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Total Synthesis of (±)-Phosphonothrixin

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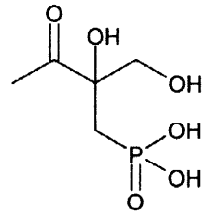
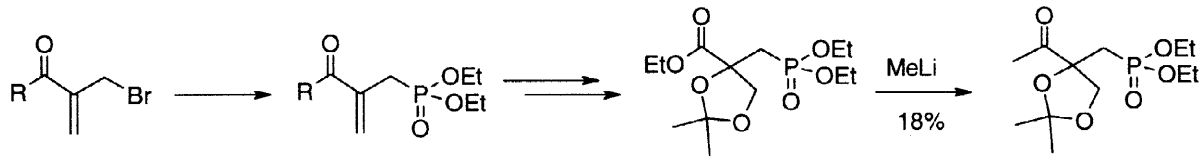
Abstract: Synthesis of the novel natural product Phosphonothrixin has been accomplished in 6 steps and 24% overall yield from the commercially available Baylis-Hillman adduct derived from acetaldehyde and methyl vinyl ketone. The synthesis features use of a trisubstituted olefin as a latent a-hydroxyketone, which formally reverses the oxidation states of the hydroxyl and carbonyl functionalities. This alleviates some of the difficulties encountered in alternative syntheses which proceed through metastable intermediates.

Relatively few compounds containing a carbon-phosphorus (C-P) bond are produced in nature.[1,2] Several herbicidal compounds which have been isolated from Actinomycetes are bialaphos[3] phosphonothricin[4] and phosalacine. Another herbicidal example is Phosphonothrixin (**1**), recently isolated from Saccharothrix sp. ST-888.[5] The isolation,[6] identification,[7] racemic synthesis[8] and asymmetric synthesis[9] of this material have been described. We were interested in evaluating **1** based on its reported broad spectrum, low use rate, post-emergent herbicidal activity.[5]



1

After failed attempts to acquire natural phosphonothrixin from external sources, we undertook its total synthesis. The first reported synthesis of **1** employed a carboxylic ester as a latent ketone.[8] This was necessary because attempted Michaelis-Becker reaction with bromomethyl allyl ketone (**3b**) resulted in the Perkow reaction and did not give any of the desired allylphosphonate **4b**.



3a R = OEt
b R = Me

4a R = OEt
b R = Me

5a

5b

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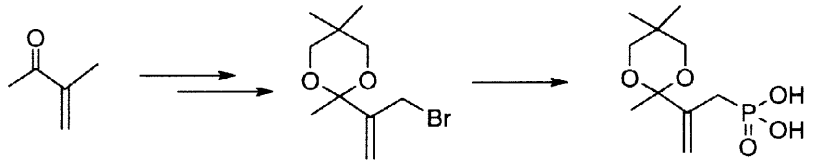
PII: S0040-4039(98)01403-8

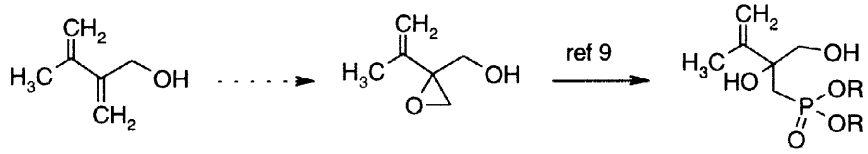
However, conversion of ester **5a** to ketone **5b** employed a low yielding methyllithium addition late in the sequence (**5a** → **5b**) which we sought to avoid.

Attempts to circumvent the methyllithium addition problem by repeating the protocol used for **3b** → **5b** using a ketal to protect the ketone in **3b** met with little success. Newly purchased commercial starting material **6** arrived partially dimerized and continued to dimerize upon standing. More importantly, synthetic intermediate **7** did not appear to be stable under standard Michaelis-Becker or Arbuzov conditions .



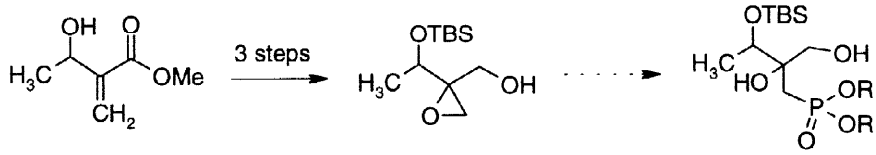
6 **7** **8**

The second reported synthesis employed an olefin as the latent ketone.[9] In our hands, however, precursor **9** was difficult to prepare and work with, complicating preparation of the epoxide.



9 **10** **11**

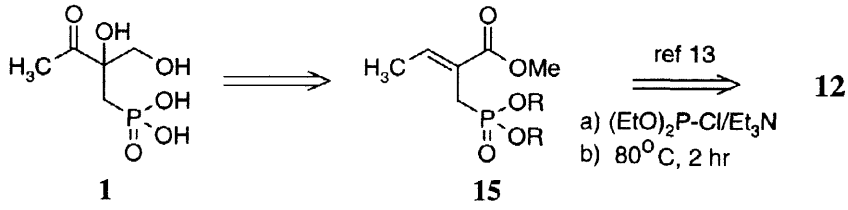
Attempts to perform a sequence analogous to **9** → **11** using a hydroxyl group as the ketone synthon (i.e. **12**) rather than a methylene in order to circumvent working with reactive acrylate and/or diene intermediates also failed. We were unable to find conditions to open the epoxide of **13** with a phosphorus nucleophile to form the C-P bond.[10] Thus, we decided to redesign the synthesis with emphasis on a) forming the C-P bond in a reliable fashion and b) avoiding unstable intermediates.



