Tetrahedron Letters 50 (2009) 3220–3223

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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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ARTICLE INFO

Article history:
Received 15 January 2009
Revised 23 January 2009
Accepted 2 February 2009
Available online 8 February 2009

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.

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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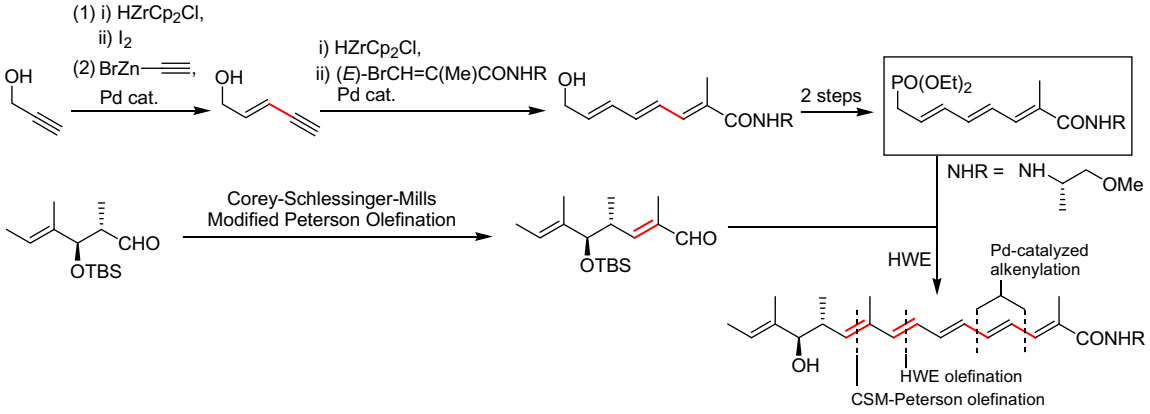
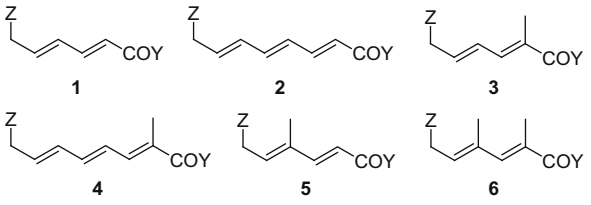
0040-4039/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2009.02.023



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.

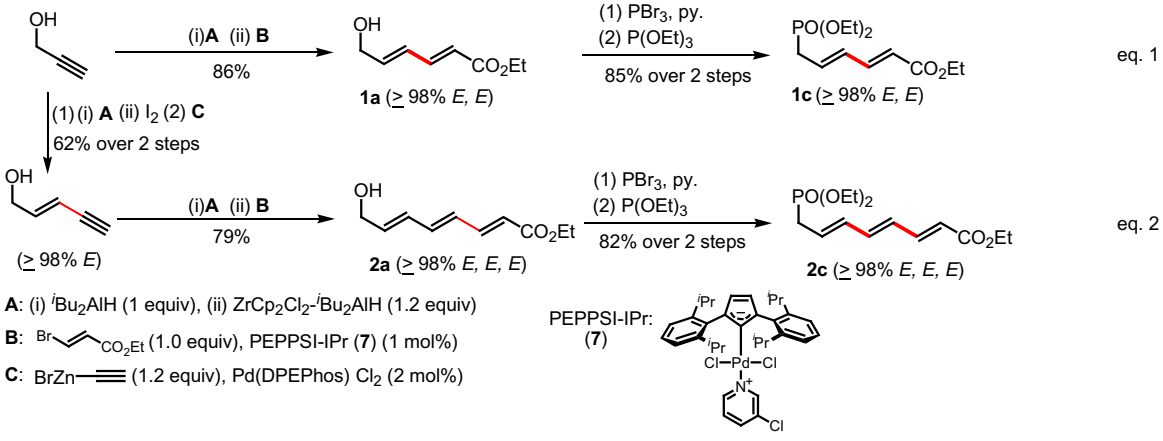
2. Synthesis of unbranched dienoates (1) and trienoates (2)

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**).