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The enantiospecific synthesis of (+)-monomorine I using a 5-*endo*-trig cyclisation strategy

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Full Research Paper

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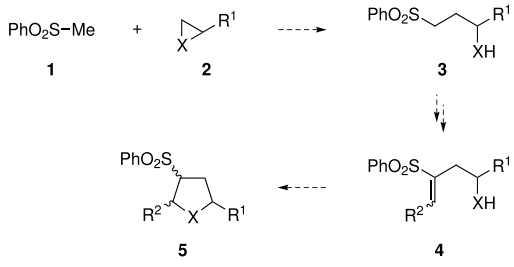
Abstract

We have developed a general strategy for the synthesis of 2,5-*syn* disubstituted pyrrolidines that is based on the multi-faceted reactivity of the sulfone moiety and a 5-*endo*-trig cyclisation. This methodology was applied to the synthesis of indolizidine alkaloid monomorine I. Two factors were key to the success of this endeavour; the first was the choice of nitrogen protecting group whilst the second was the conditions for the final stereoselective amination step. Employing a combination of different protecting groups and an intramolecular reductive amination reaction we were able to prepare (+)-monomorine I in just 11 steps from commercially available D-norleucine in a completely stereoselective manner.

Background

The abundance in natural products and drug candidates of saturated five-membered heterocycles, such as tetrahydrofurans and pyrrolidines, makes these motifs attractive targets for synthesis. Over the last decade we have developed a powerful general strategy for the preparation of such compounds based upon the multi-faceted reactivity of the sulfone group and the formally disfavoured 5-*endo*-trig mode of cyclisation. [1-6] The methodology allows the conversion of epoxides (X = O) or aziridines (X = N-PG) (**2**) into the desired trisubstituted tetrahydrofurans or pyrrolidines (**5**) *via* a series of sulfone-mediated transformations (Scheme 1). Ring-opening **2** with the sulfone-stabilised anion of **1** forms the first C-C bond and furnishes **3**. Modifica-



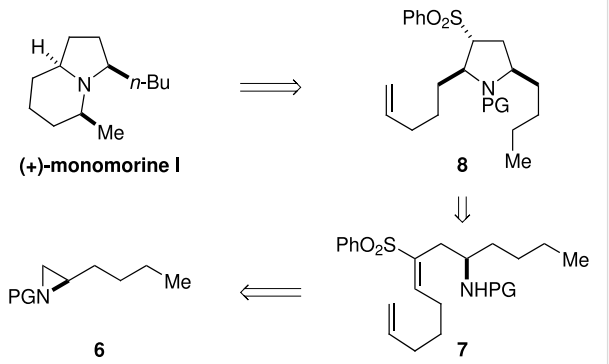
Scheme 1: General strategy for the synthesis of heterocycles *via* 5-*endo*-trig cyclisation

tion of the work of Julia [7-9] then utilises the sulfone to facilitate stereocontrolled alkenylation to give the cyclisation substrate **4**. Finally, 5-*endo*-trig cyclisation yields the desired heterocycles **5**. Overall, the sulfone moiety enables two C-C bond forming steps, allows stereocontrol of the alkene and activates the alkene to cyclisation. Furthermore, the sulfone can be used to elaborate the basic framework post-cyclisation.

In this publication we outline the application of this methodology to the synthesis of the indolizidine, (+)-monomorine I. [10-13] We have briefly described this work in a previous communication. [4]

