N-Heterocycle construction *via* cyclic sulfamidates. Applications in synthesis

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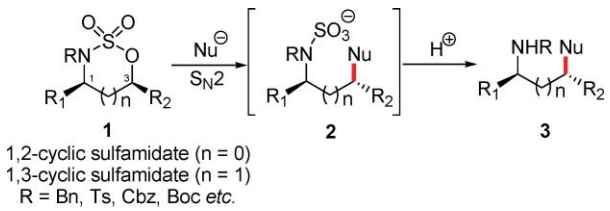
When combined with an appropriate nucleophilic component, 1,2- and 1,3-cyclic sulfamidates function as versatile precursors to a range of substituted and enantiopure heterocyclic classes. Functionalised enolates provide a direct entry to *C*-3 functionalised lactams, as exemplified by total syntheses of (−)-aphanorphine, (+)-laccarin and (−)-paroxetine. Heteroatom nucleophiles, such as thiol esters, amino esters and bromo phenols, provide concise access to a range of enantiomerically pure thiomorpholine, piperazine and benzofused heterocyclic scaffolds. The latter methodology enables a facile synthesis of the antibacteriocidal agent levofloxacin.

Introduction

Cyclic sulfamidates **1** comprise a category of synthetically versatile electrophiles that are accessible *via* readily available (and enantiomerically pure) 1,2- and 1,3-amino alcohols. Nucleophilic attack occurs almost exclusively at the oxygen-bearing carbon in a stereospecific manner (S_N2) to deliver an *N*-sulfate intermediate **2**, which may then be hydrolysed under either protic (HCl, H_2SO_4, NaH_2PO_4)[1] or Lewis acidic (BF_3/thiol or *N*-hydroxysuccinimide)[2] conditions to afford the final product **3** (Scheme 1).



Scheme 1

The reactivity profile of 1,2- and 1,3-cyclic sulfamidates (n = 0, 1) corresponds to that associated with activated aziridines and azetidines, respectively, but with several important advantages.[3] In contrast to aziridines and azetidines, the activation of cyclic sulfamidates towards nucleophilic displacement is not largely derived from ring strain, and so useful levels of reactivity are retained when moving from 5- to 6-ring systems (*cf.* aziridine → azetidine reactivity). Furthermore, cyclic sulfamidates allow flexibility with regard to the protecting group employed on nitrogen. For example, whereas aziridines often require highly activating protecting groups (such as *N*-tosyl or *N*-P(O)Ph_2), a variety of nitrogen substituents can be tolerated on cyclic sulfamidates (*e.g.* Boc, Cbz, Ts, Me, Bn)[4] with only relatively

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John F. Bower

John F. Bower was born in 1980 in Chester and obtained his MSci degree in Chemistry in 2003 from the University of Bristol. He then remained at Bristol to study for his PhD degree (2007) under the guidance of Tim Gallagher. During this time his research focused on the development of cyclic sulfamidate-based N-heterocyclic methodologies and their application to synthesis. His first postdoctoral appointment (2007–2008) was a very productive period with Prof. Michael Krische at the University of Texas, and John is currently a postdoctoral associate with Prof. Timothy Donohoe at the University of Oxford.

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small effects upon their susceptibility to nucleophilic cleavage. Perhaps the most useful reactivity trait of cyclic sulfamidates, when compared to their azacycle counterparts, is that the regioselectivity of nucleophilic attack is clear cut, occurring preferentially at the oxygen-bearing carbon, and attack at *C*-1 is not generally observed.

For the above reasons, there has been considerable interest in the synthesis and application of cyclic sulfamidates to a variety of diverse research areas. Much of these efforts have previously been summarised in an extensive and comprehensive review published by Meléndez and Lubell in 2003.[5] Our focus has been upon the exploitation of the cyclic sulfamidate reactivity profile for the synthesis of a diverse array of *N*-heterocyclic architectures. Accordingly, we have developed a number of efficient methodologies which have, in turn, been applied to syntheses of several therapeutically important targets, including current drugs and natural products. This Perspective gives an overview of our activities in this area with an emphasis on the application of these methods in target-directed synthesis.

Synthesis of cyclic sulfamidates

Before considering the heterocyclic methodologies available *via* cyclic sulfamidates, it is pertinent to briefly review the methods available for their synthesis, including relative merits and disadvantages, so as the reader can fully appreciate the substrate availability for the subsequent methodology discussion. This is all outlined under a series of headings (A–E) within Scheme 2 and serves as an update to the 2003 review.[5]

A. From 1,2- or 1,3-amino alcohols

As cyclic sulfamidates are generally considered to be amino alcohol derivatives, it is unsurprising that the most direct synthetic routes to these electrophiles involve the treatment of an amino alcohol with a reagent which can directly install the -SO_2- moiety. Approaches based upon the use of sulfuryl chloride or sulfuryl diimidazole have been successful, but only in cases involving conformationally constrained 1,2-amino alcohols, such as prolinol and amino sugar variants.[6,7] Problems with this approach arise due to competitive chlorination (for SO_2Cl_2),[8] aziridination,[9] and also, presumably, polymerisation. For these reasons, amino alcohols are generally converted to cyclic sulfamidates using a two-step approach, which proceeds *via* an intermediate cyclic sulfamidite (in an analogous manner to that employed for the synthesis of cyclic sulfates).[10] Specifically, treatment of 1,2- or 1,3-amino alcohols with $SOCl_2$,[11] in the presence of imidazole as a nucleophilic catalyst,[12] promotes the highly efficient formation of 1,2- and 1,3-cyclic sulfamidites as a mixture of epimers at sulfur.[13,14] Several methods have been investigated for the oxidation of cyclic sulfamidites, such as *m*-CPBA[6b] and $KMnO_4$,[15] but the most efficient systems utilise either catalytic RuO_4 or $RuCl_3$ and $NaIO_4$ in aqueous solvent, affording the sulfamidate products in typically greater than 80% yield. The employment of both imidazole and Et_3N in the cyclic sulfamidite formation step necessitates the isolation of this species prior to oxidation as both of these reagents inhibit ruthenium oxidants.[16] The requirement for such vigorous oxidation conditions necessarily precludes the presence of certain functionalities which are sensitive to oxidation (*e.g.* alkenes) on cyclic sulfamidates synthesised in this manner.

B. From 1,2-diols or epoxides

Nicolaou and co-workers have shown that the Burgess reagent can be used to form 1,2-cyclic sulfamidates from the corresponding 1,2-diols *via* a double alcohol activation mechanism.[4b,17] This method is notable in that it allows the direct conversion of 1,2-diols, which are often available in an enantioenriched form,[18] to electrophiles, which are then suitable for a range of downstream transformations. One limitation of the chemistry is that the regioselectivity of the process is dependent upon the stereoelectronic preferences of the substrate involved, although in many cases excellent selectivities are obtained.[6b,17] A range of readily available modified Burgess-type reagents allow access to different classes of *N*-carbamate-protected cyclic sulfamidates. A related method has also been developed by Nicolaou to enable the conversion of allylic alcohol-derived epoxides to either 5- or 6-ring cyclic sulfamidates (substrate dependant).[17b] Additionally, Hudlicky *et al.* have reported the use of the Burgess reagent for the direct conversion of simple epoxides to the corresponding 5-ring cyclic sulfamidates, albeit in generally modest yields.[19]

C. *Via* metal-catalysed nitrene insertion

Building upon early work by Breslow and Gellman,[20] Che *et al.* demonstrated that general ***inter***molecular amidation of saturated C–H bonds is possible *via* Ru- or Mn-catalysed nitrene insertion of iminoiodanes prepared *in situ*,[21] and subsequently applied these conditions ***intra***molecularly to the asymmetric synthesis of cyclic sulfamidates.[22] In concurrent work, Du Bois *et al.* reported a related Rh-catalysed protocol.[23] The sulfamate ester precursors are readily prepared by treatment of chlorosulfonyl isocyanate with formic acid (to form H_2NSO_2Cl) and then the appropriate alcohol. Cyclisation selectively forms 6-ring cyclic sulfamidates, but in cases where this is not possible, 1,2-cyclic sulfamidates are generated.[23e] Yields are good to excellent and

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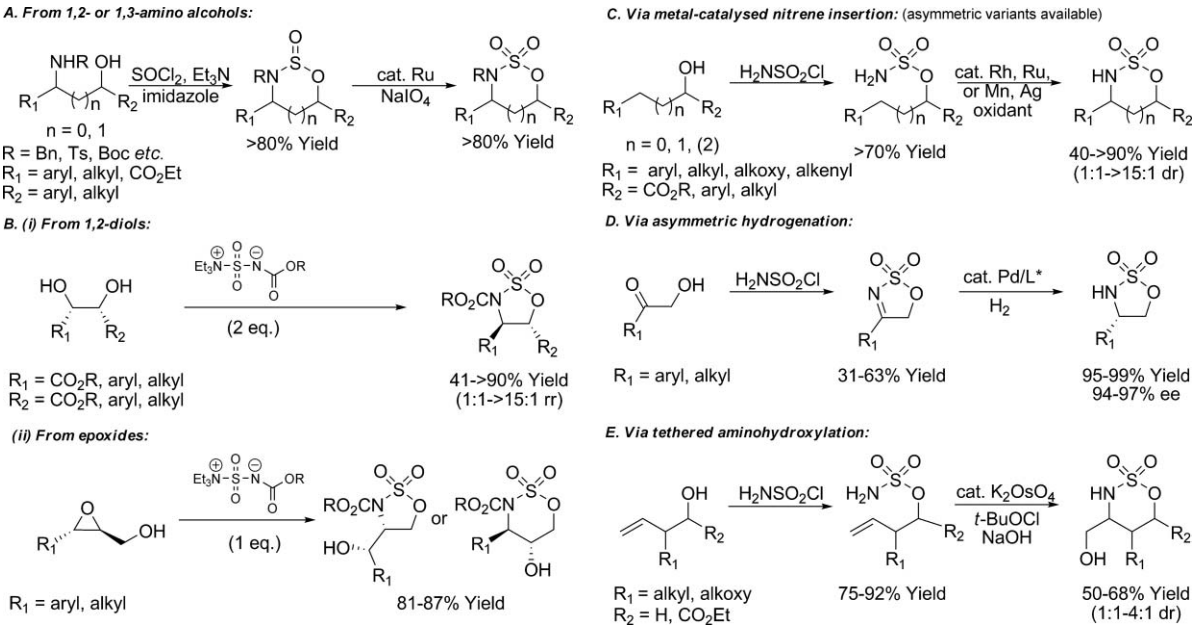


