Synthesis of β-ketophosphonates from Thioester Intermediates: A Stereocontrolled Route to the C_{29}-C_{35} Fragment of the Halichondramides

Alison N. Hulme,* Garnet E. Howells, Rachel H. Walker

Department of Chemistry, The University of Edinburgh, King's Buildings, West Mains Road, Edinburgh, EH9 3JJ, UK

e-mail: Alison.Hulme@ed.ac.uk

Received 13 May 1998

Abstract: An efficient synthesis of β-ketophosphonates from *t*-butyl thioesters using the lithium anion of either methane- or ethane-phosphonate is described. The elaboration of a range of substrates to intermediates in natural product syntheses *via* the Horner Wadsworth Emmons reaction is then discussed.

In a recent synthesis of a model for the cytotoxic marine metabolite octalactin A **1**, we identified a key target **2** (**Figure 1**).[1] Retrosynthetic analysis of this compound led us to propose a stereocontrolled boron-mediated *anti* aldol between *t*-butyl thiopropionate and a 1,7-difunctional aldehyde to set the C_7-C_8 stereochemistry. We were then faced with the problem of how to extend the carbon backbone of the resultant acyclic β-hydroxy thioester to give enone **3**, an advanced precursor to compound **2**.

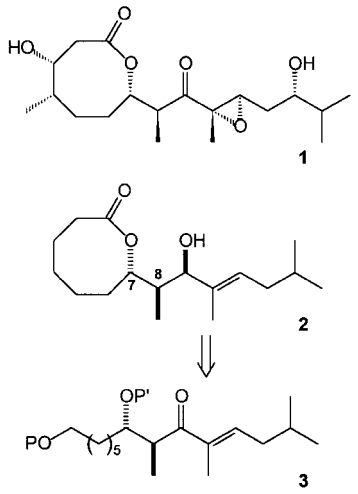
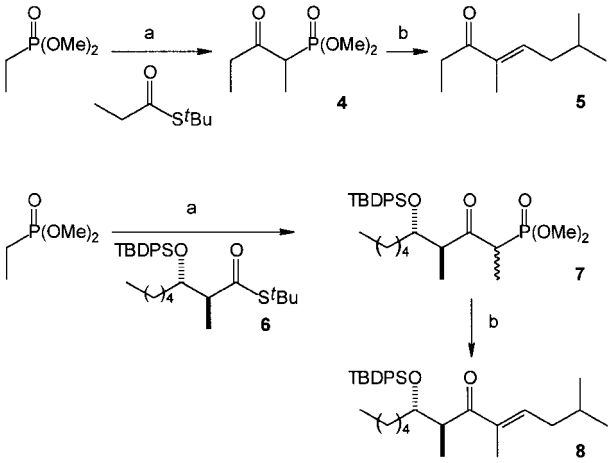


Fig. 1

Thioesters have been used as intermediates in a number of important natural product syntheses. However, their elaboration has largely been limited to the generation of carboxylic acids,[2] esters,[2f] lactones,[2f] aldehydes,[3a] and β-ketoamides.[3 b] The potential for the use of thioesters in natural product synthesis has greatly increased recently due to a number of developments in aldol methodology, where particularly difficult aspects of stereocontrol have been tackled effectively. Chiral boron reagents developed by Gennari,[4] and Masamune[5] have been shown to give high levels of both diastereo- and enantio-control with thioester substrates, resulting in the formation of *anti* aldol adducts in >95% ds and >95% ee. Similarly, in the development of new chiral Lewis acids for the catalytic asymmetric Mukaiyama acetate aldol reaction, many authors have concentrated on the use of thioester substrates.[6] Thus, new methodology for their synthetic elaboration is particularly important.

The Horner Wadsworth Emmons (HWE) reaction between alkyl phosphonates and aldehydes is frequently used for the synthesis of di- and tri-substituted double bonds.[7 a,b] The development of a number of mild conditions for the HWE reaction between β-ketophosphonates and aldehydes,[8] makes this reaction particularly suited to the synthesis of complex natural products, where it has found use both in fragment coupling,[9] and macrocyclisation reactions.[10] In a recent paper,[11] Mosset identified a number of distinct routes to the synthesis of β-ketophosphonates. Of particular relevance to this work is the reaction of α-carbanionic alkylphosphonates with a range of substrates including aldehydes (followed by oxidation),[11,12] carboxylic acid esters,[9-11,13] carboxylic acid chlorides,[11,14] *N*-methoxy-*N*-methylcarboxamides (Weinreb amides),[11,15] and 3-acylthiazolidine-2-thiones.[11,10b] In this Letter, we report an extension of this strategy to the reaction of α-carbanionic alkylphosphonates with a range of functionalised thioesters.

