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Highly stereoselective and efficient synthesis of ω-heterofunctional di- and trienoic esters for Horner–Wadsworth–Emmons reaction via alkyne hydrozirconation and Pd-catalyzed alkenylation

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Dedicated to Dr. John Birmingham (Boulder Scientific Co. whose pioneering synthesis of $ZrCp_2Cl_2$ with G. Wilkinson in 1954 led to the major development of organozirconium chemistry)

Keywords:
Pd-catalyzed alkenylation
Alkyne hydrozirconation
ω-Heterofunctional di- and trienoic esters
Horner–Wadsworth–Emmons reaction

ABSTRACT

In situ OH metalation with $^{i}Bu_2AlH$ and hydrozirconation with $HZrCp_2Cl$ of $HOCH_2C{\equiv}CH$, (*E*)-$HOCH_2CH{=}CHC{\equiv}CH$, and $HOCH_2C{\equiv}CCH_3$ followed by Pd-catalyzed alkenyl–alkenyl coupling with (*E*)-$BrCH{=}CHCO_2Et$ and (*E*)-$BrCH{=}C(Me)CO_2Et$ using PEPPSI-IPr (**7**) as a catalyst provides a highly efficient and selective (⩾98% all-*E*) route to ω-hydroxy di- and trienoic acid esters (**1a**–**6a**). The corresponding phosphonate esters (**1c**–**4c**) of ⩾98% isomeric purity can be obtained via conventional bromination–phosphonation in >80% yields. As expected, their carbonyl olefination is ca. 85–90% *E*-selective with alkyl aldehydes but ⩾98% *E*-selective with PhCHO and some α,β-unsaturated aldehydes under the conditions used.

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1. Introduction

Regio- and stereodefined alkenes including oligoenes and polyenes exhibit a variety of significant biological and medicinal activities. Until a few decades ago, they were most often prepared by aldol and related *carbonyl olefination* reactions, especially those promoted by P-, S-, and Si-functional groups.[1] In the 1970s, some fundamentally different routes to alkenes via *organometallic alkenylation*, represented by stoichiometric hydroboration—migratory insertion routes to conjugated dienes[2] and the Pd-catalyzed alkenylation using Al, Zr, Zn, B, and other metal countercations,[3] were discovered and developed. These organometallic alkenylation reactions usually display ⩾98% stereo- and regioselectivity, and the Pd-catalyzed alkenylation has been developed into the alkene synthetic method of very wide applicability. And yet, *carbonyl olefination* and *organometallic alkenylation* can be mutually more complementary than competitive. Thus, for example, alkenes containing an asymmetric carbon center in the allylic positions are most readily and widely prepared by *carbonyl olefination*, while those containing a homoallylic chiral center have been selectively and conveniently prepared by *Pd-catalyzed alkenylation*.[4] Moreover, in recent syntheses of conjugated oligoenes[5,6] (Scheme 1), it has been shown to be attractive to efficiently and selectively prepare key reagents for the Horner–Wadsworth–Emmons (HWE, hereafter) olefination by Pd-catalyzed alkenylation. It then occurred to us that little, if any, had been explored along the line of this promising and potentially useful concept.

Herein, we report highly efficient and selective syntheses of several conjugated diene- and triene-containing HWE olefination reagents via alkyne hydrozirconation[7] and Pd-catalyzed alkenyl–alkenyl cross-coupling.[3–5,8]

In view of both proven and potential synthetic values, the following set of several (all-*E*)-diene- and triene-containing HWE olefination reagents (**1c**–**4c**) were considered (Fig. 1). For various reasons, we opted for their syntheses via the corresponding ω-hydroxy (**1a**–**4a**) and ω-bromo (**1b**–**4b**) derivatives. For one thing, these hydroxy and bromo derivatives are by themselves useful reagents for various other purposes as well. Our preliminary investigation also indicated some unclarified complications and difficulties in attempted early incorporation of the desired phosphonate groups, and this potentially more convergent route is to be further explored later.

