Lewis Acid Induced Rearrangement of 1-Hetero-2,3-Epoxides. Synthesis, Reactivity and Synthetic Applications of Homochiral Thiiranium and Aziridinium Ion Intermediates

Christopher M. Rayner

School of Chemistry, University of Leeds, Leeds LS2 9JT, U.K.; email: chrisr@chem.leeds.ac.uk

Received 28 February 1996

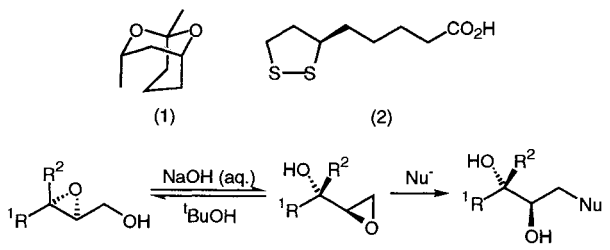
This account is dedicated to Professor Ian Sutherland on the occasion of his retirement from the University of Liverpool, September 1995.§

Abstract: 2,3-Epoxy sulfides and 2,3-epoxy amines, prepared in an optically active form *via* the Sharpless asymmetric epoxidation, both undergo a Lewis acid induced rearrangement to give the corresponding thiiranium and aziridinium ions respectively. These reactive intermediates, generated *in situ*, react efficiently with a variety of nucleophiles such as silylated aromatic heterocycles, amides, and amines, including amino acid derivatives. Imines can be used as synthetic equivalents of primary amine nucleophiles, which effectively allows selective monoalkylation with a reactive thiiranium ion intermediate. Applications of this new methodology, and mechanistic studies are also discussed.

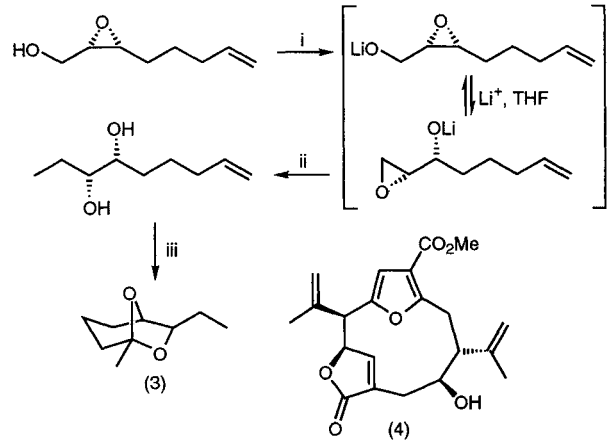
1. Introduction

One of the major advances in synthetic organic chemistry in the 1980's was the development of the Sharpless asymmetric epoxidation (SAE).[1] Few organic reactions have had a such an impact on the synthetic organic chemistry community. It was one of the first truly reliable asymmetric transformations, and also allowed access to a wide variety of optically active 2,3-epoxy alcohols which have since proved to be versatile synthetic intermediates.[2] As a Ph.D. student in the mid 1980s, it was clear to me that this reaction was of great significance, and under the guidance of my supervisors, Ian Sutherland and Philip Page at Liverpool University, we developed synthetic routes to (+)-*endo*-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]-nonane (1), an insect pheromone isolated from the bark of the Norway Spruce fir tree *Picea abies* infested by the ambrosia beetle *Trypodendron lineatum* Oliver,[3] and R-(+)-α-Lipoic acid (2), an important enzyme cofactor.[4] Both syntheses relied on the SAE as the key asymmetric step. During this work we also became aware of a process called the Payne rearrangement, which refers to the base catalysed isomerisation of 2,3-epoxy alcohols (scheme 1).[5] Such a phenomenon had been reported previously in sugar chemistry and was termed epoxide migration, however in the case of simple 2,3-epoxy alcohols the term "Payne rearrangement" has been adopted.[6,7] Although not a particularly useful process in itself, the Payne rearrangement-nucleophilic trapping procedure (PRNTP) reported independently by Sharpless[7a] and Ganem[7b] in 1983, was a much more significant development. For this procedure, the Payne rearrangement is carried out in the presence of a nucleophile which selectively reacts with the less hindered terminal epoxide in the equilibrium (scheme 1). Importantly, the PRNTP is stereospecific, and, with suitable substrates, is also regiospecific. Thus coupled with the SAE and the wide variety of homochiral 2,3-epoxy alcohols it can produce, this procedure represents a very powerful method for the synthesis of optically active 1-substituted-2,3-diols.

The inherent elegance of the PRNTP made it a very attractive reaction for use in synthesis, however it had one serious limitation. It could only be carried out in protic solvents which obviously placed a severe limitation on the range of nucleophiles which could be used. We eventually found that an analogous reaction could be carried out in aprotic solvents such as THF, if a lithium salt, particularly lithium chloride was added to the reaction mixture. We envisaged that this was acting as a Lewis acid to activate the epoxide toward ring opening and hence promoting the isomerisation. We were subsequently able to exploit this new methodology in a short synthesis of (+)-*exo*-Brevicomin (3), where MeCuCNLi was used to introduce a methyl group at C-1 (scheme 2).[8]



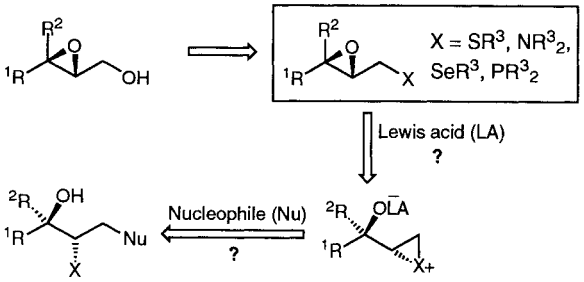
Scheme 1



Reagents: i, ^{n}BuLi (1.0 equiv.), THF, LiCl, -78 °C; ii, MeCuCNLi (3.0 equiv.), LiCl, THF, 0-25 °C, 4 days, then NH_4Cl (aq.); iii, $PdCl_2$ (cat.), $CuCl_2 \cdot 2H_2O$, THF, 25 °C, 12h.

Scheme 2

After two stimulating years with Leo Paquette carrying out the synthesis of the furanocembranolide (4),[9] I returned to the UK to take up an academic position in Leeds, and start my own research effort. At this time, my thoughts returned to the Payne rearrangement-nucleophilic trapping procedure (PRNTP). The very simple idea we had, which has since developed into some very interesting and useful chemistry, was to see whether we could develop reactions analogous to those of 2,3-epoxy alcohols, but of substrates where the alcohol moiety is replaced by some other heteroatom functionality such as a thioether, or a tertiary amine (scheme 3). We envisaged that there would be a number of significant differences. In particular, the equivalent reaction to the PRNTP would no longer be an isomerisation, and would in fact be a novel method for the generation of synthetically useful reactive intermediates such as thiiranium ions (episulfonium ions) and aziridinium salts, in an optically active form (scheme 3) (*vide infra*). In addition, the enhanced reactivity of such intermediates relative to epoxides, would allow the introduction of relatively poor nucleophiles under mild reaction conditions. Thus these systems would represent new, readily available, optically active building blocks for use in synthesis, which have a high degree of functionality, and considerable potential for stereoselective synthetic manipulation.



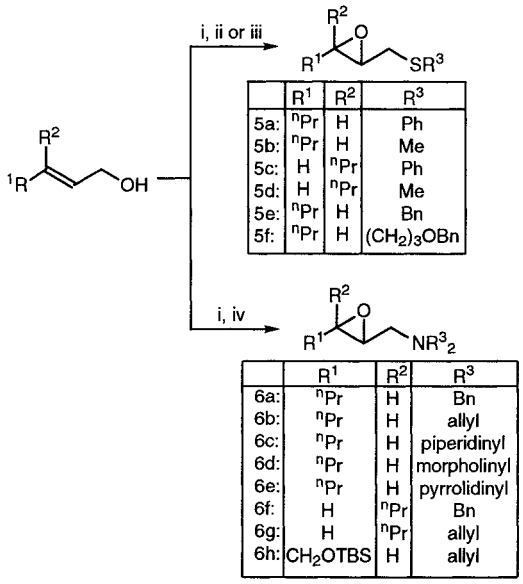
Scheme 3

We have also developed a number of synthetic transformations utilising oxidised 2,3-epoxy sulfide derivatives as new homochiral building blocks, however these have been discussed in some detail in a recent full paper and so are not included here.[10] This account describes our work to date in the development of synthetically useful procedures related to the PRNTP, developing further the chemistry of 2,3-epoxy sulfides, and also more recently the related 2,3-epoxy amine systems. We thus embarked on a journey which has since opened up many other avenues of research currently under investigation in my group.