Results and Discussion

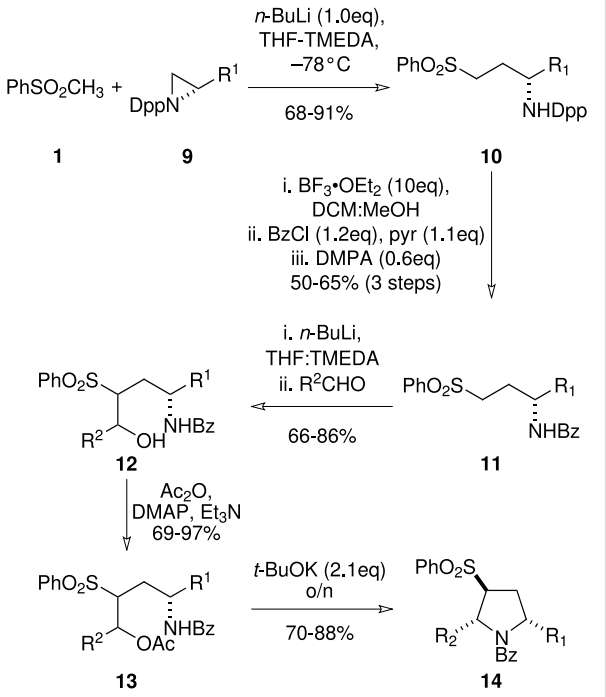
The pyrrolidine ring is an important structural motif that occurs in a range of pheromones, venoms and drug candidates. [14] In order to demonstrate the synthetic utility of the sulfone-mediated 5-*endo*-trig methodology. [3] we embarked on the total synthesis of the indolizidine alkaloid monomorine I, the trail pheromone of the Pharaoh worker ant *Monomorium pharaonis*. [10] Our initial synthetic plan is outlined in Scheme 2; aziridine **6**, prepared from D-norleucine by standard transformations, would be converted into the 2,5-*syn* disubstituted pyrrolidine core **8** *via* alkene **7**. With all the required carbon atoms in place, the final steps would involve deprotection, intramolecular hydroamination of the alkene and desulfonylation.



Scheme 2: Retrosynthesis of (+)-monomorine I

Initial studies directed towards this goal exploited the tosyl moiety as the nitrogen-protecting group (PG) and resulted in a succinct synthesis of alkenes of the type **4** (X = NTs; Scheme 1). [15] Disappointingly, all attempts to ring-close the sulfonamides proved fruitless, and it was found that desulfonylation was necessary before cyclisation could be achieved. Whilst the tosyl-based methodology permitted the synthesis of a range of simple, non-functionalised pyrrolidines **5** (X = NH), the harsh nature of the deprotection reaction, treatment with hydrobromic acid and phenol in acetic acid at reflux, led to the destruction of the the terminal alkene functionality of **7** (PG = Ts; Scheme 2) required for our synthesis of (+)-monomorine I. As a result of this set-back, a second nitrogen protecting group was assessed. The diphenylphosphinyl group (PG = $P(O)Ph_2$ = Dpp) overcame many of the problems encountered with the tosyl group; protected alkenes **4** (X = NDpp) underwent smooth 5-*endo*-trig cyclisation to furnish *N*-(diphenylphosphinyl)pyrrolidines **5** (X = Dpp) in good yields. [3,16] Furthermore, dephosphinylation was readily achieved under either Lewis acidic or Brønsted acid conditions compatible with a range of functional groups. This second-generation methodology was limited by the finding that acylation of **3** (X = NDpp) could only be achieved with non-enolisable acid chlorides, rendering it unsuitable for the synthesis of (+)-monomorine I. Ultimately, no single protecting group was found to be suitable and it was necessary to exploit a combination of protecting groups. The full evolution of the 5-*endo*-trig cyclisation-based pyrrolidine methodology will be described in a future publication.

Key to the successful synthesis of (+)-monomorine I was the use of the *N*-(benzoyl)aminosulfone **11** (Scheme 3). Benzamide **11** could be prepared from *N*-(diphenylphosphinyl)aziridine **9** by ring-opening with **1** followed by protecting group interchange. Although this strategy was not as elegant as utilising an *N*-benzoylaziridine directly, we deemed it prudent not to

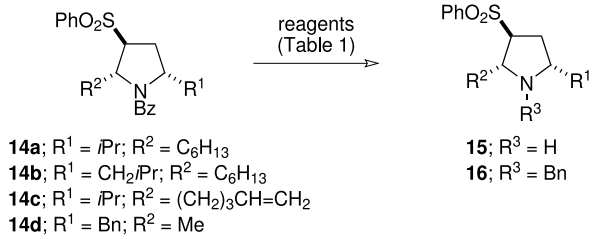


Scheme 3: The sulfone-mediated synthesis of 2,5-*syn* disubstituted pyrrolidines *via* a 5-*endo*-trig cyclisation

