SELECTIVE FUNCTIONALIZATION AND ELABORATION OF 2,5-PIPERAZINEDIONES

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of
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by

Terry William Badran
B. Sc. Hons.
Department of Organic Chemistry
The University of Adelaide
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CONTENTS

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I would like to thank my fellow laboratory members for creating a working and social enviroment with a sense of the insane. I would also like to thank the academic and technical staff, the other members of my research group and fellow students of the Organic Chemistry Department at the University of Adelaide for their valuable assistance.

STATEMENT

This thesis contains no material previously submitted for a degree or diploma in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person except where due reference is made in the text.

Terry Badran

NAME: TERRY WILLIAM BADRAN **COURSE:** Ph.D.

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PUBLICATIONS

Some of the work described in this thesis has been reported in the following publication:

"Monobromination of Symmetric Piperazine-2,5-dione Derivatives"

Badran, T. W.; Easton, C. J. *Aust. J. Chem.* **1990**, *43*, 1455.

ABSTRACT

With the intent of developing methods for the selective functionalization of amino acid residues in cyclic dipeptides, radical halogenation of diketopiperazines has been investigated. Radical bromination of such compounds allows functionalization of symmetric cyclic dipeptides at the α-carbon of one amino acid residue to afford asymmetrically substituted cyclic dipeptides.

The reactions of a symmetric diketopiperazine with two different radical halogenating agents have also been compared. It has been found that radical bromination with *N*-bromosuccinimide is more discriminating than reaction with sulfuryl chloride. Thus *N*-bromosuccinimide is the reagent of choice for the regioselective halogenation of diketopiperazines.

The relative reactivity towards bromination of *N*-alkyl and *N*-acyl substituted cyclic dipeptides has been compared. Relative to *N*-alkyl substituents, *N*-acyl substituents disfavor reaction at the α-carbon of the substituted amino acid residue. Selectivity for the reaction of glycine residues in comparison with α-substituted amino acid residues has also been observed in bromination reactions of substituted 2,5-piperazinedione derivatives.

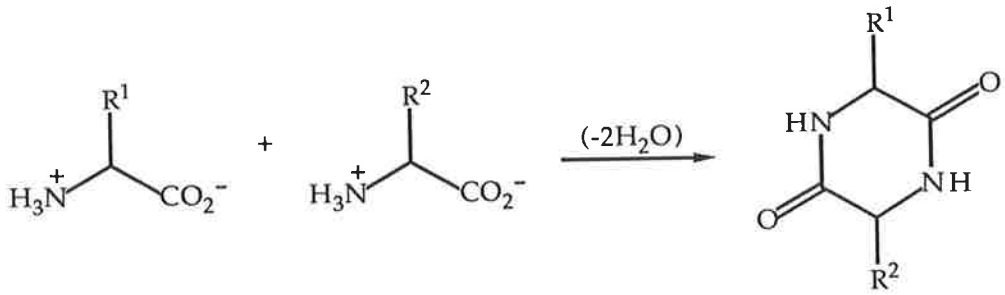
The extent of the deactivating effect of an *N*-acyl substitutent is such that an *N*-alkylglycine residue reacts preferentially to an *N*-acylglycine residue. Furthermore, in the case of 3- and 3,6-substituted di-*N*-acyldiketopiperazines, side

chains possessing activating substituents at the β-position undergo competing β-functionalization. These factors have been exploited in the synthesis of regioselectively halogenated diketopiperazines, which are suitable for further elaboration.

Three methods for elaboration of 3-bromo-2,5-piperazinediones were investigated, in order to exploit the selective functionalization of diketopiperazines. Reaction of 3-bromo-2,5-piperazinedione derivatives with methyl nitronate was found to be an unsuitable method for the preparation of β-nitroamino acid residues in diketopiperazines. Reaction of 3-bromo-2,5-piperazinedione derivatives with allyltrimethylsilane in the presence of a Lewis acid was also unsuitable for the production of allyl-substituted diketopiperazines. However, reaction of 3-bromo-2,5-piperazinedione derivatives with allyltributylstannane afforded the corresponding allyl-substituted 2,5-piperazinediones. Substituted allylstannanes have also been shown to react in this manner, and asymmetric induction in these reactions and in the preparation of deuteriated diketopiperazines from the corresponding bromides has been observed.

INTRODUCTION

Diketopiperazines or 2,5-piperazinediones constitute a large and important class of naturally occurring compounds[1,2] that are derived by the net removal of two molecules of water from two amino acid residues (Scheme 1).

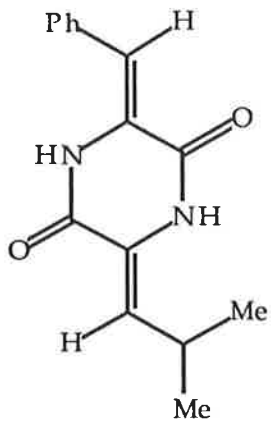


Scheme 1

These cyclic dipeptides are frequently found in high oxidation states relative to the amino acid residues from which they are derived. They are often formed during the synthesis, degradation and manipulation of peptides.[3] Diketopiperazines, both in the solid state and in solution, have been traditional models for studies of peptides[4] and proteins.[5] More recently, diketopiperazines have been used as versatile synthetic intermediates for the preparation of amino acids, amino acid derivatives and natural products both containing[6] and ultimately lacking[7] the 2,5-piperazinedione ring system.

In general, naturally occurring biologically active diketopiperazines can be classified into two major classes; those

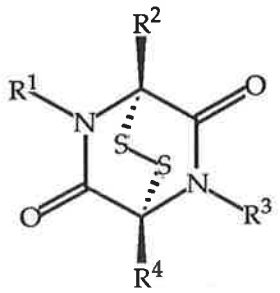
which are sulfur containing such as the gliotoxin and sporidesmin families of 2,5-piperazinediones, and those that exhibit unsaturation at both α-carbons such as Albonoursin (**1**). Previous work in the latter series has emphasized the importance of oxidized 2,5-piperazinediones as natural products. Biosynthetic studies indicate that these compounds can arise from saturated precursors.[8] By far the most studied compound of this 3,6-didehydro-2,5-piperazinedione series is Albonoursin (**1**).



1

The asymmetrically substituted Albonoursin (**1**) has been isolated from *Streptomyces albus* var. *fungatus*, *Streptomyces noursei*[9,10] and from *Actinomyces tumemacerance*.[11] Naturally occurring **1** has been found to exhibit antibacterial activity and to inhibit the growth of transplantable solid brain tumors in mice.[11] The epidithiapiperazinedione moiety **2** is common to the class of fungal metabolites which includes the gliotoxins,[12] sporidesmins,[13] hyalodendrin[14] and others.[15] Gliotoxin (**3**) was first isolated from cultures of the wood fungus *Gliocladium fimbratium*.[12] This compound has also been isolated as the metabolite of a variety of microorganisms, including *Aspergillus*

fumigatus and *Penicillium terlikowskii*.[16,17] Gliotoxin (**3**) was found to be a powerful bacteriostatic agent and to exhibit remarkable antifungal and antiviral activity.[18,19,20] However, it was precluded from therapeutic use due to its observed toxicity in animal tests.[21] The structure of the asymmetrically substituted 2,5-piperazinedione **3** was proposed in 1958[22] and its structure, stereochemistry and absolute configuration were subsequently confirmed by X-ray crystallographic analysis.[23] Since the discovery of Gliotoxin (**3**), a number of other antiobiotics containing the epidithiapiperazinedione framework **2** have been isolated and exhibit comparable activity.[24] The biological activity is considered to be associated with the epidithiapiperazinedione moiety **2**, since removal of the disulfide group results in loss of activity.[25]



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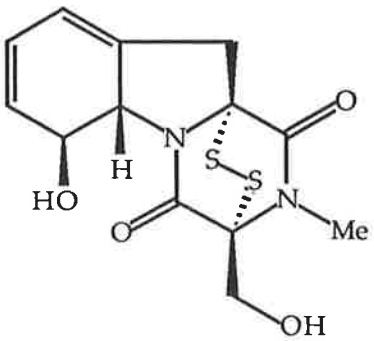
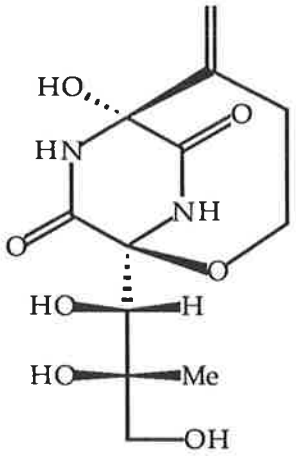


3

Another much studied, structurally unique and naturally occurring diketopiperazine which exhibits biological activity is Bicyclomycin (**4**). Bicyclomycin (**4**) now named Bicozamycin, has been obtained from *Streptomyces sapporonensis*[26] and *Streptomyces aizunensis*[27] and shown to be a broad spectrum antibiotic of low toxicity. This commercially important and

structurally unique antibiotic is now marketed on a world-wide basis as an effective agent against non-specific diarrhoea in humans and bacterial diarrhoea in calves and swine.[28]



4

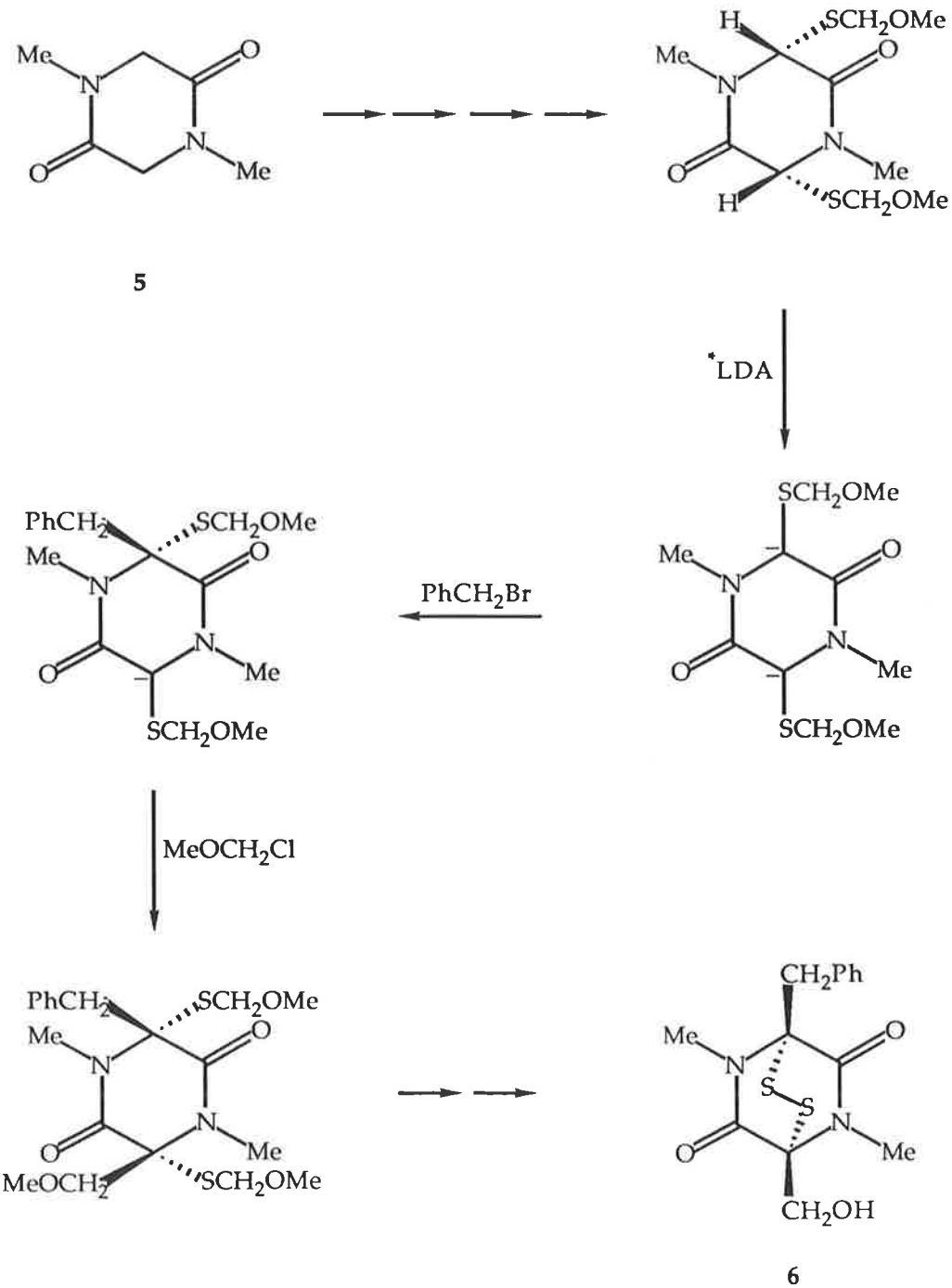
Given their natural occurrence and broad spectrum physiological activity, an intense interest has focussed on the synthesis of 2,5-diketopiperazines. The two most common methods for preparing α-carbon functionalized 2,5-piperazinediones involve (i) standard peptide coupling of two amino acids followed by cyclization[29] and (ii) α-carbanion substitution of a preformed 2,5-piperazinedione ring.[30,31] The latter approach is more generally useful, primarily because sensitive functional groups do not survive the vigorous reaction conditions associated with the former approach.

Numerous methods for the elaboration of symmetric diketopiperazines have been reported. Introduction of sulfur into a preformed ring represents one of the more successful approaches for the synthesis of epidithiapiperazinediones **2**.[32]

The most successful strategy for the synthesis of 3,6-didehydro-2,5-piperazinediones involves the condensation of aldehydes with the α-carbanions derived from deprotonation of a symmetric 2,5-piperazinedione.[33,34] One of the earliest syntheses of an epidithiapiperazinedione compound was achieved by Trown in 1968.[35] The method of Trown incorporated direct halogenation of sarcosine anhydride (**5**) at the α-carbons as the initial step of the sequence.

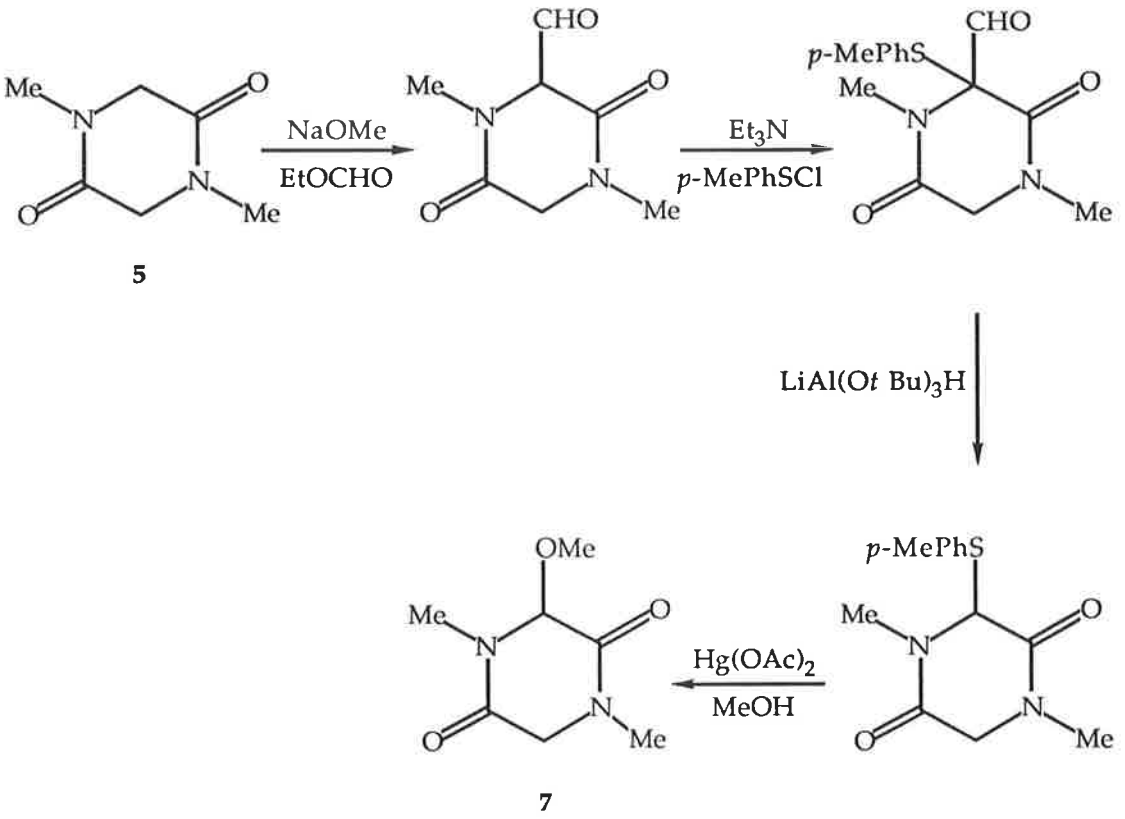
Many of the target diketopiperazines are asymmetrically substituted and asymmetric substitution of the piperazinedione ring is more difficult to achieve. The selective alkylation of dianions of 2,5-piperazinediones has been exploited in the synthesis of asymmetrically disubstituted compounds, as demonstrated in Kishi's synthesis of Hyalodendrin (**6**),[36] depicted in Scheme 2.

In early investigations for a viable approach to the synthesis of Bicyclomycin (**4**), Williams *et. al.* used carbanion chemistry in their conversion of 1,4-dimethyl-2,5-piperazinedione (**5**) to the asymmetric 1,4-dimethyl-3-methoxy-2,5-piperazinedione (**7**),[30,37,38] as shown in Scheme 3. They reported that halogenation of diketopiperazines followed by alcoholysis was not a viable method for the preparation of asymmetrically substituted products such as **7**. Instead, treatment of various glycine anhydride derivatives with *N*-bromosuccinimide (NBS) followed by alcoholysis gave exclusively 3,6-disubstituted products.[39,40]



* LDA = Lithium diisopropyl amide

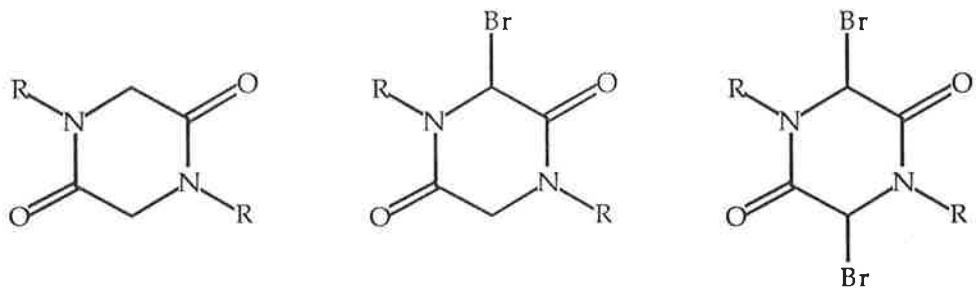
Scheme 2



5 **7**

Scheme 3

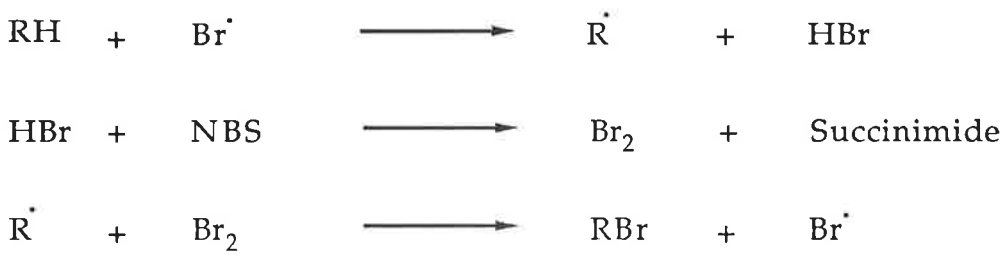
In particular, treatment of 1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**8**) with 0.9 mole equivalents of NBS gave approximately 50% of 3,6-dibromo-1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**10**) and 50% starting material **8**.



8 **9** **10**

R = CH_2Ph-*p* -OMe

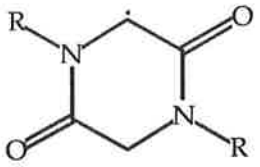
The generally accepted mechanism of bromination of reactive substrates with NBS is as shown in Scheme 4. This mechanism was originally postulated in 1953.[41] Hydrogen atom abstraction by bromine atom from the substrate forms hydrogen bromide and the substrate radical. Hydrogen bromide reacts with NBS to afford a constant but small concentration of molecular bromine. Bromine atom transfer from molecular bromine to the substrate radical affords the brominated product and bromine atom. The latter propagates the chain. Although alternative mechanisms have been proposed for brominations with NBS, the fact that the bromination of diketopiperazines can also be accomplished with bromine instead of NBS[35,42] indicates that the mechanism depicted in Scheme 4 probably applies for these systems.



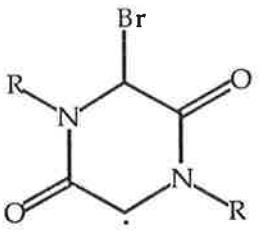
Scheme 4

3-Bromo-1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**9**) will be an intermediate in the reaction of **8** with NBS to give the dibromide **10**. The formation of **10** in preference to **9**, implies that hydrogen abstraction from **9** to give the radical **12** is considerably faster than that from **8** to give **11**. This is particularly curious in that the abstraction of hydrogen from the

monobromide **9**, is disfavored statistically in comparison with hydrogen abstraction from **8**.



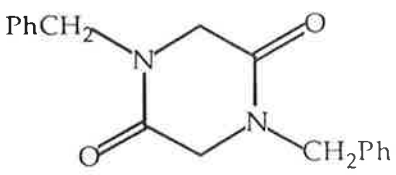
11



12

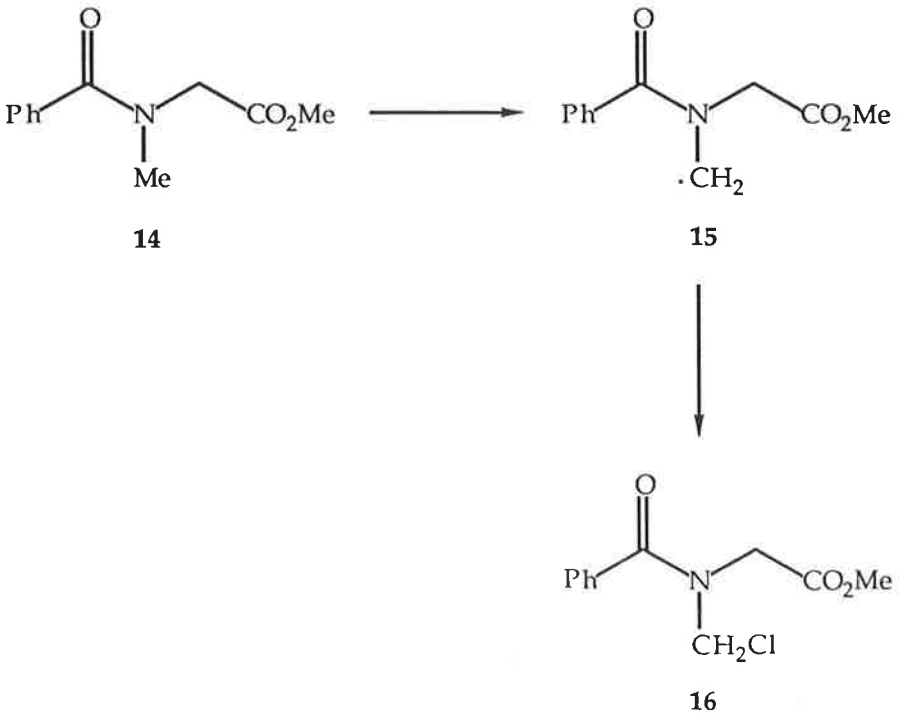
R = CH_2Ph-*p* -OMe

The aim of the work described in Chapter 1 of this thesis was to examine the halogenation of symmetric 2,5-piperazinediones and to investigate the preference for dibromination. The radical brominations of 1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**8**), 1,4-dibenzyl-2,5-piperazinedione (**13**) and 1,4-dimethyl-2,5-piperazinedione (**5**) were investigated. Additionally, the reaction of 1,4-dimethyl-2,5-piperazinedione (**5**) with sulfuryl chloride was examined as an alternative to halogenation with NBS. The motive for studying the reactions of two different halogenating reagents was to compare the selectivity in the two systems.



13

The factors known to affect the selectivity of free radical halogenation[43] include stabilization of the intermediate radicals, polar effects and steric effects. An example in which the regioselectivity of a reaction of an amino acid derivative is determined by the dominance of a polar effect, is the reaction of *N*-benzoylsarcosine methyl ester (**14**) with sulfuryl chloride.[44] Treatment of **14** with sulfuryl chloride in carbon tetrachloride gave *N*-benzoyl-*N*-chloromethylglycine methyl ester (**16**). The proposed mechanism involves abstraction of hydrogen from **14** to give the radical **15** followed by incorporation of chlorine atom to afford **16** (Scheme 5).



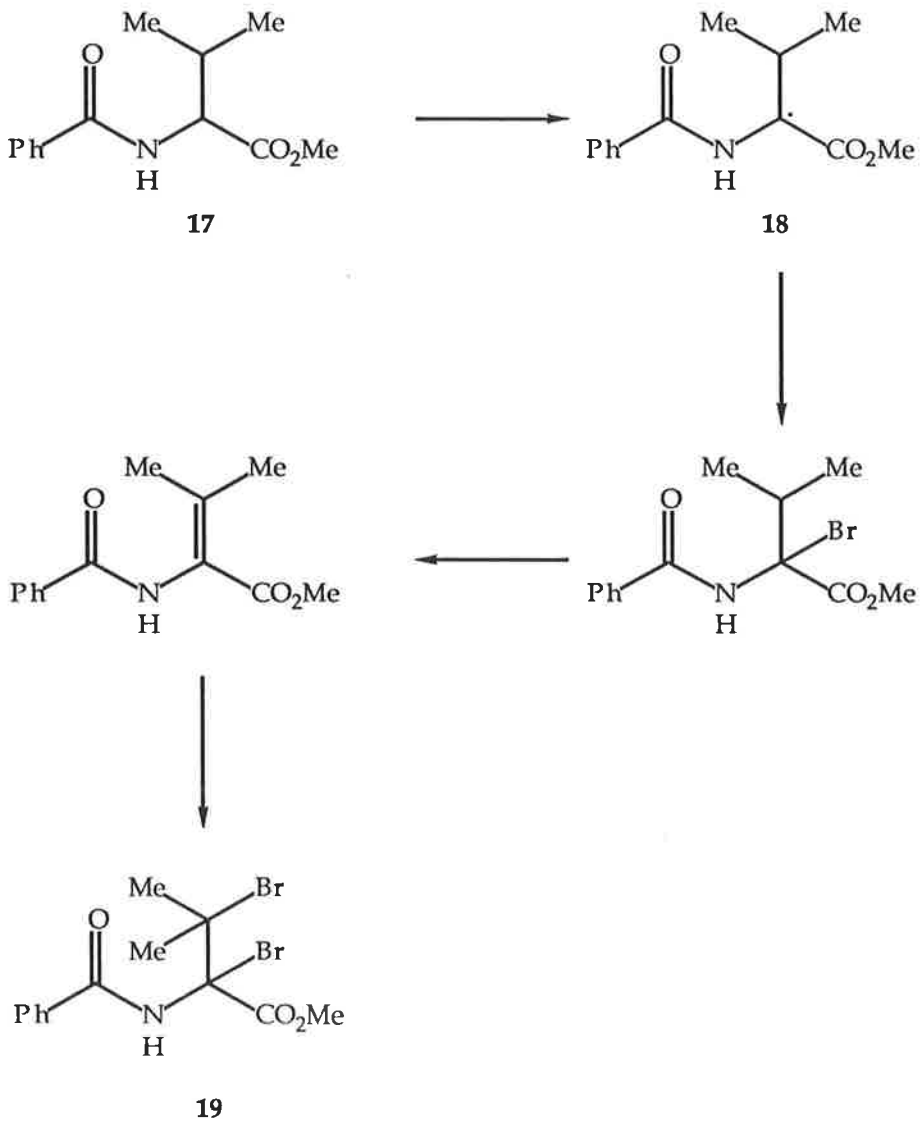
Scheme 5

The hydrogen abstracting species in the chlorination reaction are electrophilic and abstraction proceeds through a transition state of little radical character. Consequently, reaction at the α-carbon of **14** is disfavored by the inductively electron withdrawing methoxycarbonyl substituent.

Radicals such as **11** and **12** are termed captodative radicals.[45] The term captodative reflects the combined resonance effect imparted by the electron-withdrawing (capto) and electron-donating (dative) moieties. Expressions other than captodative have been coined to describe radicals of this type, such as merostabilization[46,47], by Katritzky *et. al.*, and push-pull resonance,[48,49] by Balaban. Much debate has centered on whether the combined action of both the capto and dative groups leads to synergistic stabilization of this class of radicals. A synergistic effect is deemed to be operative in stabilization of these radicals if the overall stabilizing effect of an electron-withdrawing and an electron-donating group is greater than the sum of the effects of the individual groups.[50,51,52,53,54,55,56,57] Irrespective of the existence or not of a synergistic effect, the combined action of stabilization by electron-donating and electron-withdrawing moieties greatly facilitates the formation of radicals such as **11** and **12**.

In contrast to the ease of formation of **11** and **12**, the formation of α-carbon centered radicals from di-*N*-acylated amino acid derivatives is disfavored.[58] This is illustrated by the reactions of *N*-benzoylvaline methyl ester (**17**) and

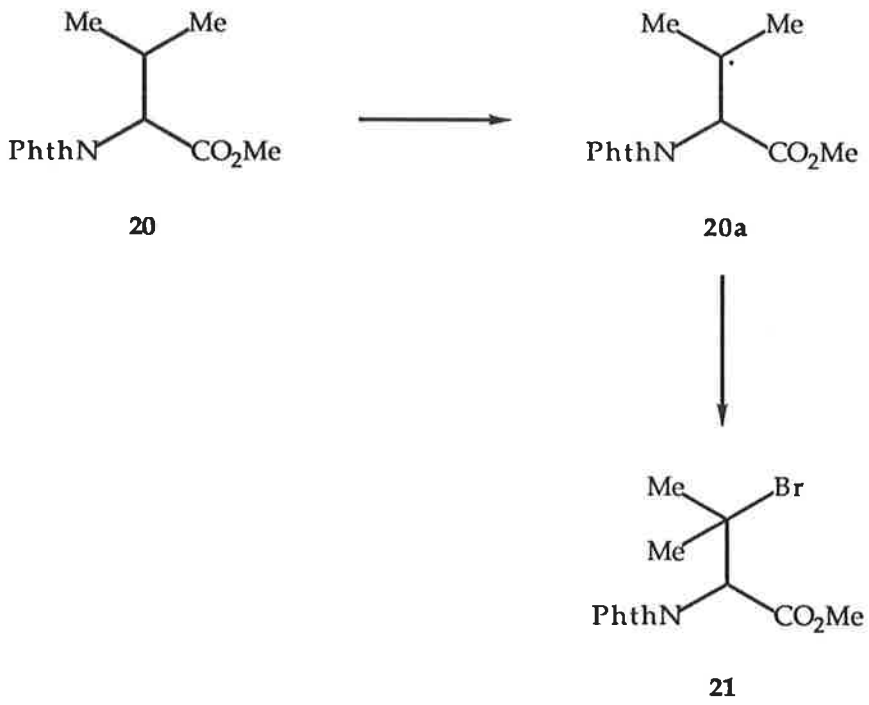
N-phthaloylvaline methyl ester (**20**) with NBS, to afford the dibromide **19** and the β-brominated amino acid derivative **21**, respectively. Reaction of **17** by hydrogen atom abstraction gives the α-centered radical **18**, followed by bromine atom incorporation, elimination of hydrogen bromide and bromine addition, to give **19** (Scheme 6).



17 **18** **19**

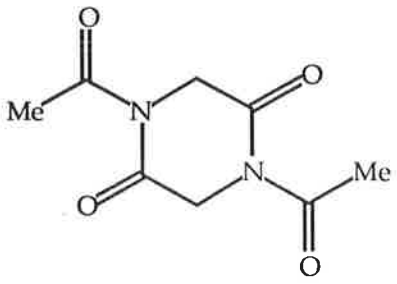
Scheme 6

In direct contrast, the abstraction of hydrogen atom from the β-carbon of **20** gives **20a**. Subsequent incorporation of bromine to the radical **20a** affords the product **21** (Scheme 7).



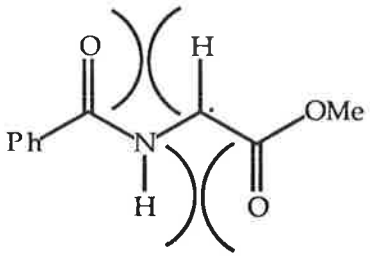
Scheme 7

It was envisaged that the contrasting effects of *N*-acyl and di-*N*-acyl substituents on the reactivity of acyclic amino acid derivatives would also affect the reactivity of cyclic dipeptides. To examine the effect of *N*-alkyl and *N*-acyl substitutents on halogenation of diketopiperazines, and thus the effect of *N*-acyl and di-*N*-acyl groups on reactivity in these systems, reactions of *N*-alkyl and *N*-acyl substituted piperazinediones such as **5** and **22** with NBS, were investigated and compared. This study is presented in Chapter 2 of the Results and Discussion of this thesis.



22

Whilst *N*-substituents are known to affect the facility of the radical reactions of amino acid derivatives, α-substituents can also affect reactivity in these systems. Radical reactions of amino acid derivatives have been observed to be selective for reaction of glycine residues.[59,60,61] This selectivity has been attributed to the relative stability and ease of formation of α-centered glycinyl radicals **23**. The greater stability of α-centered glycinyl radicals **23** in comparison to α-substituted radicals **24** of acyclic amino acid derivatives was ascribed to the ability of the former to adopt planar conformations which are relatively free of non-bonding interactions. In these conformations there is maximum delocalization of the unpaired spin density through overlap of the semi-occupied p-orbital of the radical, with the π-systems of the capto and dative groups. α-Substituted radicals **24** are destabilized compared to glycinyl radicals **23** due to the severity of the non-bonding interactions which distort the former from planarity, reducing orbital overlap and resonance stabilization of the radical, as a consequence. The larger and more bulky the α-side chain, the greater the distortion of the radical from planarity.



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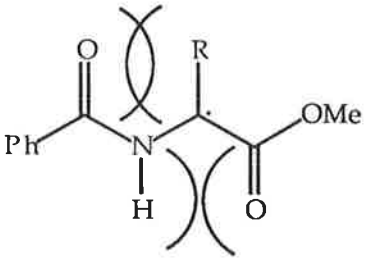


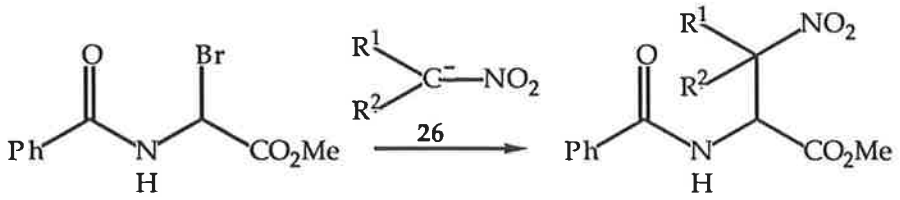
24

It was considered likely that α-substituents would also affect the reactivity of amino acid residues in cyclic dipeptides, and an investigation of the relative reactivity of glycine and α-substituted amino acid residues in diketopiperazines is presented in Chapter 2 of this thesis.

One of the objectives of the investigation of the halogenation of 2,5-piperazinediones, described in Chapters 1 and 2 of this thesis, was to develop procedures for the regioselective synthesis of asymmetrically functionalized 2,5-piperazinedione derivatives, suitable for further synthetic elaboration. Derivatives of α-haloamino acids have been utilized diversely in synthesis, as facile electrophilic glycine templates susceptible toward a variety of nucleophiles, including enamines,[62] Grignard reagents,[63] thioacetates,[64] alkyl malonates,[65,66] trialkyl phosphites and phosphines,[67] diazomethane,[68] mixed cuprates[69] and many others[69,70,71] used in conjunction with Lewis acids. By analogy with their acyclic counterparts 3,6-dibromo-2,5-piperazinedione derivatives have also been modified with a variety of oxygen[72,73] and sulfur nucleophiles.[35,39,74,75]

Elaboration of α-bromoamino acid derivatives by reaction with alkyl nitronates,[76] considered to proceed by an electron transfer mechanism,[75,77,78] and by reaction with allylic stannanes,[79,80,81] *via* radical carbon-carbon bond formation, has also been reported.

In Chapter 3 of this thesis a variety of techniques, amenable to elaboration of acyclic α-bromoglycine derivatives, have been applied to the elaboration of α-bromo-2,5-diketopiperazines. One of the chosen techniques was based on the report of the reactions of a variety of alkylnitronates **26** with *N*-benzoyl-2-bromoglycine methyl ester (**25**) to give the corresponding β-nitroamino acid derivatives **27** (Scheme 8).[76]

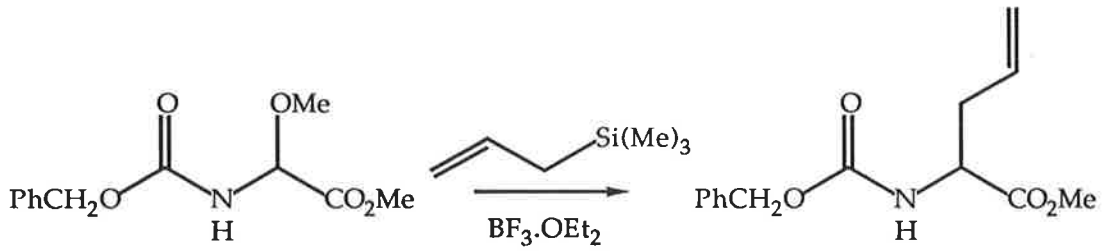


25 **27**

	R^1	R^2
(a)	H	H
(b)	Me	Me
(c)	Me	H
(d)	Ph	H
(e)	CO_2Me	H

Scheme 8

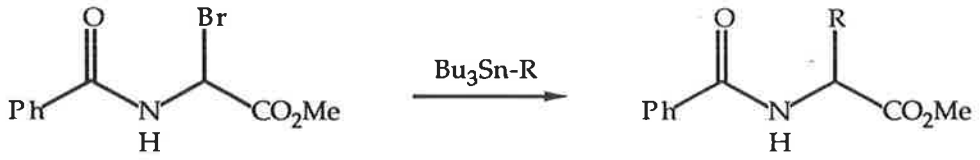
Another approach employed in the work involved the treatment of α-functionalized-2,5-diketopiperazines with allyltrimethylsilane and boron trifluoride etherate. Castelhano*et. al.* have reported the transformation of the acyclic α-methoxyamino acid derivative **28** to the corresponding α-allylamino acid derivative **29**[82] utilizing allyltrimethylsilane and boron trifluoride etherate as the allylating and Lewis acid agents, respectively (Scheme 9).



