

Phosphonate Aldehyde Annulation. A One-Pot Synthesis of δ -Hydroxy Cyclopentenoic Esters

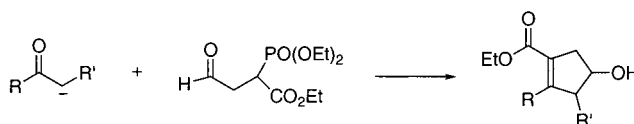
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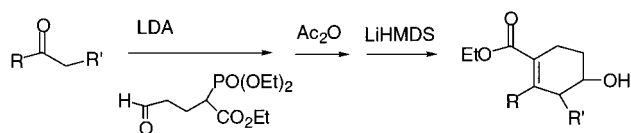
Received March 15, 2002

ABSTRACT



The reaction of ketone enolates with phosphonate aldehyde **2** afforded cyclopentenols **3** or keto esters **4** in a one-pot procedure.

The synthesis of functionalized bicyclic systems by carbanion-based annulation reactions is well established.¹ The formation of cyclohexenones via Michael addition/aldol/dehydration protocols² and the generation of cyclohexanedi-ones via Michael addition/Claisen condensation pathway³ are well-known examples. Recently, we reported that ketone enolates reacted with phosphonate aldehydes to give, after protection and cyclization, hydroxy esters.⁴ This three-step procedure shown below afforded modest overall yields of products.



In the context of understanding the effect that changes in structure have upon the soybean cyst nematode hatching

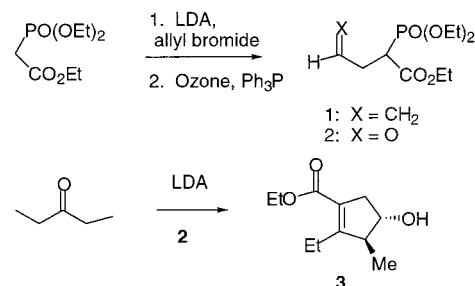
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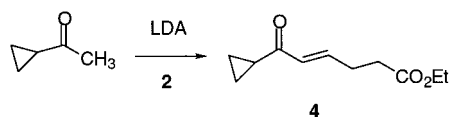
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activity of glycinoeclepin A analogues, we required several δ -hydroxy cyclopentenoic acids.⁵ We prepared phosphonate aldehyde **2** from **1**⁶ by ozonolysis of **1** at -78 °C in methylene chloride/methanol in 83% yield. The reaction of **2** with the enolate of 3-pentanone afforded hydroxy ester **3** directly in 53% yield. This compound was converted quantitatively into the acetate. The acetate was an inseparable 10:1 mixture of diastereomers as evidenced by the absorption of the acetoxy group in the proton NMR spectrum.⁷ A NOESY experiment showed that the methyl group and the methine proton attached to the carbon bearing the acetoxy group were cis.

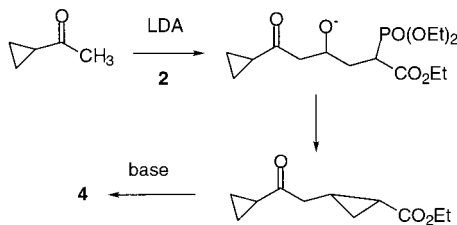


To our surprise, the reaction of methyl cyclopropyl ketone with lithium diisopropylamide (LDA) followed by the addition of **2** produced the keto ester **4** in 48% yield. Surprisingly, no product derived from the addition of the enolate of methyl cyclopropyl ketone to the aldehyde **2**

followed by anion exchange and cyclization to a hydroxy cyclopentene carboxylate was isolated. The structure of **4**



was supported by two methylene groups centered at δ 2.49 and 2.56 and by resonances at δ 6.26 ($J = 11.8$ Hz) and 6.88 ($J = 11.8$, 5 Hz) which were indicative of a trans double bond conjugated with a carbonyl group. A possible mechanism for the formation of compound **4** is depicted below. Although certain γ -hydroxy phosphine oxides have been reported by Warren and co-workers to produce cyclopropanes,⁸ this reaction appears unknown for hydroxy phosphonates. The last step in the mechanism, the base-mediated ring opening of cyclopropanes, has precedent in the work of Mitra and co-workers.⁹ In support of our structure assignment, we synthesized the methyl ester corresponding to **4** by reaction of the enolate of methyl cyclopropyl ketone with methyl 4-oxobutanoate followed by dehydration of the resulting β -hydroxy ketone with methanesulfonyl chloride and triethylamine.