2. Synthesis of 2,3-epoxy sulfide and 2,3-epoxy amine substrates

Synthesis of the required substrates was achieved using relatively straightforward chemistry summarised in scheme 4. The 2,3-epoxy alcohols required could be readily prepared in a racemic form using a $VO(acac)_2$/^{t}BuOOH epoxidation of a suitable allylic alcohol.[10] Racemates were used for much of our earlier work. Optically active 2,3-epoxy alcohols were prepared using the conventional SAE procedure with (+)-diethyl tartrate as the chiral ligand.[11] In the case of *cis*-allylic alcohols, poor yields were obtained from the $VO(acac)_2$ catalysed epoxidation, however this problem was overcome by using the SAE. Conversion of the alcohol to the phenylsulfide was best carried out directly using $PhSSPh/PBu_3$, however for dialkyl sulfides preparation of the tosylate and displacement by thiolate was the most efficient route.[12] The 2,3-epoxy amines were also prepared from the tosylate by NaI-catalysed displacement using a secondary amine.[13]

In the case of the 2,3-epoxy sulfides, the substituents were chosen so as to investigate the effects of epoxide geometry on the efficiency and stereoselectivity of the reaction, *i.e. cis* and *trans* epoxides would lead to the formation of diastereomeric products after nucleophilic trapping, potentially allowing full control of the stereochemical configuration at both the chiral centres in the final product. Also of importance was the substituent on sulfur, which would allow us to gain a better understanding of the fundamental factors controlling the generation and reactivity of thiiranium ions. In addition, it was envisaged that the S-methyl and S-benzyl thioethers would allow deprotection to the corresponding thiols, which in some cases were our final target molecules (*vide infra*).[14,15]

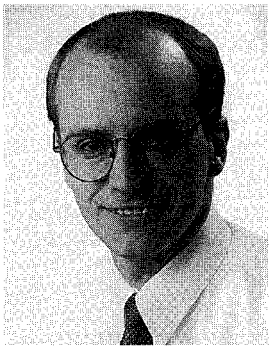


	R1	R2	R3
5a:	nPr	H	Ph
5b:	nPr	H	Me
5c:	H	nPr	Ph
5d:	H	nPr	Me
5e:	nPr	H	Bn
5f:	nPr	H	$(CH_2)_3OBn$

	R1	R2	R3
6a:	nPr	H	Bn
6b:	nPr	H	allyl
6c:	nPr	H	piperidinyl
6d:	nPr	H	morpholinyl
6e:	nPr	H	pyrrolidinyl
6f:	H	nPr	Bn
6g:	H	nPr	allyl
6h:	CH_2OTBS	H	allyl

Reagents: i, $VO(acac)_2$, ^{t}BuOOH, CH_2Cl_2 *or* $Ti(O^iPr)_4$, (+)-DET, ^{t}BuOOH, CH_2Cl_2, -78 → 0 °C; ii, R^3SSR^3, PBu_3; iii, TsCl, pyridine then R^3SNa, DMF; iv, TsCl, pyridine then $R^3{}_2NH$, NaI (cat.), DMF.

Scheme 4

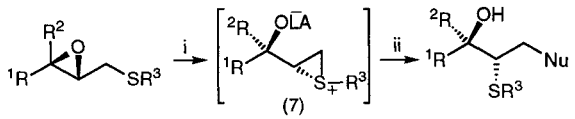


Christopher M. Rayner was born in 1963 in Burton on Trent, England. He obtained his B.Sc. in 1984, and a Ph.D. in 1987 from the University of Liverpool under the guidance of Professor Ian O. Sutherland and Dr. Philip C.B. Page as a Royal Society of Chemistry William Briggs Fellow. He then took up a postdoctoral position with Professor Leo A. Paquette at the Ohio State University as a NATO Postdoctoral Fellow. In 1989 he returned to the UK to take up his current position as Lecturer in Organic Chemistry at the University of Leeds.

In the case of the 2,3-epoxy amines, again we chose to investigate the *cis*- and *trans*-isomers, and also the N,N-diallyl- and N,N-dibenzyl-substituted amines which would allow for deprotection to the corresponding primary amines under mild conditions.[16,17,18] The use of cyclic amines such as piperidine would allow formation of interesting spirocyclic aziridinium salts.

3. Generation of thiiranium ion intermediates from 2,3-epoxy sulfides under Lewis acidic conditions: Preliminary investigations

We initially decided to investigate the 2,3-epoxy sulfides, where the alcohol group of a 2,3-epoxy alcohol is replaced by a thioether. In this case, the intermediate we hoped to generate would be the 3-alkoxy-1,2-thiiranium ion (7), which may be isolable, or could be trapped *in situ* with a suitable nucleophile (scheme 5). Thiiranium ions (episulfonium ions) are interesting and synthetically useful intermediates.[19] Their formation from β-hydroxy sulfides has been investigated by a number of groups, in particular Warren[20] and others,[21] however the use of epoxides for this type of reaction had not been reported to any significant degree.[22]

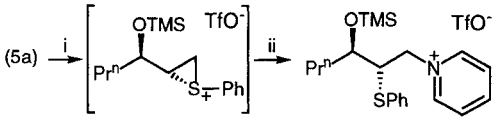


Reagents: i, Lewis acid (LA); ii, Nucleophile (Nu)

Scheme 5

The generation of a thiiranium ion from a 2,3-epoxy sulfide is not necessarily an equilibrium process like the Payne rearrangement as it is no longer an isomerisation. It may thus be possible to effectively convert all the starting material into the reactive intermediate, which can subsequently be trapped by a suitable nucleophile. This would have significant advantages over the equilibrium process. In order to mimic the role of the lithium cation which promoted the original "aprotic" Payne rearrangement, we decided to investigate the use of more conventional Lewis acids for this related transformation.

A number of thiiranium ions have been isolated and characterised.[19,23] We initially attempted to generate and isolate thiiranium ions generated by treatment of the S-phenyl *trans*-2,3-epoxy sulfide **5a** with a Lewis acid (BF_3•OEt_2 or TMSOTf) in CH_2Cl_2 at -78 °C then warming to rt.[12]



Reagents: i, TMSOTf, CH_2Cl_2, -78 °C; ii, Pyridine, -78 °C → rt.

Scheme 6

TLC showed a rapid disappearance of starting material, but no characterisable products could be observed in the ^1H NMR spectrum of the crude product. We believed that decomposition of the desired thiiranium ion/Lewis acid complex may be occurring on warming due to extraneous acid in the reaction medium, and therefore repeated the reaction, but in this case, added a base (pyridine) whilst still at -78 °C (scheme 6). After warming and removal of solvent *in vacuo*, a new compound was formed very cleanly as rather unstable colourless needles, but rather than being a thiiranium ion, was identified as the pyridinium triflate, isolated in near quantitative yield. This was a very significant result for three reasons:

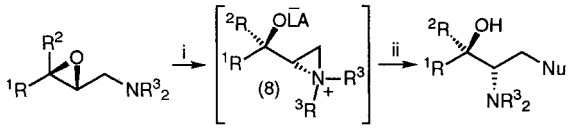
- the thiophenyl group had cleanly undergone a 1,2-migration - an observation often used to imply the intermediacy of a thiiranium ion.[20] This was good evidence that our initial concept for thiiranium ion generation was sound, but that the thiiranium ion intermediate was too unstable to be isolated. Frequently, thiiranium ions are postulated as reactive intermediates, but are not actually isolated.[19]
- the thiiranium ion intermediate had been opened exclusively at C-1 by the nucleophile, no other products being observed in the crude product mixture - this was a nice clean regiospecific reaction.
- the pyridinium salt was a single diastereoisomer by ^1H and ^{13}C NMR, which implied that the rearrangement to form the thiiranium ion was a stereospecific process, and that thiiranium ions are sufficiently configurationally stable to be useful in asymmetric synthesis.[24] This also had significant implications for other methods of enantioselective thiiranium ion generation currently under development in our group.[25]

Thus this first simple result had convinced us that we had the basis for a very powerful method for the synthesis of functionalised β-hydroxy sulfides with full regio- and stereo-chemical control. We next turned our attention to the generation of aziridinium salts from the corresponding 2,3-epoxy amines under Lewis acidic conditions.

4. Generation of aziridinium salt intermediates from 2,3-epoxy amines under Lewis acidic conditions

Aziridinium ions are well established reactive intermediates, primarily as a result of their biological activity.[26] Their use in synthesis has been much less extensively studied.[27] When we began this work there were relatively few reports of related epoxyamine/hydroxyaziridine interconversions, however more recently a number of related procedures have appeared. For example, a recent paper has described the conversion of a primary 2,3-epoxy amine to the corresponding 1,2-aziridinyl-3-ol using trimethylaluminium as catalyst.[28] Similarly, 1,2-epoxy-3-sulfonamides are reported to rearrange to the N-tosyl-1,2-aziridinemethanols under basic conditions[29] which can be reacted with suitable nucleophiles.

The main advantage of our procedure is the reactivity of aziridinium salts relative to simple aziridines and N-acyl and N-sulfonyl aziridines. This should allow reaction with relatively poor nucleophiles under mild conditions. Thus under Lewis acidic conditions we envisaged that a 2,3-epoxy amine containing a tertiary amine group would undergo transformation into a reactive aziridinium ion which could be opened with nucleophiles to form substituted β-amino alcohols (scheme 7). Note that this entire synthetic sequence would be expected to be a stereospecific process as with the corresponding thiiranium ion system.



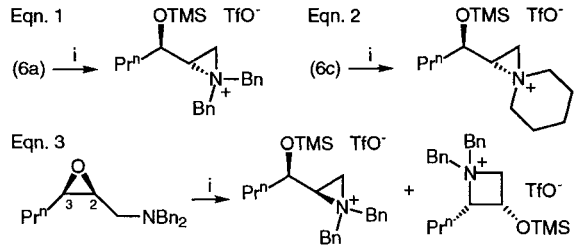
Reagents: i, Lewis acid (LA); ii, Nucleophile (Nu)

Scheme 7

Efficient methods for the generation of aziridinium salts rely on essentially two approaches, either the addition of diazomethane to an iminium ion,[30] or by neighbouring group participation by a tertiary amine adjacent to a centre with a good leaving group.[27] The latter is by far the most common method and is particularly relevant to this work. In many previous examples where aziridinium salts have been used, they have been present only as a small equilibrium concentration,[27] however this can be displaced, for example, by the use of Ag(I).[31] We believed it to be important that, for our systems, the generation of the aziridinium salt was irreversible. This would prevent the formation of piperazinium dimers, which are often side products when aziridinium salts are generated from β-haloamines.[27] Such dimerisation reactions have been shown to be the dominant pathway even in the presence of

nucleophiles, including amines and amino acids, however we have not observed such byproducts in any of our reactions (*vide infra*).

