ORGANIC LETTERS

2006
Vol. 8, No. 10
2019−2021

# Regiospecific Hydration of γ-Hydroxy-α,β-acetylenic Esters: A Novel Asymmetric Synthesis of Tetronic Acids

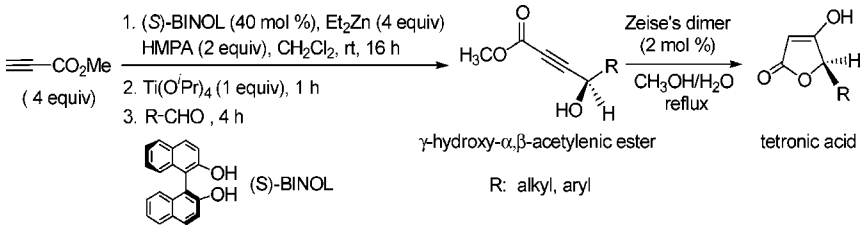
**Amaresh R. Rajaram and Lin Pu***

*Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904-4319*

*lp6n@virginia.edu*

**Received February 13, 2006**

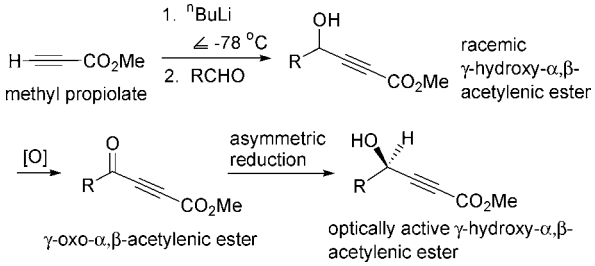
## ABSTRACT




**The optically active γ-hydroxy-α,β-acetylenic esters are obtained from the enantioselective reaction of methyl propiolate with both aliphatic and aromatic aldehydes. These compounds can undergo regiospecific hydration in the presence of Zeise's dimer, $[PtCl_2(C_2H_4)]_2$, to generate the optically active tetronic acids.**

Optically active γ-hydroxy-α,β-acetylenic esters are a class of highly functional compounds with versatile synthetic applications.[1,2] These compounds are generally prepared by oxidation of the racemic γ-hydroxy-α,β-acetylenic esters to the corresponding γ-oxo-α,β-acetylenic esters followed by asymmetric reduction (Scheme 1).[2] The racemic γ-hydroxy-α,β-acetylenic esters are normally prepared from the treatment of a propynoate, e.g., methyl propiolate, with $^n$BuLi at very low temperature, often ≤ −78 °C, followed by addition to an aldehyde.[1a] Although it would be much more efficient to synthesize the optically active γ-hydroxy-α,β-acetylenic esters by the asymmetric addition of methyl propiolate to aldehydes, no such process was developed until recently.[3,4]

**Scheme 1.** Synthesis of Optically Active γ-Hydroxy-α,β-acetylenic Esters by Asymmetric Reduction




We discovered that 1,1′-bi-2-naphthol (BINOL) in combination with $Et_2Zn$, $Ti(O^iPr)_4$, and HMPA can catalyze the highly enantioselective reaction of methyl propiolate with aromatic aldehydes at room temperature (Scheme 2).[3] In this paper, we describe a further expansion of the scope of the substrates for this reaction to include various types of ali-

(1) (a) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28−29. (b) Molander, G. A.; St. Jean, D. J., Jr. *J. Org. Chem.* **2002**, *67*, 3861−3865. (c) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2004**, *126*, 13942−13944. (e) Tejedor, D.; Garcia-Tellado, F.; Marrero-Tellado, J. J.; de Armas, P. *Chem. Eur. J.* **2003**, *9*, 3122−3131. (f) Meta, C. T.; Koide, K. *Org. Lett.* **2004**, *6*, 1785−1787.

