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Asymmetric Synthesis of α-Amino 1,3-Dithioketals from Sulfinimines (*N*-Sulfinyl Imines). Synthesis of (2*S*,3*R*)-(−)-3-Hydroxy-3-methylproline

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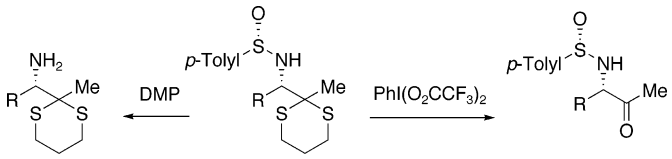
ABSTRACT

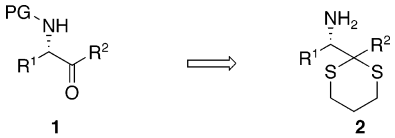


***N*-Sulfinyl α-amino 1,3-dithioketals are prepared in high de and good yield by treating sulfinimines with lithio-1,3-dithianes. Selective removal of the *N*-sulfinyl or the thioketal groups affords stable α-amino 1,3-dithioketals and *N*-sulfinyl α-amino ketones, respectively. This new sulfinimine-derived chiral building block is employed in the asymmetric synthesis of polyoxypeptin amino acid (2*S*,3*R*)-(−)-3-hydroxy-3-methylproline.**

The asymmetric syntheses of α-amino ketones **1** is currently receiving a great deal of attention because of the value of these building blocks in the asymmetric syntheses of heterocyclic compounds and natural products.[1] Generally enantiopure α-amino ketones are prepared by reaction of lithium and Grignard reagents with suitably N-protected α-amino acid derivatives; however, these syntheses are limited by the availability of the starting material.[2,3] In addition, while α-amino ketones are more stable than α-amino aldehydes, racemization can occur on storage. The harsh conditions necessary to remove the N-protecting group can also be problematic.[1,4]

There is however, another way to think about the syntheses and utilization of α-amino ketones, and that is to protect the keto group and leave the amine free for further elaboration. The keto group is then unmasked later in the synthetic sequence. α-Amino 1,3-dithianes **2** are a class of compounds that can be used in this manner because the dithioacetal group is stable to both acidic and basic conditions (Scheme 1).[5]

Scheme 1



1 **2**

PG = protecting group

Although racemic α-amino 1,3-dithianes **2** have been described,[6] the only optically active examples were those prepared from D-glucosamine.[7] Furthermore, in only one instance, a racemic example, was the 1,3-dithiane success-

(1) (a) Coppola, G.; Schuster, H. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. (c) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825.

(2) For leading references to the asymmetric synthesis of α-amino ketones, see: Paleo, M. R.; Calaza, M. I.; Sardina, F. J. *J. Org. Chem.* **1997**, *62*, 6862.

(3) For an alternative method, see: Myers, A. G.; Yoon, T. *Tetrahedron Lett.* **1995**, *36*, 9429.

(4) For reviews on α-amino aldehydes and ketones, see: (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Fisher, L. E.; Muchowski, J. M. *Org Prep. Proced. Int.* **1990**, *22*, 399.

(5) For a review of the application of 1,3-dithianes in natural product synthesis, see: Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147.

(6) (a) Wan, Y.; Angleson, J. K.; Kutateladze, A. G. *J. Am. Chem. Soc.* **2002**, *124*, 5610. (b) Mitkin, O. D.; Kurchan, A. N.; Wan, Y.; Schiwal, B. F.; Kutateladze, A. G. *Org. Lett.* **2001**, *3*, 1841. (c) Page, P. C. B.; van Niel, M. B.; Westwood, D. *J. Chem. Soc., Chem. Commun.* **1987**, 775.

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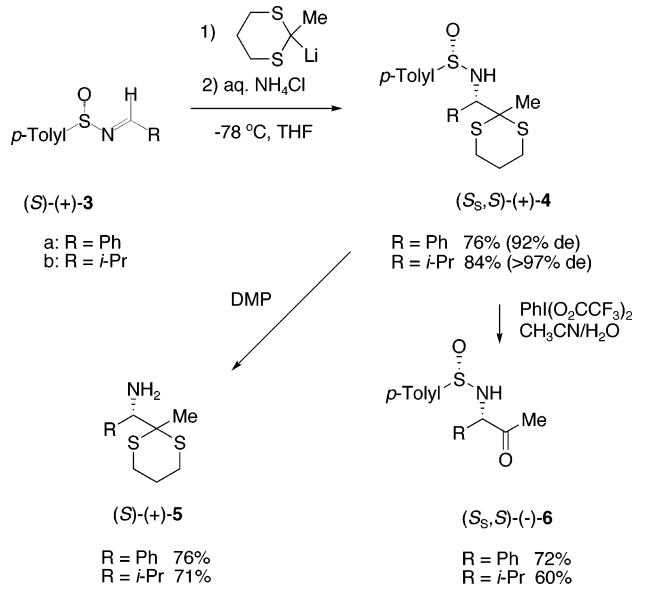
fully deprotected to give the ketone moiety.[8] We describe here a general method for the asymmetric synthesis of α-amino 1,3-dithianes **2** and the utility of this new sulfinimine-derived chiral building block for the asymmetric synthesis of α-amino ketones **1** and the polyoxypeptin amino acid (2*S*,3*R*)-(−)-3-hydroxy-3-methylproline (**14**).