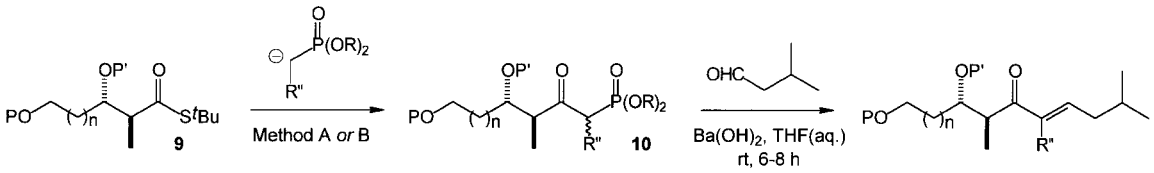
We found that we could carry out a displacement reaction on *t*-butyl thiopropionate using the lithiated anion of dimethyl ethanephosphonate (**Scheme 1**), to give the β-ketophosphonate **4** in 76% yield. This was then coupled to isovaleraldehyde using the mild activated barium hydroxide HWE conditions of Paterson,[8c] to give trisubstituted enone **5**,[7c] also in excellent yield (85%). When the displacement reaction was carried out using the *t*-butyldiphenylsilyl protected *anti* aldol adduct **6**,[16] it was similarly successful, generating β-ketophosphonate **7** as a ~3:1 mixture of diastereomers in 73% yield.[17] This could be converted *via* the HWE reaction to enone **8** in 71% yield without epimerisation of the *anti* stereochemistry derived from the aldol adduct.



Scheme 1. Reagents: a) i. *t*-BuLi, DMPU, THF, -42 °C, 1 h; ii. thioester, -78 °C, 4 h; b) isovaleraldehyde, activated $Ba(OH)_2$, THF (aq.), rt, 6-8 h

This displacement reaction was then extended to a series of *anti* aldol adducts **9**, of the type required for the generation of enone **3** (**Table 1**).[18] Although these reactions were initially conducted using *t*-BuLi in the presence of DMPU (1 eq.) (Method A), we later discovered that deprotonation by *n*-BuLi was equally effective, and that the addition of DMPU was not required (Method B). In general, the best results were obtained when the solution of the carbanion was added *via* cannula to a precooled solution of the thioester. It was also noted that the anion generated from dimethyl ethanephosphonate was considerably more sluggish in its reactions than its diethyl counterpart and generally required either a higher reaction temperature (-42 °C *c.f.* -78 °C), or longer reaction times, for the reaction to proceed to completion.

Table 1



Entry	Method	n	R	R''	P	P'	T	%Yield 10	%Yield HWE
1	A	3	Me	Me	TBS	TBS	-78 °C	69	85
2	B	3	Et	Me	TBS	TBS	-78 °C	85	91
3	B	3	Et	Me	PMB	TBS	-78 °C	86	96
4	B	5	Me	H	TBS	TBS	-78 °C	84*	70
5	A	5	Me	Me	TBS	TBDPS	-42 °C	80	82
6	B	5	Et	Me	TBS	TBS	-78 °C	94	85 (3)
7	B	8	Et	Me	TBS	TBS	-78 °C	94	88

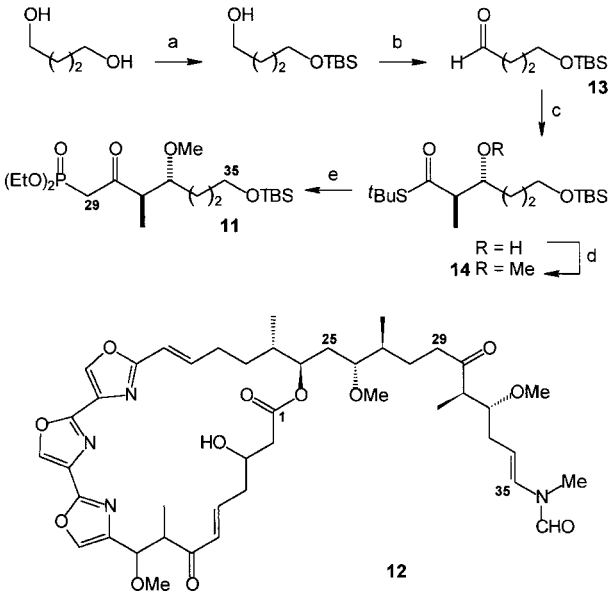
* yield based on unrecovered starting material

