



Digest paper

Recent topics of the natural product synthesis by Horner–Wadsworth–Emmons reaction



Kenichi Kobayashi*, Kosaku Tanaka III, Hiroshi Kogen*

Graduate School of Pharmaceutical Sciences, Meiji Pharmaceutical University, 2-522-1 Noshio, Kiyose, Tokyo 204-8588, Japan

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ABSTRACT

The Horner–Wadsworth–Emmons (HWE) reaction has become well established among existing methodologies for the highly stereoselective olefination of carbonyl compounds. The reliability of this reaction in terms of its robustness, high stereoselectivity, and broad substrate scope permit retrosynthetic disconnection of the olefin bond in α,β -unsaturated carbonyl intermediates in natural product synthesis. This review discusses recent applications of the HWE reaction in natural product synthesis, highlighting its use for carbon chain elongation, coupling reactions of synthetic segments, ring-closing reactions, tandem reactions including HWE olefination, and asymmetric reactions.

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Contents

Introduction	568
Carbon chain elongation	569
Iterative use of the HWE reaction	569
Use of unique HWE reagents	570
exo -Methylene formation	571
Synthesis of amino acid derivatives	572
Coupling of segments	572
Use of HWE phosphonates	572
Use of Still–Gennari-type phosphonates	572
Side chain attachment	573
Ring-closing reactions	574
Large-ring construction	574
Small-ring construction	575
Tandem reactions	576
Asymmetric reactions	577
Conclusion	582
References	582

Introduction

The Horner–Wadsworth–Emmons (HWE) reaction is widely used in organic synthesis as one of the most reliable methods for

the olefination of carbonyl compounds. This reaction originates from a first report by L. Horner in 1958 describing a novel method for the preparation of alkenes from aldehydes and ketones using the carbanions of alkyl diphenylphosphine oxides.¹ This olefination method is now regarded as the Wittig–Horner reaction,² and it was further developed by W. S. Wadsworth and W. D. Emmons. They demonstrated that phosphonate carbanions work very well in the olefination reaction compared with the triphenylphosphorus

* Corresponding authors.

E-mail addresses: kenichik@my-pharm.ac.jp (K. Kobayashi), hkogen@my-pharm.ac.jp (H. Kogen).

ylides used in the Wittig reaction, and this method for the olefination of carbonyl compounds using phosphonate carbanions is now generally known as the HWE reaction within the organic synthetic community. The HWE reaction is recognized as a robust, reliable, and widely applicable technique for C=C bond formation because of its following advantages: (1) easy preparation and high reactivity of the phosphonate reagents, (2) generally high *E* selectivity, (3) applicability under a variety of reaction conditions, and (4) broad substrate tolerance.³ In contrast to the *E* selectivity of the HWE reaction, Still–Gennari- or Ando-type phosphonates permit (*Z*)-olefins to be synthesized exclusively.^{4,5} Thus, the HWE reaction and these complementary methods possess great value for stereochemically defined C=C bond formation. In addition to the standard HWE reaction using commercially available phosphonates (e.g., triethyl phosphonoacetate), a wide range of other phosphonate reagents can be prepared and used in natural product synthesis.