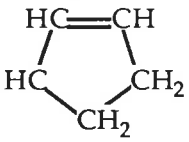
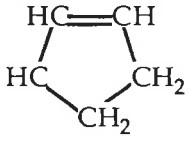
28 **29**

Scheme 9

The third approach used for the elaboration of α-halo-2,5-piperazinediones, described in Chapter 3 of this thesis utilizes the radical allyl transfer technique that has been shown to be amenable to elaborations of acyclic α-bromoglycine derivatives.[79-81] For example, treatment of *N*-benzoyl-2-bromoglycine methyl ester (**25**) with allyltributylstannanes gave the corresponding allyl glycine derivatives **30** (Scheme 10).[80,81]

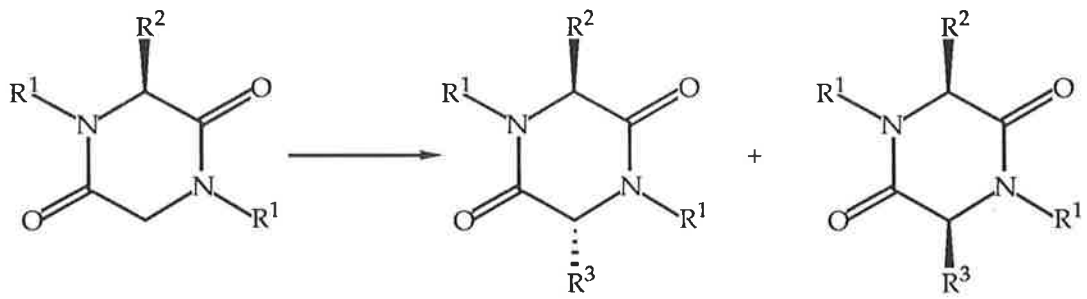


25 **30**

	Bu_3Sn-R	**30**
(a)	R = CH_2-CH=CH_2	CH_2-CH=CH_2
(b)	R = CH_2-CMe=CH_2	CH_2-CMe=CH_2
(c)	R = CH_2-CH=CHMe	CHMe-CH=CH_2
(d)	R = CHMe-CH=CH_2	CH_2-CH=CHMe
(e)	R = CMe_2-CH=CH_2	CH_2-CH=CMe_2
(f)	R = 	

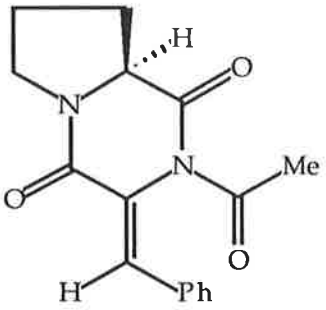
Scheme 10

Functionalization at the α-carbon of 2,5-piperazinedione derivatives, introduces a chiral center to the molecule, while, functionalization of a 3-substituted-2,5-piperazinedione at the 6-position also results in the formation of diastereomers (Scheme 11), with the possibility of **diastereoselectivity** .

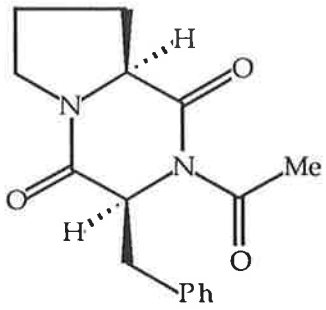


Scheme 11

The potential of an amino acid residue to act as an inbuilt chiral auxiliary and exert stereocontrol in formation of the new chiral center within a cyclic dipeptide, has been reported.[83,84] The earliest report of this phenomenon was the hydrogenation of the benzylidene derivative **31**, to afford the saturated product **32** in greater than 90% diastereomeric excess.[83]

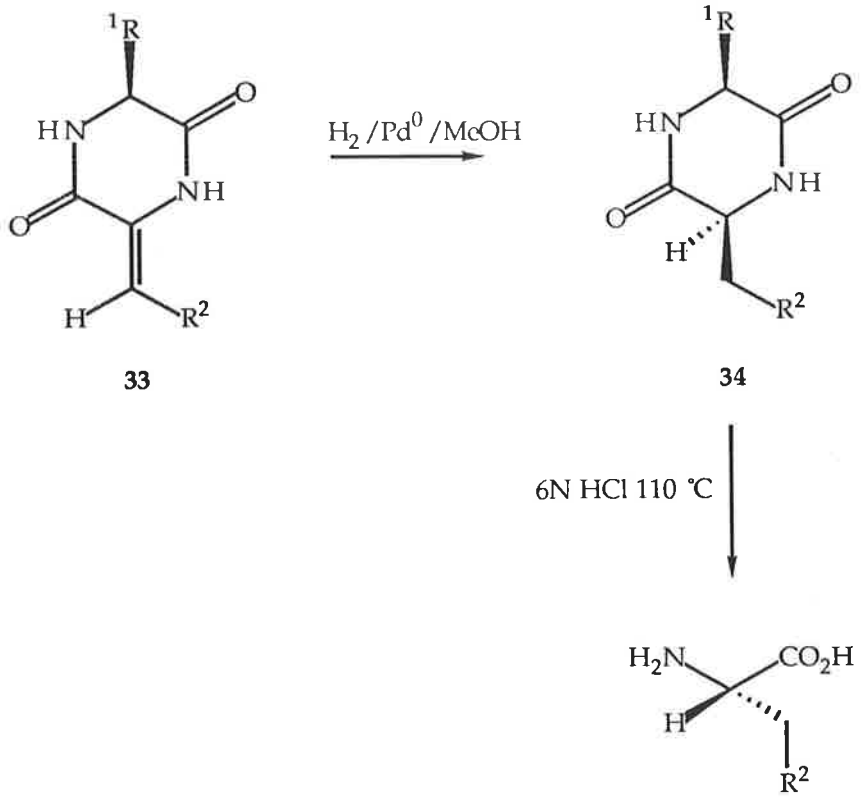


31



32

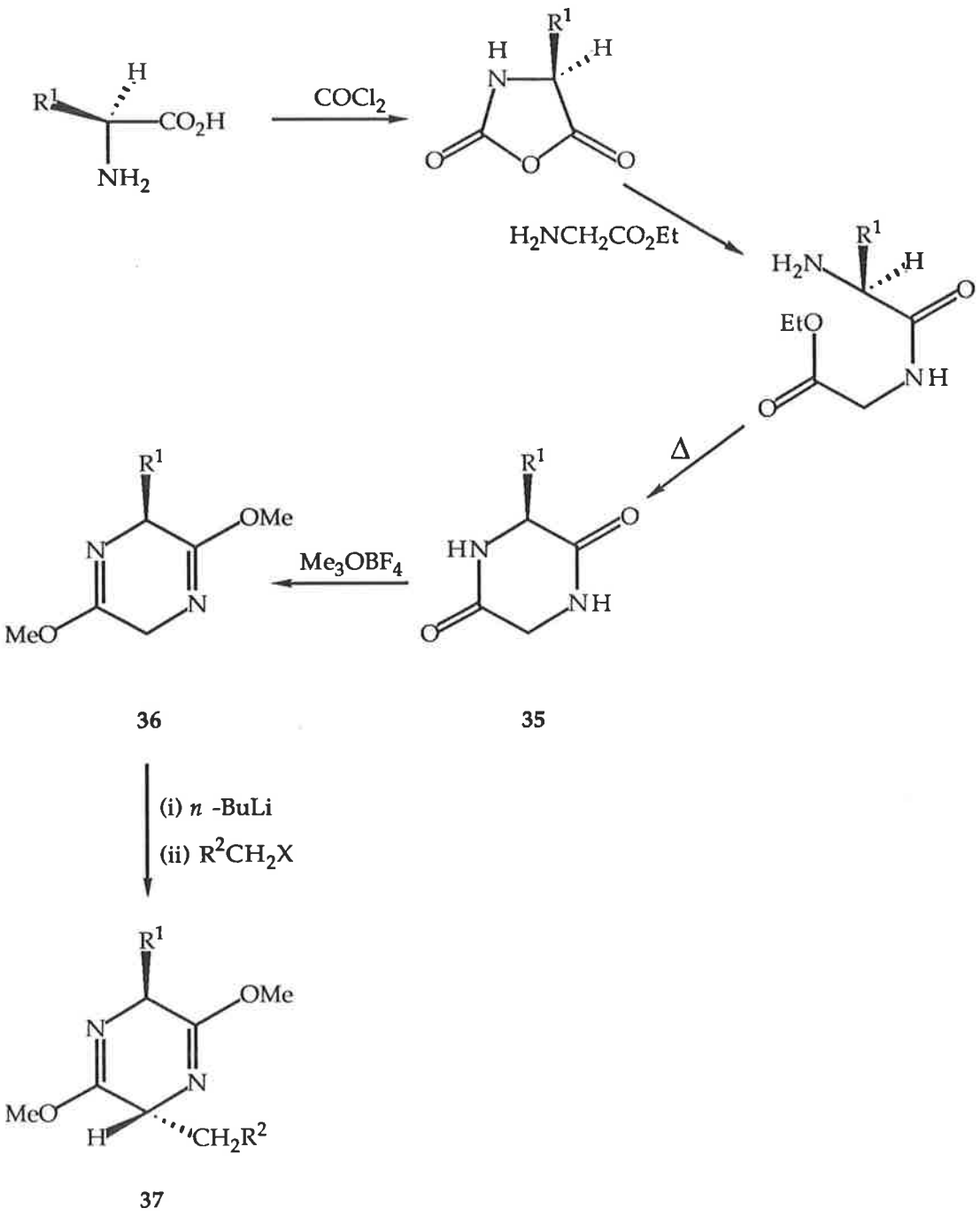
Since then there has been a number of papers by Izumiya and co-workers,[84] dealing with the preparation and stereoselective reduction of dehydropiperazinediones **33**. Catalytic hydrogenation of compounds of this type is generally observed to proceed with very high levels of asymmetric induction (Scheme 12). The saturated amino acid residue in **33** directs hydrogenation to occur from the least hindered *anti* - face of the piperazinedione ring at the unsaturated amino acid residue, affording the *syn* -product **34** in all cases.



33 **34**

Scheme 12

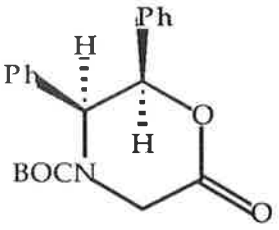
In addition, there have been reports on the elaboration of other ring systems which possess an inbuilt chiral auxiliary. Bis-lactim ethers have been used to prepare a large variety of optically active amino acids.[85,86] The general protocol involves peptide coupling of two amino acids, formation of the piperazinedione ring **35** and subsequent conversion to the bis-lactim ether **36** with trimethyloxonium **tetrafluoroborate** . The bis-lactim ether **36** is then metallated and subsequent alkylation furnishes the homologated bis-lactim ether **37** (Scheme 13). The electrophiles add *anti* - to the substituent in **36**, in a highly stereoselective manner.



36 **35**

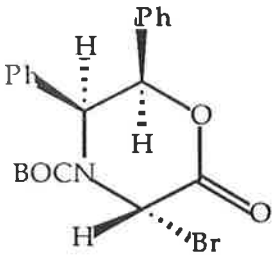
37

Scheme 13



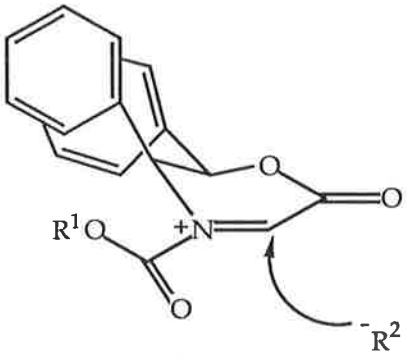
38

NBS, CCl_4

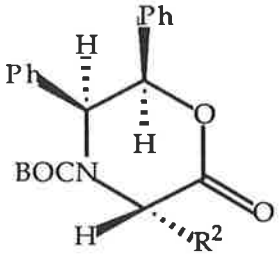


39

R^2M, solvent
$ZnCl_2$

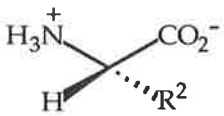


40



41

(a) H_2, Pd^0, EtOH
20-50 psi *or*
(b) Li, NH_3
THF, EtOH



for BOC = CBZ: (a) or (b)
for BOC = t-BOC: (b)

Scheme 14

The synthesis of optically active amino acids by elaboration of the α-bromides of chiral oxazinones **38** has also been reported.[70,87] Reaction of the α-bromoxazinones **39** with various organometallic reagents in the presence of zinc (II) chloride results in displacement of the halogen, providing the homologated oxazinones **41** (Scheme 14). In most cases, the reactions proceed with net retention. It is thought that the zinc (II) salt coordinates to the halogen affording an iminium species **40**, with approach of the organometallic reagent from the sterically less encumbered face of **40**, *anti* - to the two phenyl substituents.

In view of the diastereoselectivity observed in these systems, the asymmetric induction in reactions involving the elaboration of 3-halo-2,5-diketopiperazines was investigated. That work is also described in Chapter 3 of this thesis.

RESULTS and DISCUSSION

CHAPTER 1

Halogenation of Symmetric Diketopiperazines

In order to investigate reactions of symmetric cyclic dipeptides with NBS, it was necessary to synthesize substrate 2,5-diketopiperazines. 1,4-Di-(p-methoxybenzyl)-2,5-piperazinedione (**8**) and 1,4-dibenzyl-2,5-piperazinedione (**13**) were prepared by alkylation of glycine anhydride (**42**) with p-methoxybenzyl chloride and benzyl bromide,[39,88] respectively, as shown in Scheme 15. Sarcosine anhydride (**5**) and glycine anhydride (**42**) were prepared by heating the respective parent amino acids in anhydrous ethylene glycol at reflux[89] to effect the net removal of two mole equivalents of water. The anhydrides **5**, **8**, and **13** thus prepared, possessed satisfactory physical and spectral properties consistent with those reported previously.[75,90]

42

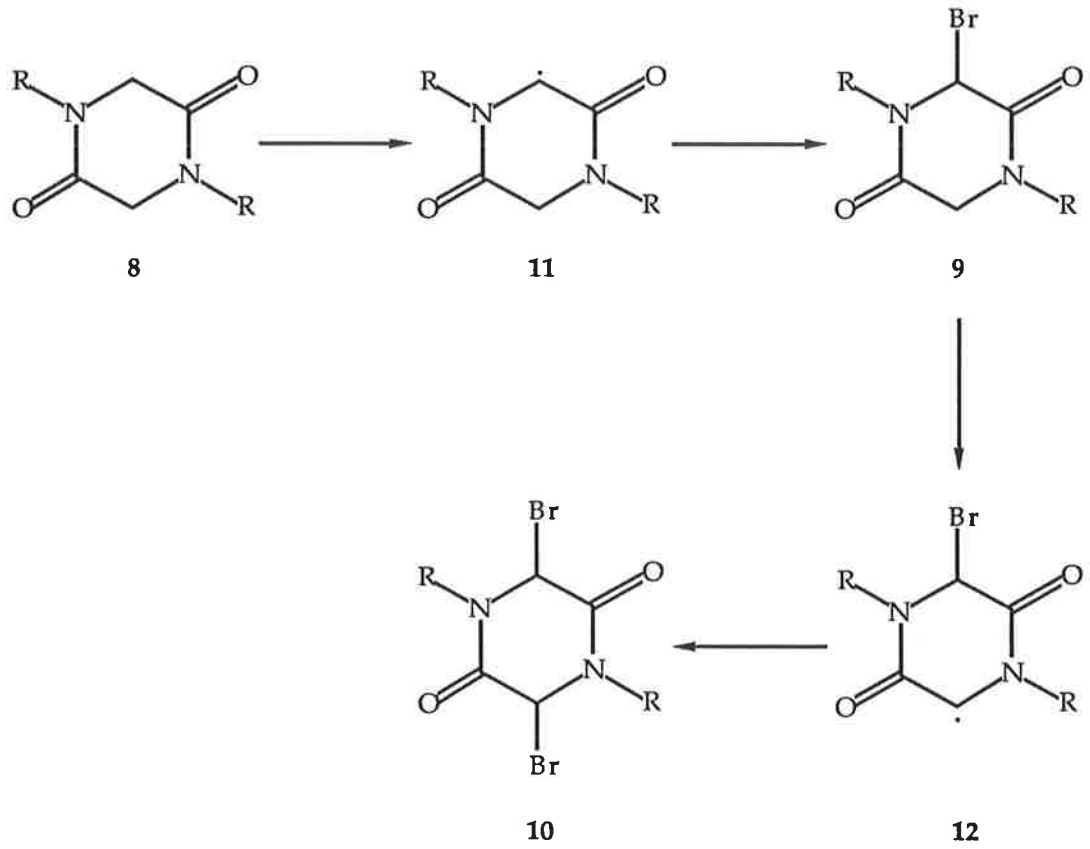
8 R = CH_2Ph-*p*-OMe

13 R = CH_2Ph

Scheme 15

1,4-Di-(p-methoxybenzyl)-2,5-piperazinedione (**8**) was treated with 0.9 mole equivalents of NBS in refluxing carbon tetrachloride under nitrogen, with reaction initiated by the presence of a trace amount of AIBN and by irradiation with a 300-W mercury lamp. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy, after evaporation of the solvent, indicated the presence of starting material **8**, the monobromide **9**, and the dibromide **10**, in the ratio *ca.* 2: 6: 1. The ^{1}H NMR spectrum showed characteristic resonances for the monobromide **9**, including AB q resonances at δ 3.82 and δ 3.94 ($J_{AB\,q}$ = 18 Hz), for the protons at the α'-carbon of the piperazinedione ring, and at δ 3.91 and δ 5.18 ($J_{AB\,q}$ = 14 Hz) and δ 4.26 and δ 4.84 ($J_{AB\,q}$ = 14.5 Hz), for the pairs of diastereotopic benzylic hydrogens, as well as a singlet resonance at δ 5.79 for the hydrogen of the carbon bearing the bromine. The dibromide **10** was identified by comparison with the ^{1}H NMR spectrum of an authentic sample, prepared by treatment of **8** with 2.1 mole equivalents of NBS. The dibromide **10** thus obtained was a single diastereomer and exhibited characteristic resonances including a singlet resonance at δ 5.87, attributable to the α-hydrogens of the piperazinedione

ring, together with an AB q resonance at δ 3.96 and δ 5.26 ($J_{AB\ q}$ = 14.5 Hz), for the diastereotopic benzylic hydrogens.

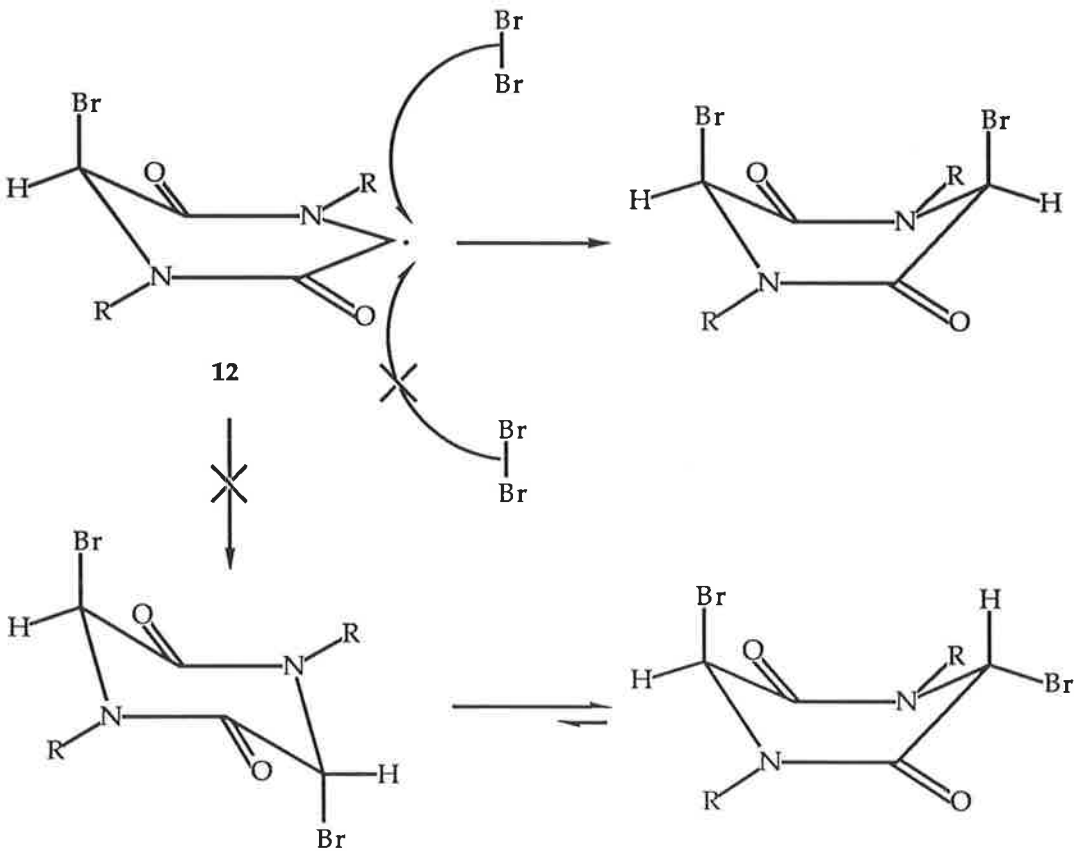


R = CH_2Ph-*p*-OMe

Scheme 16

There was no interconversion between the starting material **8**, the monobromide **9** and the dibromide **10** in carbon tetrachloride or dichloromethane, at room temperature or at reflux, unless NBS was present and either AIBN or ultra-violet light was used to initiate the reaction. On this basis it is likely that the reactions of **8** with NBS proceed through a radical pathway (Scheme 16). The diastereoselective formation of **10**

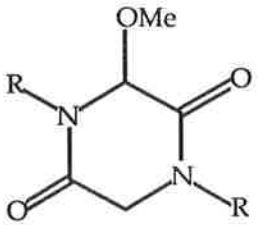
can be attributed to stereoelectronically controlled axial incorporation to the intermediate radical **12**[91,92] resulting in the formation of the thermodynamically more stable *syn*-diastereomer (Figure 1.1).[30,39,93] Previous reports have attributed *syn*-diastereoselectivity in 3,6-disubstituted diketopiperazines to a known propensity of *N,N'*-disubstituted diketopiperazines to adopt a boat-like conformation that places the 3- and 6-substituents pseudoaxial to minimize steric compression with the substituents attached to the amide nitrogen atoms.[39]



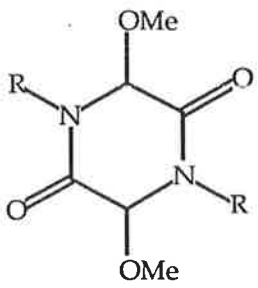
R = CH_2Ph-*p*-OMe

Figure 1.1 Incorporation of bromine to **12** to give the thermodynamically more stable *syn*-diastereomer **10**.

Since the bromides **9** and **10** were found to be insufficiently stable for isolation and purification they were converted to the corresponding ethers **43** and **45**, respectively, for characterization. The filtrate of a reaction mixture obtained by treatment of **8** with 2.1 mole equivalents of NBS was concentrated and then treated with methanol and triethylamine at 0 °C. Work-up and chromatography of the residue on silica afforded a 2: 1 mixture of the diastereomers of 3,6-dimethoxy-1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**45**), in 55% yield from **8**. The characteristic resonances in the ^{1}H NMR spectrum for the major diastereomer of the mixture were singlets at δ 3.44, for the methoxy sustituents attached to the piperazinedione ring, and δ 4.78, for the α-hydrogens, as well as an AB q resonance at δ 4.02 and δ 5.24 ($J_{AB\,q}$ = 14 Hz), for the diastereotopic benzylic hydrogens. The characteristic resonances in the ^{1}H NMR spectrum for the minor diastereomer of the mixture were singlets at δ 3.49, for the methoxy sustituents attached to the piperazinedione ring, and δ 4.64, for the α-hydrogens, as well as an AB q resonance at δ 4.06 and δ 5.11 ($J_{AB\,q}$ = 14.5 Hz), for the diastereotopic benzylic hydrogens. The mass spectrum of the mixture of diastereomers of **45** gave rise to peaks at 382 and 121, corresponding to loss of methanol from the molecular ion and production of the p-methoxybenzyl cation, respectively. The identity of **45** was established rigorously through attainment of satisfactory microanalytical data.



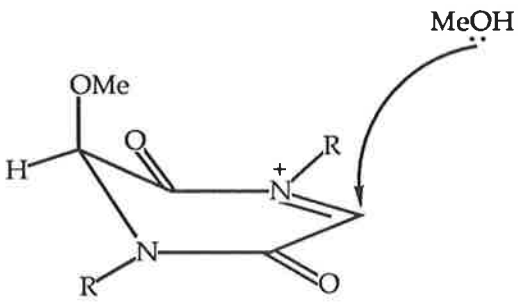
43



45

R = CH_2Ph-*p*-OMe

The formation of **45** from the dibromide **10**, is most likely to proceed through nucleophilic attack of methanol on the corresponding iminium species **44a**. Presumably, the observed diastereoselectivity reflects the preference for the formation of the *syn*-diastereomer in a stereoelectronic and thermodynamically controlled manner.[94]



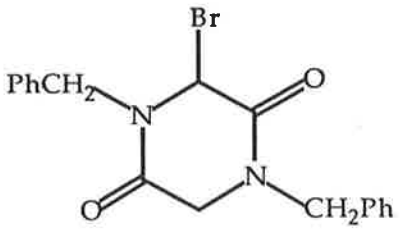
44a R = CH_2Ph-*p*-OMe
44b R = CH_2Ph
44c R = Me

Figure 1.2 Incorporation of methanol to the iminium ions **44a-c**.

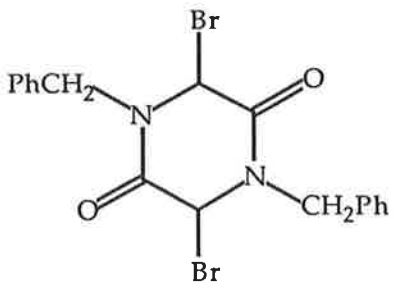
The filtrate of a mixture obtained by reaction of **8** with 0.9 mole equivalents of NBS was concentrated. Treatment with methanol and triethylamine at 0 °C, subsequent work-up and chromatography of the residue on silica, gave 1,4-di-(p-methoxybenzyl)-3-methoxy-2,5-piperazinedione (**43**), in 41% yield based on **8**. Characteristic resonances in the ^{1}H NMR spectrum of the monoether **43** were singlets at δ 3.39, for the protons of the methoxy substituent attached to the piperazinedione ring, and at δ 4.67, for the hydrogen of the carbon bearing the methoxy substituent. In addition, AB q resonances at δ 3.78 and δ 4.02 ($J_{AB\ q}$ = 18 Hz), for the hydrogens of the α'-carbon of the piperazinedione ring, and at δ 4.11 and δ 5.05 ($J_{AB\ q}$ = 14.5 Hz) and δ 4.33 and δ 4.68 ($J_{AB\ q}$ = 14.5 Hz), for the pairs of diastereotopic benzylic hydrogens, were observed. The mass spectrum of **43** gave rise to peaks at 384 and 121, attributable to the parent ion and production of the p-methoxybenzyl cation, respectively. The identity of **43** was confirmed by elemental analysis. The yield of **43** was subsequently improved to 56% by using a 9:1 mixture of carbon tetrachloride/chloroform as the solvent for the bromination reaction. This increase in chemical yield may be attributed to the greater solubility of the monobromide **9** in the mixed solvent during filtration of the succinimide byproduct.

The conditions employed for the bromination of **8** and the methoxylation technique used for the subsequent characterization of the bromides **9** and **10**, described above, were utilized in the investigation of the cyclic dipeptide derivative **13**. Reaction of 1,4-dibenzyl-2,5-piperazinedione (**13**) with 0.9 mole equivalents

of NBS and analysis of the crude reaction mixture by ^{1}H NMR spectroscopy, after evaporation of the solvent, indicated the presence of **13**, the monobromide **46** and the dibromide **47**, in the ratio *ca.* 1: 6: 1. The ^{1}H NMR spectrum showed characteristic resonances for the monobromide **46**, including AB q resonances at δ 3.87 and δ 3.99 ($J_{AB\ q}$ = 18 Hz), for the protons attached to the α'-carbon of the piperazinedione ring, and at δ 3.94 and δ 5.24 ($J_{AB\ q}$ = 14.5 Hz) and δ 4.32 and δ 4.93 ($J_{AB\ q}$ = 14.5 Hz), for the pairs of diastereotopic benzylic hydrogens, as well as a singlet resonance at δ 5.84. for the hydrogen of the carbon bearing the bromine. The dibromide **47** was identified by comparison with the ^{1}H NMR spectrum of an authentic sample, prepared by treatment of **13** with 2.1 mole equivalents of NBS.



46

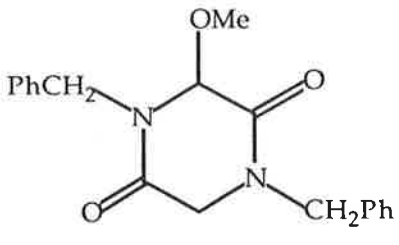


47

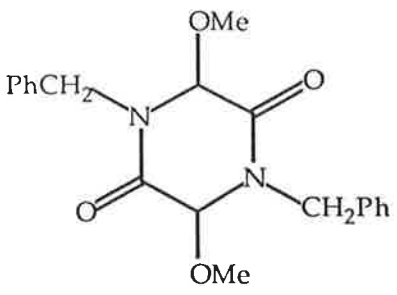
The dibromide **47** thus obtained was a single diastereomer and exhibited characteristic resonances including an AB q resonance at δ 4.03 and δ 5.34 ($J_{AB\ q}$ = 14.6 Hz), for the diastereotopic benzylic hydrogens, and a singlet resonance at δ 5.90, attributable to the hydrogens of the α-carbons. The attainment of

a single diastereomer of the dibromide **47** may be rationalized as described above for **10**.

The mixture obtained from treatment of **13** with 0.9 mole equivalents of NBS was subjected to methanolysis for characterization purposes. After work-up, chromatography of the residue on silica afforded 1,4-dibenzyl-3-methoxy-2,5-piperazinedione (**48**), in 61% yield based on **13**. Characteristic resonances in the ^{1}H NMR spectrum of the monoether **48** included singlets at δ 3.41, for the protons of the methoxy substituent, and δ 4.70, attributable to the hydrogen of the carbon bearing the methoxy substituent. In addition, AB q resonances at δ 3.80 and δ 4.06 ($J_{AB\ q}$ = 18 Hz), for the hydrogens of the α'-carbon of the piperazinedione ring, and at δ 4.18 and δ 5.15 ($J_{AB\ q}$ = 15 Hz) and δ 4.38 and δ 4.76 ($J_{AB\ q}$ = 14.5 Hz), for the pairs of diastereotopic benzylic hydrogens, were observed. The mass spectrum of **48** gave rise to peaks at 293 and 91, corresponding to loss of the methoxy group from the molecular ion and production of the benzyl cation, respectively. Elemental analytical data for **48** was also found to be satisfactory.



48

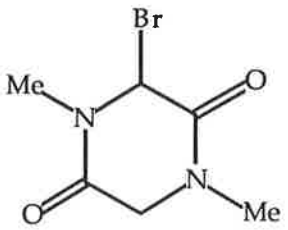


49

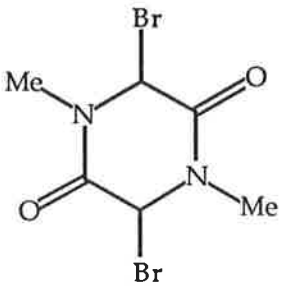
Methanolysis of the authentic sample of the dibromide **47**, work-up and subsequent chromatography afforded 1,4-dibenzyl-3,6-dimethoxy-2,5-piperazinedione (**49**), in 66% yield from **13**, as a single diastereomer. The other diastereomer could not be detected either in the crude reaction mixture or in the purified product. In the ^{1}H NMR spectrum of the diether **49** the characteristic resonances exhibited were a singlet at δ 3.46, for the protons of the methoxy sustituents attached to the piperazinedione ring, an AB q resonance at δ 4.17 and δ 5.11 ($J_{AB\ q}$ = 15 Hz), for the diastereotopic benzylic hydrogens, and a singlet resonance at δ 4.69, attributable to both α-hydrogens. The mass spectrum of **49** afforded peaks at 322 and 91, corresponding to loss of methanol from the molecular ion and production of the benzyl cation, respectively. Satisfactory elemental analytical data was obtained to unambiguously confirm the composition of **49**. By analogy with **45**, the *syn*-diastereomer of **49** would be expected to predominate. By analogy with the rationale for the selectivity reported in the formation of disulfides from dibromides such as **10** and **47**,[39] the greater diastereoselectivity in the production of **49** than **45** can be attributed to the relative stabilities of the iminium species **44b** and **44a**, respectively.[39]

The conditions employed above for the reactions of **8** and **13** with NBS, were utilized in the reactions of 1,4-dimethyl-2,5-piperazinedione (**5**), except that the reactions were carried out in refluxing dichloromethane because sarcosine anhydride (**5**) was found to be insoluble in carbon tetrachloride, the solvent most commonly used in reactions with NBS. Analysis by ^{1}H NMR

spectroscopy of the crude reaction mixture produced by treatment of **5** with 0.9 mole equivalents of NBS and evaporation of the solvent, indicated the presence of **5**, the monobromide **50** and the dibromide **51**, in the ratio *ca.* 5: 15: 1. The ^{1}H NMR spectrum showed characteristic resonances for the monobromide **50**, including singlets at δ 3.01 and δ 3.06, for the non-equivalent *N*-methyl protons, and at δ 6.02, for the hydrogen of the carbon bearing the bromine, as well as an AB q resonance at δ 3.92 and δ 4.16 ($J_{AB\ q}$ =18 Hz), for the geminal α'-protons. The dibromide **51** was identified by comparison with an authentic sample, prepared by treatment of **5** with 2.1 mole equivalents of NBS. The dibromide **51** thus obtained was a single diastereomer and exhibited singlet resonances at δ 3.10, attributable to the *N*-methyl protons, and at δ 6.13, attributable to the α-hydrogens. The attainment of a single diastereomer of the dibromide **51** may be rationalized as described above for **10**.



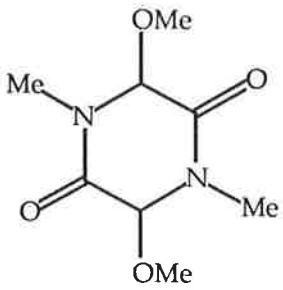
50



51

The mixture obtained from the treatment of **5** with 0.9 mole equivalents of NBS was subjected to methanolysis for characterization purposes. Work-up and subsequent chromatography afforded 1,4-dimethyl-3-methoxy-2,5-piperazinedione (**7**), in 54% yield, with spectral properties

consistent with those reported previously.[30,37] Methanolysis of the dibromide **51**, work-up and subsequent chromatography, gave 3,6-dimethoxy-1,4-dimethyl-2,5-piperazinedione (**52**) as a 3:1 mixture of diastereomers, in 68% yield as a colorless oil. Trituration of the oil with ether/light petroleum followed by slow evaporation of the solvent allowed crystallization of the minor diastereomer. Both diastereomers were found to exhibit spectral properties consistent with those reported previously.[72]



52

The above results show that the monobromides **9**, **46** and **50** can be produced through reaction of the corresponding symmetric diketopiperazines **5**, **8** and **13** with NBS. This is in direct contrast to the report by Williams and Kwast,[40] that bromination of symmetric diketopiperazines shows a strong tendency to afford dibrominated products, as illustrated by the reaction of **8** with 0.9 mole equivalents of NBS in carbon tetrachloride to give *ca.* 50% starting material **8** and *ca.* 50% of the dibromide **10**. In fact, whereas the results described above indicate that the reactions of **5, 8** and **13** are faster than those of the corresponding monobromides **9**, **46** and **50**, the results of Williams and Kwast[40] show the converse.

To obtain a quantitative measure of the relative rates of reaction of **5**, **8** and **13**, and **9**, **46** and **50**, the reactions of **5**, **8** and **13** with increasing amounts of NBS were studied. The relative percentage concentrations of **5**, **8** and **13**, and **9**, **46** and **50**, and **10**, **47** and **51**, were determined by analysis of the high field ^{1}H NMR spectra of crude reaction mixtures, as a function of the extent of bromination. The extent of bromination was measured as the summation of the concentrations of the monobromides **9**, **46** and **50** and the dibromides **10**, **47** and **51**, taking into account that bromination occurs twice in the formation of **10**, **47** and **51**. The results are expressed in both tabular (Tables 1.1 - 1.3) and graphical (Figures 1.3 - 1.5) forms.