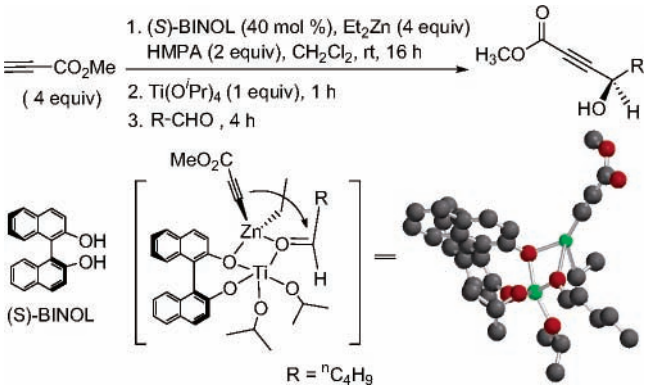
(2) (a) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867−869. (b) Noyori, R.; Yamada, T. M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717−6725. (c) Duvold, T.; Rohmer, M. *Tetrahedron Lett.* **2000**, *41*, 3875−3878. (d) Mulzer, J.; Csybowski, M.; Bats, J.-W. *Tetrahedron Lett.* **2001**, *42*, 2961−2964. (e) Johansson, M.; B. Köpcke, B.; Anke, H.; Sterner, O. *Tetrahedron* **2002**, *58*, 2523−2528.

(3) Gao, G.; Wang, Q.; Yu, X.-Q.; Xie, R.-G.; Pu, L. *Angew. Chem., Int. Ed.* **2005**, *45*, 122−125.

(4) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8−9.

10.1021/ol060377v CCC: $33.50 
**Published on Web 04/15/2006**

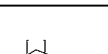
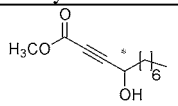
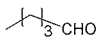
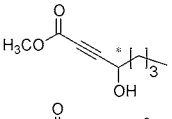
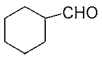
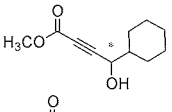
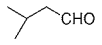
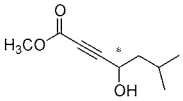
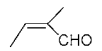
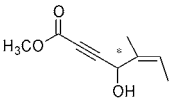
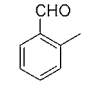
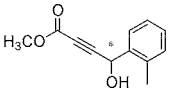
**Scheme 2.** Asymmetric Addition of Methyl Propiolate to Aldehydes




phatic aldehydes. In addition, we have discovered that the optically active $\gamma$-hydroxy-$\alpha,\beta$-acetylenic ester products can undergo a regiospecific hydration to generate tetronic acids while maintaining the optical purity. Herein these results are reported.

We first used (*S*)-BINOL to catalyze the reaction of methyl propiolate with aliphatic aldehydes in the presence of $Et_2Zn$ and $Ti(O^iPr)_4$ to synthesize the optically active $\gamma$-hydroxy-$\alpha,\beta$-acetylenic esters (Scheme 2). The results are summarized in Table 1. Good enantioselectivity has been observed for

**Table 1.** Results for the Enantioselective Addition of Methyl Propiolate to Aldehydes Catalyzed by BINOL-HMPA-Ti

| entry | aldehyde | γ-hydroxy-α,β-acetylenic ester | yield (%) | ee (%) |
|---|---|---|---|---|
| 1 |  |  | 72 | 81[a] |
| 2 |  |  | 76 | 89[a] |
| 3 |  |  | 60 | 81[a] |
| 4 |  |  | 73 | 83[a] |
| 5 |  |  | 38 | 90[a] |
| 6[3] |  |  | 96 | 91[b] |

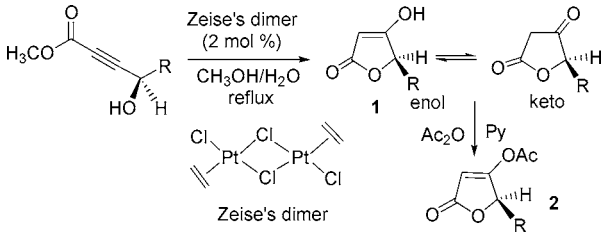
[a] Measured by analyzing the $^1$H NMR spectrum of the mandelate acetate. [b] Obtained by using a HPLC-chiral column.

