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A Synthetic and Computational Investigation into the Direct Synthesis of α-Hydroxymethylated Enones from β-Keto Phosphonates

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The synthesis of a range of α-hydroxymethylated enones has been achieved using the Villiéras modification of the Horner–Wadsworth–Emmons (HWE) reaction. Scope, limitations, and mechanistic aspects of this reaction were investigated using a combination of synthetic and computational studies. These investigations support a Schlosser–Corey type reaction mechanism that is balanced between two pathways with the outcome influenced by the steric environment of the substrate.

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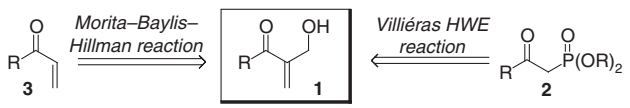
Introduction

Interception of the Wittig reaction by low temperature deprotonation and alkylation was introduced separately by Schlosser[1a] and Corey[1b] as a method for the assembly of allylic alcohols in a stereochemically well defined fashion.[1] As part of studies directed towards the synthesis of limonoid natural products,[2] a range of α-hydroxymethylated enones (e.g., **1**) were required. While these compounds can be prepared from the enone (e.g., **3**) by a Morita–Baylis–Hillman (MBH) reaction,[3] more convenient is their preparation using a Schlosser–Corey type reaction with an appropriate Horner–Wadsworth–Emmons (HWE) or stabilized Wittig reagent (Scheme 1).[4] This approach was reported by Villiéras for ester-containing HWE reagents (**2**, R = OR)[5a–c] and has been exploited in several synthetic applications.[5d–g] The analogous approach for ketone-containing HWE reagents has received little attention,[5c] while the mechanism of this reaction is yet to be probed. As a result of our synthetic needs, the well documented utility of MBH adducts,[6] and problems associated with their preparation,[3c,7] it was decided to investigate the scope and mechanism of the Villiéras approach to MBH adducts.

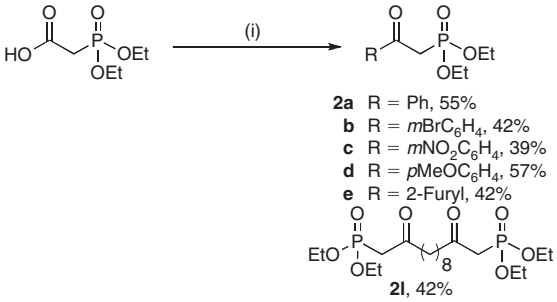
Results and Discussion

In order to undertake the proposed studies, access to a range of β-keto phosphonates **2** was required.[8] In our hands, the known acylation decarboxylation of (diethoxyphosphoryl)acetic acid (Scheme 2) proved convenient for the preparation of known (**2a**–**e**) and new (**2l**) phosphonates.[8b]

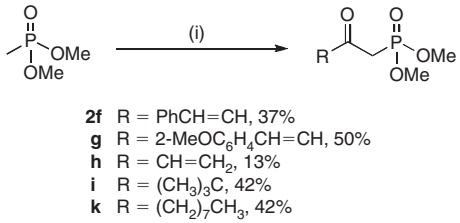
While this approach was operationally simple, it failed to provide β-keto phosphonates **2f**–**i** and **k**. These compounds were



Scheme 1.



Scheme 2. Reagents and conditions: (i) $MgCl_2$ (2.5 mol equiv.), Et_3N (4 mol equiv.), CH_3CN 18°C, and then RCOCl (1 mol equiv.), 0 → 18°C.



Scheme 3. Reagents and conditions: (i) *n*-BuLi (1 mol equiv.), CuI (1 mol equiv.) THF, −78°C → −40°C, and then RCOCl (1 mol equiv.), −40°C → 18°C.

prepared from dimethyl methylphosphonate by its corresponding cuprate (Scheme 3).[8c]

Initial studies into the Villiéras reaction explored the use of reaction conditions analogous to those reported for α-phosphonoesters.[5a] When phosphonate **2a** was reacted under these conditions the expected product **1a** formed in 41% yield accompanied by enone **3a** and phosphonate **4a** in a 5:2:1 ratio (Table 1, entry 1). While this is the first report of these by-products in a Villiéras–HWE reaction, their formation seemed in keeping with the reaction conditions, which may provide enone **3a** by a conventional HWE reaction and phosphonate **4a** from

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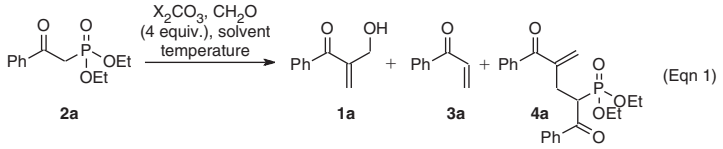
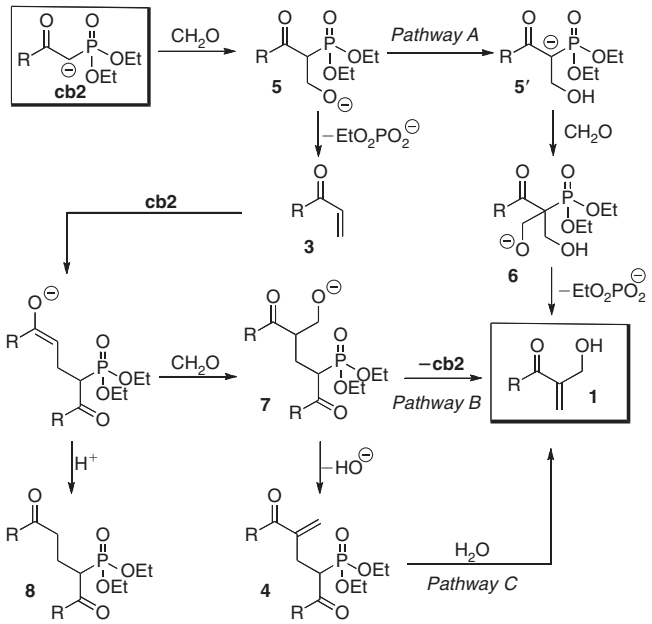
Table 1. Selected optimization of Villiéras–HWE reaction of β-keto phosphonates



