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Intramolecular thermal allenyne [2+2] cycloadditions: facile construction of the 5–6–4 ring core of sterpurene

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Abstract—A variety of 1-allenyl-2-propargyl-substituted cyclopentanol derivatives were found to undergo facile intramolecular microwave-assisted [2+2] allenyne cycloaddition reactions to generate tricyclic 5–6–4 ring systems present in the sterpurenes.

We have recently investigated a known but largely ignored tandem reaction that involves a base-catalyzed intramolecular 5-*exo* cyclization of appropriately substituted 4-pentyn-1-ols, followed by in situ thermal Claisen rearrangement of the intermediate 2-methylenetetrahydrofurans (Fig. 1).[1–8] These reactions, which provide convenient access to a number of interesting cyclohept-4-enone systems, are most conveniently performed under microwave irradiation that typically allows for greatly shortened reaction times and increased product yields.[5–8]

We were intrigued about the possibility of extending this methodology to systems that would involve the allene variant of the Claisen rearrangement.[9–12] It was envisioned that such reactions might provide a facile route to 3-alkylidene substituted cyclohept-4-enone derivatives.

The requisite allene derivatives used for this study were prepared in a straightforward fashion by first reacting the acetylide anion derived from a THP protected propargyl alcohol with different 2-propargyl-substituted cyclopentanone derivatives **1a**–**d** (Scheme 1). These reactions resulted in the formation of diastereomeric mixtures from which products having the propargyl and hydroxyl substituents either *cis* (major) or *trans* (minor) were easily separated by column chromatography. Subsequent reaction of **2a**–**d** with $LiAlH_4$ at room temperature for 30 min afforded the expected allene products **4a**–**d** as single diastereomers typically in 70–90% isolated yields. Allene products bearing aromatic substituents on the triple bond terminus were prepared in a straightforward fashion from **4a** via the Sonogashira reaction.[13]

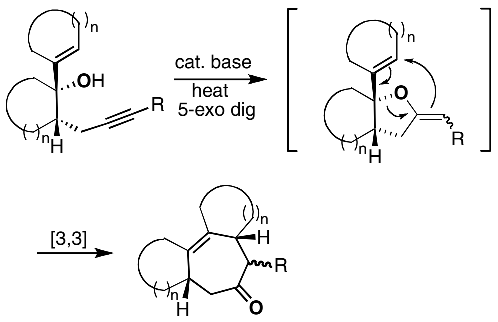

Figure 1. General method for the generation of polycyclic ring systems via tandem 5-*exo* dig cyclization/Claisen rearrangement sequence.

To assess whether these allenynes would undergo the anticipated tandem 5-*exo* cyclization/Claisen rearrangement sequence compound **4b** was subjected to microwave irradiation in the presence of catalytic MeLi. After 30 min of heating at 210 °C in the microwave oven, the starting material was consumed, and a single new product had been formed in nearly quantitative yield (Scheme 2). Interestingly, spectroscopic analysis of the isolated product was consistent with compound **5b** having the tricyclic 5–6–4 structure; none of the initially expected **6** was produced under these conditions. The reaction outcome, including yield, was further found to be independent of added base, suggesting that the formation of the observed product was mechanistically consistent with a thermal intramolecular [2+2] allenyne cycloaddition process (Scheme 2).

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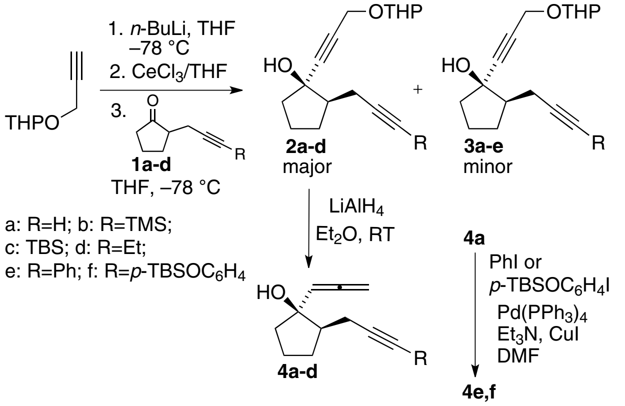
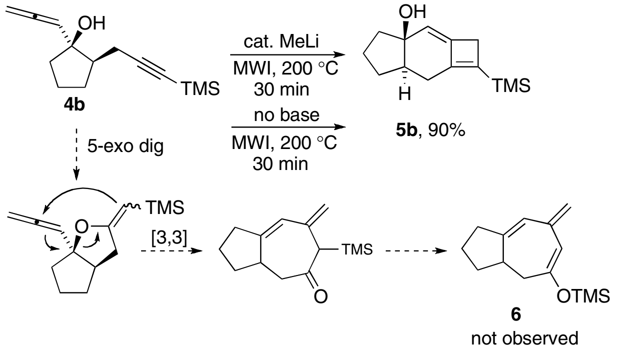
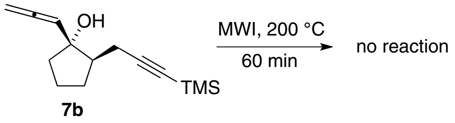


Scheme 1. Synthesis of 1-allenyl-2-propargyl-substituted cyclopentanol derivatives.



Scheme 2. Preparation of compound **6** via intramolecular [2+2] allenyne cycloaddition reaction.



