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Stereoselective Reactions of a (−)-Quinic Acid-Derived Enone: Application to the Synthesis of the Core of Scyphostatin

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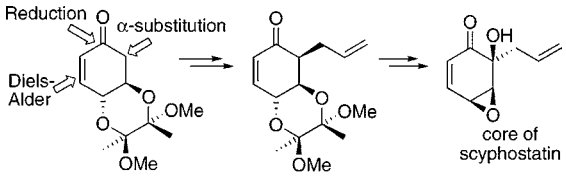
ABSTRACT

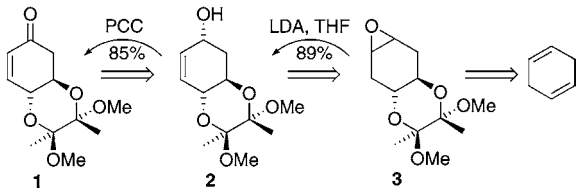


A (−)-quinic acid-derived enone, with the *trans*-1,2-diol protected as a 2,3-dimethoxybutanediyldioxy ketal, provides an excellent template for further highly stereoselective elaboration as exemplified by its conversion into the core of scyphostatin, a potent inhibitor of neutral sphingomyelinase.

The conformationally rigid cyclohexenone **1**, with the *trans*-1,2-diol protected as a 2,3-dimethoxybutanediyldioxy ketal, appears to be ideally suited to further stereoselective elaboration and therefore should prove to be a useful synthetic building block. Given our continued interest in the preparation of cyclohexane-based natural products,[1,2] we have explored the use of enone **1** in synthesis.

There are two published syntheses of enone **1**. In 2000, we reported the synthesis of racemic **1**:[3] LDA-mediated *diastereoselective* rearrangement of chiral (but racemic) epoxide **3** (prepared in three steps from 1,4-cyclohexadiene) gave allylic alcohol **2** (as a single diastereomer), and subsequent oxidation afforded enone **1** (Scheme 1). Maycock et al. then reported an efficient four-step synthesis of enone (4*R*,5*R*)-**1** starting from (−)-quinic acid[4], and it is this route to **1** that we have utilized in the present work.

Scheme 1



In this paper, we describe a range of stereoselective reactions of enone (4*R*,5*R*)-**1** and its corresponding trimethylsilyl enol ether. With both enone (4*R*,5*R*)-**1** and its enol ether, there is very little steric bias on either face for controlling stereoselective reactions of the π-systems. Indeed, we invoke subtle stereoelectronic effects to explain the highly stereoselective processes that are observed. Furthermore, to exemplify enone (4*R*,5*R*)-**1** as a useful synthetic building block, its use in the synthesis of the core of scyphostatin is also described. Scyphostatin[5] is a cyclohexenone-based naturally occurring inhibitor of neutral sphingomyelinase and has attracted significant synthetic interest of late.[2a,6]

(1) de Sousa, S. E.; O'Brien, P.; Pilgram, C. D. *Tetrahedron* **2002**, *58*, 4643.

(2) (a) Runcie, K.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 3237. (b) Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Taylor, R. J. K. *J. Org. Chem.* **1998**, *63*, 3526.

(3) Kee, A.; O'Brien, P.; Pilgram, C. D.; Watson, S. T. *Chem. Commun.* **2000**, 1521.

(4) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 166.

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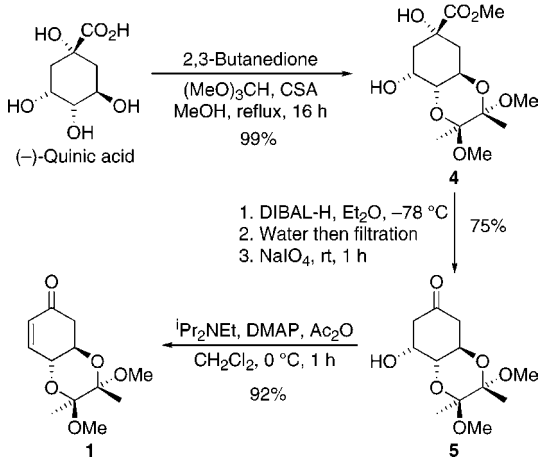
To start with, gram quantities of enone (4*R*,5*R*)-**1** were prepared from (−)-quinic acid using minor modifications to the literature route reported by Maycock et al.[4] (Scheme 2).

