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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, 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.

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 NaBH₄ gives the expected syn 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 Et₃N gave the expected, kinetically favored, furan (+)-**14** in 83% yield (Scheme 3). Oxidation of the phenyl group in (+)-**14** with RuCl₃/NaIO₄ gave the carboxylic acid **15**, which was isolated as the methyl ester with TMSCHN₂ affording

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(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.

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/Et₃N, (+)-**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. NH₃ at -78 °C afforded the (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 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

Acknowledgments

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12. Selected data: (+)-**8**, mp 109–110 °C; $[\alpha]^{20}_{\text{D}}$ 30.8 (c 0.4, CHCl₃); (–)-**10**, mp 93–95 °C; $[\alpha]^{20}_{\text{D}}$ –161.4 (c 0.42, CHCl₃); (+)-**11**, $[\alpha]^{20}_{\text{D}}$ +26.5 (c 0.7, CHCl₃); (+)-**12**, $[\alpha]^{20}_{\text{D}}$ 44.7 (c 1.3, CHCl₃); (+)-**13**, $[\alpha]^{20}_{\text{D}}$ 16.8 (c 0.81, CHCl₃); (+)-**14**, $[\alpha]^{20}_{\text{D}}$ +11.5 (c 0.68, CHCl₃); (+)-**5**, $[\alpha]^{20}_{\text{D}}$ +34.4 (c 1.1, CHCl₃); (+)-**16**, $[\alpha]^{20}_{\text{D}}$ +27.1 (c 0.72, CHCl₃); (+)-**17**, mp 152–153 °C; $[\alpha]^{20}_{\text{D}}$ +35.1 (c 0.4, CHCl₃); (+)-**18**, $[\alpha]^{20}_{\text{D}}$ +59.2 (c 0.32, CHCl₃); (+)-**19**, $[\alpha]^{20}_{\text{D}}$ +76.31 (c 0.38, CHCl₃); (+)-**20**, $[\alpha]^{20}_{\text{D}}$ +58.6 (c 0.53, CHCl₃); (+)-**4**, $[\alpha]^{25}_{\text{D}}$ +36.12 (c, 0.64, CHCl₃).

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.