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A Highly Conjunctive β-Keto Phosphonate: Application to the Synthesis of Pyridine Alkaloids Xestamines C, E, and H

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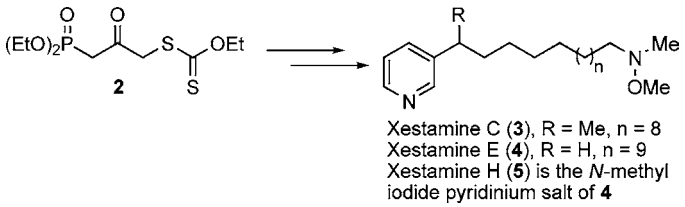
ABSTRACT



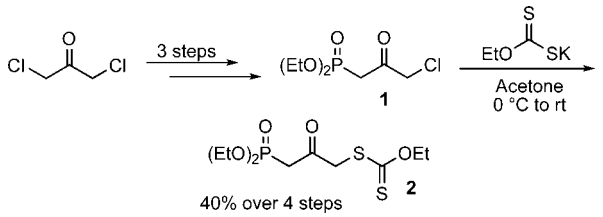
Xestamine C (**3**), R = Me, n = 8
Xestamine E (**4**), R = H, n = 9
Xestamine H (**5**) is the *N*-methyl iodide pyridinium salt of **4**

The synthesis of a novel β-keto γ-xanthyl phosphonate has been achieved. This highly conjunctive reagent has been utilized in a combination of radical and ionic reactions to create new carbon−carbon bonds. Its usefulness was demonstrated by realizing the first total synthesis of naturally occurring pyridine alkaloids xestamines C, E, and H.

Phosphonates bearing a keto function in the β position (β-keto phosphonates) are of great interest in organic synthesis. Of particular importance is their use in the Horner−Wadsworth−Emmons (HWE) olefination.[1] This well-known modification of the Wittig reaction allows an easy access to α,β-unsaturated ketones in either an intermolecular or intramolecular fashion, and it has been shown many times to be a useful tool in total synthesis.[2] β-Keto phosphonates are also valuable intermediates in the synthesis of heterocyclic cores such as quinolines,[3] pyrroles,[4] pyrazoles,[5] and naphthydrines.[6] Their synthesis is commonly achieved via the Arbuzov reaction,[7] the Michaelis−Becker reaction,[8] or by acylation of alkyl phosphonate anion.[9] They can also be formed from vinyl phosphates via a 1,3-phosphorus migration;[10] this strategy, however, appears to be limited to the formation of cyclic β-keto phosphonates.

Following our work on xanthate transfer radical chemistry,[11] we envisioned synthesizing a β-keto phosphonate **2** (Scheme 1) that would be able to undergo both group transfer radical addition to olefins and HWE reaction with aldehydes and ketones.

Scheme 1. Synthesis of Key Xanthate **2**



(1) For reviews, see: (a) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(2) For recent examples, see: (a) Mata, E. G.; Thomas, E. J. *J. Chem. Soc. Perkin Trans.* **1995**, *1*, 785. (b) Solladié, G.; Wilb, N.; Bauder, C. *J. Org. Chem.* **1999**, *64*, 5447. (c) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **2000**, *65*, 2163. (d) Lambert, W. T.; Hanson, G. H.; Benayoud, F.; Burke, S. D. *J. Org. Chem.* **2005**, *70*, 9382. (e) Crimmins, M. T.; McDougall, P. J.; Emmitte, K. A. *Org. Lett.* **2005**, *7*, 4033. (f) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S.; Cole, K. P.; Yamaguchi, J. *J. Am. Chem. Soc.* **2007**, *129*, 1760.

(3) (a) Coppola, G. M. *Synthesis* **1988**, 81. (b) Vasse, J.-L.; Goumain, S.; Levacher, V.; Dupas, G.; Quéginer, G.; Bourguigno, J. *Tetrahedron Lett.* **2001**, *42*, 1871.