2a 1a 3a 4a

Entry	X_2CO_3 [mol-%]	Solvent	t [h]	T^A [°C]	Ratio[B] **1a**:**3a**:**4a**	Yield **1a**[C] [%]
1[D]	100 (K)	H_2O	2	rt	5:2:1	41
2	100 (K)	DMSO/H_2O[E]	2	rt	24:1:37	33
3[F]	100 (K)	H_2O	2	rt	38:1:0	16
4	100 (K)	H_2O	1	0	5:2:1	45
5	10 (K)	H_2O	2	rt	12:1:0	20
6	70 (K)	H_2O	2	rt	14:1:0	66
7	70 (Na)	H_2O	2	rt	14:1:0	65
8	70 (Li)	H_2O	2	rt	14:1:1	52

[A] rt = room temperature.
[B] Ratio calculated by integration of suitably separated peaks within the ^{1}H NMR spectrum of the reaction mixture.
[C] Isolated yield following flash column chromatography.
[D] CH_2O formed in situ from paraformaldehyde.
[E] 1:1 ratio of DMSO and H_2O.
[F] Eight equivalents of formaldehyde.



Scheme 4. Proposed reaction mechanisms.

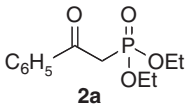
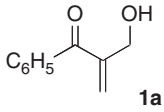
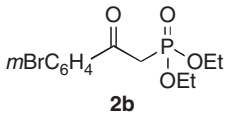
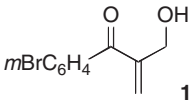
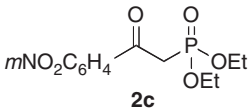
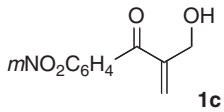
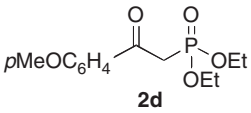
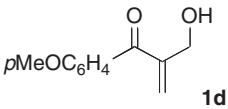
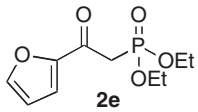
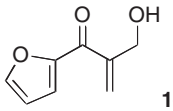
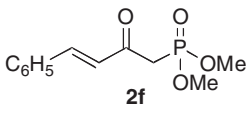
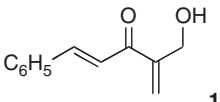
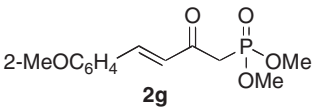
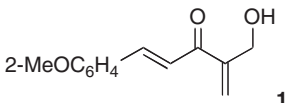
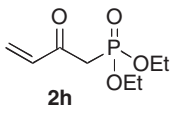
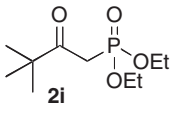
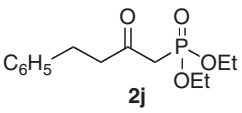
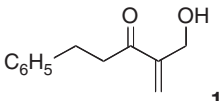
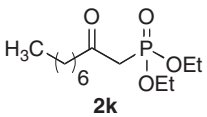
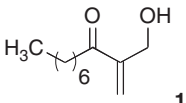
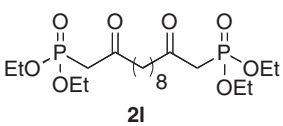
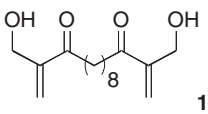
the degradation of allylic alcohol **1a**. Alternately, the formation of such by-products may be explained by the initial formation of enone **3a**, which is subsequently converted into allylic alcohol **1a** by a MBH reaction catalyzed by phosphonate **2a**.[9] In this case, the formation of **4a** would arise as a result of dehydration of a MBH intermediate, rather than elimination of phosphonate **2a** (Scheme 4).

If the reaction proceeds by pathway B/C it was reasoned that conversion of enone **3a** into allylic alcohol **1a** may be enhanced using a dimethyl sulfoxide/H_2O solvent mix known to accelerate the rate of MBH reactions.[10,11] In the event, this decreased the formation of enone **3a**, but favoured the formation of phosphonate **4a** (Table 1, entry 2). In order to increase the formation of allylic alcohol **1a** the stoichiometry of formaldehyde was increased, which resulted in a good ratio of **1a**:**3a**:**4a** (38:1:0), but lower overall yield (Table 1, entry 3). Cooling the reaction mixture had little bearing on either the ratio of products, or the yield (Table 1, entry 4). Finally, attention was turned to the stoichiometry of K_2CO_3. When 10 mol-% of K_2CO_3 was used, the ratio of **1a**:**3a**:**4a** was 12:1:0, although the yield was a mere 20% (Table 1, entry 5). Increasing the amount of base to 70 mol-% allowed the formation of allylic alcohol **1a** to be achieved in 66% yield (Table 1, entry 6) with only a trace of by-product **3a**. The use of Na_2CO_3 and Li_2CO_3 was also investigated and found to have little bearing on the reaction outcome (Table 1, entries 7 and 8).

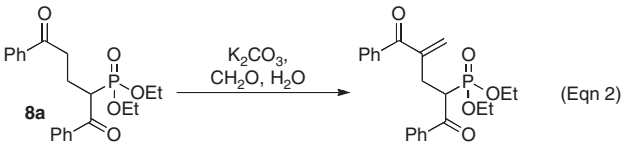
These studies indicate that with ketone-containing HWE reagents the formation of by-products **3a** and **4a** occur readily, but can be suppressed through the control of the stoichiometry of base. From a mechanistic standpoint, the formation of compounds **3a** and **4a** bring to light several possibilities in addition to the Schlosser–Corey type dialkylation originally proposed by Villiéras. In order to clarify the mechanism of this reaction and ascertain the generality of these reaction conditions, an investigation into the reaction scope was undertaken. When electron-poor aromatic, electron-rich aromatic, and heteroaromatic phosphonates were subjected to the optimized reaction conditions (Table 1, entries 2–5) they all smoothly provided products **1b**–**e** in acceptable yields, in each case accompanied by a small amount of by-product **3b**–**e**, identifiable by ^{1}H NMR spectroscopy.