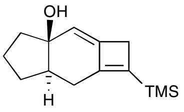
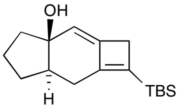
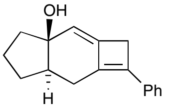
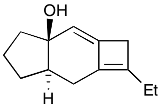
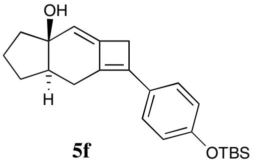
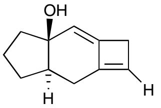
Scheme 3. Attempted [2+2] cycloaddition of **7b**.

At the time these studies were conducted, only a handful of reports involving [2+2] cycloaddition reactions of allenes and alkynes were known in the literature[14–17] and of these, only two involved an intramolecular variant of this process. In both cases, the [2+2] cycloaddition reactions were observed as by-products in molybdenum mediated Pauson–Khand reactions.[16,17] Brummond and Chen[18] later showed that bicyclo[4.2.0]-octa-1,6-dienes and bicyclo[5.2.0]nona-1,7-dienes could be accessed through [2+2] allenic cycloaddition reaction under microwave irradiation. In addition, Oh et al.[19] discovered approximately at the same time that appropriately substituted allenynes underwent similar thermal cycloaddition reactions with or without transition metal catalysts, providing a facile route to a number of bicyclic compounds. Very recently, Mukai et al.[20] demonstrated that bicyclo[6.2.0]deca-1,8-dienes, bicyclo[5.2.0]nona-1,7-dienes, and bicyclo[4.2.0]octa-1,6-dienes could be prepared using thermal [2+2] cycloaddition of allenynes.

In addition to the TMS derivative described above, we found that other allenynes bearing different substituents at the triple bond terminus could also be used to generate analogous tricyclic products. The reaction was shown to be rather general and independent of the type of substituent on the triple bond with the exception of terminal alkynes, which decomposed under the reaction conditions employed. The results from these experiments are summarized in Table 1.[21]

Interestingly, only those allenic systems having the OH and the propargylic moieties in a *cis* orientation were found to be reactive under the conditions investigated. In fact, only unreacted starting material was recovered when **7b**, the *trans* analogue of **4b**, was subjected to microwave irradiation at 200 °C (Scheme 3). Preliminary examination of molecular models suggests that the ring geometry of **4b** allows for better overlap of the terminal p-orbitals of both the allene and acetylene moieties compared to those in **7b**, which may explain the observed resistance of **7b** towards cycloaddition in this relatively rigid system.

Table 1. Intramolecular [2+2] alleneyne cycloaddition reactions of allenynes **4a**–**f**[a]

Entry	Substrate	Product	Yield (%)
1	**4b**	 **5b**	90
2	**4c**	 **5c**	85
3	**4e**	 **5e**	92
4	**4d**	 **5d**	70
5	**4f**	 **5f**	75
6	**4a**	 **5a**	0

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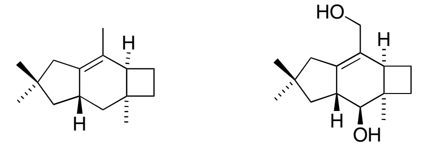
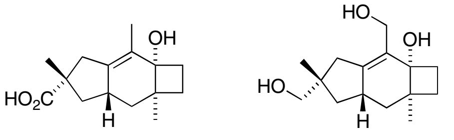
[a] All reactions were conducted in 10 mL base-washed microwave vials under MWI using phenetole as the solvent at 200 °C for 30 min except reactions affording **5e** and **5f** (entries 3 and 5), which were conducted at 150 °C for 45 min.



Sterpurene 2-Sterpurene-8,15-diol



Sterpuric acid 2-Sterpurene-6,12,15-triol

Figure 2. Structures of sterpurene and three related fungal metabolites.

Notably, the methodology described in this Letter allows a straightforward entry to the carbon skeleton of sterpurene, which is one of several closely related structures that have been isolated as metabolites of the fungus *Chondrostereum purpureum* (Fig. 2).[22] This fungus is responsible for the 'silver leaf' disease, which is widespread in North America. Although the 5–6–4 ring system and sterpurene have been synthesized before,[23] the present methodology represents a novel approach to this unique ring system.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.042.

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21. *General procedure for the allenyne [2+2] cycloaddition reaction*: Compound **4b** (63 mg, 0.27 mmol) was dissolved in 1.0 mL of phenetole and the mixture was heated under MWI at 200 °C for 30 min in a base-washed (NaOH) 10 mL microwave vial. Phenetole was then removed in vacuo and the residue was passed through a short plug of deactivated silica gel (MeOH), eluting with 10% ethyl acetate in hexanes. Solvent evaporation afforded compound **5b** (57 mg, 90%) as a clear oil. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 5.04 (s, 1H), 2.92–3.00 (m, 2H), 2.40–2.51 (m, 1H), 2.11–2.21 (m, 2H), 1.82–1.92 (m, 2H), 1.75–1.82 (m, 1H), 1.65–1.75 (m, 1H), 1.61 (s, 1H), 1.48–1.60 (m, 1H), 1.23–1.35 (m, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 156.17, 146.77, 143.38, 112.23, 78.69, 45.51, 39.41, 37.06, 28.67, 24.52, 20.10, -1.56. HRMS calcd for $C_{14}H_{22}OSi$ 234.1440, found 234.1334.
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