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Efforts toward the total synthesis of a jatrophane diterpene

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ABSTRACT

A significant effort toward the model study of jatrophane skeleton has been made. To synthesize an important synthon, Horner–Emmons–Wadsworth olefination was attempted.

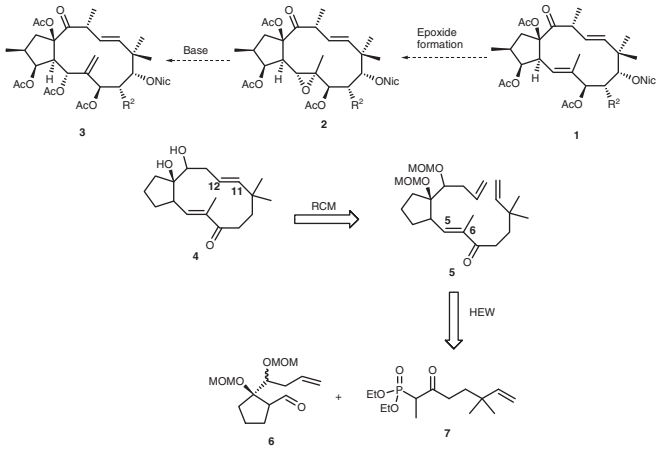
Introduction

It has been found that certain cancer cells naturally become resistant to chemotherapeutic drugs when exposed to drug over a period of time. Scientists have identified small pumps on the surface of cancer cells that actively extrude the chemotherapeutic drug from inside the cancer cell ultimately leading to the failure of chemotherapy. The developed resistance of disease-causing microbes or cells against varying drugs is commonly known as multidrug resistance (MDR).[1] Jatrophane diterpenes were isolated in 1970 by Kupchan et al. from *Euphorbia gossypiifolia*[2] which have shown potential as Pgp inhibitor. Since then a large number of jatrophane diterpenes have been isolated. Most of the jatrophane diterpenes feature a characteristic bicyclic[10.3.0]pentadecane framework.

The structural complexity of this molecule can be estimated by the numbers of stereocenters. They possess as many as 9 stereogenic centers along with C11–C12 double bond, and C6–C17 *exo*-double bond. The first total synthesis of a jatrophane diterpene was accomplished by Smith and co-workers in 1981.[3] The key step in this synthesis of normethyljatrophone was a $TiCl_4$-mediated intramolecular Mukaiyama cyclization. Stille and co-workers reported another synthetic route for the total synthesis of jatrophone in 1990.[4] The key step in their total synthesis was the intramolecular palladium-catalyzed carbonylative coupling between vinyl stannane and vinyl triflate. However, the first asymmetric total synthesis of 15-acetyl-3-propionyl-characiol was achieved by Hiersemann et al., demonstrating a reliable synthetic strategy toward the jatrophane framework.[5] A thermal intramolecular carbonyl-ene reaction was utilized to synthesize the highly substituted cyclopentane fragment.

Results and discussion

We assume that a bulky base-promoted hydrogen-abstraction can lead to a regioselective opening of an epoxide to furnish an exo-double bond. Hence the synthesis of jatrophane analogue **1** was targeted. In pursuit of a reliable synthetic pathway to access a jatrophane skeleton such as **4**, one of our main goals was to establish a reliable methodology to construct the C11–C12 trisubstituted double bond. The structural architecture of this molecule consists of a 5-membered ring *trans*-fused to a 12-membered ring.



Scheme 1. Retrosynthetic analysis of model substrate **4**.