When cinnamyl phosphonate **2f** was subjected to the reaction conditions, the expected product **1f** formed in an excellent yield of 92% (Table 2, entry 6) without any by-product **3f**. Interestingly when 2-methoxycinnamyl phosphonate **2g** (Table 2, entry 7) was allowed to react the yield was reduced, and once more by-product **3g** was identified. Unfortunately, when acrolyl chloride-derived phosphonate **2h** was subjected to the optimized reaction conditions, decomposition was observed (Table 2, entry 8).

Table 2. Scope of the tandem olefination MBH reaction

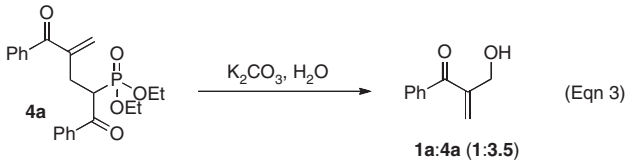
Entry	SM	Product	Yield[A] [%]
1	 **2a**	 **1a**	66
2	 **2b**	 **1b**	63
3	 **2c**	 **1c**	65
4	 **2d**	 **1d**	65
5	 **2e**	 **1e**	56
6	 **2f**	 **1f**	92
7	 **2g**	 **1g**	50
8	 **2h**	–	–[B]
9	 **2i**	–	–[C]
10	 **2j**	 **1j**	96
11	 **2k**	 **1k**	60
12	 **2l**	 **1l**	57

[A]Isolated yield following flash column chromatography.
[B]Decomposition of starting material **2h**.
[C]No reaction of starting material **2i**.



(Eqn 2)

4a:**8a** (**1**:**2.9**)



(Eqn 3)

1a:**4a** (**1**:**3.5**)

Finally, the reactions of alkyl-substituted phosphonates were investigated. While pivaloyl chloride-derived β-keto phosphonate **2i** failed to provide alcohol **1i** (Table 2, entry 9); dihydrocinnamyl phosphonate **2j** gave the expected product **1j** in high yield, without the formation of by-product **3j** (Table 2, entry 10). Similarly alkyl phosphonates **2k** and bisphosphonate **2l** provided allylic alcohols **1k** and **1l** without by-products (Table 2, entries 11 and 12).

Based on optimization and scope studies, three plausible reaction mechanisms for the Villiéras–HWE reaction can be proposed (Scheme 3). Based on a Schlosser–Corey type mechanism, as originally proposed by Villiéras,[5a] hydroxymethylation of the starting phosphonate affords alkoxide **5**, which then undergoes proton transfer to form **5′**. This intermediate subsequently reacts with a second molecule of formaldehyde to give intermediate **6**,¶ which fragments to provide compound **1** (pathway A). Alternatively, intermediate **5** may directly fragment to afford olefin **3**, which then undergoes MBH reaction catalyzed by β-keto phosphonate **2** to provide alcohol **1** directly (pathway B), or by enone **4** (pathway C).[9] The failure of the least hindered substrates **2f**, **j**, **k**, and **l** to afford any by-products would appear to suggest that the reaction occurs by a mechanism sensitive to sterics, which supports the originally proposed pathway A. Potentially, pathways B and C become operative in cases where steric crowding slows the formation of intermediate **6**. The isolation of enone **3a** clearly demonstrates that the first step in pathway B/C proceeds, however, the viability of this pathway to afford allylic alcohol **1a** remains in question.

Investigation into these mechanistic possibilities was undertaken using synthetic and computational methods. It was hoped that a kinetic analysis of the reaction could be undertaken to clarify the involvement of these pathways, however, because of the rapid nature of the reaction and its heterogeneity this was not possible. Thus, the interconversion of isolated intermediates, specifically enone **3a**, phosphonate **4a**, and ketone **8a**† was investigated. Initial studies focussed on demonstrating that phosphonate **8a** and **4a** could be converted into allylic alcohol **1a** (Eqn 2 and 3). When phosphonate **8a** was exposed to formaldehyde and K_2CO_3 after 2 h 25% conversion to compound **4a** was observed (Eqn 2), however allylic alcohol **1a** failed to form.

Similarly, when enone **4a** was dissolved in water and reacted with K_2CO_3 allylic alcohol **1a** formed (Eqn 3), but only as the minor product with most of the material remaining as unreacted starting material.

While these experiments prove that intermediates **8a** and **4a** can give rise to allylic alcohol **1a**, considering the extended reaction time required to achieve low levels of conversion, their significance appears to be minimal. Subsequent investigations focussed on the conversion of enone **3a** into allylic alcohol **1a** by a MBH reaction catalyzed by HWE reagent **2**. In order to establish this, a crossover experiment in which enone **3a** was reacted with two equivalents of nitro phosphonate **2c** (Eqn 4) was undertaken. This experiment produced none of product **1a**, which indicates that β-keto phosphonate **2c** does not undergo conjugate addition into enone **3a**. A similar crossover experiment was undertaken using phosphonate **2d**. However, as with phosphonate **2c**, compound **1a** was not identified (Eqn 5). In both of these experiments hybrid intermediates of type **8** or **4** were never observed, which clearly indicates that the anions of the β-keto phosphonates **2c** and **2d** are incapable of undergoing conjugate addition with enone **3a**.

