Letter

Synthesis of Polyconjugated Aldehydes Using a New Horner–Wadsworth–Emmons Reagent

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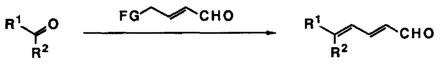
Conjugated dienals are well recognized as useful building blocks in organic synthesis. Among several possible applications, one of the most interesting is the construction of conjugated polyenes.[1] Many important classes of natural products, such as the leukotrienes[1a–e] and the lipoxins,[1f] contain polyenic units as part of their structures, and polyenes can also be used as advanced synthetic intermediates.[2]

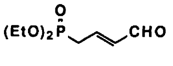
One attractive way of synthesizing dienals is to perform a condensation between a carbonyl compound and an appropriately functionalized 'Wittig-type' reagent that gives a four-carbon extension [eqn. (1)]. A few reagents that effect this transformation have been described in the literature.[3] However, keeping in mind the advantages of phosphonate reagents compared with phosphonium and arsonium ylides[4] (enhanced nucleophilicity and hence potentially greater generality, ease of workup, lower toxicity than arsenic compounds), we sought to develop a new phosphonate reagent that would effect this transformation in a one-pot procedure.[5]



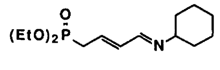
(1)

FG = functional group

In this letter, we would like to report the preparation of 4-(diethylphosphono)-2-butenal (**1**) (to the best of our knowledge, this compound has not previously been described in the literature), and the use of **1**, with the carbonyl group protected as an imine as in **2**, in Horner–Wadsworth–Emmons condensations.[6] When the carbonyl group is protected as an oxime ether the condensations work equally well, but the carbonyl group cannot be regenerated satisfactorily.

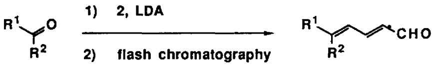


1

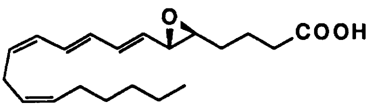


2

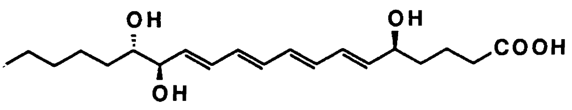
Results of condensations of **2** with a representative set of carbonyl compounds, according to eqn. (2), are summarized in Table 1.



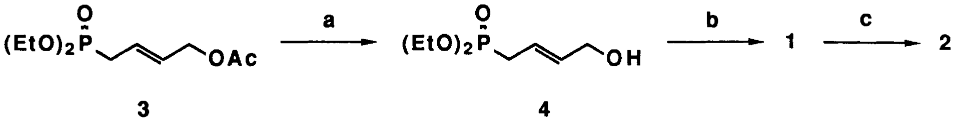
(2)



Leukotriene A4

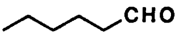
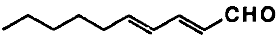
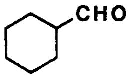
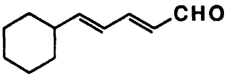
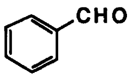
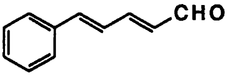
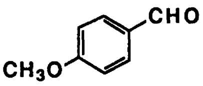
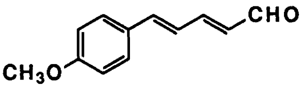
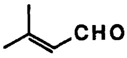
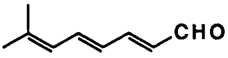
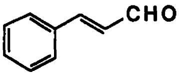
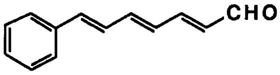
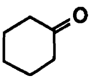
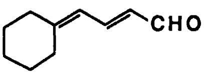
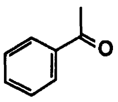
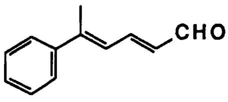


Major component of Lipoxin B



Scheme 1. a, *p*-TsOH, 10 %, EtOH, reflux, 20 h (95 %); b, CrO_3, 1 equiv., 2 M H_2SO_4, acetone, 0 °C, 45 min (70 %); c, cyclohexylamine, 1 equiv., molecular sieves, THF, RT, overnight (yield essentially quantitative as determined by NMR spectroscopy).

