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Enantioselective Synthesis of (*S*)-(+)-Pantolactone

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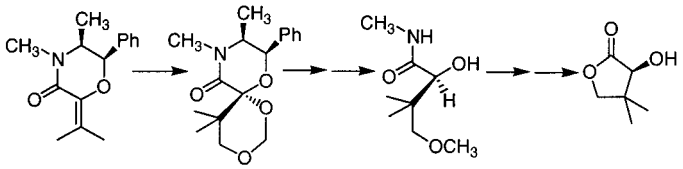
ABSTRACT



The Prins reaction of a chiral alkylidene morpholinone derived from (1*R*,2*S*)-ephedrine and 3-methyl-2-oxobutanoic acid proceeds with good diastereoselectivity to generate a spiro bis-acetal. Lewis acid mediated diastereoselective reductive cleavage of the spiro acetal and subsequent removal of the ephedrine portion generates a α-hydroxy-γ-methoxy carboxamide which is readily converted to (*S*)-(+)-pantolactone with high enantiomeric excess.

The asymmetric synthesis of pantolactone continues to be an area of active interest due to its utility as a building block in the synthesis of natural products and their analogues[1,2] and the biological activity of pantothenic acid and (*R*)-panthenol.[3] In addition, pantolactone has found application as a chiral auxiliary in asymmetric synthesis.[4] Enantiomerically enriched pantolactone has been obtained by several procedures. These include chemical[1a,5] or enzymatic[6] resolution of the racemate, microbial or catalytic asymmetric reduction of 3,3-dimethyl-2-oxobutyrolactone[7] and asymmetric functionalization of linear or cyclic precursors.[8]

We chose to examine a synthesis of pantolactone that focused on the precursor hydroxy acid rather than functionalization of the butyrolactone skeleton. The advantage of such an approach would be the ready access to pantolactone analogues. Herein, we describe a new approach to the enantioselective construction of the α,γ-dihydroxy butyric acid moiety, the precursor to pantolactone. The procedure involves a stereoselective Prins reaction[9] of an α-alkoxy acrylamide as the key step.

Acylation of (1*R*,2*S*)-ephedrine hydrochloride with 3-methyl-2-oxobutanoyl chloride generates the hemiacetal **1** which is

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(3) (a) Lipmann, F. *Science* **1954**, *120*, 855. (b) Shimizu, S,; Tani, Y.; Ogata, K. *Agric. Biol. Chem.* **1974**, *38*, 1989.

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(8) (a) Rao, A. V. R.; Rao, S. M.; Sharma. G. V. M. *Tetrahedron Lett.* **1994**, *35*, 5735. (b) Upadhya, T. T.; Gurunath, S.; Sudalai, A. *Tetrahedron: Asymmetry* **1999**, *10*, 2899. (c) Effenberger, F.; Eichhorn, J.; Roos, J. *Tetrahedron: Assymetry* **1995**, *6*, 271.

(9) For reviews on the Prins reaction, see: (a) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661. (b) Snyder, B. B. *Compr. Org. Synth.* **1991**, *2*, 527.

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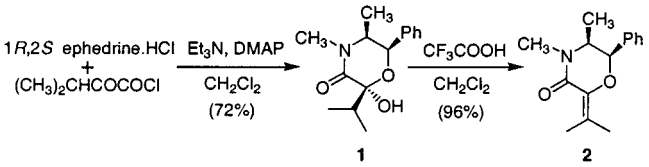
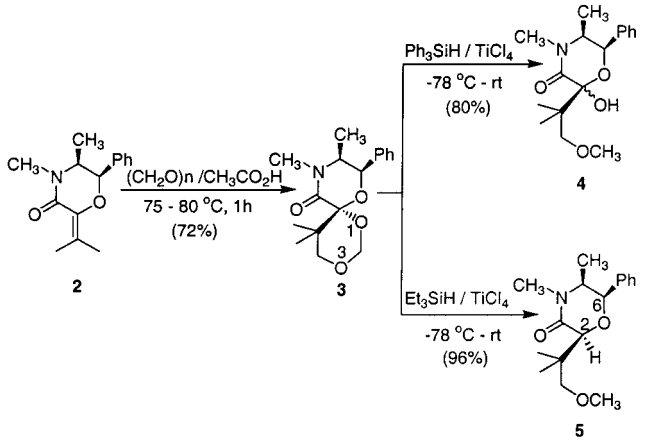
readily dehydrated to the chiral acrylamide **2**[10] in good yield (Scheme 1). This served as a starting material for this study.