While these studies indicate that pathway B/C does not give rise to the formation of allylic alcohol **1a**, the origin of enone **4a** and ketone **8a** remained to be explained. As they are not forming from the reaction of enone **3a**, it appeared likely that these materials arise as a result of degradation of allylic alcohol **1a**. When a 2:1 mixture of β-keto phosphonate **2a** and alcohol **1a** were mixed in the presence of water and K_2CO_3 after 30 min the quantity of compounds **2a** and **1a** were found to have decreased and intermediate **8a** was now observed (Scheme 5). As this reaction lacks formaldehyde, it is not possible to form enone **4a**. However, this reaction indicates that allylic alcohol **1a** is not stable under the optimized reaction conditions and can lead to the formation of degradation products.

Calculations

While synthetic studies suggest that allylic alcohol **1a** forms by pathway A, and that by-products arise as a result of competing reactions (in the case of enone **3a**) or decomposition (in the case of phosphonate **4a**), it was decided to investigate the reaction using computational approaches to gain further insight into the mechanism. The use of computational techniques to study the Wittig and HWE reaction is well documented[12] with notable work by Ando.[12c] Using a similar approach the energy profile of the reaction was calculated at *B3LYP/6-31+G** level of theory, using the software package *Gaussian 03*.[13] Incorporation of the polarization continuum solvent model (PCM, $\varepsilon = 78.69$) allowed the simulation of the reaction in water.[14] All structures were derived from the conjugate base of **2a** (Et = Me) [namely **cb2a** (Et = Me)], two formaldehyde molecules, and a potassium ion. Local minima and transition states were confirmed by zero or one negative frequency, respectively, and have been calculated for all species on pathway A and on all species up until enone **3a** on pathway B/C. As in the work of Ando, inclusion of the cation is essential – in its absence the hydroxymethylation does not proceed. Gas phase calculations predict that the barrier to forming enone **3a** is lower than that for the formation of enone **1a**. However, incorporation of the solvation model inverts these energies and provides results more consistent with the synthetic studies (Fig. 1, and with computationally derived structures in Figure S1 of the Accessory Publication). In the PCM/DFT calculations divergence of pathways A and B/C occurs at intermediate **5**. The difference in energy between the two pathways at the rate

¶The dihydroxymethylated derivative of phosphonate **2** (R = OEt) is indicated as an intermediate in the hydroxymethylation reported in Ref. [5a].

†Intermediate **8a** was prepared as described in the experimental section as a part of other optimization studies.

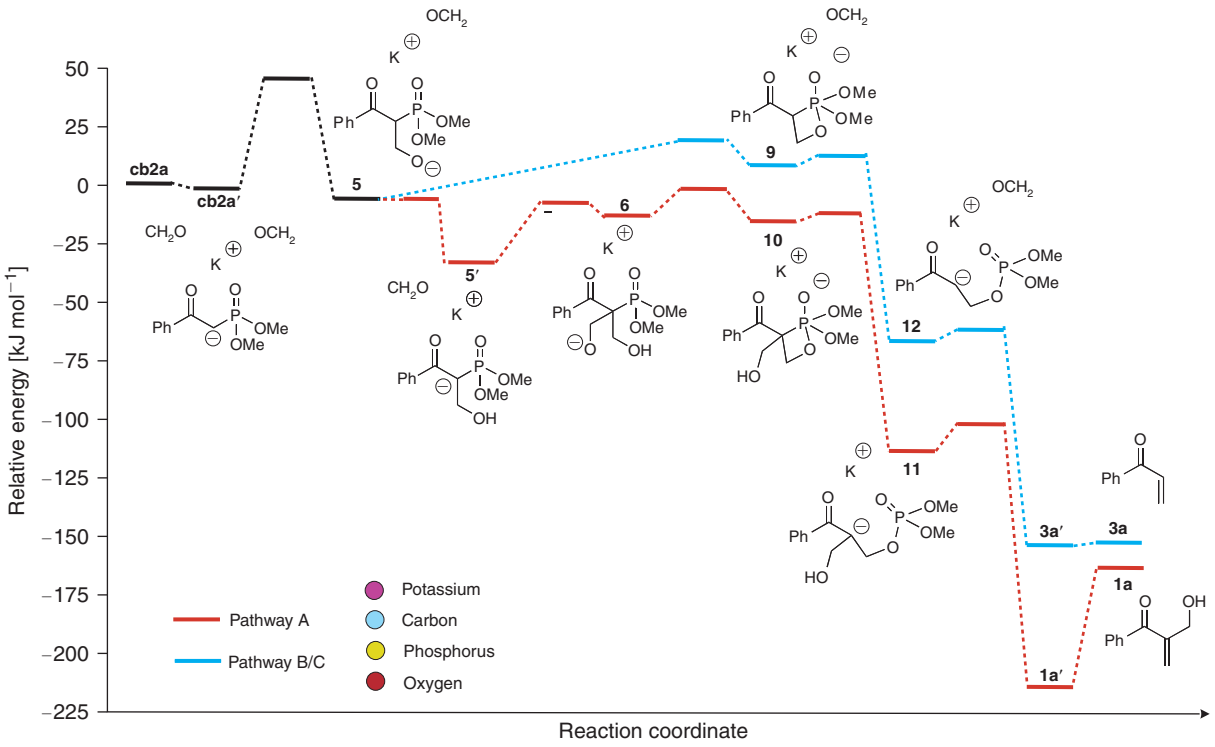
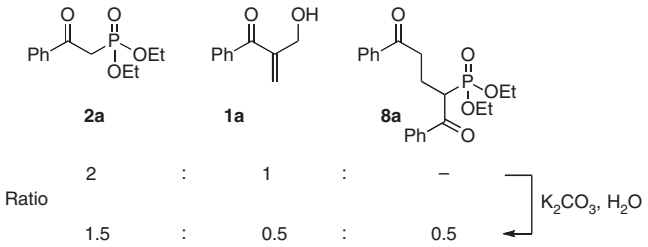


Fig. 1. Reaction coordinate calculated using PCM/*B3LYP/6-31+G**.

determining step is 36.15 kJ mol^{-1} and corresponds to the transition states for the formation of oxetane **9** in pathway B/C and oxetane **10** in pathway A. Only small barriers (~4 kJ mol^{-1}) for P–C and C–O bond cleavage isolate the oxetanes **9** and **10** from the final products **1a** and **3a**.

