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Stereoselective Synthesis of *cis*-2,6-Disubstituted Morpholines and 1,4-Oxathianes by Intramolecular Reductive Etherification of 1,5-Diketones

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Keywords: Morpholines / 1,4-Oxathianes / Diketones / Lewis acids / Reductive etherification / Natural products

A simple and efficient, Lewis acid catalysed reductive etherification strategy for the stereoselective synthesis of *cis*-2,6-disubstituted morpholines and 1,4-oxathianes starting from readily available 1,5-diketones has been developed. The strategy is used in the total synthesis of morpholine-based natural products (±)-chelonin A and formal total synthesis of (±)-chelonin C.

Introduction

In recent years, substituted six-membered 1,4-heterocycles have attracted considerable attention because of their ubiquity in natural products and drug molecules. Morpholine is an important pharmacophore and it is present in many compounds, which exhibit antimicrobial, anti-inflammatory and anti-Alzheimer's activities.[1] The natural products chelonin A (**1**) and chelonin C (**2**) have been reported to exhibit antimicrobial and anti-inflammatory activities (Figure 1).[2] (±)-Reboxetine (**3**) is used for the treatment of depression, whereas its (+)-(*S*,*S*)-enantiomer is utilised to cure fibromyalgia and neuropathic pain.[3] Similarly, the 1,4-oxathiane scaffold is also often found in many biologically active molecules; for example, the drug 1-(1,4-oxathian-2-yl)-5-fluorouracil (5-FUra) (**4**) possesses significant antitumor activity.[4a] Substituted oxathianes are important precursors in the synthesis of biologically significant 1,4-oxathiins, which are useful as fungicides and pesticides.[4b] Raphanuside (**5**) is an unusual oxathiane-fused thioglucoside isolated from the seeds of *Raphanus sativus*, a traditional Chinese herbal medicine used for expectorant, anticough, and anti-asthmatic purposes.[5] Tagetitoxin (**6**) is a phytotoxin produced by the pathogenic bacterium *Pseudomonas synringae pv.*, which targets and induces chlorosis in the apex of the host plant by specifically inhibiting chloroplast RNA polymerase.[6] Apart from that 2,6-disubstituted morpholines and 1,4-oxathianes have found use in various asymmetric transformations as chiral auxiliaries and chiral templates.[7] Recently, oxathianes have been used as glycosyl donors for stereoselective formation of 1,2-*cis*-glycosides.[8]

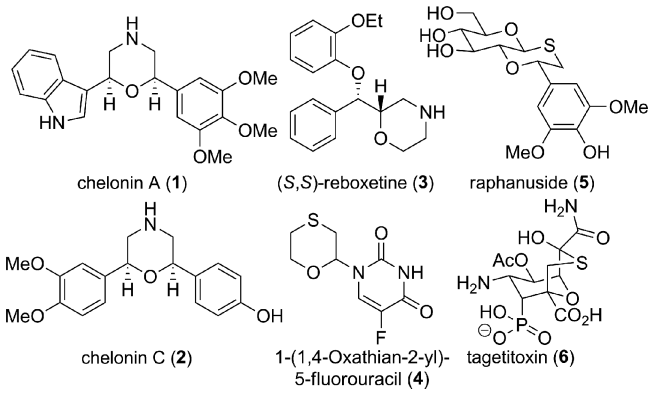

Figure 1. Morpholines and 1,4-oxathiane ring bearing natural products and bioactive molecules.

It is thus not surprising that the synthesis of 2,6-disubstituted morpholines and 1,4-oxathianes has attracted considerable attention from synthetic chemists. Over the years, good progress was made on the synthesis of 2,6-disubstituted morpholines and corresponding 2,6-disubstitued 1,4-oxathianes.[9,10] However, given the importance of these 1,4-heterocycles, a common strategy, which can give access to both morpholines, as well as oxathianes, in a highly diastereoselective manner is still desirable. In a programme directed at developing methods for the stereoselective synthesis of 1,4-heterocycles,[11] herein, we disclose a concise, reductive-etherification-based approach for the stereoselective synthesis of 2,6-disubstituted morpholines and 1,4-oxathianes starting from readily accessible 1,5-diketones.