Table 1: Deprotection of *N*-benzoylpyrrolidines

Pyrrolidine	R^1	R^2	Reagent	R^3	Product	Yield (%)
14a	*i*Pr	C_6H_{13}	HCl	H	**15a**	69
14b	CH_2*i*Pr	C_6H_{13}	HCl	H	**15b**	60
14a	*i*Pr	C_6H_{13}	Super-Hydride®	H	**15a**	69
14c	*i*Pr	$(CH_2)_3CH=CH_2$	Super-Hydride®	H	**15c**	57
14c	*i*Pr	$(CH_2)_3CH=CH_2$	DIBAL	Bn	**16c**	70
14d	Bn	Me	DIBAL	Bn	**16d**	67

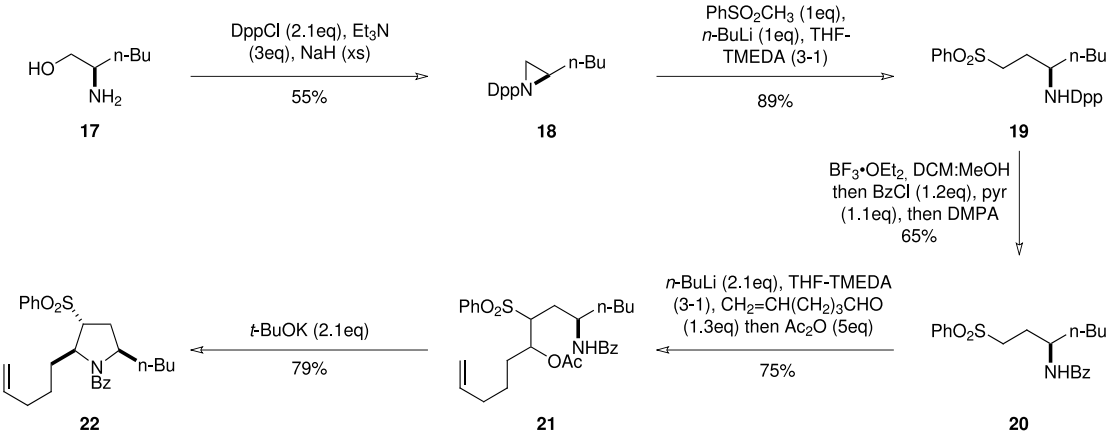
subject such a species to nucleophilic attack due to reported issues with chemoselectivity. [17] Careful optimisation obviated the need for chromatography following the protecting group exchange, and the benzamides **11** could be isolated in high purity and good yield. Hydroxyalkylation with a range of aldehydes proceeded without issue to give the β-hydroxysulfones **12** in excellent yields. The β-hydroxysulfones were then acylated under standard conditions to give **13**. Treatment of the β-acetoxysulfones **13** with two equivalents of base gave the pyrrolidines **14** directly as the product of a one-pot elimination-cyclisation cascade. The pyrrolidines were formed with complete diastereoselectivity for the 2,5-*syn* diastereoisomers. Although this stereochemical relationship could not be discerned from the ^{1}H NMR spectra of **14** due to peak broadening caused by amide rotamers, a combination of further elaboration and X-ray crystallographic analysis confirmed the assignment.



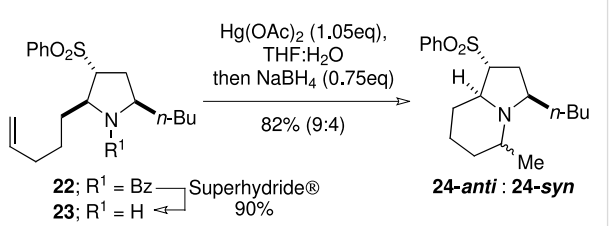
Scheme 4: The deprotection of *N*-benzoylpyrrolidines

Deprotection of simple benzoyl-protected pyrrolidines **14a** and **14b** could be achieved by acid hydrolysis (Scheme 4 and Table 1). However, as with the tosyl-based methodology, such reaction conditions were incompatible with the terminal alkene-substituted pyrrolidine **14c**. Therefore alternative deprotection conditions were investigated. Attempted base-mediated hydrolysis led to formation of the *N*-benzoylaminosulfone **11**, presumably by a sequence involving ring-opening by elimination, hydration of the electron-deficient alkenyl sulfone double bond and retro-aldol-like fragmentation. Reductive deprotection proved to be a more fruitful avenue of study. After considerable optimisation it was found that treatment of the *N*-benzoylpyrrolidines with Super-Hydride®[18] gave the free amines **15**, whilst the use of DIBAL in THF furnished the benzyl-protected pyrrolidines **16** in good yield (Scheme 4 and Table 1).

