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α-Amino 1,3-dithioketal mediated asymmetric synthesis of piperidines (L-733,060) and tetrahydrofuran glycines

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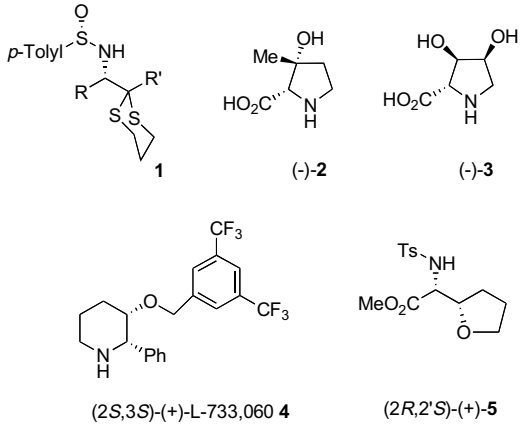
Abstract

Sulfinimine-derived α-amino 1,3-dithianes and α-amino carbonyl chiral building blocks, are utilized in asymmetric syntheses of (+)-(tetrahydrofuran-2-yl)glycine and the 2,3-disubstituted piperidine (+)-L-733,060.

Enantiomerically pure α-amino aldehydes and ketones, generally prepared from α-amino acids, are widely used chiral building blocks for asymmetric synthesis.[1] However, α-amino carbonyl compounds are notoriously unstable and rapidly epimerize and self-condense even when suitably N-protected. Many of these problems can be avoided by using *N*-sulfinyl α-amino 1,3-dithianes **1**, new sulfinimine-derived chiral building blocks for α-amino aldehyde, and ketone synthesis (Scheme 1).[2,3] These building blocks are readily prepared in high diastereomeric purity by addition of 2-lithio-1,3-dithianes to sulfinimines.[4] Acid hydrolysis affords the enantiomerically pure free amine, leaving the carbonyl group protected, resulting in unique opportunities for functional group manipulation. We employed these α-amino 1,3-dithianes in highly diastereoselective asymmetric syntheses of functionalized prolines including (−)-3-hydroxy-3-methyl proline (**2**)[2] and (−)-2,3-*trans*-3,4-*cis*-dihydroxyproline (**3**).[3] As an extension of this methodology, we describe the concise asymmetric synthesis of the 2,3-disubstituted piperidine (2*S*,3*S*)-(+)-L-733,060 (**4**) and the unnatural constrained α-amino acid (+)-(2*R*,2′S)-(+)-2-(tetrahydrofuran-2-yl)glycine (THFG **5**) from a common intermediate.



Scheme 1.

The key strategy employed in our synthesis of hydroxy prolines (−)-**2** and (−)-**3** was the cyclization of a 2-hydroxyethyl moiety (R′) in **1** to form the pyrrolidine ring. Cyclization of a 3-hydroxypropyl group (R′) in **1** would produce a piperidine ring. Addition of 2-lithium-1,3-dithiane **7**[5] to (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**6**)[6] gave *N*-sulfinyl α-amino 1,3-dithiane (S_S,*S*)-(+)-**8** in 94% de and 81% yield of the major diastereoisomer (Scheme 2). Hydrolysis of (+)-**8** with 1,3-dibromo-5,5-dimethylhydantoin (**9**) in aqueous acetone not only hydrolyzes the thioketal group, but also oxidizes the *N*-sulfinyl group to the *N*-tosyl protecting group affording (*S*)-(−)-**10** in 73% yield for the one pot sequence. Reduction of the amino ketone with $NaBH_4$ gives the expected syn

