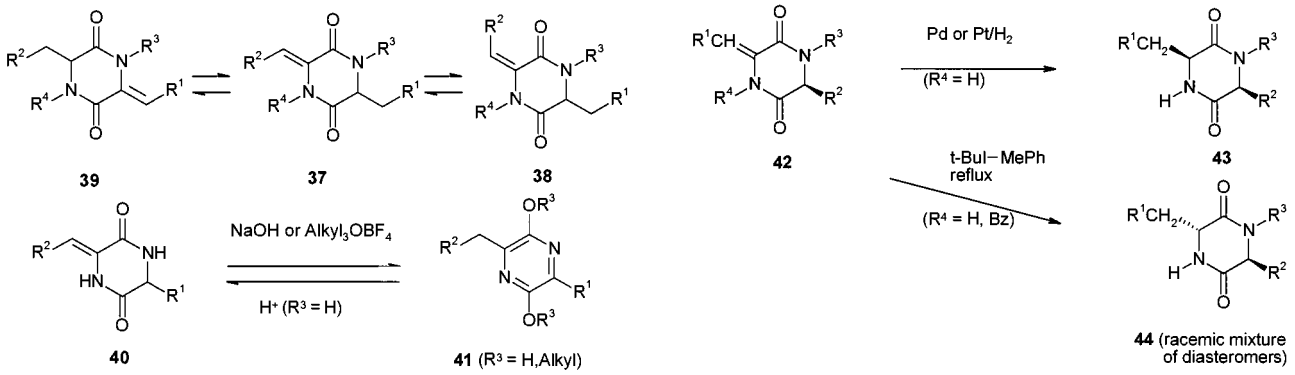
For steric reasons 3-ylidene-PDOs are usually more stable in the *Z*-configuration **37** (Scheme 8). Thus isomerisation of the *E*-isomers **38** to **37** was reported by treatment with acids.[20] Such a transformation is also possible in the opposite direction, *i.e.* from **37** to **38**, by irradiation with light (R^2 = aryl)[4,8,10,21] or, if R^2 and R^4 are large enough (*e.g.* R^2 = *i*-Pr, R^4 = Me) by treatment with acids. Under acidic or basic conditions migration of the C–C double bond of 3-ylidene-PDOs **37** can occur affording racemic isomers **39**.[13,17,22] This rearrangement is likely to occur either *via* 2,5-dihydroxypyrazines **41** (if R^3 = R^4 = H) or *via* *N*-acyliminium structures when acids are present. The former intermediates could be synthesised by treating *N*,*N*′-unsubstituted 3-ylidene-PDOs **40** with sodium hydroxide.[21] Corresponding 2,5-dialkoxypyrazines **41** were obtained with trialkyloxonium salts.

4 Hydrogenation of C=C and reduction of C=O

Catalytic hydrogenation of optically active 3-ylidene-PDOs **42** (Scheme 9) in the presence of Pd or Pt catalysts and polar solvents occurs in a highly stereoselective *syn*-fashion from the opposite side with respect to the substituent R^2 attached to the chiral ring position 6.[23] *cis*-PDOs **43** were obtained usually in excellent yields (but for R^1 = aryl) and with a wide scope of substituents. They could be cleaved by acid hydrolysis thus



