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Asymmetric synthesis of α-amino aldehydes from sulfinimine (*N*-sulfinyl imine)-derived α-amino 1,3-dithianes. Formal synthesis of (−)-2,3-*trans*-3,4-*cis*-dihydroxyproline

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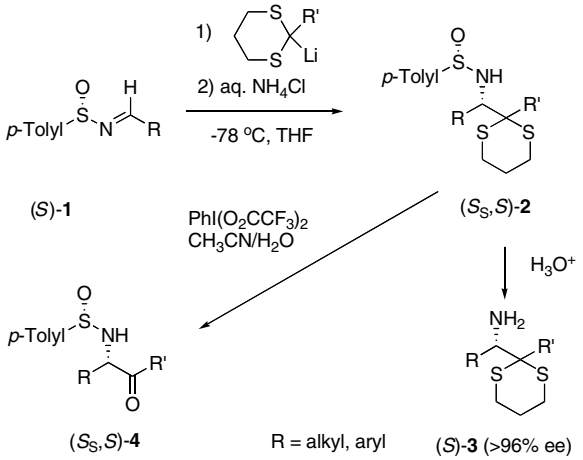
Abstract—Hydrolysis of sulfinimine-derived *N*-sulfinyl α-amino 1,3-dithianes with aqueous 1,3-dibromo-5,5-dimethylhydantoin affords the corresponding *N*-tosyl α-amino aldehydes in good yield and high enantiomeric purity. These aldehydes can be reduced to amino alcohols and undergo the Wittig reaction to give allylic amines without epimerization. The utility of this methodology is illustrated in a formal synthesis of (−)-2,3-*trans*-3,4-*cis*-dihydroxyproline.

1. Introduction

α-Amino aldehydes are extremely valuable chiral building blocks that have been widely used in the asymmetric synthesis of α-amino acids, α-amino alcohols, 1,2-diamines, allylic amines, heterocycles, and natural products.[1] Their participation in aldol reactions, cycloaddition reactions with 1,3-dienes, and reactions with various organometallic reagents add to their versatility and utility as chiral synthons.[1] However, α-amino aldehydes are notoriously unstable and easily racemized; therefore they require an N-protecting group. The choice of this group is critical for stability of the amino carbonyl moiety and for success in subsequent transformations as most involve reaction with basic types of nucleophiles. Although a number of N-protecting groups have been shown to be useful for this purpose—the choice depending on the substituents (Boc, Cbz, dibenzyl, Fmoc, PhFl)—the amino aldehydes are generally not purified prior to use because of their sensitivity to racemization.[1,2]

Often α-amino aldehydes are prepared from N-protected α-amino acids by employing a reduction step followed by reoxidation, and as such the preparation is limited by the availability of the amino acid.[1] Although a few procedures have been devised for the asymmetric synthesis of α-amino aldehydes not requiring amino acids, these methods lack generality, are restricted by the availability of the chiral starting materials, and are often multistep.[1,3] Therefore concise methods for the asymmetric synthesis of enantiopure N-protected α-amino aldehydes that do not necessitate α-amino acids as precursors are of considerable value.

Recently, we introduced a new and general method for the asymmetric synthesis of N-protected α-amino ketones involving the addition of 2-lithio-2-substituted-1,3-dithianes to enantiopure sulfinimines (*N*-sulfinyl imines) (*S*)-**1** (Scheme 1).[4–6] The resulting α-amino



Scheme 1.

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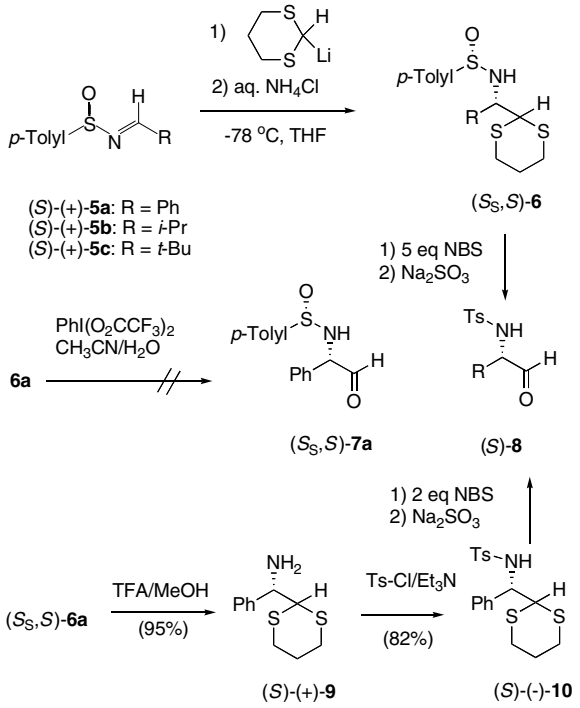
1,3-dithioketals **2** were formed in good yield with excellent diastereoselectivity. Acid hydrolysis gave the enantiomerically pure free amine **3**, which leaves the keto group protected and provides unique opportunities for functional group manipulation. Furthermore, we discovered that it was possible to hydrolyze the thioketal moiety without affecting the *N*-sulfinyl group by using the Stork reagent bis(trifluoroacetoxy)-iodobenzene.[7] The resulting *N*-sulfinyl α-amino ketone proved to be unusually stable and attests to the impressive amine protecting group ability of the sulfinyl moiety.[6] Here, we present a new and general procedure for the asymmetric synthesis of N-protected α-amino aldehydes from *N*-sulfinyl α-amino 1,3-dithioacetals.