To understand the scope and limitations of this reaction, we reacted several ketone enolates with **2**. The results are depicted in Table 1.¹⁰ All of the ketone enolates afforded either hydroxy esters or keto esters as the primary products. In a few cases as much as 5% of the keto ester was coproduced with the hydroxy cyclopentenoic ester. Increasing

(5) Glycinoeclepin A has a hydroxy cyclohexenoic acid subunit. See: Kraus, G. A.; Johnston, B.; Kongsjahju, A.; Tylka, G. *J. Agric. Food Chem.* **1994**, *42*, 1839.

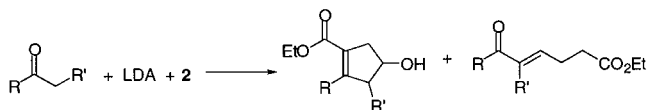
(6) Kirschleger, B.; Queignec, R. *Synthesis* **1986**, 926.

(7) Spectrum for main diastereomer of **3**: ¹H 300 MHz NMR (CDCl₃) δ 1.06 (t, $J = 7.7$ Hz, 3H), 1.08 (d, $J = 7.5$ Hz, 3H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.67–1.83 (m, 1H), 2.16–2.25 (m, 1H), 2.49 (d, $J = 16.7$ Hz, 1H), 2.67–2.69 (m, 1H), 2.90–2.98 (m, 2H), 3.92–3.99 (m, 1H), 4.18 (q, $J = 7.1$ Hz, 2H). ¹³C NMR (CDCl₃) δ 12.6, 14.5, 15.9, 21.3, 41.4, 52.8, 60.0, 77.1, 123.4, 162.7, 166.1. HRMS calcd for C₁₁H₁₈O₃ 198.1255, found, 198.1259.

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Table 1. Reactions of Enolates with **2**



| R | R' | % yield | dr | % yield |
|--------------------------------|-----------------|------------------|-------|-----------------|
| C ₂ H ₅ | CH ₃ | 53 (3) | 10:1 | 0 |
| C ₃ H ₅ | H | 0 | | 48 (4) |
| Ph | H | 40 (5) | | 0 |
| C ₅ H ₁₁ | H | 46 (6) | | 2 |
| PhCH=CH | H | 30 (7) | | 0 |
| α -tetralone | | 0 | | 36 (8) |
| 6-methyl-5-hepten-2-one | | 43 (9) | | 5 |
| C ₆ H ₅ | CH ₃ | 43 (10) | 6.5:1 | 0 |
| cyclopentanone | | 60 (11) | 7:1 | 5 |
| cyclohexanone | | 65 (12) | 5.5:1 | 5 |

the reaction temperature from -10 to 0 °C and extending the reaction time did not affect the product distribution. Interestingly, the enolates of aldehydes such as isobutyraldehyde or cyclohexane carboxaldehyde afforded only decomposition products.

There is no clear rationale for the production of unsaturated keto esters **4** and **8** in the cases of methyl cyclopropyl ketone and α -tetralone, respectively, while the other eight examples studied gave little or no unsaturated ketone. The cyclopropyl group and the rigid tetralone framework would likely present greater nonbonded interactions as the intramolecular cyclization step proceeded. Slowing the rate of cyclization might lead to an increased alkoxide concentration that would enhance the phosphonate transfer step.

The reaction of phosphonate aldehyde **2** with ketone enolates provides a convenient one-pot route to hydroxy cyclopentenoic esters. The reaction conditions are mild and should be compatible with many functional groups.

Acknowledgment. We thank Iowa State University and the Iowa Soybean Promotion Board for partial support of this work.

Supporting Information Available: Spectral data for compounds **3–12**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) **General procedure:** To a freshly prepared lithium diisopropylamide (LDA) solution (1 mmol, 2 mL) was added the ketone (1 mmol) in THF (1 mL) dropwise at -78 °C, and the reaction was stirred for 1 h at -78 °C. Aldehyde (1 mmol) in THF (1 mL) was added, and the mixture was stirred at -78 °C for 1 h. Stirring was continued until the temperature reached between -15 and -10 °C. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (2×25 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to yield crude product which was purified by flash chromatography on silica gel using ethyl acetate–hexane.