Scheme 2 Methods available for the synthesis of cyclic sulfamidates.

often provide products in high diastereoselectivity,[23b] and Du Bois has developed a particularly robust and general Rh-catalyst which is now commercially available.[24] C–H insertion into ethereal C–H bonds provides *N*,*O*-acetals which can be further functionalised *via* the corresponding iminium ion.[25] Silver-catalysed protocols have also been reported.[26]

Related Cu-, Rh- and Au-catalysed methods allow the formation of 7-ring cyclic sulfamidates where the nitrogen is part of an aziridine ring system.[27] 7-Ring cyclic sulfamidate formation can also be achieved in stereoelectronically predisposed cases[23e] or *via* metallo-nitrene/alkyne metathesis cascades.[28]

To date, a *general* asymmetric variant of these insertion approaches has not been realised. Che *et al.* have reported a chiral Ru-porphyrin complex which achieves moderate to good enantioselectivities (77–88% ee) in cases involving benzylic C–H insertion.[22a] Processes employing chiral manganese[29] and rhodium[30a,b] catalysts have been reported, but the enantioselectivites observed in these cases were low (0–55% ee). Rh-carboxamidate[30c] and Ru-PyBox[31] catalyst systems have recently been developed for efficient asymmetric nitrene insertion into benzylic and allylic C–H bonds. This represents a very significant simplification of the catalyst structure which, in turn, makes this chemistry much easier to apply.

D. *Via* asymmetric hydrogenation

Recently Zhou *et al.* reported a method for accessing enantioenriched 1,2-cyclic sulfamidates by asymmetric hydrogenation of an imine precursor.[32] Treatment of a variety of aryl- and alkyl-substituted α-hydroxyketones with sulfamoyl chloride (H_2NSO_2Cl) resulted in the formation of the corresponding cyclic imines after acid-promoted condensation. Hydrogenation of these species using a Pd-catalyst modified with f-binaphane, a chiral ferrocene-derived *bis*-phosphine, afforded the corresponding *N*-unsubstituted cyclic sulfamidates in near quantitative yields, and with excellent levels of asymmetric induction. This method is limited to the synthesis of 1,2-cyclic sulfamidates with substituents at the nitrogen-bearing carbon only.

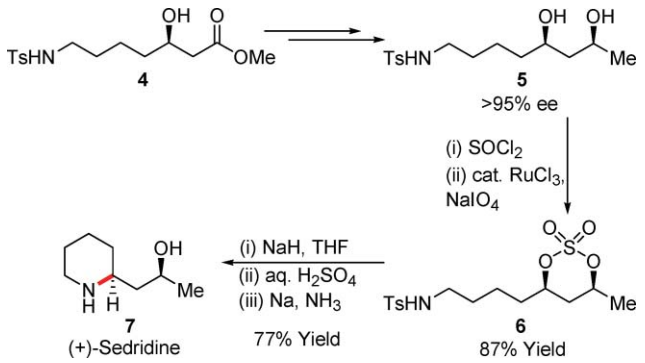
E. *Via* tethered aminohydroxylation

Kenworthy and Taylor have utilised a tethered aminohydroxylation reaction of homoallylic sulfamate esters to provide 6-ring cyclic sulfamidates possessing pendant alcohols.[33] The conditions employed are an adaptation of those used by Donohoe in the corresponding tethered aminohydroxylation of allylic carbamates.[34] This method has not been extensively investigated and presently only provides modest yields of the target products.

Emergence of a cyclic sulfamidate based *N*-heterocyclic strategy

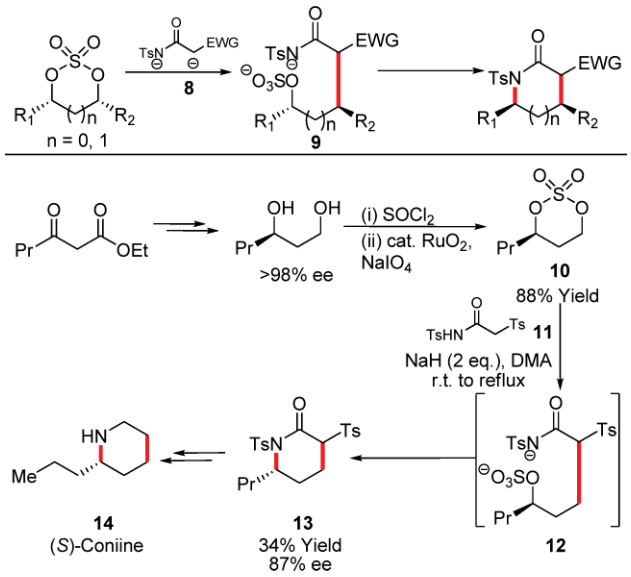
In earlier work we reported a method for pyrrolidine and piperidine construction based upon the generation and subsequent intramolecular opening of 1,3-cyclic sulfates.[35] This chemistry enabled a concise entry to (+)-sedridine, an alkaloid originally isolated from *Sedum acre* (Scheme 3). Here, asymmetric hydrogenation of the corresponding β-ketoester affords alcohol **4** in high enantiopurity, which is then advanced to diol **5** over a 4 step sequence. Formation of the 1,3-cyclic sulfate **6** and subsequent treatment with NaH achieves efficient *N*-heterocyclisation to ultimately provide (+)-sedridine **7** after *N*-deprotection.

Extension of this approach results in a [3+3] annulation protocol for the construction of piperidines by exploiting the *bis*-electrophilic nature of cyclic sulfates.[36] Specifically, dianions of type **8** react with 1,3-cyclic sulfates *via* a sequence wherein C–C bond formation precedes C–N bond formation *via* the intermediacy of *O*-sulfate **9**. The synthetic value of this chemistry was demonstrated by its application to an asymmetric synthesis of the hemlock alkaloid (*S*)-coniine **14**. Treatment of enantiopure



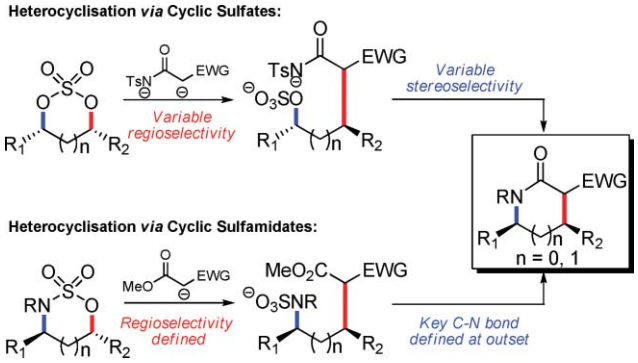
Scheme 3

cyclic sulfate **10** with the dianion derived from **11** results in *C*-alkylation, to deliver *O*-sulfate **12**, which, upon heating, undergoes C–N bond formation to afford the target piperidinone **13** in 34% yield (Scheme 4).



Scheme 4 Intermolecular heterocycle formation *via* cyclic sulfates.

While potentially powerful, this chemistry suffers from limitations with regard to control of both regiochemistry and enantiopurity over the annulation sequence. As 1,3-cyclic sulfates are *bis*-electrophiles, the site of initial C–C bond formation (when employing non-symmetric electrophiles) is not clear cut, and in many cases would lead to mixtures of piperidinone regioisomers. Perhaps more significantly, the C–N bond forming event is neither efficient nor stereospecific, and some degradation of enantiopurity was observed. This is particularly evident in the coniine case where enantiopure (>98% ee) cyclic sulfate **10** delivers the target heterocycle **13** in only 87% ee. Although this issue was solved using a two-step Mitsunobu-based approach, a more elegant and concise solution involves switching to a 1,2- or 1,3-cyclic sulfamidate-based strategy (Scheme 5). Here both of these problematic issues are resolved as (a) the site of nucleophilic attack is defined by the nature of the electrophilic substrate (occurring at the oxygen-bearing carbon) and (b) the key C–N bond is already in place.



Scheme 5 Cyclic sulfates *vs.* cyclic sulfamidates for heteroannulation.

