Natural Product Synthesis

Intramolecular Organocatalytic [3+2] Dipolar Cycloaddition: Stereospecific Cycloaddition and the Total Synthesis of (±)-Hirsutene**

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Nucleophilic catalysis represents an important subset of organocatalytic transformations.[1,5] As part of a program devoted to the design of phosphane-catalyzed C–C bond-forming reactions,[2] we recently reported the first intramolecular phosphane-catalyzed [3+2] cycloaddition of 2-butynoates with electron-deficient alkenes.[2a] A challenge inherent to the intramolecular cycloaddition resides in suppression of competitive internal redox isomerization, that is, phosphane-catalyzed conversion of the 2-alkynoates to the corresponding 2,4-dienoates.[3] Indeed, whereas diquinane formation proceeds smoothly, presumably owing to the enhanced rate of five-membered-ring formation, competitive isomerization circumvents hydrindane formation. Notably, unlike the parent intermolecular cycloaddition discovered in 1995,[4,5] which generally provides cycloadducts as mixtures of regio- and diastereomers, the intramolecular process affords cycloadducts in isomerically pure form.[2a] In this account, the first application of this intramolecular organocatalytic cycloaddition methodology in natural product synthesis is reported, as demonstrated by the synthesis of the linear triquinane hirsutene. These studies highlight the utility of this cycloaddition methodology vis-à-vis diastereoselective construction of quaternary centers and establish the intramolecular cycloaddition as a stereospecific process.

Since the first structural elucidation of a polyquinane natural product in 1966 (hirsutic acid-C, Figure 1),[6] over 250 polyquinane natural products have been isolated.[7] Over 80 of these natural products belong to the structural subset known as linear triquinanes, which are isolated from plants, microbes, and marine organisms.[7b] The discovery of structurally novel linear triquinanes continues unabated. For example, chlorinated linear triquinanes such as chloriolin C have been isolated from fungal cultures taken from a *Jaspis* marine sponge.[8] Efforts toward the synthesis of linear triquinane

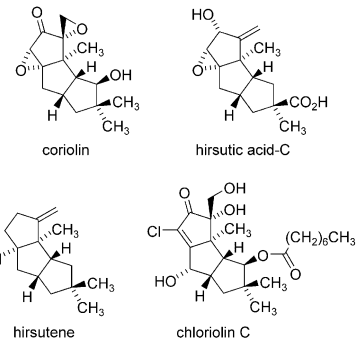

Figure 1. Representative linear triquinanes.

natural products are fueled, in part, by their biological activity. Hirustic acid-C and coriolin exhibit antibiotic and antitumor activity, respectively.[9] Owing to their novel structure, the linear triquinanes have also captured the interest of synthetic chemists as a testing ground for new cyclopentannulation strategies. In this latter capacity, hisutene, a metabolite of the basidiomycete *Coriolus consors* and presumed biogenetic precursor to coriolin and hirsutic acid-C,[10] has been the focus of considerable attention.[7] Here we present a concise and stereocontrolled approach to (±)-hirsutene based on phosphane-catalyzed intramolecular [3+2] cycloaddition methodology developed in our lab.

Retrosynthetically, hirsutene is envisioned to derive from cycloadduct **6** by means of aldol cyclization–methylenation (Scheme 1). The diquinane **6**, which contains three of the four stereogenic centers in hirsutene, will be obtained directly through phosphane-catalyzed [3+2] dipolar cycloaddition of the 1,7-enyne **5**. The cycloaddition of **5** serves as a means of exploring the utility of the intramolecular cycloaddition methodology vis-à-vis stereoselective formation of quaternary carbon centers. Moreover, by examining the cycloaddition of both (*E*)- and (*Z*)-**5**, information regarding the stereospecificity of the intramolecular cycloaddition may be obtained. Finally, cycloaddition substrate **5** will be obtained from dimethylhexenol **1** through sequential introduction of enone and ynoate moieties.

The synthesis of cycloaddition substrate **5** begins with tosylation of 3,3-dimethyl-hex-5-en-1-ol (**1**, Scheme 2).[11] Displacement of the tosylate was attempted with an assortment of acetylides under a range of conditions, but it could only be achieved with lithium acetylide ethylenediamine complex in DMSO. Under these conditions the resulting 1,7-enyne **2** is produced in 68% yield.[12] Treatment of 1,7-enyne **2** with methyllithium followed by methyl chloroformate provides the corresponding ynoate **3** in 81% yield. Selective ozonolytic cleavage of the terminal alkene residue in the presence of the ynoate occurs smoothly to provide aldehyde **4** in 85% yield. Finally, olefination of **4** using 3-diethylphosphono-2-butanone[13] occurs in 60% yield to afford cycloaddition addition substrate **5** as a 5.5:1 ratio of *E*/*Z* isomers.

The acquisition of mono(enone)–mono(ynoate) **5** sets the stage for phosphane-catalyzed cycloaddition. Gratifyingly, exposure of (*E*)-**5** to our previously defined conditions[2a] for intramolecular phosphane-catalyzed [3+2] dipolar cycloaddition results in the formation of cycloadduct **6** in 88% yield.