Method A: i. *t*-BuLi, DMPU (1 eq.), THF, 1 h; ii. thioester, -78 °C or -42 °C, 4 h; Method B: i. *n*-BuLi, THF, 1 h; ii. add to thioester in THF, -78 °C, 4 h

From these results it can be seen that a range of protecting groups is tolerated by these reaction conditions. Where the lithiated anion of dimethyl methanephosphonate was used to generate β-ketophosphonate **10**, a di-substituted double bond was generated by the HWE reaction (Entry 4). The *E*-geometry of this double bond was confirmed by the ^{1}H nmr coupling constant (J = 15.8 Hz). As with aldol adduct **6**, the reactions of dialkyl ethanephosphonate anions with aldol adducts **9** were found to produce a ~3:1 ratio of diastereomers **10**, which were converted to a single *E*-double bond geometry in the HWE reaction.[7c]

We have used these conditions in the synthesis of enone **3** (P=P'=TBS, Entry 6) which has subsequently been used in the construction of key target **2**.[1] In order to demonstrate the general applicability of this protocol we also chose to synthesise β-ketophosphonate **11**, which has been used by Pattenden as the C_{29}-C_{35} section of the halichondramide backbone (**12**, **Scheme 2**).[9d] Aldehyde **13** was generated through monoprotection of butane-1,4-diol as its *t*-butyldimethylsilyl ether,[19] followed by oxidation by *o*-iodoxybenzoic acid. Enolisation of *t*-butyl thiopropionate with Et_3N and $^cHex_2BBr$ and reaction with aldehyde **13** generated the *anti* aldol adduct in 81% yield as a single diastereomer. Subsequent methylation of the free hydroxyl was achieved using Meerwein's salt in the presence of Proton-Sponge® (Aldrich) to give protected thioester **14**. Phosphonate displacement was carried out using two equivalents of the anion following the protocol described in Method B.[18] A previously unobserved minor impurity, formed by elimination of methanol from β-ketophosphonate **11**, was noted in the ^{1}H nmr of the crude reaction mixture. However, this impurity was found to be readily separable by HPLC allowing the isolation of **11** in 64% yield.[20] Thus the synthesis was successfully completed giving (±)-**11** in 5 steps with an overall yield of 38%, which compares extremely favourably with the earlier synthesis.

In conclusion, we have developed an efficient route for the conversion of functionalised thioesters to β-ketophosphonates and we have demonstrated the addition of these β-ketophosphonates to aldehydes under mild Horner Wadsworth Emmons reaction conditions. This protocol considerably extends the options available for the elaboration of thioesters in natural product synthesis, as demonstrated by the synthesis of enone **3** and β-ketophosphonate **11**.



Scheme 2. Reagents: a) i. NaH, THF, rt, 40 min; ii. TBDMSCl, rt, 1 h (89%); b) *o*-iodoxybenzoic acid (IBX), DMSO/THF, rt, 1 h (88%); c) i. *t*-butyl thiopropionate, $^cHex_2BBr$, Et_3N, 0 °C, 2 h; ii. aldehyde **13**, 0 °C, 2 h (81%); d) Me_3OBF_4, Proton-Sponge®, 0 °C, 2 h (94%); e) i. $(EtO)_2P(O)Me$, *n*-BuLi, THF, -78 °C, 1 h; ii. thioester **14**, -78 °C, 1 h (64%)

Acknowledgements. We thank the EPSRC (GR/95309810 to G.E.H.), The University of Edinburgh (Vacation Scholarship to R.H.W.), The Royal Society and GlaxoWellcome for the support of this work.

References and Notes

1 Hulme, A. N.; Howells, G. E. *Tetrahedron Lett.* **1997**, *38*, 8245-8248.

2 a) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem.* **1995**, *60*, 6248-6249; b) Paterson, I.; Hulme, A. N. *J. Org. Chem.* **1995**, *60*, 3288-3300; c) Chamberlin, A. R.; Dezube, M.; Reich, S. H.; Sall, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 6247-6256; d) Masamune, S.; Lu, L. D.-L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* 1982, *104*, 5523-5526; e) Kaiho, T.; Masamune, S.; Toyoda,

T. *J. Org. Chem.* **1982**, *47*, 1612-1614; f) Masamune, S. *Aldrichimica Acta* **1978**, *11*, 23-32 and references cited therein.