A general trend is evident in the reactions of **5**, **8** and **13**. Initially the concentrations of the monobromides **9**, **46** and **50** increase at the expense of the corresponding starting materials **5**, **8** and **13**. As the amount of NBS is increased further the concentrations of the dibromides **10**, **47** and **51** increase, whilst those of the monobromides **9**, **46** and **50** decrease. For the consecutive reactions:

$$\mathbf{8} \xrightarrow{k_1} \mathbf{9} \xrightarrow{k_2} \mathbf{10} \qquad \text{(i)}$$

the concentration of the monobromide **9** reaches a maximum when

$$d[\mathbf{9}]/dt = k_1\,[\mathbf{8}]\,[Br^{\bullet}] - k_2\,[\mathbf{9}]\,[Br^{\bullet}] = 0 \qquad \text{(ii)}$$

At this point

$$k_1/k_2 = [\mathbf{9}]/[\mathbf{8}] \qquad \text{(iii)}$$

Table 1.1 and Figure 1.3. Percentage Molar Ratios of **8**, **9** and **10** as a Function of the Extent of Bromination with NBS

Extent of Bromination	Substrate **8**	Monobromide **9**	Dibromide **10**
0.00	1.00	0.00	0.00
0.73	0.35	0.57	0.08
0.82	0.25	0.68	0.07
0.98	0.17	0.68	0.15
1.14	0.06	0.74	0.20
1.23	0.02	0.73	0.25
1.53	0.00	0.47	0.53
1.72	0.00	0.28	0.72
1.78	0.00	0.22	0.78
2.00	0.00	0.00	1.00

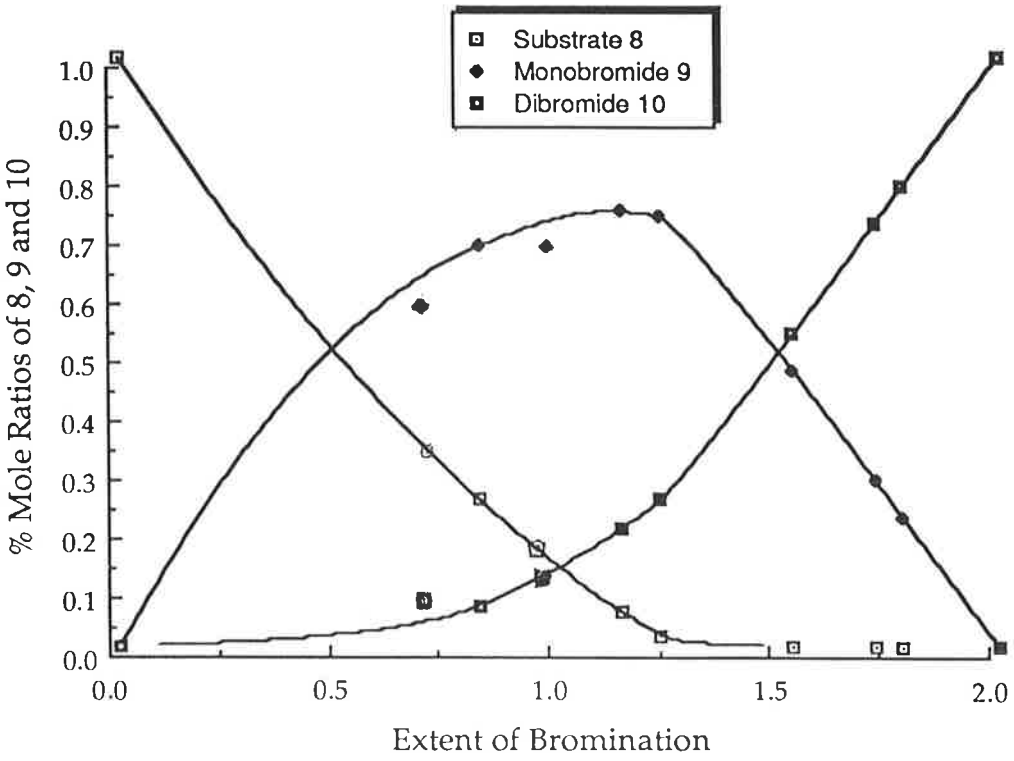


Table 1.2 and Figure 1.4. Percentage Molar Ratios of **13**, **46** and **47** as a Function of the Extent of Bromination with NBS

Extent of Bromination	Substrate **13**	Monobromide **46**	Dibromide **47**
0.00	1.00	0.00	0.00
0.77	0.31	0.61	0.08
1.02	0.11	0.76	0.13
1.22	0.00	0.78	0.22
1.39	0.00	0.61	0.39
2.00	0.00	0.00	1.00

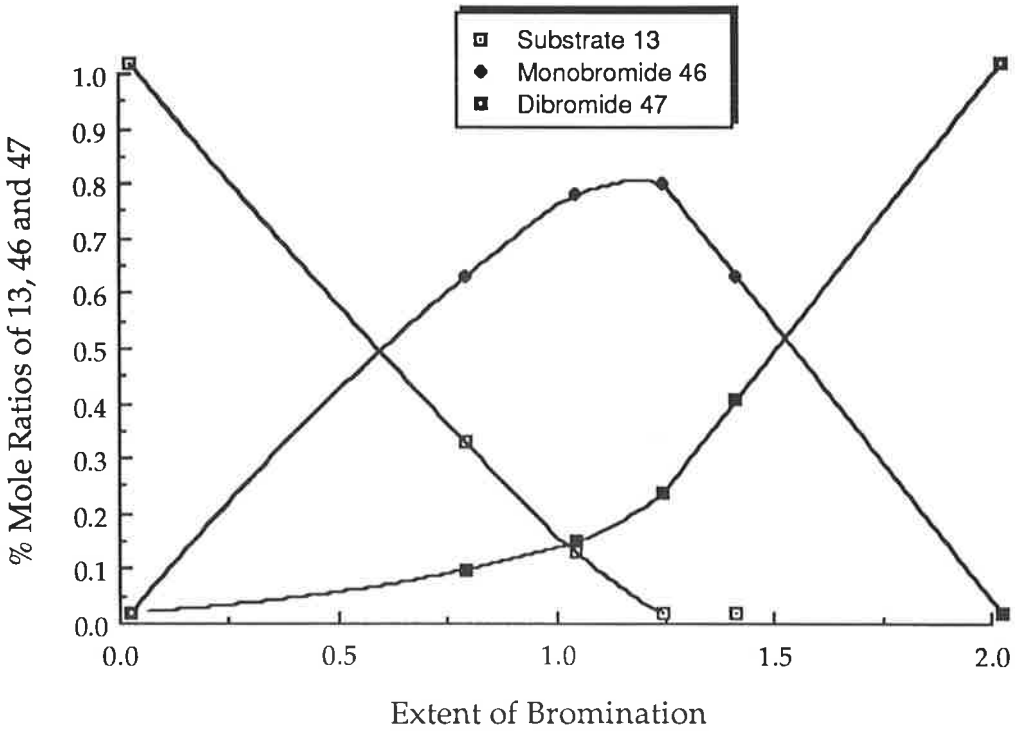
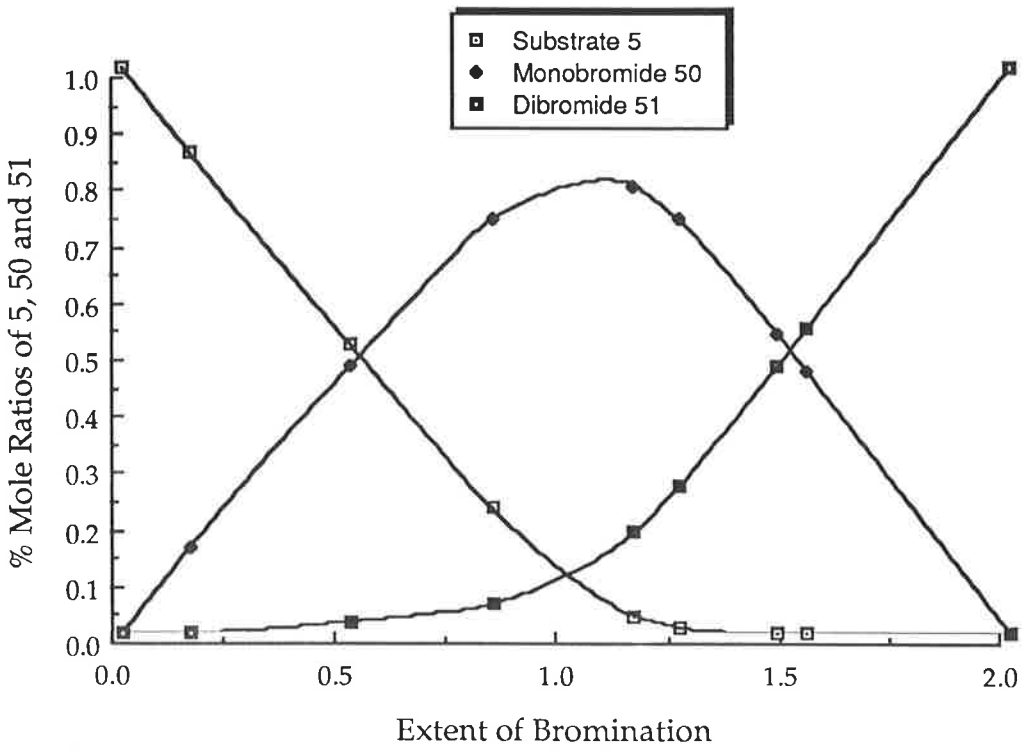


Table 1.3 and Figure 1.5. Percentage Molar Ratios of **5**, **50** and **51** as a Function of the Extent of Bromination with NBS

Extent of Bromination	Substrate **5**	Monobromide **50**	Dibromide **51**
0.00	1.00	0.00	0.00
0.15	0.85	0.15	0.00
0.51	0.51	0.47	0.02
0.83	0.22	0.73	0.05
1.15	0.03	0.74	0,20
1.23	0.02	0.79	0.18
1.25	0.01	0.73	0.26
1.47	0.00	0.53	0.47
1.54	0.00	0.46	0.54
2.00	0.00	0.00	1.00



As shown in Figure 1.3 the monobromide **9** reached a maximum concentration of over 70%, at which stage less than 10% of the starting material **8** remained. On this basis the rate constant for the reaction of **8** is at least seven times greater than that of **9**. Similar conclusions may be drawn from analysis of the reactions of **13** and **5** in an analagous manner.

In summary, the rates of reaction of **5, 8** and **13** are significantly faster than those of the corresponding monobromides **9**, **46** and **50**. This can be attributed, at least in part, to statistical factors, since there are two reactive centers in **5**, **8** and **13**, but only one in **9**, **46** and **50**, and to steric effects. It is likely that the bromine in **9**, **46** and **50** hinders approach of the hydrogen abstracting species. There is no obvious explanation for the disparity between these results and those reported by Williams and Kwast;[40] however, the syntheses of **9**, **46** and **50**, and **43**, **48** and **7** described above illustrate a direct and simple one-pot procedure for the preparation of monosubstituted 2,5-piperazinedione derivatives.

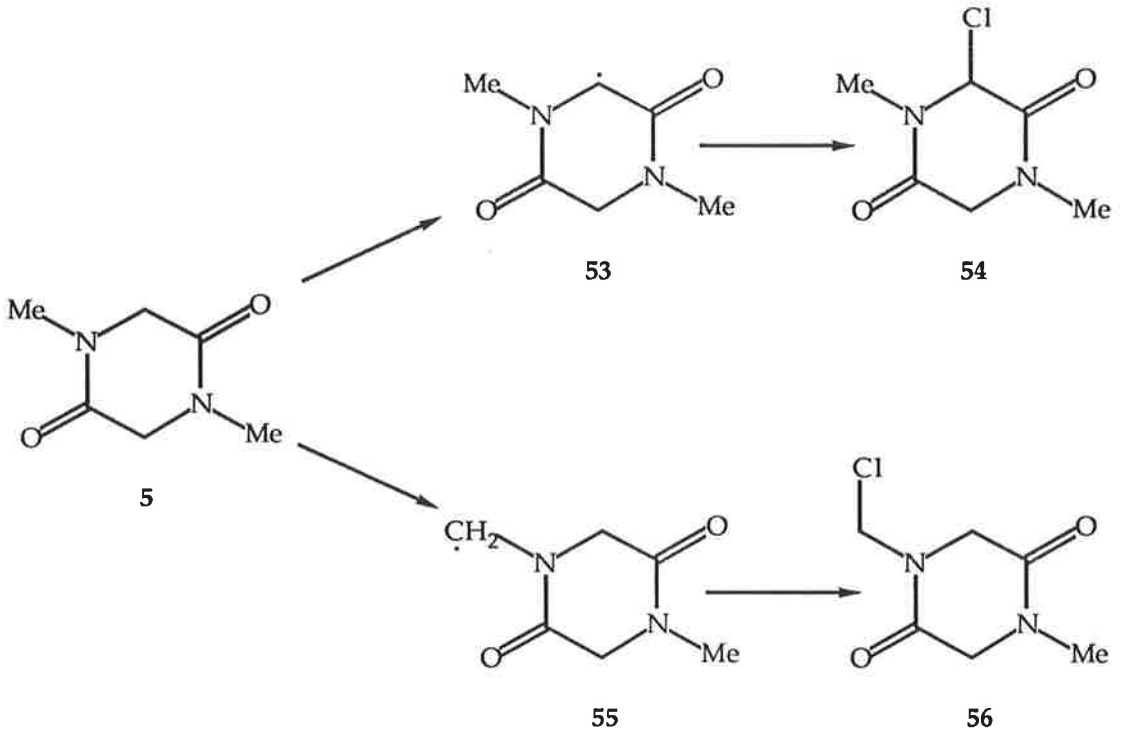
To investigate alternatives to bromination with NBS, for the functionalization of diketopiperazines, a mixture of sarcosine anhydride (**5**), 0.9 mole equivalents of sulfuryl chloride and a catalytic amount of AIBN in refluxing dichloromethane was irradiated for 0.5 h. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture, after evaporation of the solvent, indicated the presence of two major products in a *ca.* 1:1 ratio. The two products were tentatively assigned as 3-chloro-1,4-dimethyl-2,5-piperazinedione (**54**) and 1-chloromethyl-4-

methyl-2,5-piperazinedione (**56**) on the basis of their characteristic resonances. The structure of the endocyclic chloride **54** was assigned on the basis of an AB system at δ 3.93 and δ 4.25 ($J_{AB\,q}$ = 18 Hz), for the protons at the α'-carbon of the piperazinedione ring, and singlet resonances at δ 3.05, δ 3.06 and δ 5.74, attributable to the hydrogens of the *N*-methyl groups and the hydrogen of the carbon bearing the chlorine, respectively. The structure of the exocyclic **56** chloride was tentatively assigned on the basis of singlet resonances at δ 2.99 and δ 5.29, for the protons of the *N*-methyl group and the hydrogens of the *N*-methylene group, respectively, as well as a broadened singlet at δ 4.00 attributed to the α-hydrogens of the piperazinedione ring.

By analogy with the formation of **50** from **5**, the formation of 3-chloro-1,4-dimethyl-2,5-piperazinedione (**54**) likely occurs by hydrogen atom transfer from the α-carbon of **5**, with subsequent incorporation of chlorine atom to the intermediate radical **53**. Similarly, the formation of the exocyclic chloride **56** proceeds by hydrogen atom transfer to afford the radical **55**. Incorporation of chlorine atom to the radical **55** affords the exocyclic chloride **56** (Scheme 17).

The chlorides **54** and **56** were insufficiently stable for separation and isolation. In order to characterize the products (**54**) and (**56**), the mixture was subjected to methanolysis. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture, after evaporation of the solvent, indicated the presence of 3-methoxy-1,4-dimethyl-2,5-piperazinedione (**7**)

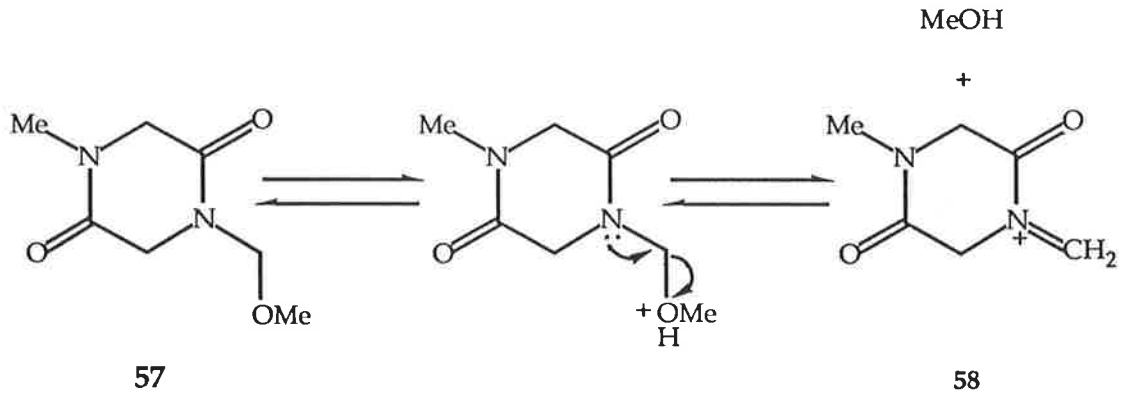
and 1-methoxymethyl-4-methyl-2,5-piperazinedione (**57**) in the ratio *ca.* 2: 1.



Scheme 17

Chromatography of the residue on silica using ethyl acetate/hexane as the eluant allowed isolation of **7**, in 19% yield based on **5**. The exocyclic methoxy product **57** decomposed on chromatography under these conditions. Considering the possibility that this was due to formation of the *N*-acyliminium species **58** (Scheme 18), the chromatography was repeated in the presence of methanol, in order to convert the putative **58** back to **57**. Thus, an enriched sample of **57** contaminated with 25% of **7**, was obtained by chromatography of the residue of the crude methanolysis reaction, on silica, using 5% methanol/chloroform as the eluant. Characteristic resonances

for **57** in the ^{1}H NMR spectrum of the enriched sample were singlet resonances at δ 3.02 and δ 3.36, attributable to the protons of the *N*-methyl group and the methyl protons of the methoxymethyl group, respectively, as well as singlet resonances at δ 4.07 and δ 4.86, attributable to the protons of the piperazinedione ring and the methylene protons of the methoxymethyl group, respectively. These and other spectral and physical properties were consistent with those reported previously.[36]



57 **58**

Scheme 18

The formation of the two chlorinated products **54** and **56** in the reaction of **5** with sulfuryl chloride can be rationalized through consideration of the polar effects operative at the sites of hydrogen abstraction in the substrate **5**, the stability of the intermediate radicals **53** and **55** and the degree of bond homolysis in the transition states for the production of the radicals **53** and **55**.[44] The difference between the two sites of hydrogen abstraction in the substrate **5** is that the endocyclic methylene has an aminocarbonyl substituent which stabilizes the

product radical **53** by resonance but inductively deactivates the substrate **5** to hydrogen abstraction by electrophilic radicals. The products from the reaction of the substrate **5** with sulfuryl chloride result from a balance between these effects.

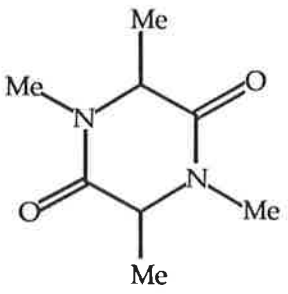
In contrast to the chlorination of **5** with sulfuryl chloride, the bromination reaction of **5** with NBS affords the endocyclic products **50** and **51** exclusively. The reaction of **5** with NBS is more sensitive to radical stability effects, since there is a greater degree of development of radical character in the transition state. The reaction of **5** to give **54** and **56** indicates that reactions of diketopiperazines with sulfuryl chloride are likely to be less discriminating than those with NBS. On this basis, NBS is likely to be the reagent of choice for the regioselective halogenation of these compounds.

RESULTS and DISCUSSION

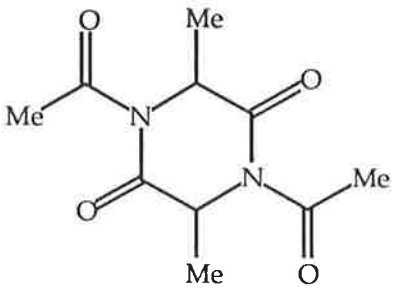
CHAPTER 2

N- and α-Substituent Effects in Diketopiperazines

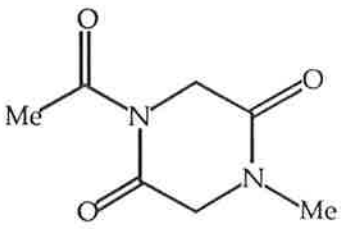
As described in the Introduction, protecting groups are known to affect the regioselectivity of halogenation of amino acid derivatives. With this in mind the effects of nitrogen substituents on the halogenation of diketopiperazines were investigated. It was envisaged that the results of these studies would provide methods for the regioselective functionalization of diketopiperazines, complementary to the monobromination procedure described in Chapter 1.



59

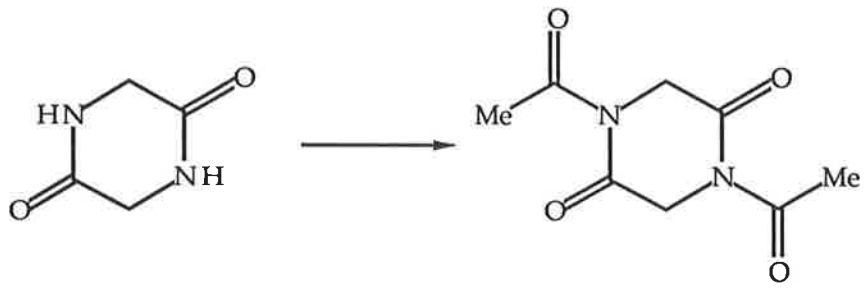


60



61

The 2,5-diketopiperazines **22**, **59**, **60** and **61** were synthesized for use in this investigation. Alanine anhydride (**62**), prepared by heating (S)-alanine in anhydrous ethylene glycol at reflux,[89] possessed satisfactory physical properties consistent with those reported previously. The preparation of 1,4-diacetyl-2,5-piperazinedione (**22**) (Scheme 19) involved heating **42** in refluxing acetic anhydride for four hours and concentration of the cooled solution. The crystals which formed on storage of the residue at -4°C overnight were recrystallized from ethyl acetate/ether. The product **22** thus obtained, possessed satisfactory physical and spectral properties consistent with those reported previously.[95]



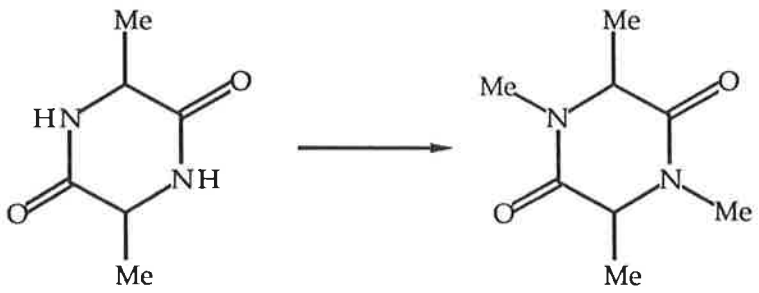
42 **22**

Scheme 19

Similar conditions were employed for the reaction of **62** to give 1,4-diacetyl-3,6-dimethyl-2,5-piperazinedione (**60**), in 81% yield as a *ca.* 1:1 mixture of diastereomers. The characteristic resonances in the ^{1}H NMR spectrum of **60** were doublet resonances at δ 1.59 and δ 1.62 (J = 7 Hz), attributable to the methyl protons of the β-carbons, singlet resonances at δ 2.53 and

δ 2.57, for the *N*-acetyl protons, and two quartets at δ 4.94 and δ 5.18 for the α-hydrogens. These and other physical and spectral properties were consistent with those previously reported.[34,96]

Alkylation of alanine anhydride (**62**) with methyl iodide (Scheme 20) gave 1,3,4,6-tetramethyl-2,5-piperazinedione (**59**), as a *ca.* 2.5: 1 mixture of diastereomers. A variety of experimental conditions were employed for this conversion.[74,97] The method of Matsunari[74] was found to be low yielding but the most successful. None of the methods used in the alkylation of **62** gave consistent results. This lack of reproducibility has been attributed to the insolubilty of the starting material **62**.[74] All attempts at separation of the diastereomers either by fractional crystallization or by chromatography on silica were unsuccessful. 1,3,4,6-Tetramethyl-2,5-piperazinedione (**59**) was found to exhibit satisfactory physical and spectral properties consistent with those previously reported.[74]

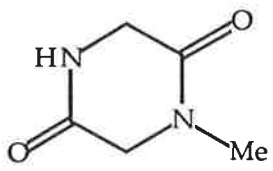


62 **59**

Scheme 20

1-Acetyl-4-methyl-2,5-piperazinedione (**61**) was prepared by acetylation of 1-methyl-2,5-piperazinedione (**63**) in an

analogous manner to the preparation of **22** and **60**. The ^{1}H NMR spectrum of the 2,5-piperazinedione **61** showed singlet resonances at δ 2.61 and δ 3.06, attributable to the protons of the *N*-acetyl and *N*-methyl substituents, respectively, and at δ 4.10 and δ 4.28, attributable to the methylene protons of the *N*-methylglycine and *N*-acetylglycine residues, respectively. These latter assignments are based on the general observation that in diketopiperazines the α-protons of *N*-acetylamino acid residues are deshielded to a greater extent than those of the corresponding *N*-alkylamino acid derivatives. The mass spectrum of **61** gave rise to peaks at 170 and 128, attributable to the molecular ion and loss of ketene (CH_2CO) from the molecular ion, respectively. The identity of **61** was confirmed by elemental analysis. 1-Methyl-2,5-piperazinedione (**63**) was prepared by heating glycylsarcosine in anhydrous ethylene glycol at reflux.[89]



63

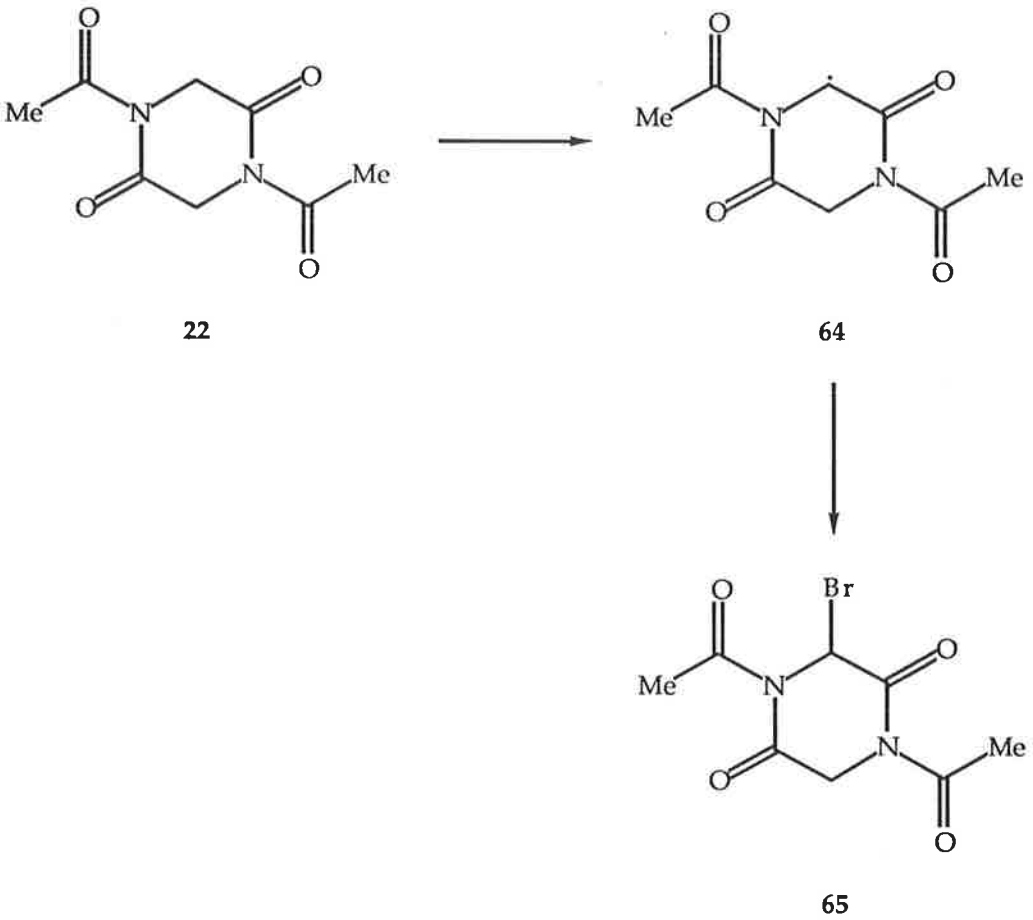
To compare the effects of *N*-acyl and *N*-methyl substituents of symmetric 2,5-piperazinediones, the relative reactivity of **5** and **22**, and **59** and **60** with NBS was investigated. Initially, the relative reactivity of sarcosine anhydride (**5**) and 1,4-diacetyl-2,5-piperazinedione (**22**) was determined by

irradiation of a mixture containing equimolar amounts of **5**, **22** and NBS in the presence of AIBN. From analysis of the ^{1}H NMR spectrum of the crude reaction mixture, after evaporation of the solvent, the only products evident were the monobromide **50** and the dibromide **51**. The bromides **50** and **51** were identified by comparison with the ^{1}H NMR spectra of authentic samples as described in Chapter 1. Traces of unreacted **5** were also detected in the reaction mixture together with more substantial quantities of unreacted **22**. No products attributable to the reaction of **22** were detected.

In a separate experiment, 1,4-diacetyl-2,5-piperazinedione (**22**) was treated with one mole equivalent of NBS in refluxing dichloromethane under nitrogen with reaction initiated by the presence of a trace amount of AIBN and by irradiation with a 300-W mercury lamp. The ^{1}H NMR spectrum of the crude reaction mixture was recorded after evaporation of the solvent. The product of the reaction was tentatively assigned as 3-bromo-1,4-diacetyl-2,5-piperazinedione (**65**) on the basis of an AB system at δ 4.32 and δ 5.28 ($J_{AB\ q}$ = 18 Hz), for the protons at the α'-carbon of the piperazinedione ring, and singlet resonances at δ 2.63 and δ 6.91, attributable to the hydrogens of the *N*-acetyl groups and the hydrogen of the carbon bearing the bromine, respectively. The bromide (**65**) was not sufficiently stable for isolation and purification. Analysis of the ^{1}H NMR spectrum of the competitive experiment between **5** and **22** indicated that none of **65** was produced.

The relative reactivity of 1,3,4,6-tetramethyl-2,5-piperazinedione (**59**) and 1,4-diacetyl-3,6-dimethyl-2,5-piperazinedione (**60**) with NBS was investigated by irradiation of a reaction mixture containing equimolar amounts of the substrates **59** and **60**, and four mole equivalents of NBS, in the presence of AIBN. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture, after evaporation of the solvent, indicated the presence of unreacted **60** and a mixture of diastereomers of 3,6-dibromo-3,6-di(bromomethyl)-1,4-dimethyl-2,5-piperazine-dione (**68**).

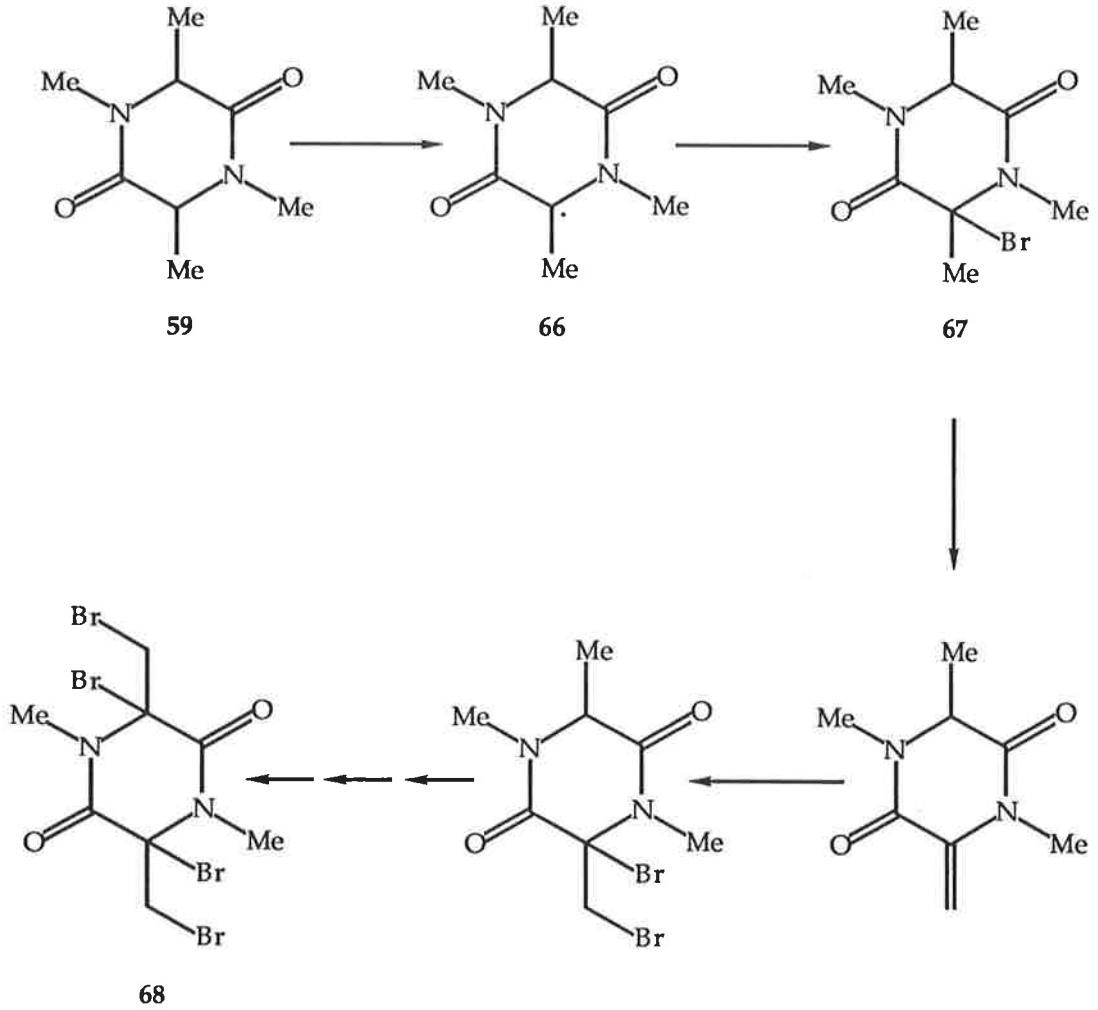
An authentic sample of the product **68**, formed in the above competitive experiment between **59** and **60**, was prepared in 81% yield, as a *ca.* 2 :1 mixture of diastereomers, by treatment of **59** with four mole equivalents of NBS[74] in refluxing dichloromethane. The characteristic resonances in the ^{1}H NMR spectrum for the major diastereomer of the tetrabromide **68** were a singlet resonance at δ 3.02, for the *N*-methyl protons, and an AB system at δ 3.62 and δ 4.15 ($J_{AB\,q}$ = 11 Hz), attributable to the geminal β-protons. The characteristic resonances in the ^{1}H NMR spectrum for the minor diastereomer of the tetrabromide **68** were a singlet resonance at δ 2.98, for the *N*-methyl protons, and an AB system at δ 3.66 and δ 3.92 ($J_{AB\,q}$ = 10.5 Hz), attributable to the geminal β-protons. From analysis of the ^{1}H NMR spectrum of the competitive experiment between **59** and **60**, no unreacted **59** remained and no products attributable to the reaction of **60** were detected.



22 64 65

Scheme 21

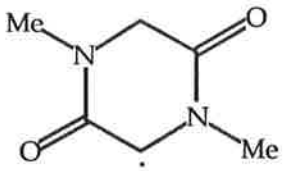
The reaction of **5** to give **50** and **51** was discussed in Chapter 1. By analogy with **5**, the reaction of **22** to give **65** likely proceeds by hydrogen abstraction from the α-carbon by bromine atom and subsequent incorporation of bromine to the radical **64** (Scheme 21). Similarly, the formation of the tetrabromide **68** from **59** initially proceeds by hydrogen abstraction from the α-carbon of the piperazinedione ring by bromine atom to give **66** and subsequent incorporation of bromine to give **67**. The product **68** is then produced through elimination of hydrogen bromide from **67**, subsequent addition of bromine and repetition of the sequence (Scheme 22).[74]



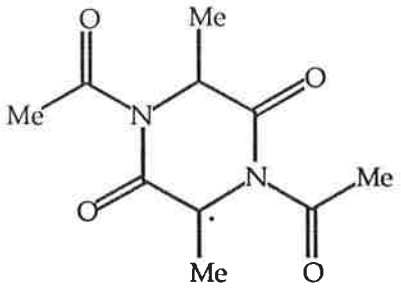
Scheme 22

In the competitive experiment, the abstraction of hydrogen atom from the α-carbon of **5** occurs in preference to the abstraction of hydrogen atom from the α-carbon of **22**. Similarly, the abstraction of hydrogen atom from the α-carbon of **59** occurs in preference to the abstraction of hydrogen atom from the α-carbon of **60**. This difference in the relative reactivity of **5** and **22**, and **59** and **60** reflects a significant preference in the rate of formation of the corresponding intermediate radicals

69 and **64**, and **66** and **70**. The radicals **69** and **66** are formed much faster than **64** and **70**, respectively.



69



70

To evaluate this observation, radical stabilization and polar effects in the transition state of hydrogen atom abstraction by bromine atom[98] must be considered. Hydrogen atom transfer to bromine atom involves a transition state of substantial radical character, hence radical stability effects are significant. In addition, because of the electrophilic nature of bromine atom, polar effects would also exert an important influence.

Consider first radical stabilization and its importance in the transition state of hydrogen atom abstraction by bromine atom.[43,99,100,101] In discussing radical stabilization the terms amido, imido, aminocarbonyl and amidocarbonyl substituents are used as defined in Figure 2.1. Stabilization of the captodative[61,102] radicals **66** and **69** will result from overlap of the semi-occupied p orbital with the π orbitals of the amido and aminocarbonyl substituents.

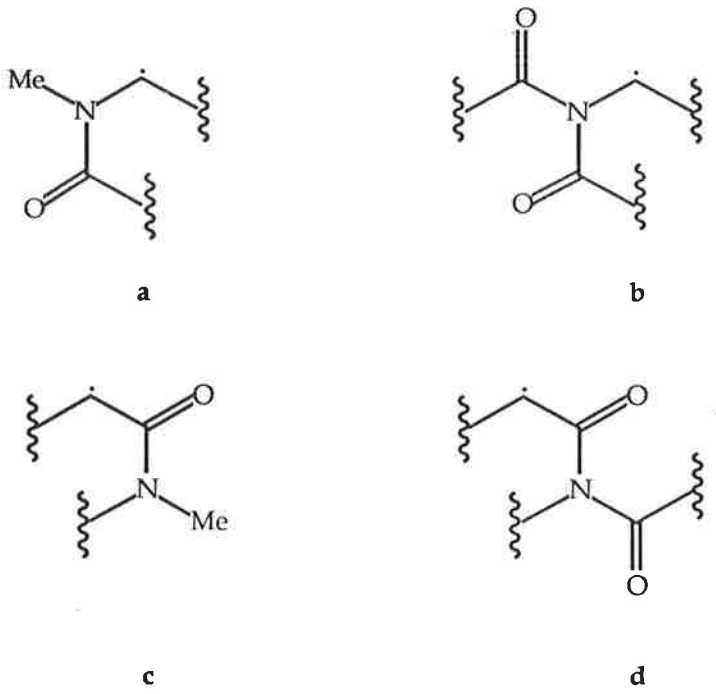


Figure 2.1 (a) amido, (b) imido,
(c) aminocarbonyl and
(d) amidocarbonyl substituted radicals

In the case of the captodative radicals **64** and **70**, stabilization results from overlap of the semi-occupied p orbital with the π orbitals of the imido and amidocarbonyl substituents. Maximum overlap of these orbitals occurs in planar conformations of the radicals **64**, **66**, **69** and **70**.

If one considers the radicals **64** and **69**, non-bonding interactions are more severe in the case of **64** than for **69** (Figure 2.2).[61] The hydrogen at the α-carbon of the radical **64** would experience greater steric interactions than the α-hydrogen of the radical **69**, imparting a greater distortion of radical **64** out of planarity, reducing resonance stabilization as a consequence. Similarly, the radical **70** will be destabilized compared to the radical **66**, to an even greater extent than in the

above case, owing to more severe non-bonding interactions with the methyl substituent at the α-carbon.

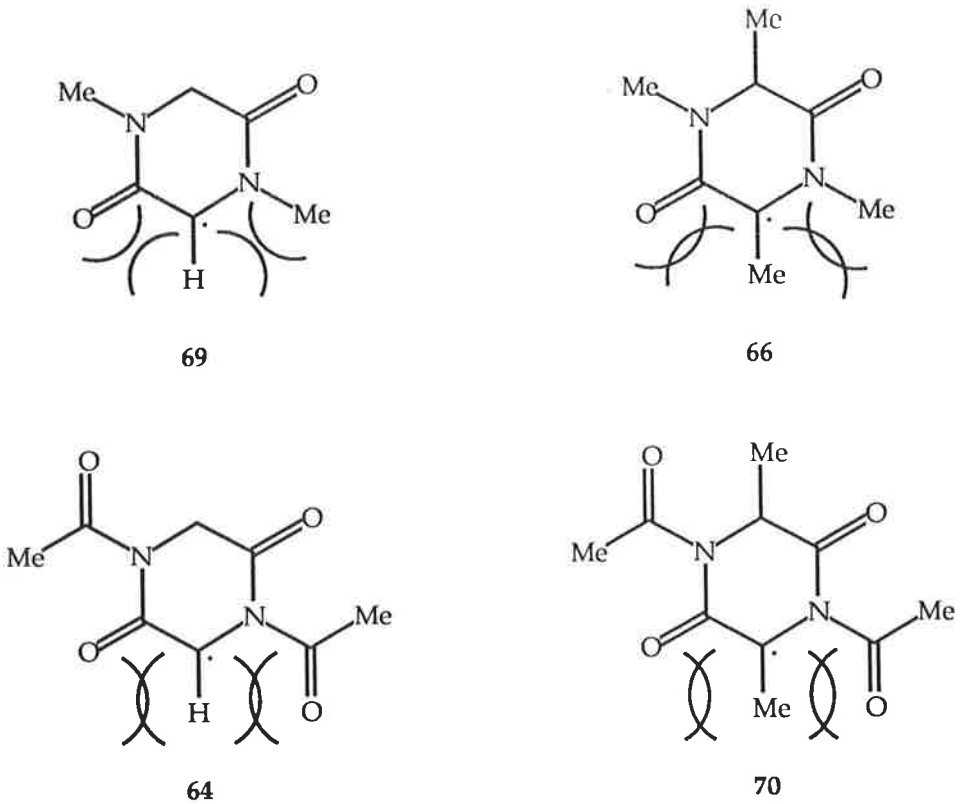


Figure 2.2 Non-bonding interactions associated with planar conformations of the radicals **64**, **66**, **69** and **70**.