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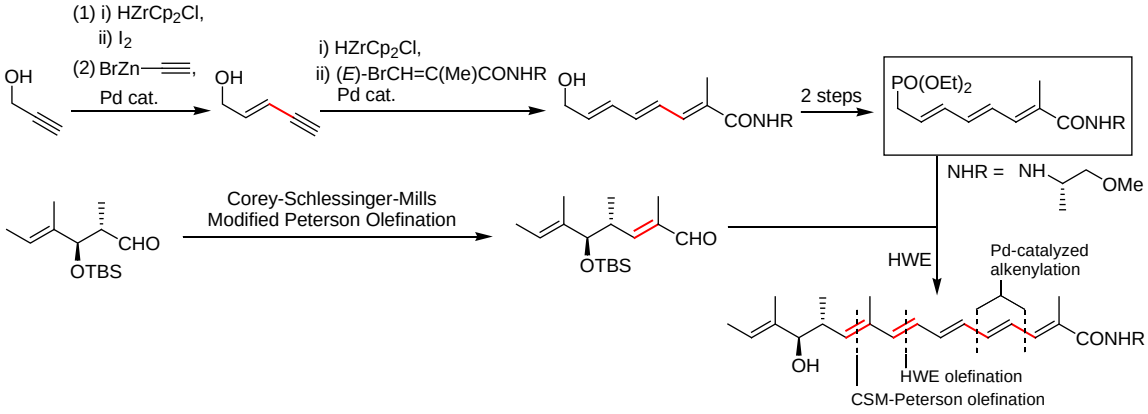
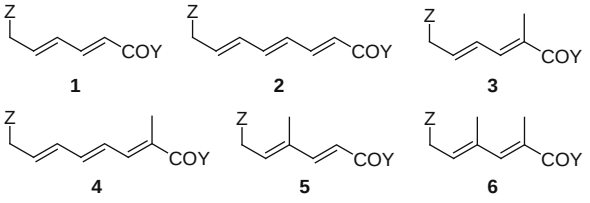


Scheme 1. Synthesis of (all-*E*)-*O*-methylmyxalamide D via carbonyl olefination-Pd-catalyzed alkenylation synergy (previously reported[5]).



a: Y = OEt, Z = OH. **b**: Y = OEt, Z = Br. **c**: Y = OEt, Z = $PO(OEt)_2$

Figure 1. (all-*E*)-Diene- and triene-containing HWE olefination reagents (**1c**–**4c**) and the corresponding OH (**1a**–**6a**) and Br (**1b**–**4b**) derivatives.

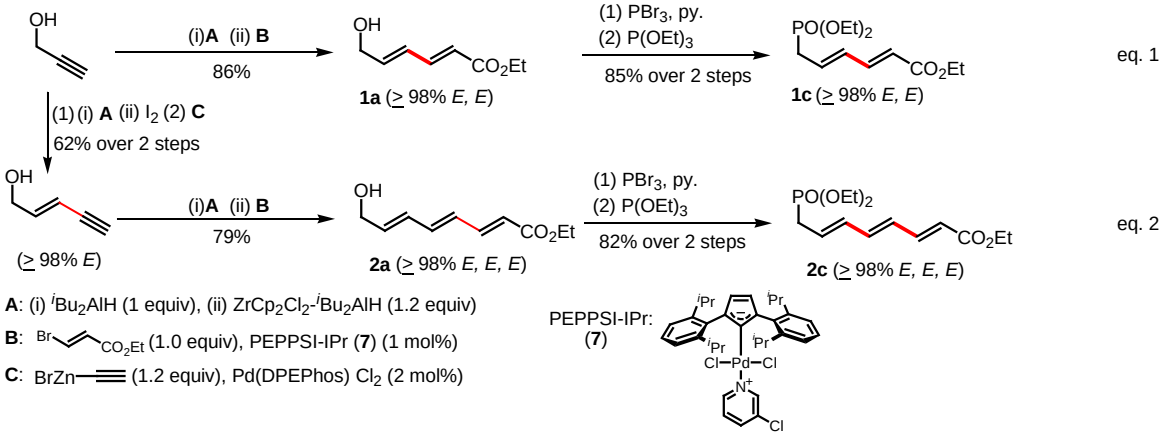
2. Synthesis of unbranched dienoates (1) and trienoates (2)

ω-Phosphonodienoate ester (**1c**) has been synthesized from a commercially available 3:1 mixture of ethyl (*E*)-4-bromocrotonate and its 2-bromo isomer in four steps in 55% overall yield via HWE olefination.[9] Both 2- and 4-bromo isomers were converted to the desired product. Despite somewhat high cost of the starting compounds, it may be considered to a reasonably satisfactory synthesis, and **1c** has been successfully used in the synthesis of oligoenes, such as amphotericin B, scyphostatin, and their oligoene fragments.[9] On the other hand, a recently reported synthesis of ethyl (all-*E*)-8-hydroxy-2,4,6-octatrienoate (**2a**) required nine steps from (*Z*)-2-butene-1,4-diol (14% overall yield).[10] As summarized in Scheme 2 **1a** and **2a**[11] of ⩾98% isomeric purity can be prepared in 86% yield in one step and 49% yield over three steps, respectively, from propargyl alcohol. In both cases, ethyl (*E*)-3-bromoacrylate[12] prepared by addition of HBr to commercially available propiolic acid followed by esterification was used as one of the key intermediates. Sequential treatment of propargyl alcohol with one equiv of $^{i}Bu_2AlH$ and hydrozirconation with $HZrCp_2Cl$, generated in situ by treating $ZrCp_2Cl_2$ with $^{i}Bu_2AlH$ in THF,[7d] cleanly produced a solution containing the hydrozirconation product in ⩾95% yield by ^1H NMR spectroscopic analysis.