3 a) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050-7051; b) Ley, S. V.; Smith, S. C.; Woodward, P. R. *Tetrahedron* **1992**, *48*, 1145-1174.

4 Gennari, C.; Moresca, D.; Vieth, S.; Vulpetti, A. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1618-1621.

5 Masamune, S.; Sato, T.; Kim, B.M. Wollmann, T. A. *J. Am. Chem. Soc.* 1986, *108*, 8279-8281.

6 a) Review: Mukaiyama, T. *Aldrichimica Acta* **1996**, *29*, 59-76; b) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363-2364; c) Review: Bach, T. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 417-419.

7 Reviews: a) Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann. Rec.* **1997**, 1283-1301; b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927; c) *E*-alkene geometry assigned on the basis of literature precedent.

8 a) Rubsam, F., Evers, A. M., Michel, C., Giannis, A. *Tetrahedron* **1997**, *53*, 1707-1714; b) Bonadies, F.; Cardilli, A.; Lattanzi, A.; Orelli, L. R.; Scettri, A. *Tetrahedron Lett.* **1994**, *35*, 3383-3386; c) Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774-776; d) Koskinen, A. M. P.; Koskinen, P. M. *Synlett* **1993**, 501-502.

9 For recent examples, see: a) Mulzer, J.; Berger, M. *Tetrahedron Lett.* **1998**, *39*, 803-808; b) Nakada, M.; Kobayashi, S.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett.* **1993**, *34*, 1035-1038; c) Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1992**, *57*, 2235-2244; d) Kiefel, M. J.; Maddock, J.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 3227-3230; e) Han, Q.; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692-7697; f) Hoffmann, R. W.; Ditrich, K. *Liebigs Ann. Chem.* **1990**, 23-29.

10 For recent examples, see: a) Stocksdale, M. G.; Ramurthy, S.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 1221-1225; b) Astles, P. C.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. I* **1997**, 845-856; c) Johnson, C. R.; Zhang, B. R. *Abstr. Papers, Am. Chem. Soc.* **1996**, *211*, 125 (ORGN); d) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1994**, *59*, 1703-1708; e) Roush, W. R.; Warmus, J. S.; Works, A. B. *Tetrahedron Lett.* **1993**, *34*, 4427-4430.

11 Delamarche, I.; Mosset, P. *J. Org. Chem.* **1994**, *59*, 5453-5457, and references cited therein.

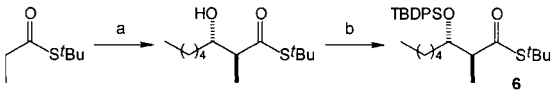
12 a) Pipelier, M.; Ermolenko, M. S.; Zampella, A.; Olesker, A.; Lukacs, G. *Synlett* **1996**, 24-26; b) Paterson, I.; Yeung, K.-S.; *Tetrahedron Lett.* **1993**, *34*, 5347-5350.

13 a) Deziel, R.; Plante, R.; Caron, V.; Grenier, L.; Llinas-Brunet, M.; Duceppe, J. S.; Malenfant, E.; Moss, N. *J. Org. Chem.* **1996**, *61*, 2901-2903; b) Neidlen, R.; Feistauer, H. *Helv. Chim. Acta* **1996,** *79*, 895-913; c) Konoike, T.; Araki, Y. *J. Org. Chem.* **1994**, *59*, 7849-7854; d) Mulzer, J.; List, B. *Tetrahedron Lett.* **1994**, *35*, 9021-9024.

14 a) Takemoto, M.; Koshida, A.; Miyazima, K.; Suzuki, K.; Achiwa, K. *Chem. Pharm. Bull.* **1991**, *39*, 1106-1111; b) Kuo, F.; Fuchs, P. L. *Synth. Commun.* **1986**, *16*, 1745-1759; c) Honda, M. Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *35*, 3857-3860.