Stabilization of the radicals **64**, **66**, **69** and **70** arises from the delocalization of unpaired spin density through interaction with the amido and imido substituents (Figure 2.3).[103] In comparison of amido substituted radicals, such as **66** and **69**, against imido substituted radicals, such as **64** and **70**, the electrons of the amide nitrogen are more available for stabilization of **66** and **69** than those of the imide nitrogen in **64** and **70**. This is because the electrons of the amide nitrogen are involved in resonance with only one carbonyl group instead of two

as in the imide system. Moreover, on generation of the amido substituted radicals **66** and **69**, the conjugation of the system is extended, whilst on generation of the imido substituted radicals **64** and **70**, cross-conjugation results.

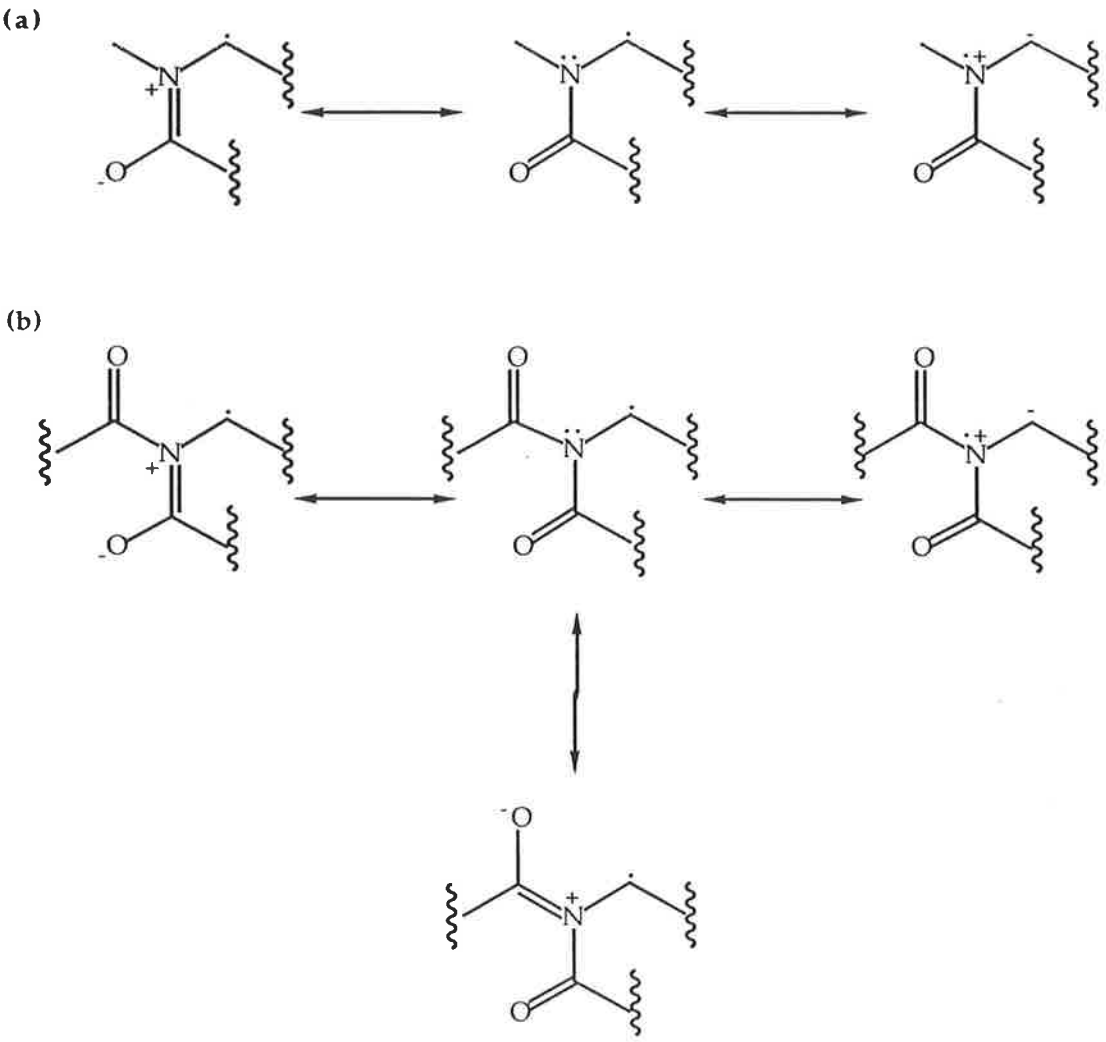


Figure 2.3 Resonance stabilization of (a) amido and (b) imido substituted radicals

Polar effects arise from the fact that a radical formed adjacent to an aminocarbonyl or amidocarbonyl substituent is resonance stabilized, but formation of such a radical by hydrogen

atom transfer to bromine atom is disfavored by a polar effect. The polar effect involves the inductive interaction between the aminocarbonyl (Figure 2.4 **(a)**) or amidocarbonyl (Figure 2.4 **(c)**) substituent and the electron deficient site of hydrogen abstraction that is developing in the transition state. Stabilization of the developing positive charge in the transition state of hydrogen abstraction, by electron donation from the amido or imido substituent, is likely to occur, rendering the nitrogen in the resonance contributors represented in Figures 2.4 **(b)** and **(d)** with a partial positive charge.

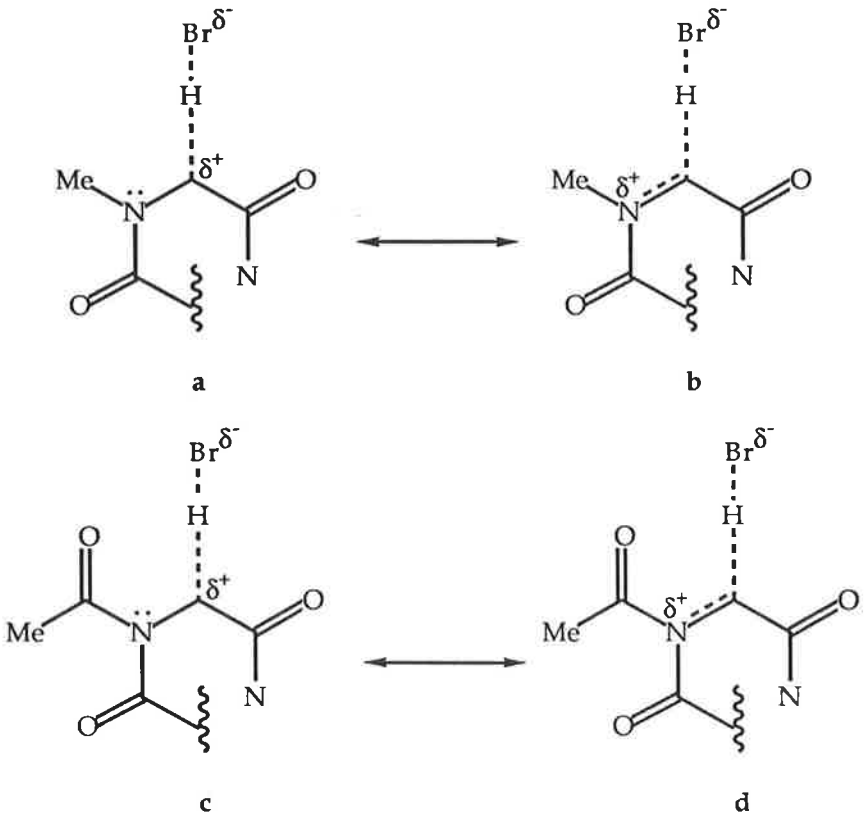


Figure 2.4 (a) and (c) Development of charge in the transition state of hydrogen abstraction by bromine atom and (b) and (d) delocalization of that charge by an amido and imido substituent

The ability of the substituents to stabilize or destabilize this charge will ultimately determine the magnitude of the polar effect. The amido substituent in **5** and **59** has the greater capacity to stabilize partial positive charge in the transition state of hydrogen abstraction than the imido substituent in **22** and **60**, because of the more available electron density on the amide nitrogen compared to that on the imide nitrogen.

From the comparison of the amido and imido substituents discussed above, it can be seen that all the factors which effect the reactivity, favor the activation of acylamino acid residues in symmetric diketopiperazines over diacylamino acid residues. These factors provide a rationale for the significantly faster reactivity of **5** over **22**, and **59** over **60**.

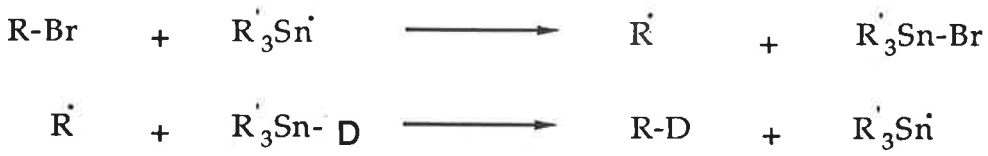
To examine the synthetic utility of the comparative deactivation of diacylamino acid residues with respect to acylamino acid residues in the regioselective functionalization of asymmetric diketopiperazines, 1-acetyl-4-methyl-2,5-piperazinedione (**61**) was treated with one mole equivalent of NBS in dichloromethane, and reaction initiated by the presence of AIBN and through irradiation with a 300-W mercury lamp. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy, after evaporation of the solvent, indicated the formation of a single bromide **71**. The characteristic resonances in the ^{1}H NMR spectrum of the crude reaction mixture for the bromide **71** were an AB q resonance at δ 3.96 and δ 4.97 ($J_{AB\ q}$ = 18 Hz), for the protons at the α'-carbon of the piperazinedione ring, and singlet resonances at δ 2.58 and δ 3.01, for the protons of the *N*-acetyl

and *N*-methyl groups, respectively, and at δ 6.09, for the hydrogen of the carbon bearing the bromine. From a comparison of the resonances of the piperazinedione ring protons in the ^{1}H NMR spectrum of the bromide **71** with those in the ^{1}H NMR spectra of the bromides **50** and **65**, the α-proton in the bromide **71** appears at approximately the same chemical shift as the α-proton in the bromide **50**. In addition, the chemical shift of the geminal α'-proton resonances in the bromide **71** is similar to the chemical shift of the α'-protons in the bromide **65**. On this basis, reaction of **61** occurs exclusively at the α-carbon of the *N*-methylglycine residue to give the bromide **71**. If reaction had occurred at the α-carbon of the *N*-acetylglycine residue the chemical shift of the resonances for the piperazinedione ring protons would be expected to be different. The resonance of the α-proton would be shifted downfield, similar to the chemical shift of the α-proton in **65**, whilst the geminal α'-proton resonances would be shifted upfield, similar to the chemical shift of the α'-protons in **50**. No products attributable to reaction at the α-carbon of the *N*-acetylglycine residue of **61** were detected.

The bromide **71** was found to be insufficently stable for isolation and purification. Attempted conversion of **71** to the corresponding methyl ether for characterization purposes afforded a complex mixture. Analysis of the ^{1}H NMR spectrum of the crude mixture indicated the presence of deacylated products. The inherent lability of *N*-acyl substituents of diketopiperazines has been previously reported.[34] Chromatography of the crude

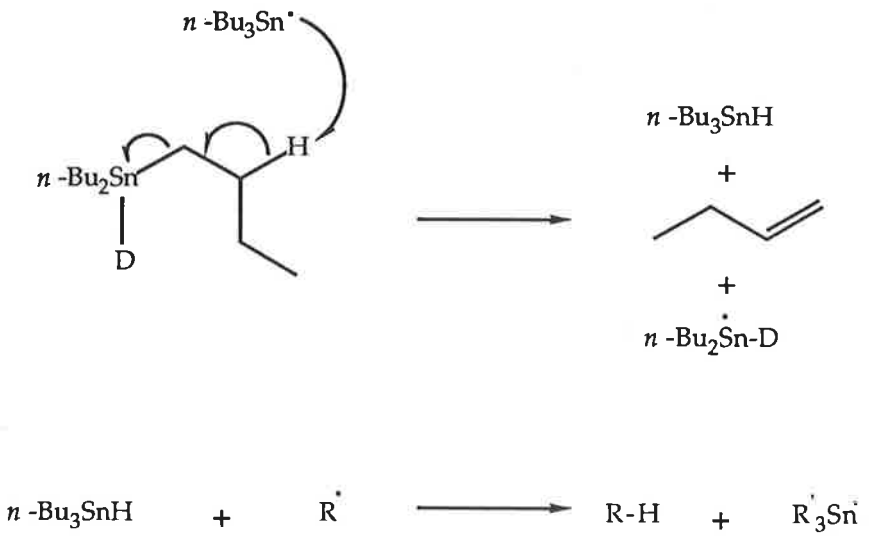
product mixture on silica did not afford any discrete products that could be readily identified.

For complete characterization purposes the crude bromide **71** was reduced with tributylstannyl deuteride[104] to afford the deuteriated product **72**. The reduction was carried out by addition of benzene, tributylstannyl deuteride and a trace amount of AIBN directly to the concentrated residue obtained from the bromination of **71**. The mixture was refluxed under a nitrogen atmosphere for four hours, allowed to cool, the solvent evaporated and the residue chromatographed on silica to remove the stannane byproducts. Analysis of the ^{1}H NMR spectrum of the deuteriated derivative **72** gave characteristic resonances for incorporation of deuterium at the α-carbon of the *N*-methylglycine residue. In particular, a broadened resonance for the residual hydrogen of the *N*-methylglycine residue, which integrated to 1.4 hydrogens, was observed. The mass spectrum of **72** showed two molecular ions at 171 and 170, and gave rise to other peaks at 129 and 128, and 43 corresponding to loss of ketene from the molecular ions and production of the acetyl cation, respectively. These peaks are in accordance with the incorporation of deuterium in **61**. By mass spectrometry the percentage deuterium incorporation in the reduced 2,5-piperazinedione **61** was 57%. Tributylstannyl deuteride was prepared by reduction of tributylstannyl chloride with lithium aluminium deuteride[105] (98% deuterium content).



Scheme 23

The mechanism of tin deuteride reduction of bromides[106] is as shown in Scheme 23. Bromine atom transfer from the substrate bromide to stannyl radical produces the substrate radical and stannyl bromide. Deuterium transfer from stannyl deuteride to the substrate radical affords the deuteriated product and stannyl radical, which propagates the chain. The percentage deuterium incorporation in a reaction is limited by a number of factors. Firstly, reactions which involve transfer of deuterium are influenced by kinetic isotope effects.[107,108,109]



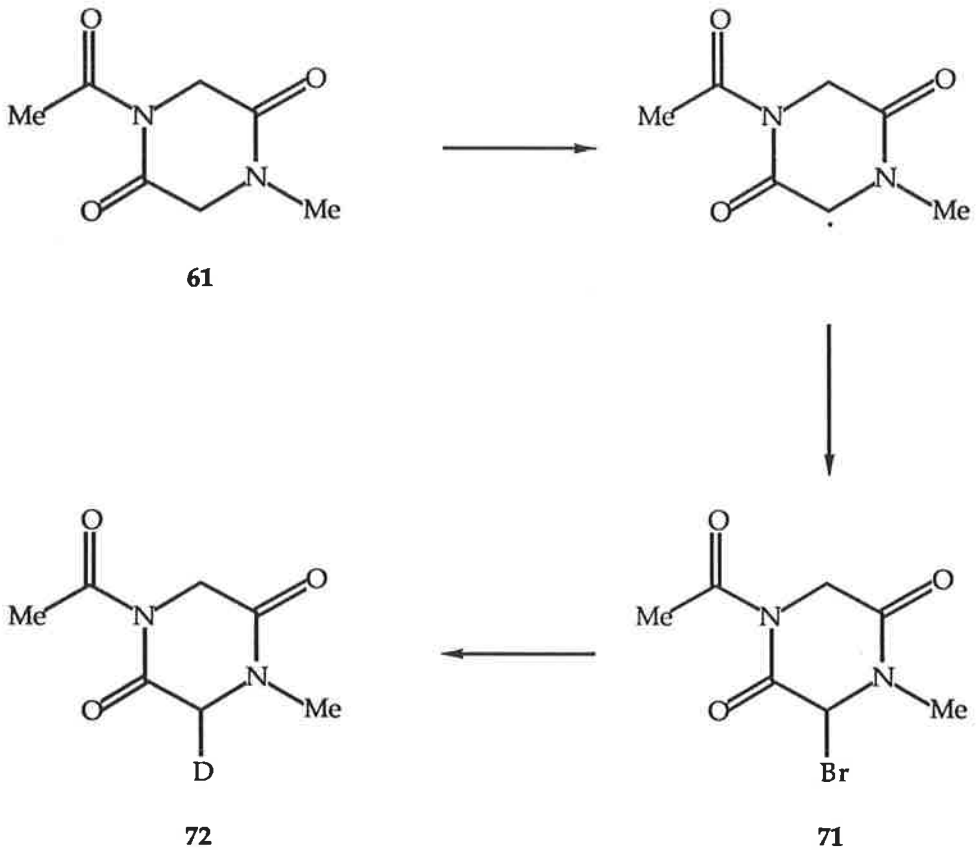
Scheme 24

Competing reaction processes resulting in net deuterium exchange are possible in the use of tributylstannyl deuteride as the reducing reagent (Scheme 24).[110] Through these effects hydrogen atom is transferred in preference to deuterium atom.In addition, particularly low deuterium incorporation may result from incomplete reaction of the substrate in the bromination reaction, resulting in lower deuterium content in the product. Limits to the accuracy of calculation of deuterium incorporation were dependent upon signal intensity and baseline noise in the ^{1}H NMR and mass spectra. Low deuterium incorporation in this case was attributed, for the most part, to the incomplete formation of the bromide **71**.

The location of deuterium at the α-carbon of the *N*-methylglycine residue in **72** is consistent with hydrogen abstraction and subsequent bromine incorporation at the *N*-methylglycine residue of **61** in the reaction with NBS (Scheme 25). The exclusive formation of the bromide **71** is demonstrative of the extent to which the diacylamino acid residue is comparatively deactivated with respect to the acylamino acid residue in reactions with NBS. This reaction is illustrative of the synthetic utility of the regioselective functionalization of asymmetric diketopiperazines.

In the work described earlier in this chapter, the effect of *N*-substituents on the regioselectivity of halogenation of 2,5-piperazinediones was investigated. The aim of the work described in this section was to investigate the effect of

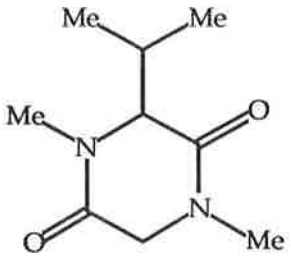
α-substituents on the reactivity of amino acid residues in 2,5-piperazinediones.



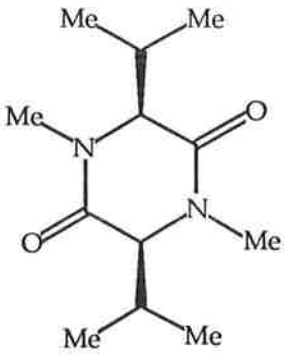
61 **72** **71**

Scheme 25

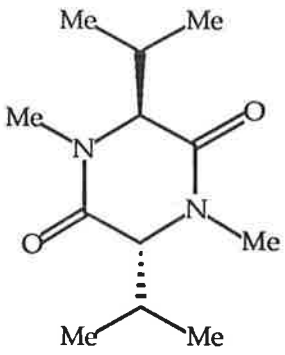
The size of a substituent at the α-carbon is known to affect the reactivity of amino acid residues within acyclic peptide derivatives.[80] However, 2,5-diketopiperazines exhibit substantial conformational rigidity which is not present to the same extent in the corresponding acyclic dipeptide derivatives, and which may substantially affect the reactivity.



73

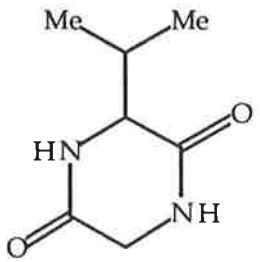


74

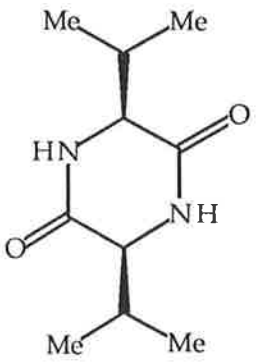


75

The 2,5-piperazinediones **73**, **74** and **75** were synthesized for use in this investigation. 1,4-Dimethyl-3-isopropyl-2,5-piperazinedione (**73**) was prepared by the alkylation of 3-isopropyl-2,5-piperazinedione (**76**) with methyl iodide. *cis*-3,6-Diisopropyl-1,4-dimethyl-2,5-piperazinedione (**74**) and *trans*-3,6-diisopropyl-1,4-dimethyl-2,5-piperazinedione (**75**) were prepared by the alkylation of valine anhydride (**77**) with methyl iodide, and separated by chromatography on silica.* 3-Isopropyl-2,5-piperazinedione (**76**) and valine anhydride (**77**) were prepared by heating glycylvaline and (S)-valine, respectively, in anhydrous ethylene glycol at reflux.[89]



76



77

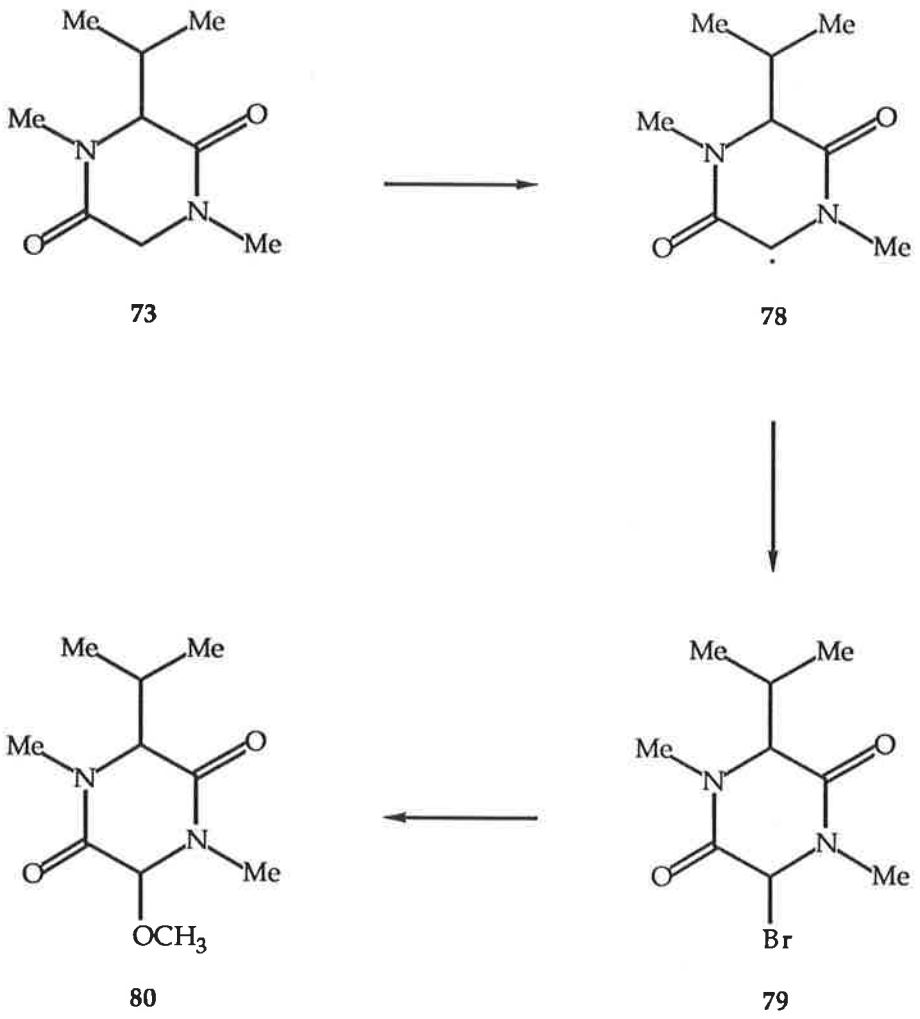
*Under the basic reaction conditions, isomerization of the *trans*-isomer (75) occurs to give (74).

The diketopiperazines **73**,[111] **74**[74], **75**[74] and **76**[112] and **77** possessed physical and spectral properties consistent with those reported previously.

In order to compare the relative reactivity of valine and glycine residues in diketopiperazines, initially the reaction of 1,4-dimethyl-3-isopropyl-2,5-piperazinedione (**73**) with one mole equivalent of NBS was investigated. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture, after evaporation of the solvent, indicated the formation of 3-bromo-1,4-dimethyl-6-isopropyl-2,5-piperazinedione (**79**) as a single diastereomer. The characteristic resonances in the ^{1}H NMR spectrum for the bromide **79** were two doublet resonances at δ 1.08 and δ 1.16 (J = 5 Hz) and a multiplet resonance centered at δ 2.62, for the non-equivalent methyl protons and the methine proton of the isopropyl group, repectively. In addition, a doublet resonance at δ 3.24 (J = 7 Hz), attributable to the α-proton of the valine residue, and singlet resonances at δ 2.99 and δ 3.06, for the protons of the *N*-methyl groups, and at δ 6.07, attributable to the proton of the α-carbon bearing the bromine, were observed. No products attributable to reaction of the valine residue were detected.

By analogy with the mechanism of formation of the dibromide **51** described in Chapter 1, the reaction of **73** with NBS to give **79** likely proceeds by hydrogen abstraction from the α-carbon of the glycine residue to give **78**. Bromine incorporation to **78** affords the bromide **79** (Scheme 26). By analogy with the rationale for the stereoselective formation of

the dibromide **10**, the formation of the bromide **79** would be expected to occur in a stereoelectronically controlled manner, to afford the thermodynamically more stable *syn*-diastereomer.



Scheme 26

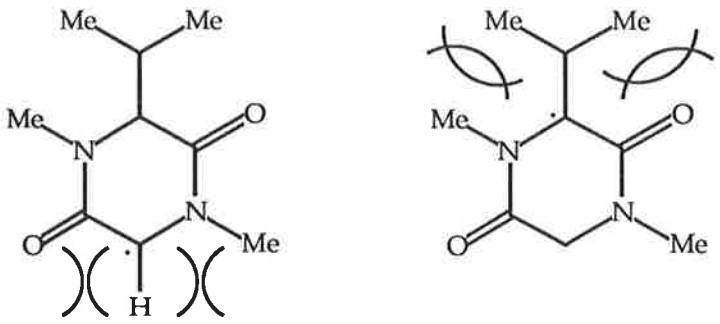
The bromide **79** was insufficiently stable for isolation and purification and was converted to the corresponding methyl ether **80** using the methanolysis procedure described in Chapter 1. Work-up and subsequent chromatography of the residue on silica gave 1,4-dimethyl-6-isopropyl-3-methoxy-

2,5-piperazinedione (**80**), in 57% yield, as a *ca.* 2: 1 mixture of diastereomers. The characteristic resonances in the ^{1}H NMR spectrum for the major diastereomer of the methyl ether **80** were two doublet resonances at δ 1.02 and δ 1.10 (J = 7 Hz) and a multiplet resonance centered at δ 2.05, ascribable to the non-equivalent methyl protons and the methine proton of the isopropyl group, repectively. In addition, a doublet resonance at δ 3.59 (J = 6 Hz), attributable to the α-proton of the valine residue, and singlet resonances at δ 3.01, δ 3.03 and δ 3.61, for the *N*-methyl protons and the methyl protons of the methoxy group, respectively, as well as a singlet resonance at δ 4.62, attributable to the proton of the α-carbon bearing the methoxy group, were observed. The characteristic resonances in the ^{1}H NMR spectrum for the minor diastereomer of the methyl ether **80** were two doublet resonances at δ 0.87 and δ 1.12 (J = 7 Hz) and a multiplet resonance centered at δ 2.05, ascribable to the non-equivalent methyl protons and the methine proton of the isopropyl group, repectively. In addition, a doublet resonance at δ 3.89 (J = 2.5 Hz), attributable to the α-proton of the valine residue, and singlet resonances at δ 2.97, δ 3.02 and δ 3.33, for the *N*-methyl protons and the methyl protons of the methoxy group, respectively, as well as a singlet resonance at δ 4.94, attributable to the proton of the α-carbon bearing the methoxy group, were observed. The mass spectrum of the methyl ether **80** afforded peaks at 214 and 184, corresponding to the molecular ion and loss of formaldehyde from the molecular ion, respectively. The identity of **80** was confirmed by elemental analysis.

The formation of **80** from the bromide **79** is most likely to proceed through nucleophilic attack of methanol on an intermediate iminium species. By analogy with the production of **45**, it would be expected that addition of methanol to the intermediate iminium ion would occur axially in a stereoelectronically controlled manner, to afford the thermodynamically more stable *syn*-diastereomer of **80**, predominantly.

The formation of **79** from **73** reflects a significant difference in the rates of formation of the α-centered radicals **78** and **81**. To account for this observation, radical stabilization in the transition state of hydrogen abstraction by bromine atom must be considered. The selectivity for the formation of tertiary radicals in preference to secondary radicals is typically a factor of twenty in reactions involving hydrogen atom transfer to bromine atom,[60,61] however, the reaction of **73** to give **79** indicates that the secondary radical **78** is formed in preference to the tertiary radical **81**. An explanation for this contrast is that captodative radicals of the type of **78** and **81** experience maximum stabilization in their planar conformations.[61,103] In comparison of the radicals **78** and **81**, the non-bonding interactions associated with the accommodation of the isopropyl group into planar conformations of **81** are much greater than those associated with the introduction of a hydrogen into planar conformations of **78** (Figure 2.5). As a result of the more severe non-bonding interactions, the distortion of the radical **81** out of planarity would be greater than in **78**, reducing resonance stabilization of the radical **81** to a greater extent, as a

consequence. This explanation parallels that used to account for the selective reaction of glycine residues in acyclic peptide derivatives.[80]



78 81

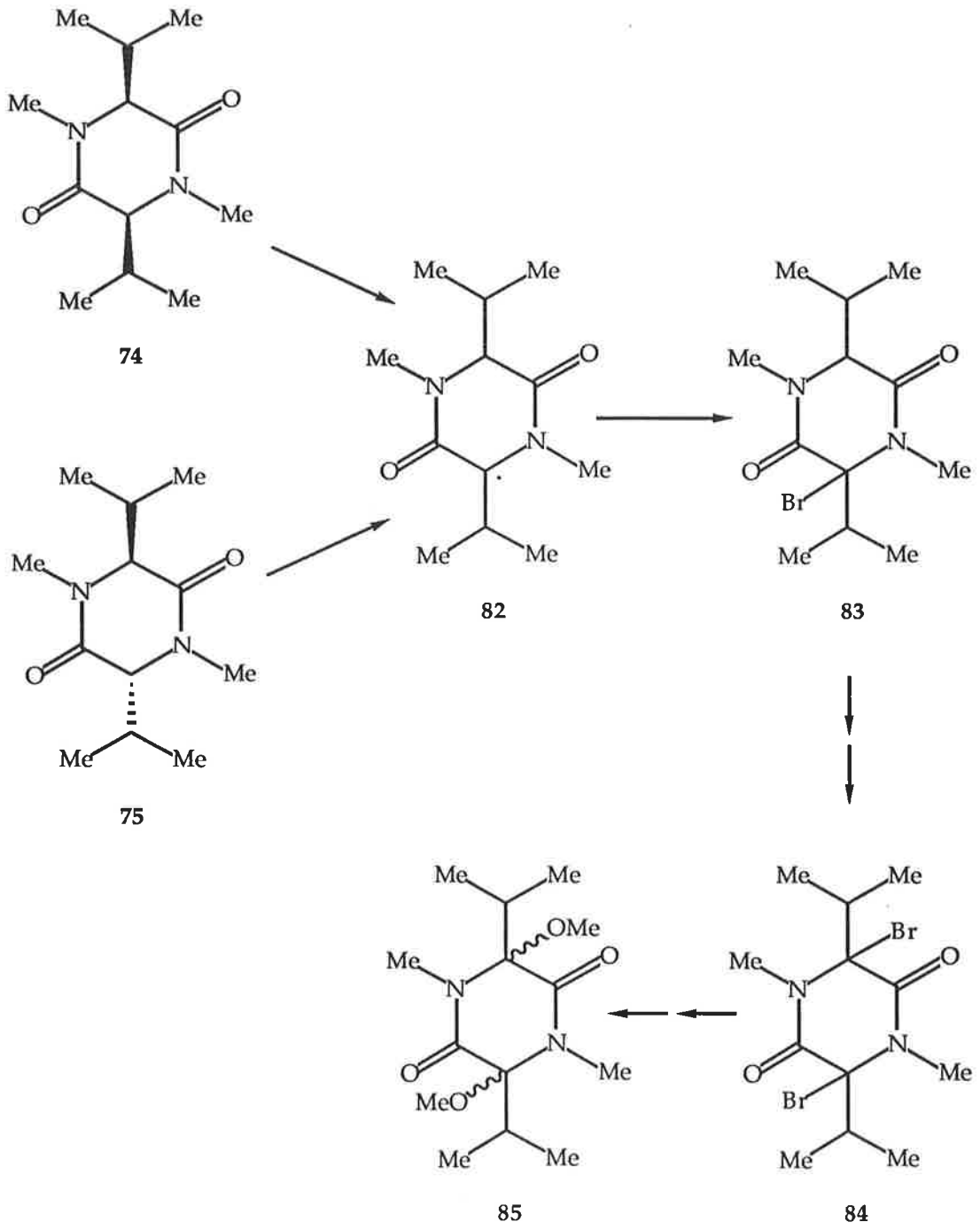
Figure 2.5 steric interactions associated with conformations of the radicals **78** and **81**.

To obtain a further comparison of the effect of α-substituents in the halogenation of 2,5-piperazinediones, the relative reactivity of sarcosine anhydride (**5**), 1,4-dimethyl-3-isopropyl-2,5-piperazinedione (**73**), *cis*-3,6-diisopropyl-1,4-dimethyl-2,5-piperazinedione (**74**) and *trans*-3,6-diisopropyl-1,4-dimethyl-2,5-piperazinedione (**75**) with NBS was investigated and compared. To compare the reactions of the *cis*-diastereomer **74** and *trans*-diastereomer **75** in the competitive experiments it was necessary to determine the products of their reactions with NBS. Initially, the products from the treatment of the *cis*-diastereomer **74** with two mole equivalents of NBS were derivatized by methanolysis of the crude reaction mixture, to allow the nature of the products to be determined. From a comparison of the ^{1}H NMR spectrum of the crude methanolysis

reaction mixture with the ^{1}H NMR spectral data reported by Matsunari,[74] both diastereomers of 3,6-diisopropyl-3,6-dimethoxy-1,4-dimethyl-2,5-piperazinedione (**85**) were observed, in approximately equal abundance, as the major products of the reaction sequence. Work-up and chromatography on silica gave only one of the diastereomers of **85**, in 28% yield based on **74**, which had physical and spectral properties consistent with those reported previously.[74]

Trans-3,6-Diisopropyl-1,4-dimethyl-2,5-piperazinedione (**75**) was treated with two mole equivalents of NBS in an analogous manner to the reaction of the*cis*-diastereomer **74**. Analysis of the ^{1}H NMR spectrum of the residue obtained from methanolysis of the crude reaction mixture, indicated that the two isomers of **85** were present, in approximately equal abundance, as the major products of the reaction sequence. Work-up and chromatography of the residue on silica gave the same isomer of **85**, in 28% yield, as was isolated from the reaction of **74**.

The initial step in the formation of **85**, from **74** or **75** by sequential treatment with NBS then methanol, most likely involves hydrogen abstraction from the substrate to give the common intermediate radical **82**. Bromine incorporation to the radical **82** affords the monobromide **83**. The dibromide **84** is then produced through repetition of the sequence. Subsequent reaction of the dibromide **84** with methanol gives the dimethoxy product **85** as a mixture of diastereomers (Scheme 27).



Scheme 27

The relative reactivity of sarcosine anhydride (**5**) and 1,4-dimethyl-3-isopropyl-2,5-piperazinedione (**73**) was determined by treatment of an equimolar mixture of **5** and **73** with one mole equivalent of NBS in dichloromethane, with

reaction initiated by the presence of AIBN and by irradiation with a 300-W mercury lamp. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture, after evaporation of the solvent, indicated the presence of residual **5** and 1,4-dimethyl-3-isopropyl-2,5-piperazinedione (**73**) in the ratio *ca.* 1: 2. Both **50** and 3-bromo-1,4-dimethyl-6-isopropyl-2,5-piperazinedione (**79**) were also detected in the mixture, with **50** as the major product. The products **50** and **79** were identified by comparison with authentic samples prepared as described above.

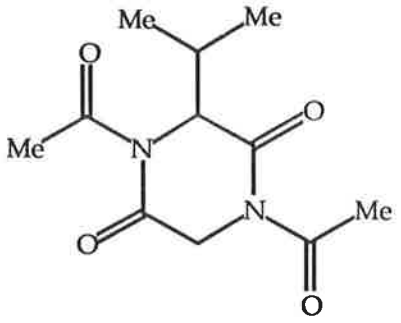
In an analogous manner, the relative reactivity of sarcosine anhydride (**5**) and *cis*-3,6-diisopropyl-1,4-dimethyl-2,5-piperazinedione (**74**) was determined by treatment of an equimolar mixture of **5** and **74** with one mole equivalent of NBS. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture, after evaporation of the solvent, indicated that similar proportions of **5** and **74** had reacted. Similarly, the relative reactivity of **5** and *trans*-3,6-diisopropyl-1,4-dimethyl-2,5-piperazinedione (**75**) was examined and analysis of the ^{1}H NMR spectrum indicated that similar proportions of **5** and **75** had reacted.

From the results of the competitive experiment, the relative reactivity of **5** and **73** indicates that the rate of formation of the radical **69** is *ca.* 2 times faster than that for the radical **78**. The preferential reactivity of the *N*-methylglycine residue of **73** and the 2: 1 ratio of the number of *N*-methylglycine residues in sarcosine anhydride (**5**) to that in **73**, accounts for the difference in the rates of formation of the radicals **69** and **78**, and the observed ratio of products.

From the results of the competitive experiments, the rate of formation of each of the intermediate radicals **69** and **82**, in the reactions of **5**, **74** and **75**, respectively, is approximately the same. The radical **82** is expected to experience severe non-bonding interactions between the *N*-methyl and aminocarbonyl substituents and the isopropyl side-chain, in planar conformations necessary for its stabilization. On this basis the rates of reaction of **74** and **75** compared to that of **5**, would appear to be anomalous. No definitive explanation can be offered for this anomaly, however, it may be that conformational strain reflected in the large degree of ring folding exhibited in **74**[113,114] and the large degree of peptide bond twisting out of the plane in **75**,[97,114] is relieved on forming the radicals **82**, facilitating the reactions.

The reaction of **73** with NBS to give **79** indicates that the selective reaction of glycine residues in 2,5-piperazinediones is a viable pathway for the regioselective functionalization of these compounds. The competitive reactions of **74**, **75** and **5** indicate that conformational effects may impose a limitation on the general viability of this method as a synthetic tool.

In order to attain further evidence for the selective halogenation of glycine residues in diketopiperazines, and to further examine the deactivating effect of *N*-acyl substituents on the reactivity of these compounds, the reactions of 1,4-diacetyl-3-isopropyl-2,5-piperazinedione (**86**) and 1,4-diacetyl-3-benzyl-2,5-piperazinedione (**87**) with NBS were investigated.