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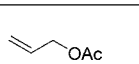
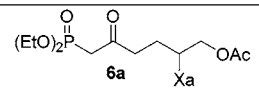
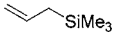
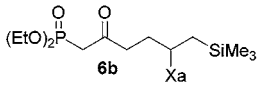
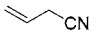
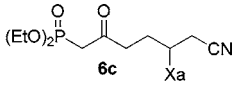
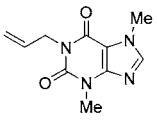
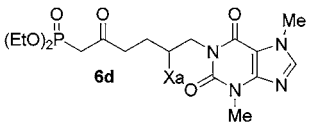
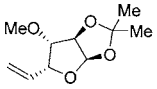
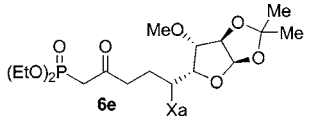
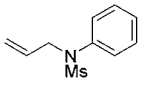
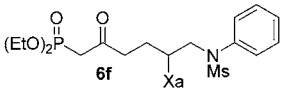
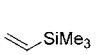
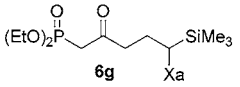
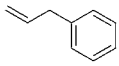
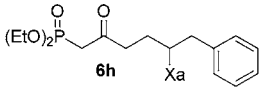
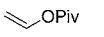
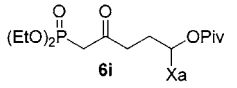
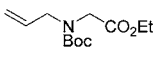
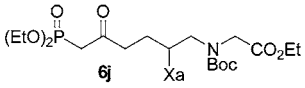
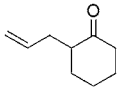
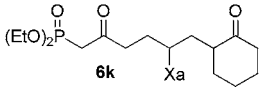
The synthesis of xanthate **2** was easily achieved in a 40% overall yield starting from commercially available 1,3-dichloroacetone via known β-keto phosphonate **1**.[12] With this highly conjunctive reagent in hand, we hoped to generate carbon−carbon bonds efficiently in both an ionic and a radical fashion at the two extremities of this novel ketone.

Table 1. Radical Addition of Xanthate **2** to Olefins **a**−**k**[a]

entry	olefin **a-k**	product **6a-k**[b]	yield[c] (%)
1		 **6a**	85
2		 **6b**	80
3		 **6c**	72
4		 **6d**	43
5		 **6e**	74
6		 **6f**	81
7		 **6g**	81
8		 **6h**	78
9		 **6i**	53
10		 **6j**	90
11		 **6k**	84

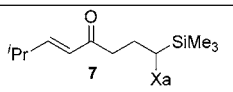
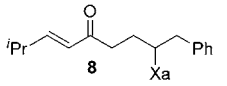
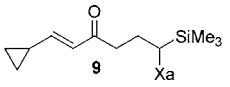
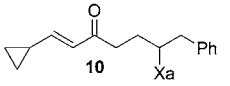
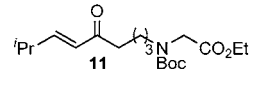
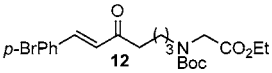
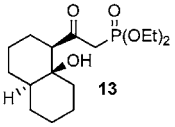
[a] Addition reactions were performed by portionwise addition of DLP (5 mol %) every 90 min to a refluxing degassed 1 M solution of **2** (1 equiv) in DCE in the presence of the olefin (2−3 equiv) until **2** had entirely reacted. [b] Xa = SC(S)OEt. [c] Isolated yields.

First, several examples of xanthate addition onto various olefins were undertaken to investigate its scope (Table 1).

Xanthate **2** afforded moderate to excellent yields of adducts **6a**−**k** when treated with a substoichiometric amount of lauroyl peroxide (DLP) (7.5−25 mol %) and the corresponding olefin **a**−**k** (2−3 equiv) in refluxing 1,2-dichloroethane (DCE). Examples include functionality that is widely used in organic synthesis such as ketones (entry 11), esters (entries 1 and 9), nitriles (entry 3), *N*,*O*-protected amino acids (entry 10), silanes (entries 2 and 7). Complex heterocycles and sugars (entries 4 and 5) were also tolerated.

We then turned our attention to the ability of these xanthate adducts (or the corresponding reduced forms **6′j** and **6′k** from **6j** and **6k**)[13] to undergo HWE olefination using sodium hydride in THF (Table 2). We were glad to see that in most cases the xanthate goup was stable under these conditions.

Table 2. HWE Olefination of Some Selected Compounds[a]

entry	substrate (**6**)	aldehyde	product[b]	yield[c] (%)
1	**6g**	^{i}PrCHO	 **7**	84
2	**6h**	^{i}PrCHO	 **8**	78
3	**6g**		 **9**	72
4	**6h**		 **10**	68
5	**6′j**	^{i}PrCHO	 **11**	80
6	**6′j**	*p*-BrPhCHO	 **12**	86
7	**6′k**	-	 **13**	70

[a] HWE reactions were performed using 1 equiv of NaH and 2 equiv of aldehyde. [b] Xa = SC(S)OEt. [c] Isolated yields.