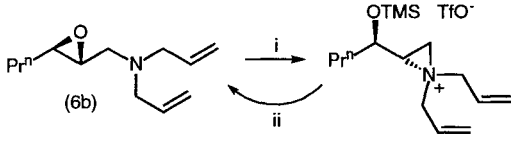
The *trans*-2,3-epoxy amine (6a), derived from dibenzylamine, was treated with trimethylsilyltrifluoro-methanesulfonate (TMSOTf) in $CDCl_3$ at -40 °C and the reaction allowed to warm to room temperature (scheme 8, eqn. 1). The ^1H NMR spectrum of the resulting solution clearly showed clean formation of the aziridinium salt, which was stable for a number of days at room temperature.[13] A similar reaction could be induced using TBDMSOTf in place of TMSOTf. Only a single diastereomeric aziridinium salt was formed consistent with the expected stereoselectivity of the rearrangement process. This was also the case for the majority of other substrates, including those derived from piperidine, forming spirocyclic aziridinium systems (eqn. 2). However, one exception was the *cis*-2,3-epoxy amine (6f) at -40 °C (eqn. 3) where we observed a small amount of side product tentatively assigned to be the azetidinium salt resulting from intramolecular epoxide opening at C-3 rather than C-2. Fortunately formation of this product could be reduced by carrying out the reaction in CH_2Cl_2 at -78 °C rather than $CDCl_3$ at -40 °C. The latter conditions were originally used to allow direct ^1H NMR analysis of the intermediate aziridinium salts.[32] In the case of the 2,3-epoxy sulfides, we have never observed any signs of products resulting from thietanium ion formation, however in some cases where low yields of products are obtained this is one possible contributing factor.



Reagents: i, TMSOTf, $CDCl_3$, -40 °C → rt.

Scheme 8

One further interesting point to note about this reaction is that it can actually be reversed. In some cases (*vide infra*), we had noticed that small amounts of the original 2,3-epoxy amine could be recovered from crude product mixtures, despite quantitative aziridinium salt formation. This indicated that formation of the salt may be reversible under suitable reaction conditions. To investigate this, the diallyl amine derived epoxy amine (6b) was treated with TMSOTf and quantitative formation of the aziridinium salt was observed by NMR. The salt was then subjected to our standard deprotection conditions (K_2CO_3/MeOH) and the original epoxy amine starting material could be recovered in good yield (scheme 9).[32] Thus it would appear that, at least in this case, desilylation and intramolecular aziridinium ion ring opening is more favourable than the competing intermolecular incorporation of methanol. In reactions of 2,3-epoxy sulfides, we sometimes also isolate quite significant quantities of recovered starting material in crude product mixtures (*vide infra*). We believe this to be due to the analogous process where the 3-alkoxy- or 3-trimethylsilyloxy-1,2-thiiranium ion is converted into starting material, however as we do not yet have proof that the initial thiiranium ion generation is quantitative we need to investigate this further.



Reagents: i, TMSOTf, CH_2Cl_2, -78 °C → rt; ii, K_2CO_3, MeOH, 87% overall yield.

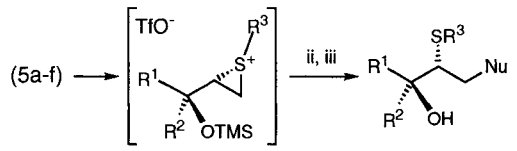
Scheme 9

It is clear from these results that we do have the desired quantitative aziridinium salt formation, rather than any equilibrium process, and this encouraged us to investigate the *in situ* nucleophilic trapping process.

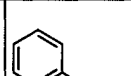
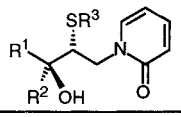
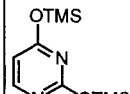
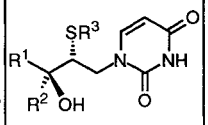
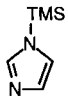
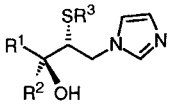
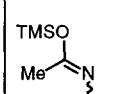
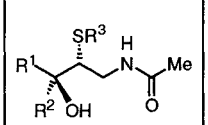
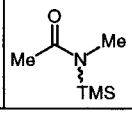
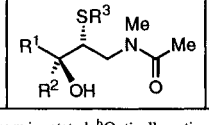
5. Investigations into the nucleophilic trapping of thiiranium and aziridinium ions with sp^2 hybridised nitrogen nucleophiles

Pyridine had worked very efficiently in our preliminary studies (scheme 6), so we chose to investigate other sp^2 hybridised nitrogen systems, and, in keeping with a general interest in the synthesis of molecules with possible biological activity, the use of silylated precursors to 2-pyridones, uracils, imidazoles, and amides were initially studied.[12] Addition of a variety of nitrogen nucleophiles to thiiranium ions generated *in situ* under the conditions we had previously established, warming to 0 °C and stirring for up to 3 days gave the corresponding O-trimethylsilyl ethers which were readily deprotected using K_2CO_3 in MeOH (table 1). In general, yields ranged from low to very good. They refer to pure products after chromatography, and are

Table 1: Results of thiiranium ion trapping experiments with silylated nitrogen heterocycles and amide nucleophiles



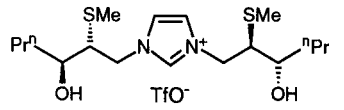
Reagents: i, TMSOTf (1.2 eq.), CH_2Cl_2, -78 °C, 10 min.; ii, Nucleophile, -78 °C → 0°C, up to 3 days; iii, K_2CO_3, MeOH, rt, 45 min.

Entry	Substrate[a]	Nucleophile	Product	Yield (%)
1	5a			81
2	5b			85
3	5a			75
4	5b			81
5	5c[b]			55[c]
6	5d			68
7	5e			53
8	5f			20
9	5a			39(83[e])
10	5b			33
11	5a			58
12	5b			54
13	5c[b]			40[d]
14	5d			44
15	5e			51
16	5a			55
17	5b			44

[a]All compounds used as racemates unless otherwise stated; [b]Optically active (>95% e.e.) 2,3-epoxysulphide used; [c]$[\alpha]_D^{25}$+36.6 (*c* 1.18, EtOH); [d]$[\alpha]_D^{25}$+47.6 (*c* 0.97, EtOH); [e]Yield based on recovered starting material.

overall yields for the 3 step sequence of thiiranium ion generation, nucleophilic trapping and deprotection. In all cases the products are single diastereoisomers and regioisomers as determined by ^{13}C NMR. Importantly, when homochiral 2,3-epoxy sulphide substrates are used, the products retain their optical activity (entries 5 and 13).

The 2-pyridones and uracils gave best yields, and the simple (S-Me, S-Ph) *trans*-2,3-epoxy sulfides were better substrates than the *cis*-isomers. The benzyloxypropyl system (5f) gave a low yield, and we propose that this may be due to a significant reduction in the reactivity of the thiiranium ion intermediate, resulting from stabilisation by coordination of the ether oxygen to the sulfonium sulfur (figure 1). We have so far been unable to confirm this directly and it is currently under further investigation. A similar effect has been observed in related systems where thiiranium ions are stabilised by adjacent coordinating substituents, which render them much less reactive than would be otherwise expected (*cf.* figure 2).[33]



(8)

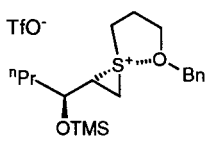


Figure 1

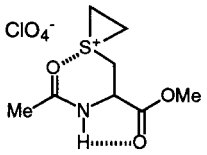
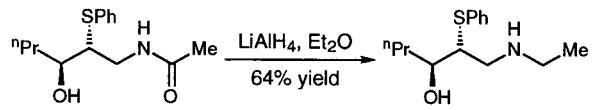


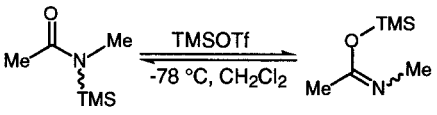
Figure 2

N-Trimethylsilylimidazole showed only low reactivity. With the S-phenyl thiiranium ion, a considerable amount of starting material could be recovered. However in the case of the S-methyl system, no starting material was observed, and only a moderate yield of products was obtained along with significant amounts (30-40%) of a byproduct. This was tentatively assigned as the *bis*-alkylated imidazolium salt (8) from the crude ^1H NMR, however we were unable to isolated it in a sufficiently pure form for full characterisation. Thus it would appear that, at least in this case, the S-alkyl thiiranium ions are more reactive than the S-phenyl systems.

In the case of the amide nucleophiles (entries 11 to 17), both gave moderate yields of the desired products. Clean N-alkylation was observed. This was proved unambiguously in one case (entry 11) by reduction of the amide product with $LiAlH_4$ (scheme 10). The product obtained was clearly the N-ethylamine. N-Methyl trimethylsilylacetamide is reported to exist as the N-silylated isomer,[34] although this would be expected to undergo O-alkylation. However it is likely that under the reaction conditions (TMSOTf), silyl migration can readily occur to give the O-trimethylsilylacetamide (scheme 11), which would be expected to undergo the observed N-alkylation.