Scheme 7

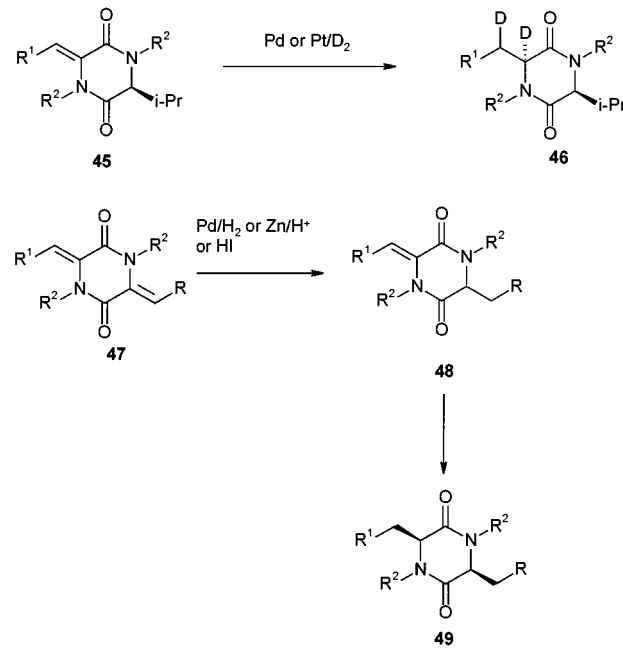


Scheme 8

giving access to enantiomerically pure amino acids. Mechanistic investigations of the catalytic deuteration of 3-ylidene-PDOs **45** gave similar results (formation of **46**).[23] But, remarkably, in some cases of *N,N′*-diBoc-protected **45** (R^2 = Boc) with R^1 = Ph no *syn*-addition was observed but instead *anti*-addition was seen, *i.e.* only a D-atom was added from the opposite side of the *i*-Pr group found at the ring position while the exocyclic C-atom of the C–C double bond was attacked from the same side. Racemic *trans*-3,6-dialkyl-PDOs **44** were obtained as major products if optically active 3-ylidene-PDOs **42** were heated with *t*-BuI. Probably HI was formed under the thermal conditions acting as hydrogenating reagent.[24]

Hydrogenation of one of the two C–C double bonds of 3,6-diylidene-PDOs **47** was achieved by catalytic hydrogenation, with zinc under acidic conditions or using HI. The hydrogenation could be stopped at the stage of 3-ylidene-PDOs **48** somehow demonstrating the higher reactivity of diylidene-PDOs **47** as compared with the resulting monoylidene-PDOs **48**. Naturally the latter could further be hydrogenated by the same reagents under more forcing conditions to racemic *cis*-3,6-dialkyl-PDOs **49**.

$LiAl(Ot\text{-}Bu)_3H$ left the C–C double bond of the 3-benzylidene-PDOs **50** unchanged (Scheme 10) but reduced the conjugated carbonyl group affording hemiaminal structures **51** which were employed in synthetic approaches to ecteinascidines *via* benzazocines **52**.[9]



Scheme 9

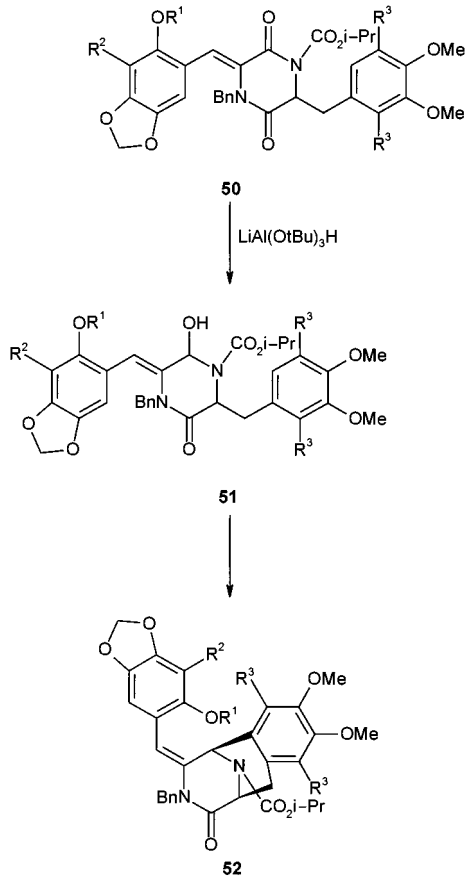
PDOs **53** gave low yields of 3-alkyl-PDOs **54** in the presence of sodium borohydride (Scheme 11).[12] The approach of the hydrogen to the 3-position occurred stereoselectively from the phase opposite to the alkyl substituent R at position 6.