Heterocyclisation employing cyclic sulfamidates and enolate nucleophiles

Reactivity of cyclic sulfamidates towards enolate nucleophiles

Cyclic sulfamidates have been shown to react with certain carbon-based nucleophiles (organocuprates,[4c] RLi,[37] cyanide[38]) in moderate to good yields. Specific examples involving enolates as nucleophiles have also been described.[38] For example, Wei and Lubell have shown that a 1,2-cyclic sulfamidate derived from serine reacts with enolates both directly and *via* an elimination-addition sequence, which results in significant loss of enantiomeric purity.[1b] In a related, but sterically more demanding, system, Boulton *et al.* reported that enolates and silyl enol ethers failed to react.[38c] A 1,3-cyclic sulfamidate derived from homoserine did, however, undergo direct nucleophilic cleavage with a stabilised enolate in modest yield.[39] More basic nucleophiles are also effective, for example lithiated diisopropylmethylphosphonate reacts with primary 1,2-cyclic sulfamidates in good yield.[40] More recently, a range of 1,2-cyclic sulfamidates possessing primary electrophilic centres were shown to react efficiently with $PhSO_2CF_2Li$.[41]

Pyrrolidinones and piperidinones *via* 1,2- and 1,3-cyclic sulfamidates

Our initial studies focussed upon evaluating the opening of a representative range of sterically and electronically distinct 1,2- and 1,3-cyclic sulfamidates **15a–g** (Fig. 1) with malonate enolate to procure *C*-3 carboxylated lactams (Table 1).[42,43]

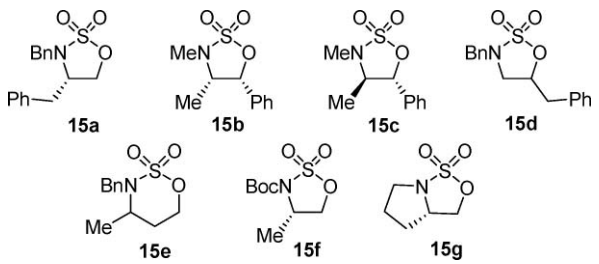
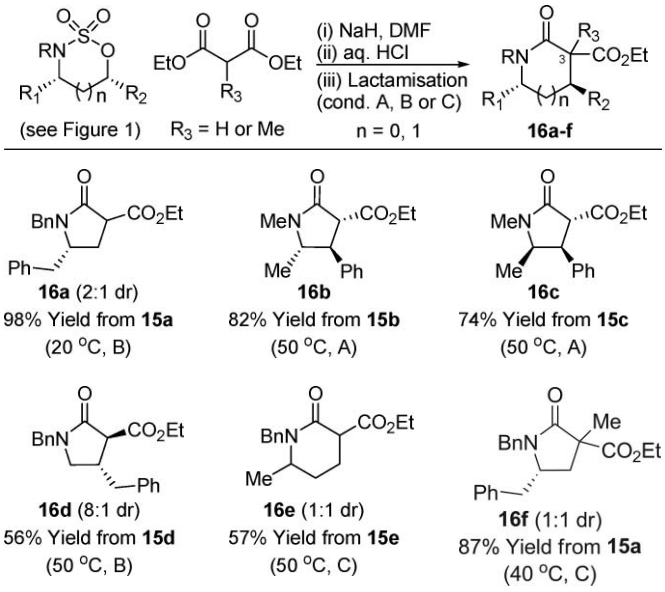


Fig. 1 Model substrates employed in methodology studies

Reaction of a range of cyclic sulfamidates with the sodium enolate of malonate in DMF was indeed successful in providing the target heterocyclic structures in good to excellent yields. These results demonstrate some very clear reactivity trends across the cyclic sulfamidate substrate range studied. Firstly, 6-ring

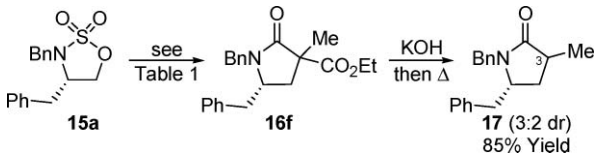
Table 1 Reactivity of cyclic sulfamidates to malonate enolates



Stage (i) reaction temperatures and stage (iii) lactamisation conditions are given in parentheses: Conditions A: spontaneous lactamisation; Conditions B: PhMe, reflux; Conditions C: NaOEt, EtOH, reflux.

cyclic sulfamidates (*e.g.* **15e**) are less reactive than their 5-ring counterparts (*e.g.* **15a,b**) as evidenced by the requirement for higher reaction temperatures and longer reaction times to effect C–O bond cleavage. Secondly, substitution (either alkyl or aryl) at the *O*-bearing carbon of the cyclic sulfamidate diminishes reactivity and necessitates elevated reaction temperatures relative to unsubstituted variants. Thirdly, the S_N2 nature of the ring cleavage event is evidenced by stereospecific formation of **16b** and **16c**; none of the alternative diastereomer was detected in either case. Fourthly, *N*-sulfate hydrolysis is readily and reliably achieved simply by addition of a small amount of aqueous HCl into the reaction medium after the initial C–C bond forming event is judged complete. Fifthly, lactamisations are case dependant: 6-ring cyclisation is slower than that observed for 5-ring formation, and for **16e** was best promoted under ethoxide mediated conditions. Indeed, for substrates possessing a higher degree of ring substitution (*e.g.* **16b** and **16c**) this occurs spontaneously upon neutralisation, in other instances, brief thermolysis of the crude alkylation product in PhMe is sufficient to promote clean lactam formation. Finally, stereochemical control at *C*-3 is observed in cases where the product embodies a neighbouring *C*-4 substituent (*i.e.* **16b–d**), presumably for thermodynamic reasons; in other cases, (**16a/e/f**) and as expected, no control is observed at this stereocentre.

Application of substituted malonate derivatives provides a convenient means of accessing *C*-3 alkylated lactams. For example, cyclic sulfamidate **15a** reacts efficiently with 2-methyl diethylmalonate to provide adduct **16f** after *N*-sulfate hydrolysis and thermal lactamisation. Base-promoted decarboxylation then provides the *C*-3 methylated variant **17** (Scheme 6). It is pertinent to note that our attempts to directly procure substrates such as **17** using simple alkyl enolates as the nucleophilic component



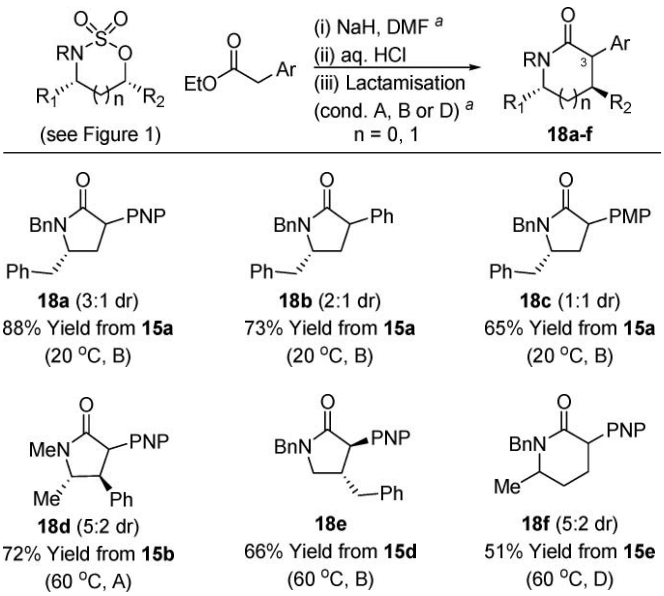
Scheme 6

(and thereby obviating the decarboxylation step) have failed. This suggests a reasonably narrow tolerance range with regard to enolate basicity *vs.* nucleophilicity.

One very attractive extension of this heteroannulation approach employs less classically stabilised aryl-substituted enolates as the nucleophilic component (Table 2).[42,43] This provides a direct method for the preparation of *C*-3 arylated lactams and also offers the opportunity to exercise kinetic control of the stereochemistry at *C*-3 of the lactam products. We have found that the anion of ethyl 4-nitrophenyl acetate reacts efficiently with a range of substrates to provide the corresponding α-arylated products **18a,d–f** in good to excellent yields. In the case of 6-ring variant **18f**, lactamisation was best achieved under cyanide (*i.e.* nucleophilic catalysis) mediated conditions. Other more electron-rich arenes also participate in this chemistry. This is exemplified using cyclic sulfamidate **15a**, where reaction with the anions of methyl phenyl acetate and methyl 4-methoxyphenyl acetate provides lactams **18b** and **18c** in 73% and 65% yield, respectively. Here, there is a trend towards diminished efficiency as the enolate component becomes more basic, but nevertheless efficient heteroannulation can be maintained.

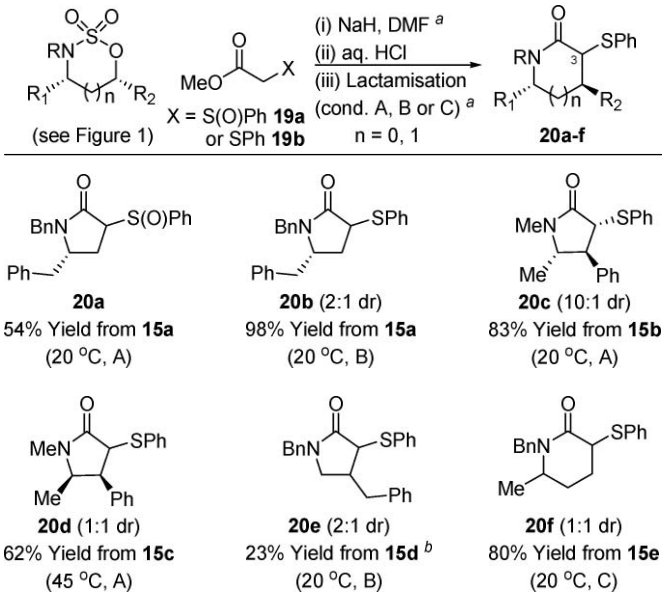
The ability to install directly substituents at the *C*-3 position of the lactam scaffold portends opportunities for developing general entries to other valuable lactam subclasses. A very useful class of chiral lactams is that consisting of 5- and 6-ring α,β-unsaturated variants for which very few general asymmetric entries exist.