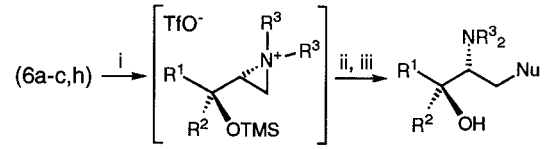
Scheme 10



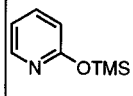
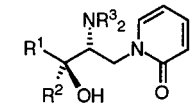
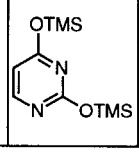
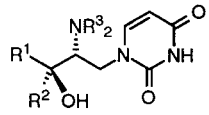
Scheme 11

The reaction of our aziridinium salts with a similar range of nucleophiles were also investigated.[13] Unfortunately the silylated acetamides were unsuccessful, only starting material being recovered. This indicates that, as one might expect, the thiiranium ion intermediates are significantly more reactive than the corresponding aziridinium salts. Fortunately, 2-trimethylsilyloxy-pyridine and *bis*-O-trimethylsilyluracil were both efficient traps for a variety of aziridinium ion intermediates (table 2).

Table 2. Coupling of aziridinium salts with silylated sp^2 hybridised nitrogen nucleophiles



Reagents: i, TMSOTf (1.2 equiv.), CH_2Cl_2, -78°C,10 min.; ii, Nucleophile, -78°C→rt., 3 - 5 days; iii, K_2CO_3, MeOH,rt., 45 min.

Entry	Substrate[a]	Nucleophile	Product	Yield (%)
1	6a			93
2	6b			83
3	6h			62[b]
4	6a			90
5	6b			86[b]
6	6c			86[c]

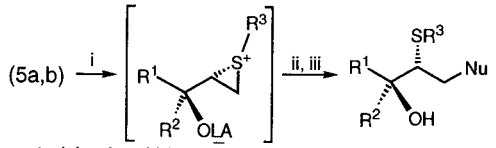
[a] All compounds used as racemates unless otherwise stated; [b] Homochiral (>96%e.e.) 2*S*,3*S*-epoxyamine used; [c] TBAF used in deprotection rather than K_2CO_3 (see text).

6. Use of secondary and primary amine nucleophile equivalents

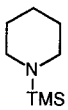
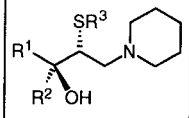
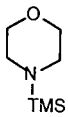
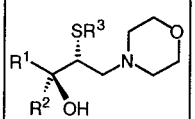
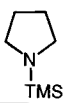
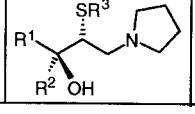
Although the systems which had worked well so far were of use, we also needed to extend the chemistry for the introduction of secondary and primary amines. In particular, as part of a general programme aimed at the synthesis of novel aminopeptidase inhibitors, we needed a system which allowed the use of α-amino ester nucleophiles (*vide infra*).[18,35] The relative success of silylated nucleophiles in our previous work led us to initially consider the use of N-trimethylsilyl amines as nucleophilic equivalents of secondary amines in the reaction (table 3). As can be seen these gave low to moderate yields of the desired products, and were more efficient if BF_3•OEt_2 was used as Lewis acid rather than TMSOTf.[12]

These yields were disappointing but acceptable, however the real problems began when we investigated the use of primary amines. Isopropylamine was chosen initially as a simple model system for an amino ester, however all attempts at coupling with a thiiranium ion resulted in isolation of the *bis*-alkylated compound (9) as the sole characterisable product. Use of a large excess of nucleophile, and modification of reaction conditions, failed to improve the selectivity of the reaction. The use of silylated primary amines, such as the stabase derivatives of isopropylamine, Ala(OMe) and Leu(OMe) and other silylated nucleophiles such as $(Me_3Si)_3N$ and $(Me_3Si)_2NMe$ in some cases gave monoalkylation products but only in <20% yield.[12] This marked something of a frustrating low point in the project - if we were to achieve our final objectives we needed to overcome this serious problem.

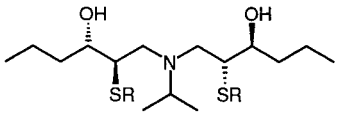
Table 3. Results of thiiranium ion trapping experiments with N-trimethylsilyl amines.



Reagents: i, Lewis acid (LA), CH_2Cl_2, -78 °C, 10 min.; ii, Nucleophile (Nu), -78 °C → 0 °C, 3 days; iii, K_2CO_3, MeOH, rt, 45 min.

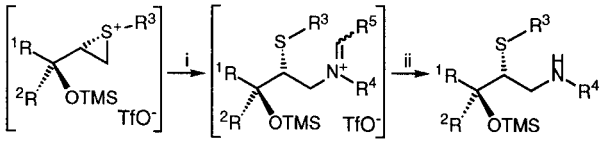
Entry[a]	Substrate	Nucleophile	Lewis acid	Product	Yield (%)
1	**5a**		TMSOTf		23
2	**5a**		BF_3•OEt_2		40
3	**5b**		TMSOTf		37
4	**5b**		BF_3•OEt_2		47
5	**5b**		BF_3•OEt_2		44
6	**5a**		BF_3•OEt_2		33
7	**5b**		BF_3•OEt_2		37

[a]All compounds used as racemates.



(9)

At this time, the student (DMG) was on a 3 month placement with his industrial sponsor. It was during this period that he had the idea that, as sp^2 hybridised nitrogen nucleophiles had worked so well previously, we may be able to use imines as synthetic equivalents of primary amines in these reactions.[36] We later found out that this approach had been used previously for the preparation of very simple secondary amines[37] however it looked like a very promising reaction and so we decided to look at it in some detail. The approach is summarised in scheme 12. Thus the imine nucleophile would be expected to undergo clean monoalkylation to give an iminium ion, which on work-up could be hydrolysed to give the desired secondary amine product.

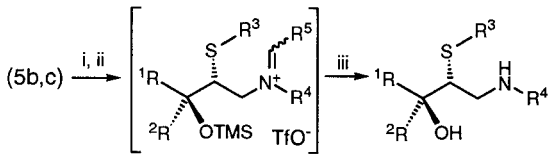


Reagents: i, $R^5CH{=}NR^4$; ii, hydrolysis.

Scheme 12

A number of simple imines derived from isopropylamine were prepared, and their efficiency as thiiranium ion trapping agents investigated using our thiiranium ion system (table 4, entries 1-3). The almost immediate success we achieved was very gratifying. The iminium triflate intermediates were formed in almost quantitative yield and could be isolated, however they were generally hydrolysed using aqueous K_2CO_3 during work-up, which also served to deprotect the trimethylsilyl ether. Note that yields are for the 4 step reaction sequence, *viz.* thiiranium ion generation, iminium ion formation, hydrolysis, and deprotection. We believe the isolated yields of the final products are somewhat reduced because of problems with the purification and handling of these polar products.[36]

Table 4. Use of imines as synthetic equivalents for the selective monoalkylation of primary amines



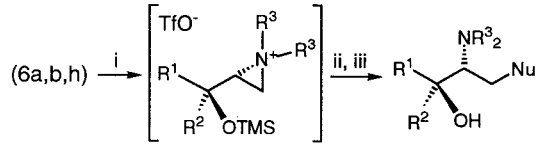
Reagents: i, TMSOTf, CH_2Cl_2, -78 °C, 10 min.; ii, $R^5CH{=}NR^4$, 0 °C, 72 h.; iii, K_2CO_3 (aq.), 3h., rt.

Entry	Substrate	H_2N-R^4	R^5	Yield
1	**5b**	$^iPrNH_2$	C_6H_5	37[a]
2	**5b**	$^iPrNH_2$	(4-MeO)C_6H_4	63[a]
3	**5b**	$^iPrNH_2$	Me	70[a]
4	**5c**	$^iPrNH_2$	(4-MeO)C_6H_4	57
5	**5c**	$PhNH_2$	(4-MeO)C_6H_4	66[b]
6	**5c**	$BnNH_2$	(4-MeO)C_6H_4	46

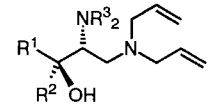
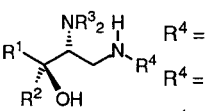
[a]Racemic 2,3-epoxy sulfide used; [b]Isolated as O-trimethylsilyl ether

It can be seen that the *p*-anisaldehyde imine (entry 2) and acetaldehyde imine (entry 3) were of similar efficiency, however the instability of the latter meant that for reproducibility the *p*-anisaldehyde

Table 5. Results of nucleophilic trapping of aziridinium salts with simple primary and secondary amines



Reagents: i, TMSOTf (1.2 equiv.), CH_2Cl_2, -78°C,10 min.; ii, Nucleophile, -78°C→rt., 3 - 5 days; iii, K_2CO_3, MeOH,rt., 45 min.

Entry	Substrate[a]	Nucleophile	Product	Yield (%)
1	6a		X = CH_2	60
2	6b		X = CH_2	67
3	6a		X = O	92
4	6b		X = O	90
5	6f		X = O	58
6	6h		X = O	59[b]
7	6a			67
8	6b			88
9	6a	Bu^n—NH_2	R^4=^{n}Bu	44[c]
10	6a	$^iPrNH_2$	 R^4 = ^{i}Pr	47
11	6b	$^iPrNH_2$	R^4 = ^{i}Pr	49
12	6a	NH_3 (liq.)	R^4 = H	65[d]

[a] All compounds used as racemates unless otherwise stated; [b] Homochiral (>96%e.e.) 2*S*,3*S*-epoxyamine used. [c] 12% bis-alkylated product also isolated; [d] Reaction carried out at -30 °C, only monoalkylated product observed.