We encountered some difficulty, however, with xanthate adduct **6i**, which decomposed rapidly when treated with

(4) Attanasi, O. A.; Filippone, P.; Giovagnoli, D.; Mei, A. *Synthesis* **1994**, 181.

(5) Almirante, N.; Benicchio, A.; Cerri, A.; Fedrizzi, G.; Marazzi, G.; Santagostino, M. *Synlett* **1999**, 299.

(6) Hsiao, Y.; Rivera, N. R.; Yasuda, N.; Hughes, D. L.; Reider, P. J. *Org. Lett.* **2001**, *3*, 1101.

(7) (a) Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307. (b) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415.

(8) Koh, Y. J.; Oh, D. Y. *Tetrahedron Lett.* **1993**, *34*, 2147.

(9) (a) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374. (b) Narkunan, K.; Nagarajan, M. *J. Org. Chem.* **1994**, *59*, 6386.

(10) (a) Hammond, G. B.; Calogeropoulo, T.; Wiemer, D. F. *Tetrahedron Lett.* **1986**, *27*, 4625. (b) Calogeropoulo, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185. (c) An, Y.-Z.; An, J.; Wiemer, D. F. *J. Org. Chem.* **1994**, *59*, 8197. (d) An, J.; Wilson, J. M.; An, Y.-Z.; Wiemer, D. F. *J. Org. Chem.* **1996**, *61*, 4040. (e) Baker, T. J.; Wiemer, D. F. *J. Org. Chem.* **1998**, *63*, 2613.

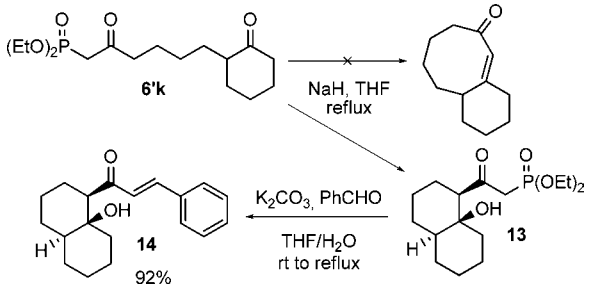
(11) (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus Sulfur Silicon Relat. Elem.* **1999**, *153*, 137. (c) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (d) Quiclet-Sire, B.; Zard, S. Z. *Chem. Eur. J.* **2006**, *12*, 6002.

(12) Corbel, B.; Medinger, L.; Haelters, J.-P.; Sturtz, G. *Synthesis* **1985**, 1048.

(13) Xanthate reductions were performed with a combination of 2 equiv of DLP in propan-2-ol (10 mL/mmol). See: Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5877.

sodium hydride. In addition, no intramolecular reaction product was detected with xanthate adduct **6k** under these conditions. When the reaction was performed at reflux, we observed the formation of *trans*-decalin **13** (entry 7) in a 70% isolated yield. Presumably, the strain incurred in forming an 8-membered ring is too great for the expected HWE pathway to occur. Anion equilibration at higher temperature led to the formation of more accessible *trans*-decalin **13**. Subsequent HWE reaction with benzaldehyde gave *trans*-decalin **14** in 92% yield (Scheme 2).

Scheme 2. HWE Olefination of Unexpected Compound **13**



We decided next to apply the key conjunctive reagent to short and convergent syntheses of antimicrobial pyridine alkaloids xestamines C (**3**), E (**4**), and H (**5**) (Figure 1).

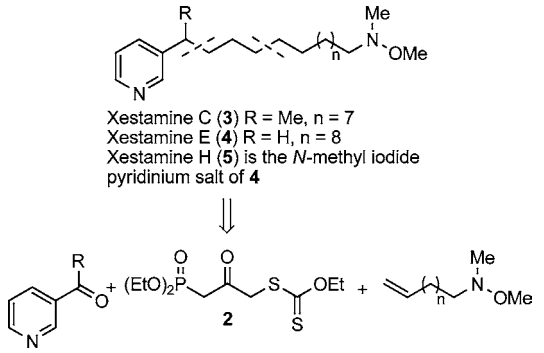


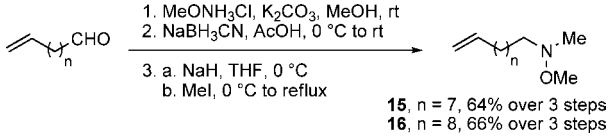
Figure 1. Retrosynthetic analysis of xestamines C, E, and H.