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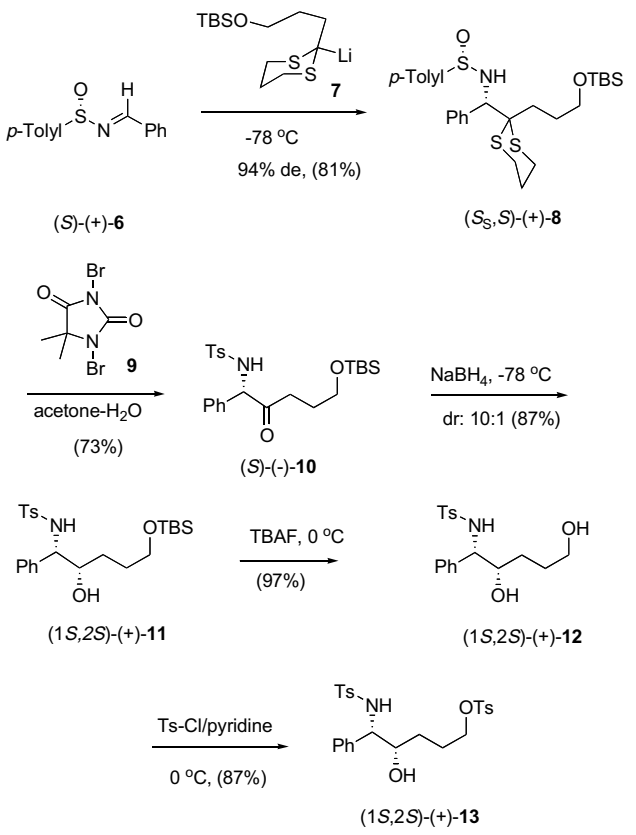
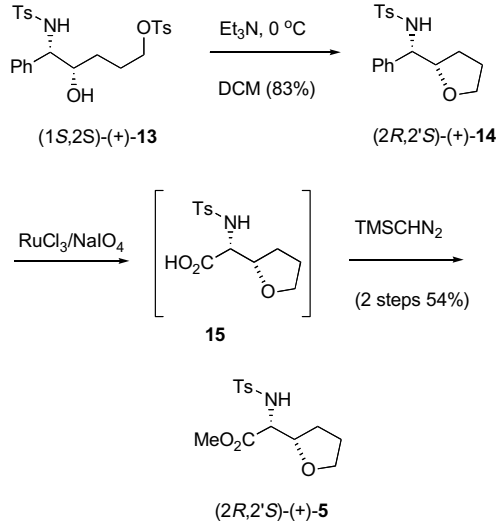


Scheme 2.

alcohol (1*S*,2*S*)-(+)-**11** (dr = 10:1) in 87% yield of the major diastereoisomer. Selective tosylation of the primary alcohol in (+)-**12** was readily accomplished with TsCl/pyridine affording (1*S*,2*S*)-(+)-**13** in 87% yield.

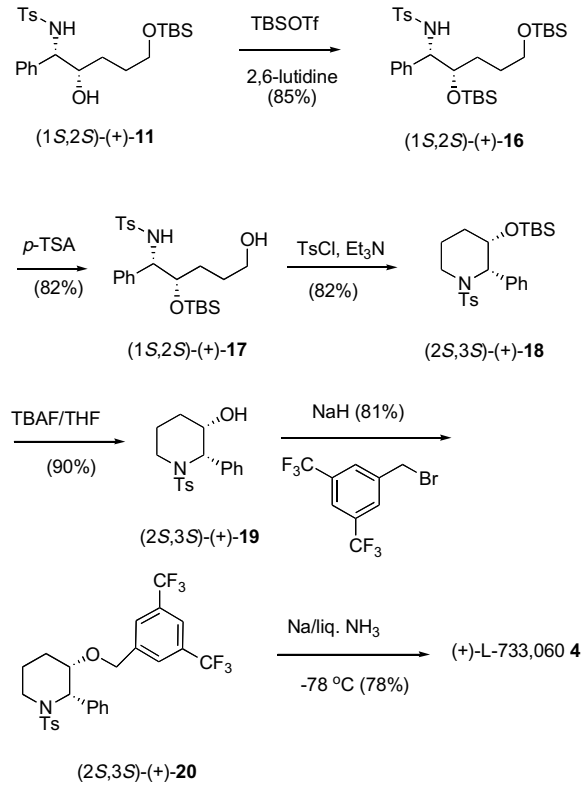
Next, treatment of amino alcohol (+)-**13** with Et_3N gave the expected, kinetically favored, furan (+)-**14** in 83% yield (Scheme 3). Oxidation of the phenyl group in (+)-**14** with $RuCl_3/NaIO_4$ gave the carboxylic acid **15**, which was isolated as the methyl ester with $TMSCHN_2$ affording (2*R*,2′*S*)-(+)-**5** in 54% for the two steps.[7] Conformationally constrained unnatural amino acids such as (+)-**5** are in demand for the synthesis of constrained peptide surrogates, which have increased potency, stability, bioavailability, and selectivity.



