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Tandem oxidation–Wittig–Wittig sequences for the preparation of functionalised dienoates

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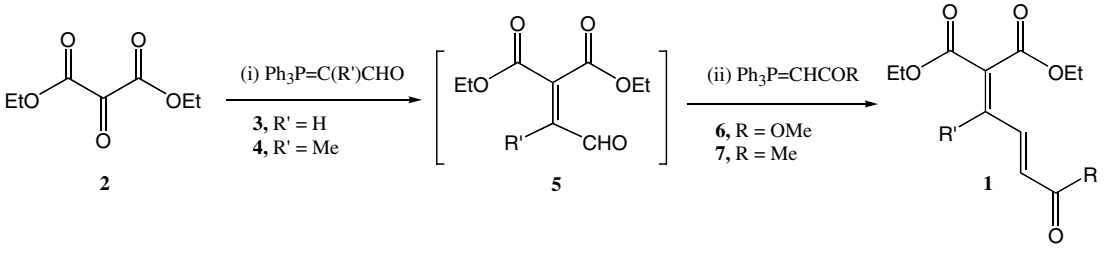
Abstract—A range of functionalised dienes and trienes have been prepared by one-pot processes in which alcohol oxidation is accompanied by in situ Wittig homologation using Trippett's reagent [(triphenylphosphoranylidene)acetaldehyde] followed by addition of a second stabilised phosphorane. This procedure has been applied to α-hydroxy carbonyl compounds and activated benzylic alcohols.

As part of a natural product study, we required easy access to a range of oxygenated dienoates **1**. Diethyl ketomalonate **2** seemed a logical starting material and its transformation could have been accomplished by a single Wittig-type elaboration,[1] or a stepwise sequence. However, we were attracted by the possibility of carrying out the one-pot tandem procedure shown in Scheme 1, as all of the starting materials are commercially available. Thus, the aim was to convert ketomalonate **2** into a two/three carbon homologated aldehyde **5** using (triphenylphosphoranylidene)acetaldehyde (Trippett's reagent, **3**), or its α-methyl analogue **4**,[2] and then to carry out the second Wittig elaboration in situ to produce the target compounds **1**. This approach obviously relies on the fact that the conjugated aldehyde intermediate **5** is less reactive than the original carbonyl substrate, but several such examples were given by Trippett and Walker in their original publication,[2] and it seemed likely to be the case when employing such a reactive carbonyl substrate as a ketomalonate.

Therefore, the one-pot, tandem Wittig sequence using diethyl ketomalonate **2** outlined in Scheme 1 was investigated and the results are gathered in Table 1.[3] Using (triphenylphosphoranylidene)acetaldehyde **3** as the initial Wittig reagent, followed by phosphoranes **6** or **7**, the expected adducts **1a** and **1b**[4] were obtained in reasonable, unoptimised isolated yields (entries i and ii). When the methyl-substituted phosphorane **4** was employed in the first step, the reaction proceeded much more slowly (24 h vs. 1 h) but the expected adduct **1c** was obtained, albeit in modest yield (entry iii).

We have recently described one-pot tandem oxidation processes (TOP) in which manganese dioxide-mediated alcohol oxidations have been combined with



Scheme 1.

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Table 1. Double Wittig elaboration of diethyl ketomalonate **2**[a]

Entry	Phosphorane (i)	Phosphorane (ii)	Product	Isolated yield (%)
i	$Ph_3PCHCHO$ **3**	Ph_3PCHCO_2Me **6**	**1a**, R′ = H, R = OMe	82[b]
ii	$Ph_3PCHCHO$ **3**	$Ph_3PCHCOMe$ **7**	**1b**, R′ = H, R = Me	69[b]
iii	$Ph_3PC(Me)CHO$ **4**	Ph_3PCHCO_2Me **6**	**1c**, R′ = Me, R = OMe	54[c]

[a] In toluene at rt using **3** or **4** (1 equiv) followed by **6** or **7** (1.1 equiv); *E*-alkenes predominated (>95%).
[b] Both steps (i) and (ii) carried out for 1 h.
[c] Step (i) carried out for 24 h, step (ii) for 3 h.

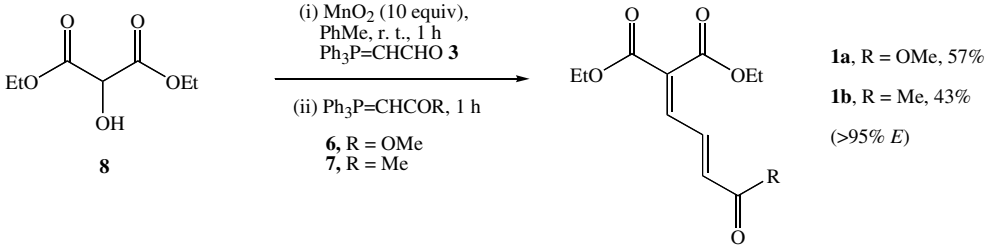
phosphorane olefination.[5] It was therefore of interest to further elaborate the above procedure by incorporation of an oxidative step (Scheme 2). Thus, alcohol **8**[6] was treated with MnO_2 and Trippett's reagent **3** followed by phosphoranes **6** and **7** and we were pleased to find that **1a**[7] and **1b** were formed in reasonable isolated yields (57% and 43%, respectively) via an oxidation–Wittig–Wittig sequence.