Table 2 Reactivity of cyclic sulfamidates to aryl-stabilised enolates

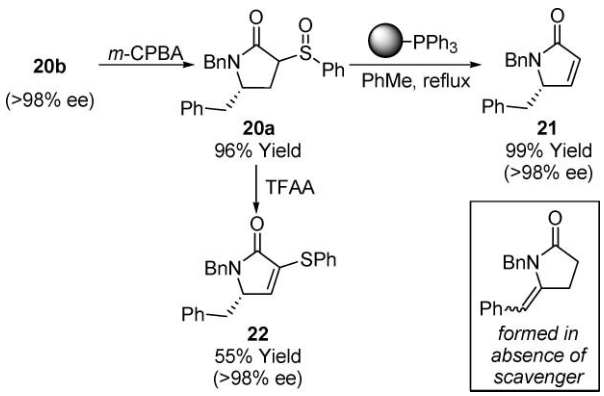


[a] See Table 1 footnotes; Conditions D: cat. NaCN, MeOH, reflux. PNP = *p*-nitrophenyl; PMP = *p*-methoxyphenyl.

Table 3 Reactivity of cyclic sulfamidates to sulfur-stabilised enolates



[a] See Table 1 footnotes. [b] *N*-Benzyl cinnamyl amine by-product was isolated in 37% yield (see text).

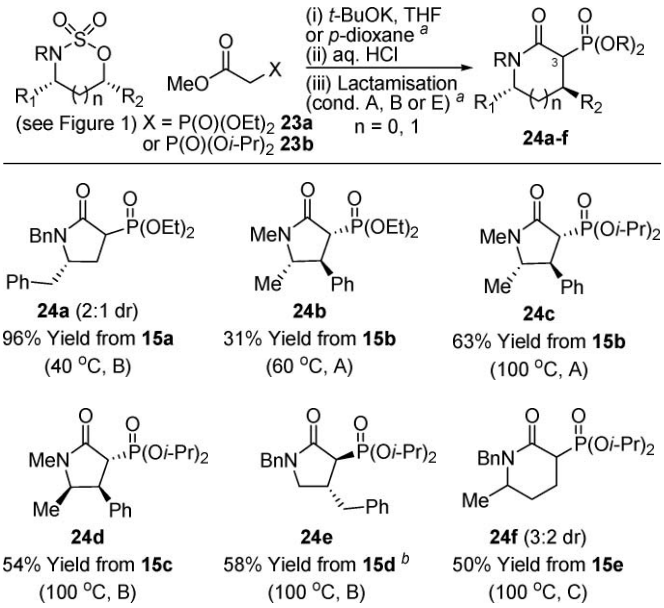


Scheme 7 Manipulation of α-sulfenyl lactam **20b**.

In our approach we are able to capitalise on the remarkably efficient nucleophilic cleavage suffered by cyclic sulfamidates in the presence of sulfur-stabilised enolates (Table 3 and Scheme 7).[44]

We began by examining the reaction of cyclic sulfamidate **15a** with α-sulfinyl-substituted nucleophile **19a**, which reacted at room temperature to provide lactam **20a** after *N*-sulfate hydrolysis and spontaneous lactamisation. Unfortunately, extension of this strategy to other, less reactive, cyclic sulfamidates was not possible, as the higher reaction temperatures required to effect C–O cleavage promoted competing (but premature) sulfoxide elimination[45] which always led to complex mixtures of products. As such, we reverted to the use of an α-phenylsulfenyl group (*i.e.* as in **19b**) on the enolate component. This was successful in providing a range of α-sulfenylated lactams **20b–f** in good to excellent yields. The increased basicity of this nucleophile is, however, evident in the case of **20e**, where a substantial amount of *N*-benzyl cinnamyl amine (the product of β-elimination from **15d**) was also formed.

Table 4 Reactivity of cyclic sulfamidates to phosphonate-stabilised enolates



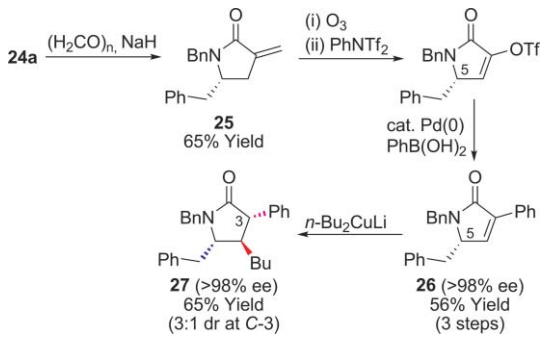
[a] See Table 1 footnotes; Conditions E: *p*-xylene, reflux. [b] *N*-Benzyl cinnamyl amine by-product was isolated in 7% yield.

Oxidation of α-sulfenylated lactams then either enables thermal sulfoxide elimination or Pummerer rearrangement to provide access to unsaturated lactams **21** and **22**, respectively. Thermal sulfoxide elimination to provide the corresponding unsaturated variant **21** presented a difficult challenge. Although phenyl sulfoxide elimination occurs readily at *approx.* 100 °C, complications arose as the sulfenic acid by-product caused scrambling of the double bond position to afford the isomeric enamine as the major product. A scavenger for the sulfenic acid was clearly necessary, but conventional basic additives (such as Na_2CO_3) were not suitable, as target **21** was highly susceptible to base-induced epimerisation at *C*-5. We found that polymer-bound PPh_3 provided a convenient and efficient solution to this problem, enabling access to alkene **21** in 93% overall yield (from **15a**) and, importantly, with no detectable level of epimerisation.[46] These conditions were generally applicable to other substrates studied. Pummerer rearrangement to afford vinyl sulfides, such as **22**, was more facile and proceeded without any erosion of the integrity of the *C*-5 stereochemistry (Scheme 7).

The corresponding exocyclic α,β-unsaturated lactams provide another particularly attractive class of heterocyclic scaffold. Here, synthetic access is achieved by reaction of a cyclic sulfamidate with a phosphonate-stabilised enolate (Table 4).[42,47] The resulting α-phosphono lactams **24a–f** are then amenable to double bond installation *via* Wadsworth–Emmons olefination.[48] While cyclic sulfamidate **15a** reacted efficiently with the enolate of triethyl phosphonoacetate **23a** (to provide lactam **24a** in essentially quantitative yield), other less reactive substrates (*e.g.* conversion of **15b** to **24b**) were not tolerant of these conditions. Specifically, we found that the elevated temperatures required to achieve C–O bond cleavage in these cases led to competitive decomposition

of the enolate component, presumably *via* nucleophilic attack at phosphorus.[49] A somewhat counterintuitive solution involved switching to a more hindered diisopropyl variant **23b** as the nucleophilic component. Here, nucleophilic attack at phosphorus is suppressed and coupling with a range of cyclic sulfamidates is achievable to provide the corresponding α-phosphonolated targets **24c–f** in good yield.

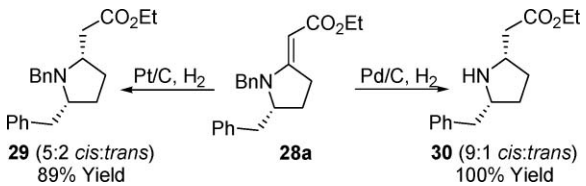
Both diethyl- and diisopropylphosphono lactams function as suitable precursors for Wadsworth–Emmons reactions with a range of aldehydes and ketones. Levels of diastereocontrol depend on both the substitution pattern of the phosphono lactam and the nature of the alkoxy groups at phosphorus. It should be noted that the corresponding products represent particularly versatile building blocks for diversity-oriented synthesis. This is exemplified by the conversion of **24a** to **27** using a sequence of ozonolysis, triflation, Suzuki coupling[50] (to afford **26**) and cuprate 1,4-addition. Notably, no erosion of the sensitive *C*-5 stereochemistry is observed and trisubstituted lactam **27** is accessible in >98% ee, thereby enabling the modular introduction of substituents at all ring positions (Scheme 8).