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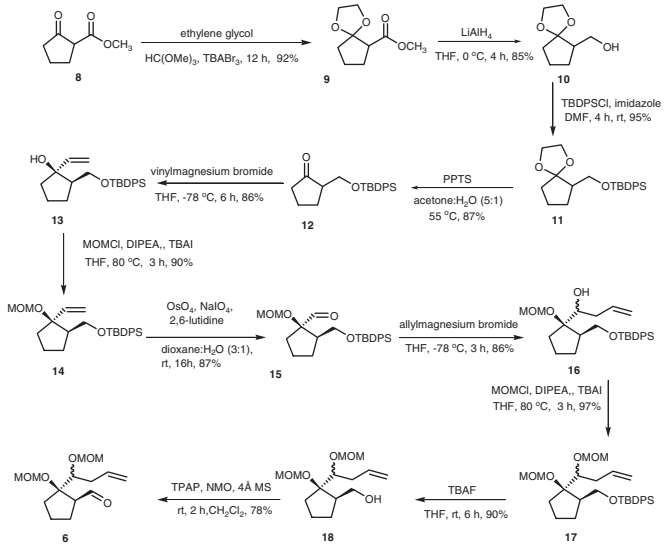
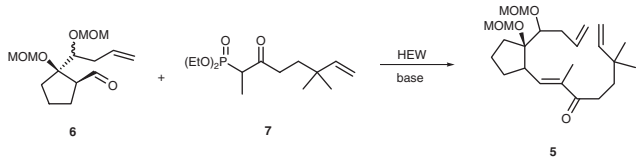


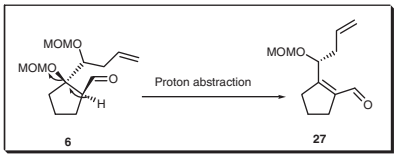
Scheme 2. Synthesis of aldehyde **6**.

Our retrosynthesis involves forming the C11–C12 olefinic double bond by employing the ring-closing metathesis (RCM)[6] from bis-MOM-triene **5**, which might be synthesized from Horner–Emmons–Wadsworth olefination (HEW)[7] using aldehyde **6** and phosphonate **7** (Scheme 1).[8]

Synthesis of racemic aldehyde **6** commenced with cyclopentanone methylcarboxylate **8** (Scheme 2). First, we protected the ketone as the ketal with ethylene glycol and trimethyl orthoformate.[9] The primary alcohol was obtained by the reduction of ester **9** with $LiAlH_4$ and was protected as the TBDPS ether.[10] We chose TBDPS as the protecting group because we wanted it to serve two purposes: (1) the bulky nature of this group should assist in a stereoselective vinyl addition on an adjacent ketone, which is relevant to the synthesis of our target; and (2) the Si-protecting group would give us the flexibility of late stage deprotection and would avoid undesirable deprotection of other protected alcohols. In the initial phase of our research, we used a *p*-methoxyphenyl group (PMP) for protecting this hydroxyl group. While stereoselective vinyl addition worked well, the ceric ammonium nitrate-mediated deprotection of the PMP group in a later stage was low yielding



Scheme 4. Attempted HEW reaction.



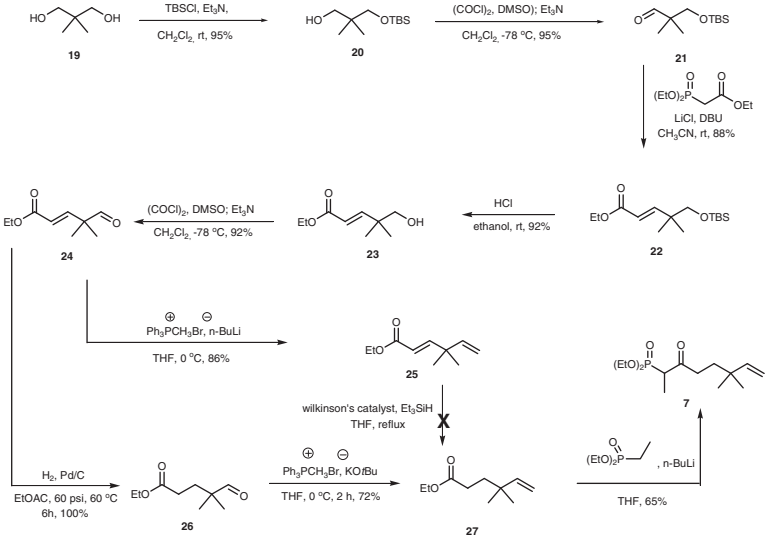
Scheme 5. Rationale for the failure of the key HEW reaction.