5 Radical addition to the C–C double bond

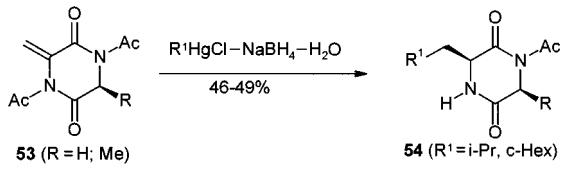
Although 3-ylidene-PDOs are composed of a didehydroamino acid moiety and thus should be prone to formation of radicals at the 3-position according to the concept of the capto-dative effect radical reactions seem not to be favoured by such systems. Addition of organomercurates to the 3-methylidene-

6 Nucleophilic addition to the exocyclic position of the C–C double bond

In general, Michael acceptor properties of 3-ylidene-PDOs seem to be weak, *i.e.* addition of nucleophiles to the exocyclic



Scheme 10



53 (R = H; Me) **54** (R^1 = i-Pr, c-Hex)

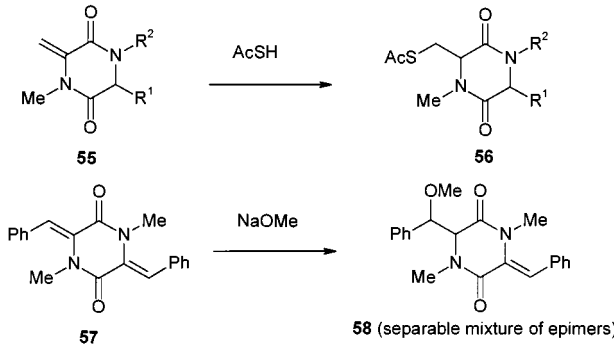
Scheme 11

position of the C–C double bond is not preferred. Thus proline derived **74** turned out to be reluctant to react with various nucleophiles such as alkoxides, mercaptanes, amines or CH-acidic compounds. But reactivity of 3-ylidene-PDOs with nucleophiles is increased in methylidene-PDOs such as **55** or in 3,6-diylidene-PDOs (*e.g.* **57**, **59** or **64**). Thus thioacetic acid could be added to the methylidene-PDOs **55** and sodium methoxide to the dibenzylidene-PDO **57** affording mono-adducts **56**[17, 20] and **58** (Scheme 12).[15] Unlike the latter product the analogous monoadducts **60** and **62** derived from the 3,6-dimethylidene-PDO **59** and thiols or aziridine still possess a reactive 3-methylidene-PDO moiety. Thus further nucleophilic addition was possible under more forcing conditions affording functionalised 3,6-dialkyl-PDOs **61** and **63**, respectively.[14]

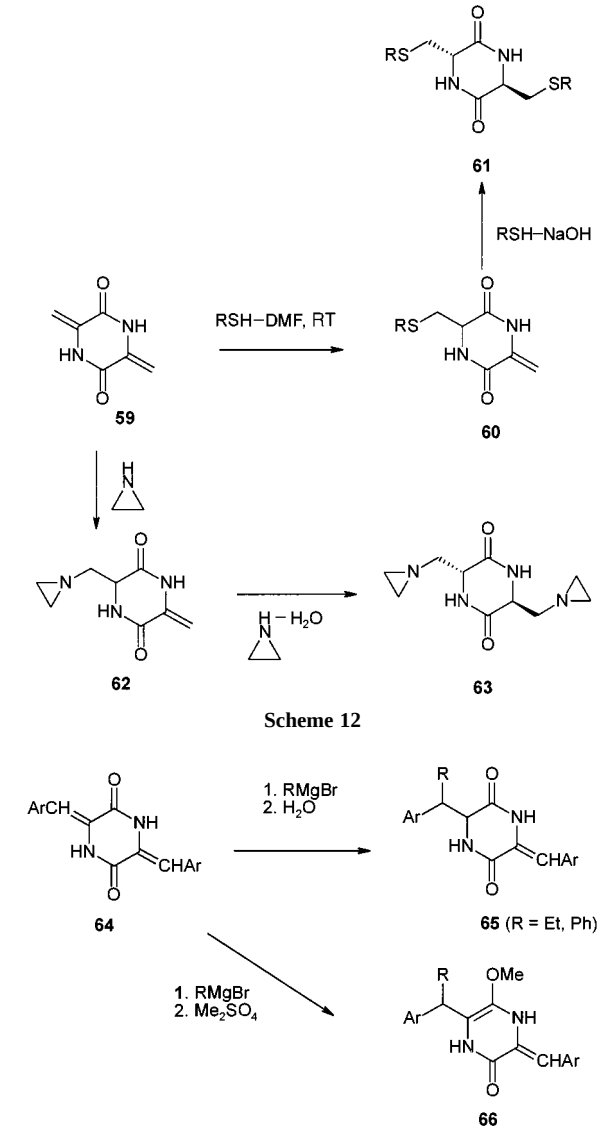
Grignard addition to 3,6-diarylidene-PDOs **64** afforded monoadducts **65** even with an excess of Grignard reagent or corresponding O-methylated products **66** after quenching with dimethyl sulfate (Scheme 13).[25]