These computational results concur with the synthetic studies and indicate that the formation of allylic alcohol **1a** occurs by a lower energy pathway than the formation of enone **3a**. The magnitude of this difference is somewhat larger than the synthetic studies suggest, however, this may be a result of the limitations of our computational model, which simplifies the solvent mixture.

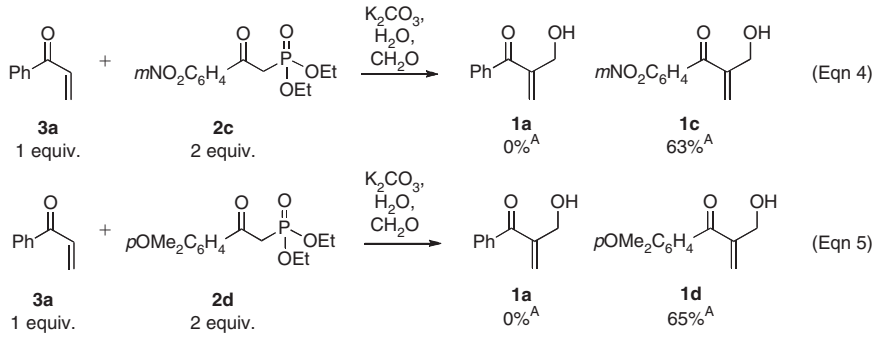


Scheme 5.

Conclusions

Based on DFT studies, and the observed by-product formation in the experimental studies, it appears that formation of the allylic alcohol **1** is more energetically favourable than the formation of enone **3**. With substrates less sterically demanding than a phenyl group (R = cinnamyl, hydrocinnamyl, etc.) this difference in transition-state energy is large enough that the allylic alcohol **1** is the only product formed. Crossover experiments indicate that when enone **3** forms it is unlikely to react further to provide allylic alcohol **1**; and that phosphonates **4a** and **8a** arise from the degradation of product **1a**. These results and the DFT/PCM studies indicate that the formation of allylic alcohol **1a** is occurring by a Schlosser–Corey type mechanism as originally proposed by Villiéras (pathway A).

Through the course of these studies it has been demonstrated that the Villiéras modification of the HWE reaction is a viable method for the synthesis of known and new MBH adducts.



[A]Yields were determined based on ^{1}H NMR analysis.

The reaction proceeds rapidly in all cases, and when unhindered HWE reagents are used, gives rise to the desired product in high yield and without any by-products. By employing synthetic and theoretical studies the first direct evidence for the reaction mechanism proposed by Villiéras has been obtained.

Experimental

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded in $CDCl_3$ on a Varian Mercury 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei or a Varian DRX 500 spectrometer operating at 500 MHz for proton and 125 MHz for carbon. Signals arising from the residual protio-forms of the solvent were used as the internal standard. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer RXI FTIR Spectrometer. Samples were analyzed as thin films on NaCl plates and IR band intensities are expressed as s = strong, m = medium, w = weak, and br = broad. Low-resolution mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker BioApex 47e FTMS fitted with an Analytical electrospray source using NaI for accurate mass calibration. Low-resolution (EI) mass spectra were also recorded on a VG Micromass 70/70F mass spectrometer with an ion source temperature of 200°C and electron impact energy of 70 eV. Melting points were measured on a Stuart hot-stage microscope apparatus. Flash column chromatography was performed on silica gel (Davisil LC60A, 40–63 μm silica media) using compressed air or nitrogen. TLC was performed using aluminium-backed plates coated with 0.2 mm silica (Merck, DC-Platten, Kieselgel; 60 F_{254} plates). Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable stain followed by heating.

Starting materials and reagents were purchased from Sigma–Aldrich and were used as supplied or, in the case of some liquids, distilled. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Concentration under reduced pressure was performed on a rotary evaporator with the water bath temperature not exceeding 40°C.

Experimental Procedures for the Synthesis of Phosphonates

*(E)-Dimethyl 4-(2-Methoxyphenyl)-2-oxobut-3-enylphosphonate (**2g**)*

Using a modification to the procedure reported by Nesterov et al.[8c] dimethyl methylphosphonate was acylated with 2-methoxy cinnamyl chloride to yield the *title compound* as a yellow oil (1.45 g, 50%). R_f 0.3 (EtOAc). (Found: 307.0656 $[M+Na]^+$. $C_{20}H_{40}O_8P_2$ requires: 307.0711 $[M+Na]^+$.) ν_{max}/cm^{-1} 3473.0br, 2956.1m, 1682.6m, 1651.8m, 1597.3s, 1248.9s, 1027.9s. δ_H (500 MHz) 7.97 (1H, d, *J* 17), 7.56 (1H, dd, *J* 7.5, 1.5), 7.38 (1H, tm, *J* 7.5), 6.97 (1H, t, *J* 7.5), 6.92 (1H, dd, *J* 7.5, 1.5), 6.91 (1H, d, *J* 17), 3.90 (3H, s), 3.81 (6H, d, *J* 11), 3.36 (2H, d, *J* 23). δ_C (125 MHz) 191.5 (d, *J* 6.4), 158.8, 140.5, 132.4, 129.1, 126.3, 123.1, 120.9, 111.3, 55.7, 53.2 (d, *J* 6.5), 39.4 (d, *J* 129). *m/z* (ESI) 307.0 (100%) $[M+Na]^+$, 285.1 (8) $[M+H]^+$.