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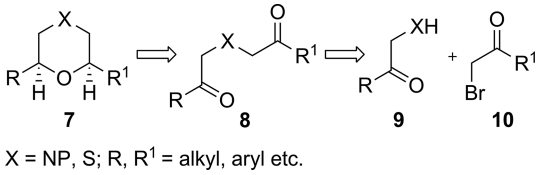
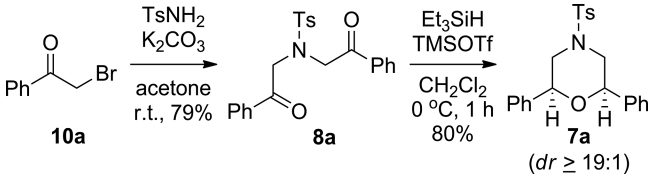
Results and Discussion

Olah and co-workers reported only one example of the synthesis of tetrahydropyran from 1,5-diketone using reductive etherification by employing TMSOTf and triethylsilane.[12] Interestingly, this reaction has received very little attention subsequently. Based on this, we envisioned that the 1,4-heterocycles **7** could be readily synthesised from the 1,5-diketones **8** by a Lewis acid catalysed intramolecular reductive etherification reaction. The unsymmetrically substituted 1,5-diketones **8** ($R \neq R^1$) could be readily prepared by the alkylation of α-amino- or α-mercapto ketones **9** with appropriate α-bromoketones **10** (Scheme 1). On the other hand, the symmetrically substituted 1,5-diketones **8** ($R = R^1$) could be assembled by dialkylation of *p*-toluenesulfonamide or sodium sulfide with α-bromoketones **10**.



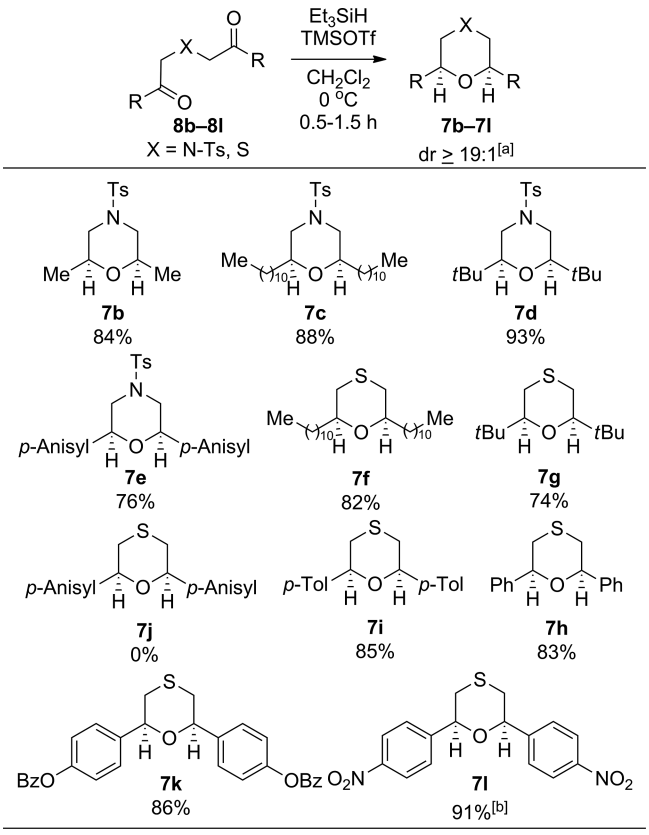
Scheme 1. Retrosynthesis for 2,6-disubstituted morpholine and 1,4-oxathianes **7**.

To test the feasibility of this proposed strategy, the diketone **8a** was prepared by treating phenacyl bromide (**10a**) with *p*-toluenesulfonamide with K_2CO_3 as the base. The diketone **8a**, when subjected to an intramolecular reductive etherification reaction by treatment with TMSOTf (1.1 equiv.) and Et_3SiH (2 equiv.), gave *meso*-2,6-diphenyl morpholine (**7a**) in good yield and excellent diastereoselectivity (Scheme 2). The *cis*-stereochemistry of the product was confirmed by comparison of the spectroscopic data with that reported earlier.[11a,13]



Scheme 2. Stereoselective synthesis of *meso*-2,6-diphenyl morpholine (**7a**) by a reductive etherification reaction.