2. Synthesis of α-amino 1,3-dithianes and α-amino aldehydes

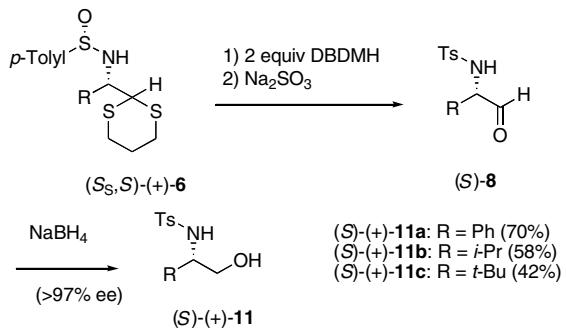
Addition of 1.5 equiv of the preformed −78 °C THF solution of 2-lithio-1,3-dithiane to sulfinimines (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**5a**), (*S*)-(+)-*N*-(isobutylidene)-*p*-toluenesulfinamide (**5b**), and (*S*)-(+)-*N*-(2,2-dimethylpropylidene)-*p*-toluenesulfinamide (**5c**) gave the corresponding *N*-sulfinyl α-amino-1,3-dithianes (S_S,*S*)-(+)-**6a** (73%, 82% de), (S_S,*S*)-(+)-**6b** (70%, 72% de) and (S_S,*S*)-(+)-**6c** (72%, 96% de) in good yield and de (Scheme 2). Chromatography gave the pure diastereoisomers. However, when (+)-**6a** (R = Ph) was treated with the Stork reagent, decomposition occurred and the corresponding aldehyde **7a** was not detected in the proton NMR of the crude reaction mixture (Scheme 2). When the hydrolysis of (+)-**6a** was carried out using 5 equiv of NBS in aqueous acetone for 10 min, followed by quenching with sodium sulfite, and extraction with methylene chloride, concentration resulted in a solid. The proton NMR spectrum of this material, which was remarkably clean, exhibited absorption at δ 9.4 ppm, which suggested that the desired α-amino aldehyde **7a** had indeed been formed. Less than 2–3% of the succinimide by-product was detected by NMR. On the other hand, the methyl protons attributed to the *p*-toluenesulfinyl group had shifted downfield from 2.23 in **6a** to 2.31 ppm. This suggested that the *p*-toluenesulfinyl group had been oxidized, under the hydrolysis conditions, to give the *N*-tosyl α-amino aldehyde **8a**. Attempts at chromatographic purification of **8a** resulted in decomposition. In an effort to find evidence that the *N*-sulfinyl group in **7a** had been oxidized, the *N*-sulfinyl group in (+)-**6a** was replaced with a tosyl group to give (*S*)-(−)-**10**. This was easily accomplished by treating (+)-**6a** with TFA/MeOH to give the amino 1,3-dithioacetal (+)-**9** in 95% yield. Reaction of (+)-**9** with *p*-toluenesulfonyl chloride in Et_3N afforded (*S*)-(−)-**10** in 82% yield. Subsequent hydrolysis of **10** using the NBS protocol gave a product whose proton NMR was identical to that obtained on hydrolysis of (+)-**6a** (Scheme 2).

Having established that *N*-tosyl α-amino aldehyde (*S*)-**8** was formed under the reaction conditions, it was necessary to determine its enantiomeric purity. This was accomplished by reduction of the crude aldehyde with 5 equiv of $NaBH_4$ to give the known 1,2-amino alcohol (*S*)-(+)-**11**, which was then transformed to its Mosher ester (Scheme 3). The literature specific rotation of (*S*)-(+)-**11**[8] and its Mosher ester indicated that the enantiomeric purity of the amino alcohol was >97% ee. This means the enantiomeric purity of the intermediate α-amino aldehyde **8a** is better than 97% ee. Similar results were observed for **8b** and for **8c**.