Scheme 8

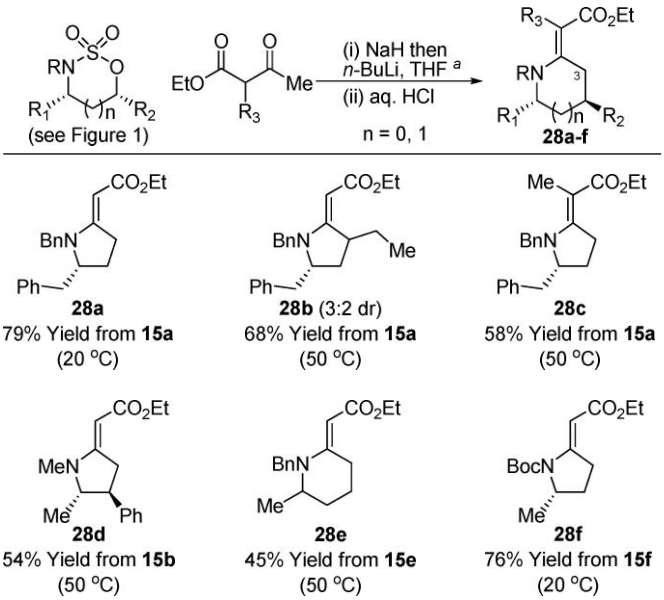
Alkylidene pyrrolidines and piperidines *via* cyclic sulfamidates

In the work discussed so far, nucleophilic cleavage of the cyclic sulfamidate has been followed by *N*-sulfate hydrolysis and then heterocyclisation *via* lactamisation. In order to develop a versatile strategy for the synthesis of alkylidene pyrrolidines and piperidines, we investigated the opening of cyclic sulfamidates with the dianion of ethyl acetoacetate and related nucleophiles (Table 5).[51,52] Here, nucleophilic cleavage occurs with moderate ease across a range of substrates. *N*-Sulfate hydrolysis is followed by facile condensation onto the intermediate ketone to provide the targets **28a–f** in moderate to excellent yield. Of note is the versatility of this strategy, which enables facile variation of the *N*-protecting group and the introduction of substituents at all ring positions. Reduction of the products provides an easy entry to substituted homoprolines (*e.g.* **29** and **30**; Scheme 9) and homopipecolinic acid derivatives (*via* reduction of **28e**).[53]



Scheme 9 Reductive manipulation of **28a**.

Table 5 Alkylidene pyrrolidines and piperidines *via* cyclic sulfamidates



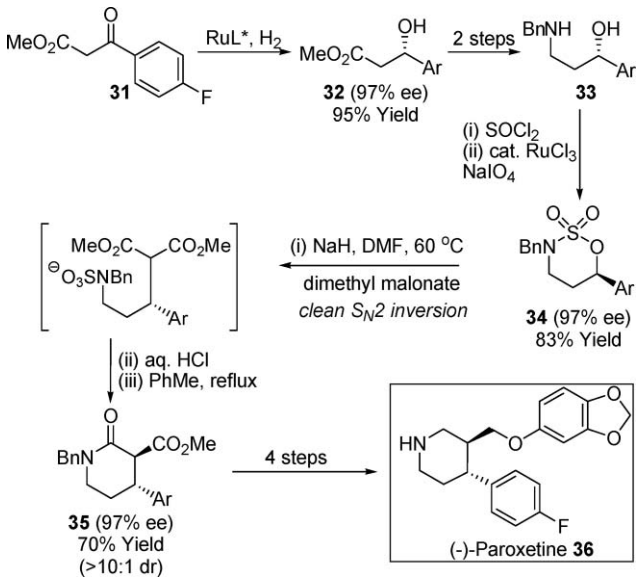
[a] See Table 1 footnotes.

Assessing stereochemical fidelity: S_N2 cleavage of 1,3-cyclic sulfamidates

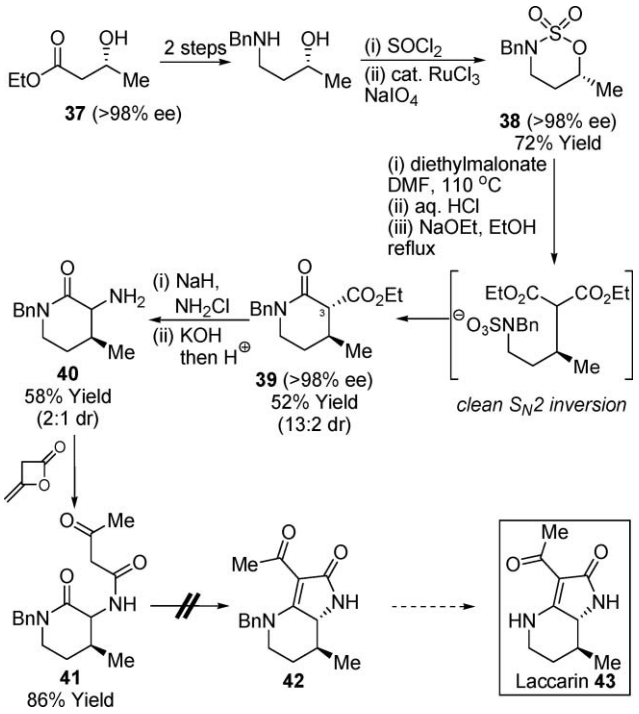
Piperidines represent a privileged therapeutic heterocyclic class.[54] In this regard, synthetic access to enantiopure 3,4-disubstituted piperidines represents a particularly challenging task. Our approach relies upon the stereospecific cleavage of *C*-3 substituted 1,3-cyclic sulfamidates with synthetically valuable *enolate* nucleophiles to ultimately provide *trans*-3,4-disubstituted lactams.[55] Prior to this work, diastereoselective cleavage of 1,3-cyclic sulfamidates with *heteroatom* nucleophiles had been reported, but these reactions were subject to internal stereocontrol mechanisms.[23a] We chose to evaluate this specific aspect of the methodology by focussing on the synthesis of two biologically and structurally interesting 3,4-disubstituted piperidine targets, the anti-depressant (–)-paroxetine[56] and the fungal-derived alkaloid (+)-laccarin.[57] Here, the strategy to both compounds involves the cleavage of either a *C*-3-*aryl*- or *C*-3-*alkyl*-substituted 1,3-cyclic sulfamidate with an enolate nucleophile.

Our route to paroxetine, which proceeds in 24% overall yield, is shown in Scheme 10. Asymmetric hydrogenation of β-ketoester **31** affords alcohol **32** in excellent yield and enantiopurity.[58] This intermediate is then converted to amino alcohol **33** over two steps. Treatment with $SOCl_2$ followed by Ru-catalysed oxidation affords cyclic sulfamidate **34** (97% ee) in short order and good overall yield. Treatment of this species with the anion of malonate, followed by *N*-sulfate hydrolysis and thermally promoted lactamisation delivers the target 3,4-disubstituted piperidinone **35** in excellent yield and with no detectable loss of enantiopurity, thereby demonstrating clean S_N2 cleavage of the *C*-3-*arylated* 1,3-cyclic sulfamidate. Conversion of intermediate **35** to (–)-paroxetine **36** is then readily achieved.

(+)-Laccarin **43** is a fungal metabolite which was first isolated in 1996 from *Laccaria vinaceoavellanea*;[57] prior to our work no



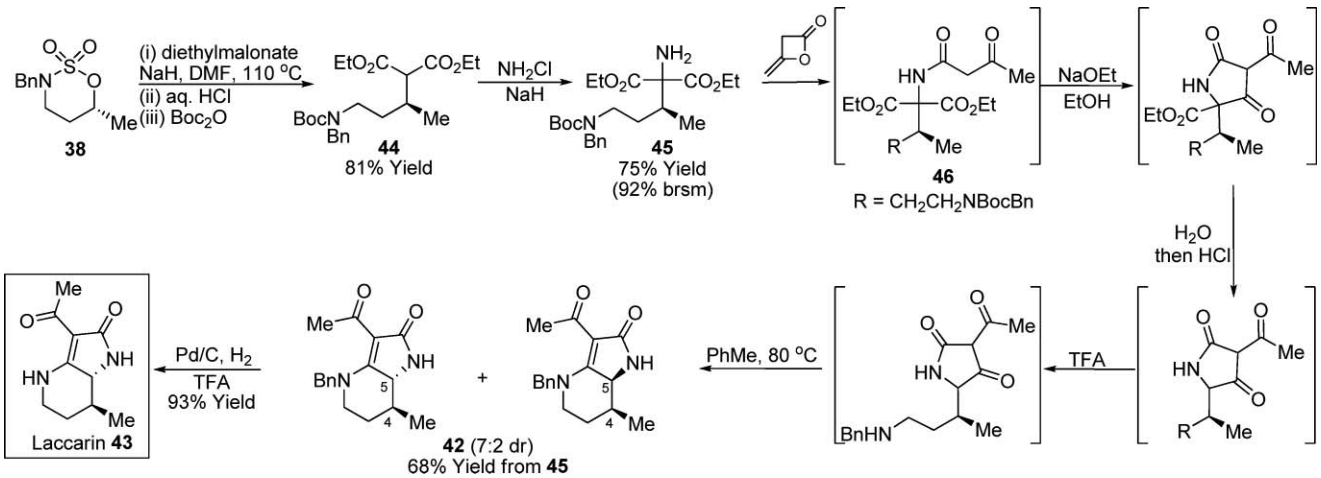
Scheme 10 Synthesis of (−)-paroxetine.



Scheme 11 Claisen condensation approach to (+)-laccarin.

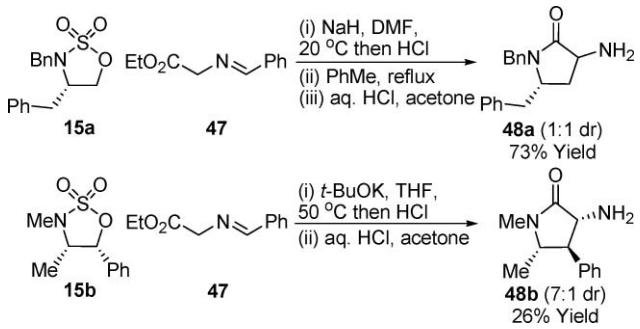
total synthesis of laccarin had been reported, and the absolute configuration of **43** remained unknown. Our approach to the 3,4-disubstituted piperidine core of **43** is analogous to that employed for (−)-paroxetine. Here (Scheme 11), cyclic sulfamidate **38** (>98% ee) is readily synthesised from commercially available alcohol **37**. Displacement of this species with the anion of malonate, followed by *N*-sulfate hydrolysis and (slow) thermally promoted lactamisation, delivers the target piperidinone **39** in moderate yield; importantly, no erosion of enantiopurity was observed, thereby demonstrating clean S_N2 cleavage of, in this case, a *C*-3-*alkylated* 1,3-cyclic sulfamidate. Dowd amination of the piperidinone adduct **39** with freshly generated monochloramine[59] followed by decarboxylation (to provide **40**) and treatment with diketene affords adduct **41** in 50% overall yield. Our plan was to promote a Claisen-type condensation to provide the bicyclic core (**42**) of laccarin, but this proved problematic despite extensive investigation.