Tetraethyl 2,11-dioxododecane-1,12-diyldiphosphonate (***2l***). Using the procedure described by Kim et al.,[8b] however with 0.5 equivalents of sebacoyl chloride and 1 equivalents of all other reagents the title compound was prepared as a yellow oil (1.98 g, 42%). R_f 0.2 (10% MeOH:EtOAc). (Found: 493.2093 $[M+Na]^+$. $C_{20}H_{40}O_8P_2$ requires: 493.2096 $[M+Na]^+$.) ν_{max}/cm^{-1} 3474.5br, 2982.7s, 2931.5s, 2855.8m, 1715.6s, 1394.6m, 1368.8m, 1254.9s br, 1025.2s br. δ_H (500 MHz) 3.98–4.05 (8H, m), 2.95 (4H, d, *J* 23.0), 2.48 (4H, t, *J* 7.0), 1.42–1.45 (4H, m), 1.21 (12H, t, *J* 7.0), 1.13–1.15 (8H, m). δ_C (125 MHz) 202.2 (2C), 62.5 (d, *J* 6.5, 4C), 44.0 (2C), 42.3 (d, *J* 126, 2C), 29.1 (2C), 28.8 (2C), 23.3 (2C), 16.3 (d, *J* 6.0, 4C). *m/z* (ESI) 471.2 (70%) $[M+H]^+$, 493.1 (100) $[M+Na]^+$.

General Method for α-Hydroxymethylation Reaction

To a stirred solution of phosphonate **2** (0.5 mmol) in aqueous formaldehyde (2.0 mmol in 2 mL of H_2O), K_2CO_3 (0.7 mL of a 0.5 M aqueous solution, 0.35 mmol) was added dropwise. The reaction mixture was allowed to stir for 1 h, at which time the mixture was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with brine (3 × 5 mL), dried ($MgSO_4$), and concentrated under vacuum. The resulting residue was purified by flash column chromatography to afford, after concentration of the appropriate fractions, the title compound. The reaction mixture derived from the reaction of phosphonate **2a** when separated by column chromatography (silica gel, 50% EtOAc/hexane) afforded enone **3a** (R_f 0.7) along with the major product allylic alcohol **1a** (R_f 0.4) in a ratio of 14:1.

*2-(Hydroxymethyl)-1-phenylprop-2-en-1-one (**1a**)*

Obtained as a clear oil (54 mg, 66%). R_f 0.4 (50% EtOAc/hexane). ν_{max}/cm^{-1} 3417.4s br, 1652.9s, 1597.3m, 1447.6m, 1321.8m, 978.5m. δ_H (500 MHz) 7.75–7.76 (2H, m), 7.55–7.58 (1H, m), 7.44–7.48 (2H, m), 6.12 (1H, s), 5.83 (1H, s), 4.51 (2H, s). δ_C (125 MHz) 196.4, 146.7, 137.6, 132.8, 129.8, 128.6, 127.5, 63.1.

*1-(3-Bromophenyl)-2-(hydroxymethyl)prop-2-en-1-one (**1b**)*

Obtained as a white solid (74 mg, 63%). R_f 0.3 (35% EtOAc/hexane). Mp 41.4–49.8°C. (Found: 238.9709 $[M-H^\bullet]^+$. $C_{10}H_9BrO_2$ requires: 238.9708 $[M-H^\bullet]^+$.) ν_{max}/cm^{-1} 3105.8m br, 1645.1s, 1625.6m, 1562.2m, 1419.2w, 1078.0m. δ_H (500 MHz) 7.86 (1H, t, *J* 2.0), 7.64–7.69 (2H, m), 7.33 (1H, t, *J* 8.0), 6.19 (1H, t, *J* 0.5), 5.81 (1H, s), 4.49 (2H, s). δ_C (125 MHz) 196.5, 146.3, 139.4, 135.7, 132.5, 130.2, 128.2, 128.2, 122.8, 63.0. *m/z* (EI) 239 (17%) $[M-H^\bullet]^+$, 185 (42), 161 (100), 155 (34), 115 (13), 85 (8).

*2-(Hydroxymethyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**1d**)*

Obtained as a clear oil (63 mg, 65%). R_f 0.3 (35% EtOAc/hexane). (Found: 193.0863 $[M-H^\bullet]^+$. $C_{10}H_{12}O_3$ requires: 193.0865 $[M-H^\bullet]^+$.) ν_{max}/cm^{-1} 3434.2s br, 2935.6m, 1647.0m, 1600.0s, 1509.3m, 1309.1m, 1260.3s, 1166.5s. δ_H (500 MHz) 7.80 (2H, d, *J* 9.0), 6.93 (2H, d, *J* 9.0), 6.05 (1H, t, *J* 1.0), 5.73 (1H, s), 4.47 (2H, s), 3.86 (3H, s). δ_C (125 MHz) 197.0, 163.6, 146.5, 132.2, 130.0, 125.7, 113.8, 63.7, 55.7. *m/z* (ESI) 215.1 (100%) $[M+Na]^+$.

*1-(Furan-2-yl)-2-(hydroxymethyl)prop-2-en-1-one (**1e**)*

Obtained as a clear oil (43 mg, 56%). R_f 0.2 (35% hexane/EtOAc). (Found: 175.0366 $[M+Na]^+$. $C_8H_8O_3$ requires: 175.0371 $[M+Na]^+$.) ν_{max}/cm^{-1} 3412.6s br, 2872.0m, 1646.3s, 1618.0m, 1560.8m, 1465.5s, 1391.1m, 1324.3m. δ_H (500 MHz) 7.65 (1H, dd, *J* 1.5, 1.0), 7.20 (1H, dd, *J* 4.0, 1.0), 6.54 (1H, dd, *J* 4.0, 1.5), 6.20 (1H, d, *J* 0.5), 6.06 (1H, s), 4.45 (2H, s). δ_C (125 MHz) 183.5, 152.0, 147.5, 146.3, 125.6, 120.5, 112.4, 63.3. *m/z* (ESI) 175.0 (100%) $[M+Na]^+$.

