Novel Synthesis of Trisubstituted Olefins for the Preparation of the C16–C30 Fragment of Dolabelide C

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Supporting Information

ABSTRACT: A silicon-tether ring-closing metathesis strategy is reported for the synthesis of trisubstituted olefins flanked by allylic or homoallylic alcohols, which are difficult to obtain by classical ring-closing or cross-metathesis reactions. In addition, a novel Peterson olefination reaction has been developed for the preparation of the allyldimethylsilane precursors, which are versatile synthetic intermediates. This method was then applied to the synthesis of the C16–C30 fragment of dolabelide C.

Numerous natural products of the polyketide family encompass an E trisubstituted olefin with a methyl substituent. Among these, callipeltoside A® and dolabelide C® possess an allylic alkoxy substituent on the lone substituent of the trisubstituted olefin (motif highlighted in red in Figure 1). Hoye and co-workers attempted to close the macrocycle in callipeltoside by ring-closing metathesis (RCM) reaction to form the C10–C11 trisubstituted alkene.1b Unfortunately, only starting materials were recovered, or truncated products were obtained when using relay ring-closing metathesis strategies,3 highlighting the lack of efficiency of metathesis reactions for hindered substrates. During our previous studies toward the synthesis of dolabelide C,4 we constructed the C16–C30 fragment5 using a cross metathesis (CM) reaction between Z disubstituted enone 1 and gem-disubstituted olefin 2 to form trisubstituted olefin 3 (Scheme 1). Any attempt at CM between the corresponding allylic alcohol (protected or not) and olefin 2 led to dimerization of the allylic alcohol partner. Similarly, the monosubstituted enone dimerized under the metathesis conditions. The optimized yield of the desired E trisubstituted enone 3 was only 47%, because Z enone 1 isomerized into the unreactive E isomer in the presence of metathesis catalysts, showing the limitations of CM for the synthesis of highly hindered trisubstituted olefins.6 We thus devised an intramolecular version of this coupling reaction, relying on a silicon-tether ring-closing metathesis. This strategy has been employed frequently in natural product synthesis, but in most cases the silicon is attached to two oxygen atoms.7 The RCM reaction of substrates possessing an O−Si−C linkage is far less common, and there are few examples involving the formation of trisubstituted olefins from allylsilanes, all of which involve cyclic substrates.8 Herein we report the synthesis of acyclic trisubstituted olefins by coupling of allylic alcohols with...
allyldimethylsilanes, followed by RCM and tether cleavage of the resulting silyl ethers (Scheme 1).

The first objective of this work was to find an efficient synthesis of allyldimethylsilanes from easily available starting materials. While numerous examples of conversion of esters into allyltrimethylsilanes by Peterson olefination have been described,9 to our knowledge there is no report of the synthesis of the corresponding allyldimethylsilanes using this method. Treatment of esters 4a–c with 2 equiv of the Grignard reagent derived from chloromethyldimethylsilane 5 in the presence of cerium trichloride,10 followed by elimination of dimethylsilanol by stirring the unpurified β-hydroxysilanes with silica gel in dichloromethane, gave the desired allyldimethylsilanes 6a–c (Scheme 2).11 These silanes are versatile intermediates that can be easily chlorinated,12a oxidized,12b or used in the hydrolysislation of alkyln carbonyl compounds.12c Silanes 6a–c were reacted with allylic alcohol 7 under the dehydrogenative conditions reported by Ito and Sawamura et al.13 to furnish silyl ethers 8a–c in good yields (as 1:1 mixtures of diastereomers for 8b and 8c). RCM of 8a–c with 5–10 mol % of the Grubbs 2 catalyst proceeded uneventfully to furnish cyclic ethers 9a–c in moderate to excellent yields.

Tether cleavage proved to be more difficult than anticipated. When compound 9b was subjected to the conditions employed by Miller and Li for the removal of their allylic silicon tether (KF, KHCO3, 1:1 THF/MeOH),8a diol 10b was obtained in 16% yield along with 41% of recovered 9b (Scheme 3). All attempts to improve this yield by using alternative fluoride sources such as TBAF, KF, or CsF led to complete conversion to either isomerized product 11b or elimination product 12b. When 9b was treated with Sc(OTf)3 in toluene, only elimination product 12b′ was formed.

We finally resorted to a two-step process to circumvent the problems described above. The six-membered ring of 9a and 9c was first opened with methyllithium2a and the resulting allytrimethylsilanes 13a and 13c were desilylated with TBAF in wet DMF at 65 °C, giving moderate yields of 10a and 10c along with the corresponding isomerized 11a and 11c as easily separable minor products (Scheme 4).