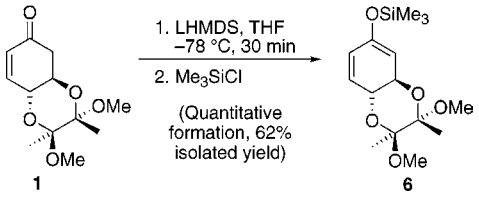
Scheme 2



In a one-step process (reported as unpublished work in a review article[7]), (−)-quinic acid was converted into bis-ketal **4** with concomitant methyl ester formation (99% yield). The 2,3-dimethoxybutanediyldioxy ketal group, introduced by Ley and co-workers,[7,8] selectively protects the *trans*-1,2-diol and provides a conformational lock in enone (4*R*,5*R*)-**1**. Conversion of bis-ketal **4** into ketone **5** via ester reduction and subsequent cleavage of the 1,2-diol following the published procedure proved to be problematic in our hands. Eventually, reproducible yields of 75% over the two steps were obtained using a modified workup procedure after the DIBAL-H step (see Supporting Information for full details). Elimination of the hydroxyl group in ketone **5** proceeded uneventfully to furnish enone (4*R*,5*R*)-**1**.

Initially, we envisaged exploring α-functionalization of enone (4*R*,5*R*)-**1** via its enolate. To demonstrate that the enolate could be formed without elimination of the *β*-alkoxyl group, enone (4*R*,5*R*)-**1** was deprotonated with LHMDS in THF at −78 °C for 30 min and then reacted with Me_3SiCl. After workup, analysis by ^1H NMR spectroscopy indicated quantitative formation of silyl enol ether **6** (62% isolated yield after chromatography; Scheme 3). Satisfied that the enolate could be generated without *β*-elimination, we investigated alkylation reactions of the lithium enolate. Direct

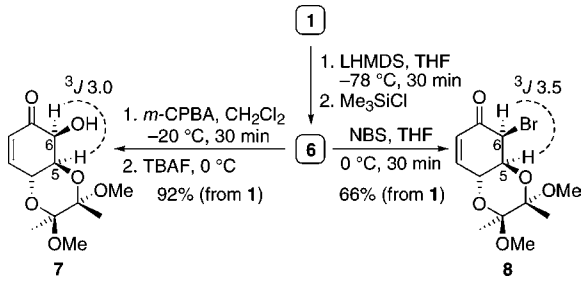
Scheme 3



alkylation of the lithium enolate of **1** with allyl halides under a variety of conditions met with complete failure. Therefore, our attention switched to reactions of silyl enol ether **6**.

Two very useful transformations of silyl enol ether **6** were found: reaction with *m*-CBPA (Rubottom oxidation[9]) followed by treatment with TBAF gave **7** (92% yield), and reaction with NBS gave **8** (66% yield), both as single diastereomers (Scheme 4). In both adducts **7** and **8**, the

Scheme 4



relative stereochemistry was assigned on the basis of the small ^3J coupling constant of 3.0−3.5 Hz between H-5 (known axial orientation due to the bis-ketal protecting group) and H-6.

The exclusive axial attack on silyl enol ether **6** using *m*-CPBA and NBS as electrophiles is noteworthy. High levels of stereoselectivity using these types of reactions are usually governed by steric factors, and in previously reported reactions of conformationally locked but sterically unbiased silyl enol ethers with *m*-CPBA[10] or NBS,[11] the sense and degree of stereoselectivity is quite varied and not predictable. The complete stereocontrol exhibited by electrophilic attack on silyl enol ether **6** (which has no obvious steric bias) is a consequence of the conformational rigidity imparted by the trans-diequatorial-protected 1,2-diol *and* the stereoelectronic preference for axial attack on the electron-rich C-6 (avoiding a twist boat conformation[12]).