7 Acid catalysed addition of nucleophiles to the ring position of the C–C double bond

If thioacetic acid or hydrosulfide were reacted with 3-methylidene-PDOs in the presence of an acid or Lewis acid the nucleophilic attack did not occur at the exocyclic position of the



55 **56** **57** **58** (separable mixture of epimers)



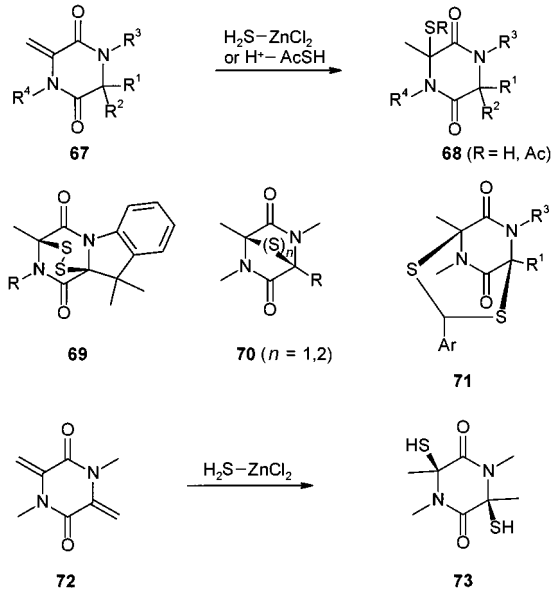
59 **60** **61** **62** **63**

Scheme 12

64 **65** (R = Et, Ph) **66**

Scheme 13

C–C double bond (see previous chapter) but at the ring carbon due to formation of intermediate *N*-acyliminium salts **10** (E = H).[16,17 20] 3-Mercapto-PDOs **68** were formed (Scheme 14), which are particularly interesting if a second mercapto function is found at position 6 (R^2 = SH), *i.e.* if either R^2 = SH in the starting material **67** or a suitable leaving group (R^2 = Cl, OH, OMe, SAc) is substituted by SH. Such 3,6-dimercapto-PDOs **68** (R^2 = SH) allowed an oxidative ring closure (I_2–pyridine) to the epidithiapiperazinedione moiety (**69**, **70**) a common class of fungal metabolites with interesting pharmacological properties.[16] An alternative route to **70** is possible from 3,6-dimethylidene-PDOs **72** by two-fold addition of hydrosulfide in the presence of $ZnCl_2$ *via* dithiols **73**. Similarly, ethanethiol was added twice to 3,6-diylidene-PDOs.[20] Bridged dithioacetals **71**



