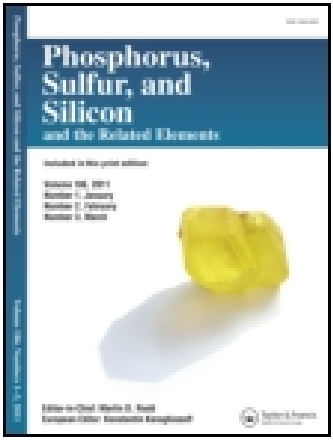

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Synthetic Applications of Asymmetric Horner-Wadsworth-Emmons Condensations: Approaches to Marine Natural Products

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Synthetic Applications of Asymmetric Horner-Wadsworth-Emmons Condensations: Approaches to Marine Natural Products

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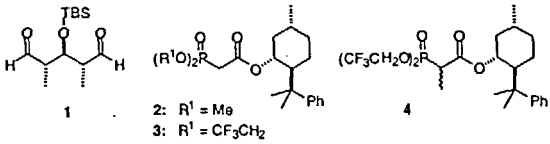
Asymmetric HWE condensations of *meso*-dialdehyde **1** with chiral phosphonates containing 8-phenylmenthol very directly generate chiral moieties that are seen in a number of cytotoxic natural products. The HWE reactions proceed in good yields with synthetically useful geometric and diastereoselectivities. Also, we demonstrate the applicability of the HWE products to the synthesis of biologically active marine natural products.

Keywords: asymmetric Horner-Wadsworth-Emmons condensation; chiral phosphonate; desymmetrization; doliculide; *meso*-dialdehyde

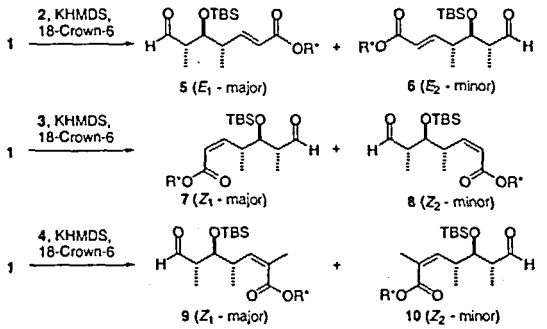
INTRODUCTION

The basic concept of asymmetric Wittig or Horner-Wadsworth-Emmons (HWE) reactions and related condensations has been studied in several laboratories, including our own[1]. The underlying principle of an HWE desymmetrization is the ability of the chiral phosphonate reagent to distinguish between enantiotopic aldehyde units in the *meso*-dialdehyde. The enantioselectivity of the reaction and the alkene geometry of the



resulting product are controlled by choice of chiral auxiliary and phosphonate substituent, respectively.

Scheme 1 and the Table summarize the asymmetric HWE condensations of *meso*-dialdehyde **1** with phosphonate reagents **2**-**4**, bearing (1*R*,2*S*,5*R*)-8-phenylmenthol as the chiral auxiliary.



SCHEME 1. HWE Condensation Products.

TABLE. Results of HWE Condensations with **1**.

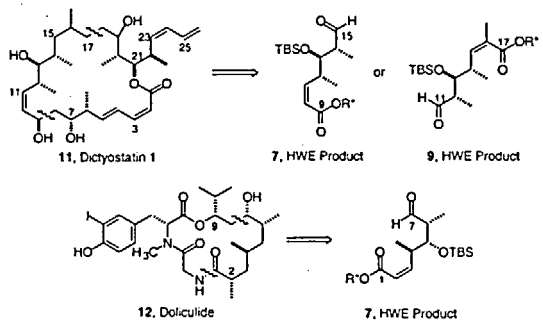
Entry	Conditions	Yield	(*E*):(*Z*)	(E_1):(E_2)
1	**2**, -100 °C, 6.5 h	**5**: 53%	>98 : 2	95 : 5
			(Z):(*E*)	(Z_1):(Z_2)
2	**3**, -85 °C, 6.25 h	**7**: 83%	98 : 2	>99 : 1
3	**4**, -78 °C, 25 h	**9**: 84% @ 50% conv.	>98 : 2	98 : 2

Dimethyl phosphonoacetate **2**, which bears electron-donating alkoxy substituents on the phosphorus, reacts with **1** to produce (*E*)-alkene **5** with excellent geometric

selectivity and good diastereoselectivity (Table, entry 1). Phosphonoacetate **3**, which contains electron-withdrawing trifluoroethoxy substituents, reacts with **1** to form (*Z*)-alkene **7** (Table, entry 2). This reaction occurs exclusively at the opposite carbonyl to that which reacts in the HWE condensation with the (*E*)-selective phosphonate **2**. Trisubstituted (*Z*)-alkene **9** is formed from an HWE reaction of phosphonopropionate **4** with **1** (Table, entry 3). The enantiotopic selectivity of **4** is opposite to that observed for phosphonoacetate **3**.

SYNTHETIC APPLICATIONS

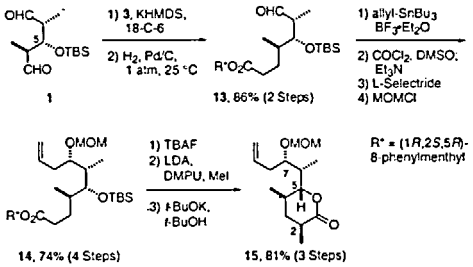
Asymmetric HWE condensations of *meso*-dialdehydes and racemic monoaldehydes generate very directly chiral subunits that are seen in a number of natural products that may serve as lead compounds for the development of new anticancer drugs. Among the more recently reported cytotoxic compounds are dictyostatin 1[12] [**11**, see C(9)-C(15) and C(11)-C(17) subunits] and doliculide[13] [**12**, see C(1)-C(7) subunit], both of which are active at the ng/mL level against human cancer cell lines.



Although doliculide has been synthesized[14] by the same group that reported its isolation, our HWE reactions will provide an approach that is quite different from, and shorter than, the previous synthesis. Lactone **15** represents the C(1)-C(9) fragment and was obtained in nine steps with an overall yield of 52% (Scheme 2).

In summary, we have described some of our most recent results in our continuing efforts to expand the scope of asymmetric HWE condensations. By varying the

electronic nature of the phosphonate substituent, we obtained both (*E*)- and (*Z*)-products with good diastereoselectivities. These products are useful intermediates in the synthesis of biologically active natural products.



SCHEME 2. Synthetic progress towards Doliculide (**12**).

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