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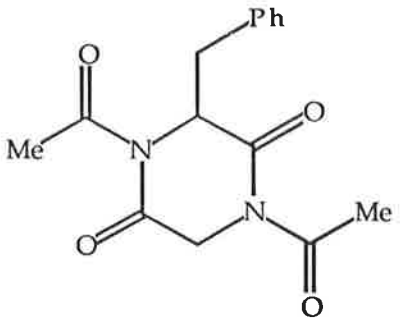
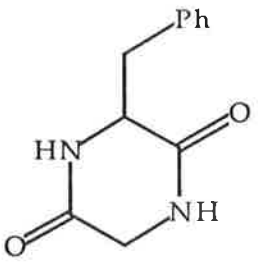


87

The 2,5-piperazinediones **86** and **87** were obtained by the acetylation of 3-isopropyl-2,5-piperazinedione (**76**) and 3-benzyl-2,5-piperazinedione (**88**), respectively, by utilization of the procedure for the acetylation of **42** to give **22**. The characteristic resonances in the ^{1}H NMR spectrum of 1,4-diacetyl-3-isopropyl-2,5-piperazinedione (**86**) were two doublet resonances at δ 0.99 and δ 1.10 (J = 6.5 Hz) and a multiplet centered at δ 2.04, for the non-equivalent methyl protons and the methine proton of the isopropyl group, repectively. In addition, there were two singlet resonances at δ 2.57 and δ 2.60, for the methyl protons of the *N*-acetyl substituents, an AB q resonance at δ 4.09 and δ 5.11 ($J_{AB\ q}$ = 19 Hz), attributable to the geminal α-protons of the piperazinedione ring, and a doublet resonance at δ 5.01 (J = 10 Hz), for the methine α'-proton of the piperazinedione ring. The identity of **86** was confirmed by elemental analysis. 1,4-Diacetyl-3-benzyl-2,5-piperazinedione (**87**) gave satisfactory physical and spectral properties consistent with those previously reported.[115]



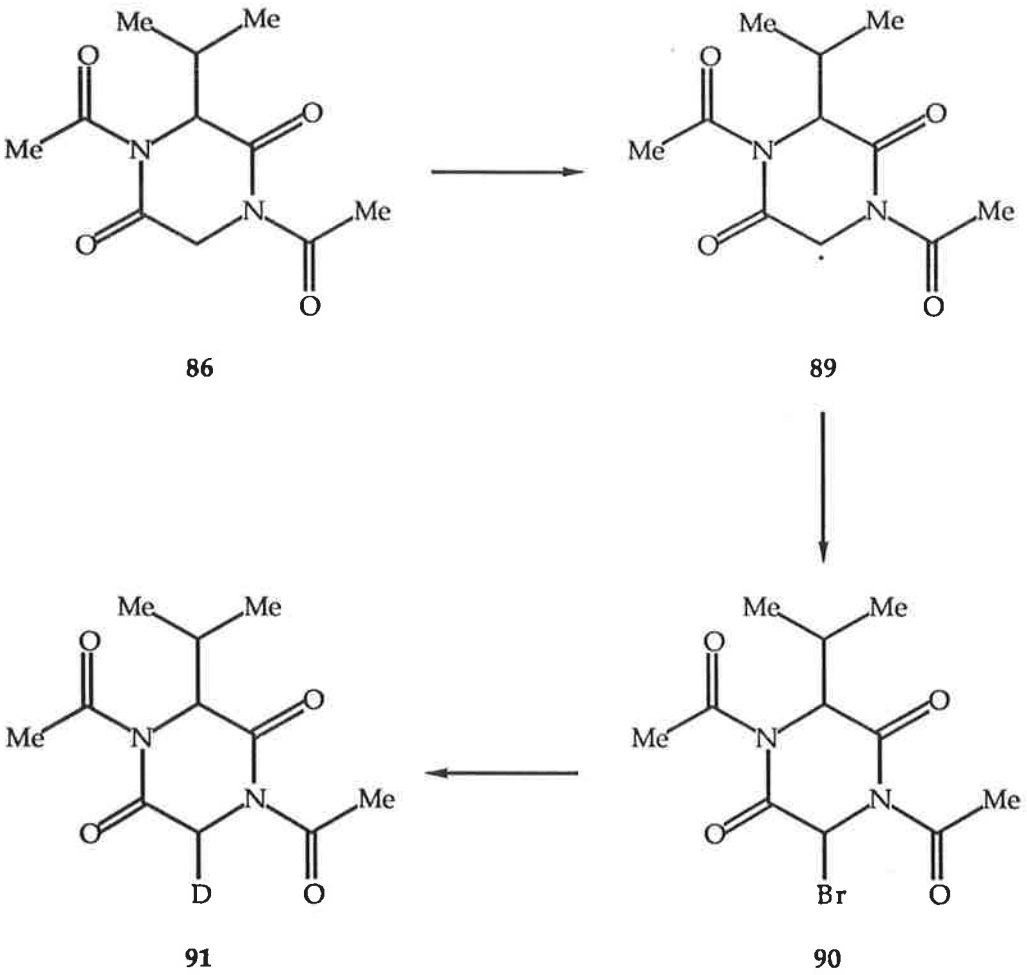
88

1,4-Diacetyl-3-isopropyl-2,5-piperazinedione (**86**), one mole equivalent of NBS and a trace of AIBN were dissolved in a solvent mixture of carbon tetrachloride/dichloromethane (10: 7) and the mixture was refluxed and irradiated for 0.5 h. Evaporation of the solvent and chromatography of the residue on silica gave 3-bromo-1,4-diacetyl-6-isopropyl-2,5-piperazinedione (**90**) as a single diastereomer, in 80% yield, and unreacted starting material **86**, in 7% yield. The characteristic resonances in the ^{1}H NMR spectrum of the piperazinedione **90** were two doublet resonances at δ 0.99 and δ 1.19 (J = 7 Hz) and a multiplet centered at δ 2.85, attributable to the methyl protons and the methine proton of the isopropyl group, repectively. In addition, there were singlet resonances at δ 2.61, δ 2.63 and δ 6.92, for the methyl protons of the *N*-acetyl substituents and for the hydrogen of the carbon bearing the bromine, respectively, as well as a doublet resonance at δ 5.08 (J = 10.5 Hz), for the methine α'-proton of the piperazinedione ring. The mass spectrum of **90** gave rise to peaks at 278, 276 and 239, corresponding to the loss of ketene and the loss of bromine from the molecular ions, respectively. The identity of **90** was substantiated by elemental analysis.

The reaction of **86** with NBS to give **90** likely proceeds by hydrogen abstraction from the α-carbon of the glycine residue to give **89**, with subsequent incorporation of bromine to give **90**. As described above for related examples, the *syn*-diastereomer of **90** would be expected to predominate as a result of a combination of stereoelectronic effects and greater thermodynamic stability.

In order to further characterize the bromide **90**, 6-deuterio-1,4-diacetyl-3-isopropyl-2,5-piperazinedione (**91**) was produced through treatment of the bromide **90** with tributylstannyl deuteride in refluxing benzene for 4 h (Scheme 28). The solvent was evaporated and the residue chromatographed on silica to remove the stannane byproducts. By comparison of the mass spectrum of **91** with the mass spectrum of the non-deuteriated analogue **86**, the deuterium incorporation in the deuteriated derivative **91** was calculated to be 85%. The characteristic resonances in the ^{1}H NMR spectrum of the deuteriated derivative **91** were analogous to those of the non-deuteriated analogue **86**, with the exception that the resonances centered at δ 4.04 and δ 5.00, were of reduced intensity. The ^{1}H and ^{2}H NMR spectra of **91** indicated that of the 85% of deuterium incorporated at the α-carbon of the *N*-acetylglycine residue, 67% corresponded to the ^{1}H NMR resonance at δ 4.04 and 33% to that at δ 5.00.

The 2: 1 ratio of deuterium at δ 4.04 to that at δ 5.00 reflects a diastereomeric preference for the incorporation of deuterium with tributylstannyl deuteride at the α-carbon of the *N*-acetylglycine residue.



Scheme 28

The diastereoselectivity observed in the formation of the deuteriated derivative **91** can be explained by stereoelectronically controlled incorporation of deuterium to the intermediate radical **89**, to afford the thermodynamically more stable *syn*-diastereomer, predominantly.

3-Benzyl-1,4-diacetyl-2,5-piperazinedione (**87**) was treated with one mole equivalent of NBS and a trace of AIBN in dichloromethane and irradiated for 3.5 h. The solvent was

removed by concentration under reduced pressure and the crude reaction mixture was then treated *in situ* with tributylstannyl deuteride. The solvent was evaporated and the stannane byproducts removed by chromatography of the residue on silica, to give a mixture of the deuterides **94** and **97**. A comparison of the mass spectrum of the mixture of **94** and **97** with that of the non-deuteriated analogue **87** showed that the total deuterium content was 54%. Comparison of the ^{1}H and ^{2}H NMR spectra of the deuteriated products **94** and **97** with the ^{1}H NMR spectrum of the starting material **87** allowed the position of deuterium incorporation to be determined. Integration of the spectra showed that of the total deuterium incorporation, 54% was located at the α-carbon of the *N*-acetylglycine residue in the form of **94**, and 46% at the benzylic carbon of the phenylalanine residue in the form of **97**. The preferred conformation about the α-β bond of a phenylalanine residue in cyclic dipeptides is the one in which the aromatic ring is in closest proximity to the 2,5-diketopiperazine ring.[116] As a consequence, the α-hydrogen of the glycine residue in **88** which is *cis* to the benzyl substituent exhibits an anisotropy due to the shielding of the phenyl ring of 1.0ppm.[72,117] By analogy, the α-hydrogen of the *N*-acetylglycine residue in **87** which is *cis* to the benzyl substituent exhibits an anisotropy such that the difference in the ^{1}H NMR chemical shift of the geminal α-protons, is 1.85ppm. Analysis of the ^{1}H and ^{2}H NMR spectra of the mixture of **94** and **97** indicated that of the 54% of deuterium incorporated at the α-carbon of the *N*-acetylglycine residue in the form of **94**, 65% corresponded to the ^{1}H NMR resonance at δ 4.48 and 35% to that at δ 2.63.

In the ^{1}H NMR spectrum of **87**, the resonance for the α-proton of the *N*-acetylglycine residue *cis* to the benzyl substituent is of higher field than the resonance for the α-proton *trans* to the benzyl substituent. Based on this assignment of the resonances of the α-protons, the deuterium incorporation in **94** is *ca.* 1.8 times greater *trans* to the benzyl substituent, than *cis* to the benzyl substituent.

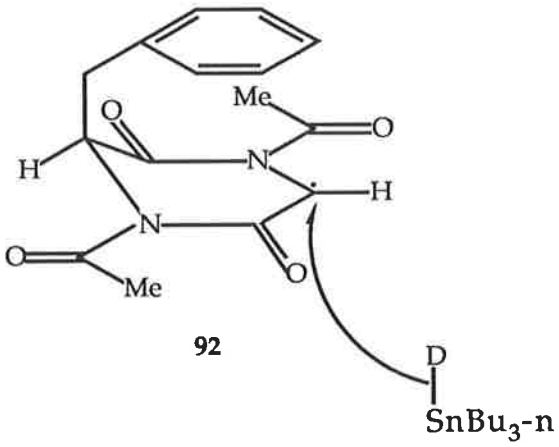
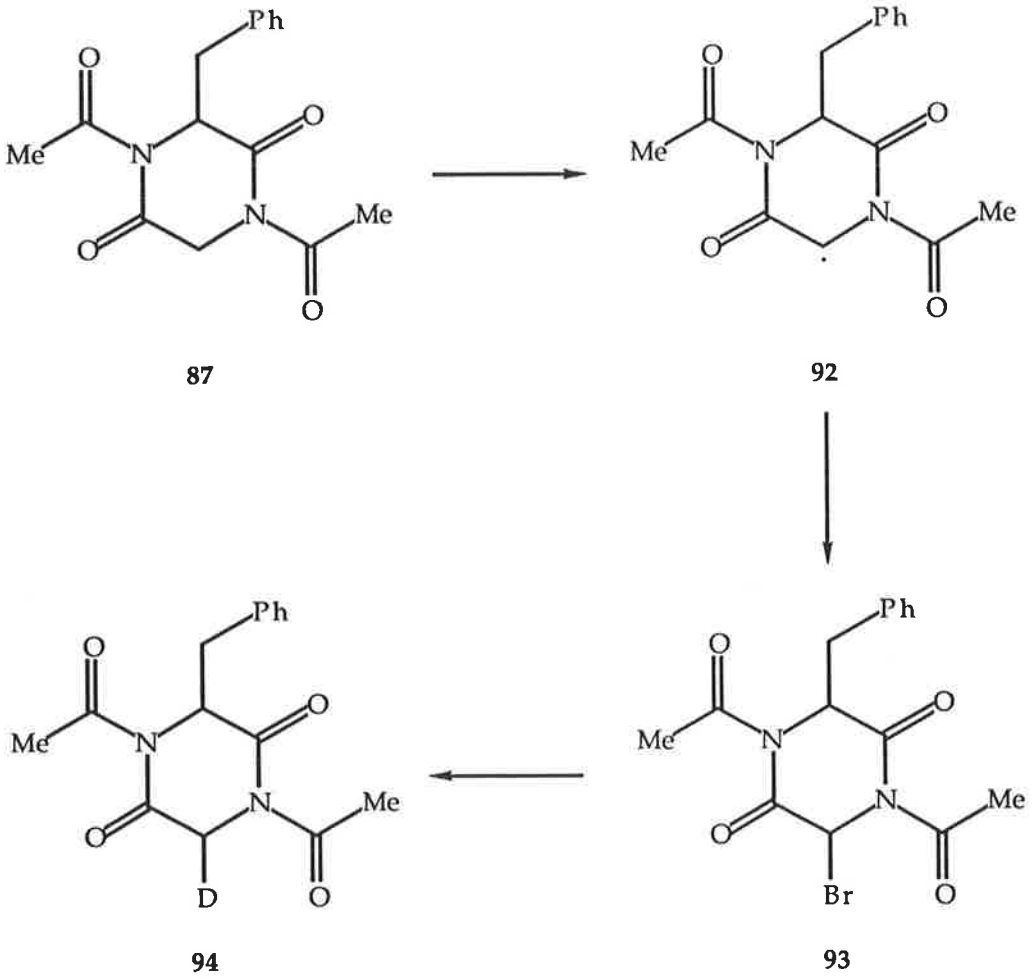


Figure 2.6 steric interactions associated with incorporation of deuterium to **92**.

The diastereoselectivity observed in the formation of the deuteriated derivative **94**, can be explained by steric control of the incorporation of deuterium to the intermediate radical **92** from the least hindered face of the 2,5-piperazinedione ring (Figure 2.6).

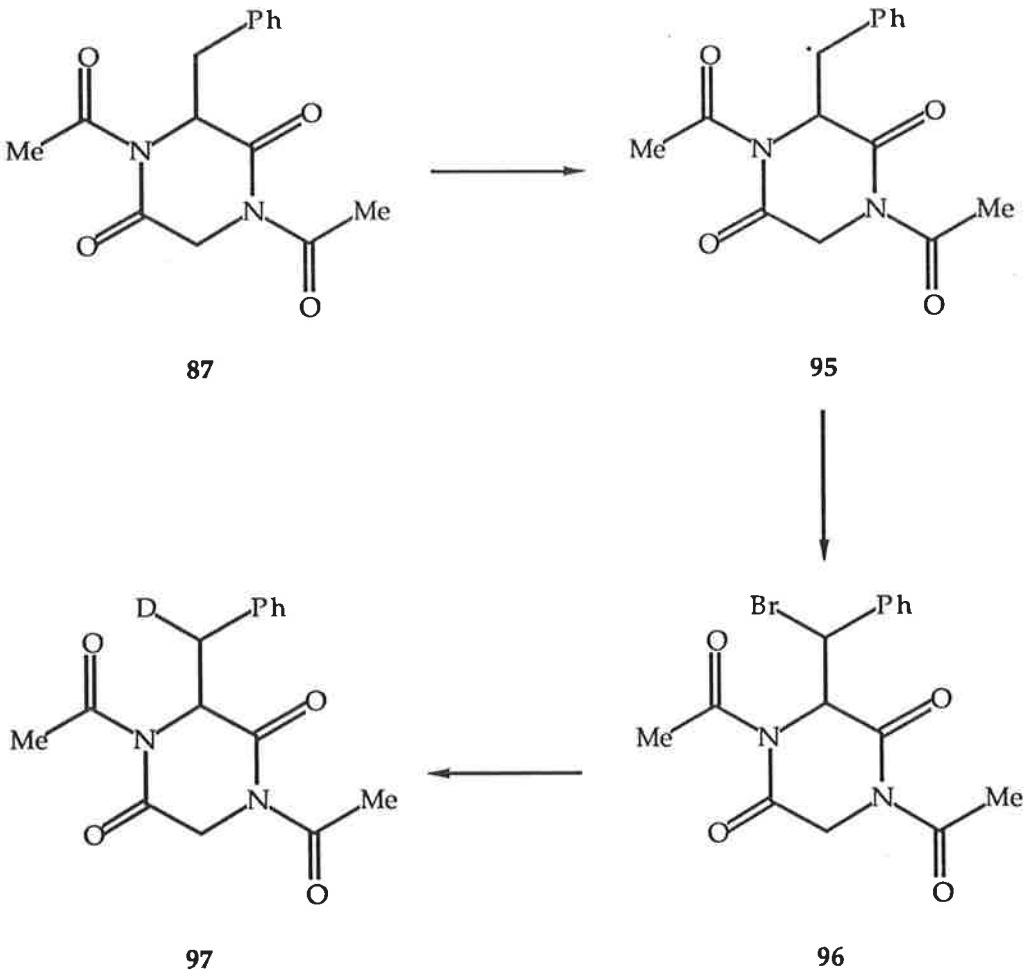
The formation of the deuteriated derivative **94** indicates that the reaction of **87** with NBS likely proceeds by hydrogen abstraction from the α-carbon of the *N*-acetylglycine residue to

give **92**, with subsequent incorporation of bromine to give **93** (Scheme 29).



Scheme 29

Similarly, the production of the deuteriated derivative **97** in the reaction of **87**, likely proceeds by hydrogen abstraction from the benzylic carbon of the phenylalanine residue to give **95**, with subsequent incorporation of bromine to give **96** (Scheme 30). The abstractions of hydrogen atom to give **92** and **95** are competing processes.



Scheme 30

There was no evidence of reaction at the α-carbons of the valine and phenylalanine residues in **86** and **87**, respectively. On this basis, the production of **90** and **93** reflect selective reactions at the α-carbons of glycine residues, complementary to the formation of **79** from **73**. From the exclusive production of **90** in the reaction of **86**, it is evident that the extent of the deactivating effect of an *N*-acyl substituent in a diketopiperazine is not great enough to direct functionalization to an unactivated side-chain. Comparatively, the production of **96**, in competition with **93**, indicates that the effect of an *N*-acyl substituent is

sufficient for reaction of an activated side-chain to occur. These reactions indicate the extent to which α-substituents and *N*-acyl substituents affect the regioselectivity of reactions of diketopiperazines.

CHAPTER 3

Elaboration of Functionalized 2,5-Piperazinediones

The reactions described in Chapters 1 and 2 of the Results and Discussion of this thesis illustrate procedures for the regioselective functionalization of 2,5-diketopiperazines. In order to examine the synthetic potential of those procedures, reactions of the halogenated diketopiperazines were investigated.

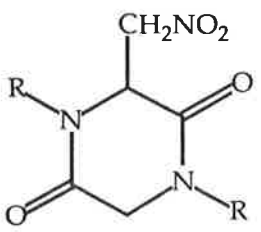
Initially, the reaction of 3-bromo-1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**9**) with methyl nitronate was examined. Crude 3-bromo-1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**9**) was prepared by reaction of **8** with NBS as described above, and separated from the succinimide byproduct by filtration of the cooled reaction mixture. The filtrate was concentrated and the bromide **9** was dissolved in anhydrous terahydrofuran (THF). Nitromethane anion was generated by addition of *n*-butyl lithium to a solution of one equivalent of nitromethane in dry THF and hexamethylphosphoric triamide (HMPA) (6: 1) at -78 °C. The THF solution of the bromide **9** was then added to the methyl nitronate solution at -78 °C. After 4 h at that temperature the reaction was quenched by addition of acetic acid. Work-up and chromatography of the residue on silica gave 1,4-di-(p-methoxybenzyl)-3-hydroxy-2,5-piperazinedione (**100**), in 46%

yield based on the quantity of **8** used to prepare the bromide **9**. Characteristic resonances in the ^{1}H NMR spectrum of **100** were a singlet at δ 3.82, for the protons of the methoxy groups, and AB q resonances at δ 4.09 and δ 5.07 ($J_{AB\ q}$ = 14.5 Hz), at δ 4.41 and δ 4.63 ($J_{AB\ q}$ = 14.5 Hz) and at δ 3.82 and δ 4.09 ($J_{AB\ q}$ = 17.5 Hz), for the pairs of diastereotopic benzylic hydrogens and for the geminal protons at the α'-carbon of the piperazinedione ring, respectively. In addition, a doublet resonance at δ 4.93 (J = 7 Hz), for the hydrogen of the α-carbon bearing the hydroxyl group, a doublet resonance at δ 7.10 (J = 7 Hz), for the intramolecularly hydrogen bonded hydroxyl proton, and multiplet resonances at δ 6.88-6.93 and δ 7.20-7.25, for the aromatic protons, were observed. Addition of deuterium oxide resulted in the collapse of the doublet resonance at δ 4.93 to give a singlet resonance. The hydroxy substituted diketopiperazine **100** possessed other physical and spectral data consistent with the assigned structure and was further characterized by comparison with an authentic sample prepared by addition of water to the crude bromide **9**.

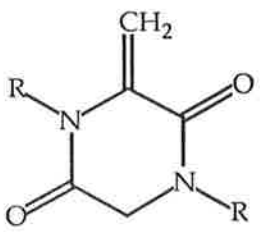
A minor component obtained by chromatography of the product of the reaction of **46** with methyl nitronate was tentatively assigned the structure 1,4-di-(p-methoxybenzyl)-3-methylidene-2,5-piperazinedione (**99**) on the basis of singlet resonances at δ 3.77 and δ 3.80, for the protons of the methoxy substituents, and at δ 4.08, for the geminal protons of the piperazinedione ring, as well as singlet resonances at δ 4.61 and δ 4.90, ascribale to the benzylic protons, in the ^{1}H NMR spectrum. In addition, two doublet resonances at δ 4.99 and

δ 5.86 (J = 1.2 Hz), for the geminal vinylic protons, and four doublet resonances at δ 6.84, δ 6.88, δ 7.13 and δ 7.25 (each with J = 8.5 Hz), for the aromatic protons, were observed.

The reaction of **46** with methyl nitronate was carried out in an analogous manner to that of **9**. Work-up of the reaction mixture gave 1,4-dibenzyl-3-hydroxy-2,5-piperazinedione (**101**), in 42% yield based on the quantity of **13** used to prepare the bromide **46**. Characteristic resonances in the ^{1}H NMR spectrum of **101** were AB q resonances at δ 4.11 and δ 5.06 ($J_{AB\ q}$ = 15 Hz), at δ 4.43 and δ 4.70 ($J_{AB\ q}$ = 15 Hz) and at δ 3.84 and δ 4.16 ($J_{AB\ q}$ = 17.5 Hz), for the pairs of diastereotopic benzylic hydrogens and for the geminal protons at the α'-carbon of the piperazinedione ring, respectively. Additionally, doublet resonances at δ 4.93 (J = 7 Hz) and δ 6.53 (J = 7 Hz), for the hydrogen of the α-carbon bearing the hydroxyl group and for the intramolecularly hydrogen bonded hydroxyl proton, respectively, as well as a multiplet resonance at δ 7.25-7.37, for the aromatic protons, were observed. Addition of deuterium oxide to the NMR sample resulted in the collapse of the doublet resonance at δ 4.93 to give a singlet resonance. The product **101** possessed other physical and spectral data consistent with the assigned structure.

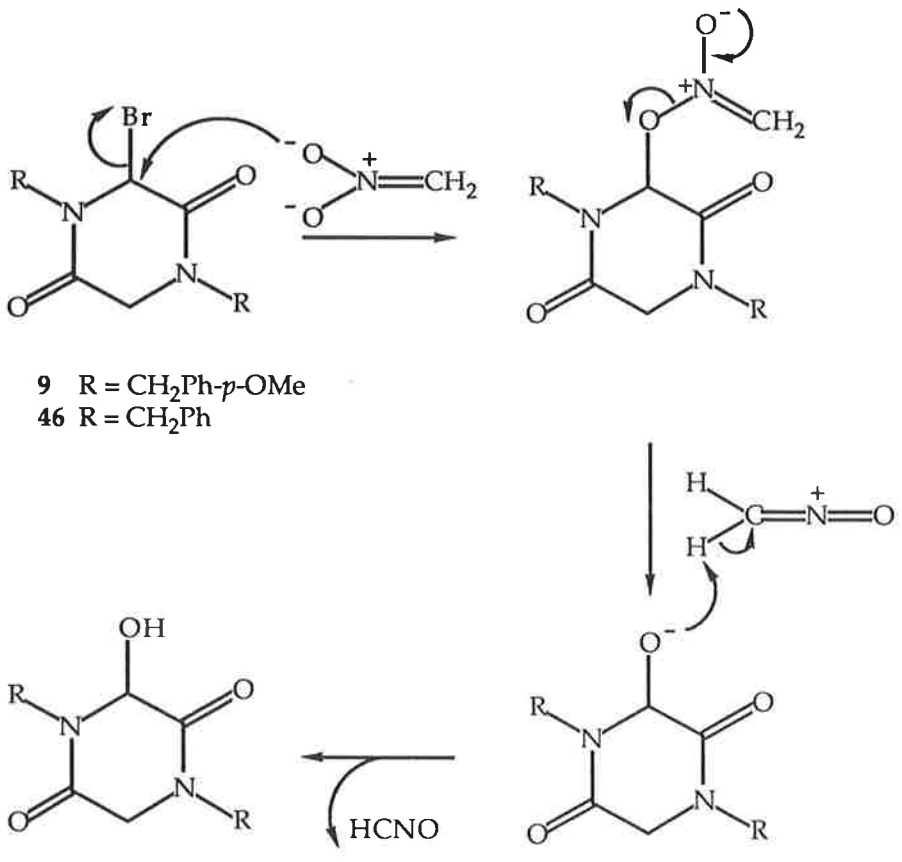


98 R = CH_2Ph-*p*-OMe



99 R = CH_2Ph-*p*-OMe

The formation of **99** in the reaction of **9**, in very low yield, may be attributed to alkylation of the nitronate on carbon, to give **98**. Subsequent elimination of nitrous acid from **98** affords the product **99**. It is unlikely that the hydroxy substituted diketopiperazines **100** and **101** are formed as a result of hydrolysis of the corresponding bromides **9** and **46**, as these products were obtained when the reactions were carried out under strictly anhydrous conditions. Instead, the formation of **100** and **101**, from **9** and **46**, repectively, can be rationalized as shown in Scheme 31.



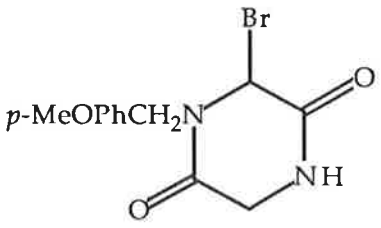
9 R = CH_2Ph-*p*-OMe
46 R = CH_2Ph

100 R = CH_2Ph-*p*-OMe
101 R = CH_2Ph

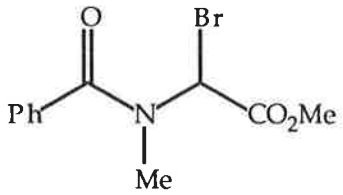
Scheme 31

Initially, nucleophilic attack at the α-carbon of each of the piperazinedione rings by methyl nitronate gives the oxygen alkylated intermediates. Collapse of the intermediates affords the products **100** and **101**. Thus, the alkylation reactions of the monobromides **9** and **46** with the anion of nitromethane occur almost exclusively on oxygen.

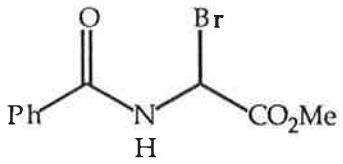
Oxygen alkylation in the reactions of **9** and **46** with methyl nitronate parallels the typical reaction of alkyl nitronates,[118,119,120] whilst carbon alkylation in reactions of alkyl nitronates[77,78] with acyclic α-bromoamino acids are atypical.[76] To determine the cause of this contrast, the reactions of 6-bromo-1-p-methoxybenzyl-2,5-piperazinedione (**102**), *N*-benzoyl-2-bromosarcosine methyl ester (**103**) and *N*-benzoyl-2-bromoglycine methyl ester (**25**) with methyl nitronate were examined.



102

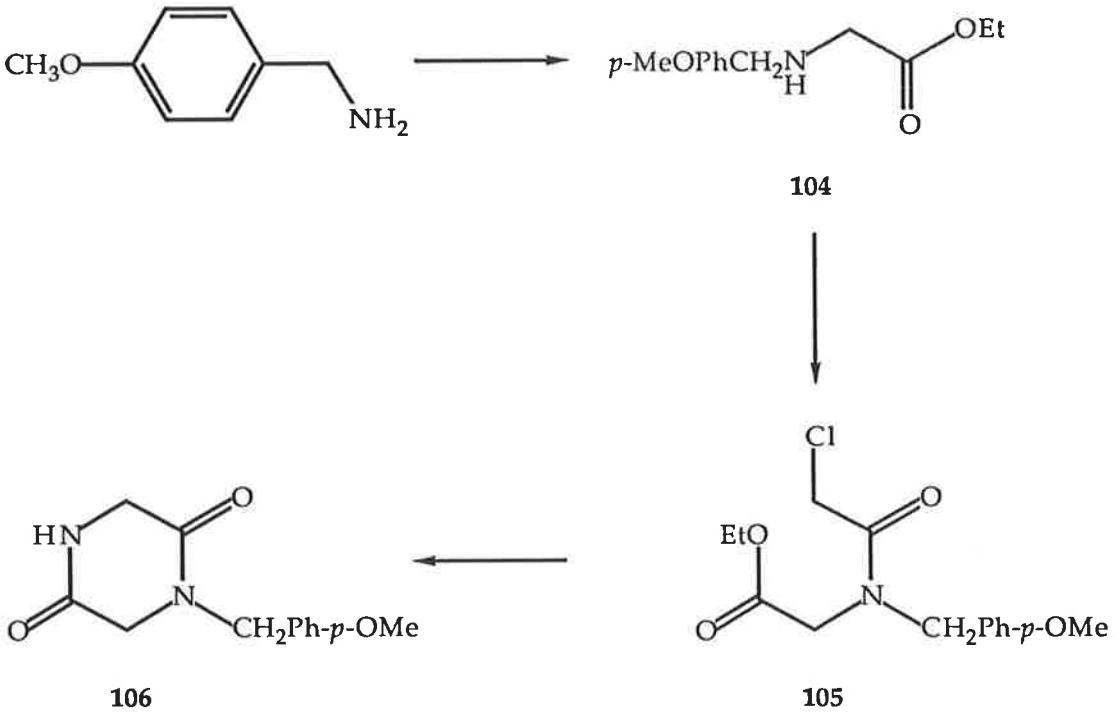


103



25

1-p-Methoxybenzyl-2,5-piperazinedione (**106**) required for this study was prepared in a three step sequence according to the reported literature procedure (Scheme 32).[121]



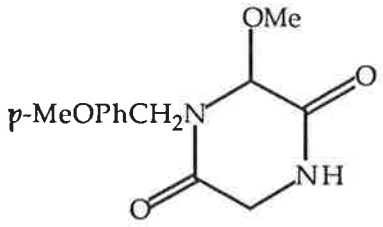
Scheme 32

Slow addition of ethyl bromoacetate at 0 °C to one mole equivalent of p-methoxybenzylamine and 1.1 mole equivalents of triethylamine in ethyl acetate gave crude *N*-p-methoxybenzylglycine ethyl ester (**104**) in 90% yield after work-up. The glycine derivative **104** was not purified but was used directly in the next step of the sequence. One mole equivalent of chloroacetylchloride in ether was added over 1.5 h to a solution of **104** and one mole equivalent of triethylamine in ether. Work-up and chromatography of the residue on silica afforded

N-chloroacetyl-*N*-p-methoxybenzylglycine ethyl ester (**105**) in quantitative yield. The chloroacetyl derivative **105** was dissolved in methanol and a stream of ammonia passed through the solution at -20 °C until the methanol was saturated. The reaction mixture was stirred for a further hour, allowed to warm to room temperature and stirring continued overnight. The precipitate which formed was collected, washed with methanol and dried, to yield 1-p-methoxybenzyl-2,5-piperazinedione (**106**), in 80% yield.

The reaction of 1-p-methoxybenzyl-2,5-piperazinedione (**106**) with one mole equivalent of NBS followed by treatment of the product *in situ* with methanol and triethylamine gave, after work-up and chromatography, 6-methoxy-1-p-methoxybenzyl-2,5-piperazinedione (**107**), in 52% yield based on **106**. The characteristic resonances in the 1H NMR spectrum of the monoether **107** were singlets at δ 3.40 and δ 3.80, for the protons of the methoxy substituents of the piperazinedione and aromatic rings, respectively, as well as a broad signal at δ 7.53, for the amide proton, and a doublet at δ 4.57 (J = 1.2 Hz), attributable to the hydrogen of the α-carbon bearing the methoxy substituent. In addition, an AB q resonance at δ 4.10 and δ 5.13 ($J_{AB\ q}$ = 14.5 Hz), for the diastereotopic benzylic hydrogens, as well as one half of an AB q resonance at δ 4.16 ($J_{AB\ q}$ = 18 Hz), attributable to the pseudoaxial geminal proton of the α'-carbon of the piperazinedione ring, were observed. The pseudoequatorial geminal proton of the α'-carbon of the piperazinedione ring is additionally coupled to the amide proton and is observed as a doublet of one half of an AB q resonance at δ 3.95 ($J_{AB\ q}$ = 18

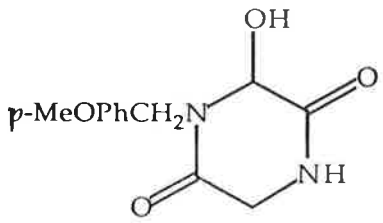
Hz, J = 4.0 Hz). The protons of the aromatic ring appear as doublet resonances at δ 6.87 and δ 7.21 (J = 8.5 Hz). The hydrogen of the α-carbon bearing the methoxy substituent is held in the 'W' configuration[122] with respect to the amide proton and experiences long-range coupling. A plausible explanation for the coupling experienced by only one of the protons of the α'-carbon with the vicinal amide proton is that the α'-protons have unequal dihedral angles, indicating that the piperazinedione ring is in a non-planar conformation.[116]



107

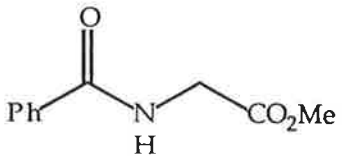
Verification of the assignment of resonances in the ^{1}H NMR spectrum of the monoether **107** was obtained by homonuclear decoupling at the chemical shift of the amide proton. The partially decoupled spectrum showed characteristic resonances of an AB system at δ 3.95 and δ 4.16 ($J_{AB\ q}$ = 18 Hz), and a singlet at δ 4.57. This confirms that one of the protons at the α'-carbon and the proton at the α-carbon are coupled with the amide proton. The mass spectrum of **107** gave rise to peaks at 264 and 121, attributable to the molecular ion and production of the p-methoxybenzyl cation, respectively. The elemental composition of **107** was substantiated by satisfactory microanalytical data.

The production of **107** indicates that reaction of **106** occurs *via* the bromide **102**. Although there is no definitive explanation for the regioselectivity observed in the reaction of **106** with NBS, it may be that the *N*-p-methoxybenzyl substituent facilitates reaction at the C6 carbon through delocalization of charge developed in the transition state of the hydrogen transfer process. A sample of the crude bromide **102** was treated with two equivalents of methyl nitronate to afford a solid upon work-up and chromatography. The product was tentatively assigned as 6-hydroxy-1-p-methoxybenzyl-2,5-piperazinedione (**108**) on the basis of its ^{1}H NMR spectrum, which showed a singlet resonance at δ 3.80, for the protons of the methoxy group, and an AB q resonance at δ 3.93 and δ 4.17 ($J_{AB\ q}$ = 18 Hz), for the geminal protons at the α'-carbon of the piperazinedione ring. In addition, an AB q resonance at δ 4.09 and δ 5.19 ($J_{AB\ q}$ = 14.5 Hz), attributable to the diastereotopic benzylic hydrogens, and a singlet resonance at δ 4.89, for the proton of the carbon bearing the hydroxy group, and two doublet resonances at δ 6.87 and δ 7.24 ($J_{AB\ q}$ = 9 Hz), attributable to the aromatic protons, were observed. Long-range and vicinal, α-proton to amide proton couplings were detectable but not resolved, due to exchange of the amide proton with the solvent, causing a broadening in the α-proton resonances. Thus, alkylation of the bromide **102** with the anion of nitromethane occurs on oxygen, in an analogous manner to the reactions of the monobromides **9** and **46** described above.



108

N-Benzoylsarcosine methyl ester (**14**) was prepared by esterification of sarcosine with methanol and thionyl chloride, followed by treatment of the intermediate methyl ester hydrochloride with benzoyl chloride and triethylamine. Methyl hippurate (**109**) was prepared by esterification of hippuric acid with methanol and thionyl chloride. The products **14** and **109** were found to exhibit satisfactory physical and spectral properties consistent with those previously reported.[123,124]

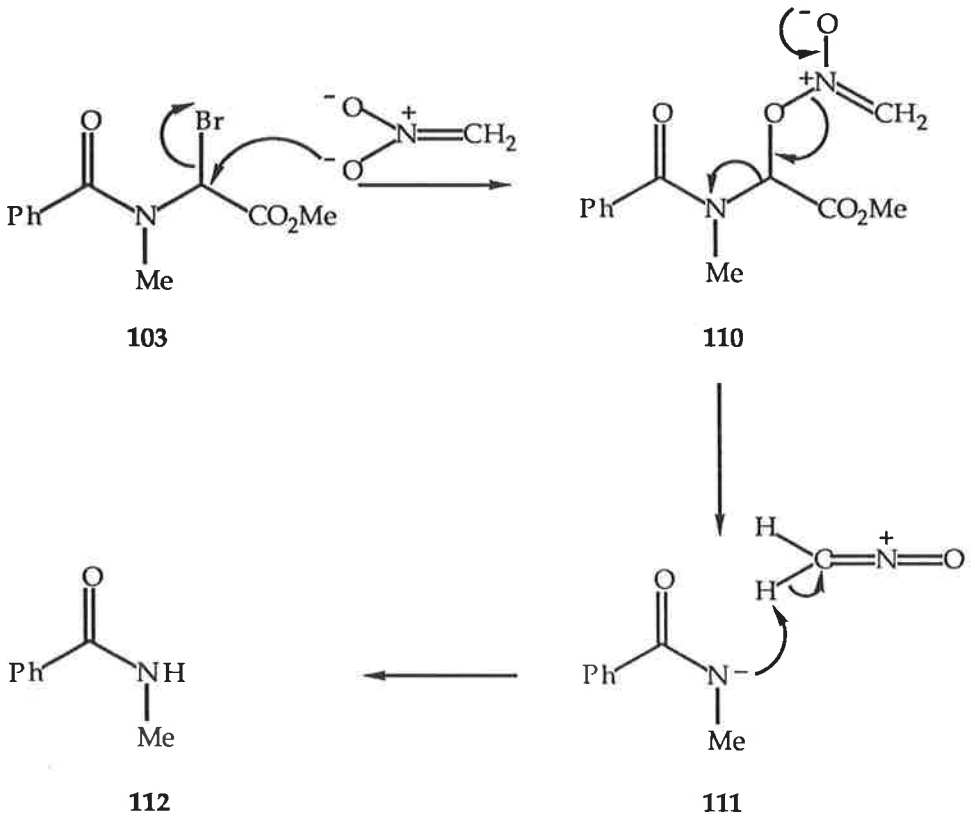


109

N-Benzoylsarcosine methyl ester (**14**) was treated with one equivalent of NBS to give *N*-benzoyl-2-bromosarcosine methyl ester (**103**).[125] The bromide **103** obtained upon filtration to remove the succinimide byproduct and evaporation of the solvent, was dissolved in THF and added to one equivalent of the nitromethane anion, prepared as described for reaction with **9**. After work-up and chromatography of the residue on silica the sole product was *N*-methylbenzamide (**112**), which was obtained in 56% yield based on **14**. *N*-Methylbenzamide (**112**) was

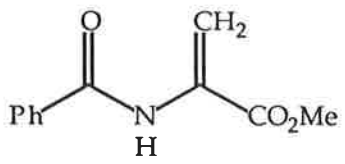
identified by comparison of its spectral properties with literature spectral data.