The xestamine family is part of a wide variety of naturally occurring pyridine alkaloids such as the theonelladin family,[14] the niphatesine family,[14c,15] the ikimine family,[15b,16] or the cribochaline family.[17]

Xestamine C was isolated from the Caribbean sponge *Xestospongia wiedenmayeri* in 1990,[18] and xestamine E was isolated (along with inseparable xestamine D) in the Bahamas from the sponge *Calyx podatypa* in 1991 as well as xestamine H (along with inseparable xestamine G).[19] Larock et al. reported the first synthesis of a member of the xestamine family (xestamine D) using palladium-catalyzed coupling of 3-iodopyridine, 1,13-tetradecadiene, and *N*,*O*-dimethylhydroxylamine.[20] To our knowledge no other synthesis of any xestamines has been realized.

Our work started with the straightforward synthesis of *N*,*O*-dimethylhydroxylamines **15** and **16** starting from the corresponding aldehydes (Scheme 3). (When $n = 7$, the aldehyde was prepared by oxidation of the corresponding 9-decen-1-ol using PCC in dichloromethane following the reported procedure.[21])

Scheme 3. Synthesis of Olefinic *N*,*O*-Dimethylhydroxylamines



Treatment of these aldehydes with *N*-methoxyammonium chloride and potassium carbonate in methanol gave the corresponding oximes which were reduced with sodium cyanoborohydride in acetic acid to afford *O*-methylhydroxylamines. Subsequent *N*-methylation using NaH and methyl iodide yielded the desired *N*,*O*-dimethylhydroxylamines **15** and **16** in 64% and 66% overall yield, respectively. They were then submitted to the xanthate transfer radical reaction with xanthate **2**. These reactions proceeded smoothly under the usual conditions to give the corresponding adducts **17** and **18** in 69 and 65% yield respectively. Reductive removal of the xanthate groups was then readily accomplished using DLP (2 equiv) in propan-2-ol (10 mL/mmol) to afford β-keto phosphonates **19** and **20** in 80 and 83% yield, respectively (Scheme 4). Horner−Wadsworth−Emmons olefination using either 3-acetylpyridine (in refluxing THF) or nicotinaldehyde (room temperature in THF) gave the corresponding α,β-unsaturated carbonyl compounds **21** an **22** in good yield. The lower yield obtained in the case of **21** can be explained by the lower reactivity of the carbonyl in 3-acetylpyridine as compared to that of nicotinaldehyde.

Nevertheless, it is noteworthy that the β-keto phosphonate allows a facile introduction of the methyl group α to the pyridine ring for the synthesis of xestamine C. Moreover,

(14) (a) Kobayashi, J.; Murayama, T.; Ohizumi, Y. *Tetrahedron Lett.* **1989**, *30*, 4833. (b) Rao, A. V.; Reddy, G. R.; Rao, B. V. *J. Org. Chem.* **1991**, *56*, 4545. (c) Teubner, A.; Gerlach, H. *Liebigs Ann. Chem.* **1993**, *2*, 161. (d) Tsunoda, T.; Uemoto, K.; Ohtani, T.; Kaku, H.; Ito, S. *Tetrahedron Lett.* **1999**, *40*, 7359.

(15) (a) Kobayashi, J.; Murayama, T.; Kosuge, S.; Kanda, F.; Ishibashi, M.; Kobayashi, H.; Ohizumi, Y.; Ohta, T.; Nozoe, S.; Sasaki, T. *J. Chem. Soc., Perkin Trans.* **1990**, *1*, 3301. (b) Kobayashi, J.; Zeng, C. M.; Ishibashi, M.; Shigemori, H.; Sasaki, T.; Mikami, Y. *J. Chem. Soc., Perkin Trans.* **1992**, *1*, 1291. (c) Rao, A. V. R.; Reddy, G. R. *Tetrahedron Lett.* **1993**, *34*, 8329. (d) Bracher, F.; Papke, T. *J. Chem. Soc., Perkin Trans.* **1995**, *1*, 2323. (e) Bracher, F.; Papke, T. *Monatsh. Chem.* **1996**, *127*, 91.

(16) (a) Carroll, A. R.; Scheuer, P. J. *Tetrahedron* **1990**, *46*, 6637. (b) Bracher, F.; Papke, T. *Nat. Prod. Lett.* **1994**, *4*, 223.

(17) Nicholas, G. M.; Molinski, T. F. *Tetrahedron* **2000**, *56*, 2921.