To solve this, a step reordering was undertaken (Scheme 12). Thus, upon cleavage and subsequent *N*-sulfate hydrolysis of the cyclic sulfamidate **38**, immediate trapping of the intermediate amine as its *N*-Boc derivative (6-ring lactamisation is slow) afforded adduct **44** in good overall yield. Amination of this species (to give **45**) followed by treatment with diketene afforded **46**, which was cyclised under base-mediated conditions. Subsequent decarboxylation (by addition of water and then acid to the reaction medium), *N*-Boc hydrolysis and condensation provided *N*-benzyl laccarin **42** along with the corresponding *C*-5-epimer; despite extensive experimentation we were unable to convert the minor (and undesired) *C*-5-epimer to laccarin. The whole sequence (from **45**) was conducted efficiently without isolation of any of the intermediates and *N*-debenzylation of **42** provided (+)-laccarin **43** (in 18% overall yield), the optical rotation and CD data of which were in full agreement with that reported for the natural product.



Scheme 12 Completion of the synthesis of (+)-laccarin.

It should be noted that direct cleavage of cyclic sulfamidates, such as **38**, with glycine-derived enolates would lead directly to *C*-3 aminated lactams and thereby obviate the need to perform separate amination and decarboxylation steps (*cf* **39** to **40**). This has been achieved using the Stork glycine enolate equivalent **47**,[60] but this chemistry is only efficient for more reactive substrates (*e.g.* **15a** to **48a**) and was not as tolerant of more demanding cyclic sulfamidates such as **15b** (Scheme 13).[43,61]



Scheme 13 Direct synthesis of α-amino lactams.

(–)-Aphanorphine: evaluating cyclic sulfamidate-based routes

(–)-Aphanorphine **49** was isolated from the freshwater blue-green alga *Aphanizomenon flos-aquae* and is remarkable in its structural resemblance to benzomorphan analgesics such as pentazocine **50** and eptazocine **51** (Fig. 2).[62,63] Our synthesis of (–)-aphanorphine provides a particularly striking demonstration of the versatility of the cyclic sulfamidate heterocyclisation strategy. Here, we were able to rapidly synthesise and evaluate three distinct lactam precursors to the 3-benzazepine core of the natural product.[64,65]

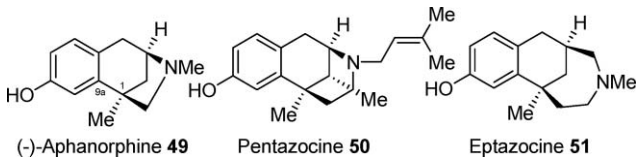
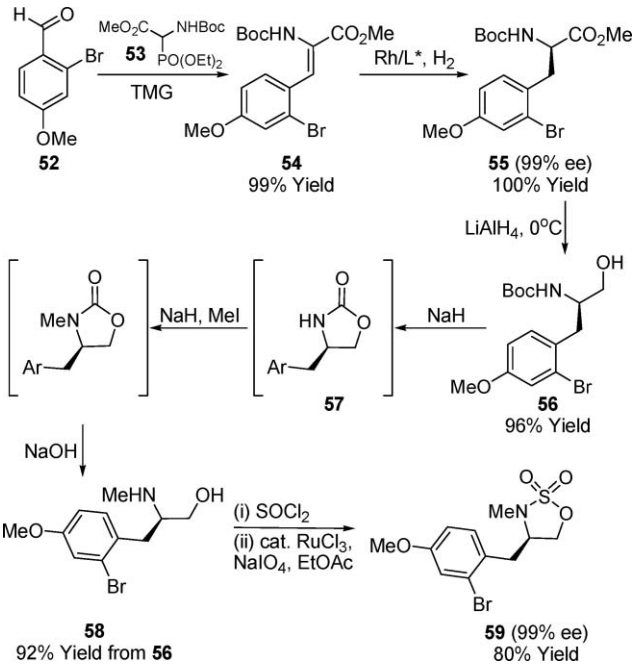


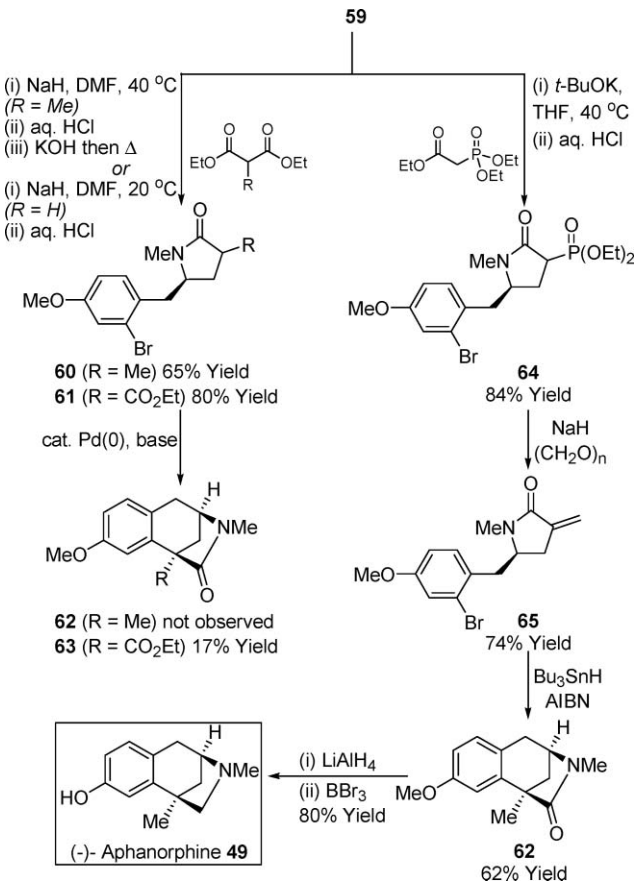
Fig. 2

Our synthesis of **49** commenced with constructing the appropriate 1,2-cyclic sulfamidate **59** in asymmetric fashion (Scheme 14). Reaction of *o*-bromoanisaldehyde **52** with **53** (with tetramethylguanidine, TMG) provided dehydroamino ester **54**, which underwent smooth asymmetric hydrogenation to deliver amino ester **55**.[66] Direct reduction of both the ester and *N*-Boc group of this species to amino alcohol **58** was not possible due to competing reductive debromination. Instead, and by exploiting the proximity (and under-appreciated reactivity) of the *N*-Boc residue, low temperature chemoselective ester reduction (to **56**) was followed by a one-pot procedure involving conversion of the resulting alcohol to cyclic carbamate **57**, *in situ N*-methylation, and then carbamate hydrolysis to afford amino alcohol **58** in excellent yield. Conversion to the cyclic sulfamidate **59** was then achieved *via* the corresponding cyclic sulfamidite. Here, the presence of an oxidatively sensitive *p*-methoxybenzyl group necessitated the use of EtOAc[6a] (rather than MeCN) as the co-solvent for the Ru-catalysed oxidation step.



Scheme 14 Synthesis of cyclic sulfamidate **59**.

With cyclic sulfamidate **59** in hand, a range of cyclisation precursors were readily synthesised and investigated (Scheme 15). We initially chose to evaluate Pd-catalysed cyclisation protocols.



Scheme 15 Completion of the synthesis of (–)-aphanorphine **49**.

The most obvious approach to achieve cyclisation involved Pd-catalysed enolate α-arylation of α-methylated lactam **60**, which was readily synthesised by reaction of cyclic sulfamidate **59** with methyl diethylmalonate and subsequent base-mediated decarboxylation of the resultant lactam.[67] Unfortunately, under a range of Pd-catalysed conditions, ***only*** reductive debromination of the aryl halide was observed. As more stabilised enolates are generally better coupling partners for this kind of reaction, attention turned to α-ester lactam **61** as a substrate for Pd-catalysed arylation. Although arylation to give **63** occurred, this was low yielding due to competing debromination and decarboxylation as a consequence of the high temperatures required.