The formation of *N*-methylbenzamide (**112**) in the reaction of **103** with methyl nitronate can be explained through initial nucleophilic attack of the methyl nitronate to displace bromide ion, to give **110**. The intermediate **110** then collapses to give deprotonated *N*-methylbenzamide (**111**), with the product **112** being formed upon quenching of the reaction mixture with acid (Scheme 33). No glyoxylate byproducts from this process were isolated. These were presumably lost in the aqueous work-up. Thus, O-alkylation of methyl nitronate is the major reaction pathway in the reaction of **103**.



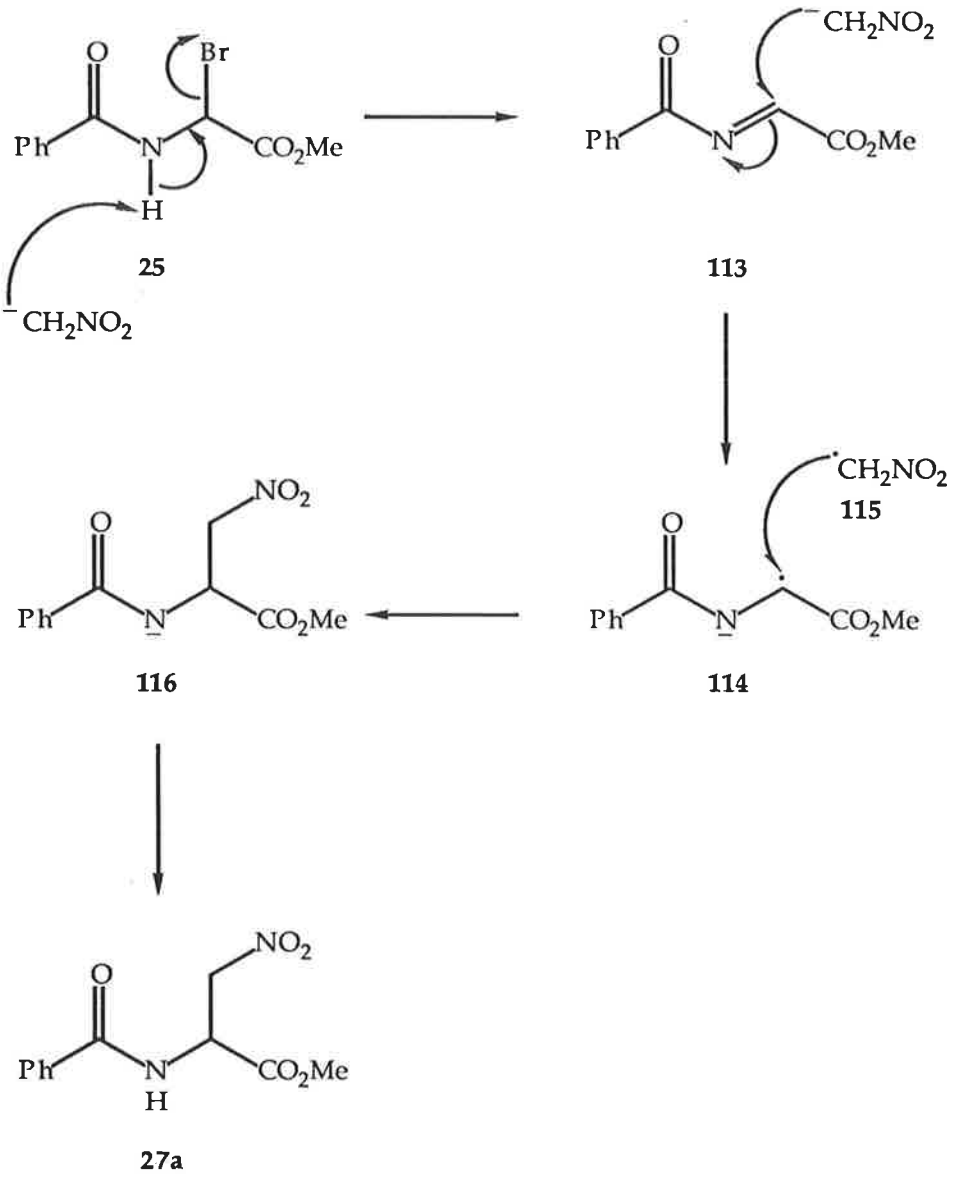
Scheme 33

N-Benzoylglycine methyl ester (**109**) was treated with one equivalent of NBS to give *N*-benzoyl-2-bromoglycine methyl ester (**25**).[125] The bromide **25** was dissolved in THF and added to two equivalents of the nitromethane anion, in a similar manner as to that described previously.[76] Work-up and chromatography of the residue on silica gave *N*-benzoyl-3-nitroalanine methyl ester (**27a**), in 54% yield, and methyl 2-benzamidopropenoate (**117**), in 2% yield, based on **109**. The products **27a** and **117** had physical and spectral properties consistent with those reported previously.[76]



117

A mechanistic pathway for the formation of **27a**, by the reaction of **25** with methyl nitronate, has been reported (Scheme 34),[76] initially involving elimination of hydrogen bromide to afford the *N*-acylimine **113**. Subsequent electron transfer from the second equivalent of the nitroalkane anion to the *N*-acylimine **113** gives the radical anion **114** and the nitromethane radical **115**. Combination of the nitromethane radical **115** and the radical anion **114** gives the amidate **116**. Quenching of the reaction with acid affords the product **27a**. The dehydroalanine derivative **117** is formed by elimination of nitrous acid from **27a**.

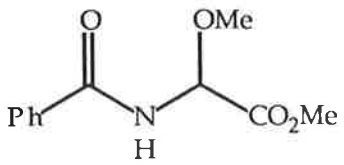


Scheme 34

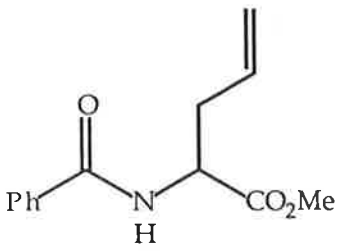
The different course of reaction of methyl nitronate with **25**, compared to **9**, **46**, **102** and **103** may be attributed to the inability of the latter compounds to afford *N*-acylimines by hydrogen bromide elimination. Clearly, if the corresponding *N*-acyliminium ions are formed in the reactions of **9**, **46**, **102** and **103**, oxygen alkylation of methyl nitronate, rather than electron transfer, is the favored reaction pathway. On this basis,

reactions with alkyl nitronates are unsuitable for elaboration of functionalized diketopiperazines.

The reactivity of functionalized diketopiperazines with allyltrimethylsilane in the presence of boron triflouride etherate was also investigated. There was no reaction on treatment of 6-methoxy-1-p-methoxybenzyl-2,5-piperazinedione (**107**) with 3.15 mole equivalents of allyltrimethylsilane and 3.25 mole equivalents of boron triflouride etherate. Unreacted **107** was recovered quantitatively from the mixture after work-up. Furthermore, even greater excesses of either allyltrimethylsilane or boron triflouride etherate failed to induce reaction. The bromides **102** and **90** were also inert under these conditions. However, when the substrate was 2-methoxy-*N*-benzoylglycine methyl ester (**118**) the allylated product **30a** was produced in 65% yield and had physical and spectral properties identical to those previously reported.[82] The reaction of **118** under conditions in which **102**, **107** and **90** were inert, indicates that the formation of **30a** probably occurs *via* the intermediate *N*-acylimine **113**.



118



30a

The failure of functionalized diketopiperazines to react by ionic allylation led to an investigation of homolytic allylation

reactions of these compounds using allyltributylstannane. Allyltributylstannane was prepared using the reported magnesium-induced halide coupling procedure. Allyl bromide and tributylstannyl chloride were the halides of choice, used for the coupling reaction. Initially, the allylation reaction of 3-bromo-1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**9**) was examined. The crude bromide **9**, prepared by treatment of **8** with one equivalent of NBS and evaporation of the solvent, was dissolved in dry benzene. Two mole equivalents of allyltributylstannane and a trace amount of AIBN were added and the mixture was refluxed for 4 h under a nitrogen atmosphere. The solvent was evaporated and the stannane byproducts removed by chromatography of the residue on silica, to afford 3-allyl-1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**119**), in 36% yield based on **8**.

Characteristic resonances in the ^{1}H NMR spectrum of the allylated product **119** were multiplet resonances centered at δ 2.60 and δ 5.60, for the allylic protons and for the non-terminal vinylic proton, respectively, as well as singlet resonances at δ 3.75 and δ 3.76, for the protons of the methoxy groups. In addition, AB q resonances at δ 3.76 and δ 3.91 ($J_{AB\,q}$ = 17.5 Hz), for the geminal protons at the α'-carbon of the piperazinedione ring, and at δ 3.98 and δ 5.17 ($J_{AB\,q}$ = 14.5 Hz) and δ 4.16 and δ 4.82 ($J_{AB\,q}$ = 14.5 Hz), for the pairs of diastereotopic benzylic hydrogens, were observed. Doublet resonances at δ 5.05 (J = 9.5 Hz) and δ 5.09 (J = 15.5 Hz), attributable to the terminal vinylic protons in a *cis* and *trans* relationship to the non-terminal vinylic proton, respectively, and at δ 6.84 (J = 8.5 Hz) and δ 7.18

(J = 8.5 Hz), ascribable to the aromatic protons, as well as a triplet resonance at δ 3.99 (J = 5 Hz), for the methine proton of the α-carbon, were observed. Coupling of the non-terminal vinylic proton resonances was not resolved. The mass spectrum of **119** gave rise to peaks at 394, 353 and 121, corresponding to the molecular ion, loss of the allylic moiety from the molecular ion and production of the p-methoxybenzyl cation, respectively.

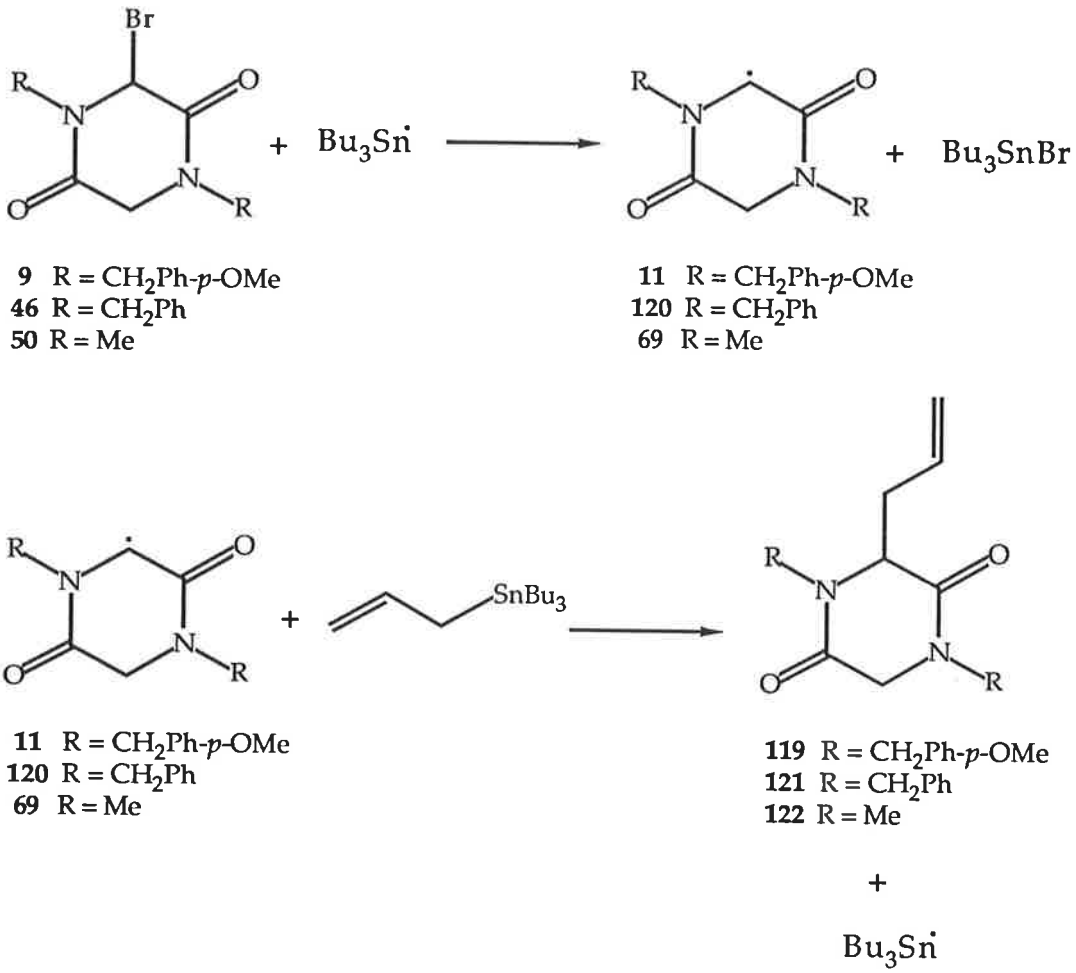
The crude bromide **46**, prepared by treatment of **13** with NBS was treated with allyltributylstannane as described for **9**. The solvent was removed and the residue chromatographed on silica to afford 3-allyl-1,4-dibenzyl-2,5-piperazinedione (**121**). Characteristic resonances in the ^{1}H NMR spectrum of the allylated product **121** were multiplet resonances centered at δ 2.62 and δ 5.62, for the allylic protons and for the non-terminal vinylic proton, respectively, as well as AB q resonances at δ 3.80 and δ 3.95 ($J_{AB\,q}$ = 17.5 Hz), for the geminal protons at the α'-carbon of the piperazinedione ring, and at δ 4.03 and δ 5.27 ($J_{AB\,q}$ = 14.5 Hz) and δ 4.25 and δ 4.89 ($J_{AB\,q}$ = 15 Hz), for the pairs of diastereotopic benzylic hydrogens. In addition, doublet of doublet resonances at δ 5.06 (J = 1.5 and 9 Hz) and δ 5.11 (J = 1.5 and 16 Hz), attributable to the terminal vinylic protons in a *cis* and *trans* relationship to the non-terminal vinylic proton, respectively, a multiplet resonance centered at δ 7.28, ascribable to the aromatic protons, as well as a triplet resonance at δ 4.02 (J = 5 Hz), for the methine proton of the α-carbon, were observed. The mass spectrum of **121** gave rise to peaks at 334, 293 and 91, corresponding to the molecular ion, loss of the

allylic moiety from the molecular ion and production of the benzyl cation, respectively.

Additionally, the crude bromide **50**, obtained from the reaction of **5** with NBS, was treated with two equivalents of allyltributylstannane, in an analogous manner as for the allylation reactions of the bromides **9** and **46**, to afford 3-allyl-1,4-dimethyl-2,5-piperazinedione (**122**), in 36% yield based on **5**. Characteristic resonances in the ^{1}H NMR spectrum of the allylated product **122** were multiplet resonances centered at δ 2.68, δ 5.20 and δ 5.69, attributable to the allylic protons, the terminal geminal vinylic protons and the non-terminal vinylic proton, respectively. In addition, singlet resonances at δ 2.98 and δ 3.00, for the *N*-methyl protons, an AB q resonance at δ 3.83 and δ 4.06 ($J_{AB\,q}$ = 17.5 Hz), for the geminal protons at the α'-carbon of the piperazinedione ring, and a triplet resonance at δ 4.01 (J = 4.5 Hz), for the methine proton of the α-carbon, were observed. The mass spectrum of **122** gave rise to peaks at 182 and 141, corresponding to the molecular ion and loss of the allylic moiety from the molecular ion.

The production of **119**, **121** and **122** in the reactions of **9**, **46** and **50**, respectively, can be rationalized as shown in Scheme 35. Bromine transfer from **9**, **46** and **50** to stannyl radical gives the corresponding radicals **11**, **120** and **69**. Allyl group transfer from the allylstannane to the radicals **11**, **120** and **69** affords the corresponding allyl substituted piperazinediones **119**, **121** and **122** and stannyl radical which propagates the chain reactions. The production of **119**, **121** and **122** indicates that reaction of α-halogenated diketopiperazines

with allyltributylstannane is a viable method for elaboration of these compounds.



9 R = CH_2Ph-*p*-OMe
46 R = CH_2Ph
50 R = Me

11 R = CH_2Ph-*p*-OMe
120 R = CH_2Ph
69 R = Me

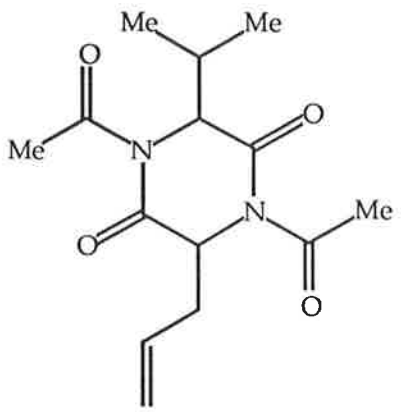
11 R = CH_2Ph-*p*-OMe
120 R = CH_2Ph
69 R = Me

119 R = CH_2Ph-*p*-OMe
121 R = CH_2Ph
122 R = Me

Scheme 35

The introduction of an allyl group into a diketopiperazine, i.e., the conversion of **5**, **8** and **13**, to **119**, **121** and **122**, respectively, results in a new chiral center. To investigate the diastereoselectivity of allyl group incorporation in a 3-alkyl substituted diketopiperazine, the reaction of 3-bromo-1,4-diacetyl-6-isopropyl-2,5-piperazinedione (**90**) with two equivalents of allyltributylstannane in refluxing benzene in the presence of AIBN, for 17 h, was studied. Evaporation of the

solvent and chromatography of the residue afforded 3-allyl-1,4-diacetyl-6-isopropyl-2,5-piperazinedione (**123**) as a single diastereomer, in 60% yield. Characteristic resonances in the ^{1}H NMR spectrum of the allyl product **123** included a multiplet resonance centered at δ 2.75, for the allylic protons, a doublet resonance at δ 4.76 (J = 4.5 Hz), attributable to the methine proton of the piperazinedione ring of the valine residue, and a multiplet resonance centered at δ 5.53, for the non-terminal vinylic proton. In addition, doublet of doublet resonances at δ 4.90 (J = 3.5 and 5.5 Hz), at δ 5.05 (J = 1.5 and 15 Hz) and at δ 5.09 (J = 1.5 and 9.5 Hz), attributable to the methine proton of the piperazinedione ring of the allylglycine residue and the geminal vinylic protons, respectively, were observed. The mass spectrum of the allyl substituted product **123** gave rise to peaks at 280, 238 and 43, corresponding to the molecular ion, loss of ketene from the molecular ion and production of the acetyl cation, respectively. The composition of the allylated product **123** was confirmed by elemental analysis.

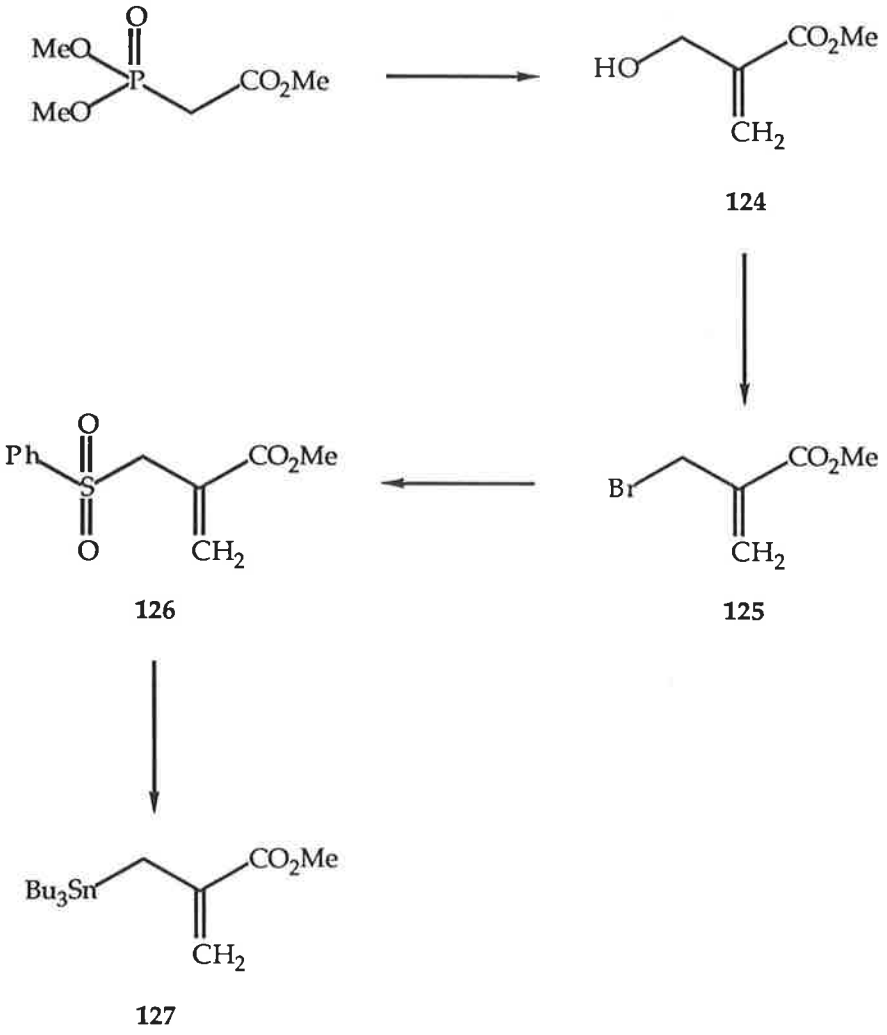


123

There was no evidence for the formation of the diastereomer of **123**, either in the crude reaction mixture or in the products isolated from chromatography of the reaction mixture on silica. The product **123** is assumed to be the *syn*-diastereomer as a result of the thermodynamically preferred mode of allyl group transfer to the intermediate radical **89**.

In order to assess the generality of this diastereoselective allylation, the reaction of 3-bromo-1,4-diacetyl-6-isopropyl-2,5-piperazinedione (**90**) with methyl α-tributylstannylmethyl-acrylate (**127**) was examined. Methyl α-tributylstannylmethyl-acrylate (**127**) required for use in this investigation, was prepared in a four step process (Scheme 36). Reaction of trimethyl phosphonoacetate with an aqueous solution of formaldehyde and potassium carbonate gave methyl α-hydroxy-methylacrylate (**124**). Methyl α-hydroxymethylacrylate (**124**) was converted to methyl α-bromomethylacrylate (**125**) by treatment with phosphorous tribromide. Methyl α-phenyl-sulfonylmethylacrylate (**126**) was prepared in 33% yield, by treatment of the bromide **125** with two equivalents of sodium phenyl sulfinate. Characteristic resonances in the ^{1}H NMR spectrum of the product sulfone **126** were singlet resonances at δ 3.58 and δ 4.16, for the methyl ester and methylene protons, respectively, and at δ 5.91 and δ 6.50, for the vinylic protons, as well as multiplet resonances centered at δ 7.60 and δ 7.86, attributable to the protons of the aromatic ring. The mass spectrum gave rise to peaks at 240 and 176, corresponding to the molecular ion and the loss of sulfur dioxide from the molecular ion, respectively. The compositions of **124**, **125** and **126** were

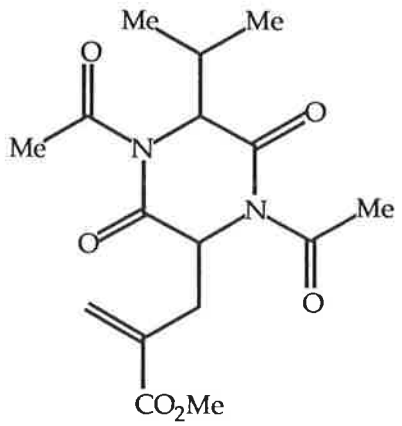
confirmed by elemental analysis. The sulphone was treated with two mole equivalents of tributylstannyl hydride to give the unstable methyl α-tributylstannylmethylacrylate (**127**) in 29% yield. All attempts to remove trace impurities from the allyl stannane **127** were unsuccessful and the crude material was used in reactions with the bromide **90**.



Scheme 36

The bromide **90** was treated with two equivalents of methyl α-tributylstannylmethylacrylate (**127**) in refluxing benzene in the presence of AIBN, for 10 h. Evaporation of the solvent and

chromatography of the residue afforded 1,4-diacetyl-6-isopropyl-3-(2-methoxycarbonyl)-allyl-2,5-piperazinedione (**128**) in 17% yield. Characteristic resonances in the ^{1}H NMR spectrum of **128** included a doublet of an AB q resonance at δ 3.00 and δ 3.04 (J = 3.5 Hz and $J_{AB\ q}$ = 14 Hz) and at δ 3.22 and δ 3.27 (J = 7 Hz and $J_{AB\ q}$ = 14 Hz), for the allylic protons, a doublet of doublets resonance at δ 5.05 and δ 5.07 (J = 3.5 and 7 Hz), for the methine proton of the piperazinedione ring of the allylated residue, and a doublet resonance at δ 4.78 (J = 4.5 Hz), attributable to the methine proton of the piperazinedione ring of the valine residue. In addition, singlet resonances at δ 5.64 and at δ 6.25, attributable to the vinylic protons, were observed. The mass spectrum of the product **128** gave rise to peaks at 338, 296, and 42, corresponding to the molecular ion, loss of ketene from the molecular ion and production of a ketene cation, respectively.



128

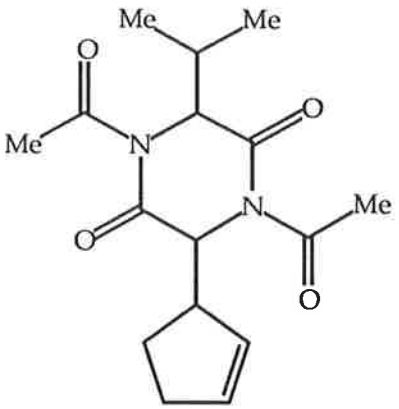
The product **128** was determined to be formed as a single diastereomer within the limits of detection by ^{1}H NMR

spectroscopy, and is assumed by analogy with the formation of the single diastereomer of **123** to be of *syn*-stereochemistry, as a result of the preferred mode of allyl group transfer to the intermediate radical **89** to give the thermodynamically most stable product.

The reaction of the bromide **90** with cyclopent-2-enyltributylstannane (**130**) was also examined. The allylic stannane **130** was synthesized for use in this investigation of these elaborations. 3-Bromocyclopentene (**129**), prepared by the reaction of cyclopentene with one equivalent of NBS, was used immediately in the magnesium-induced halide coupling reaction with tributylstannyl chloride, to afford cyclopent-2-enyltributylstannane (**130**). The bromide **90** was treated with two equivalents of cyclopent-2-enyltributylstannane (**130**) in refluxing benzene in the presence of AIBN. After 24 h the solvent was evaporated and the stannane byproducts removed by chromatography of the residue on silica, to give 3-(cyclopent-2-enyl)-1,4-diacetyl-6-isopropyl-2,5-piperazinedione (**131**) as a *ca.* 1:1 mixture of two diastereomers, in 12% yield. The ^{1}H NMR spectrum of **131** showed characteristic doublet resonances at δ 4.83 (J = 4 Hz), δ 4.84 (J = 4 Hz), δ 5.06 (J = 3.5 Hz) and δ 5.18 (J = 5.5 Hz), one for each of the methine piperazinedione ring protons of each diastereomer. No other diastereomer of **131** was detected in the products isolated from chromatography of the reaction mixture on silica.

129

130



131

The production of **131** from the radical **89** involves the formation of two new chiral centers and the possible formation of four diastereomers. That only two diastereomers of **131** were detected indicates that one chiral center is formed diastereoselectively. Presumably the selectivity occurs at the C3 carbon of the piperazinedione ring, by analogy with the diastereoselectivity observed in the reactions of **90** with allyltributylstannane and **127**.

The allyl transfer reactions of **90** to give **123**, **128** and **131** exhibit much greater diastereoselectivity than the homolytic reaction of **90** with tributylstannyl deuteride to give **91**. This can be attributed to the higher activation energy for the allyl transfer process. In order to develop a more diastereoselective synthesis of **91**, the reaction of 3-bromo-1,4-diacetyl-6-isopropyl-2,5-piperazinedione (**90**) with deuterium in the presence of a palladium catalyst was investigated. The bromide **90** was dissolved in anhydrous tetrahydrofuran and deuterium oxide, and 0.3 mole equivalents of palladium chloride were added. The mixture was stirred under an atmosphere of

deuterium, overnight. Filtration of the reaction mixture through celite, work-up and chromatography of the residue gave the deuteriated piperazinedione **91**, in 40% yield. The deuteriated piperazinedione **91**, prepared in this manner showed identical resonances in the ^{1}H NMR spectrum to those of the non-deuteriated analogue **86**, with the exception that the resonances at δ 4.04 and δ 5.00 were of reduced intensity. By comparison of the mass spectrum of **91** with that of the non-deuteriated analogue **86**, the deuterium incorporation in **91** was calculated to be 92%. The ^{1}H and ^{2}H NMR spectra of **91** indicated that deuterium was incorporated at the α-carbon of the *N*-acetylglycine residue, of which 89% was incorporated at δ 5.00 and 11% at δ 4.04 to the isopropyl substituent.

Thus, the reaction of **90** with deuterium over palladium chloride is not only more stereoselective but also results in the reverse stereochemical outcome compared to the reaction of **90** with tributylstannyl deuteride. On this basis, the predominant diastereomer of **91** obtained by deuterogenolysis of the bromide **90**, is likely to be the *anti*-diastereomer as palladium catalyzed hydrogenolysis reactions are known to proceed with inversion of configuration. This outcome parallels the results of hydrogenolysis reactions of epoxides, benzylamine and benzyl alcohol derivatives over palladium catalysts.[126,127,128,129,130] Both the rate and stereochemical outcome of hydrogenolysis reactions may be influenced not only by the metal catalyst used but also by the nature of the leaving group,[126,127,131,132] by the reaction solvent and by the amount of hydrogen retained on the catalyst.[132] In general, the rate of hydrogenolysis is increased

when the bond being cleaved is weaker. The backside displacement of the leaving group to form the metal bound intermediate with inversion of configuration, is more favorable with a better leaving group. The inversion process in the formation of **91** is favored not only by the use of a palladium catalyst but also by the use of bromide ion as the leaving group.

The production of **123**, **128** and **131** in the reactions of **90** with allyltributylstannane, **127** and **130**, respectively, illustrates procedures for the diastereoselective elaboration of diketopiperazines. The synthesis of **91** by deuterogenolysis of **90** provides a complementary method for the synthesis of stereochemically enriched deuterioglycines, from a readily available precursor **90**, with valine as the chiral auxiliary.

CONCLUSION

Radical bromination is a viable method for the monofunctionalization of symmetric glycine anhydride derivatives. The attractiveness of the technique is its direct simplicity. Polar effects are observed in reactions of symmetric diketopiperazines with sulfuryl chloride, however, the regioselectivity is not high enough to warrant exploitation of the method in synthesis.

From the examination of the factors governing the comparative effects of *N*-alkyl and *N*-acyl substituents in cyclic dipeptides it can be seen that partial charge stabilizing effects play a significant role in determining the relative reactivity of amino acid residues of such piperazinediones. Relative to *N*-alkyl substituents, *N*-acyl substituents deactivate the substituted amino acid toward functionalization. The reactions are also selective for glycine residues in 3-substituted diketopiperazines.

The selectivity of bromination of amino acid residues in diketopiperazines can be influenced through the choice of *N*-substituents and the presence or absence of α-substituents. Thus, to an extent, the selectivity of functionalization of a diketopiperazine can be predicted and directed as required for a particular synthesis.

3-Bromo-2,5-piperazinedione derivatives are suitable templates from which allyl, substituted allyl and deuteriated amino acid derivatives can be prepared.

The methodology for the elaboration of symmetric diketopiperazines *via* the allylation technique has considerable potential for synthesis of this class of important and naturally occurring compounds. An important aspect of the application of this technique is that the functionalization and elaboration of a 3-substituted diketopiperazine proceeds with a high degree of stereoselectivity. Optically active allylglycine derivatives and related compounds are of interest as mechanism based enzyme inhibitors, whilst deuteriated amino acid derivatives are utilized in the study of biochemical reactions.

EXPERIMENTAL

Melting points were measured using a Kofler hot-stage melting point apparatus under a Reichert microscope and are uncorrected.

Elemental analyses were carried out by the Canadian Microanalytical Service Ltd., New Westminster, Canada.

Infrared spectra were recorded on a Hitachi 270-30 spectrophotometer. Electron impact mass spectra and accurate mass measurement of ions were recorded on an AEI MS-3010 spectrometer. Fast atom bombardment (FAB) mass spectra were recorded on a Vacuum Generators ZAB 2HF spectrometer. Only the major fragments are given with their relative abundances shown in parentheses.

^{1}H NMR spectra were recorded on either a Varian T-60, Jeol JNM-PMX60, Bruker CXP-300 or Bruker ACP-300 spectrometer. Unless otherwise stated, ^{1}H NMR spectra were recorded as dilute solutions in deuteriochloroform using tetramethylsilane as an internal standard. The characteristic resonances of the spectra are expressed in text as follows: s, singlet; d, doublet; t, triplet; q, quartet; AB system, AB quartet; d of an AB system, d of an AB quartet; m, multiplet; br s, broad singlet; br, broad.

^{2}H NMR spectra were recorded on a Bruker CXP-300 spectrometer. They were determined in deuteriochloroform.

^{13}C NMR spectra were recorded on a Bruker ACP-300 spectrometer. They were determined in deuteriochloroform using tetramethylsilane as an internal reference.

Chromatography was carried out by either Dry Flash Column Chromatography[133] or by Flash Column Chromatography[134] using Merck silica gel grade 60 HF_{254} for the former and grade 60 PF_{254} for the latter.

All organic extracts were dried over anhydrous sodium sulfate or anhydrous magnesium sulfate.

All solvents were purified by standard procedures.[135] In particular, **dichloromethane** and chloroform were washed with water, dried and distilled before use in order to remove ethanol. Hexane refers to the fraction of light petroleum of bp 66-68 °C. Glycine anhydride (**42**), sarcosine anhydride (**5**) and all dipeptides were obtained from Sigma chemical company.

Work described in Chapter 1

1,4-Di-(p-methoxybenzyl)-2,5-piperazinedione (8)

Glycine anhydride (**42**) (5 g, 44 mmol) was suspended in dry dimethylformamide (DMF) (600 ml) and sodium hydride (3.29 g, 80% in paraffin oil, 110 mmol) and p-methoxybenzylchloride (34.3 g, 219 mmol) added. The mixture was stirred under a nitrogen atmosphere overnight and the DMF removed by distillation under reduced pressure. The residue was taken up in ethyl acetate, and the organic phase washed with water, saturated sodium chloride solution and dried. The solvent was removed *in vacuo* and the product recrystallized from chloroform, to give **8** (14.2 g, 91%) as colorless needles; mp 205.5-206 °C; ^{1}H NMR δ 3.80 (6 H, s), 3.96 (4 H, s), 4.51 (4 H, s), 6.85-6.88 (4 H, m), 7.18-7.21 (4 H, m); MS, *m/z* 354 (19), 121 (100); exact mass calcd for $C_{20}H_{22}N_2O_4$ *m/e* 354.15678, found 354.15795.

3-Bromo-1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (9)

A mixture of 1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**8**) (1.03 g, 2.9 mmol) and NBS (0.46 g, 2.61 mmol) in carbon tetrachloride (50 ml) in the presence of AIBN (*ca.* 5 mg) was irradiated for 0.5 h at reflux under a nitrogen atmosphere. The reaction mixture was cooled and then filtered and the solvent

removed *in vacuo* to give a residue comprised of the starting material **8**, the monobromide **9** and the dibromide **10** in the ratio *ca.* 2: 6: 1, as determined by ^{1}H NMR spectroscopy. Characteristic resonances in the ^{1}H NMR spectrum of **9** were δ 3.80 (3 H, s), 3.81 (3 H, s), 3.82, 3.94 (1 H each, AB system, J = 18 Hz), 3.91, 5.18 (1 H each, AB system, J = 14 Hz), 4.26, 4.84 (1 H each, AB system, J = 14.5 Hz), 5.79 (1 H, s), 6.6-6.9 (4 H, m), 7.1-7.3 (4 H, m).

3,6-Dibromo-1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (10)

Reaction of 1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**8**) (1.03 g, 2.9 mmol) and NBS (1.08 g, 6.1 mmol) in carbon tetrachloride (50 ml) as described above for the preparation of **9**, gave the crude dibromide **10**. ^{1}H NMR δ 3.81 (6 H, s), 3.96, 5.26 (2 H each, AB system, J = 14.5 Hz), 5.87 (2 H, s), 6.85-6.95 (4 H, m), 7.20-7.25 (4 H, m).

1,4-Di-(p-methoxybenzyl)-3-methoxy-2,5-piperazinedione (43)

The crude mixture containing the bromide **9** (prepared as described above) was cooled to 0 °C and methanol (40 ml) and triethylamine (0.5 ml, 3.6 mmol) added. The reaction mixture was stirred at this temperature for 2 h, filtered and concentrated. The residue was dissolved in chloroform, washed with water, dried, concentrated and the resultant oil chromatographed on

silica (eluant, 85% ethyl acetate-hexane) to give **43** (0.46 g, 41%) (recrystallized from ethyl acetate-hexane), calculated from **8**; mp 96.5-97 °C; ^{1}H NMR δ 3.39 (3 H, s), 3.79 (6 H, s), 3.78, 4.02 (1 H each, AB system, *J* = 18 Hz), 4.11, 5.05 (1 H each, AB system, *J* = 14.5 Hz), 4.33, 4.68 (1 H each, AB system, *J* = 14.5 Hz), 4.67 (1 H, s), 6.8-6.9 (4 H, m), 7.1-7.3 (4 H, m); MS, *m/z* 384 (M^+, 2), 121 (100); exact mass calcd for $C_{21}H_{24}N_2O_5$ *m/e* 384.16703, found 384.16852. Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.6; H, 6.3; N, 7.3. Found: C, 65.4; H, 6.2; N, 7.2.

Alteration of the solvent mixture to carbon tetrachloride/chloroform (9: 1) gave **43** in 56% yield based on **8**. The increase in chemical yield may be attributed to the greater solubility of **43** in the mixed solvent during filtration of the succinimide byproduct.