Scheme 1



Initial investigations on the Prins reaction of **2** were conducted with aqueous formaldehyde as the electrophile. Sulfuric acid catalyzed reaction of **2** with aqueous formaldehyde in dioxane at 80−85 °C generated the spiro bisacetal **3** (41%) as a single diastereomer. However, this reaction was capricious and frequently generated unwanted products in significant amounts or failed to give **3**. Changing the solvent to acetic acid was beneficial, and the Prins reaction of **2** with paraformaldehyde in acetic acid at 75−80 °C in the presence of a catalytic amount of concentrated sulfuric acid consistently generated **3** in 70−72% yield (Scheme 2). The stereochemistry at the spiro acetal stereo-

Scheme 2

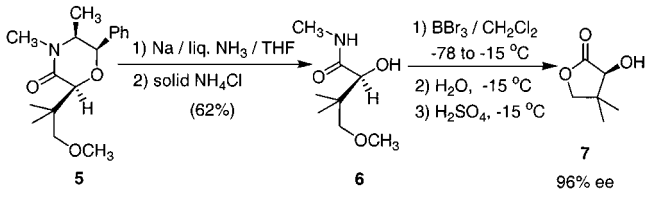


center is assigned by analogy to other reactions of the oxocarbenium ion intermediate in the ephedrine-derived template.[10] It is noteworthy that several alkylidene morpholinones varying in substitution on the double bond are also readily available.[10] These should serve as substrates for the Prins reaction in the synthesis of pantolactone analogues in which an alkyl group replaces the *gem*-dimethyl functionality. Having constructed the requisite 2,2-dimethyl-4-hydroxy portion of the target butyric acid, we next investigated the reduction of the spiro acetal to generate the α-hydroxy acid functionality.

Treatment of **3** with $Ph_3SiH/TiCl_4$ in CH_2Cl_2 at −78 °C followed by an aqueous workup generated the hemiacetal **4** as a mixture of diastereomers. Presumably, $TiCl_4$ coordinates with the exocyclic oxygen (O1, Scheme 2) in the spiro acetal **3** to generate an endocyclic oxocarbenium ion which is inaccessible for reduction by Ph_3SiH due to steric reasons. Facile reduction of the methylenedioxy acetal followed by reaction with water generates **4**. Replacement of Ph_3SiH with the sterically less demanding Et_3SiH is beneficial and furnishes **5** in 96% yield (ds >95/5). Lewis acid coordination to O3 in **3** followed by acetal cleavage (Scheme 2) would generate a free hydroxymethyl group in the product. However, this reaction path was not observed since there was no evidence of the corresponding product. Reasons for the regioselective Lewis acid coordination in **3** are unclear at present. It is plausible that the reaction is governed by the stability of the more substituted endocyclic oxocarbenium ion. The opposing dipole of the amide carbonyl may also be a stabilizing factor. The stereochemistry of the newly generated stereocenter was assigned as *S* from a NOESY experiment that indicated a *syn* orientation of the hydrogens on C2 and C6 in morpholinone **5** (Scheme 2). The stereoselectivity is an outcome of a stereoelectronically controlled axial reduction of the intermediate oxocarbenium ion.

Morpholinone **5** is a protected version of the requisite α,γ-dihydroxy butyric acid precursor to pantolactone. Dissolving metal reduction of **5** proceeds rapidly (10−15 s) at −78 °C to generate the α-hydroxy-γ-methoxy butyramide **6** in 62% yield (Scheme 3). Conversion of **6** to (*S*)-pantolactone was

Scheme 3



achieved by a one-pot reaction sequence. The primary hydroxyl group in **6** was liberated by demethylation with BBr_3 in CH_2Cl_2 at −78 °C. Subsequent acid-catalyzed lactonization at −15 °C, which presumably involves a very facile intramolecular acyl transfer from nitrogen to oxygen, furnished (*S*)-(+)-pantolactone in 68% yield and 96% ee[11] from **6** ($[\alpha]^{25}_D = +51.6$ (*c* 2, H_2O); lit.[12] $[\alpha]^{25}_D = +50.1$ (*c* 2, H_2O)).

The simplicity of the above synthetic sequence makes it viable for the synthesis of pantolactone on a preparative scale. In this regard, it is noteworthy that several grams of the key intermediate **5** can be prepared readily.

In conclusion, an enantioselective synthesis of (*S*)-pantolactone has been achieved by employing a novel, stereo-

(10) Pansare, S. V.; Ravi, R. G.; Jain, R. P. *J. Org. Chem.* **1998**, *63*, 4120.

(11) Determined by GC analysis of the Mosher ester derivative with *R*-MTPA. Column: BP1 (nonpolar) 100% dimethylpolysiloxane; 0.53 mm id; nitrogen as carrier gas (3.8 mL/min); injection temperature 280 °C; column temperature 140 °C−280 °C at 10 °C/min; t_R(minor) 9.54 min, t_R(major) 9.87 min.

(12) Stiller, E. T.; Harris, S. A.; Finkelstein, J.; Keresztesy, J. C.; Folkers, K. *J. Am. Chem. Soc.* **1940**, *62*, 1785.

selective Prins reaction of a chiral alkylidene morpholinone as the key step. Since (1*S*,2*R*)-ephedrine is also commercially available, (*R*)-pantolactone should be readily available by this method. Current efforts focus on the synthesis of pantolactone analogues and other reactions of **2** and related alkylidene morpholinones.

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Supporting Information Available: Experimental methods, spectroscopic data with assignments, ^{1}H and/or ^{13}C NMR spectra for compounds **3**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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