Synthesis of α-Amino-1,3-dithianes. Addition of 1.5 equiv of a preformed −78 °C THF solution of 2-lithio-2-methyl-1,3-dithiane to sulfinimines (*S*)-(+)-*N*-benzylidene-*p*-toluenesulfinamide (**3a**) and (*S*)-(+)-*N*-isobutylidene-*p*-toluenesulfinamide (**3b**) readily gave the corresponding *N*-sulfinyl α-amino-1,3-dithianes (S_S,*S*)-(+)-**4a** and (S_S,*S*)-(+)-**4b** (Scheme 2).[9,10] The diastereoselectivities, determined

Scheme 2



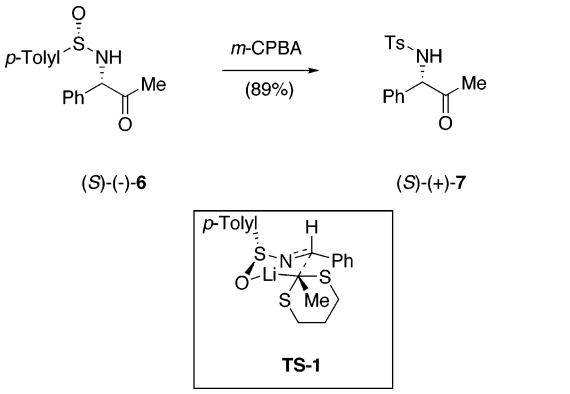
by ^{1}H NMR on the crude reaction mixtures, were excellent (92−97% de), and the yields of the major diastereoisomers, isolated by flash chromatography, were very good (76−84%).

Selective removal of the *N*-sulfinyl group in (+)-**4** can be accomplished in several ways. Treatment of the *N*-sulfinyl α-amino 1,3-dithianes **4** with the Dess−Martin periodinane (DMP) reagent afforded the corresponding amino 1,3-dithianes (*S*)-(+)-**5a** and (*S*)-(+)-**5b** in 76 and 71% yield, respectively (Scheme 2).[11] The usual method for removing *N*-sulfinyl groups in sulfinamides, TFA/H_2O, also works (see below).[8] A chiral shift reagent experiment indicated that the C−N stereocenter in (+)-**5a** was not compromised in the deprotection step.

Unless α-amino ketones are suitably N-protected, they are unstable and generally cannot be isolated.[1,4] Consequently, a method for the selective hydrolysis of the dithioketal moiety, in the presence of the *N*-sulfinyl group in (+)-**4**, is required if *N*-sulfinyl α-amino 1,3-dithianes are to be useful chiral building blocks (Scheme 1). It is unlikely that the *N*-sulfinyl group would survive most of the traditional methods for thioketal hydrolysis, i.e., mercury(II) salts and oxidative conditions.[12] However, we found that bis(trifluoroacetoxy)iodobenzene [$PhI(O_2CCF_3)_2$], described earlier by Stork and Zhao for selective thioacetal hydrolysis, proved to be ideal for this purpose.[13] Treatment of **4a**,**b** with 2 equiv of $PhI(O_2CCF_3)_2$ in acetonitrile−water afforded methyl ketones (S_S,*S*)-(−)-**6a** and (S_S,*S*)-(−)-**6b** in 72 and 60% isolated yields (Scheme 2). The fact that racemization was not detected in **6** further illustrates the unique nitrogen protecting group abilities of the sulfinyl group.[9]

Chelation-control arguments, based on six-membered chairlike transition states where the metal ion is chelated to the sulfinyl oxygen, have been used to rationalize the chiral recognition for the addition of enolates, Grignard reagents, DIBAL-H, and Et_2AlCN to sulfinimines.[9d,14] On the other hand, steric arguments have been evoked to explain the stereochemical preference in additions of benzyl Grignard, α-metallo phosphonates, 1,3-dipoles, and glycine iminoester enolates to sulfinimines.[9d,14] The absolute configuration of the newly created stereogenic center in (+)-**4** was determined to be (*S*)- by *m*-CPBA oxidation of **6a** to (*S*)-(+)-**7**, which has a known absolute configuration (Scheme 3).[15] This

Scheme 3



assignment means that 2-methyl-2-lithio-1,3-dithiane additions to sulfinimines fall into the chelation-control category and may go through a transition state such as **TS-1** (Scheme 3).