The yields given for the amino alcohols (*S*)-**11** are overall yields for several steps including oxidation, hydrolysis, and reduction beginning with the *N*-sulfinyl α-amino 1,3-dithiane **6**. The fact that these overall yields ranged from 42% for R = *t*-Bu to 70% for Ph suggest that the intermediate *N*-tosyl α-amino aldehydes (*S*)-**8** are formed in good yield and in high enantiomeric purity. In these studies we observed that hydrolysis with 2 equiv of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) resulted in much improved yields of the α-amino aldehydes **8** over NBS. Importantly, none of



Scheme 2.



Scheme 3.

the 5,5-dimethylhydantoin by-products were detected in the proton NMR of the crude reaction mixture.

Our studies suggest that the *N*-tosyl group is a particularly effective protecting group for α-amino aldehydes. We attribute this effect to its ability to stabilize anions at nitrogen and thus inhibiting base-catalyzed epimerization. Interestingly there are very few examples of an *N*-arylsulfonyl group being used to protect an α-amino aldehyde,[9,10] with the possible exception of Rapoport, who demonstrated the utility of *N*-arylsulfonyl protecting groups in many transformations of amino acids including modifications of the carboxyl group to give α-amino ketones.[10] Removal is effected without epimerization via reduction with sodium naphthalide or cleavage with HBr in HOAc.[11] In our studies, we have found that Na/NH_3 (liq) is particularly effective for removal of this protecting group.[4]

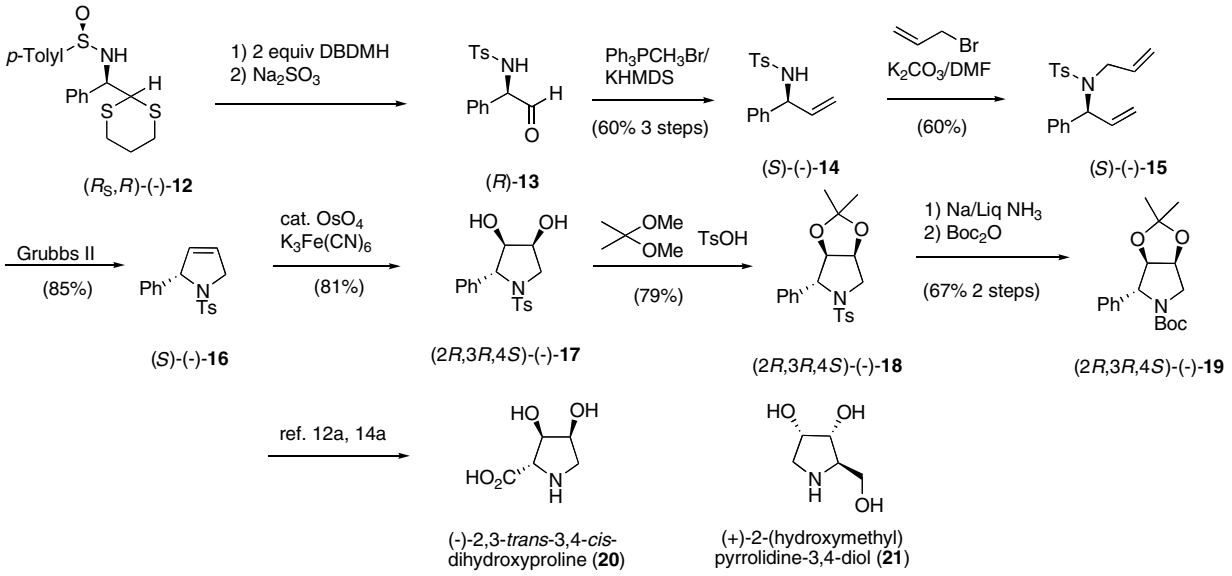
3. Formal synthesis of (−)-2,3-*trans*-3,4-*cis*-dihydroxyproline

Polyhydroxy pyrrolidines and prolines (azasugars) are common constituents of many biologically active natural products and are potent glycosides inhibitors.[12] As such they may be useful in treating cancer, diabetes, and various viral infections. To illustrate the utility of our new α-amino 1,3-dithiane derived α-amino aldehydes, we present a concise formal asymmetric synthesis of (−)-2,3-*trans*-3,4-*cis*-dihydroxyproline (**20**), a naturally occurring amino acid isolated from the marine mussel *Mytilus edulis*.[13,14]

