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Expeditious and Efficient Annulation Protocol for the Synthesis of α,β-Unsaturated δ-Lactones from β-Keto Esters

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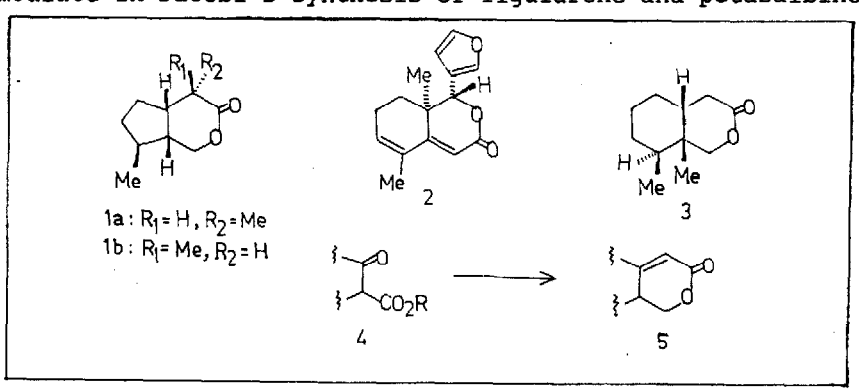
Abstract: β-Keto esters **6a-e** are transformed into β-keto alcohols **7a-e**, which are homologated to phosphonates **9a-e**. Intramolecular Horner-Wadsworth-Emmons reaction affords δ-lactones **10a-d** in excellent overall yields.

The occurrence of lactonic functionality is a ubiquitous structural element in natural products possessing a wide range of biological activity.[1] In particular, lactones fused to a carbocyclic ring are common in biologically active natural products and as synthetically versatile precursors. For example, iridomyrmecin (**1a**)[2a] is a natural insecticide, isoiridomyrmecin (**1b**)[2b] is a constituent of defense secretion in ants, pyroangolensolide (**2**)[2c] is formed by pyrolysis of methyl angolensate, and bicyclic δ-lactone **3**[2d] is an advanced intermediate in Jacobi's synthesis of ligularone and petasalbine.



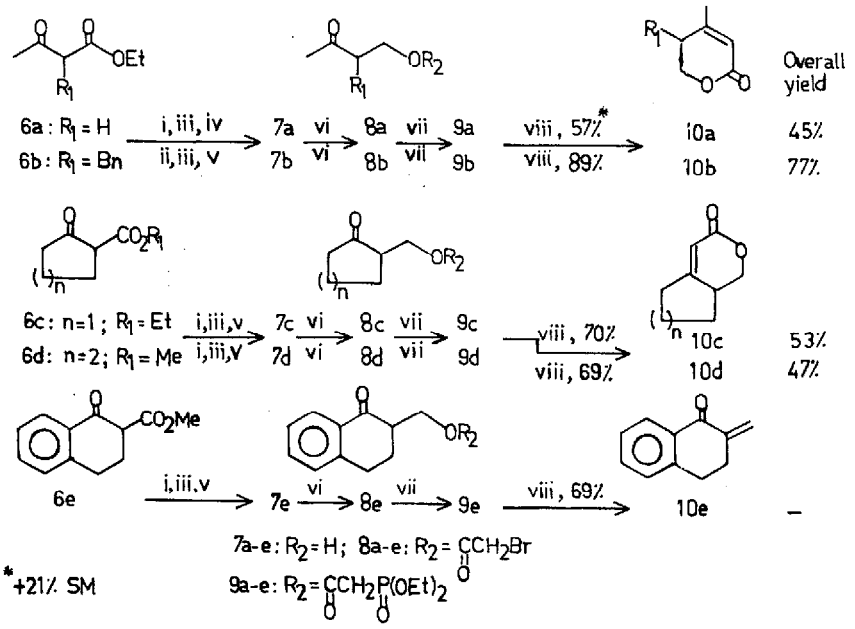
A number of synthetic methods and approaches have been reported for the synthesis of mono- and bicyclic lactones.[3] We were interested in developing a general and flexible sequence for the synthesis of α,β-unsaturated δ-lactones from β-keto esters (such as 4 ---> 5) with the objective of applying it to the synthesis of lactones of type 1-3. We report in this Letter an expeditious, highly efficient and adaptable annulation protocol for the transformation of β-keto esters to α,β-unsaturated δ-lactones employing intramolecular Horner-Wadsworth-Emmons (IMHWE) reaction as the key step.