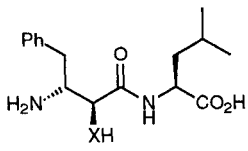
imines were preferred. The acetaldehyde-derived imines were generally used without purification immediately after preparation, and tended to give coloured products (this could be suppressed by addition of $^{i}PrNH_2$ prior to work-up) whereas the anisaldehyde imines could be purified prior to use and generally gave cleaner products. For this reason the anisaldehyde imines were chosen for further investigation into the effect of the nature of the amine structure on the reaction. The benzaldehyde imine was clearly inferior in this reaction.

Thus a series of anisaldehyde-derived imines were all reacted with the same 2,3-epoxy sulfide substrate. The reactions generally proceeded with similar efficiency. One interesting point to note is the unusual stability of the O-trimethylsilyl ether obtained by reaction of the phenylimine, which allowed its isolation without *in situ* deprotection under the conditions required for imine hydrolysis. Thus use of this procedure gives the required secondary amines, which are the desired products of overall selective monoalkylation of primary amines by the thiiranium ion.

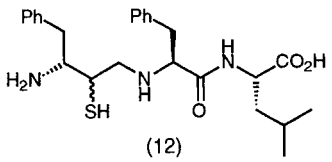
With the aziridinium salt systems, the polyalkylation of primary and secondary amine nucleophiles was not such a problem, probably due to the lower reactivity of the aziridinium ion intermediates (table 5). Only a small amount of *bis*-alkylation was observed with a simple primary amine nucleophile (entry 9), and we were even able to use ammonia with no appreciable polyalkylation (entry 12).

7. Synthesis of new potential aminopeptidase inhibitors

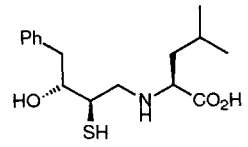
One of the original ideas behind this work, in addition to fundamental reactive intermediate chemistry, was to apply this new methodology to the synthesis of molecules of biological relevance. We became interested in the synthesis of structural analogues of the potent aminopeptidase inhibitor bestatin (10)[38] and its mercapto analogue α-thiolbestatin (11) which has slightly higher activity.[39] Such compounds are of considerable importance, having activity as immune response modifiers,[40] analgesics by enkephalinase inhibition,[41] and antitumour and antimicrobial properties believed to be associated with their abilities to inhibit cell surface aminopeptidases.[42]



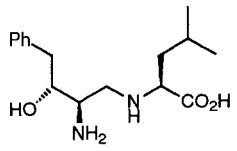
(10) Bestatin, X = O
(11) α-Thiolbestatin, X = S



(12)



(13)



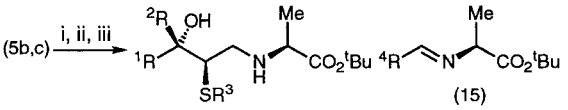
(14)

Also of importance to our work was a series of peptide-derived amino alcohols and amino thiols including (12) which have also shown high activity (1nM) as aminopeptidase inhibitors.[43] By analogy with (12) we reasoned that the amide carbonyl group of bestatin and related compounds may not be necessary for activity, although it is known that the alcohol group (or presumably the thiol group) is required.[39] Because the situation regarding binding in these types of compound remains unclear, we felt it would be of interest to embark on a programme to synthesise related potential novel aminopeptidase inhibitors [*e.g.* (13, 14)], to further probe the structural requirements for aminopeptidase inhibitory activity, and in addition, provide access to novel peptide isosteres.[44]

For our approach to be viable, we needed to develop methodology where thiiranium ion and aziridinium salt intermediates could be coupled with amino acid derivatives under mild conditions. Our previous results with thiiranium ions and imines derived from simple primary amines led us to consider their use in this reaction. We thus investigated the couplings of imines derived from amino esters (table 6). Importantly, to get the relative stereochemistry required for bestatin-like systems, 2,3-epoxy alcohol precursors derived from *cis*-alkenes were required, although it was also important that the reaction was successful with systems derived from *trans*-alkenes, which would give the opposite relative stereochemistry at C-2 and C-3.

Previous results had indicated that the acetaldehyde and anisaldehyde-derived imines were most efficient for this reaction (table 4). Such imine derivatives of Ala(O^tBu) were prepared and investigated in the thiiranium ion trapping reaction sequence (table 6). As can be seen from the limited number of examples, moderate yields of the desired products were obtained using procedures slightly modified from our previous work. In this case, iminium ion hydrolysis was carried out using $NaHCO_3$ (aq.), followed by AcOH/MeOH to remove trimethylsilyl group. We had previously used K_2CO_3 (aq.) which accomplished both reactions in one step, but we felt that with these more sensitive systems, racemisation and/or ester hydrolysis could be an important side reaction. Note that yields are for the 4 step reaction sequence (*viz.* thiiranium ion generation, iminium ion formation, hydrolysis, and deprotection) and purification. The desired products were obtained in reasonable overall yield as single diastereoisomers as determined by ^1H and ^{13}C NMR, indicating complete retention of stereochemical integrity throughout the reaction sequence. It was also possible to use $BF_3{\cdot}OEt_2$ instead of TMSOTf in the reaction with only slight decrease in the efficiency of the reaction (entry 3).

Table 6. Coupling of thiiranium ions with imines derived from amino esters



Reagents: i, TMSOTf, CH_2Cl_2, -78 °C, 10 min.; ii, (15), temp., time; iii, $NaHCO_3$ (aq.); AcOH, MeOH; $NaHCO_3$ (aq.).

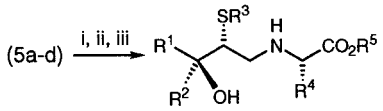
Entry	R^1	R^2	R^3	Temp. °C	Time (h)	R^4 (15)	Yield
1	H	^{n}Pr	Ph	0	72	(4-MeO)C_6H_4	44
2	^{n}Pr	H	Me	-78	12	Me	40[a]
3	^{n}Pr	H	Me	-78	12	Me	34[a,b]

[a]Isopropylamine added at -78°C prior to workup;
[b]$BF_3{\cdot}OEt_2$ used in place of TMSOTf.

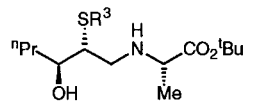
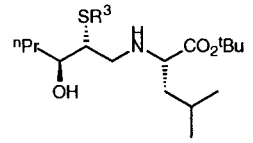
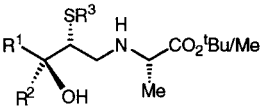
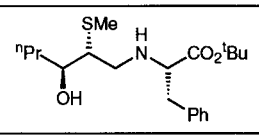
The modest yields observed with this procedure, meant that there was still considerable room for improvement. It was at this time that we began to notice rather unusual temperature effects in the coupling reaction. We observed that similar yields of products could be obtained if the coupling reaction was carried out at 0 °C for 3 days, or at -78 °C for 12 hours (table 6). This we believe has important implications for the nature of the reactive intermediates involved in the reaction (section 8). In addition, with the acetaldehyde imines, the products were often coloured, however this could be suppressed if isopropylamine was added immediately prior to work up. Fortunately, the student carrying out this work was a very competent and careful experimentalist, and he noticed that a small amount of a side product had been formed which turned out to be the product of selective monoalkylation of isopropylamine by our thiiranium ion intermediate. Thus, carrying out the entire reaction at -78 °C rather than our previously optimised conditions (0 °C, 3 days), with a primary amine nucleophile, we envisaged that we may be able to get more significant yields of monoalkylated products. We thus began to investigate this reaction further.

To our disappointment, isopropylamine still gave mainly the *bis*-alkylated product under these modified reaction conditions, however amino esters gave only products of clean monoalkylation, in better yield than using the imine systems, and with additional recovery of starting material in some cases (table 7). Thus we got something of a break here - although simple primary amines underwent polyalkylation hence requiring the imine methodology, our desired systems, the amino esters, were significantly more selective and gave only the desired products - so much for model studies !

Table 7. Coupling of thiiranium ions with amino esters



Reagents: i, Lewis acid, CH_2Cl_2, -78 °C, 10 min.; ii, Aminoester, -78 °C, 4 → 24 h.; iii, $NaHCO_3$ (aq.); AcOH, MeOH, rt, 3 h.; $NaHCO_3$ (aq.).

Entry	Substrate	Amino ester	Product	Yield[a] (%)
1	5b	Ala(O^tBu)		54(74)
2	5b	Ala(O^tBu)		49[b]
3	5a	Ala(O^tBu)		48(84)
4	5b	Leu(O^tBu)		54
5	5a	Leu(O^tBu)		58(87)
6	5d	Ala(O^tBu)		44
7	5c	Ala(O^tBu)		43(78)
8	5b	Ala(OMe)		53[c]
9	5b	Phe(O^tBu)		49

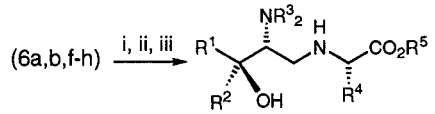
[a] Values in parentheses are yields based on recovered starting material; [b] BF_3•OEt_2 used as Lewis acid rather than TMSOTf; [c] Methyl ester

The reaction is successful for 2,3-epoxy sulfides derived from *cis*- and *trans*-alkenes, both as the S-methyl and S-phenyl thioethers. The *tert*-butyl esters of alanine, leucine (required for bestatin-like systems), and phenyl alanine, were chosen as typical amino acid substrates and were found to be equally effective. In addition, for the one example investigated (entry 8), a methyl ester was as efficient as the *tert*-butyl ester. The use of BF_3•OEt_2 as Lewis acid in place of TMSOTf (entry 2), resulted in only marginal decrease in the efficiency of the overall process. Again, in all cases the products were isolated as single diastereoisomers as determined by ^1H and ^{13}C NMR.