3,6-Dimethoxy-1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (45)

Similar treatment of the dibromide **10** (prepared as described above) with methanol (40 ml) and triethylamine (1.0 ml, 7.2 mmol), followed by work-up and chromatography (eluant, 50% ethyl acetate-hexane), gave **45** (0.66 g, 55%) as a 2.3: 1 mixture of diastereomers, calculated from **8**. The diastereomers could not be separated and were characterized as a mixture; mp 108-115 °C (recrystallized from ethyl acetate-hexane); ^{1}H NMR major diastereomer δ 3.44 (6 H, s), 3.80 (6 H, s), 4.02, 5.24 (2 H each, AB system, *J* = 14 Hz), 4.78 (2 H, s), 6.8-7.3 (8 H, m) minor diastereomer δ 3.49 (6 H, s), 3.81 (6 H, s), 4.06, 5.11 (2 H each, AB

system, J = 14.5 Hz), 4.64 (2H, s), 6.8-7.3 (8H, m); MS, *m/z* 383 (7), 382 (31), 121 (100); exact mass calcd for $C_{22}H_{26}N_2O_6$ *m/e* 414.18035, found 414.17908. Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.8; H, 6.3; N, 6.8. Found: C, 63.3; H, 6.4; N, 6.9.

1,4-Dibenzyl-2,5-piperazinedione (13)

Glycine anhydride (**42**) (5 g, 44 mmol) was suspended in dry DMF (600 ml) and sodium hydride (3.29 g, 80% in paraffin oil, 110 mmol) and p-methoxybenzylchloride (34.3 g, 219 mmol) added. The mixture was stirred under a nitrogen atmosphere overnight and the DMF removed by distillation under reduced pressure. The residue was taken up in ethyl acetate, and the organic phase washed with water, saturated sodium chloride solution and dried. The solvent was removed *in vacuo* and the product recrystallized from chloroform, to give **13** (11.5 g, 89%) as colorless needles (recrystallized from chloroform); mp 174.5-176.5 °C (lit.[90] mp 178-180 °C); ^{1}H NMR δ 3.99 (4 H, s), 4.63 (4 H, s), 7.40-7.45 (10 H, m); MS, *m/z* 294 (14), 91 (100); exact mass calcd for $C_{18}H_{18}N_2O_2$ *m/e* 294.13604, found 294.13683.

3-Bromo-1,4-dibenzyl-2,5-piperazinedione (46)

Treatment of 1,4-dibenzyl-2,5-piperazinedione (**13**) (1.0 g, 3.4 mmol) with 0.9 mole equivalents of NBS (0.61 g, 3.4 mmol) as described above for the preparation of **9** gave a residue comprised of the starting material **13**, the monobromide **46** and the dibromide **47** in the ratio *ca.* 1: 6: 1, as determined by ^{1}H NMR

spectroscopy. Characteristic resonances in the ^{1}H NMR spectrum for the monobromide **46** were δ 3.87, 3.99 (1 H each, AB system, J = 18 Hz), 3.94, 5.24 (1 H each, AB system, J = 14.5 Hz), 4.32, 4.93 (1 H each, AB system, J = 14.5 Hz), 5.84 (1 H, s), 7.20-7.40 (10 H, m).

1,4-Dibenzyl-3,6-dibromo-2,5-piperazinedione (47)

Reaction of 1,4-dibenzyl-2,5-piperazinedione (**13**) (1.03 g, 3.5 mmol) and NBS (1.28 g, 7.2 mmol) in carbon tetrachloride (50 ml) as described above for the preparation of **9**, gave the crude dibromide **47**. ^{1}H NMR δ 4.03, 5.34 (2 H each, AB system, J = 14.5 Hz), 5.90 (2 H, s), 7.30-7.40 (10H, m).

1,4-Dibenzyl-3-methoxy-2,5-piperazinedione (48)

The crude mixture containing the bromide **46** (prepared as described above) was treated with methanol (40 ml) and triethylamine (0.5 ml, 3.6 mmol), followed by work-up and chromatography (eluant, 40% ethyl acetate-hexane) to give **48** (0.67 g, 61%) (recrystallized from chloroform-hexane) calculated from **13**; mp 87.5-88 °C; ^{1}H NMR δ 3.41 (3 H, s), 3.80, 4.06 (1 H each, AB system, J = 18 Hz), 4.18, 5.15 (1 H each, AB system, J = 15 Hz), 4.38, 4.76 (1 H each, AB system, J = 14.5 Hz), 4.70 (1 H, s), 7.20-7.40 (10 H, m); MS, *m/z* 293 (94), 91 (100); exact mass calcd for $C_{19}H_{20}N_2O_3$ *m/e* 324.1469, found 324.1474. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.4; H, 6.2; N, 8.6. Found: C, 70.1; H, 6.0; N, 8.4.

1,4-Dibenzyl-3,6-dimethoxy-2,5-piperazinedione (49)

Similar treatment of the dibromide **47** (prepared as described above) with methanol (40 ml) and triethylamine (1.0 ml, 7.2 mmol), followed by work-up and chromatography (eluant, 30% ethyl acetate-hexane) gave a colorless oil. The oil was then dissolved in ether (5 ml) and set aside. The product **49** (0.82 g, 66%) crystallized as a single diastereomer (calculated from **13**); mp 169-171.5 °C (recrystallized from ethyl acetate-hexane). The other diastereomer was not detected in the crude reaction mixture or in the product after purification; ^{1}H NMR δ 3.46 (6 H, s), 4.17, 5.11 (2 H each, AB system, J = 14 Hz), 4.69 (2 H, s), 7.25-7.35 (10 H, m); MS, *m/z* 322 (43), 91 (100); exact mass calcd for $C_{20}H_{22}N_2O_4$ *m/e* 354.15795, found 354.15746. Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.8; H, 6.3; N, 7.9. Found: C, 67.6; H, 6.2; N, 8.0.

3-Bromo-1,4-dimethyl-2,5-piperazinedione (50)

Treatment of 1,4-dimethyl-2,5-piperazinedione (**5**) (1.0 g, 7.0 mmol) with 0.9 mole equivalents of NBS (1.13 g, 6.3 mmol) in dichloromethane* as described above for the preparation of **9** gave a residue comprised of the starting material **13**, the monobromide **50** and the dibromide **51** in the ratio *ca.* 5: 15: 1, as determined by ^{1}H NMR spectroscopy. Characteristic resonances in the ^{1}H NMR spectrum of **50** were ^{1}H NMR δ 3.01 (3H, s), 3.06 (3H, s), 3.92, 4.16 (1H each, AB system, J = 18 Hz), 6.02 (1H, s).

*Dichloromethane was used in the bromination reactions of **5**, as the substrate **5** was insoluble in carbon tetrachloride, the solvent most commonly used in bromination reactions with NBS.

3,6-Dibromo-1,4-dimethyl-2,5-piperazinedione (51)

Reaction of 1,4-dimethyl-2,5-piperazinedione (**13**) (1.0 g, 7.0 mmol) and NBS (2.57 g, 14.4 mmol) in dichloromethane (50 ml) as described above for the preparation of **50**, gave the crude dibromide **51**. ^{1}H NMR δ 3.10 (6H, s), 6.13 (2H, s).

1,4-Dimethyl-3-methoxy-2,5-piperazinedione (7)

The crude mixture containing the bromide **50** (prepared as described above) was treated with methanol (40 ml) and triethylamine (0.5 ml, 3.6 mmol), followed by work-up and chromatography (eluant, 90% ethyl acetate-hexane) to give **7** (0.65 g, 54%) (calculated from **5**); bp 155-174 °C, 0.08 torr (block); ^{1}H NMR δ 3.00 (3 H, s), 3.05 (3 H, s), 3.48 (3 H, s), 3.88, 4.18 (1 H each, AB system, J = 18 Hz), 4.77 (1 H, s).

Spectral characteristics of **7** were found to be consistent with those previously reported.[30]

3,6-Dimethoxy-1,4-dimethyl-2,5-piperazinedione (52)

Similar treatment of the dibromide **51** (prepared as described above) with methanol (40 ml) and triethylamine (1.0 ml, 7.2 mmol), followed by work-up and chromatography (eluant,

90% ethyl acetate-hexane) gave a colorless oil **52** (0.96 g, 68%) as a 3: 1 mixture of diastereomers. The oil was then dissolved in ether (5 ml) and the solvent allowed to evaporate. The minor diastereomer crystallized from the oil and was washed with 15% ether-hexane, mp 115-118 °C (lit.[72] mp 118-119 °C); ^{1}H NMR major diastereomer δ 3.13 (6H, s), 3.57 (6H, s), 4.78 (2H, s) minor diastereomer δ 3.13 (6 H, s), 3.45 (6 H, s), 4.92 (6H, s).

Spectral characteristics of **7** were found to be consistent with those previously reported.[72]

Reaction of 1,4-dimethyl-2,5-piperazinedione (5) with sulfuryl chloride

A mixture of 1,4-dimethyl-2,5-piperazinedione (**5**) (0.25 g, 1.77 mmol) and sulfuryl chloride (0.13 ml, 1.59 mmol) in dichloromethane (20 ml) in the presence of AIBN (*ca.* 5 mg), was irradiated for 0.5 h at reflux under a nitrogen atmosphere. The reaction mixture was cooled and the ^{1}H NMR spectrum of the crude reaction mixture recorded after removal of the solvent *in vacuo*. The principal products of the residue were the two chlorides **54** and **56** present in a *ca.* 1: 1 ratio. Due to the instability of the chloride mixture, the chlorides **54** and **55** could not be separated or adequately purified. The endocyclic chloride **54** and the exocyclic chloride **56** were tentatively identified on the basis of their characteristic resonances in the ^{1}H NMR spectrum of the crude reaction mixture. Resonances attributed to the endocyclic chloride in the ^{1}H NMR spectrum were δ 3.05 (3 H, s), 3.06 (3 H, s), 3.93, 4.25 (1 H each, AB system, J = 18 Hz), 5.74

(1 H, s) and resonances for the exocyclic chloride were δ 2.99 (3 H, s), 4.00 (4 H, br s), 5.29 (2 H, s).

The crude chlorination mixture decomposed rapidly on exposure to air affording a white solid. The deprotection of the *N*-methoxymethyl protecting group in cyclic dipeptides with boron trihalides to give the *N*-unsubstituted products has been reported.[36] This deprotection is considered to proceed through an *N*-halomethyl substituent analogous to the exocyclic chloride **56**.

Reaction of 1,4-dimethyl-2,5-piperazinedione (5) with sulfuryl chloride followed by methanol

Methanol (40 ml) and sodium acetate (1.0 g, 12.1 mmol) were added directly to the residue obtained from concentration of the chlorination mixture. The methanolysis reaction was stirred at room temperature under a nitrogen atmosphere overnight. The solvent was evaporated and the residue dissolved in chloroform. The organic phase was washed with water, saturated sodium chloride solution and dried. The solvent was removed *in vacuo*. Analysis of the ^{1}H NMR spectrum of the residue showed characteristic resonances corresponding to a *ca.* 2: 1 mixture of **7** and **57**. Chromatography of the residue on silica (eluant, 90% ethyl acetate-hexane) gave **7** in 19% yield with spectral and physical properties identical to those described above. None of the exocyclic product could be isolated, as analysis of the ^{1}H NMR spectrum of a mixed fraction isolated from the column indicated that **57** had undergone acid catalyzed decomposition on the silica.

Chromatography of the residue on silica (eluant, 5% methanol-chloroform) gave **7** with spectral and physical properties identical to those described above and a sample of the exocyclic methoxy product **57** contaminated with some of **7**. Complete separation of **57** from **7** was not achieved. The exocyclic methoxy product **57** was assigned on the basis of its resonances in the ^{1}H NMR spectrum of the enriched sample at δ 3.02 (3 H, s), 3.36 (3 H, s), 4.07 (4 H, br s), 4.86 (2 H, s).

Spectral characteristics of the enriched sample of the exocyclic methoxy product **57** were found to be consistent with those previously reported.[36]

Work described in Chapter 2

3,6-Dimethyl-2,5-piperazinedione (62)

Prepared according to the reported procedure.[89]

3,6-Dimethyl-2,5-piperazinedione (**62**) was prepared by suspension of S-alanine (5 g, 56 mmol) in anhydrous ethylene glycol (30ml) and reflux of the mixture for 0.5 h. The solution was then allowed to cool and the resultant solution stored at -4 °C overnight. The crystalline product was isolated by vacuum filtration and recrystallized from ethanol/water to give **62** (2.8 g, 70%).

1,4-Diacetyl-2,5-piperazinedione (22)

Glycine anhydride (**42**) (5 g, 44 mmol) was suspended in dry acetic anhydride (50 ml) and the mixture refluxed for 4 h. The solution was allowed to cool and the solution concentrated to *ca.* 2 ml by reduced pressure distillation. The residue was left to crystallize overnight in the freezer and the crystals which formed were recrystallized from ethyl acetate/ether to give **22** (7.4 g, 85%) as colorless needles; mp 98-99 °C (lit.[95] mp 99.5-100.5 °C); ^{1}H NMR δ 2.60 (6 H, s), 4.66 (4 H, s).

Spectral characteristics of **22** were found to be consistent with those previously reported.[95]

1,4-Diacetyl-3,6-dimethyl-2,5-piperazinedione (60)

3,6-Dimethyl-2,5-piperazinedione (**62**) (1.0 g, 7 mmol) was acetylated in dry acetic anhydride (50 ml) using the procedure described above to give **60** as colorless needles as a *ca.* 1: 1 mixture of diasteromers (1.29 g, 81%), which were not separated but instead recrystallized from ethyl acetate/ether; mp 133-138 °C (lit.[96] mp 132 °C); ^{1}H NMR δ 1.59 (6 H, d, *J* = 7 Hz), 1.62 (6 H, d, *J* = 7 Hz), 2.53 (6 H, s), 2.57 (6 H, s), 4.94 (2 H, q, *J* = 7 Hz), 5.18 (2 H, q, *J* = 7 Hz).

1-Methyl-2,5-piperazinedione (63)

1-Methyl-2,5-piperazinedione (**63**) was prepared by cyclization of glycylsarcosine (4.94 g, 34 mmol) according to the procedure described above for the preparation of **62** and recrystallized from ethanol and decolorizing charcoal to give **63** (3.44 g, 79%) as colorless needles; mp 143-144.5 °C (lit.[114] mp 145-146 °C); ^{1}H NMR δ 3.06 (3 H, s), 4.06 (4 H, br s), 7.45 (1 H, br s).

Spectral characteristics of **63** were found to be consistent with those previously reported.[114]

The relative reactivity of 1,4-dimethyl-2,5-piperazinedione (5) and 1,4-diacetyl-2,5-piperazinedione (22) with NBS

An equimolar mixture of 1,4-dimethyl-2,5-piperazinedione (**5**) (0.38 g, 2.65 mmol), 1,4-diacetyl-2,5-piperazinedione (**22**) (0.52 g, 2.64 mmol) and NBS (0.47 g, 2.64 mmol) in dichloromethane (30 ml) was irradiated for 0.5 h in the presence of AIBN (*ca.* 5 mg) at reflux under a nitrogen atmosphere. The reaction mixture was cooled and the ^{1}H NMR spectrum of the crude reaction mixture recorded after removal of the solvent *in vacuo*. The bromides **50** and **51** were present together with more substantial quantities of **22**. None of the product bromide **65** resulting from bromination of **22** was detected.

Reaction of 1,4-diacetyl-2,5-piperazinedione (22) with NBS

A mixture of 1,4-diacetyl-2,5-piperazinedione (**22**) (0.5 g, 2.5 mmol) and NBS (0.45 g, 2.5 mmol) in dichloromethane (20 ml) in the presence of AIBN (*ca.* 5 mg) was irradiated for 0.5 h at reflux under a nitrogen atmosphere. The reaction mixture was cooled and the ^{1}H NMR spectrum of the crude reaction mixture recorded after removal of the solvent *in vacuo*. The product was tentatively assigned as 3-bromo-1,4-diacetyl-2,5-piperazinedione (**65**) on the basis of resonances in the ^{1}H NMR δ 2.63 (6 H, s), 4.38, 5.32 (1 H each, AB system, J = 18 Hz), 6.91 (1 H, s).

The relative reactivity of 1,3,4,6-tetramethyl-2,5-piperazinedione (59) and 1,4-diacetyl-3,6-dimethyl-2,5-piperazinedione (60)with NBS

An equimolar mixture of 1,4-diacetyl-3,6-dimethyl-2,5-piperazinedione (**60**) (118 mg, 0.52 mmol), 1,3,4,6-tetramethyl-2,5-piperazinedione (**59**) (88 mg, 0.52 mmol) and four mole equivalents of NBS (370 mg, 2.07 mmol) in dichloromethane (20 ml) was irradiated for 0.5 h, in the presence of AIBN (*ca.* 5 mg) at reflux under a nitrogen atmosphere. The reaction mixture was cooled and the ^{1}H NMR spectrum of the crude reaction mixture recorded after removal of the solvent *in vacuo*. A mixture of diastereomers of the tetrabromide **68** and unreacted **60** were present. No products attributable to reaction of **60** were detected.

1,3,4,6-Tetramethyl-2,5-piperazinedione (59)

Prepared according to the reported procedure.[74]

To 3,6-dimethyl-2,5-piperazinedione (**62**) (2.30 g, 16 mmol) in dried DMF was added sodium hydride (1.03 g, 80% in paraffin oil, 34 mmol) portionwise over 0.5 h with stirring. After the evolution of hydrogen had ceased the reaction was cooled to 0 °C and methyl iodide (2.3 ml, 37 mmol) was added dropwise. Stirring was maintained for a further 0.5 h at room temperature upon complete addition of the methyl iodide. The DMF was removed by reduced pressure distillation, the residue

dissolved in chloroform and the organic phase washed with water and dried. The solvent was removed *in vacuo* and the product recrystallized from ether to give **59** (0.8 g, 29%) as a *ca.* 2.5: 1 mixture of diastereomers (colorless needles). All attempts to separate the diastereomers, either by fractional crystallization of the mixture (from ether) or by chromatography on silica were unsuccessful; mp 75-82 °C (lit.[136] mp 121-123 °C for the 3S,6S and 135-136 °C for the 3S,6R diastereomers); 1H NMR major diastereomer δ 1.53 (6 H, d, J = 7.5 Hz), 2.98 (6 H, s), 3.95 (2 H, q, J = 7.5 Hz) minor diastereomer δ 1.50 (6 H, d, J = 7.5 Hz), 2.98 (6 H, s), 3.88 (2 H, q, J = 7.5 Hz).

3,6-Dibromo-3,6-di(bromomethyl)-1,4-dimethyl-2,5-piperazinedione (68)

1,3,4,6-Tetramethyl-2,5-piperazinedione (**59**) (1.0 g, 5.9 mmol) and NBS (4.2 g, 24 mmol) in dichloromethane (50 ml) in the presence of AIBN (*ca.* 5 mg) was irradiated for 0.5 h at reflux under a nitrogen atmosphere. The reaction mixture was cooled and then filtered and the solvent removed *in vacuo* to give **68** (2.34 g, 82%) as a *ca.* 1.8: 1 mixture of diastereomers; mp 154-160 °C decomposed (lit.[74] mp 186-188 °C decomposed, for a single diastereomer of **68**); ^{1}H NMR major diastereomer δ 3.02 (6 H, s), 3.62, 4.15 (2 H each, AB system, J = 11 Hz) minor diastereomer δ 2.98 (6 H, s), 3.66, 3.92 (2 H each, AB system, J = 10.5 Hz).

1-Acetyl-4-methyl-2,5-piperazinedione (61)

1-Acetyl-4-methyl-2,5-piperazinedione (**61**) was prepared from 1-methyl-2,5-piperazinedione (**63**) (2.7 g, 21 mmol) by the acetylation procedure used in the preparation of **22**, to give **61** (3.30 g, 92%); mp 60-61 °C (recrystallized from ethyl acetate-ether); ^{1}H NMR δ 2.62 (3 H, s), 3.06 (3 H, s), 4.17 (2 H, s), 4.44 (2 H, s); MS, *m/z* 170 (M^+, 21), 128 (89), 43 (100), 42 (89). Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.25; H, 5.60; N, 16.42.

Reaction of 1-acetyl-4-methyl-2,5-piperazinedione (61) with NBS

A mixture of 1-acetyl-4-methyl-2,5-piperazinedione (**61**) (0.41 g, 2.4 mmol) and NBS (0.42 g, 2.4 mmol) in dichloromethane (25 ml) in the presence of AIBN (*ca.* 5 mg), was irradiated for 0.5 h at reflux under a nitrogen atmosphere. The reaction mixture was cooled and the ^{1}H NMR spectrum of the crude reaction mixture recorded after removal of the solvent *in vacuo*. The product was assigned as 1-acetyl-3-bromo-4-methyl-2,5-piperazinedione (**71**) on the basis of resonances in the ^{1}H NMR δ 2.58 (3 H, s), 3.01 (3 H, s), 3.96, 4.97 (1 H each, AB system, J = 18 Hz), 6.09 (1 H, s).

Reaction of 1-acetyl-4-methyl-2,5-piperazinedione (61) with NBS followed by reaction with tributylstannyl deuteride

Tributylstannyl deuteride (two mole equivalents), benzene (40 ml) and AIBN were added to the crude reaction mixture of 1-acetyl-3-bromo-4-methyl-2,5-piperazinedione (**71**), prepared as described above, and the mixture refluxed for 4 h. The solvent was removed under reduced pressure and the residue chromatographed on silica (eluant, 50% ethyl acetate-hexane) to give the deuteriated product **72** (0.25 g, 62%) based on **61**. 57% $^{2}H_{1}$ incorporation; ^{1}H NMR similar to that of **61** except that δ 4.17 (~1.4 H, br) instead of 4.17 (2 H, s); MS, *m/z* 171 (M^+, 34), 170 (M^+, 21), 129 (100), 128 (89).

1,4-Dimethyl-3-isopropyl-2,5-piperazinedione (73)

Reaction of 3-isopropyl-2,5-piperazinedione (**76**) (2.74 g, 17.6 mmol) with two mole equivalents of sodium hydride (1.09 g, 80% in paraffin oil, 36.4 mmol) in DMF and subsequent quenching with methyl iodide, as described for the preparation of **59**, gave **73** (recrystallized from ether) (2.06 g, 64%) as colorless needles; mp 118-120 °C (lit.[111] mp 122-124 °C); ^{1}H NMR δ 0.98 (3 H, d, J = 7 Hz), 1.12 (3 H, d, J = 7 Hz), 2.20 (1 H, m), 3.02 (3 H, s), 3.06 (3 H, s), 3.79 (1 H, d, J = 4 Hz), 3.82, 4.20 (1 H each, AB system, J = 18 Hz).

Spectral characteristics of **73** were found to be consistent with those previously reported.[111]

***cis*-3,6-Diisopropyl-1,4-dimethyl-2,5-piperazinedione (74) and *trans*-3,6-diisopropyl-1,4-dimethyl-2,5-piperazinedione (75)**

The diketopiperazine **77** (7.0 g, 35.5 mmol) was methylated using the methylation procedure decribed for the conversion of **62** to **59**. The *cis*- and *trans*- methylated products were separated by fractional crystallization from ether or by the more expedient method of dry flash column chromatography on silica (eluant, an increasing polarity grade of ethyl acetate-hexane); to give **74** (***cis*-**) (2.25 g, 28%); mp 106-107 °C (lit.[97] mp 106-107 °C); ^{1}H NMR δ 1.15 (6 H, s), 1.18 (6 H, s), 2.10 (2 H, m), 3.03 (6 H, s), 3.52 (2 H, d, *J* = 9 Hz); and **75** (**trans**-) (3.05 g, 38%); mp 143.5-145 °C (lit.[97] mp 143-144 °C); ^{1}H NMR δ 0.87 (6 H, s), 1.20 (6 H, s), 2.30 (2 H, m), 2.97 (6 H, s), 3.86 (2 H, d, *J* = 2.5 Hz).

Spectral characteristics of **74** and **75** were found to be consistent with those previously reported.[97]

3-Isopropyl-2,5-piperazinedione (76)

3-Isopropyl-2,5-piperazinedione (**76**) was prepared by cyclization of glycylvaline (2.0 g, 11.5 mmol) according to the procedure described above for the preparation of **63**. The product was recrystallized from ethyl acetate/ethanol to afford **76** as colorless needles (1.65 g, 92%); mp 243-246 °C (when the racemate was used as the starting material) and 259-262 °C (when the starting material was Gly-S-Val) (lit.[112] mp 264-265 °C for cyclic Gly-S-Val); ^{1}H NMR $CDCl_3$ and one drop ($^2H_6$)

DMSO δ 0.84 (3 H, d, *J* = 7 Hz), 0.97 (3 H, d, *J* = 7 Hz), 2.14 (1 H, m), 3.57 (1 H, d, *J* = 4 Hz), 3.67, 3.92 (1 H each, AB system, *J* = 18 Hz), 8.08 (2 H, br).

Spectral characteristics of **76** were found to be consistent with those previously reported.[114]

3S,6S-Diisopropyl-2,5-piperazinedione (77)

3S,6S-Diisopropyl-2,5-piperazinedione (**77**) was prepared as described above for **62**, by cyclization of S-valine to give colorless needles in 65% yield upon recrystallization from ethanol; ^{1}H NMR $CDCl_3$ / ($^2H_6$) DMSO δ 1.14 (6 H, d, *J* = 7 Hz), 1.26 (6 H, d, *J* = 7 Hz), 2.49 (2 H, m), 3.97 (2 H, d, *J* = 11.5 Hz), 8.28 (2 H, br).

Reaction of 1,4-dimethyl-3-isopropyl-2,5-piperazinedione (73) with NBS

1,4-Dimethyl-3-isopropyl-2,5-piperazinedione (**73**) (0.81 g, 4.4 mmol) was treated with NBS (0.78 g, 4.4 mmol) in dichloromethane (50 ml) as described above for the preparation of **50**. The reaction mixture was cooled and the ^{1}H NMR spectrum of the crude reaction mixture recorded after removal of the solvent *in vacuo*. 3-Bromo-1,4-dimethyl-6-isopropyl-2,5-piperazinedione (**79**) was observed as a single diastereomer in the crude reaction mixture; ^{1}H NMR δ 1.08 (3 H, d, *J* = 5 Hz), 1.16 (3 H, d, *J* = 5 Hz), 2.62 (1 H, m), 2.99 (3 H, s), 3.06 (3 H, s), 3.78 (1 H, d, *J* = 7 Hz), 6.07 (1 H, s).

Reaction of 1,4-dimethyl-3-isopropyl-2,5-piperazinedione (73) with NBS followed by reaction with methanol

The crude mixture containing the bromide **79** (prepared as described above) was treated with methanol (40 ml) and triethylamine (0.5 ml, 3.6 mmol) as described for the conversion of **9** to **43**. Chromatography (eluant, 90% ethyl acetate-hexane) of the residue obtained from aqueous work-up gave 1,4-dimethyl-6-isopropyl-3-methoxy-2,5-piperazinedione (**80**) (0.53 g, 57%) as a *ca.* 2: 1 mixture of diastereomers as a white powder (calculated from **73**). The diastereomers could not be separated by chromatography on silica; mp 49-62 °C; ^{1}H NMR major diastereomer δ 1.02 (3 H, d, *J* = 7 Hz), 1.10 (3 H, d, *J* = 7 Hz), 2.05 (1 H, m), 3.01 (3 H, s), 3.03 (3 H, s), 3.59 (1 H, d, *J* = 6 Hz), 3.61 (3 H, s), 4.62 (1 H, s) minor diastereomer δ 0.87 (3 H, d, *J* = 7 Hz), 1.12 (3 H, d, *J* = 7 Hz), 2.05 (1 H, m), 2.97 (3 H, s), 3.02 (3 H, s), 3.33 (3 H, s), 3.89 (1 H, d, *J* = 2.5 Hz), 4.94 (1 H, s); MS, *m/z* 214 (M^+, 2), 184 (100). Anal. Calcd for $C_{10}H_{18}N_2O_3$: 56.06; H, 8.47; N, 13.07. Found: C, 55.90; H, 8.41; N 13.10.

Reaction of *cis*-3,6-diisopropyl-1,4-dimethyl-2,5-piperazinedione (74) with NBS followed by reaction with methanol

cis-3,6-Diisopropyl-1,4-dimethyl-2,5-piperazinedione (**74**) (0.27 g, 1.19 mmol) was treated with NBS (0.43 g, 2.39 mmol) in dichloromethane (25 ml) as described above for the preparation of

50. The reaction mixture was allowed to cool and the solvent removed *in vacuo*. Methanolysis of the crude reaction mixture as described above for the conversion of **9** to **43**, followed by aqueous work-up and removal of the solvent *in vacuo* gave a residue in which both diastereomers of 3,6-diisopropyl-3,6-dimethoxyl-1,4-dimethyl-2,5-piperazinedione (**85**) were observed in the ^{1}H NMR spectrum. Chromatography of the residue (eluant, 90% ethyl acetate-hexane) gave 3,6-diisopropyl-3,6-dimethoxy-1,4-dimethyl-2,5-piperazinedione (**85**) (95 mg, 28%); mp 107-110 °C (lit.[74] mp 113-115 °C); ^{1}H NMR δ 0.98 (6 H, d, *J* = 7 Hz), 1.20 (6 H, d, *J* = 7 Hz), 2.39 (1 H, m), 3.00 (6 H, s), 3.15 (3 H, s).

Spectral characteristics of **85** were found to be consistent with those of **3f** compound A, reported by Matsunari.[74] The diastereomer of **85** observed in the ^{1}H NMR spectrum of the crude reaction mixture but not isolated had resonances corresponding to those of **3f** compound B [74] δ 1.12 (6 H, d, *J* = 7 Hz), 1.22 (6 H, d, *J* = 7 Hz), 2.20 (1 H, m), 2.80 (6 H, s), 3.11 (3 H, s).

Reaction of *trans*-3,6-diisopropyl-1,4-dimethyl-2,5-piperazinedione (75) with NBS followed by reaction with methanol

In an identical manner to the reaction of **74** with NBS and then methanol, *trans*-3,6-diisopropyl-1,4-dimethyl-2,5-piperazinedione (**75**) (0.27 g, 1.19 mmol) was treated with NBS (0.43 g, 2.39 mmol) and then methanol. The ^{1}H NMR spectrum of the crude methanolysis reaction mixture was recorded after

removal of the solvent *in vacuo*. Both diastereomers of **85** were observed but upon chromatography of the residue (eluant, 90% ethyl acetate-hexane) on silica only one diastereomer of **85** was isolated (95 mg, 28%).

The isolated product had identical physical and spectral characteristics to the product isolated above and was found to be consistent with those of **3f** compound A, reported by Matsunari.[74]

The relative reactivity of 1,4-dimethyl-2,5-piperazinedione (5) and 1,4-dimethyl-3-isopropyl-2,5-piperazinedione (73) with NBS

An equimolar mixture of 1,4-dimethyl-2,5-piperazinedione (**5**) (163 mg, 1.2 mmol), 1,4-dimethyl-3-isopropyl-2,5-piperazinedione (**73**) (211 mg, 1.2 mmol) and NBS (205 mg, 1.1 mmol) in dichloromethane (25 ml) was irradiated for 0.5 h, in the presence of AIBN (*ca.* 5 mg) at reflux under a nitrogen atmosphere. The reaction mixture was cooled and the ^{1}H NMR spectrum of the crude reaction mixture recorded after removal of the solvent *in vacuo*. Analysis of the ^{1}H NMR spectrum indicated the presence of the monobromides **50** and **79** in a *ca.* 2: 1 ratio. Additionally the starting materials **5** and **73** were present in a *ca.* 1: 2 ratio. The products and starting materials were identified by comparison of the resonances in the ^{1}H NMR spectrum of mixture with the characteristic resonances of authentic samples of the products **50** and **79** and starting materials **5** and **73**.

The relative reactivity of 1,4-dimethyl-2,5-piperazinedione (5) and *cis*-3,6-diisopropyl-1,4-dimethyl-2,5-piperazinedione (74) with NBS

An equimolar mixture of 1,4-dimethyl-2,5-piperazinedione (**5**) (98 mg, 0.7 mmol), *cis*-3,6-diisopropyl-1,4-dimethyl-2,5-piperazinedione (**74**) (156 mg, 0.7 mmol) and NBS (123 mg, 0.7 mmol) in dichloromethane (25 ml) was irradiated for 0.5 h, in the presence of AIBN (*ca.* 5 mg) at reflux under a nitrogen atmosphere. The reaction mixture was cooled and the ^{1}H NMR spectrum of the crude reaction mixture recorded after removal of the solvent *in vacuo*. Analysis of the ^{1}H NMR spectrum indicated that similar proportions of **5** and **74** had reacted. The substrates were identified by comparison of the resonances in ^{1}H NMR spectrum of the mixture with the characteristic resonances of authentic samples.

The relative reactivity of 1,4-dimethyl-2,5-piperazinedione (5) and *trans*-3,6-diisopropyl-1,4-dimethyl-2,5-piperazinedione (75) with NBS

An equimolar mixture of 1,4-dimethyl-2,5-piperazinedione (**5**) (126 mg, 0.88 mmol), *trans*-3,6-diisopropyl-1,4-dimethyl-2,5-piperazinedione (**75**) (200 mg, 0.88 mmol) and NBS (158 mg, 0.89 mmol) in dichloromethane (25 ml) was irradiated for 0.5 h, in the presence of AIBN (*ca.* 5 mg) at reflux under a nitrogen atmosphere. The reaction mixture was cooled and the ^{1}H NMR spectrum of the crude reaction mixture recorded after removal of

the solvent *in vacuo*. Analysis of the ^{1}H NMR spectrum indicated that similar proportions of **5** and **74** had reacted. The substrates were identified by comparison of the resonances in ^{1}H NMR spectrum of the mixture with the characteristic resonances of authentic samples.

1,4-Diacetyl-3-isopropyl-2,5-piperazinedione (86)

1,4-Diacetyl-3-isopropyl-2,5-piperazinedione (**86**) was prepared from 3-isopropyl-2,5-piperazinedione (**76**) (3.9 g, 25 mmol) by the acetylation procedure used in the preparation of **22**. The product was recrystallized from ethyl acetate/hexane to give **86** as colorless needles (3.5 g, 58%); mp 80-81 °C ; ^{1}H NMR δ 0.99 (3 H, d, J = 6.5 Hz), 1.10 (3 H, d, J = 6.5 Hz), 2.04 (1 H, m), 2.57 (3 H, s), 2.60 (3 H, s), 4.09, 5.11 (1 H each, AB system, J = 19 Hz), 5.01 (1 H, d, J = 10 Hz); MS, *m/z* 240 (M^+, 5), 157 (90), 43 (100); exact mass calcd for $C_{11}H_{16}N_2O_4$ *m/e* 240.11101, found 240.11155. Anal. Calcd for $C_{11}H_{16}N_2O_4$: 54.99; H, 6.71; N, 11.66. Found: C, 54.72; H, 6.74; N 11.64.

3-Benzyl-1,4-diacetyl-2,5-piperazinedione (87)

1,4-Diacetyl-3-benzyl-2,5-piperazinedione (**87**) was prepared from 3-benzyl-2,5-piperazinedione (**88**) (3.3 g, 16.5 mmol) by the acetylation procedure used in the preparation of **22**. The product was recrystallized using decolorizing charcoal in ethyl acetate/ethanol to give **87** as a colorless solid (4.1 g, 86%); mp 87 °C (lit.[115] mp 85 °C); ^{1}H NMR δ 2.49 (3 H, s), 2.51

(3 H, s), 3.16 (1 H, d of an AB system, J = 5.5 Hz and J = 14 Hz), 3.27 (1 H, d of an AB system, J = 4.5 Hz and J = 14 Hz), 2.63, 4.48 (1 H each, AB system, J = 19 Hz), 5.38 (1 H, t, J = 5.5 Hz); MS, *m/z* 288 (56), 91 (100); exact mass calcd for $C_{15}H_{16}N_2O_4$ *m/e* 288.11101, found 288.11189. Anal. Calcd for $C_{15}H_{16}N_2O_4$: 62.49; H, 5.59; N, 9.72. Found: C, 62.55; H, 5.64; N 9.72.

Spectral characteristics of **87** were found to be consistent with those previously reported.[115]

3-Benzyl-2,5-piperazinedione (88)

3-Benzyl-2,5-piperazinedione (**88**) was prepared by cyclization of glycylphenylalanine (3.0 g, 13.5 mmol) according to the procedure described above for the preparation of **62** and was recrystallized from aqueous ethanol to give **88** (2.24 g, 81%) as a colorless granular powder; starting material **88** was racemic- mp 275-277 °C (lit.[112] mp 282-283 °C for the racemic cyclic dipeptide).

3-Bromo-1,4-diacetyl-6-isopropyl-2,5-piperazine-dione (90)

A mixture of 1,4-diacetyl-3-isopropyl-2,5-piperazinedione (**86**) (0.4 g, 1.67 mmol), NBS (0.30 g, 1.67 mmol) and AIBN (*ca.* 5 mg) in carbon tetrachloride/ dichloromethane (10: 7 ml) was irradiated for 0.5 h at reflux under a nitrogen atmosphere. The reaction mixture was then cooled and the solvent removed *in*

vacuo. The product was purified by chromatography of the residue (eluant, 20% ethyl acetate-hexane) on silica. 3-Bromo-1,4-diacetyl-6-isopropyl-2,5-piperazinedione (**90**) (0.42 g, 80%) was isolated as a colorless oil and as a single diastereomer, together with unreacted **86** (28 mg, 7%); ^{1}H NMR δ 0.99 (3 H, d, *J* = 6.5 Hz), 1.19 (3 H, d, *J* = 7 Hz), 2.85 (1 H, m), 2.61 (3 H, s), 2.63 (3 H, s), 5.08 (1 H, d, *J* = 10.5 Hz), 6.92 (1 H, s); MS, *m/z* 278 (3), 276 (3), 239 (100), 155 (99), 42 (100); exact mass calcd for ($C_{11}H_{15}BrN_2O_4$-C_2H_2O) *m/e* 276.01095, found 276.00985. Anal. Calcd for $C_{11}H_{15}BrN_2O_4$: 41.40; H, 4.74; N, 8.78. Found: C, 41.77; H, 4.74; N 9.32.

6-deuterio-1,4-diacetyl-3-isopropyl-2,5-piperazine-dione (91)

Method 1-Preparation by reduction with tributystannyl deuteride

Tributylstannyl deuteride (0.59 g, 2.03 mmol), benzene (15 ml) and AIBN (*ca*. 5 mg) were added to the bromide **90** (0.36 g, 1.13 mmol) and the mixture refluxed for 4 h. The solvent was removed under reduced pressure and the residue chromatographed on silica (eluant, 20% ethyl acetate-hexane) to give the deuteriated product **91** (149 mg, 55%); 85% $^2H_1$ incorporation; The ^{1}H NMR spectrum was similar to that of **86** except that δ 4.04 (~0.08 H, br) instead of 4.09 (1 H, half an AB pattern, *J* = 19 Hz) and δ 5.00 (~0.25 H, br) instead of 5.01 (1 H, half an AB pattern, *J* = 19 Hz); $^2H_1$ NMR spectrum integrated to 67% $^2H_1$ at

δ 4.04 and 33% $^2H_1$ at δ 5.00; MS, *m/z* 241 (M^+, 7), 240 (M^+, 1), 157 (92), 43 (100).