A more robust approach involves reductive Heck cyclisation onto *exo*-alkene **65**.[68] This species was available *via* reaction of cyclic sulfamidate **59** with triethyl phosphonoacetate (to afford phosphonate **64**) and subsequent Wadsworth–Emmons olefination with formaldehyde. Unfortunately, under Pd-catalysed conditions, only debromination and double bond isomerisation were observed. Ultimately, the failure of Pd-catalysed cyclisation approaches prompted the evaluation of alternative protocols. Gratifyingly, treatment of alkene **65** with Bu_3SnH/AIBN promoted efficient cyclisation to afford **62** in 62% yield, along with lesser amounts of a formal 1,5-hydrogen atom abstraction product.[69] The conversion of **62** to (–)-aphanorphine **49** is readily achieved using known protocols.[63ac]

Heterocyclisation employing cyclic sulfamidates and heteroatom nucleophiles

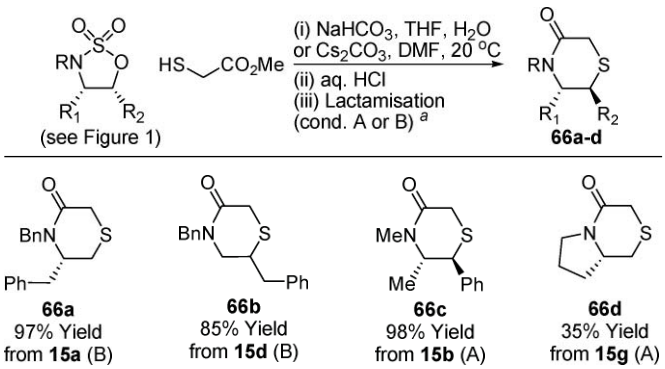
Reactivity of cyclic sulfamidates towards heteroatom nucleophiles

Although the bulk of our investigations have centred around combining enolate nucleophiles with cyclic sulfamidates, related strategies exploiting the more clearly defined reactivity profiles of heteroatom nucleophiles and 1,2-cyclic sulfamidates have also been explored. The reactivity of cyclic sulfamidates towards heteroatom nucleophiles has been extensively studied and reviewed.[5] Sulfur-based nucleophiles, such as thiols and thioacetate, react cleanly and efficiently, even in cases of cyclic sulfamidates possessing tertiary electrophilic centres.[70] Azides are also generally highly effective,[22a] although amines are often less efficient due to competing elimination processes.[38c] Perhaps the most problematic class of heteroatom nucleophiles are those based on oxygen (*e.g.* alcohols), which are often prone to detrimental side reactions due to competing elimination processes or nucleophilic attack at sulfur.[6a,71]

Thiomorpholinones and piperazinones *via* 1,2-cyclic sulfamidates

In early work, we demonstrated that reaction of 1,2-cyclic sulfamidates with thiols possessing a pendant ester group allows a sequence of nucleophilic ring cleavage, *N*-sulfate hydrolysis, and cyclisation to deliver substituted and enantioenriched thiomorpholinones **66a–d**.[72] This chemistry is relatively insensitive to the steric demands of the cyclic sulfamidate partner and substrates possessing both primary and secondary electrophilic centres uniformly provide the target thiomorpholinones in excellent yield. In the case of bicyclic prolinol-derived cyclic sulfamidate **15g**, this process was less efficient and afforded only 35% yield of the target bicycle. The reasons for the inefficiency of this reaction are unclear but were tentatively attributed to slow hydrolysis of the intermediate *N*-sulfate (Table 6).

Table 6 Thiomorpholinones *via* 1,2-cyclic sulfamidates

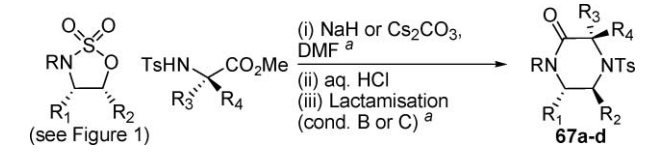


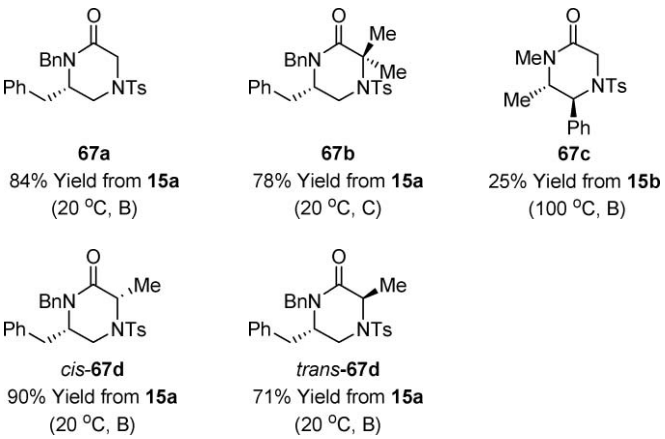
[a] See Table 1 footnotes.

Extension of this chemistry to the synthesis of piperazinones is also readily achieved using a range of *N*-tosyl amino ester nucleophiles.[72] Here, reaction efficiency is more sensitive to the structure of the cyclic sulfamidate. For example, while phenylalanine-derived cyclic sulfamidate **15a** reacts efficiently to provide the target **67a** in high yield, ephedrine-derivative **15b**, which possesses a secondary electrophilic centre, is less efficient, possibly due to competing elimination processes, and adduct **67c** was isolated in only 25% yield. Primary amine nucleophiles are not suitable for this chemistry because, in these cases, facile double *N*-alkylation was observed. It is, however, notable that this approach accommodates nucleophiles possessing epimerisable stereocentres as demonstrated by the diastereospecific synthesis of *cis*- and *trans*-**67d**; in these cases none of the other diastereomer was detected. More hindered nucleophiles can also be employed, although, in the case of **67b**, where thermal lactamisation was difficult, efficient cyclisation necessitated the use of base-mediated conditions (Table 7).

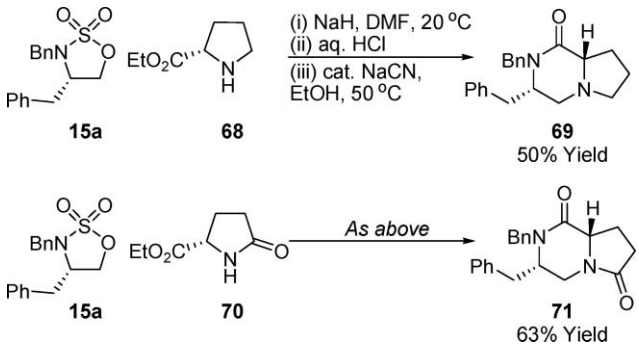
Bicyclic systems, of which praziquantel (the drug compound of choice in the control and treatment of schistosomiasis) is an example, can be constructed by employing different types of amino-based nucleophiles.[72] For example, cyclic sulfamidate **15a** reacted efficiently with proline ethyl ester **68** to afford adduct **69** in good overall yield.[73] Lactamisation of this species was investigated under a variety of conditions. Importantly, it was shown that base-mediated cyclisation was unsuitable because, and though still chemically efficient, epimerisation occurred to produce **69** as a 1 : 1 mixture of diastereomers. Although thermal lactamisation circumvented this epimerisation problem, cyclisation under these conditions was slow and lower yielding. A convenient solution to this issue employed nucleophilic catalysis using cyanide-catalysed conditions to deliver the adduct **69** in 50% yield and with no detectable epimerisation. Analogous problems were encountered when ethyl (*S*)-pyroglutamate **70** was employed as the nucleophilic component, but under cyanide-mediated cyclisation conditions no epimerisation of the product **71** was observed (Scheme 16).[74]

Table 7 Piperazinones *via* 1,2-cyclic sulfamidates





[a] See Table 1 footnotes.



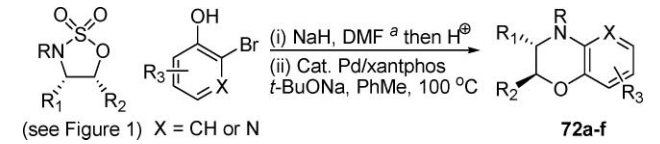
Scheme 16

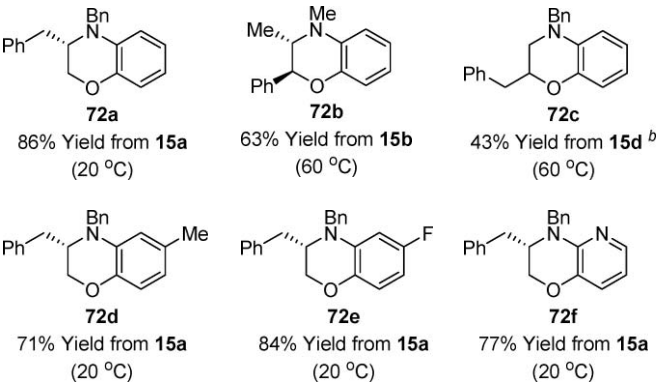
1,4-Benzoxazines and related benzofused heterocycles *via* cyclic sulfamidates

Cyclisation *via* Pd-catalysed C(sp^2)–N bond formation opens up further possibilities, and in this regard we have shown that the opening of cyclic sulfamidates with 2-bromophenol and related species allows a two-pot sequence of annulation, *N*-sulfate hydrolysis and Pd-catalysed amination to afford substituted and enantiopure benzoxazines (Table 8).[75] These compounds represent subunits of natural products and are also of medicinal value.[76]

A representative range of cyclic sulfamidates undergo smooth nucleophilic cleavage between r.t. and 60 °C with the sodium anion of 2-bromophenol and related nucleophiles, to deliver the corresponding adducts in high yield (60–99%) after *N*-sulfate hydrolysis.[77] Pd(0)-catalysed cyclisation is then efficiently promoted using a $Pd(OAc)_2$/xantphos/*t*-BuONa system.[78] Under these conditions, a range of 1,2-cyclic sulfamidates are converted to the target benzoxazines **72a–f** in good to excellent overall yields. It should be noted that the ring cleavage products derived from 1,3-cyclic sulfamidates (such as **15e**) did not cyclise under the conditions used, and only decomposition (including competing C–Br reduction) was observed, thereby reflecting the difficulty of 7-ring formation.[79]