67 **68** (R = H, Ac) **69** **70** (*n* = 1,2) **71** **72** **73**

Scheme 14

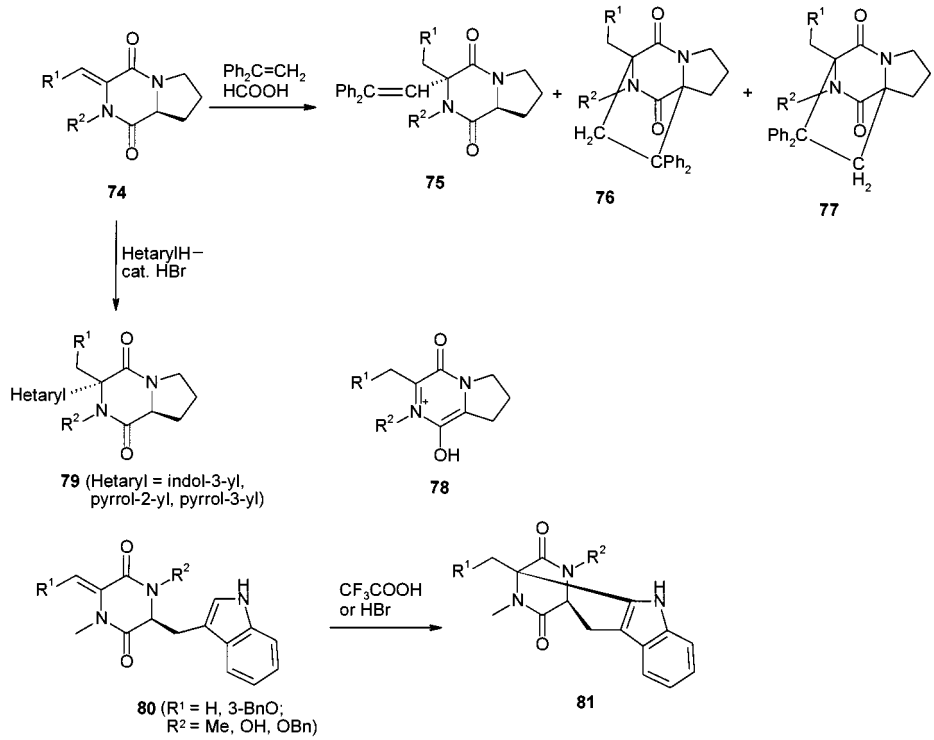
useful for the total synthesis of *Sporidesmin A*, a compound causing facial eczema, a serious disease of sheep, could be obtained by BF_3-catalysed addition of hydrosulfide in the presence of anisaldehyde or with a 5-anisyl-1,2,3,4-oxatrithiane to dimethylidene-PDO **72** or 5-acetylthio-3-methylidene-PDO **67** (R^2 = SAc), respectively.[26] Some natural products such as gliotoxin comprising the disulfide moiety **70** exhibit very high antifungal activity.

In the presence of catalytic amounts of acids it is also possible to add C-nucleophiles to the endocyclic position of the C–C double bond of 3-ylidene-PDOs. Thus treatment of **74** with 1,1-diphenylethene gave optically active 3-alkyl-3-diphenylvinyl-PDOs **75** mostly accompanied by racemic cycloadducts **76** and **77** (Scheme 15).[27] While **75** are derived from intermediate *N*-acyliminium salts **10** (E = H) again the formation of cycloadducts **76** and **77** requires alternative enolised *N*-acyliminium intermediates **78** which give a Diels–Alder reaction with diphenylethene. π-Excess *N*-heterocycles such as pyrrole or indole can also act as C-nucleophiles in acid catalysed addition to 3-ylidene-PDOs **74.** Enantiopure PDOs **79** were obtained consisting of proline and an α-quaternary amino acid.[22] Both PDOs **75** and **79** represent promising candidates for hydrolytic cleavage forming novel optically active α-amino acids. Introduction of indole to the 3-position of 3-ylidene-PDOs could also be achieved in an intramolecular fashion giving rise to interesting bridged PDOs **81** which were obtained in synthetic approaches towards naturally occurring phytotoxines.[28]

8 Addition of electrophiles to the C–C double bond and oxidation

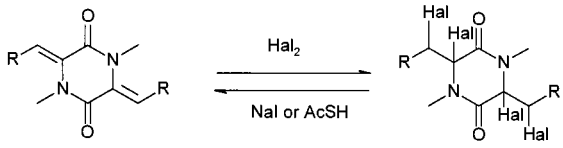
The enamine character of 3-ylidene-PDOs enables the addition of electrophilic halogen atoms or phenylselanyl to the exocyclic position (formation of **10** with E = halogen or PhSe), followed by addition of a nucleophile, *e.g.* halide, hydroxide or alkoxide to the ring position of the starting C–C double bond. Thus bromine or chlorine gave two-fold addition to both C–C double bonds of 3,6-diylidene-PDOs **82** affording tetrahalo-PDOs **83** (Scheme 16).[15, 29]