Addition of ethyl (*E*)-3-bromoacrylate (1.0 equiv) and 1.0 mol % of PEPPSI-IPr (**7**)[13] obtained from Aldrich Chemical Co. for 6 h at 23 °C provided after the standard workup and chromatography (silica gel, 30% EtOAc in hexanes) **1a** of ⩾98% *E*,*E* in 86% yield. Conversion of **1a** to **1c** via **1b** proceeded uneventfully with full retention of the *E* configuration in 85% yield over two steps. Although the overall efficiency and selectivity of this particular synthesis may be roughly comparable to those of the previously developed HWE route,[7] the Pd-catalyzed alkenylation route is readily adaptable to the syntheses of other related compounds without major modification of the synthetic strategy, as detailed in Schemes 2 and 3. Distinct advantages of the synthesis of **2a**–**c** reported herein over the previously reported one[10] should be clear.

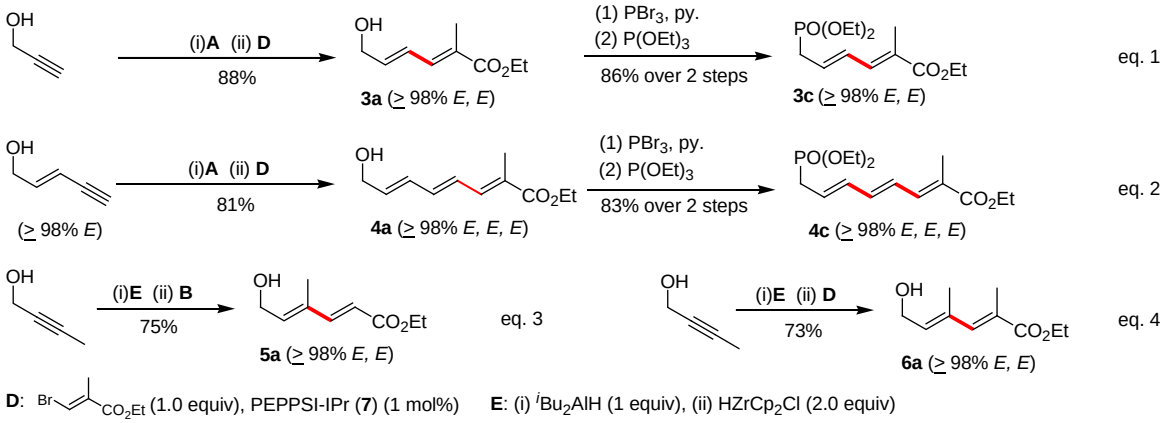
3. Synthesis of methyl-branched dienoates (3, 5, and 6) and trienoates (4)

As pointed out above, the Pd-catalyzed alkenylation route to ω-heterofunctional di- and oligoenoic acid derivatives is conceptually straightforward and potentially widely adaptable besides being



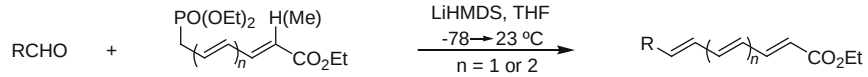
Scheme 2. Synthesis of unbranched dienoates (**1a**) and trienoates (**2a**) and the corresponding HWE olefination reagents (**1c** and **2c**).

efficient and highly selective (generally ⩾98% stereoselective). Thus, the use of ethyl (*E*)-β-bromomethacrylate readily prepared by sequential treatment of inexpensive ethyl methacrylate with Br_2 and NaOH in 90% yield[14] in place of ethyl (*E*)-bromoacrylate provided **3a** (⩾98% *E*,*E*) in one step in 88%, which was readily converted to **3c** via **3b** in 86% yield over two steps with full retention



Scheme 3. Synthesis of methyl-branched dienoates (**3, 5,** and **6**) and trienoates (**4**).