Our synthesis begins with the epimer of (S_SS)-(+)-**6a**, (R_SR)-(−)-**12**, which is hydrolyzed to give the crude *N*-tosyl α-amino aldehyde (*R*)-**13** (Scheme 4). On treatment with the Wittig reagent generated from methyl triphenylphosphonium bromide and KHMDS, allylic amine (*S*)-(−)-**14** was obtained in 60% yield for the three steps. The diene, (*S*)-(−)-**15**, prepared from (−)-**14** and allyl bromide, was subjected to ring-closing metathesis employing the Grubbs second-generation catalyst to give the unsaturated pyrrolidine (−)-**16** in 85% yield. Dihydroxylation of (−)-**16** with $K_3Fe(CN)_6$/cat. OsO_4 occurred exclusively *anti* to the phenyl group affording diol (−)-**17**, which, upon protection as the acetonide by reaction with dimethoxy propane, gave (−)-**18** in 79% isolated yield. Reductive removal of the *N*-tosyl group was accomplished with Na/liq NH_3 and, without purification, the secondary amino group was Boc protected to give (−)-**19**. (2*R*,3*R*,4*S*)-(−)-*N*-*tert*-butoxycarbonyl-3,4-dihydroxy-2-phenyl-pyrrolidine isopropylidene acetal (**19**) has been transformed by Riera and co-workers via $RuCl_3/NaIO_4$ oxidation of the phenyl group to the carboxylic acid, to produce the proline,[12a] which on hydrolysis gave (−)-2,3-*trans*-3,4-*cis*-dihydroxyproline (**20**).[14a] Intermediate (−)-**19** can also be used in the construction of the azasugar (+)-2-(hydroxymethyl)pyrrolidne-3,4-diol (**21**).[12b]

4. Summary

In summary, hydrolysis of sulfinimine-derived *N*-sulfinyl α-amino 1,3-dithianes with aqueous NBS, or better with 1,3-dibromo-5,5-dimethylhydantoin, affords the corresponding *N*-tosyl α-amino aldehydes in good yield and in high enantiomeric purity. Because α-amino acids are not required as precursors and because of the great structural diversity of available sulfinimines,[6] this protocol represents an important new method for the enantioselective synthesis of valuable α-amino aldehyde chiral building blocks for asymmetric synthesis. The *N*-tosyl α-amino aldehydes are sufficiently stable to epimerization to undergo further elaboration such as reduction to amino alcohols and in the Wittig reaction to produce allyl amines.[15]



Scheme 4.

Acknowledgements

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15. Selected compound properties: (+)-**6a**: 172–174 °C (dec.); $[\alpha]_D^{20}$ +69.8 (*c* 1.0, $CHCl_3$); (+)-**6b**: mp 94–96 °C; $[\alpha]_D^{20}$ +51.8 (*c* 1.1, $CHCl_3$); (+)-**6c**: colorless oil, $[\alpha]_D^{20}$ +15.4 (*c* 1.91, $CHCl_3$); (+)-**9**: viscous liquid, $[\alpha]_D^{20}$ +39.4 (*c* 1.0, $CHCl_3$); (−)-**10**: mp 121–122 °C; $[\alpha]_D^{20}$ −61.2 (*c* 0.52, $CHCl_3$); (+)-**11a**: mp 105–106 °C [lit.[8] mp 106 °C]; $[\alpha]_D^{20}$ +79.2 (*c*, 1.0, $CHCl_3$), [lit.[8] $[\alpha]_D^{25}$ +81.5 (*c*, 1.0, $CHCl_3$); (+)-**11b**: mp 89–90 °C [lit.[16] mp 88–89 °C]; $[\alpha]_D^{20}$ +30.7 (*c* 0.5, $CHCl_3$), [lit.[16] $[\alpha]_D^{25}$ +29.4 (*c*, 0.837, $CHCl_3$); (+)-**11c**: mp 111–112 °C; $[\alpha]_D^{20}$ +10.3 (*c* 1.45, $CHCl_3$); (−)-**12**: mp 173 (dec), $[\alpha]_D^{25}$ −68.6 (*c*, 0.7, $CHCl_3$); (−)-**14**; colorless liquid, $[\alpha]_D^{25}$ −49.4 (*c*, 0.7, $CHCl_3$), [lit,[17] $[\alpha]_D^{25}$ −50.2 (*c*, 1.32, $CHCl_3$); (−)-**15**: viscous liquid, $[\alpha]_D^{20}$ −67.4 (*c* 1.15, $CHCl_3$); (−)-**16**: viscous liquid, $[\alpha]_D^{20}$ −37.4 (*c* 1.0, $CHCl_3$); (−)-**17**: viscous liquid, $[\alpha]_D^{20}$ −24.9 (*c* 0.8, $CHCl_3$); (−)-**18**: viscous liquid, $[\alpha]_D^{20}$ −28.9 (*c* 0.5, $CHCl_3$); (−)-**19**: mp 99 °C, [lit.[12a] mp 98–100 °C]; $[\alpha]_D^{25}$ −49.4 (*c*, 0.7, $CHCl_3$), [lit.[12a] $[\alpha]_D^{25}$ −48.14 (*c*, 1.4, $CHCl_3$).
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