The ring halogen atoms of **83** could be further substituted by alcohols or water to corresponding 3,6-dialkoxy or 3,6-dihydroxy-PDOs such as **86** (Scheme 17). Interaction of sodium iodide or thiols with **83** did not cause substitution but elimination to the starting 3,6-diylidene-PDOs **82**.[29] PDOs with alkoxyhalo or hydroxyhalo structures **86** were also directly obtained by reaction of 3,6-diylidene-PDOs **84** with *N*-halosuccinimides and alcohols or water, respectively.[15] Just one C–C double bond was affected (formation of monoaddition products **85**) if equimolar quantities of the reagents were used.[15] The halogen atoms of haloalkylalkoxy-PDOs **85**[15], **86**[15] and others[28] could reductively be removed with H_2/Pd affording alkylalkoxy-PDOs such as **88** and **89**. This reaction was also used in the synthesis of thaxtomines, which are herbicide toxins produced by *Streptomyces* and *Actinomyces* species.[28] A haloalkylhydroxy-PDO **85** (R^1 = H) served as precursor for the



74 **75** **76** **77** **79** (Hetaryl = indol-3-yl, pyrrol-2-yl, pyrrol-3-yl) **78** **80** (R^1 = H, 3-BnO; R^2 = Me, OH, OBn) **81**

Scheme 15



Scheme 16

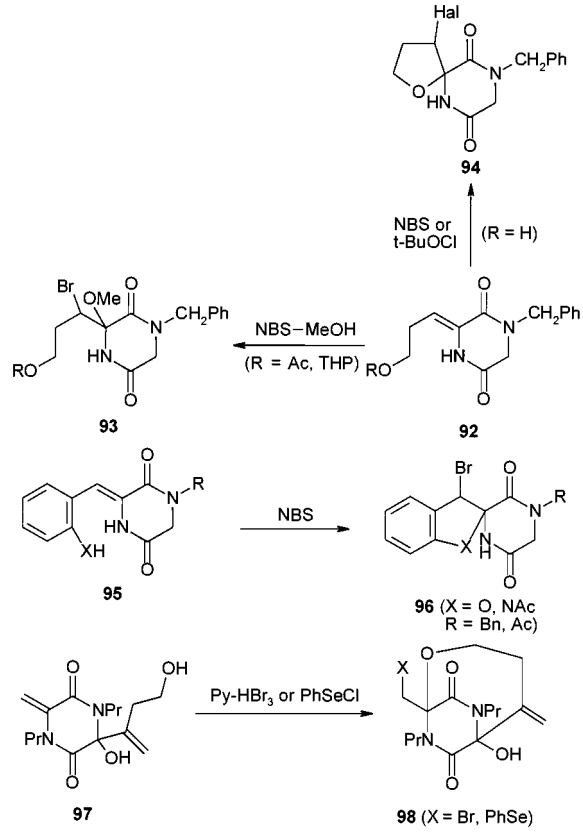
oxirane **87** by intramolecular nucleophilic substitution.[15] The bromine–alkoxide addition also happened with racemic monoarylidene-PDOs[28] and the chiral 3-benzylidene-PDO **90**[27] allowing the synthesis of optically active addition products **91** in the latter case.

The NBS–methoxide addition was further possible to the ω-functionalised 3-propylidene-PDOs **92** if the terminal OH group is protected (R = Ac, tetrahydropyranyl; formation of **93**). In the presence of a free hydroxy group intramolecular halohydroxyalkylation occurred in the presence of NBS or t-BuOCl (Scheme 18).[30] The resulting spiro-PDOs **94** possess the main skeletons of the natural products *bicyclomycin* and *aspirochlorin*. In a similar manner the phenol and aniline derivative **95** gave the spirobenzofuran **96** (X = O) or spiroindole **96** (X = NAc) upon treatment with NBS.[10] As has been shown in the transformation of the 6-hydroxybutenyl-3-methylidene-PDO **97** into the bicyclic product **98** an intramolecular attack of a hydroxy group after prior attack of bromine or phenylselenyl chloride at the exocyclic position of the double bond can also occur if the hydroxyalkyl group is found at position 6 of a 3-ylidene-PDO. The product **98** represents a substructure of *Bicyclomycin*.[31]