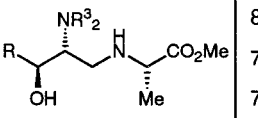
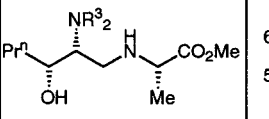
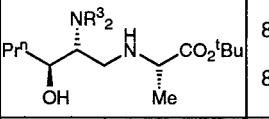
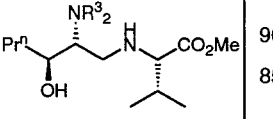
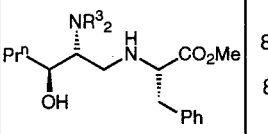
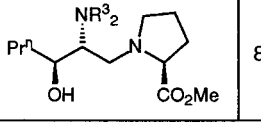
This methodology now demonstrates the potential of using amino acid based nucleophiles for reactions with thiiranium ion intermediates, and we are currently developing this chemistry further to prepare systems more closely related to thiobestatin (11) and other related biologically active systems.[35]

We then turned to aziridinium salt intermediates, and investigated their reaction with amino esters. This turned out to be relatively simple (table 8) with no sign of polyalkylation as would be expected from our previous results, and coupling occurring smoothly over a few days at room temperature. The reaction is equally successful for both methyl and *tert*-butyl amino esters, which has important consequences for subsequent synthetic manipulation (*vide infra*). Again, in all cases the products were isolated as single diastereoisomers as determined by ^1H and ^{13}C NMR.

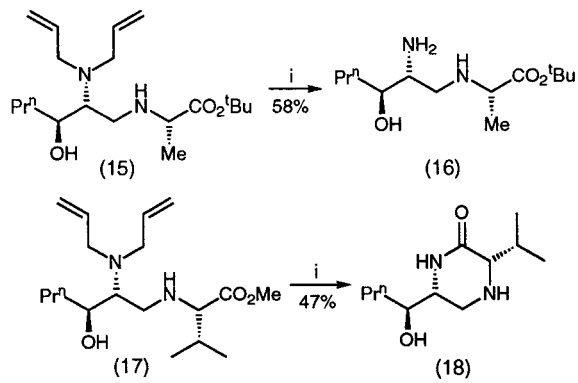
Table 8. Coupling of amino esters with aziridinium salts derived from 2,3-epoxy amines



Reagents: i, TMSOTf , CH_2Cl_2, -78°C → rt; ii, Amino ester, rt,3-5 days; iii, AcOH, MeOH; iv, $NaHCO_3$, H_2O.

Entry	Substrate	Amino ester	Product	Yield (%)
1	6a	Ala(OMe)		86
2	6b	Ala(OMe)		79
3	6h	Ala(OMe)		74
4	6f	Ala(OMe)		62
5	6g	Ala(OMe)		57
6	6a	Ala(O^tBu)		88
7	6b	Ala(O^tBu)		84
8	6a	Val(OMe)		90
9	6b	Val(OMe)		85
10	6a	Phe(OMe)		88
11	6b	Phe(OMe)		81
12	6a	Pro(OMe)		87

This new methodology allows for the coupling of amino acid residues with adjacent amino alcohol functionality, under very mild conditions. The aziridinium salt intermediates are sufficiently reactive to couple with relatively weak nucleophiles such as primary amines, whereas procedures involving less reactive aziridine derivatives (e.g. N-acyl- and N-sulfonyl-aziridines) would require harsher reaction conditions which could compromise the stereochemical integrity of the amino acid moiety.[28]



Reagents: i, $(PPh_3)_3RhCl$, CH_3CN, H_2O, Δ.

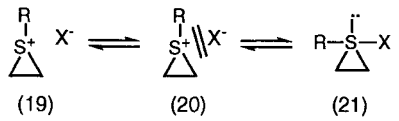
Scheme 13

The main drawback of our procedure is that primary amines are usually the eventual target molecules, and so the tertiary amine groups in our products must be deprotected. We have carried out some initial studies on this (scheme 13), and have shown that this is possible under very mild conditions.[18] So far we have seen no indication that racemisation is a problem in our systems. Interestingly the *tert*-butyl ester (15, from entry 7, table 8) is cleanly deprotected to give the required primary amine (16), whereas the methyl ester (17, from entry 9, table 8) is deprotected but cyclises under the reaction conditions to give the 2-ketopiperazine (18). Further studies on improving the yield and generality of these and other deprotection strategies are currently underway, along with the synthesis of systems more closely related to bestatin (10) and other biologically active molecules using our new chemistry.

8. The nature of the reactive intermediates - mechanistic studies

The generation of aziridinium ions from 2,3-epoxy amines, and their nucleophilic trapping reactions proceeded in a relatively straightforward manner. However, reactions involving the thiiranium ion intermediates tended to be considerably less reliable. Their capricious nature, we believe, indicates that things are considerably more complex than might first appear. We have seen indications that S-aryl thiiranium ions are less reactive than their S-alkyl counterparts, as might be expected on electronic grounds. More surprising however, was the effect of temperature on the reactivity of our thiiranium ions (*e.g.* tables 6 and 7, *cf.* table 1). We have for some time been concerned that although thiiranium ions are generally considered to be highly electrophilic species, our original optimum reaction conditions of 0 °C over a period of days were consistent with a much less reactive intermediate. The surprising observation that similar, if not better yields could be obtained after shorter reaction times (4-24h) at considerably lower temperatures (-78 °C), would tend to indicate that the nature of the reacting species (the "thiiranium ion intermediate") is different in either case.

In fact, reactions of thiiranium salts can be more complex than might at first be envisaged, mainly because of the variety of potential intermediates involved.[19] Thus, thiiranium ions (19) are one extreme possible structure, and episulfuranes (21), where the anionic counterion is covalently bonded to the sulfur atom, lies at the other end of the spectrum, with various degrees of ion pairing in between (20).

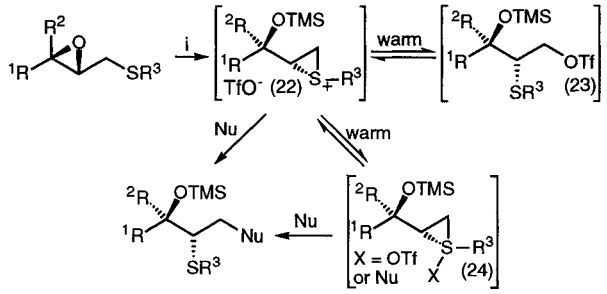


(19) (20) (21)

Episulfuranes are proposed as intermediates in reactions of halogens with episulfides,[45] halide ions with thiiranium ions,[46] and sulfenyl halides with alkenes.[19] Molecular orbital calculations have indicated that in the gas phase, an episulfurane structure is more stable than the corresponding sulfonium salt[47] and some have been isolated and characterised.[48] Alternatively, it has been proposed that, in some cases, thiiranium ions may be in equilibrium with ring opened intermediates.[49] This, of course is the idea behind neighbouring group participation reactions of β-halosulfides and related systems.

We believe that a possible explanation for our observations is that at -78 °C, the intermediate in the reaction is essentially a free thiiranium ion which reacts with nucleophiles in the usual manner (scheme 14).

If the reaction is allowed to warm, some interaction with the nucleophile or counterion (TfO^-) can now occur, either by formation of a β-thioalkyltriflate (23), or an episulfurane-like intermediate (24). These react with an external nucleophile probably *via* a small equilibrium concentration of the thiiranium ion with a corresponding decrease in observed rate of reaction.



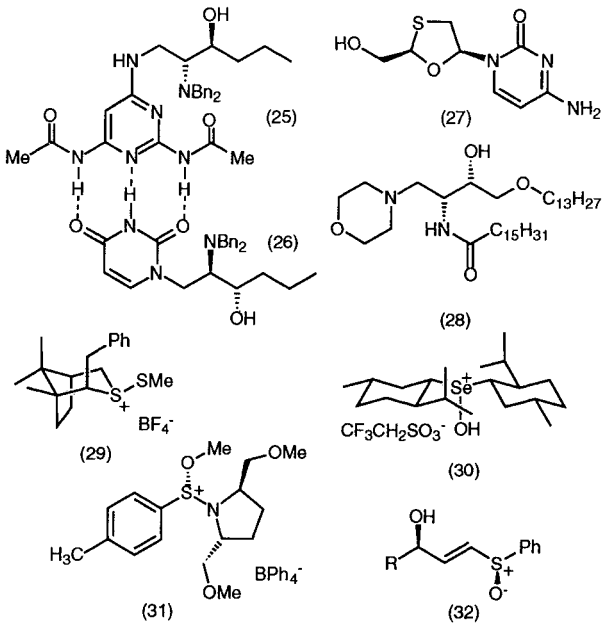
Reagents: i, TMSOTf, CH_2Cl_2, -78 °C.