After successful synthesis of the morpholine derivative **7a**, we turned our attention towards expanding the scope of this strategy for the synthesis of differently substituted symmetrical morpholines and oxathianes. The diketones **8b**–**8e** required for the synthesis of morpholines were prepared by alkylation of *p*-toluene sulfonamide with α-bromo ketones **10** by following a slight modification of the reported protocol.[14] On the other hand, the diketones **8f**–**8l** required for the synthesis of 1,4-oxathianes were readily assembled by alkylation of Na_2S with α-bromo ketones **10** following literature methods.[15] All the diketones **8b**–**8l** were then subjected to reductive etherification by using Et_3SiH and TMSOTf to give the corresponding disubstituted morpholines **7b**–**7e** and 1,4-oxathiane derivatives **7f**–**7l** in moderate to good yields (Scheme 3). In general, primary (methyl as well as long chain) and tertiary alkyl groups, phenyl and aryl groups substituted with moderately electron-releasing or moderately electron-withdrawing groups were tolerated under the reaction conditions employed. When a *p*-anisyl group was present as the substituent in the diketone, the oxathiane **7j** was not formed, instead the ketone Ar–CO–CH_2–S–CH_2–CH_2–Ar (**11**) and Ar–CH_2–CH_2–S–CH_2–CH_2–Ar [Ar = *p*-(MeO)C_6H_4–] **12** were obtained in 45 and 36% yield, respectively. Interestingly, the *p*-anisyl group was tolerated in the morpholine synthesis and the product **7e** was obtained in good yield. Formation of the reduced ketone in the former case is perhaps the outcome of a combination of the strong electron-releasing anisyl group and neighbouring group participation by sulfur. When the electron-withdrawing nitro group was present as a substituent in the diketone **8l**, not only were higher amounts of Lewis acid (4 equiv.) and Et_3SiH (6 equiv.) required for the reaction to proceed to completion, but also the time required was slightly longer (3.5 h) to give the product **7l**. In all cases, the formation of 1,4-heterocycles **7b**–**7l** proceeded with excellent diastereoselectivity and only formation of the *cis*-isomer was observed. The stereochemistry was assigned based on spectroscopic data and further



Scheme 3. Stereoselective synthesis of symmetrical *meso*-2,6-disubstituted morpholines and 1,4-oxathianes **7b**–**7l**. [a] In all cases, the *dr* was determined on the crude reaction mixtures by ^1H NMR spectroscopy. [b] TMSOTf (4 equiv.) and Et_3SiH (6 equiv.) was used and reaction time was 3.5 h.

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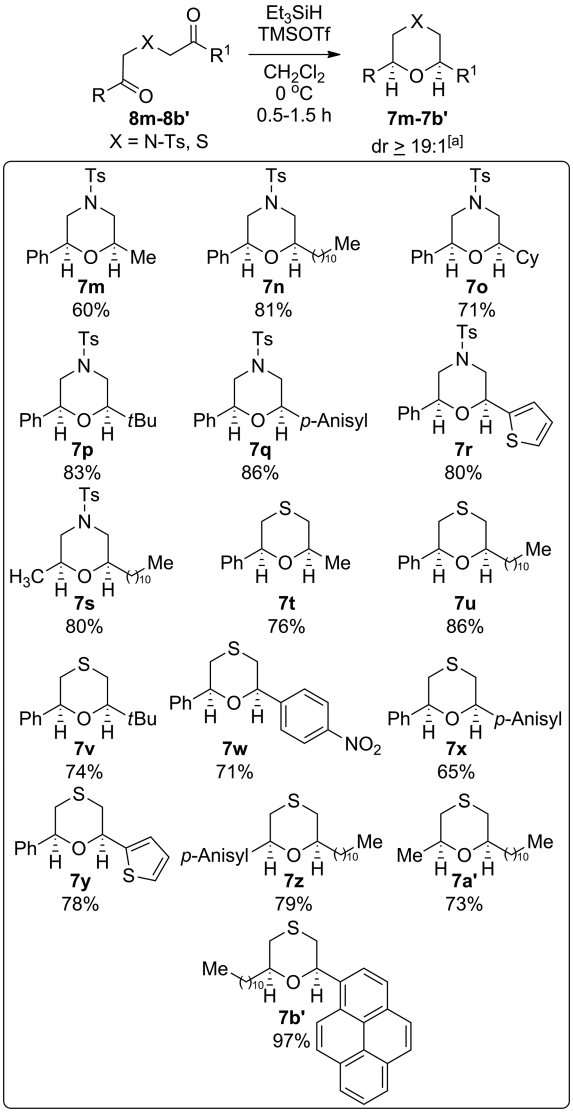
confirmed by single-crystal X-ray diffraction studies on the morpholine **7d** and the 1,4-oxathianes **7k** and **7l**.[16]