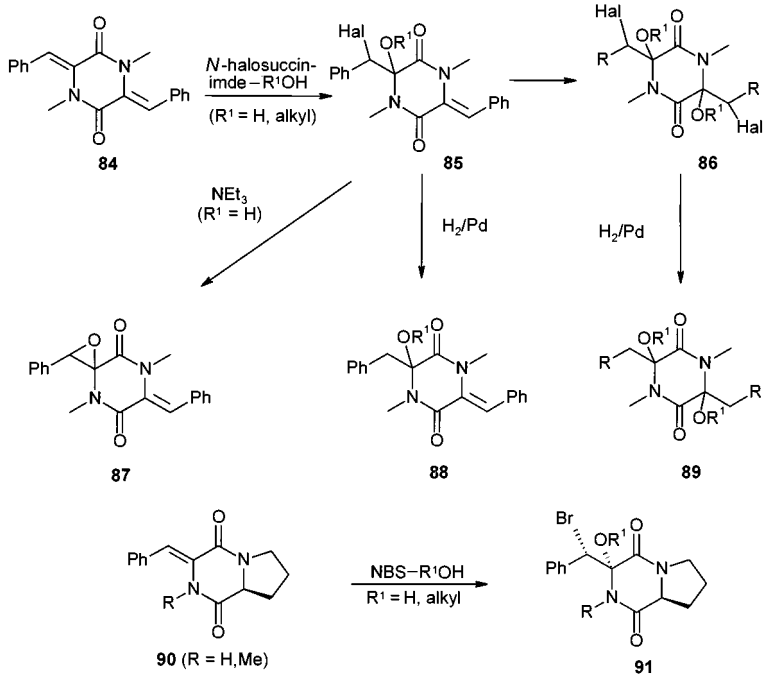
Reaction of the 3-ethylidene-PDO **99** with benzeneselenenyl chloride in the presence of AcOK–AcOH gave 3-hydroxy-3-(1-phenylselanylethyl)-PDO **100** (Scheme 19).[32] Similar additions of benzeneselenenyl choride and alcohols in pyridine were achieved in a stereoselective manner if chiral 3-alkylidene-PDOs **74** were used.[27] Remarkably, treatment of condensed 3-ylidene-PDOs **101** with NBS or Br_2 in the presence of THF–water gave diols **102** together with corresponding monohydroxy products obviously because of hydrolysis of the expected bromohydrin.[19, 33, 34] Diols **102** are found in naturally occurring *Fumitramorgins*.

cis-Hydroxylation with OsO_4 was applied to 3-ylidene-PDOs affording diols **102-A**[34] or **103**.[11] This reaction was stereoselective and could be applied to the synthesis of fungal metabolites. Bisacetoxylation of the non-chiral 3-ylidene-PDO **104** with lead tetraacetate afforded the diacetoxyproduct **105** (X = OAc) (Scheme 20) which allowed further substitution of the endocyclic acetoxy group or of both acetoxy groups by nucleophiles such as H_2O, H_2O_2 or H_2S.[35]

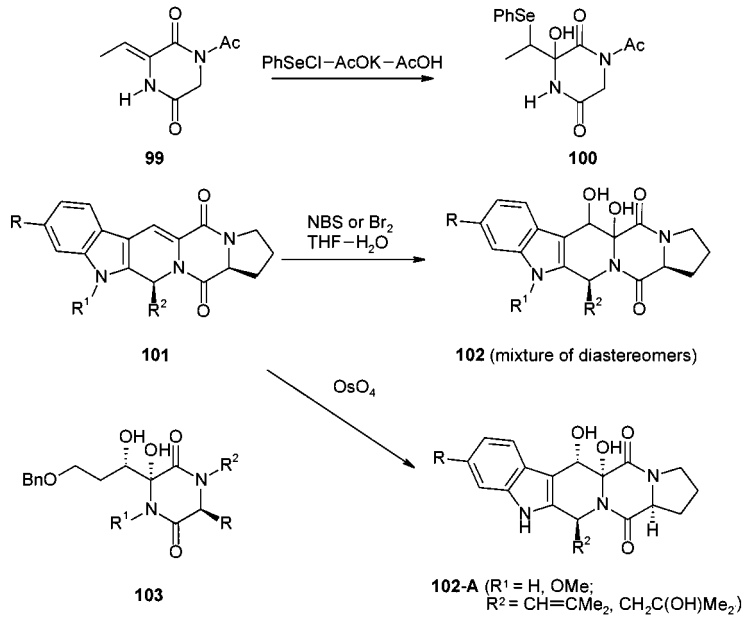
Epoxidation of 3-ylidene-PDOs **106** was achieved with *m*-chloroperbenzoic acid or with dimethyldioxirane and could also