Table 1
Reactions conditions applied for HEW reaction

Base	Temperature	Solvent	Result
n-BuLi	−78 °C	THF	Elimination
$Ba(OH)_2$	rt to reflux	THF	No reaction
K_2CO_3	rt	THF	No reaction
NaH	25–35 °C	DME	Elimination

and inconsistent. Deketalization[11] of compound **11** under acidic condition afforded us cyclopentanone **12** in 87% yield, which upon treatment with vinylmagnesium bromide gave the tertiary alcohol as a single isomer and the relative stereochemistry was confirmed by NOE as **13**. The tertiary alcohol subsequently was protected as the MOM ether to obtain **14** in 87% yield.[12] The one-pot oxidative cleavage of olefin resulted in aldehyde **15**.[13] Allylation of compound **15** using allylmagnesium bromide produced homoallylic alcohol **16** as a mixture of diastereomers in the ratio of 1:1. The resultant secondary alcohol was protected as a MOM ether to yield bis-MOM ether **17**. TBAF-mediated desilylation was achieved at room temperature to yield primary alcohol **18**.[14]

We employed three different oxidation methods for the synthesis of aldehyde **6**. Pyridinium dichromate (PDC)[15] resulted in modest yield of aldehyde and required long reaction time and the workups were often very capricious given the amount of



Scheme 3. Synthesis of phosphonate **7**.

reagent used. Swern conditions proved to be harsh on our substrate as we encountered an elimination of one of the MOM group in low yield.[16] Given the sensitive nature of substrate, we opted for a milder oxidation. TPAP/NMO condition was found to be ideal for this transformation and gave the requisite aldehyde **6** in 78% yield.[17]

The synthesis of phosphonate **7** began with mono-TBS protection of *neo*-pentyl glycol. Subsequent Swern oxidation gave aldehyde **21**. Ester **22** was generated in a good yield upon subjection of aldehyde to Horner–Emmons–Wadsworth olefination.[18] Alcohol **23** was obtained after TBS-deprotection under acidic conditions; after which Swern oxidation afforded aldehyde **24** in 92% yield. A Wittig olefination was employed to convert aldehyde into diene **25** (Scheme 3).[19] After repeated failures in performing the desired regioselective reduction of a double bond utilizing Wilkinson's catalyst along with triethylsilane, we modified our synthetic scheme.

α,β-Unsaturated ester **24** was hydrogenated under 60 psi hydrogen atmosphere using Pd/C (Scheme 4). Saturated ester **26** was obtained and subjected to Wittig olefination to yield ester **27,** which upon treatment with lithiated ethylphosphonate furnished the target phosphonate **7.**

We were now set for the key HEW olefination between bis-MOM aldehyde **6** and phosphonate **7** to provide triene **5.** Unfortunately, the two fragments did not couple under various conditions. Frequently, we observed that one of the $MOMO^-$ groups of aldehyde **6** was being eliminated (Scheme 5). We rationalized the elimination of $MOMO^-$ group was made possible through the deprotonation of α-carbon hydrogen, followed by an E1cb mechanism.

Apparently, aldehyde **6** is sensitive and prone to β-elimination even under the mildest basic conditions. Nevertheless we attempted to couple the two fragments under various conditions employing different bases but to our disappointment none of these methods afforded the desired product **5** (Table 1).

Generally, we observed the β-eliminated product **27** when we employed strong bases such as *n*-BuLi and NaH, and the use of milder bases resulted in no reaction. Another reason which might be hindering the formation of the desired enone **5** is the fact that aldehyde **6** is sterically congested, thereby slowing down the nucleophilic addition step. An alternative pathway to furnish enone with inducing minimal structural changes in the existing synthetic scheme is under investigation and is subjected for future communication.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.080.

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