Acylation of alcohol 7a (obtained from keto ester 6a under standard conditions) with α-bromoacetyl bromide (8a, 96%) followed by Arbuzov reaction with $(EtO)_3P$ afforded phosphonate 9a (96%) (Scheme 1). The seemingly trivial IMHWE reaction of phosphonate 9a to anhydromevalonolactone (10a)[4] was problematic. Exposure of 9a to standard olefination conditions[5] (t-BuOK, THF or t-BuOH; NaH, THF; K_2CO_3, MeOH; Cs_2CO_3, i-PrOH) at temperatures varying from 0 °C to reflux provided none of the expected lactone; either the SM was recovered unchanged or consumed in a deleterious side reaction.

Closer inspection of the acidic sites α to carbonyl in phosphonate 9a revealed that a plethora of reactions can ensue upon treatment with base (Scheme 2). In order to circumvent the possibility of β-elimination (path d) we attempted Masamune and Roush's[6] LiCl/amine conditions for effecting HWE reaction in base-sensitive systems. To our gratification, subjecting a solution of phosphonate 9a in CH_3CN to LiCl/DBU for 1h afforded an easily separable mixture of anhydromevalonolactone (10a)[4] (57%) and unreacted phosphonate (21%). The use of weaker amine/salt systems, e.g. $(i\text{-}Pr)_2NEt/LiCl$[6] and $Et_3N/LiBr$[7] also yielded a mixture of lactone and SM.[8] This result is presumably a consequence of competetion between olefination (path a) and enolate exchange followed by protonation (paths b+c) in Scheme 2. We reasoned that sluggish enolate exchange in a more congested system (9b, R=Bn) should overcome this complication.

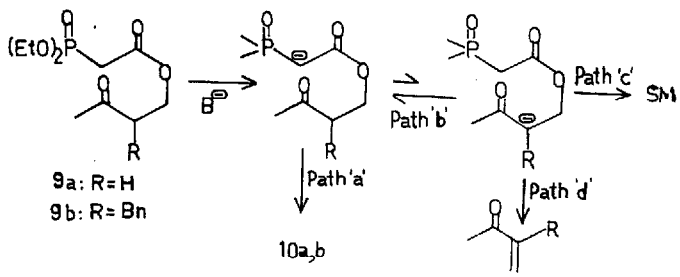
Indeed, treatment of phosphonate 9b derived from 3-benzyl-4-hydroxy-2-butanone (7b)[9] under optimal conditions afforded benzyl lactone 10b in 89% yield;[10] no unreacted SM was detected in the crude residue. In a similar manner bicyclic δ-lactones 10c and 10d[11] were synthesised from ethyl 2-oxocyclopentane carboxylate (6c) and methyl 2-oxocyclohexane carboxylate (6d) in 53% and 47% overall yields, respectively.

α-Tetralone was elaborated to phosphonate 9e without event. Cyclisation under IMHWE conditions afforded none of the expected



Reaction conditions: i) p-TsOH, $(CH_2OH)_2$, PhH, 80 °C; ii) CSA, $(CH_2OH)_2$, PhH, 80 °C; iii) LAH, ether, 0 °C; iv) p-TsOH, acetone, rt; v) 10% aq. $(COOH)_2$, silica gel, CH_2Cl_2, rt; vi) $BrCH_2C(O)Br$, pyridine, 0 °C; vii) $(EtO)_3P$, PhMe, 100 °C; viii) DBU, LiCl, MeCN, rt.

SCHEME 1



Path a: IMHWE reaction; Path b: Enolate exchange; Path c: Protonation; Path d: β-Elimination.

SCHEME 2

tricyclic lactone. Instead, β-methylene-α-tetralone (**10e**)[12] was isolated in 69% yield after silica gel chromatography. It is likely that slower IMHWE reaction (path a) and facile enolisation (path b) in enones compared to ketones leads to exclusive β-elimination (path d) product (Scheme 2).

