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A Concise, Enantioselective Approach to (−)-Quinic Acid

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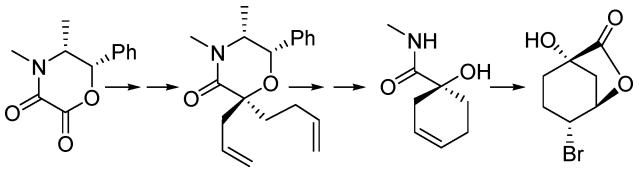
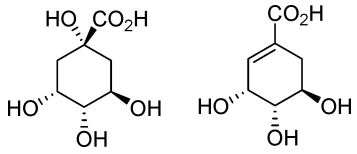
ABSTRACT



An expedient, enantioselective synthesis of a key precursor to (−)-quinic acid has been achieved from an ephedrine-derived morpholine-dione. The salient features of this approach are a highly diastereoselective conversion of the dione to a dialkenyl morpholinone and a subsequent ring-closing metathesis reaction. Removal of the ephedrine portion generates an enantiomerically enriched hydroxycyclohexene carboxamide that is readily converted to the quinic acid precursor.

Quinic acid (**1**) is found in plants and microorganisms and has a regulating role in the biosynthesis of aromatic compounds in the shikimate pathway.[1] The biosyntheses of quinic acid and shikimic acid (**2**) are interlinked and both are targets in the search for new herbicidal, antifungal, antibacterial, and antiparasitic agents that may not affect mammals.[2] In addition, quinic acid is a chiral starting material in the synthesis of viral neuraminidase inhibitors for the treatment of influenza.[3] Consequently, the enantioselective synthesis of quinic acid[4] and its analogues[5] has attracted interest in recent years. Interestingly, depending on the synthetic strategy, both quinic and shikimic acid can be accessed through common intermediates and a route to quinic acid potentially provides access to shikimic acid as well.[6]

Herein, we describe an efficient, enantioselective approach to (−)-quinic acid from readily available precursors. Our approach focuses on the asymmetric construction of the α-hydroxy acid moiety in quinic acid and begins with the enantiomerically pure morpholine-dione **3**[7] that is conveniently prepared (55%) from commercially available (1*S*,2*R*)-ephedrine hydrochloride and oxalyl chloride. Treat-



1 **2**

Figure 1. (−)-Quinic acid (**1**) and (−)-shikimic acid (**2**).

(1) (a) Haslam, E. *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, C., Eds.; Springer-Verlag: New York, 1996; Vol. 69, p 158. (b) Dewick, P. M. *Nat. Prod. Rep.* **1998**, *15*, 7 and references therein.

(2) (a) Kozlowski, M. C.; Tom, N. J.; Seto, C. T.; Sefler, A. M.; Bartlett, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 2128. (b) Roberts, F.; Roberts, C. W.; Johnson, J. J.; Kyle, D. E.; Krell, T.; Coggins, J. R.; Coombs, G. H.; Milhous, W. K.; Tzipori, S.; Ferguson, D. J. P.; Chakrabarti, D.; McLeod, R. *Nature* **1998**, *393*, 801.

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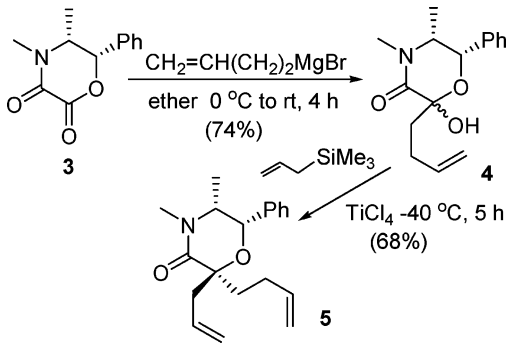
ment of **3** with the Grignard reagent derived from 4-bromobutene cleanly generated the hemiacetal **4** in 74% yield. The diastereoselectivity of the process was moderate (5/1) and the stereochemistry of the major diastereomer was not determined. The hemiacetal in **4** was readily allylated ($TiCl_4$, allyltrimethylsilane, −40 °C) to provide the dialkylated glycolamide derivative **5** (68%) as a single diastereomer (^1H NMR, Scheme 1).

Scheme 1

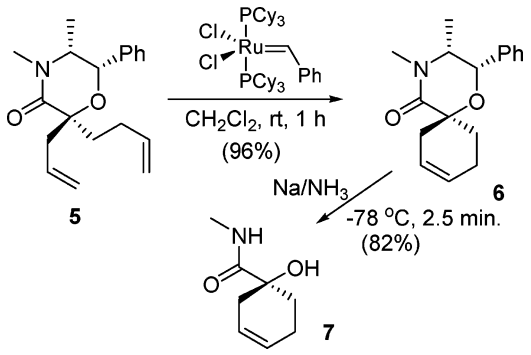


At this stage, the stereochemistry of the newly generated stereocenter in **5** was assigned the "*S*" configuration on the basis of a NOE experiment, which indicated a syn orientation of the allyl group and the benzylic hydrogen in the morpholinone ring.[8] The overall conversion of the dione **3** 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.[4f,9] The approach may be beneficial when the reactivity of the electrophile is a limitation.

The diene **5** is an excellent substrate for a ring-closing metathesis reaction. Thus, treatment of **5** with the Grubbs (generation I) catalyst (7 mol %, CH_2Cl_2, room temperature) cleanly generated the spiro-morpholinone **6** (96%), which contains the key α-hydroxy acid functionality and the carbon skeleton necessary for quinic acid (Scheme 2).