In view of these results, we decided to explore the scope of this process with more useful alcohol substrates. Initially, the one-pot oxidation–Wittig–Wittig sequence was studied using α-hydroxyacetophenone **9** (Scheme 3). Oxidation in the presence of Trippett's reagent **3** followed by addition of phosphorane **6** or **7** gave the expected dienes **10**[8] and **11**.[9,10] In a similar manner, the use of the methyl-substituted phosphorane **4** in combination with stabilised phosphorane **6** gave diene **12** in 64% yield, although as before in reactions involving **4**, a much longer reaction time was required compared to the corresponding reaction involving **3** (24 h vs. 1 h). It is also noteworthy that this initial Wittig reaction with **4** is not particularly stereoselective, with diene **12** being isolated as a mixture of 2*E*,4*E*- and 2*E*,4*Z*-isomers (*ca.* 2:1).

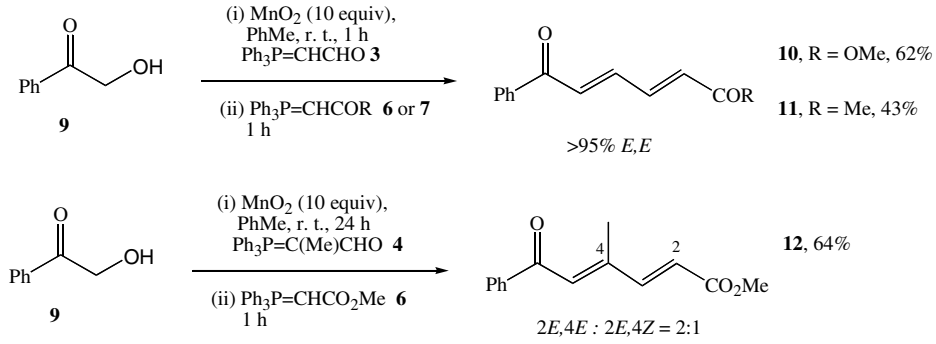
The oxidation–double Wittig sequence with phosphoranes **3** and **6** was also carried out on the α-hydroxy ester, ethyl glycolate **13** (Scheme 4). Using the conditions as before, the expected dienoate **14**[11] was obtained, albeit in low yield, along with the corresponding triene **15** (13%), which is formed by an oxidation–triple Wittig sequence (**3** then **3** then **6**). This reaction did not produce other by-products and so the low yields may be due to the volatility of the products.

The production of triene **15** encouraged us to explore triene formation with other substrates. The most promising result was achieved using α-hydroxyacetophenone with MnO_2 and 2 equiv of Trippett's reagent **3** in the first step followed by treatment with phosphorane **6** (Scheme 4). This produced triene **16**[12] in 47% yield along with diene **10** in 29% yield. Optimisation of this triene-producing sequence should be straightforward.

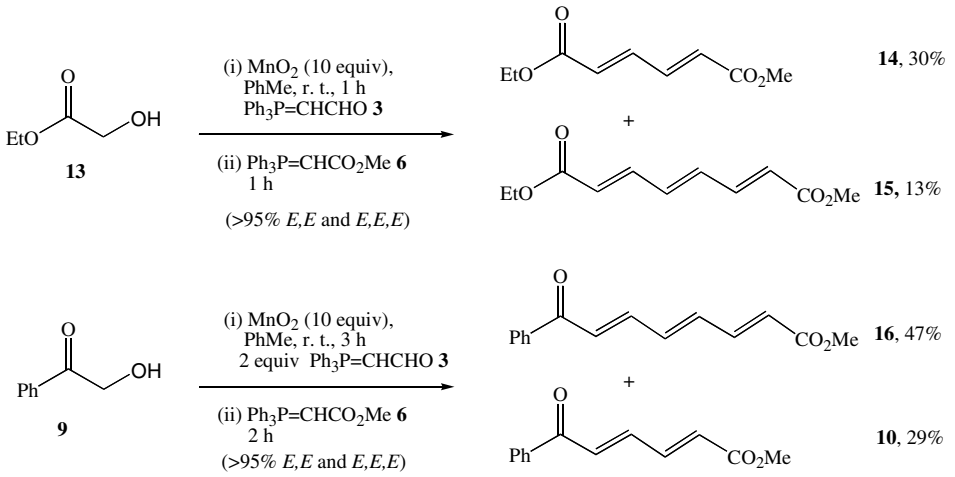
Finally, preliminary investigations were carried out to extend this methodology to benzylic alcohols and related systems (Scheme 5). These reactions were extremely slow at room temperature and so, with 4-nitrobenzyl alcohol **17a**, various solvents were screened at elevated temperatures. Thus, a mixture of alcohol



