Highly Diastereoselective Synthesis of Decalin Skeletons with Quaternary Carbon Centers via the Tandem Oxy-Cope/Ene/Claisen Reaction

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ABSTRACT

The highly diastereoselective cascade sequence of three successive thermal pericyclic reactions of 1,2-divinylcyclohexanol allyl and propargyl ethers is described. This novel tandem process provides an efficient synthesis of sesqui- and diterpenoid skeletons having a quaternary carbon at C9.

The creation of asymmetric quaternary carbon centers is a problem frequently encountered in diterpene synthesis. Although there exists a broad range of methods capable of generating new carbon–carbon bonds, the establishment of quaternary centers in the proper configuration is among the most restrictive in organic chemistry.1 Herein, we present a new synthetic method based on tandem oxy-Cope/transannular ene/Claisen reaction sequences that can generate up to four contiguous stereogenic centers including two quaternary carbons at C5 and C9 (eq 1). The thermal oxy-Cope/ene reaction of 1 generates in situ 1,5-hexadiene enol ether intermediate 2, which is properly set up for a subsequent Claisen rearrangement to afford bicyclic lactol 3.

This cascade reaction creates a quaternary carbon at C9 and gives direct access to the core of structurally complex diterpenes such as tetrodecamycin (4) and dihydroxychiliolide (5) (Figure 1). The combination of pericyclic reactions constitutes a powerful synthetic strategy to make multiple carbon–carbon bonds in an efficient manner.2 Previous work from this laboratory established that the tandem combination of oxy-Cope/ene reaction of 1,2-divinylcyclohexanols results in rapid assembly of polycyclic compounds possessing a

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bridgehead alcohol. The synthetic utility of this process in organic synthesis was demonstrated by the total synthesis of (+)-arteannuin M. Initial experiments were performed using allyl ether to establish the reaction conditions (Scheme 1). Allyl ether was readily prepared from 6 via allylic oxidation followed by etherification. Substrate was dissolved in deoxygenated toluene and DBU (2 equiv) and heated in a sealed quartz cell at 220 °C for 1 h in a CEM microwave to give lactol in 70% yield. We have recently demonstrated that the tandem oxy-Cope/ene reaction of 1,2-divinylcyclohexanols occurs 10- to 300-fold faster when irradiated with microwaves than heating with a conventional oven. 1H and 13C NMR and GC-MS of the reaction mixture indicated the presence of only two diastereomers (anomeric position). To correctly determine the diastereomeric ratio of the tandem process, the crude lactol mixture was oxidized with TPAP to afford the corresponding lactone in 70% yield as the sole diastereomer (dr > 98%).


(6) Nonpolar solvents such as toluene do not absorb microwaves; therefore, a glass coated ferrite disk was placed inside the reaction cell. Ferrite readily absorbs microwaves energy and transmits heat to the reaction mixture through conduction. This microwave oven is equipped with fiber optic probes placed inside the reaction cell to monitor the temperature and pressure of the reaction.

Table 1. Tandem Oxy-Cope/Ene/Claisen Reaction of 1,2-Divinylcyclohexanols Allyl and Propargyl Ether

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /> 75%, dr &gt; 98%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /> 60%, dr &gt;98%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /> 76%, dr &gt; 98%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /> 75%, dr &gt; 98%, E/Z = 89:11</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /> 98%, dr &gt; 98%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /> 68%, dr &gt; 98%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /> 81%, dr &gt; 98%</td>
</tr>
</tbody>
</table>

*a Diastereomeric ratio was determined by 500 MHz 1H NMR. *b Diastereomeric ratio was determined using the corresponding lactone. *c Diastereomeric ratio was determined using the corresponding diol.

Figure 1. Structure of tetrodecamycin (4) and dihydroxychilide (5).
Depending on the pattern of substitution on the terminal allyl ether, additional tertiary or quaternary carbons adjacent to C9 can be introduced onto the molecule.

To prove this, differentially substituted allyl and propargyl ethers were prepared according to Scheme 1. The ethers were heated in toluene to give the corresponding lactols in 60–98% yield (Table 1). We were pleased to observe that the tandem process is highly diastereoselective in all cases. Indeed, the thermal transformation of 10 and 11 (entries 1 and 2) led to one-pot stereocontrolled syntheses of lactol 17 and 18 each possessing four contiguous stereogenic centers in 75% and 60% yield, respectively (dr > 98%). NMR spectroscopy and X-ray analysis established the relative configuration of the bicyclic products.

On the basis of these results, we turned our attention toward the generation of a bicyclic core having two contiguous quaternary centers at C9 and C11. Heating 12 at 200 °C for 60 min gave the desired lactol 19 in 76% (entry 3). Interestingly, enol ether 20 was isolated as a single isomer in 15% yield (E/Z > 98%). Completion of the reaction involves a prolonged exposure of 20 to heat, which resulted in the formation of degradation products.

The high diastereoselectivity of this triple tandem reaction can be explained by the mechanism depicted in Figure 2. At first glance, the thermal oxy-Cope rearrangement of 10 leads to enol 25, which tautomerizes in situ to produce the ketone 26. This ketone can adopt two chairlike conformations at the transition state, A and B. A close examination of the transition state B reveals a pseudo-1,3-diaxial O-allyl-ring methylene interaction. Therefore, this favors the transition state A over B as the reactive conformer to provide the enol 27. Finally, the Claisen rearrangement proceeds anti to the bridgehead alcohol at C5 to afford the desired bicyclic product 17.

To support the proposed mechanism, ether 28 was heated at 220 °C for 1 h (Scheme 2). 1H NMR of the crude reaction mixture indicated the formation of only one enol ether 29 (E/Z > 98%). This result confirms without ambiguity the highly diastereoselective transannular ene reaction in the tandem process.

Encouraged by these results, the synthesis of two contiguous asymmetric quaternary carbons was investigated. Contrary to all expectations, the treatment of 13 under thermal conditions gave 21 as the sole isomer (dr at C9 > 98% and E/Z = 89:11) (entry 4). The formation of this lactol can be rationalized via a competitive 1,3-type rearrangement of the enol intermediate 13a (Scheme 3) to give the rearrangement product 21. The mechanism of this rearrangement is currently under investigation. In the propargyl ether series 14 and 15, respectively, (Table 1, entries 5 and 6) gave upon heating at 220 °C exclusively the expected tricyclic allene

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(9) It was observed that a prolonged exposure of 17 (entry 1) with DBU at 220 °C resulted in a partial epimerization at C11 (23%). The replacement of DBU by triethylamine afforded 17 in 75% without epimerization at C11.

(10) The olefin geometry was established by NOE experiment.

(11) The structure of 21 was elucidated by 2D-NMR COSY and NOESY experiments.
In summary, we have developed a highly diastereoselective tandem process based on a sequence of three successive pericyclic reactions. The isolation of enol ether intermediates 20 and 29 having an $E$ olefin geometry strongly supports the proposed mechanism depicted in Figure 2. This strategy, which offers a simple and efficient method for the synthesis of a bicyclic ring having a quaternary center at C9, is currently being used in the total synthesis of tetrodecamycin (4) and dihydroxychiliolide (5).

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**Supporting Information Available:** Spectroscopic data for compounds 7–24, 28, and 29, the corresponding lactones of 17, 18, 21–23 and the corresponding diol of 19, and ORTEP views of the corresponding lactone of 17 and 18. This material is available free of charge via the Internet at http://pubs.acs.org.

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