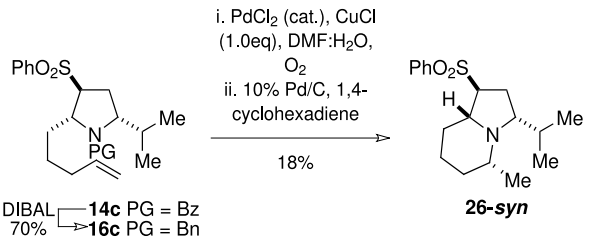
With the chemistry now in place to undertake the synthesis of (+)-monomorine I, the initial target, pyrrolidine **22**, was



Scheme 5: Synthesis of *N*-benzoyl protected pyrrolidine required for the preparation of (+)-monomorine I



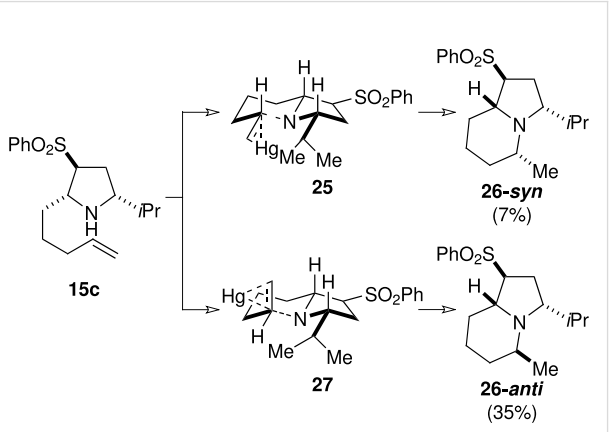
Scheme 6: Mercury-mediated hydroamination



Scheme 8: Model study for the reductive amination-based cyclisation

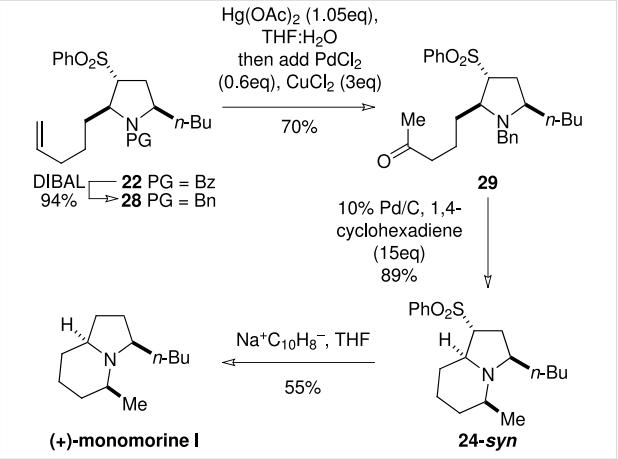
prepared. Commercially available D-norleucine was reduced to the amino alcohol **17**. [19] This was then converted into the benzoyl-protected aminosulfone **20** *via* the diphenylphosphinylaziridine **18,** which was ring-opened to give **19**, followed by protecting group exchange (Scheme 5). Formation of the dianion of **20** by exposure to two equivalents of *n*-butyllithium, followed by reaction with hex-5-enal and *in situ* trapping of the intermediate alkoxides gave the ester **21** as predominantly one diastereoisomer. Finally, one-pot elimination-cyclisation, promoted by two equivalents of potassium *tert*-butoxide, furnished the 2,5-*syn*-pyrrolidine **22** as a single diastereoisomer. Concurrently with the synthesis of **22**, the *iso*propyl model system, **14c**, was prepared using analogous chemistry.