Scheme 3.

To prepare a piperidine from (+)-**11** required protection of the 2-hydroxy group as the OTBS ether. Treatment of (+)-**16** with *p*-TSA at 0 °C for less than 30 min made it possible to selectively deprotect the primary OTBS, affording (+)-**17** in 82% yield (Scheme 4). With TsCl/Et_3N, (+)-**17** gave piperidine (+)-**18** in 88% yield and the hydroxy piperidine (+)-**19** was obtained in 90% yield using TBAF. Etherification of the hydroxy group with NaH and 3,5-bis(trifluoromethyl)benzyl bromide gave (2*S*,3*S*)-(+)-**20**. Finally, *N*-tosyl deprotection with Na/liq. NH_3 at −78 °C afforded (2*S*,3*S*)-(+)-L-733,060 (**4**) in 78% yield (Scheme 4).[8,9] (+)-L-733,060 (**4**) is a potent neurokinin substance P receptor antagonist, which exhibits strong antiemetic activity.[10]

In summary, the utility of α-amino 1,3-dithianes as chiral building blocks for the asymmetric synthesis of heterocycles has been demonstrated by the preparation of amino furan (+)-THFG-**5** and 2,3-disubstituted piperidine (+)-L-733,060 (**4**) from common amino diol intermediate (+)-**11**.[12] In particular, our synthesis of (+)-**4** in 11 steps under nine operations (18% overall yield) from sulfinimine (+)-**6** is one of the most concise to date. 2,3-Disubstituted piperidines are structural units found in natural products and



Scheme 4.

several drug candidates,[11] and the structural diversity of available sulfinimine-derived α-amino 1,3-dithianes make this protocol well suited for enantiomer and analog synthesis.[10]

Acknowledgment

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12. Selected data: (+)-**8**, mp 109–110 °C; $[\alpha]_D^{20}$ 30.8 (*c* 0.4, $CHCl_3$); (−)-**10**, mp 93–95 °C; $[\alpha]_D^{20}$ −161.4 (*c* 0.42, $CHCl_3$); (+)-**11**, $[\alpha]_D^{20}$ +26.5 (*c* 0.7, $CHCl_3$); (+)-**12**, $[\alpha]_D^{20}$ 44.7 (*c* 1.3, $CHCl_3$); (+)-**13**, $[\alpha]_D^{20}$ 16.8 (*c* 0.81, $CHCl_3$); (+)-**14**, $[\alpha]_D^{20}$ +11.5 (*c* 0.68, $CHCl_3$); (+)-**5**, $[\alpha]_D^{20}$ +34.4 (*c* 1.1, $CHCl_3$); (+)-**16**, $[\alpha]_D^{20}$ +27.1 (*c* 0.72, $CHCl_3$); (+)-**17**, mp 152–153 °C; $[\alpha]_D^{20}$ +35.1 (*c* 0.4, $CHCl_3$); (+)-**18**, $[\alpha]_D^{20}$ +59.2 (*c* 0.32, $CHCl_3$); (+)-**19**, $[\alpha]_D^{20}$ +76.31 (*c* 0.38, $CHCl_3$); (+)-**20**, $[\alpha]_D^{20}$ +58.6 (*c* 0.53, $CHCl_3$); (+)-**4**, $[\alpha]_D^{25}$ +36.12 (*c*, 0.64, $CHCl_3$).