*(E)-4-(Hydroxymethyl)-1-phenylpenta-1,4-dien-3-one (**1f**)*

Obtained as a white solid (86.6 mg, 92%). R_f 0.4 (35% EtOAc/hexane). Mp 83.4–85.6°C. (Found: 189.0914 $[M+H]^+$, 211.0729 $[M+Na]^+$. $C_{12}H_{12}O_2$ requires: 189.0916 $[M+H]^+$, 211.0735 $[M+Na]^+$.) ν_{max}/cm^{-1} 3194.57w br, 1654.20m, 1596.27s, 1449.35m. δ_H (500 MHz) 7.70 (1H, d, *J* 15.5), 7.59–7.60 (2H, m), 7.40–7.42 (3H, m), 6.29 (1H, d, *J* 15.5), 6.21 (1H, s), 6.08 (1H, t, *J* 1.5), 4.45 (2H, d, *J* 6.0), 2.66 (1H, t, *J* 6.0, OH). δ_C (125 MHz) 191.9, 148.0, 144.7, 134.8, 130.9, 129.2, 128.7, 125.0, 121.2, 63.2. *m/z* (ESI) 211.2 (73%) $[M+Na]^+$, 193.9 (5), 181.2 (6), 159.0 (8).

*2-(Hydroxymethyl)-5-phenylpent-1-en-3-one (**1j**)*

Obtained as a clear oil (91 mg, 96%). R_f 0.3 (35% hexane/EtOAc). (Found: 191.1069 $[M+H]^+$. $C_{12}H_{14}O_2$ requires: 191.1072 $[M+Na]^+$.) ν_{max}/cm^{-1} 3436.4s br, 2930.5m, 1673.4s, 1495.9m, 1453.6m. δ_H (500 MHz) 7.26–7.30 (2H, m), 7.19–7.21 (3H, m), 6.10 (1H, s), 6.00 (1H, t, *J* 1.5), 4.32 (2H, s), 3.04 (2H, tm, *J* 8.0), 2.94 (2H, t, *J* 8.0). δ_C (125 MHz) 201.6, 147.0, 141.2, 128.7, 128.6, 126.4, 125.5, 62.7, 39.8, 30.2. *m/z* (ESI) 213.1 (100%) $[M+Na]^+$.

*2-(Hydroxymethyl)dec-1-en-3-one (**1k**)*

Obtained as a clear oil (55 mg, 60%). R_f 0.4 (35% EtOAc/hexane). (Found: 183.1394 $[M-H^{\bullet}]^+$. $C_{11}H_{20}O_2$ requires: 183.1385 $[M-H^{\bullet}]^+$.) ν_{max}/cm^{-1} 3167.6m br, 2927.5s, 2849.0m, 1663.3s, 1467.7m, 1401.1w. δ_H (500 MHz) 6.09 (1H, s), 5.98 (1H, t, *J* 1.0), 4.29 (2H, s), 2.68 (2H, t, *J* 7.5), 1.59 (2H, t, *J* 7.0), 1.22–1.30 (8H, m), 0.86 (3H, t, *J* 7.0). δ_C (125 MHz) 203.1, 147.0, 125.1, 62.8, 38.1, 31.9, 29.4, 29.3, 24.5, 22.8, 14.3. *m/z* (EI) 183 (2%) $[M-H^{\bullet}]^+$, 100 (36), 85 (100), 81 (20), 57 (20).

*2,13-Bis(hydroxymethyl)tetradeca-1,13-diene-3,12-dione (**1l**)*

Obtained as a white solid (81 mg, 57%). R_f 0.3 (EtOAc). Mp 88.7–91.5°C. (Found: 305.1726 $[M+Na]^+$. $C_{16}H_{26}O_4$ requires: 305.1729 $[M+Na]^+$.) ν_{max}/cm^{-1} 3198.6br, 2909.9s, 2848.0m, 1662.7s, 1465.3m, 1408.4w. δ_H (500 MHz) 6.10 (2H, s), 5.99 (2H, s), 4.31 (4H, s), 2.69 (4H, t, *J* 7.5), 1.59–1.62 (4H, m), 1.30 (8H, s). δ_C (125 MHz) 203.1, 147.0, 125.3, 63.0, 38.0, 29.4, 29.3, 24.4. *m/z* (ESI) 305.3 (100%) $[M+Na]^+$.

During the optimization studies phosphonate **2a** (0.5 mmol) was reacted as detailed in Table 1 and produced, along with allylic alcohol **1a**, enone **3a**, and phosphonate **4a**. For the ratio of these by-products in each specific optimization see Table 1.

*1-Phenylprop-2-en-1-one (**3a**)*

Obtained as a clear oil. R_f 0.7 (1/1, v/v, EtOAc in hexane). ν_{max}/cm^{-1} 2925.3m, 1671.9s, 1608.5m, 1447.9m, 1403.9m. δ_H (500 MHz) 7.95(3) (1H, d, *J* 8.0), 7.95(1) (1H, d, *J* 8.0), 7.58 (1H, t, *J* 8.0), 7.49 (2H, t, *J* 8.0), 7.17 (1H, dd, *J* 17, 11), 6.44 (1H, dd, *J* 17, 2.0), 5.94 (1H, dd, *J* 11, 2.0, 1H). δ_C (75 MHz) 191.5, 137.7, 133.4, 132.8, 130.6, 129.1, 129.0.

*Dimethyl 4-Benzoyl-1-oxo-1-phenylpent-4-en-2-ylphosphonate (**4a**)*

Obtained as a clear oil. R_f 0.2 (50% hexane/EtOAc). (Found: 373.1202 $[M+H]^+$. $C_{20}H_{21}O_5P$ requires: 373.1205 $[M+H]^+$.) ν_{max}/cm^{-1} 3409.0br, 2926.3m, 1679.7s, 1596.9m, 1448.8m, 1259.8m, 1035.4br. δ_H (500 MHz) 7.97–7.98 (2H, m), 7.53–7.57 (3H, m), 7.43–7.49 (3H, m), 7.33–7.36 (2H, m), 5.99 (1H, s), 5.65 (1H, s), 4.67 (1H, ddd, *J* 22.5, 9.5, 5.0), 3.77 (3H, d, *J* 11.0), 3.75 (3H, d, *J* 11.0), 3.19–3.25 (2H, m). δ_C (75 MHz) 197.9, 195.9, 144.0 (d, *J* 13.1), 137.5 (d, *J* 13.8), 133.8, 132.5, 130.4, 129.6, 129.0, 128.9, 128.7, 128.4, 53.6 (d, *J* 6.9), 53.5 (d, *J* 6.9), 45.2 (d, *J* 128.2), 31.4 (d, *J* 4.3). *m/z* (ESI) 395.2 (100%) $[M+Na]^+$.