In conclusion, the method works best for α-substituted β-keto esters **6b-d** which bodes well for the eventual application in the synthesis of lactones **1-3**. Studies are currently under way in this direction and to synthesise δ-lactones of a different structural type.

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References and Notes:

1. a) Ohloff, G. *Fortschr. Chem. Org. Naturstoffe.* **1978** 35 431. b) Brand, J. M.; Young, J. C.; Silverstein, R. M. *ibid.* **1979** 37 1.
2. a) Mathews, R. S.; Whitesell. J. K. *J. Org. Chem.* **1975** 40 3312. b) Callant, P.; Ongena, R.; Vandewalle M. *Tetrahedron* **1981** 37 2085. c) Fukuyama, Y.; Tokroyama, T. *Tetrahedron Lett.* **1973** 4869. d) Jacobi, P. A.; Craig, T. A.; Walker D. G.; Arrick, B. A.; Frechette, R. F. *J. Am. Chem. Soc.* **1984** 106 5585.
3. a) Carlson, R.M.; Oyler, A. R.; Peterson, J. R. *J. Org. Chem.* **1975** 40 1610. b) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1980** 45 4117. c) Yoshida, T.; Saito, S. *Chemistry Lett.* **1982** 1587. d) Khan, H. A.; Paterson, I. *Tetrahedron Lett.* **1982** 23 5083. e) Helquist, P. in *Strategies and Tactics in Organic Synthesis;* Ed. Lindberg, T.; Academic Press: New York, 1989; pp 163-189. f) Hanzawa, Y.; Ishizawa, S.; Ito, H.; Kobayashi, Y.; Taguchi, T. *J. Chem. Soc., Chem. Comm.* **1990** 394. g) Kido, F.; Sinha, S. C.; Abiko, T.; Watanabe, M.; Yoshikoshi, A. *J. Chem. Soc., Chem. Comm.* **1990** 418.
4. a) White, J.D.; Carter, J.P.; Kezar, H.S. *J. Org. Chem.* **1982** 47 929. b) Herold, P.; Mohr, P.; Tamm, Ch. *Helv. Chim. Acta.* **1983** 66 744.
5. Wadsworth, W.S. *Org. Reactions* **1977** 25 73.
6. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai. T. *Tetrahedron Lett.* **1984** 25 2183.
7. Rathke, M.W.; Nowak, M. *J. Org. Chem.* 1985 50 2624.
8. Longer reaction time was required (1 day).
9. Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.; Albizati, K.F. *J. Am. Chem. Soc.* **1990** 112 6965.
10. Experimental procedure: Exposure of phosphonate **9b** (0.1 mmol, 36 mg) to IMHWE reaction conditions described in reference 6 provided 29 mg of crude material which was chromatographed to furnish trace amounts of elimination product (<5%; exocyclic methylene protons at δ 5.96, 5.52) followed by 18 mg (89%) of pure lactone **10b**. 1H NMR (100 MHz, CDCl3): δ 7.40-7.00 (m, 5H); 5.72 (d, J=2Hz, 1H); 4.22-3.98 (m, 2H); 3.00-2.40 (m, 3H); 1.92 (d, J=2Hz, 3H). IR (Neat, cm-1): 3500 (br, w), 3050, 2950, 1720, 1450, 1400, 1320, 1285, 1265, 1235, 1160, 1105, 1045, 1020, 880, 760, 710. Low-resolution MS: M+ 202, PhCH2+ 91.
11. Lactone **10c**: 1H NMR: δ 5.72 (br d, J=3Hz, 1H); 4.48 (dd, J=12,7Hz, 1H); 3.88 (dd, J=12,10Hz, 1H); 3.00-2.20 (m, 3H); 2.05-1.50 (m, 4H). IR: 1720 cm-1 (partial). LRMS: M+ 138. Lactone **10d**: 1H NMR: δ 5.68 (br s, 1H); 4.30 (dd, J=12,8Hz, 1H); 3.84 (t, J=12Hz, 1H); 2.60-1.30 (m, 9H). IR: 1715 cm-1 (partial). LRMS: M+ 152.
12. Gras, J-L *Org. Syn.* **1981** 60 88.

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