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(7) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53.

(8) Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Poisson, J.-F.; Warriner, S. L.; Wesson, K. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2023.

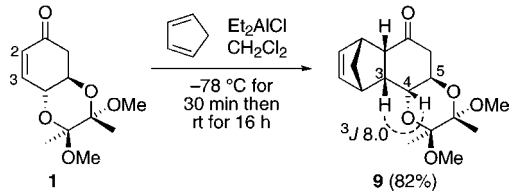
(9) Rubottom, G. M.; Gruber, J. M.; Juve, H. D.; Charleson, D. A. *Org. Synth.* **1986**, *64*, 118.

(10) (a) Jones, T. K.; Denmark, S. E. *J. Org. Chem.* **1985**, *50*, 4037. (b) Baudouy, R.; Maliverney, C. *Tetrahedron* **1988**, *44*, 471. (c) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523. (d) Majewski, M.; Irvine, N. M.; MacKinnon, J. *Tetrahedron: Asymmetry* **1995**, *6*, 1837. (e) Minor, K. P.; Overman, L. E .*Tetrahedron* **1997**, *53*, 8927.

(11) (a) Parker, K. A.; Dermatakis, A. *J. Org. Chem.* **1997**, *62*, 6692. (b) Kreiser, W.; Körner *Helv. Chim. Acta* **1999**, *82*, 1610. (c) Paquette, L. A.; Wang, X. *J. Org. Chem.* **1994**, *59*, 2052.

We have already noted that Luche reduction ($NaBH_4$/$CeCl_3$) of enone (4*R*,5*R*)-**1** occurs via axial attack of hydride on the C═O group to give the corresponding allylic alcohol.[3] To further probe the stereoelectronic preferences in this system, enone (4*R*,5*R*)-**1** was subjected to a Diels−Alder reaction. Thus, enone (4*R*,5*R*)-**1** was converted into a single diastereomer of Diels−Alder adduct **9** on reaction with cyclopentadiene in the presence of Et_2AlCl (82% isolated yield; Scheme 5).[13]

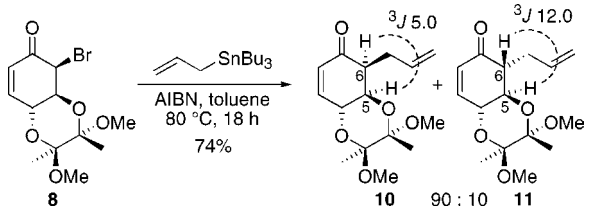
Scheme 5



Adduct **9** was identified as the expected *endo*-diastereomer by a 6.1% NOE between an alkene proton and H-5. Further NOE analysis together with a ^3J coupling constant of 8.0 Hz between H-3 and H-4 allowed assignment of the C-3/C-4 stereochemistry. This highly stereoselective Diels−Alder reaction also proceeds via a stereoelectronically preferred axial attack on the electron-deficient C-3 carbon.

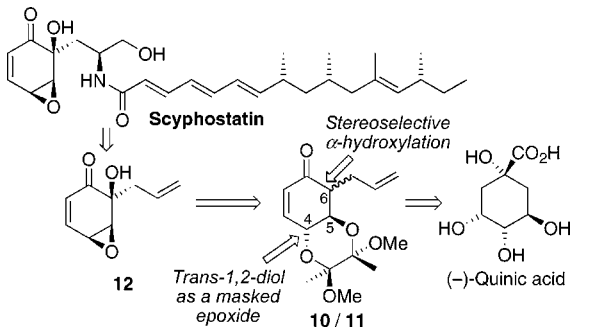
For our proposed scyphostatin studies (vide infra), we wished to incorporate an α-allyl side chain onto enone (4*R*,5*R*)-**1**, but as discussed, direct allylation of the lithium enolate was not successful. Instead, we investigated Keck allylation[14] of α-bromo enone **8** using allyltributyltin and AIBN. Additionally, this would provide a further test of the preferential axial attack on the sp^2 carbon α to the carbonyl in enone (4*R*,5*R*)-**1**. Reaction of α-bromo enone **8** with allyltributyltin at 80 °C in toluene (with AIBN) gave a 74% isolated yield of an inseparable 90:10 mixture of α-allylated enones **10** and **11**, identified by analysis of the ^3J coupling constants between H-5 and H-6 (Scheme 6). Thus, an sp^2-hybridized radical at C-6 undergoes preferential axial attack.