15 a) Blackwell, C. M.; Davidson, A. H.; Launchbury, S. B.; Lewis, C. N.; Morrice, E. M.; Reeve, M. M.; Roffey, J. A. R.; Tipping, A. S.; Todd, R. S. *J. Org. Chem.* **1992**, *57*, 1935-1937; b) Dufour, M.-N.; Jouin, P.; Poncet, J.; Pantaloni, A.; Castro, B. *J. Chem. Soc., Perkin Trans. I* **1986**, 1895-1900.

16 Aldol adduct **6** was prepared in two steps from *t*-butyl thiopropionate and hexanal, as shown below:



a) i. LDA, -78 °C, 1 h; TMSCl, -78 °C → rt, 1 h; ii. hexanal, $BF_3.OEt_2$, -78 °C, 1 h (86%); b) TBDPSCl, DMF, imidazole, rt, 24 h (77%)

17 In this and subsequent reactions, the relative stereochemistry α to the phosphonate was not determined.

18 Typical procedure for Method B: to a solution of diethyl ethanephosphonate (5.84 g, 35.11 mmol) in THF (20 ml) was added *n*-BuLi (1.54 M solution in hexanes, 22.80 ml, 35.11 mmol) dropwise at -78 °C under an atmosphere of argon. After stirring for 50 min at -78 °C the light yellow solution was transferred *via* cannula into a solution of thioester **9** (Entry 6, 4.02 g, 7.98 mmol) in THF (15 ml) at -78 °C and the resulting solution was stirred for a further 50 min before carefully pouring onto a saturated aqueous solution of NH_4Cl (150 ml). The mixture was extracted with CH_2Cl_2, washed with brine, dried ($MgSO_4$) and the volatiles removed under reduced pressure. Purification of the crude material by flash chromatography with hexane/EtOAc (3:2) as eluent afforded the β-ketophosphonate **10** (Entry 6) as a clear oil 4.23 g (94%).

10 (P=P'=TBS, n=5), 3.3:1 mixture of diastereomers: IR (neat) 1712, 1251 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 4.26-4.06 (4H, m, $P(OCH_2CH_3)_2$), 4.02-3.95 (0.23H, m, C*H*OTBS), 3.94-3.84 (0.77H, m, C*H*OTBS), 3.63 (2H, t, *J* = 6.4 Hz, CH_2OTBS), 3.55-2.98 (2H, m, C*H*C(O) and C*H*P(O)), 1.65-1.20 (13H, m, CH_2 x 5, $CH(CH_3)P(O)$), 1.37 (6H, t, *J* = 7.1 Hz, CH_2CH_3 x 2), 1.15 (0.7H, d, *J* = 7.3 Hz, CH(OTBS)CHCH_3), 1.02 (2.3H, d, *J* = 6.6 Hz, CH(OTBS)CHCH_3), 0.93 (9H, s, $C(CH_3)_3$), 0.90 (2.1H, s, $C(CH_3)_3$), 0.89 (6.9H, s, $C(CH_3)_3$), 0.08 (6H, s, $SiCH_3$), 0.07 (3.7H, $SiCH_3$), 0.00 (2.3H, $SiCH_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) major diastereomer 209.1 (d, $^2J_{P-C}$ = 3.6 Hz), 74.7, 63.07, 62.3 (2C, d, $^2J_{P-C}$ = 6.7 Hz), 50.7, 48.2 (d, $^1J_{P-C}$ = 25.5 Hz), 33.4, 32.7, 29.6, 25.9 (3C), 25.8, 25.7 (3C), 22.8, 18.2, 17.8, 16.2 (2C), 12.4, 10.4 (d, $^2J_{P-C}$ = 5.7 Hz), -4.5, -4.8, -5.4 (2C), minor diastereomer 208.9 (d, $^2J_{P-C}$ = 4.5 Hz), 73.1, 63.14, 62.3 (2C, d, $^2J_{P-C}$ = 6.7 Hz), 50.3, 45.0 (d, $^1J_{P-C}$ = 28.6 Hz), 33.4, 32.7, 29.6, 25.9 (3C), 25.8, 25.7 (3C), 24.5, 18.2, 17.9, 16.2 (2C), 12.3, 11.4 (d, $^2J_{P-C}$ = 6.9 Hz), -4.7, -4.8, -5.4 (2C); FABMS 581 (24%, $[M+H]^+$), 523 (100), 449 (78), 279 (99).

19 McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388-3390.

20 We are grateful to Prof. Pattenden for supplying spectral data for **11**, which was found to be in good agreement with our own data.