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Enantioselective synthesis of (*R*)-homocitric acid lactone

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Abstract—An expedient enantioselective approach to (*R*)-homocitric acid lactone from an ephedrine-derived morpholine-dione, a cationic glycolate equivalent, is described.

(*R*)-Homocitric acid (**1**, Fig. 1) is a key intermediate in the biosynthesis of L-lysine, an essential amino acid in some yeast and fungi,[1] and it is also a component of the Fe–Mo cofactor in nitrogenase.[2] The unique biological profile of homocitric acid is of interest in the development of antifungal therapies[3] and in the elucidation of the intricacies of nitrogen fixation.[4] Studies toward these objectives require access to enantiomerically enriched (*R*)-homocitric acid and its analogues,[5] neither of which are commercially available in significant amounts. Consequently, the enantioselective synthesis of homocitric acid, invariably isolated as its γ-lactone **2** (Fig. 1), has been actively investigated in recent years.[6] Syntheses of the racemate have also been reported recently.[7] In addition, it has been observed that the alkyl citrate, isocitrate, or α-alkyl malate motifs, which are close congeners of homocitrates, are key pharmacophoric units in several bioactive alkaloids, glycosides and antifungal agents.[8] This has added to the interest in substituted α-hydroxy di- and tri-carboxylic acid derivatives in recent years.

Our approach to (*R*)-homocitric acid is based on the double alkylation of a chiral oxalic acid derivative, the ephedrine-derived morpholinedione **3**,[9] which functions as a cationic glycolate equivalent. The dione **3** is easily prepared from commercially available 1*R*,2*S*-ephedrine and ethyloxalyl chloride in good yield (85%). Treatment of **3** with butenylmagnesium bromide generated the hemiacetal **4** (82%, Scheme 1). The diastereoselectivity of the process was moderate (1/1–5/1, depending on the reaction temperature) and the stereochemistry of the major diastereomer was not determined. The hemiacetal in **4** was readily allylated ($TiCl_4$, allytrimethylsilane, −40 °C) to furnish the dialkylmorpholinone **5** (68%) as a single diastereomer (98% ee).[10] The newly generated stereocenter in **5** was assigned the '*R*' configuration on the basis of an NOE experiment, which indicated a *syn* orientation of the allyl group and the benzylic hydrogen in the morpholinone ring. This result is probably the outcome of a stereoelectronically controlled axial allylation of the oxocarbenium ion in a boat-like transition state assembly (Scheme 1).[11]

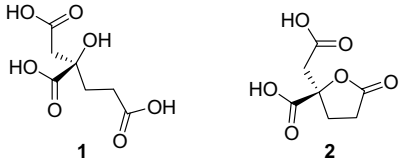
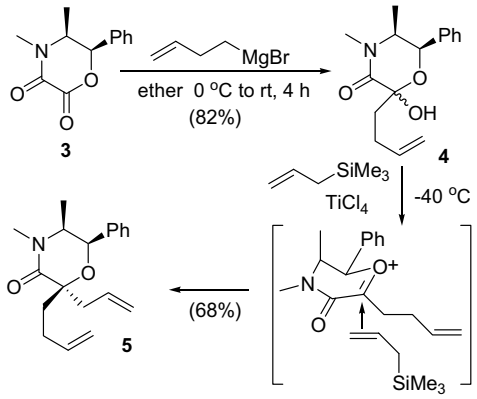


Figure 1. (*R*)-Homocitric acid (**1**) and (*R*)-homocitric acid lactone (**2**).



Scheme 1. Diastereoselective double alkylation of morpholinone **3**.

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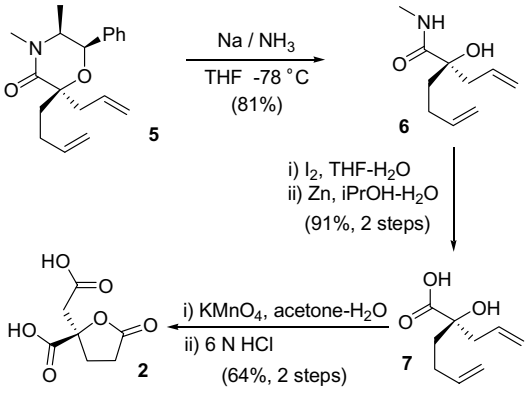
The overall conversion of the dione **3** to the dialkyl glycolamide **5** constitutes an asymmetric dialkylation of a chiral oxalic acid derivative. This procedure is an alternative to conventional approaches to chiral α,α-dialkylated glycolic acid derivatives that are based on sequential dialkylation of glycolate anions.[12] The approach may be advantageous when the S_N2 reactivity of the electrophile is a limitation in the anion alkylation protocol. Having constructed the required α-hydroxy stereocenter in the target molecule, we proceeded to remove the ephedrine portion in **5**. Dissolving metal reduction of **5** (Na/NH_3, −78 °C) provided the hydroxy amide **6** in good yield (81%, Scheme 2). Details of the homobenzylic C–N bond cleavage in **5** are not known at present. It is plausible that, at some stage in the reduction, a benzylic carbanion is generated and it undergoes facile β-elimination of the *N*-acyl moiety.[13] We next investigated the hydrolysis of the secondary amide in **6**. Not surprisingly, this proved to be a challenging task. Heating **6** in aqueous acids led to multiple products, some of which were presumably derived from intramolecular alcohol-alkene etherification reactions of **6**. Basic hydrolysis conditions resulted in decomposition. Attempts to activate the amide by N-nitrosation[14] were unsuccessful as were the efforts to convert the amide into an iminium species or an imidate ester. We therefore decided to utilize a two step procedure for achieving the required transformation. Treatment of **6** with iodine (2.5 equiv) gave a mixture of products. These are probably obtained by iodolactonization involving the amide and the allyl group and iodoetherification of some of the iodolactone by reaction of the tertiary alcohol with the butenyl group to generate a spiro ring system. Fortunately, when the crude product mixture was subjected to dehalogenative elimination with zinc, the hydroxy acid **7** was obtained in excellent yield (91%, Scheme 2). The efficiency of the dehalogenation reaction lends some credence to the proposed reactions of **6** with iodine, since the lactonization as well as the iodoetherification products should readily generate **7** after metallation with zinc.

The final step of the synthesis required the oxidative cleavage of the terminal alkenes in **7** to the carboxylic acids. This was readily achieved by treatment of **7** with aq $KMnO_4$ and $NaIO_4$ in acetone (Scheme 2). Acidification of a sodium bicarbonate extract of the crude reaction product furnished (*R*)-homocitric acid γ-lactone (64%, 98% ee, $[\alpha]_D^{23}$ −57.0 (*c* 1, H_2O); lit.[6c] $[\alpha]_D^{20}$ −48.9 (*c* 0.38, H_2O)). It may be noted that the use of labeled butenyl Grignard reagents[15] prepared from 4-bromobutene deuterated at C-4 should allow the introduction of deuterium in the lactone ring of **2**. Similarly, the use of deuterated allyltrimethylsilanes[16] should provide access to homocitrate that is deuterated in the acetate side chain. The synthesis is therefore well suited for the preparation of labeled homocitrates[5a] that may be of interest in biological studies.



Scheme 2. Synthesis of (*R*)-homocitric acid lactone.

Acknowledgements

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Supplementary data

Experimental methods, spectroscopic data with assignments, ^1H and ^{13}C data for all compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.005.

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