Scheme 14

We are currently investigating this hypothesis further, but it is clear that although I have used the term "thiiranium ion" throughout this account it should be appreciated that this may be a gross simplification of the actual nature of the intermediates involved in the reaction.

9. Future work

One of our favourite and most efficient nucleophiles for trapping both our aziridinium and thiiranium ion intermediates, has been *bis*-(O-trimethylsilyl)uracil. We are currently exploiting this chemistry further by synthesising novel hydrogen bonding systems based at least partly on systems available using our methodology.[50] For example, we have recently shown that the uracil (25) and the pyrimidine (26) form a hydrogen bonded dimer in $CDCl_3$. We are currently investigating this further for potential application in the areas of antisense oligonucleotide therapy and materials. This also developed our interests in other aspects of nucleoside chemistry, such as our recently reported enantioselective synthesis of Lamivudine (27).[51]



(25) (26) (27) (28) (29) (30) (31) (32)

Having now established the basis of the amino acid coupling methodology to both aziridinium salts and thiiranium ions, we are now in a position to synthesise potential amino peptidase systems such as (13) and (14), which more closely resemble bestatin (10). We are also working on the synthesis of the morpholine derivative (28),[32] which is related to systems recently reported to be strong inhibitors glucosylceramide synthase, a promising cancer chemotherapy target.[52] This work also has considerable potential in combinatorial chemistry which we are now beginning to develop further. We are also investigating alternative methods of enantioselective thiiranium ion generation using homochiral sulfenylsulfonium salts such as (29).[25]

Our work on the oxidation of 2,3-epoxy sulfides[10] led to our work on selenoxide-sulfonic acid salts (30), which are stable crystalline selenoxide equivalents, and also efficiently oxidise sulfides to sulfoxides.[53] It also led to our work on the use of aminosulfoxonium salts (*e.g.* 31) as novel electrophiles for enantioselective C-C bond formation,[54] and an investigation into the diasteresoselectivity for the addition to E-γ-hydroxy-α,β-unsaturated sulfoxides (*e.g.* 32).[55] Thus many of our current research themes can be traced back to our original simple idea of developing the chemistry of 1-hetero-2,3-epoxides.

10. Conclusion

There is no doubt that aziridinium salts and thiiranium ions are both useful reactive intermediates. Conceptually they are very similar in how they may be generated and used, however our experience has shown there to be significant differences in their utility. The aziridinium salts are less reactive than the corresponding thiiranium ions. Whilst this somewhat restricts the range of nucleophiles which can be used, the generally superior yields and more predictable reactivity makes aziridinium salts considerably more "user friendly". We hope this work will encourage more synthetic chemists to consider these reactive intermediates as useful building blocks for asymmetric synthesis.

Acknowledgements. My sincere thanks go to my Ph.D. students Duncan M. Gill and Quanying Liu for carrying out the vast majority of this work. I am also indebted to their Industrial supervisors, Dr. Neil A. Pegg (Glaxo Research and Development) and Dr. Allan P. Marchington (Pfizer Central Research) for their advice and encouragement. I am also grateful to Andrew D. Westwell for early contributions in this area. Financial support from Glaxo Research and Development, Pfizer Central Research, ICI Strategic Research Fund, EPSRC, the Nuffield Foundation, the Royal Society, the CVCP, and the University of Leeds, is also gratefully acknowledged.

References and Notes

§ This account was part of a lecture given at the Royal Society of Chemistry meeting to celebrate the retirement of Prof. I.O. Sutherland, University of Liverpool, 18th. September 1995.

1. Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc .*, **1980**, *102*, 5974; Hill, J.G.; Finn, M.G.; Sharpless, K.B. *Asymmetric Synthesis*, ed. J.D. Morrison, Academic Press, New York, 1985, Vol. 5.
2. Pfenninger, A. *Synthesis*, **1986**, 89; Rossiter, B.E. *Asymmetric Synthesis*, ed. Morrison, J.D., Academic Press, New York. 1985, Vol. 5; Johnson, R.A.; Sharpless, K.B. in *Comprehensive Organic Synthesis*, ed. Trost, B.M., Pergamon Press, Oxford, 1991, vol. 7, chap. 3.2, pp. 389.
3. Page, P.C.B.; Rayner, C.M.; Sutherland, I.O. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 2403.
4. Page, P.C.B.; Rayner, C.M.; Sutherland, I.O. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1615; Ger. Offen., DE, 3,629,116 (Cl.C07C143/68). *Chem. Abstr.* **1988**, *109*, P92664q.
5. Payne, G.B. *J. Org. Chem.*, **1962**, *27*, 3819.
6. Buchanan, J.G.; Sable, H.Z., in "Selective Organic Transformations", ed. Thyagarajan, B.S., Wiley, New York, **1972**, *25*, 109.
7. a) Sharpless, K.B.; Behrens, C.H.; Katsuki, T.; Lee, A.W.M.; Martin, V.S.; Takatani, M.; Viti, S.M.; Walker, F.J.; Woodard, S.S. *Pure Appl. Chem.*, **1983**, *55*, 589; b) Wrobel, J.E.; Ganem, B. *J. Org. Chem.*, **1983**, *48*, 3761.
8. Page, P.C.B.; Rayner, C.M.; Sutherland, I.O. *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1375; for independent recognition of this work see: Ganem, B. *Chemtracts-Organic Chemistry*, **1990**, *3*, 381.
9. Paquette, L.A.; Doherty, A.M.; Rayner, C.M. *J. Amer. Chem. Soc.*, **1992**, *114*, 3910; Rayner, C.M.; Astles, P.C.; Paquette, L.A. *J. Amer. Chem. Soc.*, **1992**, *114*, 3926; see also: Paquette, L.A. *Chemtracts-Organic Chemistry*, **1992**, *5*, 141.
10. Westwell, A.D.; Thornton-Pett, M.; Rayner, C.M. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 847 and refs. cited therein.
11. Sharpless, K.B.; Exon, C.M.; Regenye, R. *Org. Synth.*, **1984**, *63*, 66.
12. Gill, D.M.; Pegg, N.A.; Rayner, C.M. *Tetrahedron*, in press.
13. Liu, Q.; Simms, M.J.; Boden, N.; Rayner, C.M. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 1363.
14. For example by Pummerer rearrangement of the corresponding sulfoxide and hydrolysis, see: De Lucchi, O.; Miotti, U.; Modena, G. *Organic Reactions*, **1990**, *40*, 157.
15. Corrie, J.E.T.; Hlubucek, J.R.; Lowe, G. *J. Chem. Soc., Perkin Trans. I*, **1977**, 1421; Sakakibara, S.; Shimonishi, Y.; Kishida, Y.; Okada, M.; Sugihara, H. *Bull. Chem. Soc. Japan*, **1967**, *40*, 2164.
16. Laguzza, B.C.; Ganem, B. *Tetrahedron Lett.*, **1981**, *22*, 1483; Moreau, B.; Lavielle, S.; Marquet, A. *Tetrahedron Lett.*, **1977**, *18*, 2591; Sundberg, R.J.; Hamilton, G.S.; Laurino, P.J. *J. Org. Chem.*, **1988**, *53*, 976.
17. Hartung, W.H.; Simonoff, R. *Org. React.*, **1953**, *7*, 275; Jacobi, P.A.; Martinelli, M.J.; Polanc, S. *J. Amer. Chem. Soc.*, **1984**, *106*, 5594; Overman, L.E.; Mendelson, L.T.; Jacobsen, E.J. *J. Amer. Chem. Soc.*, **1983**, *105*, 6629.
18. Liu, Q.; Marchington, A.P.; Boden, N.; Rayner, C.M. *Synlett*, **1995**, 1037.
19. Rayner, C. M. in "Organosulfur Chemistry Series", ed. Page, P.C.B., Pergamon Press, 1995, chapter 3; see also Capozzi, G.; Modena, G.; Pasquato, L. in "The chemistry of sulphenic acids and their derivatives", ed. Patai, S., J. Wiley, Chichester, 1990, chapter 10.
20. Bird, P.; Eames, J.; Fallis, A.G.; Jones, R.V.H.; Roddis, M.; Sturino, C.F.; O'Sullivan, S.; Warren, S.; Westwell, M.S.; Worrall, J. *Tetrahedron Lett.*, **1995**, *36*, 1909 and references cited therein; Coldham, I.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1637.
21. Williams, D.R.; Phillips, J.G. *Tetrahedron*, **1986**, *42*, 3013; Trost, B.M.; Shibata, T. *J. Am. Chem. Soc.*, **1982**, *104*, 3225; Trost, B.M.; Shibata, T.; Martin, S.J. *ibid*, **1982**, *104*, 3228; see also ref. 19.
22. For other reports of 2,3-epoxy sulfide derivatives see: Derzhinskii, A.R.; Konyushkin, L.D.; Lutsenko, A.I. *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1984**, *11*, 2652; Fruchier, A.; Morangues, V.; Petrus, C.; Petrus, F. *Bull. Chem. Soc. France*, **1984**, *II*, 173; Fujisawa, T.; Itoh, T.; Nakai, M.; Sato, T. *Tetrahedron Lett.*, **1985**, *26*, 771; Itoh, T.; Yoshinaka, A.; Sato, T.; Fujisawa, T. *Chemistry Lett.*, **1985**, 1679; Apparao, S.; Schmidt, R.R. *Synthesis*, **1987**, 896; Gu, X.P.; Ikeda, I.; Okahara, M. *Bull. Chem. Soc. Japan*, **1987**, *60*, 667; Kalugin, V.E.; Litvinov, V.P. *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1991**, *18*, 2829; Niyazymbetov, M.E.; Konyushkin, L.D.; Niyazymbetova, Z.I.; Kalugin, V.E.; Litvinov, V.P.; Petrosyan, V.A. *Tetrahedron Lett.*, **1991**, *32*, 1099; Takano, S.; Sugihara, Y.; Ogasawara, K. *Synlett*, **1992**, 668; Takano, S.; Sugihara, Y.; Ogasawara, K. *Tetrahedron Lett.*, **1993**, *34*, 845; Miyauchi, H.; Nakamura, T.; Ohashi, N. *Bull Chem. Soc. Japan*, **1995**, *68*, 1731.
23. See for example: Oki, M.; Nakanishi, W.; Fukunaga, M.; Smith, G.D.; Duax, W.L.; Osawa, Y. *Chemistry Lett.*, **1975**, 1277; see also ref. 19.
24. Toshimitsu, A.; Hirosawa, C.; Tanimoto, S. *Tetrahedron Lett.*, **1991**, *32*, 4317.
25. Archer, N.J.; Rayner, C.M.; Bell, D.; Miller, D. *Synlett*, **1994**, 617; see also: Lucchini, V.; Modena, G.; Pasquato, L. *J. Chem. Soc., Chem. Commun.*, **1994**, 1565.
26. Jones, G.B.; Mathews, J.E. *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 93 and refs. cited therein.
27. Steiger, A.; Pyun, H.-J.; Coates, R.M. *J. Org. Chem.*, **1992**, *57*, 3444; Evans, D.A.; Mitch, C.H. *Tetrahedron Lett.*, **1982**, *23*, 285; Pfeil, E.; Harder, U. *Angew. Chem. Int. Edn. Engl.*, **1967**, *6*, 178; Picq, D.; Anker, D.; Rousset, C.; Laurent, A. *Tetrahedron Lett.*, **1983**, *24*, 5619; see also refs. 30 and 31.
28. Moulines, J.; Charpentier, P.; Bats, J.-P.; Nuhrich, A.; Lamidey, A.-M. *Tetrahedron Lett.*, **1992**, *33*, 487; see also: Najime, R.;