Table 1. Condensations of carbonyl compounds with **2**/LDA.[a]

Entry	Carbonyl compound	Equiv. of **2** (reaction time/h)[b]	Product	Yield/% (isomerdistribution)[c]
1		1.5 (2)		78 (84:14:2)
2		1.4 (19)		70 (90:7:3)
3		1.4 (18)		65 (94:4:2)
4		1.2 (15)		73 (93:6:1)
5		1.2 (15)		45 (88:9:3)
6		1.2 (6)		25 (90:7:3)
7		1.4 (20)		73 (98:2)
8		2.9 (111)[d]		77 (80:18:2)[e]

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[a] For a typical experimental procedure, see the text. [b] Reaction time at 0–25 °C. [c] 2*E*,4*E* : 2*E*,4*Z* : 2*Z*,4*E*; *E*:*Z* in entry 7. [d] This reaction time may well be unnecessarily long. [e] The assignment of the isomers was confirmed by NOE measurements.

It can be seen that saturated aliphatic and aromatic carbonyl compounds, both aldehydes (entries 1–4) and ketones (entries 7, 8) give good yields of the desired products. So far, conjugated aldehydes (entries 5, 6) give lower yields (the conditions have not been optimized). Although we do not have any evidence, one plausible explanation is that Michael addition of the phosphonate anion can give rise to side reactions in these cases.[7] According to NMR spectroscopy and HPLC the all-*E* isomer is the main product in all reactions, accompanied by 4–18 % of the 4*Z*-isomer and small amounts (1–3 %) of the 2*Z*-isomer.

To summarize, we have shown that (**2**) is a useful reagent for the synthesis of polyconjugated aldehydes. At present, we are studying the scope and limitations of this and related reagents, as well as synthetic applications based on this chemistry. The results of these studies will be published in full detail in forthcoming papers.

Experimental

The aldehyde **1** and the corresponding imine **2** were synthesized as described in Scheme 1, starting with 1-acetoxy-4-(diethylphosphono)-2-butene[8] (**3**).

Acid-catalysed transesterification of **3** (*E*:*Z* = 9:1) gave the alcohol **4**[9] (*E*:*Z* = 9.1) in almost quantitative yield. Oxidation of **4** with Jones reagent, under controlled conditions,[10] gave the aldehyde **1** (*E*:*Z* = 98:2) in good yield. As **1** is fairly sensitive towards base, it was purified by flash chromatography[11] on deactivated silica [prepared by dissolving water (10–15 % by weight of silica) in THF, adding the silica and evaporating the solvent]. Reaction of **1** with cyclohexylamine gave the imine **2** as a 2:3 mixture of aldimine and dienamine tautomers [determined by NMR spectroscopy (only the *E*,*E*-isomer of the dienamine tautomer could be detected); see also Ref. 6(c)]. Compound **2** was not isolated, but instead a solution of **2** in THF was used as such in the condensations.

A typical experimental procedure for the condensation of **2** with a carbonyl compound is described below (reaction with *p*-methoxybenzaldehyde). To a solution of **1** (258 mg, 1.25 mmol) in 3 ml of dry THF, at 25 °C under an argon atmosphere, was added dropwise cyclohexylamine (158 μl, 1.30 mmol) over 1 min. After 1 h, 250 mg of molecular sieves (3Å) were added, and the bright orange solution was stirred slowly overnight. The resulting solution was added dropwise over 15 min to a solution of LDA (from 1.25 mmol diisopropylamine and 1.20 mmol butyllithium in hexane) in 2 ml of THF at −78 °C. After 1 h, *p*-methoxybenzaldehyde (136 mg, 1.0 mmol) dissolved in 0.5 ml of THF was added, and 1 h later, the solution was warmed to 25 °C and stirred at this temperature for 15 h. Then, 5 ml H_2O was added, the resulting mixture was extracted with ether (3×20 ml), and the organic phase was dried with $MgSO_4$. Evaporation of the solvent gave the intermediate 5-(*p*-methoxyphenyl)-2,4-pentadienal cyclohexylimine in crude form as an orange-red solid, which was hydrolysed during flash chromatography [25 g Merck silica gel 60, 230–400 mesh; hexane:ethyl acetate (80:20) as the eluent]. Obtained was 138 mg (73 %) of 5-(*p*-methoxyphenyl)-2,4-pentadienal (2*E*,4*E* : 2*E*,4*Z* : 2*Z*,4*E* = 93:6:1) as a yellow solid, together with 7 mg (5 %) of unreacted *p*-methoxybenzaldehyde. The product isomers separated fairly well during this chromatographic hydrolysis; 124 mg of the product was collected as essentially pure *E*,*E*-isomer. All new compounds gave satisfactory spectral data. Isomer distributions are based on ^1H NMR data (integrals for the aldehyde protons).

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