Scheme 6



To demonstrate the usefulness of these highly stereoselective reactions of enone (4*R*,5*R*)-**1** in synthesis, we identified the core of scyphostatin (Scheme 7) as a viable target. Scyphostatin was isolated in 1997[5] from a mycelial extract of *Dasyscyphus mollisimus*, and it remains the most potent inhibitor of the enzyme neutral sphingomyelinase

Scheme 7



(N-SMASE). To date, no total synthesis of scyphostatin has been reported, although several approaches to core structures have appeared recently.[2a,6]

Our strategy toward α-allyl scyphostatin model core **12** is outlined in Scheme 7. Two key features are (i) stereoselective α-hydroxylation of a silyl enol ether derived from α-allyl enone **10** or **11** in which axial attack at C-6 (analogous to **6** → **7**, see Scheme 4) would establish the required α-hydroxyl relative stereochemistry in **12** and (ii) use of the protected *trans*-1,2-diol functionality in **10** or **11** as a masked epoxide in which subsequent regioselective activation of the less sterically hindered C-4 hydroxyl group would lead to the required epoxide stereochemistry in **12**. Furthermore, the absolute stereochemistry of the core of scyphostatin can be derived from that present in (−)-quinic acid via this approach. Katoh et al. have also utilized (−)-quinic acid as starting material in a different approach to scyphostatin core compounds.[6d,e]

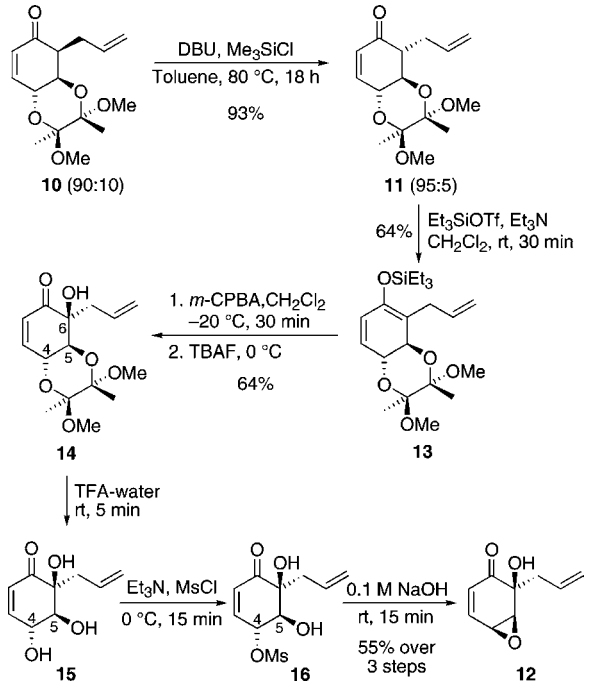
The details of the successful and highly stereoselective synthesis of scyphostatin model core **12** are outlined in Scheme 8. First of all, we discovered that it was not possible to convert the major α-allyl diastereomer **10** into a silyl enol ether (e.g., **13**) using either LHMDS/Me_3SiCl or Et_3N/R_3-SiX (R = Me or Et; X = Cl or OTf). Presumably, an axially oriented proton at C-4 (equatorial allyl group as in **11**) is required to facilitate silyl enol ether formation, and so conditions for epimerizing **10** into **11** (equatorial allyl group) were sought. Some epimerization of **10** into **11** was observed using NaOMe in methanol, but it was accompanied by decomposition (probably via elimination of the *β*-alkoxyl group). More success was obtained using DBU in toluene at 80 °C, but after 16 h, epimerization was only partially complete. Therefore, we attempted to directly form a

(12) (a) Matthews, R. S.; Girgenti, S. J.; Folkers, E. A. *J. Chem. Soc., Chem. Commun.* **1970**, 708. (b) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 1000. (c) Skaddan, M. B.; Wüst; Katzenellenbogen, J. A. *J. Org. Chem.* **1999**, *64*, 8108.