Dissolving metal reduction of **6** (Na/NH_3, −78 °C) removed the ephedrine portion to give the hydroxy amide **7**

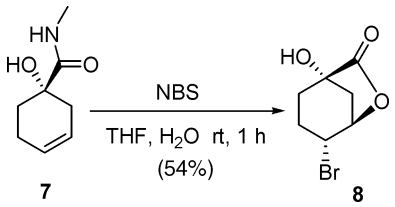
Scheme 2



in good yield (82%, Scheme 2) and 96% ee.[10] Details of the homobenzylic C−N bond cleavage in **6** 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.[11]

The formal synthesis of (−)-quinic acid was achieved by bromolactonization of **7**. Treatment of **7** with *N*-bromosuccinimide in moist THF at ambient temperature generated the bromolactone **8** (54% (unoptimized), 96% ee, Scheme 3).

Scheme 3



Spectroscopic data for lactone **8** were in agreement with those reported earlier[4f,12] and the optical rotation confirmed the "*S*" configuration at the α-carbon in the lactone ($[\alpha]_D$ −11.1, *c* 2, CH_2Cl_2; lit.[4f] $[\alpha]_D$ −9.1°, *c* 1.36, CH_2Cl_2 for material with 82% ee). This also confirmed the absolute stereochemistry of **5**.

To the best of our knowledge, this is the shortest and most efficient synthesis of enantiomerically enriched (−)-**8**. The only other asymmetric synthesis[4f] of (−)-**8** employs an enantiomerically enriched dioxolanone (a chiral glycolate derivative with 80% ee) as the starting material, which is obtained by a multistep synthesis from D-mannitol, and the key α,α-dialkylation of the dioxolanone proceeds with low diastereoselectivity (2/1). The present method represents a significant improvement since it requires fewer steps, and the dialkylglyolamide derivative **5** is easily prepared with high diastereoselectivity.

(5) (a) González, C.; Carballido, M.; Castedo, L. *J. Org. Chem.* **2003**, *68*, 2248. (b) Box, J. M.; Harwood, L. M.; Humphreys, J. L.; Morris, G. A.; Redon, P. M.; Whitehead, R. C. *Synlett* **2002**, 358. (c) An, M.; Toochinda, T.; Bartlett, P. A. *J. Org. Chem.* **2001**, *66*, 1326. (d) González-Bello, C.; Coggins, J. R.; Hawkins, A. R.; Abell, C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 849.

(6) See refs 4a, 4b, and 4d.

(7) For a synthesis of *ent*-**3** see: Rudchenko, V. F.; Shtamburg, V. G.; Pleshkova, A. P.; Kostyanovskii, R. G. *Bull Acad. Sci. USSR Div. Chem. Sci.* (*Engl. Transl.*) **1981**, *30*, 825. For a preparation *rac*-**3** see: Drefahl, G.; Hartmann, M.; Skurk, A. *Chem. Ber.* **1963**, *96*, 1011.

(8) This result can be explained by a stereoelectronically controlled axial allylation of the intermediate oxocarbenium ion in a boatlike transition state assembly. Pansare, S. V.; Ravi, R. G.; Jain, R. P. *J. Org. Chem.* **1998**, *63*, 4120.

(9) Ley, S. V.; Diez, E.; Dixon, D. J.; Guy, R. T.; Michel, P.; Natrass, G.; Sheppard, T. D. *Org. Biomol. Chem.* **2004**, *2*, 3608 and references therein.

(10) Determined by HPLC analysis on a Chiralpak AD-H column; see the Supporting Information for details.

(11) For examples of homobenzylic C−O bond cleavage in Na/NH_3 reduction, see: Samizu, K.; Ogasawara, K. *Tetrahedron Lett.* **1994**, *43*, 7989.

Racemic bromolactone **8**[12] and its iodo-analogue **9**[13] (Figure 2) are easily converted to the oxabicyclooctene

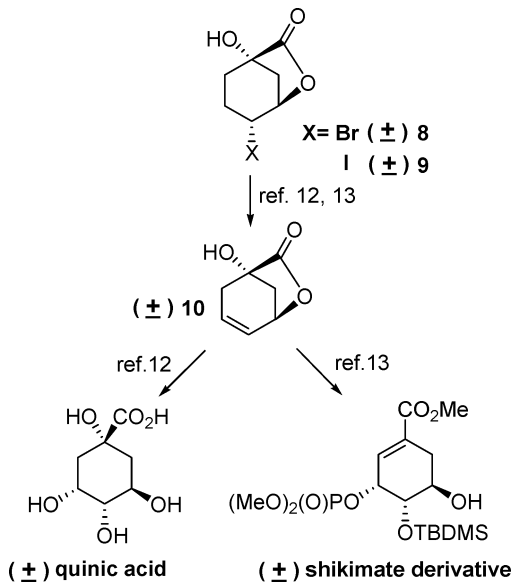


Figure 2. Halolactones **8** and **9** as precursors to quinic acid and shikimates.

derivative **10**[12,13] by dehydrohalogenation and subsequently to racemic quinic acid[12] (two steps) and a racemic, protected 3-phospho shikimate derivative[13] (four steps). Hence, the present synthetic route to enantiomerically enriched **8** establishes a route to enantiomerically enriched quinic acid and shikimic acid derivatives.

In conclusion, we have developed a short, enantioselective route to (−)-quinic acid that is extendable to shikimic acid derivatives. It is noteworthy that this method should provide access to either enantiomer of these biologically important metabolites since both enantiomers of ephedrine are commercially available. The oxalate dialkylation is an alternative to the conventional dialkylation of glycolate enolates and has potential for applications in the synthesis of polyhydroxylated cyclopentanes and cyclohexanes, as well as functionalized medium-sized carbocycles, by variation of the alkenyl groups in morpholinone **5**. We are currently investigating these and other applications of **3** and its enantiomer.

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

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(13) Bartlett, P. A.; McQuaid, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7854.