*Diethyl 1,5-Dioxo-1,5-diphenylpentan-2-ylphosphonate (**8a**)*

Formaldehyde (0.15 mL of a 10% aqueous solution, 0.5 mmol) was added over 1 h using a syringe pump to a stirred solution of phosphonate **2a** (128.1 mg, 0.5 mmol) in K_2CO_3 (1 mL of a 2 M aqueous solution, 0.5 mmol). The reaction mixture was diluted with brine (5 mL), extracted into ether (3 × 5 mL) and dried ($MgSO_4$). Following filtration and concentration under reduced pressure, purification by flash column chromatography (1/1, v/v, EtOAc in hexane) afforded *ketone **8a*** (99.0 mg, 51% yield) as a clear oil. R_f 0.15 (50% hexane/EtOAc). (Found: 411.1335 $[M+Na]^+$. $C_{21}H_{25}O_5P$ requires: 411.1337 $[M+Na]^+$.) ν_{max}/cm^{-1} 3409.0br, 2926.3m, 1679.7s, 1596.9m, 1448.8m, 1259.8m, 1035.4br. δ_H (500 MHz) 8.00–8.03 (2H, m), 7.89–7.92 (2H, m), 7.52–7.59 (2H, m), 7.41–7.49 (4H, m), 4.41 (1H, ddd, *J* 23.0, 9.0, 5.0), 4.03–4.16 (4H, m), 3.24 (1H, dt, *J* 10.5, 7.0), 2.95 (1H, dt, *J* 10.5, 7.0), 2.55–2.62 (1H, m), 2.41–2.48 (1H, m), 1.24 (3H, t, *J* 7.5), 1.18 (3H, t, *J* 7.5). δ_C (75 MHz) 199.5, 196.5 (d, *J* 5.5), 137.6, 136.9, 133.8, 133.5, 129.1, 128.9, 128.3, 63.1 (d, *J* 4.1), 62.9 (*J* 4.1), 46.3 (d, *J* 127.9), 36.4 (d, *J* 11.9), 22.4 (d, *J* 4.5), 16.5 (d, *J* 6.4), 16.4 (d, *J* 6.4) (1 signal overlapping). *m/z* (ESI) 411.2 (100%) $[M+Na]^+$.

*Conversion of Phosphonate **8a** into Enone **4a** (Eqn 2)*

To a stirred solution of phosphonate **8a** (144 mg, 0.5 mmol) in aqueous formaldehyde (2.0 mmol in 2 mL of H_2O), K_2CO_3 (0.7 mL of a 0.5 M aqueous solution, 0.35 mmol) was added dropwise. The reaction mixture was allowed to stir for 2 h, at which time the mixture was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with brine (3 × 5 mL), dried ($MgSO_4$), and concentrated under vacuum. Analysis of the residue by ^1H NMR spectroscopy indicated the presence of enone **4a** and starting material **8a** in a ratio of 1:2.9.

*Conversion of Enone **4a** into Allylic Alcohol **1a** (Eqn 3)*

A solution of enone **4a** (200 mg, 0.5 mmol) in K_2CO_3 (0.7 mL of a 0.5 M aqueous solution, 0.35 mmol) was allowed to stir for 2 h, after which the mixture was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with brine (3 × 5 mL), dried ($MgSO_4$), and concentrated under vacuum. Analysis of the residue by ^1H NMR spectroscopy indicated the presence of allylic alcohol **1a** and enone **4a** in a ratio of 1:3.5.

*Reaction of Phosphonate **2c** and **2d** in the Presence of Enone **3a** (Eqn 4 and 5)*

A solution of enone **3a** (67 mg, 0.5 mmol) and phosphonate **2c** (301 mg, 1 mmol) or **2d** (286 mg, 1 mmol) in aqueous formaldehyde (2.0 mmol in 2 mL of H_2O) and K_2CO_3 (2.1 mL of a 0.5 M aqueous solution, 1.05 mmol) were allowed to stir for 2 h, after which the mixture was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were washed with brine (3 × 5 mL), dried ($MgSO_4$), and concentrated under vacuum. Analysis of the residue by ^1H NMR spectroscopy indicated

the absence of any allylic alcohol **1a** and the formation of enones **1c** and **1d**, respectively.

*Addition of Phosphonate **2a** to Allylic Alcohol **1a***

A mixture of phosphonate **2a** (512 mg, 2.0 mmol) and allylic alcohol **1a** (162 mg, 1 mmol) was treated with K_2CO_3 (1 mL of a 2 M aqueous solution, 0.5 mmol) and stirred magnetically for 0.5 h. The reaction mixture was diluted with brine (5 mL), extracted into ether (3 × 5 mL), and dried ($MgSO_4$). Following filtration and concentration, the residue was analyzed by ^{1}H NMR spectroscopy and phosphonates **2a**, allylic alcohol **1a**, and ketone **8a** identified in a ratio of 3:1:1.

Accessory Publication

Accessory publication contains ^{1}H NMR spectra (**1l**, **2l**, **4a**, and **8a**) and ^{13}C NMR spectra (**1l**, **2l**, and **8a**) of indicated structures. Also available are documents detailing the computational methods used along with the Cartesian coordinates of all computed structures, and vibrational frequencies of minima and transition states. The documents are available from the Journal's website.

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