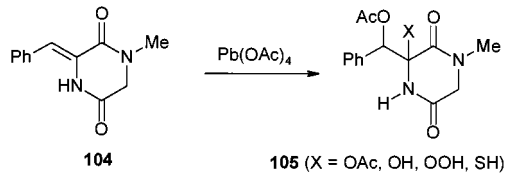
Scheme 18



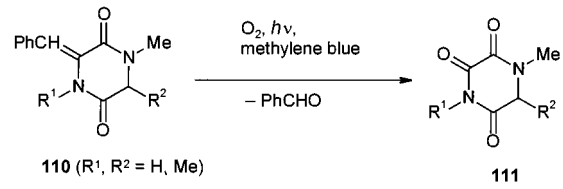
Scheme 17



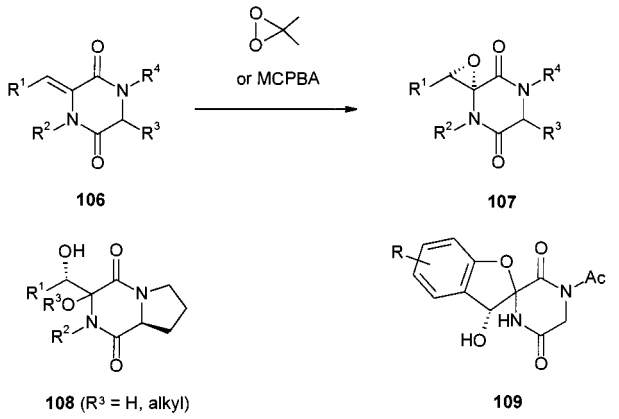
Scheme 19



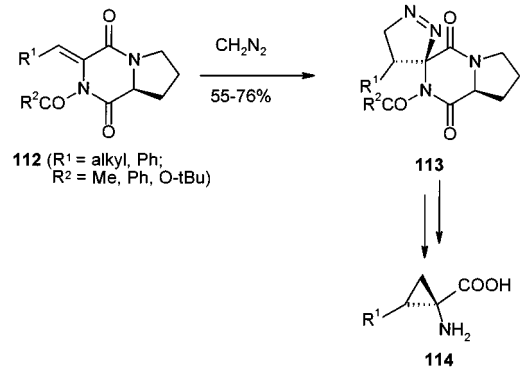
Scheme 20



Scheme 22



Scheme 21



Scheme 23

be used to synthesise optically active oxiranes **107** (Scheme 21).[27, 36] In some cases diols **108** (R^3 = H) were obtained instead due to easy hydrolysis.[27] Corresponding alkoxy-substituted ring opening products **108** (R^3 = alkyl) were available by treatment of oxiranes **107** with alcohols.[27] Epoxidation of a 3-(*o*-hydroxybenzylidene)-PDO led to the spiro-PDO **109** *via* an intermediate oxirane.[8] Reaction of 3-benzylidene-PDOs **110** with singlet oxygen disrupts the benzylidene group affording piperazinetriones **111** (Scheme 22).[35] Whether this reaction runs *via* intermediate peroxides or iminium salts is not clear. Similar C–C bond cleavage to piperazinetriones was achieved by ozonolysis.[13]

9 Dipolar cycloadditions

3-Ylidene-PDOs do not seem to be favoured for 1,3-dipolar cycloadditions. The highly reactive diazomethane however could be reacted with the proline derived PDOs **112** affording pyrazolines **113** (Scheme 23). These products were further changed to optically active *allo*-coronamic acids **114**.[37] The cycloaddition was highly stereoselective but, remarkably occurred with opposite phase selectivity as compared with the epoxidation (see Scheme 21).

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