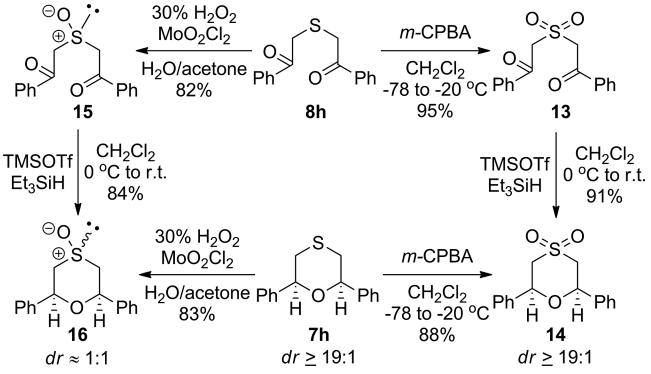
We next turned our attention towards expanding the scope of the reaction to unsymmetrically substituted morpholines and oxathianes. Various unsymmetrically substituted aza-1,5-diketones **8m**–**8s** and thio-1,5-diketones **8t**–**8b′** were then subjected to the optimised reductive etherification conditions with TMSOTf and Et_3SiH. The reaction was found to be general and *cis*-2,6-disubstituted morpholines **7m**–**7s** and 1,4-oxathianes **7t**–**7b′** were obtained in good yields and excellent diastereoselectivities (Scheme 4). As for the symmetrical cases, both alkyl and aryl substituents were tolerated. It was found that when activated aryl groups were present in the diketones **8x**, controlling the reaction time, the amount of Lewis acid and Et_3SiH and the temperature was crucial for getting good yields of the 1,4-oxathianes **7x**. Typically, formation of over-reduction products was observed with more equivalents of Et_3SiH and TMSOTf. Interestingly, no such effect was observed during the formation of morpholine **7q**. However, the diastereoselectivity in all cases was excellent and the *cis*-diastereomer was the only detectable isomer formed. The stereochemistry of the products was assigned based on NOE experiments and it was further confirmed by single-crystal X-ray diffraction studies on the morpholine **7o**.[16]



Scheme 4. Stereoselective synthesis of unsymmetrical (±)-2,6-disubstituted morpholines and 1,4-oxathianes **7m**–**7b′**. [a] In all cases, the *dr* was determined on the crude reaction mixtures by ^1H NMR spectroscopy.

The stereochemical outcome of all these reactions can be rationalised based on the model proposed earlier, wherein the substituent on the cyclic oxonium ion intermediate occupies a pseudoequatorial orientation to reduce steric interaction and the incoming hydride nucleophile is delivered from the axial direction to result in a chair conformation for the 1,4-heterocyclic product.[11a,17]

Sulfoxides and sulfones are important functional groups in organic synthesis. It was thought that expanding this method to the synthesis of cyclic sulfoxides and sulfones would be useful. To test this, the diketone **8h** was converted to sulfone **13** using *m*-CPBA. When sulfone **13** was subjected to reductive etherification conditions, the reaction proceeded smoothly leading to the ether **14** in excellent yield and diastereoselectivity. In a similar manner, the sulfoxide **15** was prepared from the ketone **8h**, by using Chand's sulfoxidation protocol.[18] Interestingly, when the sulfoxide was subjected to reductive etherification conditions, the product **16** was formed in very good yields as an approximately 1:1 mixture of diastereomers (with respect to sulfoxide stereocenter). However, the relative orientation of 2,6-substituents on both the diastereomers of **16** was *cis*. The structures of sulfone **14** and the sulfoxide **16** were further confirmed by independent synthesis from the 1,4-oxathiane **7h** (Scheme 5).



Scheme 5. Reductive etherification reaction for the synthesis of sulfone **14** and sulfoxide **16**.