the reaction of methyl propiolate with a linear (entries 1 and 2), α-branched (entry 3), and $\beta$-branched aliphatic aldehyde (entry 4). High enantioselectivity was also observed for the addition to an $\alpha,\beta$-unsaturated aldehyde, though the yield is not high (entry 5). The result in entry 6 for the addition to an *ortho*-substituted aromatic aldehydes was reported,[3] and it is included here because of the subsequent hydration study (vide infra). On the basis of the previous study,[3] the products generated from (*S*)-BINOL should have a *R*-configuration and those from (*R*)-BINOL should have a *S*-configuration.

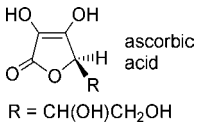
The mechanism for the BINOL-catalyzed alkyne addition to aldehydes is unknown at the current stage. An intermediate shown in Scheme 2 is only a tentative hypothesis provided to help us understand this process. The molecular modeling structure of this intermediate was established with the PC Spartan-Semiempirical PM3 program. In this intermediate, the ethyl group on the zinc center is down in order to avoid the steric interaction between its α-sp$^3$ carbon and the 3-H of the (*S*)-BINOL ligand. The alkyl group of the aldehyde is up in order to avoid the steric interaction with the ethyl group on the zinc and to reduce the interaction with the isopropoxy groups on the titanium. The alkynyl group on the zinc will then attack the *si* face of the aldehyde to give the observed (*R*)-propargylic alcohol product.

We studied the hydration of the optically active $\gamma$-hydroxy-$\alpha,\beta$-acetylenic esters by using Ziese's dimer as the catalyst.[5,6] In a refluxing $CH_3OH/H_2O$ (3:1) solution, the hydration of a $\gamma$-hydroxy-$\alpha,\beta$-acetylenic ester occurred with water attacking the $\beta$-position specifically to generate tetronic acids of general formula **1** (Scheme 3). The 300 MHz $^1$H NMR

**Scheme 3.** Regiospecific Hydration of $\gamma$-Hydroxy-$\alpha,\beta$-acetylenic Esters Catalyzed by Zeise's Dimer




spectra of these tetronic acids generally showed that both the keto and enol tautomers were present in solution. This compound belongs to the family of the biologically significant tetronic acids.[7,8] One of the best known examples of tetronic acids is vitamin C (ascorbic acid).

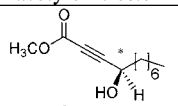
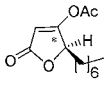
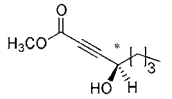
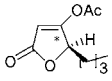
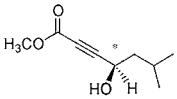
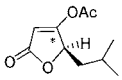
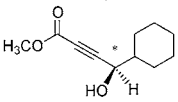
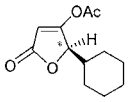
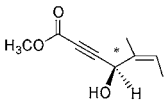
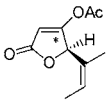
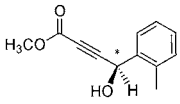
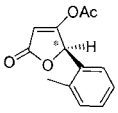



In the catalytic hydration of the optically active $\gamma$-hydroxy-$\alpha,\beta$-acetylenic esters, 2 mol % of the Zeise dimer was used.

(5) Hiscox, W.; Jennings, P. W. *Organometallics* **1990**, *9*, 1997−1999.
(6) Jenning, P. W.; Hartman, J. W.; Hiscox, W. C. *Inorg. Chim. Acta* **1994**, *222*, 317−322.
(7) (a) Tejedor, D.; Garcia-Tellado, F. *Org. Prep. Proced. Int.* **2004**, *36*, 33−59. (b) Roggo, B. E.; Petersen, F.; Delmendo, R.; Jenny, H. B.; Peter, H. H.; Roesel, J. *J. Antibiot.* **1994**, *47*, 136−142. (c) Effenberger, F.; Syed, J. *Tetrahedron: Asymmetry* **1998**, *9*, 817−825 and references therein.