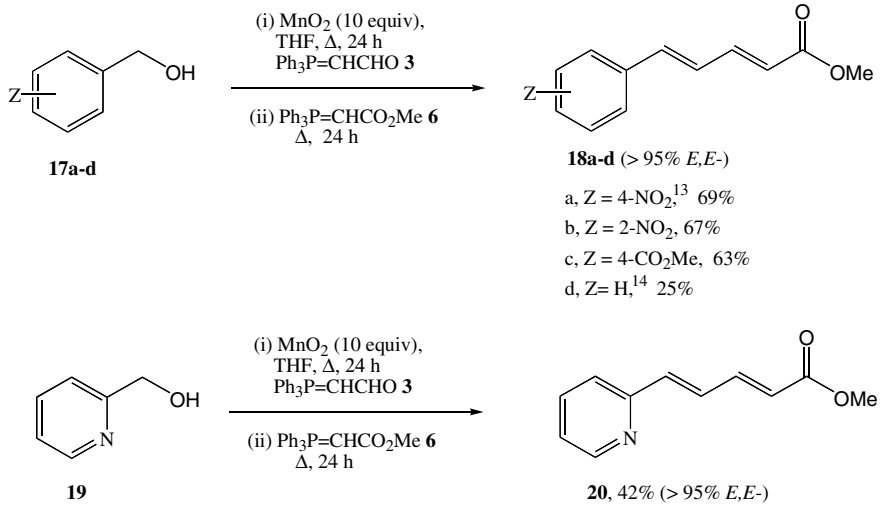
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

17a, MnO_2, and phosphorane **3** was heated in various solvents for 24 h; phosphorane **6** was then added and the mixture heated for a further 24 h. This study showed that THF at reflux was optimum (yield of **18a**,[13] 69%; CH_2Cl_2, Δ, 54%; DMF, 100 °C, 54%; PhMe, Δ, 34%).

The low reactivity of phosphorane **3** leads to a limitation of this procedure with benzylic alcohols; only those which produce more reactive electron-defficient aldehyde intermediates undergo Wittig elaboration in reasonable times. Thus, in addition to 4-nitrobenzyl alcohol **17a**, the 2-nitro- and 4-carbomethoxy- analogues **17b** and **17c** and 2-pyridylmethanol **19**, gave reasonable yields of adducts (42–69%) whereas benzyl alcohol itself produced diene **18d**[14] in only 25% yield.

In summary, a range of functionalised dienes have been prepared by one-pot processes in which alcohol oxidation is accompanied by in situ Wittig homologation using Trippett's reagent **3**, or its α-methyl derivative **4**, followed by addition of a second stabilised phosphorane. This procedure has been applied to α-hydroxy carbonyl compounds and activated benzylic alcohols. Preliminary studies have been carried out in which an oxidation–triple Wittig sequence has been used to prepare functionalised trienes. We are currently optimising these telescoped processes and investigating their applications in target molecule synthesis.

Acknowledgements

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7. Representative procedure: tandem oxidation–Wittig–Wittig reaction to prepare dienoate **1a**. A mixture of diethyl hydroxymalonate **8**[6] (176 mg, 1 mmol), (triphenylphosphoranylidine) acetaldehyde (304 mg, 1 mmol), activated manganese dioxide (Aldrich 21764-6, 869 mg, 10 mmol) and powdered 4 Å molecular sieves (1 g) in toluene (7 ml) were stirred at room temperature for 1 h. After this time methyl (triphenylphosphoranylidine) acetate (368 mg, 1.1 mmol) was added and the reaction stirred for a further 1 h. The mixture was then filtered through a pad of silica and washed with diethyl ether (50 ml) and the solvent removed in vacuo. The mixture was then purified by flash chromatography on silica gel eluting with a petroleum ether–ethyl acetate (4:1) mixture to give product **1a** (145 mg, 57%); ν_{max} (film) 1721 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.22–1.28 (6H, m, $2\times OCH_2CH_3$), 3.71 (3H, s, OCH_3), 4.20–4.28 (4H, m, $2\times OCH_2CH_3$), 6.23 (1H, d, *J* 15.2 Hz, RCH=C*H*CO_2Me), 7.26 [1H, d, *J* 11.8 Hz, $(EtO_2C)_2C$=C*H*R], 7.47 (1H, dd, *J* 15.2 Hz, 11.8 Hz, RC*H*=CHCO_2Me); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 14.1 (CH_3), 52.1 (CH_3), 61.9 (CH_2), 61.9 (CH_2), 130.8 (CH), 132.2 (C), 137.3 (CH), 139.7 (CH), 163.5 (C), 164.2 (C), 165.8 (C); *m*/*z* (CI) 274 (MNH_4, 6%), 257 (MH, 100), 197 (8), 183 (6); HRMS (CI) [MH^+], found 257.1030; $C_{12}H_{17}O_6$ requires 257.1025 (1.8 ppm error).
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