Pilard, S.; Vaultier, M. *Tetrahedron Lett.*, **1992**, *33*, 5351; Kowollik, W.; Janairo, G.; Voelter, W. *Justus Liebigs Ann. Chem.*, **1988**, 427; Tanner, D.; Somfai, P.; *Tetrahedron*, **1988**, *44*, 619.
29. Nakai, K.; Ibuka, T.; Otaka, A.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *Tetrahedron Lett.*, **1995**, *36*, 6247.
30. Leonard, N.J.; Jann, K. *J. Amer. Chem. Soc.*, **1962**, *84*, 4806; Leonard, N.J.; Jann, K.; Paukstelis, J.V.; Steinhardt, C.K. *J. Org. Chem.*, **1963**, *28*, 1499.
31. Leonard, N.J.; Ning, R.Y.; Booth, R.L. *J. Org. Chem.*, **1965**, *30*, 4357.
32. Liu, Q.; Marchington, A.P.; Rayner, C.M., unpublished results.
33. Henkel, J.G.; Amato, G.S. *J. Med. Chem.*, **1988**, *31*, 1279; see also: Reetz, M. T.; Seitz, T. *Angew. Chem. Int. Ed. Engl.*, **1987**, *26*, 1028.
34. Yoder, C.H.; Copenhafer, W.C.; DuBeshter, B. *J. Am. Chem. Soc.*, **1974**, *96*, 4283; Birkofer, L.; Ritter, A. *Angew. Chem. Int. Edn. Engl.*, **1965**, *4*, 417; Knapp, S.; Rodriques, K.E. *Tetrahedron Lett.*, **1985**, *26*, 1803.
35. Gill, D.M.; Pegg, N.A.; Rayner, C.M. *Tetrahedron Lett.*, **1995**, *36*, 8327.
36. Gill, D.M.; Pegg, N.A.; Rayner, C.M. *Synlett*, **1995**, 1275.
37. Lucier, J.J.; Harris, A.D.; Korosec, P.S. *Org. Synth., Coll. Vol. 5*, **1973**, 736; Wawzonek, S.; McKillip, W.; Peterson, C.J. *Org. Synth., Coll. Vol. 5*, **1973**, 758.
38. Nishizawa, R.; Saino, T.; Takita, T.; Suda, H.; Aoyagi, T.; Umezawa, H. *J. Med. Chem.*, **1977**, *20*, 510.
39. Ocain, T.D.; Rich, D. *J. Med. Chem.*, **1988**, *31*, 2193.
40. Dunlap, B.E.; Dunlap, S.A.; Rich, D.H. *Scand. J. Immunol.*, **1984**, *20*, 237; Schorlemmer, H.; Basslet, K.; Sedlacek, H. *Cancer Res.*, **1983**, *43*, 4148; see also ref.39.
41. Barclay, R.K.; Phillips, M.A. *Biochem. Biophys. Res. Commun.*, **1980**, *96*, 1732; Roques, B.P.; Fournie-Zaluski, M.C.; Soroca, E.; Lecomte, J.M.; Malfroy, B.; Lloreus, C.; Schwartz, J.-C. *Nature (London)*, **1980**, *288*, 286.
42. Norman, B.H.; Morris, M.L. *Tetrahedron Lett.*, **1992**, *33*, 6803 and refs. cited therein.
43. Gordon, E.M.; Godfrey, J.D.; Delaney, N.G.; Asaad, M.M.; Von Langen, D.; Cushman, D.W. *J. Med. Chem.*, **1988**, *31*, 2199.
44. For other examples see: Askin, D.; Wallace, M.A.; Vacca, J.P.; Reamer, R.A.; Volante, R.P.; Shinkai, I. *J. Org. Chem.*, **1992**, *57*, 2771; Fincham, C.I.; Higginbottom, M.; Hill, D.R.; Horwell, D.C.; O'Toole, J.C.; Ratcliffe, G.S.; Rees, D.C.; Roberts, E. *J. Med. Chem.*, **1992**, *35*, 1472; Hoffman, R.V.; Kim, H.-O. *Tetrahedron Lett.*, **1992**, *33*, 3579; Thompson, W.J.; Ball, R.G.; Darke, P.L.; Zugay, J.A.; Thies, J.E. *Tetrahedron Lett.*, **1992**, *33*, 2957; Baker, W.R.; Condon, S.L. *Tetrahedron Lett.*, **1992**, 33, 1581; Poss, M.A.; Reid, J.A. *Tetrahedron Lett.*, **1992**, *33*, 1411.
45. Villa, J.L., U.S. Patent 3725337 (cl.260145.8R; C08g) 1973, *Chem. Abstr.*, **1973**, *79*, 19734v.
46. Owsley, P.C.; Helmkamp, G.K.; Rettig, F.M. *J. Amer. Chem. Soc.*, **1969**, *91*, 5239; Bakker, S.; Kellog, R.M.; Raynolds, P.; Zonnebelk, S. *J. Amer. Chem. Soc.*, **1974**, *96*, 3146.
47. Csizmadia, V.M.; Schmid, G.H.; Mezey, P.G.; Csizmadia, I.G. *J. Chem. Soc., Perkin Trans. II*, **1977**, 1019.
48. Carretero, J.C.; Garcia Ruano, J.L.; Rodriguez, J.H. *Tetrahedron Lett.*, **1987**, *28*, 4593.
49. Trost, B.M.; Shibata, T. *J. Am. Chem. Soc.*, **1982**, *104*, 3225; Trost, B.M.; Shibata, T.; Martin, S.J. *J. Am. Chem. Soc.*, **1982**, *104*, 3228; see also: Caserio, M.C.; Kim, J.K., *J. Am. Chem. Soc.*, **1982**, *104*, 3231.
50. Liu, Q.; Wilson, R.J.; Rayner, C.M., unpublished results.
51. Milton, J.; Brand, S.; Jones, M.F.; Rayner, C.M. *Tetrahedron Asymmetry*, **1995**, *6*, 1903; *idem, Tetrahedron Lett.*, **1995**, *36*, 6961; Brand, S.; Jones, M.F.; Rayner, C.M. *Tetrahedron Lett.* **1995**, *36*, 8493; Brand, S.; Fletcher, S.J.; Jones, M.F.; Rayner, C.M., unpublished results.
52. Carson, K.G.; Ganem, B. *Tetrahedron Lett.*, **1994**, *35*, 2659.
53. Procter, D.J.; Rayner, C.M. *Tetrahedron Lett.*, **1994**, *35*, 1449; Procter, D.J.; Lovell, S.J.; Rayner, C.M. *Synlett*, **1994**, 204; Procter, D.J.; Thornton-Pett, M.; Rayner, C.M. *Tetrahedron*, in press.
54. Pickersgill, I.F.; Marchington, A.P.; Rayner, C.M. *J. Chem. Soc., Chem. Commun.*, **1994**, 2597; Pickersgill, I.F.; Marchington, A.P.; Thornton-Pett, M.; Rayner, C.M. *J. Chem. Soc., Chem. Commun.*, **1995**, 647.
55. Westwell, A.D.; Forristal, I.; Lawson, K.R.; Rayner, C.M., unpublished results.