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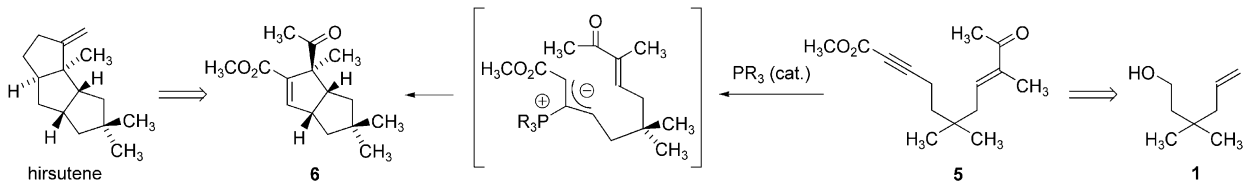
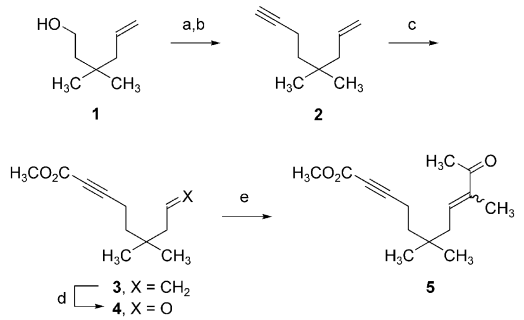


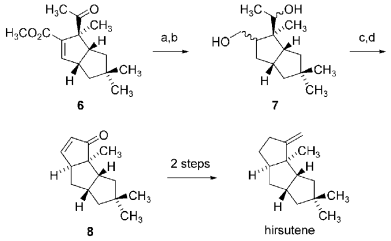
Scheme 1. Retrosynthetic analysis of hirsutene based on a phosphane-catalyzed [3+2] dipolar cycloaddition.



Scheme 2. Preparation of cycloaddition substrate **5**. Conditions: a) TsCl, Pyr, 0 °C, 76 %; b) LiC≡CH, DMSO, 5 °C, 68 %; c) CH_3Li, THF, −78 °C, then $ClCO_2CH_3$, −30 °C, 81 %; d) O_3, CH_2Cl_2, −78 °C, then PPh_3, 85 %; e) 3-diethylphosphono-2-butanone, NaH, THF, 35 °C, 60 %, 5.5:1 *E*/*Z* ratio. DMSO = dimethyl sulfoxide, Pyr = pyridine, Ts = toluenesulfonyl.

Moreover, **6** is obtained as a single stereoisomer with placement of the methyl residue on the concave face of the diquinane ring system, that is, formation of the quaternary center occurs readily and with a stereochemistry consistent with the structural features of hirsutene. To probe the stereospecificity of the cycloaddition, (*Z*)-**5** was exposed to identical conditions. Formation of the epimeric diquinane *epi*-**6** is observed, without any detectable formation of the cycloadduct derived from (*Z*)-**5**. These results firmly establish the intramolecular phosphane-catalyzed [3+2] dipolar cycloaddition as a stereospecific process. This result is significant in view of the fact that evidence for both stepwise and concerted mechanisms exists for related intermolecular cycloadditions.[4e,5] A model accounting for the stereospecific cycloaddition of (*E*)- and (*Z*)-**5** is given below (Scheme 3).

Elaboration of cycloadduct **6** to hirsutene is achieved in six manipulations. Hydrogenation of **6** followed by $LiAlH_4$ reduction occurs in yields of 93 % and 92 %, respectively, to provide diol **7** as a mixture of diastereomers. Swern modification of the Moffatt oxidation provides an intermediate keto-aldehyde in 78 % yield, which upon exposure to base affords the aldol cyclodehydration product **8** in 95 % yield as a single stereoisomer. Enone **8** is identical in all respects to the previously reported material, which has been converted to hirsutene in two manipulations.[14] As such, the synthesis of **8** represents a formal total synthesis of (±)-hirsutene. Whereas the previously reported material is prepared in 18 steps from 2,2′-dimethylpentenal, the present route allows access to enone **8** in 12 steps from the very same precursor (Scheme 4).



Scheme 4. Conversion of cycloadduct **6** to (±)-hirsutene. Conditions: a) H_2, Pd/C, CH_3OH, 25 °C, 93 %; b) $LiAlH_4$, Et_2O, 25 °C, 92 %; c) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then TEA, 78 %; d) KOH, Bu_4NOH (aq), THF/Et_2O (1:1), reflux, 95 %. TEA = triethylamine.

In summation, intramolecular phosphane-catalyzed [3+2] dipolar cycloaddition enables a concise approach to the linear triquinane hirsutene, whereby three contiguous stereogenic centers, including a quaternary center, are created in a single manipulation with control of relative stereochemistry. In addition to demonstrating the applicability of this methodology vis-à-vis triquinane synthesis, these studies also reveal that the intramolecular cycloaddition is stereospecific. Future studies will be devoted to the design of related phosphane-catalyzed transformations including enantioselective variants of the methodology reported herein.

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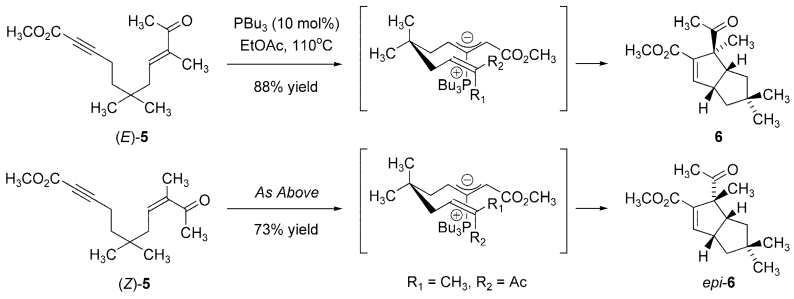
Keywords: cycloaddition · natural products · organocatalysis · phosphanes



Scheme 3. Phosphane-catalyzed cycloaddition of **5** is stereospecific.

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