

A Novel Method of Highly Enantioselective Synthesis of γ -Hydroxy- β -Keto Phosphonates *via* Allene Oxides

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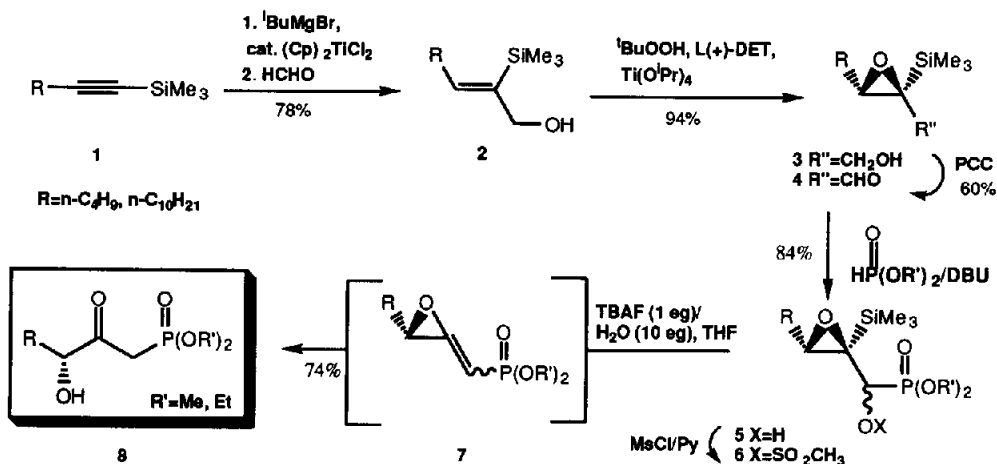
Abstract: *Optically active γ -hydroxy- β -keto phosphonates **8** (96-97% ee) were obtained starting from 1-trimethylsilyl-1-alkynes **1** by employing chiral allene oxides for introduction of α -hydroxy carbonyl functionality.*

β -Keto phosphonates are commonly employed as synthetic reagents, particularly in the Horner-Wadsworth-Emmons reaction.¹⁾ The commonly used methods for preparing β -keto phosphonates are the Arbuzov reaction²⁾ and acylation of phosphonate anions³⁾. Both methods suffer from individual restrictions and have common limitations. The Arbuzov reaction of trialkyl phosphites and α -halo ketones is limited to the highly reactive α -halo ketones, due to poor nucleophilicity of phosphites and the Perkow reaction⁴⁾ to give enol phosphates. The acylation of alkyl phosphate anions suffers from the limited availability of alkyl phosphonates and low reactivities resulting from the proton exchange between the usually more acidic β -keto phosphonates generated and the 1-lithio alkyl phosphonates used as starting materials. In contrast to the significant progress⁵⁾ that has expanded the original scope of the Horner-Wadsworth-Emmons condensation, relatively little work has appeared⁶⁾ on new syntheses of β -keto phosphonates.

In connection with our work⁷⁾ on the application of chiral allene oxides for the synthesis of α -substituted carbonyl compounds, we would like to report a highly enantioselective, mild method for the preparation of γ -hydroxy- β -keto phosphonates (96-97% ee) by using allene oxide methodology⁸⁾ for introduction of the α -hydroxy carbonyl functionality.

The starting compounds, 1-trimethylsilyl-1-alkynes **1**, (*cf.* the Scheme) were transformed into (2*S*,3*S*)-epoxy-aldehydes **4** in a three step protocol:⁹⁾ i) hydromagnesiation¹⁰⁾ of **1** and reaction with formaldehyde to form (*E*)-allylic alcohols **2** ii) Sharpless asymmetric epoxidation¹¹⁾ [tBuOOH and L-(+)-diethyl tartrate/Ti(O^{*i*}Pr)₄] followed by iii) PCC oxidation of **3**. The optical purity of the epoxides **3** (97% ee) was established by their transformation into MTPA esters. Aldehydes **4** were subsequently reacted with dialkyl phosphites (R'O)₂P(O)H (R'=Me, Et) in the presence¹²⁾ of DBU in THF solution giving a mixture of diastereomeric alcohols **5** which subsequently were transformed into mesylates **6**. Compounds **6** were prepared with the aim to serve as allene oxides precursors for a fluoride promoted elimination process. Thus, treatment of a THF solution of **6** at room temperature with 1 eq of TBAF and 10 eq of H₂O provided allene oxides **7** which could be opened by water *in situ* to yield the required (*R*)- γ -hydroxy- β -keto phosphonates **8**¹³⁾. The optical purity of the phosphonates **8** (96-97% ee by ¹H NMR with Eu(hfc)₃ of **8** protected with ^tBuMe₂SiCl) was demonstrated to be the same as silyl epoxides **3**.

By application of the method described above various (*R*)- or (*S*)- γ -hydroxy- β -keto phosphonates (depending on the chiral catalyst used for the Sharpless epoxidation) may be obtained for further transformation into the desired chiral products.



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- 13) Experiments were carried out in 1 mmol scale. Analytical data for **8** (R=n-C₄H₉, R'=C₂H₅); b.p.=140-142 °C/0.4 mmHg (Kugelrohr); $[\alpha]_D^{20} = +11.1^\circ$ (c 0.6, CH₂Cl₂); IR (CHCl₃): 3408 (OH), 1715 (C=O) and 1027 [P(OEt)₂] cm⁻¹; ¹H NMR (CDCl₃): 0.91 (3H, t, J 7.5, CH₃), 1.34 (3H, t, J 7.0, OCH₂CH₃), 1.35 (3H, t, J 7.0, OCH₂CH₃), 1.3-1.45 (4H, m, CH₂), 1.53-1.65 (1H, m, CH₂), 1.75-1.85 (1H, m, CH₂), 3.21 and 3.37 (2H, dqAB, J_{AB} 13.1, J_{PH} 23.2, CH₂-P), 4.1-4.25 (5H, m, OCH₂- and CH-OH); ³¹P (CDCl₃): 20.47 (triplet of quintet, J 23 and 7.5); ¹³C (CDCl₃): 13.93, 16.38 (d, J_{CP} 8.4), 22.46, 27.25, 33.22, 38.67 (d, J_{CP} 26.3), 63.10 (d, J_{CP} 6.6), 77.49; MS: 267 (M+1, 1%), 238 (1), 221 (1), 209 (2), 179 (8), 152 (100), 125 (92), 108 (28), 97 (35); MS-HR: C₁₁H₂₃O₅P requires 266.1283, found 266.1305.

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