(13) For examples of related Diels−Alder reactions, see: (a) Jeroncic, L. O.; Cabal, M.-P.; Danishefsky, S. J.; Shulte, G. M. *J. Org. Chem.* **1991**, *56*, 387. (b) Millan, D. S.; Pham, T. T.; Lavers, J. A.; Fallis, A. G. *Tetrahedron Lett.* **1997**, *38*, 795.

(14) (a) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829. (b) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079. (c) Umehare, M.; Honnami, H.; Hishida, S.; Kawata, T.; Ohba, S.; Zen, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 562. (d) Bamford, S. J.; Luker, T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **2000**, *2*, 1157.

Scheme 8



trimethylsilyl enol ether from the 90:10 mixture of **10** and **11** by reaction with DBU and Me_3SiCl in toluene at 80 °C for 18 h. To our surprise and delight, almost complete epimerization was observed: we isolated a 93% yield of a 95:5 mixture of **11** and **10**. Silyl enol ether formation was never observed under these conditions.

The remainder of the synthesis of scyphostatin core **12** proceeded as anticipated. Thus, the 95:5 mixture of **11** and **10** was converted into silyl enol ether **13** (64% isolated yield) using Et_3SiOTf/Et_3N. Rubottom oxidation of **13** using the same conditions as for **6** → **7** (see Scheme 4) furnished a single diastereomer of α-hydroxy enone **14** (64% isolated yield). The expected axial attack at C-6 was confirmed by a 3.2% NOE between the hydroxyl proton and H-4 and by NOEs between H-5 and protons on the allyl side chain. The conversion of α-hydroxy enone **14** into model core compound **12** was carried out via three steps without isolation of any of the intermediates. Deprotection of the bis-ketal protecting group using TFA−water[8] was followed by mesylation using 1 equiv of mesyl chloride. Finally, treatment of the crude mesylate with 0.1 M aqueous NaOH (Katoh's conditions[6d,e]) gave epoxy enone **12** {$[\alpha]_D$ +31.6 (*c* 0.35 in $CHCl_3$)} as the only isolable diastereomeric product in 55% yield over the three steps. The ^{1}H NMR spectrum of **12** in acetone-d_6 was identical to that reported for racemic **12**,[2a] thus confirming the epoxide stereochemistry and establishing that regioselective mesylation of the least hindered C-4 hydroxyl group in **15** must have occurred. Thus, a highly stereoselective, 11-step synthesis of enantiomerically pure scyphostatin core **12** starting from (−)-quinic acid has been achieved.

In summary, we report a selection of highly stereoselective reactions of enone (4*R*,5*R*)-**1** (derived from (−)-quinic acid). These include, α-hydroxylation, α-bromination, C=O reduction, Diels−Alder reaction with cyclopentadiene, and radical α-allylation. In particular, enone (4*R*,5*R*)-**1** can be converted in just eight steps into a scyphostatin model core compound **12** in enantiomerically pure form. On the basis of our findings, it seems likely that enone (4*R*,5*R*)-**1** will be a useful building block for future synthetic endeavors.

Acknowledgment. We thank the BBSRC and Hoffman-La-Roche for a CASE award (to L.M.M.) and Dr. Graeme McAllister for carrying out the NOE experiments.

Supporting Information Available: Full details on the synthesis of enone (4*R*,5*R*)-**1** and on the synthesis, characterization, and ^{1}H NMR spectra of all intermediates en route to epoxy enone **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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