Deprotection of **22** and **14c** was readily achieved with Super-Hydride® to give the free amines **23** and **15c**, which were subjected to mercury-mediated hydroamination (Scheme 6 and Scheme 7). [20] Cyclisation of **23** proceeded in good yield to give a 9:4 mixture of two indolizidines, epimeric at the C-5 methyl group **24-*anti*** and **24-*syn*** (Scheme 6). Cyclisation of the *iso*propyl analogue **15** proceeded with improved stereoselectivity to give a 5:1 mixture of epimeric indolizidines **26-*anti*** and **26-*syn*** (Scheme 7). Presumably, the increased steric bulk of the *iso*propyl group is responsible for the higher *anti*-selectivity. Assignment of the relative stereochemistry of the epimeric pairs proved problematic due to difficulties encountered during separation, and the presence of overlapping signals in the ^{1}H NMR spectrum. Finally, a combination of X-ray diffraction analysis and comparison of the ^{1}H NMR showed that the major diastereoisomer in each case was the undesired C-5 epimer, with the methyl group residing in the axial position. Naturally, we had assumed that the diastereoisomer in which all the substituents adopted a pseudo-equatorial orientation would have been formed preferentially. Yet inspection of the possible transition states for the cyclisation **25** *vs*. **27** reveals that the axial methyl may be favoured so as to minimize the strain associated with the eclipse of the C-3 and C-5 substituents (Scheme 7). Branching of the *iso*propyl substituent would cause greater interaction than the butyl group, and therefore would lead to an increase in selectivity.



Scheme 7: Proposed transition state for mercury-mediate hydroamination

The findings described above dictated that an alternative cyclisation strategy be investigated. It was anticipated that intramolecular reductive amination of a pendant methyl ketone would furnish the correct diastereoisomer, because the hydride source would be expected to approach the iminium ion from the less sterically demanding face, with the C-9 stereocentre being the controlling factor. [21] Both the benzoyl protecting group and the free amine were deemed incompatible with such a strategy. Therefore, **22** and **14c** were converted into the benzyl-protected pyrrolidines **28** and **16c** respectively by partial reduction with DIBAL-H (s Scheme 8 and Scheme 9). Wacker oxidation[22] of the *iso*propyl model compound **16c** gave the desired methyl ketone, which was subjected to transfer hydrogenation. [23] The latter reaction precipitated a reaction cascade commencing with deprotection of the *N*-benzylpyrrolidine followed by intramolecular reductive amination to give the desired indolizidine **26-*syn*** as a single diastereoisomer in 18% yield for the two steps. Whilst the yield of this unoptimised reaction was not satisfactory, we were pleased to observe that only the desired diastereoisomer was formed.



Scheme 9: The synthesis of (+)-monomorine I

Oxidation of the terminal alkene of **28** under Wacker conditions proved highly capricious and was ultimately abandoned in favour of a more reliable oxymercuration protocol. [24] Under these conditions the methyl ketone **29** was isolated in 70% yield (Scheme 9). Catalytic transfer hydrogenation led to sequential debenzylation and intramolecular reductive amination to furnish **24-*syn*** as a single diastereoisomer in excellent yield. Desulfonylation was achieved by brief exposure of **24-*syn*** to sodium naphthalenide in THF to furnish (+)-monomorine I, which showed ^{1}H and ^{13}C NMR, IR, mass spectral and optical rotation characteristics in agreement with published values. [25] Short reaction times were found to be crucial to the success of this reaction.

In summary, we have developed a highly stereoselective 5-*endo*-trig cyclisation reaction that facilitates the preparation of 2,5-*syn* disubstituted pyrrolidines. We have used this transformation as the key step in the synthesis of the indolizidine alkaloid, (+)-monomorine I. The synthesis was achieved in nine steps from the readily available aziridine **18**, and compares favourably with other total syntheses in the literature.

See Supporting Information File 1 for full experimental data.

Supporting Information

Supporting Information File 1

The enantiospecific synthesis of (+)-monomorine I using a 5-*endo*-trig cyclisation strategy: full experimental data. Full preparative details of all compounds prepared are reported, together with their spectroscopic data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-39-S1.doc]

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