Table 1
HWE olefination of aldehydes with ω-phosphonooligoenoic acid derivatives



Entry	RCHO		(Yield, Purity)
1	^{n}PrCHO	(**1c**)	84% (*E*,*E*,*E*/*E*,*E*,*Z* = 10/1)
2	CH_3CHO	(**2c**)	81% (*E*,*E*,*E*,*E*/*E*,*E*,*E*,*Z* = 8/1)
3	PhCHO	(**1c**)	82% (≥98% *all E*)
4	PhCHO	(**2c**)	78% (≥98% *all E*)
5	TBSO	(**1c**)	87% (*E*,*E*,*E*/*E*,*E*,*Z* = 10/1)
6	TBSO	(**1c**)	85% (*E*,*E*,*E*/*E*,*E*,*Z* = 6/1)
7	OTBS	(**4c**)	80% (≥98% *all E*)

of stereochemistry (Eq. 1 in Scheme 3). Similarly, sequential treatment of 2-butyn-1-ol with one equiv of $^{i}Bu_2AlH$ and 2.0 equiv (*not* 1.2 equiv) *of HZrCp$_2$Cl* followed by addition of ethyl (*E*)-3-bromoacrylate or ethyl (*E*)-3-bromomethacrylate and 1.0 mol % of PEPPSI-IPr (**7**) gave methyl-branched dienoate **5a** or **6a** in 73–75% yield with ⩾98% isomeric purity (Eqs. 3 and 4). As in the recently reported preparation of (*E*,*E*,*E*)-$(EtO)_2P(O)CH_2(CH{=}CH)_2CH{=}C(Me)CONHR$, where R is (*S*)-$CH(Me)CH_2OMe$ as shown in Scheme 1,[5] the corresponding Et ester **4c** was readily prepared from (*E*)-$HOCH_2CH{=}CHC{\equiv}CH$ and (*E*)-$BrCH{=}C(Me)CO_2Et$ via **4a** and **4b** in 3 steps in 67% overall yield (Eq. 2 in Scheme 3).

4. Horner–Wadsworth–Emmons olefination of aldehydes with 1c–4c

Although many examples of the HWE olefination of aldehydes with ω-phosphonooligoenoic acid derivatives, such as **1c**,[7] are known, detailed and precise description of the reaction itself prior to fractional purification are relatively limited. With ⩾98% pure **1c** and **2c** in hand, their HWE reaction with several representative alkyl-, aryl-, and alkenyl-containing aldehydes were examined. The experimental results are summarized in Table 1, and the results obtained under the conditions used reveal the following: (1) Alkyl aldehydes, regardless of the presence or absence of proximal branching groups and/or free and protected OH groups, exhibited the *E*-selectivity of 85–90%. Chromatographic purification (silica gel) did provide the major all *E* isomers as >98% pure compounds in 70–80% isolated yields. (2) In sharp contrast, use of PhCHO (entries 3 and 4) and alkenyl-containing aldehyde (entry 7) produced the desired products of ⩾98% purity in good yields. However, the corresponding reactions of crotonaldehyde and (*E*)-cinnamaldehyde under the same reaction conditions led to disappointingly low yields of 34% and 36%, respectively. Clearly, further optimization of the reaction parameters is needed.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.023.

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11. Representative procedure: *Ethyl (2E, 4E, 6E)-8-hydroxy-2,4,6-octatrienoate* (**2a** in Scheme 2). To a solution of Cp_2ZrCl_2 (1.75 g, 6 mmol) in THF (20 mL) cooled to 0 °C was added slowly a solution of $^{i}Bu_2AlH$ (6.0 mL, 1 M in hexane, 6.0 mmol) under argon. This mixture was stirred for 30 min at 0 °C, and a solution of O-aluminated propargyl alcohol prepared from (*E*)-2-penten-4-yn-1-ol (0.41 g, 5 mmol) and $^{i}Bu_2AlH$ (5.0 mL, 1 M in hexane, 5.0 mmol) was added at −78 °C. The mixture was stirred at 23 °C until a homogeneous solution resulted (ca. 0.5 h) and was added to ethyl (*E*)-3-bromoacrylate (0.89 g, 5.0 mmol) and PEPPSI-IPr (34 mg, 0.05 mmol) in THF (10 mL). After stirring at 23 °C for 4 h, the reaction mixture was quenched with water, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (silica gel, 30% EtOAc in hexanes) gave **2a** (0.72 g, 79%, ⩾98% isomerically pure) as light yellow wax..
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