Reaction of 3-benzyl-1,4-diacetyl-2,5-piperazinedione (87) with NBS followed by tributylstannyldeuteride

3-Benzyl-1,4-diacetyl-2,5-piperazinedione (**87**) (161 mg, 0.56 mmol) and NBS (99 mg, 0.56 mmol) in dichloromethane (15 ml) in the presence of AIBN (*ca.* 5 mg) was irradiated for 3.5 h at reflux under a nitrogen atmosphere. The reaction mixture was allowed to cool and the solvent removed *in vacuo.* Tributylstannyl deuteride (0.23 g, 0.78 mmol), benzene (15 ml) and AIBN (*ca.* 5 mg) were added to the crude reaction mixture, and the mixture refluxed for 4 h. The solvent was removed under reduced pressure and the residue chromatographed on silica (eluant, 35% ethyl acetate-hexane) to give the deuteriated products **94** and **97** in (104 mg, 64%) combined yield based on **87**. 54% $^2H_1$ incorporation; ^1H NMR similar to that of **87**; $^2H_1$ NMR spectrum- Of the 54% $^2H_1$ incorporated, 46% was incorporated at the benzylic carbon at δ 3.27 in the form of **97**, whilst 54% $^2H_1$ was incorporated in the form of **94**, with 35% $^2H_1$ at δ 2.63 and 65% $^2H_1$ at δ 4.48; MS, *m/z* 289 (M^+, 24), 288 (M^+, 17), 247 (21), 246 (11), 92 (89), 91 (100).

Work described in Chapter 3

Reaction of 1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (8) with NBS followed by reaction with methyl nitronate

A solution of butyllithium (2.34 M in hexane, 0.81 ml, 1.9 mmol) was added dropwise to a solution of nitromethane (0.10 ml, 115 mg, 1.9 mmol) in THF (10 ml) and HMPA (2 ml) maintained at -78 °C. A solution of 3-bromo-1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**9**) (*ca.* 1.7 mmol), prepared as described above from 1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**8**) (0.61 g, 1.7 mmol) and NBS (0.30 g, 1.7 mmol), in THF (6 ml) was then added at -78 °C. After 4 h at that temperature the mixture was dissolved in ethyl acetate (50 ml), washed with saturated aqueous sodium bicarbonate solution (2 x 30 ml), dried and concentrated. The combined aqueous layers were extracted with chloroform (2 x 30 ml) and the organic phase dried. The portion of the residue that was soluble in hot ethyl acetate was chromatographed on silica (eluant, 50% ethyl acetate-hexane) to give a product which was tentatively assigned as 1,4-di-(p-methoxybenzyl)-3-methylidene-2,5-piperazinedione (**99**) (18 mg, 3%) (calculated from **8**), on the basis of its resonances in the ^{1}H NMR spectrum; ^{1}H NMR δ 3.77 (3 H, s), 3.80 (3 H, s), 4.08 (2 H, s), 4.61 (2 H, s), 4.90 (2 H, s), 4.99 (1 H, d, J = 1.2 Hz), 5.86 (1

H, d, J = 1.2 Hz), 6.84 (2 H, d, J = 8.5 Hz), 6.88 (2 H, d, J = 8.5 Hz), 7.13 (2 H, d, J = 8.5 Hz), 7.25 (2 H, d, J = 8.5 Hz).

The portion of the residue that was insoluble was washed with hot ethyl acetate (3 x 10 ml) and the insoluble white powder collected by vacuum filtration. The product was recyrstallized from chloroform /methanol and identified as 1,4-di-(p-methoxybenzyl)-3-hydroxy-2,5-piperazinedione (**100**) (0.29 g, 46%) (calculated from **8**); mp 204 °C decomposed; IR 3460, 3120, 1645, 1615, 1515, 1245 cm^{-1}; ^1H NMR ($CDCl_3$/($^2H_6$) DMSO) δ 3.82 (6 H, s), 3.82, 4.09 (1 H each, AB system, J = 17.5 Hz), 4.09, 5.07 (1 H each, AB system, J = 14.5 Hz), 4.41, 4.63 (1 H each, AB system, J = 14.5 Hz), 4.93 (1 H, d exchangeable, J = 7 Hz), 6.88-6.93 (4 H, m), 7.10 (1 H, d exchangeable, J = 7 Hz), 7.20-7.25 (4 H, m); FAB MS, *m/z* 371 (M+H), 121 (100).

The hydroxyl proton appears as a low intensity broad absorbance in the IR spectrum. This phenomenon can be attributed to intramolecular hydrogen bonding of the hydroxyl proton to the neighbouring amide carbonyl oxygen which is consistent with the low field resonance of the hydroxyl proton in the ^1H NMR. Addition of deuterium oxide resulted in collapse of the signal at δ 4.93 to give a singlet and the disappearance of the resonance at δ 7.10 in the ^1H NMR spectrum.

Reaction of 1,4-dibenzyl-2,5-piperazinedione (13) with NBS followed by reaction with methyl nitronate

Reaction of 3-bromo-1,4-dibenzyl-2,5-piperazinedione (**46**), prepared as described above from 1,4-dibenzyl-2,5-piperazinedione (**13**) (0.99 g, 3.4 mmol) and NBS (0.60 g, 3.4 mmol), with methyl nitronate (3.55 mmol) gave a residue, which upon addition of hot ethyl acetate (3 x 10 ml) gave a white powder. The insoluble white powder, collected by vacuum filtration and recyrstallized from chloroform /methanol was identified as 1,4-dibenzyl-3-hydroxy-2,5-piperazinedione (**101**) (0.44 g, 42%) (calculated from **13**); mp 193.5 °C decomposed; IR 3415, 3135, 1655, 1610, 1510, 1240 cm^{-1}; ^1H NMR ($CDCl_3$ / ($^2H_6$) DMSO) δ 3.84, 4.16 (1 H each, AB system, *J* = 17.5 Hz), 4.11, 5.06 (1 H each, AB system, *J* = 15 Hz), 4.43, 4.70 (1 H each, AB system, *J* = 15 Hz), 4.93 (1 H, d exchangeable, *J* = 7 Hz), 6.53 (1 H, d exchangeable, *J* = 7 Hz), 7.25-7.37 (10 H, m); FAB MS, *m/z* 311 (M+H), 91 (100).

The hydroxyl proton appears as a broad low intensity absorbance in the IR spectrum, attributable to intramolecular hydrogen bonding with the neighbouring amide carbonyl oxygen. This is consistent with the low field resonance of the hydroxyl proton in the ^1H NMR spectrum. Addition of deuterium oxide resulted in collapse of the signal at δ 4.93 to give a singlet and the disappearance of the resonance at δ 6.53 in the ^1H NMR spectrum.

N-p-Methoxybenzylglycine ethyl ester (104)

Ethyl bromoacetate (12.2 g, 73 mmol) was added dropwise over 0.5 h to a stirred solution of *p*-methoxybenzylamine (10.0 g, 73 mmol) and triethylamine (11.0 g, 109 mmol) in ethyl acetate (150 ml) at 0 °C. Upon complete addition the reaction mixture was stirred at room temperature for a further 4 h. Water (30 ml) was added to the mixture, the organic layer separated, washed with saturated sodium chloride solution (20 ml) and dried. The crude product was obtained by filtration and concentration of the resultant solution under reduced pressure. The crude product was purified by dry flash column chromatography on silica (eluant, an increasing polarity grade of ethyl acetate-hexane) to give **104** as a colorless oil (18.5 g, 88%); ^{1}H NMR δ 1.28 (3 H, t, J = 7 Hz), 1.87 (1 H, br s), 3.41 (2 H, s), 3.77 (2 H, s), 3.83 (3 H, s), 4.21 (2 H, q, J = 7 Hz), 6.87 (2 H, d, J = 9 Hz), 7.27 (2 H, d, J = 9 Hz).

N-Chloroacetyl-*N*-p-methoxybenzylglycine ethyl ester (105)

Prepared by the literature procedure.[121]

Chloroacetyl chloride (5.87 g, 52 mmol) was added over 0.5 h to a solution of *N*-p-methoxybenzylglycine ethyl ester (**104**) (11.3 g, 50 mmol), and triethylamine (5.09 g, 50 mmol) in ether (110 ml) at -10 °C. After addition the solution was stirred for a further 1 h at -10 °C then for 4 h at room temperature. The reaction mixture was quenched with water and the organic layer dried and evaporated. The residue was purified

by dry flash column chromatography on silica (eluant, grade of ethyl acetate-hexane) to give **105** as a colorless oil (15 g, 100%); ^{1}H NMR δ 1.26 (3 H, t, *J* = 7 Hz), 3.84 (3 H, s), 4.03 (2 H, s), 4.18 (2 H, q, *J* = 7 Hz), 4.26 (2 H, s), 4.66 (2 H, s), 6.90 (2 H, d, *J* = 9 Hz), 7.21 (2 H, d, *J* = 9 Hz).

1-p-Methoxybenzyl-2,5-piperazinedione (106)

Prepared by the literature procedure.[121]

N-Chloroacetyl-*N*-p-methoxybenzylglycine ethyl ester (**105**) (12.7 g, 42 mmol) was dissolved in methanol (100 ml). A stream of ammonia was passed through the solution at -20 °C until the methanol was saturated (*ca.* 2 h). The reaction mixture was stirred for a further 1 h at -20 °C, allowed to warm to room temperature and stirring continued for 24 h. The precipitate that formed was collected washed with methanol (2 x 10 ml) and dried. The product **106** (8.11 g, 82%) was obtained as colorless needles; mp 229-231 °C (lit.[121] 230-232 °C); ^{1}H NMR (CD_3OD: $CDCl_3$ 2: 1) δ 3.81 (3 H, s), 3.86 (2 H, s), 4.03 (2 H, s), 4.55 (2 H, s), 6.90 (2 H, d, *J* = 8.5 Hz), 7.23 (2 H, d, *J* = 8.5 Hz) 7.46 (1 H, br s); ^{13}C NMR (CD_3OD: $CDCl_3$ 2: 1) δ 44.6 (CH_2), 48.3 (CH_2), 48.9 (CH_2), 56.13 (CH_3), 114.00 (CH), 126.56 (C, q), 129.57 (CH), 159.22 (C, q), 163.79 (C, q), 165.87 (C, q); MS, *m/z* 234 (M^+, 29), 121 (100).

Spectral characteristics of **106** were consistent with those previously reported.[121]

Reaction of 1-p-methoxybenzyl-2,5-piperazinedione (106) with NBS followed by reaction with methanol

A mixture of 1-p-methoxybenzyl-2,5-piperazinedione (**106**) (1.0 g, 4.27 mmol) and NBS (0.76 g, 4.27 mmol) in chloroform (40 ml) in the presence of AIBN (*ca.* 5 mg) was irradiated for 0.5 h at reflux under a nitrogen atmosphere. The mixture was allowed to cool and the solvent removed *in vacuo*. Methanol (40 ml) and triethylamine (0.65 g, 6.4 mmol) were added to the residue at 0 °C and the reaction mixture stirred for 2 h at ambient temperature. Evaporation of the solvent and chromatography of the residue on silica (eluant, 5% methanol-60% ethyl acetate-hexane) gave 6-methoxy-1-p-methoxybenzyl-2,5-piperazinedione (**107**) (0.58 g, 52%) (calculated from **106**) as a colorless solid; mp 124-125 °C (recrystallized from chloroform); ^{1}H NMR δ 3.40 (3 H, s), 3.80 (3 H, s), 3.95 (1 H, d of half an AB system, J = 4 Hz and J = 18 Hz), 4.16 (1 H, half an AB system, J = 18 Hz), 4.10, 5.13 (1 H each, AB system, J = 14.5 Hz), 4.57 (1 H, d, J = 1.2 Hz), 6.87 (2 H, d, J = 8.5 Hz), 7.21 (2 H, d, J = 8.5 Hz), 7.53 (1 H, br s); ^{13}C NMR δ 44.69 (CH_2), 46.92 (CH_2), 55.23 (CH_3), 56.13 (CH_3), 84.61 (CH), 114.17 (CH), 127.09 (C, q), 130.01 (CH), 159.37 (C, q), 164.98 (C, q), 165.52 (C, q); MS, *m/z* 264 (M^+, 12), 121 (100); exact mass calcd for $C_{13}H_{16}N_2O_4$ *m/e* 264.11186, found 264.11101. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.2; H, 6.05; N, 10.73.

Reaction of 1-p-methoxybenzyl-2,5-piperazinedione (106) with NBS followed by reaction with methyl nitronate

A mixture of 1-p-methoxybenzyl-2,5-piperazinedione (**106**) (0.30 g, 1.3 mmol) and NBS (0.23 g, 1.3 mmol) in chloroform (15 ml) in the presence of AIBN (*ca.* 5 mg) was irradiated for 0.5 h at reflux under a nitrogen atmosphere. The reaction mixture was cooled and the solvent removed *in vacuo*. Carbon tetrachloride (2 x 15 ml) was then added and the solution filtered rapidly under a nitrogen atmosphere. The resultant solution was concentrated under reduced pressure and the product bromide **102**, dissolved in anhydrous THF (5 ml) under a nitrogen atmosphere. Reaction of the bromide **102**, with methylnitronate (2.65 mmol) as described above, gave an extremely insoluble solid 6-hydroxy-1-p-methoxybenzyl-2,5-piperazinedione (**108**) (0.11 g, 35%) as a colorless solid (calculated from **106**); mp 224-225 °C decomposed; ^{1}H NMR ($^2H_6$ DMSO) δ 3.80 (3 H, s), 3.93, 4.17 (1 H each, AB system, J = 18 Hz), 4.09, 5.19 (1 H each, AB system, J = 14.5 Hz), 4.89 (1 H, s), 6.87 (2 H, d, J = 9 Hz), 7.24 (2 H, d, J = 9 Hz). No resonance attributable to the hydroxyl proton was observed in the ^{1}H NMR spectrum. A FAB MS spectrum and mass spectral data could not be obtained.

***N*-benzoylsarcosine methyl ester (14)**

Thionyl chloride (14.7 g, 124 mmol) was added dropwise to methanol (125 ml) at 0 °C. A suspension of sarcosine (10 g, 112

mmol) in methanol (20 ml) was then added to the stirred solution. The mixture was stirred at ambient temperature overnight and the solvent removed *in vacuo*. The crude product was suspended in chloroform (120 ml) and dimethylaminopyridine (*ca.* 50 mg) and triethylamine (11 g, 109 mmol) added. The mixture was cooled to 0 °C and a solution of benzoyl chloride (15.8 g, 112 mmol) and triethylamine (23 g, 228 mmol) was added slowly over 0.5 h. Upon complete addition of the benzoyl chloride solution the reaction mixture was stirred for a further 2 h and the reaction mixture filtered. The filtrate was washed with water (2 x 50 ml), then with saturated sodium bicarbonate solution (50 ml), dried and concentrated. The product **14** was distilled to give a colorless viscous oil (18.5 g, 80%); bp 130 °C 0.4mm (lit.[123] 115 °C 1mm) ^{1}H NMR δ 3.10 (3 H, br s), 3.74 (3 H, br s), 4.09 (2 H, br), 7.47 (5 H, m).

Spectral characteristics of **14** were found to be consistent with those previously reported.[125]

Reaction of *N*-benzoylsarcosine methyl ester (14) with NBS followed by reaction with methyl nitronate

Reaction of *N*-benzoyl-2-bromosarcosine methyl ester (**103**), prepared as described above from *N*-benzoyl-sarcosine methyl ester (**13**) (0.31 g, 1.48 mmol) and NBS (0.26 g, 1.48 mmol), with methyl nitronate (1.48 mmol) gave *N*-methylbenzamide (**112**) (112 mg, 56%) after work-up and chromatography of the residue on silica (eluant, 60% ethyl acetate-hexane); mp 75-77 °C (lit.[137] 78 °C); ^{1}H NMR δ 2.95 (3 H, d, J = 5.5 Hz), 6.77 (1 H, br),

7.40 (3 H, m), 7.76 (2 H, m); MS, *m/z* 135 (M^+, 36), 134 (27), 105 (100), 77 (70).

Spectral characteristics of **112** were found to be consistent with those previously reported.[138]

An aliquot was removed from the reaction 5 min. after addition of the bromide solution to the methyl nitronate, concentrated under reduced pressure and the ^1H NMR spectrum recorded. *N*-methylbenzamide (**112**) was identified as the principal component of the reaction mixture, indicating that the product is not formed upon aqueous work-up.

N-benzoylglycine methyl ester (109)

Thionyl chloride (6.6 g, 56 mmol) was added dropwise to methanol (100 ml) at 0 °C. Hippuric acid (10 g, 56 mmol) was then added and the mixture stirred at ambient temperature overnight. The solvent was removed *in vacuo* to give **109** (10.6 g, 98%); mp 82-84 °C (lit.[62] 82.5-84 °C); ^1H NMR δ 3.86 (3 H, s), 4.31 (2 H, d, J = 5 Hz), 6.65-7.28 (1 H, br), 7.37-7.70 (3 H, m), 7.83-8.03 (2 H, m).

Spectral characteristics of **109** were found to be consistent with those previously reported.[125]

Reaction of *N*-benzoylglycine methyl ester (109) with NBS followed by reaction with methyl nitronate

N-benzoyl-2-bromoglycine methyl ester (**25**), prepared from reaction of*N*-benzoylglycine methyl ester (**109**) (0.32 g, 1.63 mmol) and NBS (0.29 g, 1.63 mmol), treated with methyl nitronate (3.43 mmol) as described above, gave methyl 2-benzamido-3-nitropropanoate (**27a**) (221 mg, 54%) and methyl-2-benzamidoprop-2-enoate (**117**) (10 mg, 3%) after work-up and chromatography of the residue on silica (eluant, 35% ethyl acetate-hexane) (calculated from **109**); **27a**, mp 117-119 °C (lit.[76] 118-119 °C); ^{1}H NMR δ 3.88 (3 H, s), 4.99 (1 H, dd, *J* = 3.5 Hz and *J* = 15 Hz), 5.10 (1 H, dd, *J* = 3 Hz and *J* = 15 Hz), 5.17 (1 H, dt, *J* = 3.5 Hz and *J* = 7 Hz), 7.13 (1 H, br s), 7.44-7.59 (3 H, m), 7.80-7.83 (2 H, m); MS, m/z 205 (95), 105 (100), 193 (66), 77 (79). **117** was assigned on the basis of resonances in the ^{1}H NMR spectrum; ^{1}H NMR δ 3.88 (3 H, s), 5.99 (1 H, d, *J* = 1.5 Hz), 6.79 (1 H, d, *J* = 1.5 Hz), 7.43-7.56 (3 H, m), 7.81-7.86 (2 H, m), 8.55 (1 H, br s).

Spectral characteristics of **27a** and **117** were found to be consistent with those previously reported.[76]

Methyl 2-methoxy-2-benzamidoethanoate (118)

A mixture of *N*-benzoylglycine methyl ester (**109**) (2.00 g, 10.4 mmol) and NBS (1.84 g, 10.4 mmol) in carbon tetrachloride (50 ml) in the presence of AIBN (*ca.* 5 mg) was irradiated for 0.5 h at reflux under a nitrogen atmosphere. The reaction mixture was

cooled and then filtered and the solvent removed *in vacuo*. Methanol (40 ml) and triethylamine (1.26 g, 12.4 mmol) were added to the residue at 0 °C and the reaction mixture stirred for 2 h at ambient temperature. Evaporation of the solvent, chromatography of the residue on silica (eluant, 50% ethyl acetate-hexane) and recrystallization of the product (ether) gave **118** (2.2 g, 96%) (calculated from **109**) as colorless needles; mp 86-87 °C (lit.[139] mp 86-87 °C); ^{1}H NMR δ 3.54 (3 H, s), 3.84 (3 H, s), 5.79 (1 H, d, *J* = 9 Hz), 7.27 (1 H, br d, *J* = 9 Hz), 7.51 (3 H, m), 7.86 (2 H, d, *J* = 7 Hz).

Spectral characteristics of **118** were found to be consistent with those previously reported.[139]

Methyl 2-benzamidopent-4-enoate (30a)

Methyl 2-methoxy-2-benzamidoethanoate (0.5 g, 2.24 mmol) was dissolved in dichloromethane (30 ml) and the solution cooled to 0 °C. Allyltrimethylsilane (0.81 g, 7.07 mmol) and boron trifluoride etherate (1.04 g, 7.29 mmol) were then added. The cooling bath was removed and the reaction stirred at room temperature overnight. The residue was purified by flash column chromatography on silica (eluant, 30% ethyl acetate-hexane) to give **30a** as colorless crystals (0.34 g, 65%); mp 78-79 °C (lit.[81] mp 78-79 °C); ^{1}H NMR δ 2.64 (2 H, m), 3.72 (3 H, s), 4.83, 4.87 (1 H, dt, *J* = 6 Hz and *J* = 7 Hz), 5.13 (2 H, m), 5.76 (1 H, m), 7.17 (1 H, br d, *J* = 7 Hz), 7.42 (3 H, m), 7.80 (2 H, m); MS, *m/z* 233 (M^+, 3), 105 (100), 77 (32), 51 (11).

Spectral characteristics of **30a** were found to be consistent with those previously reported.[81]

Allyltributylstannane

Prepared by the literature procedure.[140]

To a stirred suspension of magnesium turnings (4.1 g, 171 mmol) in anhydrous THF (20 ml) was added dropwise at 5 °C a solution containing allylbromide (18.6 g, 154 mmol) and tributylstannyl chloride (25 g, 76.8 mmol) in THF (50 ml). After the addition was completed, the reaction was heated cautiously to reflux for 2 h, then cooled to 0 °C. The reaction was quenched slowly with a saturated solution of ammonium chloride (30 ml) followed by filtration through celite under aspirator vacuum and concentration of the filtrate. Ether was added and the organic phase separated, washed with water (2 x 100 ml), once with brine and dried. The organic phase was concentrated to give a yellow oil which was purified by bulb to bulb distillation to afford allyltributylstannane as a colorless oil (23.0 g, 91%); bp 60 °C 0.03mm (lit.[140] 88 °C 0.2mm); ^{1}H NMR δ 0.7-1.0 (9 H), 1.05-1.65 (18 H), 1.8 (2 H, d, J = 9 Hz), 4.8 (2 H, m), 6.1 (1 H, m).

Spectral characteristics of allyltributylstannane were found to be consistent with those previously reported.[140]

3-Allyl-1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (119)

A mixture of 1,4-di-(p-methoxybenzyl)-2,5-piperazinedione (**8**) (0.40 g, 1.13 mmol) and NBS (0.20 g, 1.13 mmol) in carbon tetrachloride (20 ml) in the presence of AIBN (*ca.* 5 mg) was irradiated for 0.5 h at reflux under a nitrogen atmosphere. The reaction mixture was cooled and the solvent removed *in vacuo*. The bromide **9** was dissolved in dry benzene (15 ml), allyltributylstannane (0.49 g, 1.47 mmol) and AIBN (*ca.* 5 mg) were added, and the mixture refluxed for 4 h. The mixture was allowed to cool and the solvent evaporated under reduced pressure. The residue was chromatographed on silica (eluant, 45% ethyl acetate-10% chloroform-hexane) to give **119** (160 mg, 36%) (calculated from **8**); mp 100-101 °C (recrystallized from chloroform); ^{1}H NMR δ 2.60 (2 H, m), 3.75 (3 H, s), 3.76 (3 H, s), 3.76, 3.91 (1 H each, AB system, J = 17.5 Hz), 3.98, 5.17 (1 H each, AB system, J = 14.5 Hz), 4.16, 4.82 (1 H each, AB system, J = 14.5 Hz), 5.05 (1 H, d, J = 9.5 Hz), 5.09 (1 H, d, J = 15.5 Hz), 5.60 (1 H, m), 6.84 (4 H, d, J = 8.5 Hz), 7.18 (4 H, d, J = 8.5 Hz); MS, *m/z* 394 (M^+, 100), 353 (22), 121 (33); exact mass calcd for $C_{23}H_{26}N_2O_4$ *m/e* 394.18925, found 394.19014.

3-Allyl-1,4-dibenzyl-2,5-piperazinedione (121)

Reaction of 3-bromo-1,4-dibenzyl-2,5-piperazinedione (**46**), prepared as described above from 1,4-dibenzyl-2,5-piperazinedione (**13**) (1.43 g, 4.85 mmol) and NBS (0.86 g, 4.85 mmol), with

allyltributylstannane (4.66 g, 28 mmol) as described for the conversion of **9** to **119**, gave 3-allyl-1,4-dibenzyl-2,5-piperazinedione (**121**) (0.58 g, 36%) as a colorless viscous oil, after chromatography of the residue on silica (eluant, 40% ethyl acetate-20% chloroform-hexane) (calculated from **13**); ^{1}H NMR δ 2.62 (2 H, m), 4.02 (1 H, t, *J* = 5.0 Hz), 3.80, 3.95 (1 H each, AB system, *J* = 17.5 Hz), 4.03, 5.27 (1 H each, AB system, *J* = 14.5 Hz), 4.25, 4.89 (1 H each, AB system, *J* = 15 Hz), 5.06 (1 H, dd, *J* = 1.5 Hz and *J* = 9 Hz), 5.11 (1 H, dd, *J* = 1.5 Hz and *J* = 16 Hz), 5.62 (1 H, m), 7.18-7.38 (10 H, m); MS, *m/z* 334 (M^+, 4), 293 (37), 91 (100); exact mass calcd for $C_{21}H_{22}N_2O_2$ *m/e* 334.16813, found 334.16862.

3-Allyl-1,4-dimethyl-2,5-piperazinedione (122)

Reaction of 3-bromo-1,4-dimethyl-2,5-piperazinedione (**50**), prepared as described above from 1,4-dimethyl-2,5-piperazinedione (**5**) (2 g, 14.0 mmol) and NBS (2.51 g, 14.0 mmol), with allyltributylstannane (2.09 g, 28 mmol) as described for the conversion of **9** to **119**, gave 3-allyl-1,4-dimethyl-2,5-piperazinedione (**122**). The product was initially purified by removal of the larger portion of the stannane byproducts by dry flash chromatography of the residue on silica (eluants, 15% ethyl acetate-hexane then 50% isopropanol-ethyl acetate). The residue obtained from the more polar gradient was further purified by flash chromatography on silica (eluant, 15% isopropanol-ethyl acetate) to give **122** (0.92 g, 36%) (calculated from **5**); mp 56.5-58 °C; ^{1}H NMR δ 2.68 (2 H, m), 2.98 (3 H, s), 3.00 (3 H, s), 3.83,

4.06 (1 H each, AB system, J = 17.5 Hz), 4.01 (1 H, t, J = 4.5 Hz), 5,20 (2 H, m), 5.69 (1 H, m); MS, *m/z* 182 (M^+, 15), 141 (100), 113 (93), 42 (98); exact mass calcd for $C_9H_{14}N_2O_2$ *m/e* 182.10553, found 182.10549.

3-Allyl-1,4-diacetyl-6-isopropyl-2,5-piperazinedione (123)

3-Bromo-1,4-diacetyl-6-isopropyl-2,5-piperazinedione (**90**) (360 mg, 1.13 mmol) was dissolved in dry benzene (12 ml), allyltributylstannane (0.59 g, 2.03 mmol) and AIBN (*ca.* 5 mg) were added, and the mixture refluxed for 6 h. Thin layer chromatography of the reaction mixture indicated that unreacted bromide was still present. An additional portion of AIBN (*ca.* 5 mg) was added and the reaction mixture was refluxed for a further 11 h. The mixture was allowed to cool and the solvent evaporated under reduced pressure. The residue was chromatographed on silica (eluant, 13% ethyl acetate-hexane) to give **123** (190 mg, 60%) as colorless needles; mp 67.5-69 °C (recrystallized from ethyl acetate-hexane); ^{1}H NMR δ 0.82 (3 H, d, J = 7 Hz), 1.00 (3 H, d, J = 7 Hz), 2.08 (1 H, m), 2.42 (3 H, s), 2.47 (3 H, s), 2.75 (2 H, m), 4.76 (1 H, d, J = 4.5 Hz), 4.90 (1 H, dd, J = 3.5 Hz and J = 5.5 Hz), 5.03, 5.08 (1 H, dd, J = 1.5 Hz and J = 15 Hz), 5.07, 5.11 (1 H, dd, J = 1.5 Hz and J = 9.5 Hz), 5.53 (1 H, m); MS, *m/z* 280 (M^+, 13), 238 (30), 197 (82), 43 (100); exact mass calcd for $C_{14}H_{20}N_2O_4$ *m/e* 280.14230, found 280.14163. Anal. Calcd for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.27; H, 7.19; N, 10.00.

Methyl α-hydroxymethylacrylate (124)

Prepared by the literature procedure used for synthesis of the ethyl ester analogue.[141]

To a mixture of trimethylphosphonoacetate (22.8 g, 125 mmol) and a 37% aqueous solution of formaldehyde (40.5 ml, 500 mmol) agitated at 600 r.p.m. at room temperature, was added a saturated solution of potassium carbonate (30.2 g in 27 ml, 220 mmol) over 0.5 h. On completion of the addition stirring was maintained for a further hour, at which point the reaction was quenched by addition of saturated ammonium chloride solution (50 ml) and extracted with ether (3 x 50 ml). The combined organic layers were dried and the solvent evaporated *in vacuo*. The remaining oil was distilled to give the product (5.8 g, 40%); bp 43-45 °C 0.15 mm; IR 3455, 1720, 1638, 1155, 1110 cm^{-1}; ^1H NMR (CCl_4) δ 3.79 (3 H, s), 4.33 (2 H, br s), 5.85 (1 H, s), 6.27 (1 H, s),; Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.00; H, 6.67.

Spectral characteristics of **124** were found to be similar to those previously reported for the ethyl ester analogue.[141]

Methyl α-bromomethylacrylate (125)

Prepared by the literature procedure used for synthesis of the ethyl ester analogue.[141]

To a stirred solution of methyl α-hydroxymethylacrylate (**124**) (5.46 g, 47 mmol) in dry ether (50 ml) at -10 °C was added

phosphorous tribromide (5.79 g, 21.4 mmol). The reaction was allowed to warm to room temperature and stirring maintained for a further 3 h. Water (25 ml) was then added at -10 °C, the mixture extracted with hexane (3 x 50 ml) and the organic extracts dried and concentrated. Distillation of the residue gave the product **125** (5.86 g, 70%); bp 70 °C 13 mm; IR 1725, 1630, 1145 cm^{-1}; ^1H NMR (CCl_4) δ 3.83 (3 H, s), 4.17 (2 H, s), 5.97 (1 H, s), 6.33 (1 H, s); MS, *m/z* 96 (75), 80 (82), 69 (80), 59 (100); exact mass calcd for $C_5H_7O_2Br$ *m/e* 177.96294, found 177.96223. Anal. Calcd for $C_5H_7O_2Br$: C, 33.55; H, 3.94. Found: C, 33.53; H, 3.97.

Spectral characteristics of **125** were found to be similar to those previously reported for the ethyl ester analogue.[141]

Methyl α-phenylsulfonylmethylacrylate (126)

Prepared by the literature procedure outlined for synthesis of the ethyl ester analogue.[142]

A mixture of methyl α-bromomethylacrylate (**125**) (5.48 g, 30.6 mmol) and sodium phenylsulfinate (10.06 g, 61.3 mmol) and methanol (50 ml) were refluxed for 12 h the solution allowed to cool and the solvent evaporated *in vacuo*. The residue was dissolved in chloroform (100 ml), washed with water (2 x 80 ml) and dried. The organic phase was filtered and concentrated to give a colorless oil which crystallized upon standing to give the crude product (8.66 g). Chromatography of the residue (eluant, gradient: ethyl acetate-hexane) allowed separation of a byproduct

to give the desired product **126** (4.56 g, 47%) which was recrystallized from ethyl acetate-ether; mp 89.5-90 °C; IR 1725, 1630, 1585, 1320, 1145, 1130 cm^{-1}; ^1H NMR (CCl_4) δ 3.58 (3 H, s), 4.16 (2 H, s), 5.91 (1 H, s), 6.50 (1 H, s), 7.60 (3 H, m), 7.86 (2 H, m); MS, *m/z* 209 (13), 176 (22), 141 (49), 99 (31), 78 (100); exact mass calcd for $C_{11}H_{12}O_4S$ *m/e* 240.04563, found 240.04516. Anal. Calcd for $C_{11}H_{12}O_4S$: C, 54.99; H, 5.03. Found: C, 54.72; H, 5.10.

Methyl α-tributylstannylmethylacrylate (127)

Prepared by the literature procedure outlined for synthesis of the ethyl ester analogue.[142]

Tributylstannyl hydride (11 g, 38 mmol), benzene (110 ml) and AIBN (*ca.* 10 mg) were added to methyl α-phenylsulfonyl-methylacrylate (**126**) (4.56 g, 19 mmol) and the mixture refluxed for 2 h. The solvent was removed under reduced pressure and the residue chromatographed on silica (eluant, gradient: hexane then ether) to give an oil which crystallizes on standing (1.46 g, 29%). The residue obtained from chromatography was distilled under reduced pressure in an effort to remove the impurity, however this was unsuccessful. Thus, the allyl stannane reagent used could not be purified and was used with some impurity present. ^1H NMR δ 0.67-1.10 (9 H), 1.13-1.70 (18 H), 2.00 (2 H, d, *J* = 1.5 Hz), 3.77 (3 H, s), 5.33 (1 H, d, *J* = 1.5 Hz), 5.85 (1 H, d, *J* = 1.5 Hz).

1,4-Diacetyl-6-isopropyl-3-(2-methoxycarbonyl)-allyl-2,5-piperazinedione (128)

To 3-bromo-1,4-diacetyl-6-isopropyl-2,5-piperazinedione (**90**) (199 mg, 0.62 mmol), dissolved in dry benzene (10 ml), were added methyl α-tributylstannylmethylacrylate (**127**) (0.48 g, 1.24 mmol) and AIBN (*ca.* 5 mg) and the mixture refluxed for 5 h. An additional portion of AIBN (*ca.* 5 mg) was added and refluxing of the mixture continued for a further 5 h. The mixture was allowed to cool and the solvent evaporated under reduced pressure. The product was isolated after chromatography of the residue on silica (eluant, 10% ethyl acetate-hexane) to give **128** (36 mg, 17%) as a low melting solid; mp 49-51.5 °C; ^{1}H NMR δ 0.86 (3 H, d, J = 7 Hz), 1.07 (3 H, d, J = 7 Hz), 2.14 (1 H, m), 2.50 (3 H, s), 2.55 (3 H, s), 3.00, 3.04 (1 H each, d of AB system, J = 3.5 Hz and J = 14 Hz), 3.22, 3.27 (1 H each, d of AB system, J = 7 Hz and J = 14 Hz), 3.71 (3 H, s), 4.78 (1 H each, d, J = 4.5 Hz), 5.05, 5.07 (1 H, dd, J = 3.5 Hz and J = 7 Hz), 5.64 (1 H, s), 6.25 (1 H, s); MS, *m/z* 338 (M^+, 4), 296 (41), 239 (8), 197 (63), 155(29), 42 (100); exact mass calcd for $C_{16}H_{22}N_2O_6$ *m/e* 338.14778, found 338.14855.

3-Bromocyclopentene (129)

Cyclopentene (6.8 g, 0.1 mmol), NBS (17.8 g, 0.1 mmol) and AIBN (*ca.* 10 mg) were dissolved in carbon tetrachloride (100 ml) and the mixture irradiated at reflux for 0.5 h. The solution was then cooled to 0 °C and the mixture filtered. The

filtrate was concentrated and the residue distilled immediately, to give **129** as a colorless oil (4.2 g, 28%); bp 42-46 °C 30mm.

Cyclopent-2-enyltributylstannane (130)

3-Bromocyclopentene (4.2 g, 28 mmol) (**129**) was used immediately after its preparation and distillation. Reaction of **129** with magnesium (0.75 g, 31 mmol) and tributylstannyl chloride (4.6 g, 14 mmol) as described above for the preparation of allyltributylstannane, gave the crude product which was purified by bulb to bulb distillation to afford **130** as a colorless oil (3.6 g, 71%); bp 160 °C 0.05mm (lit.[104] bp 160 °C 0.04-0.06mm); ^{1}H NMR δ 0.66-1.03 (9 H), 1.10-1.57 (18 H,), 1.7-2.47 (5 H), 5.43-5.97 (2 H, m).

Spectral characteristics of **130** were found to be consistent with those previously reported.[104]

3-[Cyclopent-2-enyl]-1,4-diacetyl-6-isopropyl-2,5-piperazinedione (131)

3-Bromo-1,4-diacetyl-6-isopropyl-2,5-piperazinedione (**90**) (314 mg, 0.98 mmol) was dissolved in dry benzene (10 ml), cyclopent-2-enyltributylstannane (**130**) (0.70 g, 1.97 mmol) and AIBN (*ca.* 5 mg) were added, and the mixture refluxed for 24 h. An additional portion of AIBN (*ca.* 5 mg) was added to the reaction mixture after 5 h and refluxing allowed to continue. The mixture was allowed to cool and the solvent evaporated under reduced

pressure. The product was isolated after chromatography of the residue on silica (eluant, 10% ethyl acetate-hexane) ~~as a low melting solid (36 mg, 12%) (eluant, 10% ethyl acetate-hexane)~~ to give **131** as a mixture of diastereomers as a colorless low melting solid (36 mg, 12%); mp 41-46°C ; ^{1}H NMR δ 0.86 (3 H, d, *J* = 6.5 Hz), 1.10 (3 H, d, *J* = 6.5 Hz), 1.31 (2 H, m), 1.98 (1 H, m), 2.23 (2 H, m), 2.40 (3 H, s), 2.51 (3 H, s), 3.35 (1 H, m), 4.84 (1 H, d, *J* = 4 Hz), 5.06 (1 H, d, *J* = 3.5 Hz), 5.50 (1 H, m), 5.63 (1 H, m) and δ 0.86 (3 H, d, *J* = 7 Hz), 1.12 (3 H, d, *J* = 7 Hz), 1.56 (2 H, m), 1.98 (1 H, m), 2.23 (2 H, m), 2.45 (3 H, s), 2.51 (3 H, s), 3.44 (1 H, m), 4.83 (1 H, d, *J* = 4 Hz), 5.18 (1 H, d, *J* = 5.5 Hz), 5.87 (2 H, m); MS, *m/z* 306 (M^+, 2), 264 (28), 240 (42), 42 (100); exact mass calcd for $C_{16}H_{22}N_2O_4$ *m/e* 306.15795, found 306.15712.

Addition of more AIBN or alteration of the solvent to toluene or chlorobenzene was accompanied by a small increase in chemical yield (14%) but gave significant amounts of decomposition material.

6-deuterio-1,4-diacetyl-3-isopropyl-2,5-piperazinedione (91)

Method 2-Preparation by reduction with deuterium in the presence of deuterium oxide

3-Bromo-1,4-diacetyl-6-isopropyl-2,5-piperazinedione (**90**) (453 mg, 1.42 mmol) was dissolved in anhydrous THF (8 ml)/ deuterium oxide (2 ml) and palladium chloride (76 mg, 0.42 mmol) added. The flask was charged with a deuterium atmosphere and

the reaction stirred at ambient temperature overnight. The mixture was filtered through a pad of celite and chloroform (3 x 5 ml) was then passed through the celite bed. Chloroform (15 ml) was added to the filtrate and the organic layer dried and filtered. The solvent was concentrated under reduced pressure and the residue obtained was chromatographed on silica (eluant, 20% ethyl acetate-hexane) to give the deuteriated product **91** (137 mg, 40%); 92% $^{2}H_{1}$ incorporation; The ^{1}H NMR spectrum was similar to that of **86** except that δ 4.04 (~0.35 H, br) instead of 4.09 (1 H, half an AB pattern, J = 19 Hz) and the peak at δ 5.00 (~0.02 H, br) instead of 5.01 (1 H, half an AB pattern, J = 19 Hz); $^{2}H_{1}$ NMR spectrum integrated to 11% $^{2}H_{1}$ at δ 4.04 and 89% $^{2}H_{1}$ at δ 5.00.

If the above reaction is performed in the absence of deuterium oxide the product obtained is the hydrogenolysis product **86**, in comparable yield to that obtained above.

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