Finally, the method was used in the stereoselective total synthesis of (±)-chelonin A (**1**) and the formal synthesis of (±)-chelonin C (**2**) isolated from *Chelonaplysilla* sp.[2] The first total synthesis of (±)-chelonin A (**1**) was reported by Somei et al. The key steps of their synthesis involved the ring opening of the epoxide with amino alcohol, acid catalysed cyclisation of the diol followed by removal of the *N*-methoxy group to obtain (±)-chelonin A.[19] For the total synthesis of (±)-chelonin A (**1**), the requisite diketone **17**

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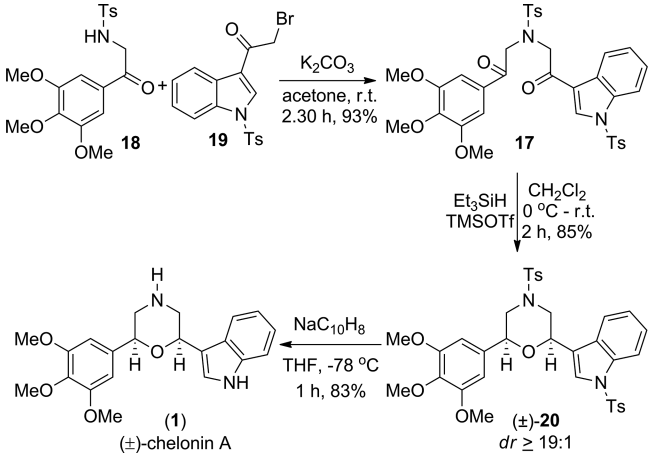
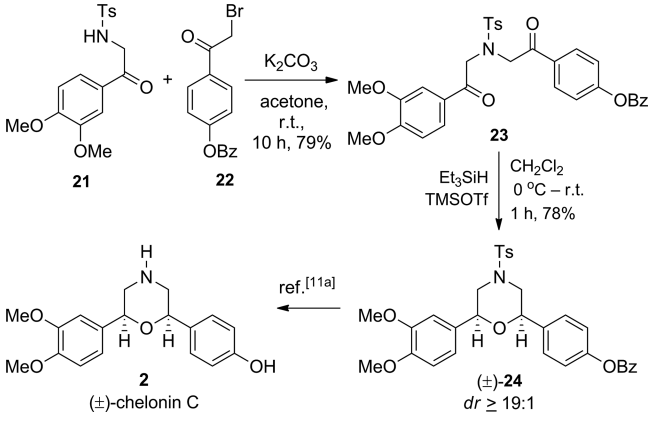
was prepared by alkylation of amine **18** with the bromide **19** (Scheme 6). The diketone **17** on subjecting to reductive etherification reaction gave the corresponding protected (±)-chelonin A **20** in good yield and excellent diastereoselectivity. Deprotection of tosyl group in (±)-morpholine **20** was effected by using sodium naphthanalide to give (±)-chelonin A (**1**) the data of which was found to be in good agreement with those reported in the literature.[2]



Scheme 6. Total synthesis of (±)-chelonin A (**1**).

We next turned our attention towards the formal synthesis of (±)-chelonin C (**2**). To this end, alkylation of the amine **21** with the bromide **22** with potassium carbonate as the base gave the diketone **23**. Reductive etherification reaction on the diketone **23** gave the (±)-morpholine derivative **24** in good yield and diastereoselectivity. Since we have already shown that the deprotection of the tosyl group in **24** can be done by using sodium naphthanalide to give (±)-chelonin C (**2**), this constitutes a formal total synthesis of (±)-chelonin C (**2**) (Scheme 7).[11a]



Scheme 7. Formal total synthesis of (±)-chelonin C (**2**).

Conclusions

We have developed a Lewis acid catalysed reductive etherification based approach for the stereoselective synthesis of 2,6-disubstituted morpholines as well as 1,4-oxathianes starting from diketones. Both symmetrical as well as unsymmetrical derivatives could be prepared in high yields and excellent diastereoselectivities. The method could be used for the construction of cyclic sulfoxide- or sulfone-containing 1,4-heterocycles. Finally, it was used in the synthesis of (±)-chelonin A and C.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterisation data along with copies of the ^{1}H and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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