The resulting product **1** was then treated with acetic anhydride and pyridine, which quantitatively converted both the enol and keto tautomers of **1** to the acetate **2** (Scheme 3). The ee of the acetate was determined by using a GC-$\beta$-cyclodextrin column. As the results summarized in Table 2

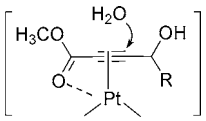
**Table 2.** Results for the Conversion of the $\gamma$-Hydroxy-$\alpha,\beta$-acetylenic Esters to **2**

| entry | γ-hydroxy-α,β-acetylenic ester | acetate of tetronic acid (**2**) | yield (%) | ee (%) |
|---|---|---|---|---|
| 1 |  |  | 55 | 80 |
| 2 |  |  | 66 | 83 |
| 3 |  |  | 61 | 74 |
| 4 |  |  | 78 | 82 |
| 5 |  |  | 46 | 90 |
| 6 |  |  | 41 | 92[b] |

[a] Obtained by using GC-$\beta$-cyclodextrin column. [b] Estimated (>95% reliable) since baseline resolution was not achieved.

show, the enantiomeric purities of the tetronic acid products are all very similar to those of the starting aliphatic $\gamma$-hydroxy-$\alpha,\beta$-acetylenic esters (entries 1−5). The $\gamma$-hydroxy-$\alpha,\beta$-acetylenic ester derived from *o*-methylbenzaldehyde also gave the hydration product with high enantiomeric purity (entry 6). We tested the hydration of other aromatic $\gamma$-hydroxy-$\alpha,\beta$-acetylenic esters, but significantly reduced enantiomeric purity was observed. It appears that the product derived from the *ortho*-substituted benzaldehyde has a stable chiral configuration under the reaction conditions, whereas the chiral configurations of the products derived from *para*- and *meta*-substituted benzaldehydes are not especially stable.

The intermediate **3** is proposed for the Pt(II)-catalyzed hydration of the $\gamma$-hydroxy-$\alpha,\beta$-acetylenic esters.[5,6] In **3**, the electron-withdrawing effect of the ester group, the Lewis acidity of the Pt(II) center, and the chelate effect in the coordination of the acetyleneic ester to the Pt(II) center might have all contributed to the observed regiospecific hydration.



**3**

In summary, we have demonstrated that the optically active $\gamma$-hydroxy-$\alpha,\beta$-acetylenic esters can be obtained from the enantioselective reaction of methyl propiolate with both aliphatic and aromatic aldehydes. These compounds can undergo regiospecific hydration in the presence of Zeise's dimer, a Pt(II) complex, to generate the optically active tetronic acids. This work provides a new and efficient asymmetric synthesis of the biologically significant tetronic acids.

**Acknowledgment.** Support of this work from the National Institute of Health (R01GM58454/R01EB002037) is gratefully acknowledged.

**Supporting Information Available:** Synthesis and characterization of the $\gamma$-hydroxy-$\alpha,\beta$-acetylenic esters and tetronic acids. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060377V

(8) (a) Boll, P. M.; Sorensen, E.; Balieu, E. *Acta Chem. Scand*. **1968**, *22*, 3251−3255. (b) Witiak, D. T.; Tehim, A. K. *J. Org. Chem.* **1990**, *55*, 1112−1114. (c) Datta, A.; Schmidt, R. R. *Synlett* **1992**, 429−430. (d) Datta, A.; Datta, D.; Schmidt, R. R. *Tetrahedron Lett*. **1992**, *33*, 8035−8038. (e) Desmaële, D. *Tetrahedron* **1992**, *48*, 2925−2934.