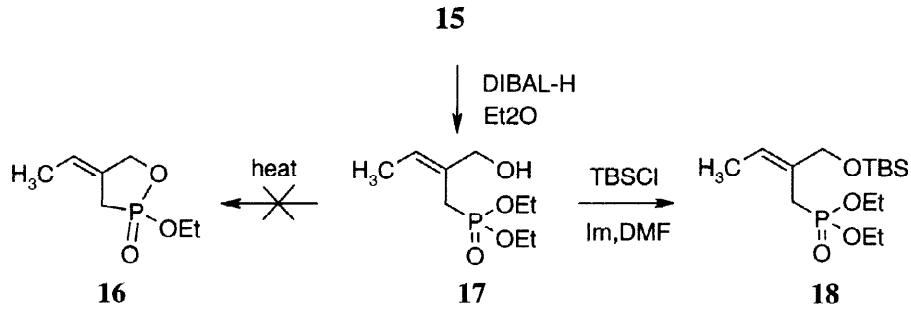
12 **13** **14**

The synthetic challenge of this molecule was to form the C-P bond while chemodifferentiating three oxygen functionalities. In particular, installing the ketone has led to the use of reactive intermediates such as **6** and **9**. The difference in the approach we envisioned compared to previous approaches toward **1** was use of a trisubstituted olefin as a latent a-hydroxyketone. As **15** can be readily derived from **12**, the oxidation states of the hydroxyl and carbonyl functionalities are formally reversed with respect to previous

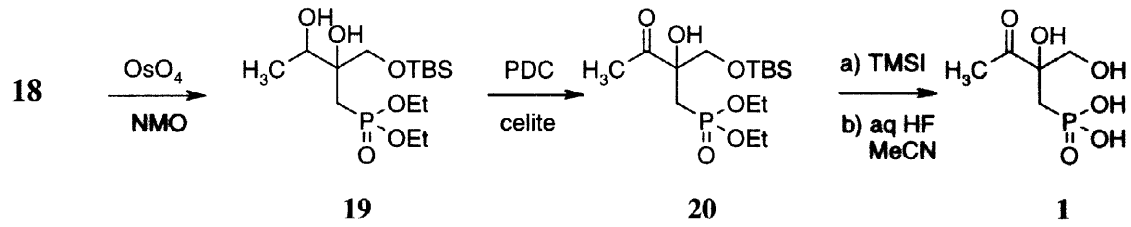
approaches. The use of commercially available starting material **12**,[11] the Baylis-Hillman adduct methyl 3-hydroxy-2-methylene butyrate derived from acetaldehyde and methyl acrylate,[12] allowed us to avoid many of the previously described pitfalls.



Thus, **12** was phosphorylated with diethyl chlorophosphite in the presence of triethylamine and then heated to 80 °C for 2 hours to give exclusively the *E*-allylphosphonate **15** in 60% yield after chromatography, forming the key C-P bond via an intramolecular Arbuzov rearrangement as reported by Janecki and Bodalski.[13,14] Reduction of the carboxylic ester (2.5 eq. DIBAL-H, Et_2O, 0°C; 79% yield) gave primary alcohol **17**. It was hoped that alcohol **17** would internally protect itself by closing to produce the 5-membered ring phosphinate **16**. However, this was not observed, and we were forced to protect the primary alcohol.



Silyl protection of primary alcohol **17** (1.1 eq. TBSCl/imidazole, DMF; 94% yield) gave silyl ether **18**. Vicinal dihydroxylation (cat. OsO_4/NMO, CH_2Cl_2; 80% yield) to diol **19** followed by oxidation of the resultant secondary alcohol (2 eq. PDC/celite, CH_2Cl_2; 80% yield) gave protected phosphonothrixin **20**. Deprotection to the salt-free protonated phosphonic acid was achieved in 83% yield first using an excess of TMSI in CH_2Cl_2 to cleave the phosphonate ester, followed by aqueous HF in MeCN to cleave the TBS group and any silylated hydroxyls created by use of excess TMSI. The volatile by-products were easily removed on a rotary evaporator and trituration of the residue with Et_2O removed residual silylated materials. Dissolution in water, separation of insolubles, and concentration produced spectroscopically pure phosphonothrixin (**1**).



19 **20** **1**

Synthesis of the novel natural product Phosphonothrixin has been accomplished in 6 steps and 24% overall yield from the commercially available Baylis-Hillman adduct **12**. The synthesis highlights use of a trisubstituted olefin as a latent a-hydroxyketone. As this results in the oxidation states of the hydroxyl and carbonyl functionalities being formally reversed, difficulties we encountered pursuing alternative syntheses were avoided.

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References and Notes

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8. Nakamura, K.; Kimura, K.; Kanno, H.; Takahashi, E; *J. Antibiotics*, **1995**, *48*, 1134.
9. Nakamura, K. and Yamamura, S. *Tetrahedron Lett.*, **1997**, *38*, 437.
10. $TMSOP(OEt)_2$, dialkyl phosphite anions and various coordinating counterions such as Mg^{2+} and I ntramolecular displacement with tethered dialkyl or trialkyl phosphites all failed in our hands.
11. Approximately $2 per gram from Aldrich.
12. For a review: Basavaiah, D.; Rao, P.; Hyma, R. *Tetrahedron*, **1996**, *52*, 8001.
13. Janecki, T. and Bodalski, R. *Synthesis*, **1990**, 799.
14. The major *E*-isomer was purified away from the < 5% minor Z- isomer by column chromatography.