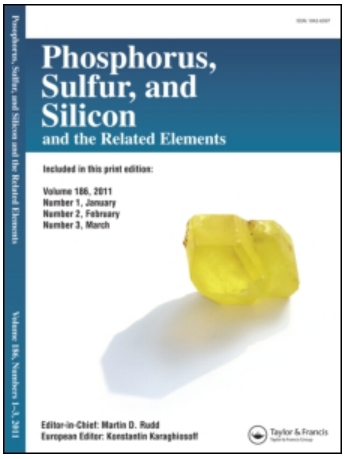

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Asymmetric Horner-Wadsworth-Emmons Reactions with *Meso*-Dialdehydes: Scope, Mechanism, and Synthetic Applications

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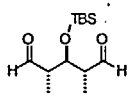
Asymmetric Horner-Wadsworth-Emmons reactions between chiral phosphonate reagents and various *meso*-dialdehydes have been investigated. A mechanistic model useful for rationalizing the experimentally observed stereoselectivities is presented. Furthermore, strategies for applying these reactions to the stereocontrolled preparation of chiral heterocyclic building blocks have been developed.

Keywords: asymmetric Horner-Wadsworth-Emmons reaction; chiral phosphonate; desymmetrization; *meso*-dialdehyde; chiral heterocycles

INTRODUCTION

In recent years, the area of asymmetric Wittig-type reactions has received increasing attention.[1l] We have studied several aspects of such reactions,[1l] including the use of *meso*-dialdehydes (e.g., **1**-**3**) as substrates in asymmetric Horner-Wadsworth-Emmons (HWE) reactions.[1b]



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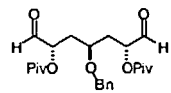

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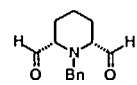

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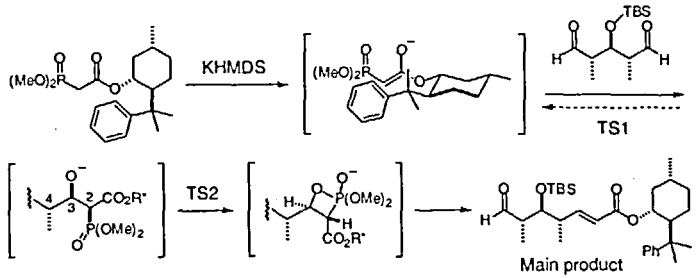
RESULTS

Mechanism

We have recently investigated the mechanistic details of these HWE reactions both by *ab initio* calculations on simplified models[3] and by molecular mechanics modelling of the actual systems.[4] Our current mechanistic model for the stereoselectivity in the asymmetric HWE reactions is illustrated by the example in Scheme 1.



Key factors:

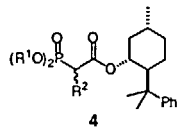
Chiral auxiliary	-> Absolute configuration at C(2)
R group in (RO)$_2$P(=O)	-> Relative stereochemistry at C(2)/C(3)
Substrate α-stereocenters	-> Relative stereochemistry at C(3)/C(4)

SCHEME 1. Factors determining product stereochemistry.

These studies indicate that the relative energies of the oxyanion and oxaphosphetane intermediates involved depend strongly on both reactant structures and reaction conditions. An interesting observation is that C-H···O hydrogen bonding between one of the alkoxy groups on phosphorus and the developing oxyanion can stabilize (*Z*)-selective forms of the transition state for the initial addition step. As illustrated in Scheme 1, several different factors combine to selectively favor one single diastereomeric form of the intermediates out of the eight theoretically possible. The chiral auxiliary controls from which face of the phosphonate enolate the reaction takes place. Our experimental studies have shown that the structure of the substituents on phosphorus controls the overall geometric selectivity, and that the influence of the substrate stereocenters depends on the specific reaction conditions. It is also clear that the whole reaction path (i.e, both the initial addition step and the subsequent ring closure) must be taken into consideration in the molecular mechanics modelling.

New Reagents

Our modelling studies serve as a basis for the design and evaluation of new chiral reagents. The most efficient reagents we have used to date are the ones of type **4**, which contain 8-phenylmenthol as a chiral auxiliary. We are presently investigating reagents of type **5**, which have shown promising results in initial kinetic resolutions of racemic monoaldehydes, as exemplified below.



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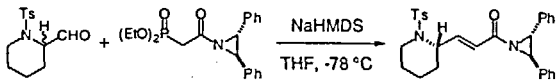
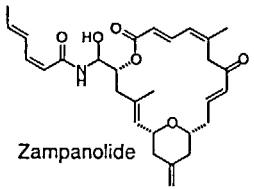


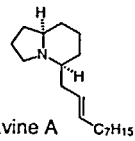
(Racemic; 2.2 equiv) **5** 82%, (*E*):(*Z*) = 96:4, d.r.(*E*) = 90:10

Application in synthetic approaches to chiral heterocycles

A range of natural products with interesting and potentially useful biological activity, e.g. zampanolide[5] and piclavine A,[6] contain heterocyclic substructures which might be derived from asymmetric HWE reactions with *meso*-dialdehyde substrates.

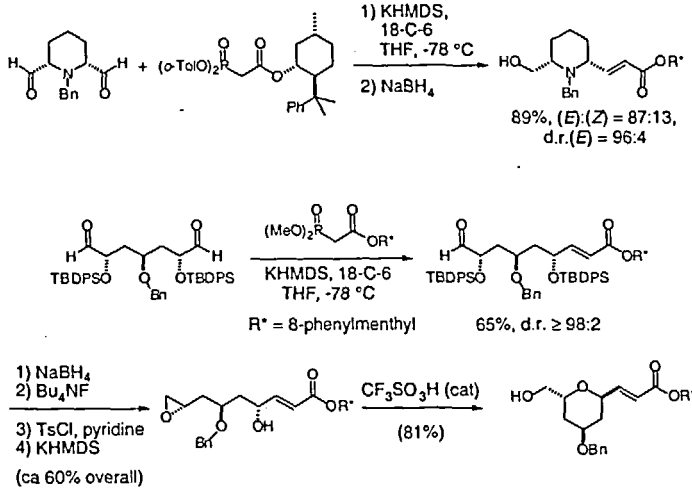


Zampanolide



Piclavine A

We have recently developed general strategies, based on asymmetric HWE reactions, which can be applied to the preparation of appropriately functionalized chiral heterocyclic building blocks (Scheme 2). In one approach, a cyclic *meso*-dialdehyde is desymmetrized to give a chiral HWE product, while an alternative strategy utilizes an asymmetric HWE reaction followed by a stereospecific ring closure to the heterocycle. By using reactions which proceed with either overall retention or inversion of stereochemistry in the ring closure step, the latter strategy enables construction of either *cis*- or *trans*-substituted derivatives, respectively.



SCHEME 2. Examples of strategies for synthesis of heterocyclic building blocks via asymmetric HWE reactions.

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