This new methodology can also be applied to the synthesis of trisubstituted olefins flanked by homoallylic alcohols. Silanes 6a and 6c were coupled with homoallylic alcohol 14a or 14b under copper catalysis to give silyl ethers 15aa, 15ac, and 15ba in good yields (Scheme 5). Formation of the seven-membered
silyl ethers was easier than that of the corresponding six-membered rings 16aa, 16ac, and 16ba, requiring only 2.5 mol % of Grubbs 2 catalyst. This is probably due to the lesser steric hindrance around the monosubstituted olefin, which is not branched at the allylic position in this case. When the two-step protocol for tether cleavage was performed on compounds 16, the desired homoallylic alcohols 18 were obtained as 1:1 inseparable mixtures with the corresponding isomerized products. Fortunately, Tamao−Kumada oxidation of the cyclic silyl ethers 16aa, 16ac, and 16ba furnished diols 17aa, 17ac, and 17ba in good yields. Subsequent selective transformation of the primary alcohols into the corresponding bromides and reduction of these bromides (without intermediate purification) with Superhydride gave the desired homoallylic alcohols 18aa, 18ac, and 18ba.

We next turned to the synthesis of the C16−C30 fragment of dolabelide C using this silicon-tether RCM strategy. The synthesis started from compound 19 that we had prepared for our previous synthesis of this fragment (Scheme 6). Ozonolysis of the terminal alkene followed by vinyl Grignard addition to the resulting aldehyde afforded allylic alcohol 23 in good overall yield but as a 1:1 inseparable mixture of diastereomers at C23. To circumvent this problem, compound 19 was transformed into the corresponding primary allylic alcohol 21 via conjugated ester 20 by CM with methyl acrylate followed by DIBAL-H reduction of the ester. The C23 stereocenter was installed by Sharpless asymmetric epoxidation with 10:1 diastereoselectivity, and epoxide 22 was converted into the secondary allylic alcohol 23 by reduction of the intermediate iodoepoxide in 91% overall yield. Dehydrogenative coupling of alcohol 23 with silane (+)-6c furnished silyl ether 24 in good yield. When compound 24 was stirred with 20 mol % of the Grubbs 2 catalyst in dichloromethane at reflux for 3 days, cyclic silyl ether 25 was obtained in only 43% yield, along with 23% recovered 24 (Table 1, entry 1). Compound 24 features a branched allylic alcohol, which decreases its reactivity toward olefin metathesis compared to model substrates 8a−c. Performing the reaction at 70 °C in 1,2-dichloroethane slightly improved the yield (entry 2). Interestingly, changing the solvent to toluene improved both the conversion and the yield (entry 3). Higher temperatures and longer reaction times were not beneficial because they led to decomposition of the silyl ethers. We then screened different Hoveyda−Grubbs 2 catalysts. The Hoveyda−Grubbs 2 catalyst improved the yield to 76% (entry 4). The Zhan-1B catalyst proved disappointing (entry 5), but the Nitro-Grela and the Umicore catalysts were superior (entries 6−8), with an 81% yield obtained with the UmicoreM71SIMes complex. Finally, the silicon tether was cleaved using solid TBAF in DMF, and compound 26 was obtained in 79% yield for the two steps, along with 13% of the isomerized product.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>yield 25</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Grubbs 2</td>
<td>CH₂Cl₂</td>
<td>43% (56% brsm)⁵</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs 2</td>
<td>1,2-DCE</td>
<td>57% (66% brsm)</td>
</tr>
<tr>
<td>3</td>
<td>Grubbs 2</td>
<td>Toluene</td>
<td>63% (78% brsm)</td>
</tr>
<tr>
<td>4</td>
<td>Hoveyda-Grubbs 2</td>
<td>Toluene</td>
<td>76% (87% brsm)</td>
</tr>
<tr>
<td>5</td>
<td>Zhan-1B</td>
<td>Toluene</td>
<td>46% (58% brsm)</td>
</tr>
<tr>
<td>6</td>
<td>Nitro-Grela</td>
<td>Toluene</td>
<td>79% (84% brsm)</td>
</tr>
<tr>
<td>7</td>
<td>UmicoreM73SIMes</td>
<td>Toluene</td>
<td>74% (88% brsm)</td>
</tr>
<tr>
<td>8</td>
<td>UmicoreM71SIMes</td>
<td>Toluene</td>
<td>81% (quant. brsm)</td>
</tr>
</tbody>
</table>

⁴Reaction performed at 40 °C. ⁵brsm = based on recovered starting material. ⁶DCE = dichloroethane.
Experimental procedures, characterization data and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES