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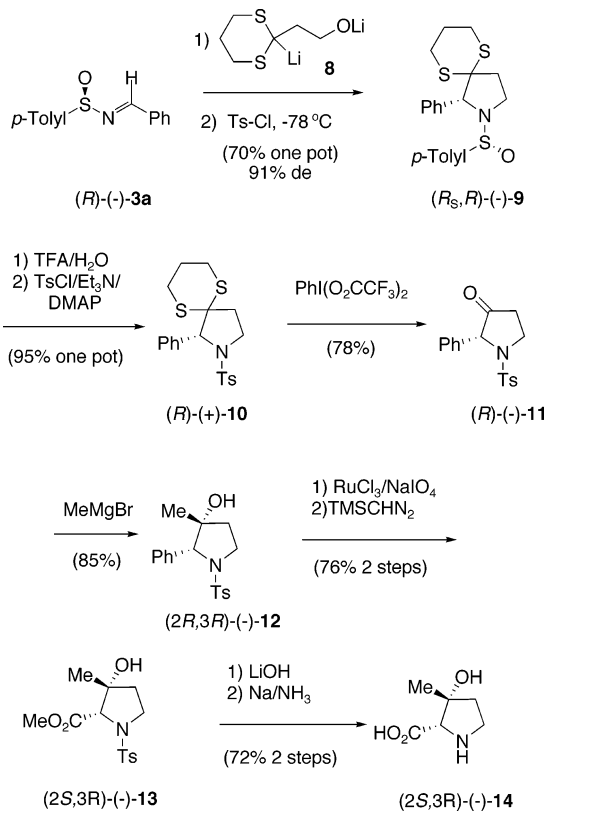
(10) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403.

(11) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *4*, 575. These workers reported the used DMP as a selective method for removal of thioketals and thioacetals.

(−)-3-Hydroxy-3-methylproline. The aim of new synthetic methodology is to solve important problems in synthesis. To highlight the utility of our new chiral building block, we employed an α-amino 1,3-dithiane in the asymmetric synthesis of (2*S*,3*R*)-(−)-3-hydroxy-3-methylproline (**14**). This nonproteinogenic amino acid is a key component of the polyoxypeptins, a 19-membered cyclic hexadepsipeptide antibiotic reported to be a potent inducer of apoptosis in human pancreatic andenocarcinoma ASPC-1 cells.[16,17]

Our synthetic strategy was to use the phenyl group as a masked carboxylic acid and to construct the pyrrolidine heterocycle directly from a substituted dithiane and benzaldehyde-derived sulfinimine (*R*)-(−)-**3a**. To this end, a preformed −78 °C solution of 1.5 equiv of dilithio species **8**, prepared from 2-(2-hydroxyethyl)-1,3-dithiane,[18] was added to (*R*)-(−)-**3a** at −78 °C (Scheme 4). Addition of Ts-Cl and quenching gave pyrrolidine (−)-**9** in 91% de and 70% isolated yield of the major diastereoisomer for the single-flask reaction. Next, the *N*-sulfinyl group was removed (TFA/H_2O) and replaced with a tosyl group in one operation. The thioketal in (+)-**10** was hydrolyzed with $PhI(O_2CCF_3)_2$ affording the 3-oxo pyrrolidine (*R*)-(−)-**11** in 78% yield. The ketone, on treatment with excess methylmagnesium bromide, gave alcohol (−)-**12** as a single isomer in 85% yield. Oxidation of the phenyl group to the carboxylic acid (−)-**12** was easily affected by $RuCl_3/NaIO_4$. To facilitate isolation, the acid was immediately converted to the methyl ester (2*S*,3*R*)-(−)-**13** with $TMSCHN_2$. Attempts to remove the *N*-tosyl group in the crude acid resulted in low conversions to (−)-**14** (20−30%). Alternatively, the somewhat longer sequence involving hydrolysis of the methyl ester in (−)-**13** and then reductive removal of the *N*-tosyl group with Na/liquid NH_3 gave (2*S*,3*R*)-(−)-3-hydroxy-3-methylproline (**14**) in 72% yield (Scheme 4).[19] Recognizing that a number of the 10 steps are one-flask transformations, we consider our synthesis of this amino acid to be one of the most concise to date.

Scheme 4



In summary, sulfinimines and lithio-1,3-dithianes afford *N*-sulfinyl-α-amino-1,3-thianes **4** in high de and good yields. This new sulfinimine-derived chiral building block can be selectivly deprotected to give either α-amino-1,3-dithianes **5** or *N*-sulfinyl α-amino ketones **6** as stable entities. The synthetic utility of *N*-sulfinyl-α-amino-1,3-thianes is illustrated by the asymmetric synthesis of the polyoxypeptins amino acid (2*S*,3*R*)-(−)-3-hydroxy-3-methylproline (**14**).

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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