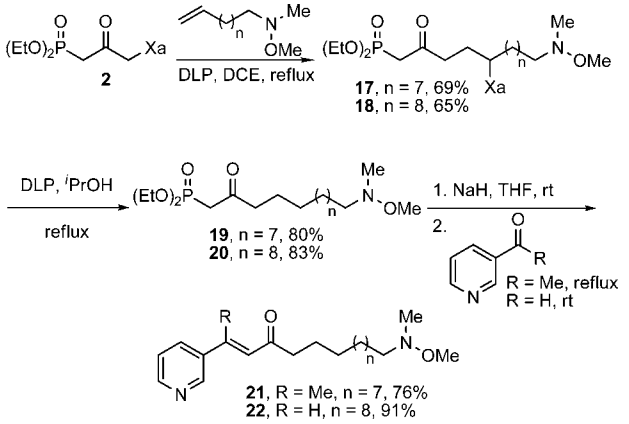
(18) Sakemi, S.; Totton, L. E.; Sun, H. H. *J. Nat. Prod.* **1990**, *53*, 995.

(19) Stierle, D. B.; Faulkner, D. J. *J. Nat. Prod.* **1991**, *54*, 1134.

(20) (a) Larock, R. C.; Wang, Y. *Tetrahedron Lett.* **2002**, *43*, 21. (b) Wang, Y.; Dong, X.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 3090.

(21) Qin, X.; Tzvetkov, T.; Liu, X.; Lee, D.-C.; Yu, L.; Jacobs, D. C. *J. Am. Chem. Soc.* **2004**, *126*, 13232.

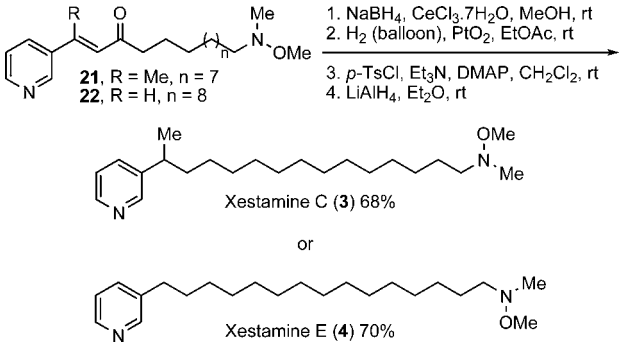
Scheme 4. Key Steps in the Synthesis of Xestamines C and E



compounds **21** and **22** could easily provide access to various analogues of xestamines C and E by further chemical transformations of the α,β-unsaturated ketone moiety.

The last steps of the synthesis were achieved using straightforward chemistry (Scheme 5). α,β-Unsaturated carbonyl compounds **21** an **22** were reduced to the corresponding allylic alcohols **23** and **24** in 95 and 98% yield respectively, using Luche conditions.[22]

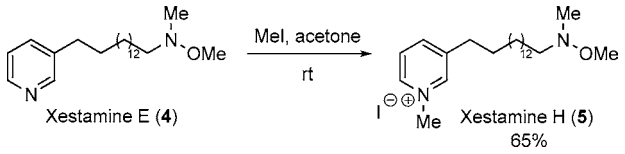
Scheme 5. Final Steps in the Synthesis of Xestamines C and E



Alcohols **23** and **24** were submitted to hydrogenation using a platinum oxide catalyst to afford alcohols **25** and **26** in 99% yield. Subsequent tosylation using *p*-toluenesulfonyl chloride (1.5 equiv), triethylamine (1.5 equiv), and catalytic DMAP gave tosylates **27** and **28** in 77 and 75% yield, respectively. Reduction with excess LAH (5 equiv) in dry ether gave the final compounds, xestamines C (**3**) (94% yield) and E (**4**) (96% yield).

Finally, *N*-methylation of xestamine E using methyl iodide in acetone afforded the *N*-methyl iodide salt, xestamine H (**5**) in 65% yield (Scheme 6).

Scheme 6. Synthesis of Xestamine H



In summary, we have developed a useful synthetic β-keto γ-xanthyl phosphonate that is able to create two new carbon−carbon bonds in both a radical and an ionic manner. We have shown that it adds to various olefins in xanthate radical transfer reactions and that the resultant compounds undergo HWE olefination to form α,β-unsaturated ketones. Moreover, we successfully demonstrated its high conjunctivity by completing the first total synthesis of antimicrobial xestamines C, E, and H. Their syntheses were achieved in 29%, 34%, and 22% overall yield, respectively, starting from xanthate **2**.

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Supporting Information Available: Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702590F

(22) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.