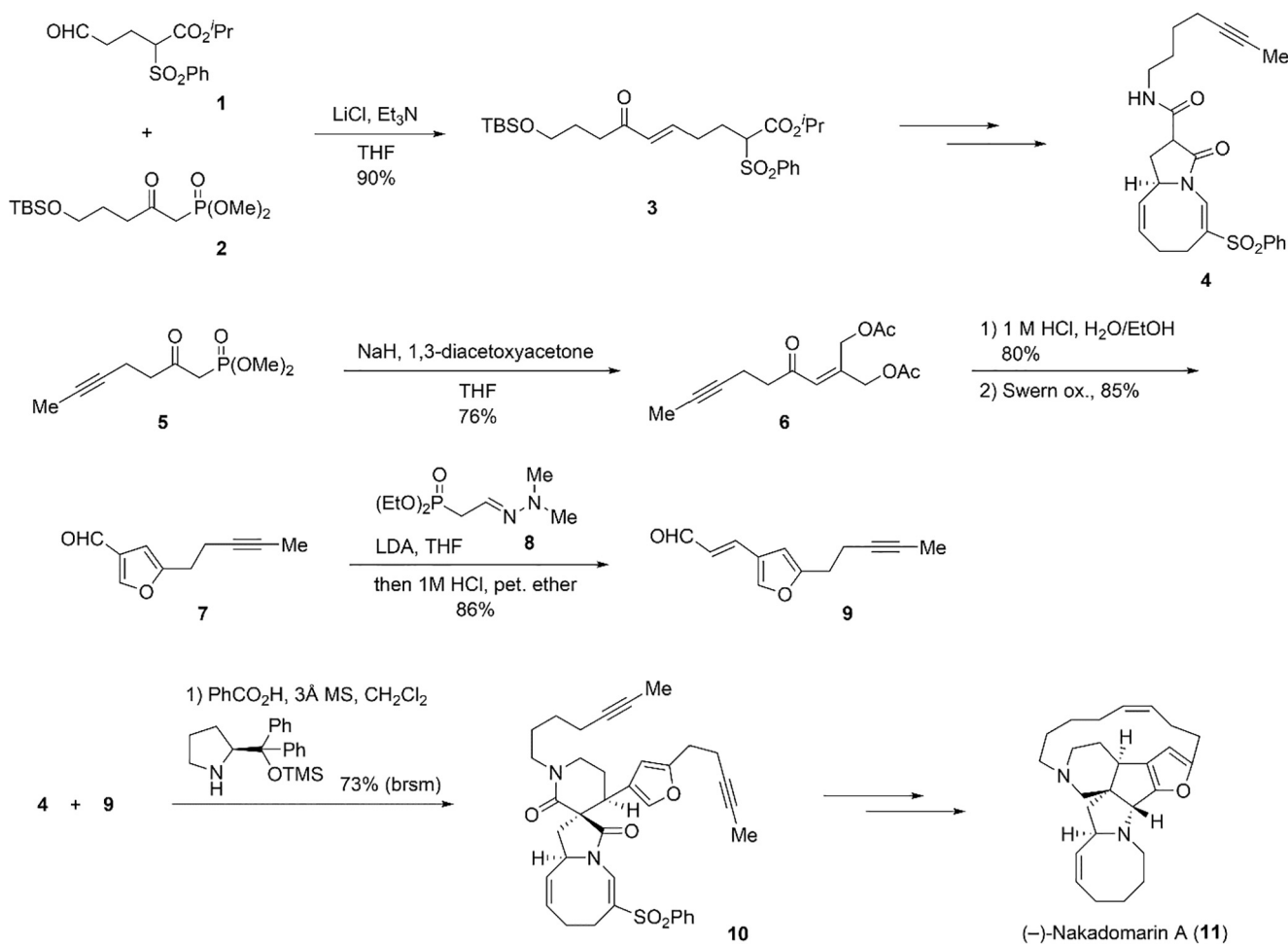
In this review, we discuss recent developments in this decade in the use of the HWE reaction as a key step in natural product synthesis from a slightly different perspective of the previous reviews by Orelli et al.,⁶ including the application of this reaction to carbon chain elongation, coupling of various-sized synthetic segments, intramolecular ring-closing reactions, tandem reactions using reactive HWE products, and asymmetric reactions using chiral phosphonates, and this paper covers the latest applications of the HWE reaction. Although numerous synthetic strategies to complex natural products can be devised through careful retrosynthetic analysis, in some cases the HWE reaction is recognized as the only viable means for successful assembly of the desired structure.^{7–10}

Carbon chain elongation

Iterative use of the HWE reaction

The HWE reaction is one of the most reliable methods for carbon chain elongation, and the reaction is often used multiple times in the synthesis of a single natural product. Boeckman and co-workers used three different HWE reactions in their total synthesis of the manzamine alkaloid (–)-nakadomarin A (**11**), which exhibits a wide range of biological activities.¹¹ In the early stage of their preparation of the bicyclic lactam segment **4**, they used the HWE reaction between aldehyde **1** and phosphonate **2** to obtain enone **3** (Scheme 1). In their synthesis of another segment of nakadomarin A, **9**, the HWE reaction of 1,3-diacetoxyacetone with phosphonate **5** was used to generate enone **6**. Subsequent acid-catalyzed furan formation followed by Swern oxidation afforded furaldehyde **7**, which was subjected to a third HWE reaction with iminophosphonate **8** followed by acidic hydrolysis to deliver β-furyl aldehyde **9**. After the coupling reaction between **4** and **9** in the presence of an organocatalyst, the total synthesis of (–)-nakadomarin A (**11**) was achieved in six steps.

Kishi and co-workers reported the total synthesis of metabolite **17** isolated from the frog pathogen *Mycobacterium liflandii*.¹² In their synthesis, they employed an iterative HWE approach to construct the tetraenoic acid moiety of the side chain of the targeted natural product. Thus, the HWE reaction was repeated four times with good *E/Z* stereoselectivities of 94/6 (first cycle), 98/2 (second cycle), 98/2 (third cycle), and 95/5 (fourth cycle) to produce



Scheme 1. Boeckman's synthesis of (–)-nakadomarin A (**11**).

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