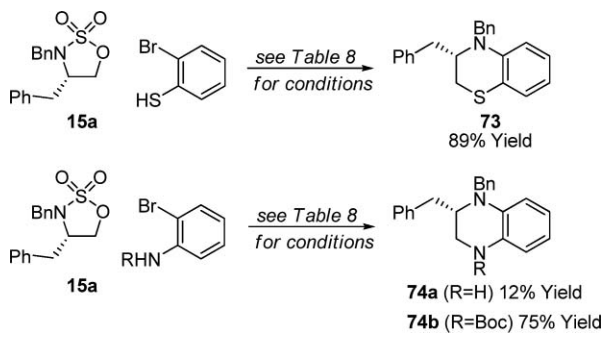
Table 8 1,4-Benzoxazines *via* 1,2-cyclic sulfamidates





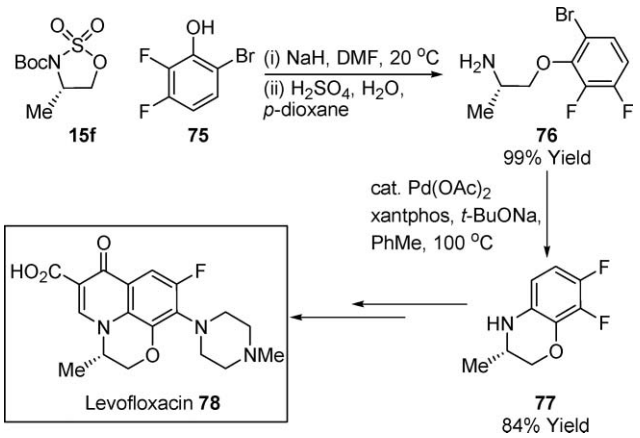
[a] See Table 1 footnotes. [b] *N*-Benzyl cinnamyl amine by-product was also isolated in 22% yield after the nucleophilic cleavage step.

Extension of this two step protocol also allows access to thio- and aza- variants **73** and **74** (Scheme 17). Opening of cyclic sulfamidate **15a** with 2-bromoaniline was not efficient, possibly due to competing elimination processes, and afforded the ring cleavage adduct in only 56% yield. Cyclisation of this species was also inefficient using this first generation approach, and quinoxaline **74a** was obtained in low overall yield. However, simply using the corresponding Boc-protected aniline provided the differentially protected quinoxaline **74b** in 75% overall yield using the same reaction sequence as outlined in Table 8.



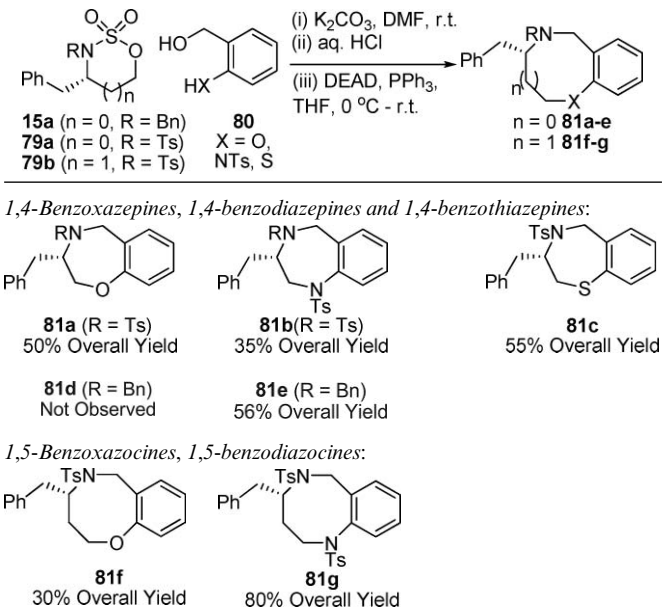
Scheme 17 Benzothiazines and quinoxalines *via* 1,2-cyclic sulfamidates.

(–)-Levofloxacin **78**, a major antibiotic drug marketed in Europe by Sanofi-Aventis, is active against both gram-positive and gram-negative bacteria and is prescribed for a wide range of infections.[80] The major challenge associated with providing an efficient entry to **78** lies in identifying concise asymmetric entries to the chiral benzoxazine core **77** associated with this drug target.[81] Our approach to levofloxacin relied upon combining alanine-derived



Scheme 18 Synthesis of levofloxacin.

Table 9 Synthesis of higher benzofused heterocycles *via* 1,2- and 1,3-cyclic sulfamidates



cyclic sulfamidate **15f** with phenol **75** (Scheme 18). Treatment of cyclic sulfamidate **15f** with the anion of **75** resulted in smooth nucleophilic ring cleavage to generate adduct **76** in essentially quantitative yield. In this case concomitant removal of both the *N*-sulfate *and N*-Boc moieties could be achieved in the same pot by employing 10% H_2SO_4 in *p*-dioxane for the hydrolysis step. Exposure of **76** to Pd(0)-mediated ring closure conditions then cleanly afforded the core **77** of levofloxacin **78** in 84% yield. Conversion of this intermediate to **78** in three further steps has been reported.[80,81g]

Extension of this approach to a broader range of substrates provides a versatile and highly direct entry to homologated benzofused variants **81a–c,e–g**, (Table 9).[82] In these cases, displacement of 1,2- or 1,3-cyclic sulfamidates (**15a**, **79a,b**) with the mono-anion of phenols, anilines and thiophenols **80** provides intermediates which are setup for cyclisation under Mitsunobu conditions *via* an *O*-, *N*- or *S*-quinone methide.[83] Cyclisation to provide the 7-ring species **81a–c,e**, is generally highly efficient and provides the desired heterocycles in serviceable yields over the two-step sequence.[84] Note that in certain cases (*e.g.* **15a** to **81e**), the intermediacy of a reactive quinone methide enables the employment of an NHBn group as the nucleophile under Mitsunobu conditions. The successful application of this chemistry to the synthesis of the enantiomerically pure substituted 8-ring variants, 1,5-benzoxazocine **81f** and 1,5-benzodiazocine **81g**, has also been demonstrated.

Again, the potential for the application of this chemistry is clear. For example, the tetrahydro-1,4-benzothiazepines S107 and JVT519 (Fig. 3) are currently being evaluated for treating conditions linked to stabilization of cardiac ryanodine receptors (RyR1), which leak Ca^{2+} when subjected to stress.[85]

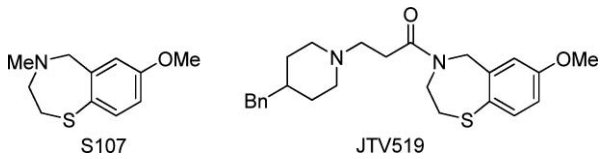


Fig. 3 RyR1 ligands based on the 1,4-benzothiazepine scaffold.

It is important to note that the methodologies described herein represent the basis of a broad and general approach to benzofused heterocyclic arrays. These scaffolds represent a growing area of therapeutically privileged frameworks and, as such, the synthetic blueprints outlined here have widespread utility for the generation of novel compound libraries of direct and topical medicinal chemistry interest.

Conclusions

The work covered in this Perspective article highlights a general and robust strategy for the synthesis of substituted and (where appropriate) enantiomerically and diastereomerically pure *N*-heterocycles by exploiting the availability and reactivity of 1,2- and 1,3-cyclic sulfamidates. Importantly, through the combination of cyclic sulfamidates as reactive alkylating agents with a wide variety of carbon- and heteroatom-based nucleophiles, a remarkable range of heterocyclic architectures are available.[86] Of note is the regiochemical predictability and ease with which various substitution patterns may be achieved. Additionally, the heterocyclic products obtained *via* these cyclic sulfamidate-based heteroannulation sequences are often readily advanced to other heterocyclic subclasses. The synthetic value of the methodology is aptly demonstrated by applications in synthesis, as showcased by highly efficient approaches to (–)-paroxetine, (+)-laccarin, (–)-aphanorphine and levofloxacin. It is the authors hope that these studies will provide practical solutions to synthetic challenges in both industry and academia.

Acknowledgements

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(PERCH-CIC), Commission on Higher Education, Thai Ministry of Education is also acknowledged.

Notes and references

1 For examples using HCl, see: (*a*) G. F. Cooper, K. E. McCarthy and M. G. Martin, *Tetrahedron Lett.*, 1992, **33**, 5895–5896. For examples using NaH_2PO_4, see: (*b*) L. Wei and W. D. Lubell, *Can. J. Chem.*, 2001, **79**, 94–104.

2 Examples: (*a*) B. M. Kim and S. M. So, *Tetrahedron Lett.*, 1998, **39**, 5381–5384; (*b*) S. B. Cohen and R. L. Halcomb, *J. Am. Chem. Soc.*, 2002, **124**, 2534–2543; (*c*) E. K. Dolence, G. Mayer and B. D. Kelly, *Tetrahedron: Asymmetry*, 2005, **16**, 1583–1594.

3 For a discussion on the nucleophilic cleavage of aziridines, see: X. E. Hu, *Tetrahedron*, 2004, **60**, 2701–2743.

4 For selected examples, see: (*a*) J. J. Posakony, J. R. Grierson and T. J. Tewson, *J. Org. Chem.*, 2002, **67**, 5164–5169; (*b*) K. C. Nicolaou, X. Huang, S. A. Snyder, P. B. Rao, M. Bell and M. V. Reddy, *Angew. Chem., Int. Ed.*, 2002, **41**, 834–838; (*c*) M. K. Pound, D. L. Davies, M. Pilkington, M. M. de Pena Vaz Sousa and J. D. Wallis, *Tetrahedron Lett.*, 2002, **43**, 1915–1918.

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