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A Convenient Route to Fused 5-7-6 Tricyclic Ring Systems

Timo V. Ovaska,[a]* Jayme L. Roark,[a] Christina M. Shoemaker,[a] and Jon Bordner[b]

[a]Department of Chemistry, Connecticut College, New London, CT 06320, USA
[b]Central Research Division, Pfizer, Inc., Groton, CT 06340, USA

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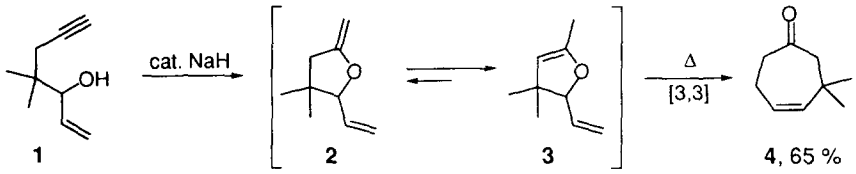
Abstract: An efficient and operationally simple route to fused tricyclic 5-7-6 ring systems was achieved through a consecutive 5-exo-dig cyclization/Claisen rearrangement process. The entire sequence can be conducted in one pot without isolation of intermediates.

The formation of heterocyclic ring systems by intramolecular addition of an anionic heteroatom center to unactivated triple bonds is generally difficult to achieve due to the reversibility and unfavorable equilibria associated with such isomerizations.[1] Nevertheless, successful 5-exo-dig cyclization reactions involving appropriately substituted 4-alkyl-1-ols have been documented in the literature.[1,2] For example, Marvell and Titterington[2b] reported that 4,4-dimethyl-1-hepten-6-yn-3-ol (**1**) undergoes a base-catalyzed cyclization to afford 5-ethenyl-2-methylene-4,4-dimethyltetrahydrofuran (**2**) which, although easily isomerized to the thermodynamically more stable endocyclic dihydrofuran derivative (**3**), could be trapped in situ under high-temperature conditions through a subsequent [3,3]-sigmatropic rearrangement (Scheme 1) providing cycloheptenone **4** in 65 % yield.[3]



Scheme 1

Despite this encouraging early report, the synthetic potential of the consecutive 5-exo-dig cyclization–Claisen rearrangement process as a general method to complex cycloheptane-containing ring systems has not been explored. Herein, we report the initial results of our investigation probing the synthetic utility of this methodology as a route to the fused tricyclic 5-7-6 ring system which constitutes the core structure of several important terpenoid natural products.[4]

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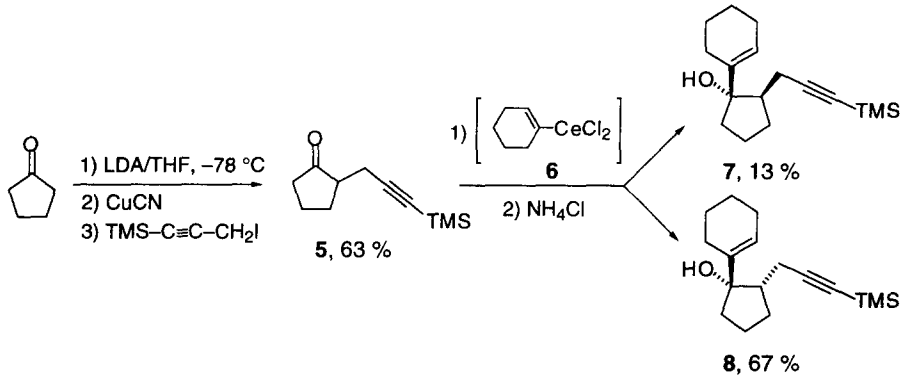
The starting materials required for our intial studies were prepared in a straightforward manner as depicted in Scheme 2. Thus, following the general procedure of Posner et al.,[5] cyclopentanone was treated with LDA and then with trimethyl 3-iodo-1-propynylsilane in the presence of catalytic amounts of cuprous cyanide to provide 2-(3-trimethylsilyl-2-propynyl)cyclopentanone (**5**) in 63 % yield. Treatment of this ketone with the vinylic organocerium compound **6**, prepared *in situ* from 1-bromocyclohexene via lithium-halogen exchange using *t*-BuLi followed by addition of $CeCl_3$,[6] afforded the acetylenic alcohols **7** and **8** as a 1:5 ratio of readily separable diastereomers in an overall yield of 80 %. The analogous TBDMS and phenyl derivatives were prepared similarly.[7]

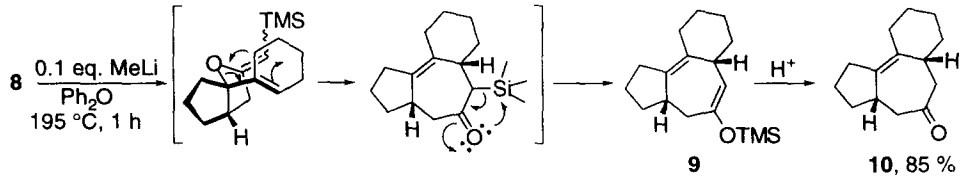


Scheme 2

Cycloisomerizations and the subsequent Claisen rearrangements were effected in a single reaction vessel simply by heating solutions of the acetylenic alcohols in anhydrous diphenyl ether under an atmosphere of argon and in the presence of catalytic amounts of MeLi. The reaction conditions and results from these experiments are summarized in Table 1. Thus, the tricyclic ketone **10** was produced in 85 % isolated yield when a solution of **8** in Ph_2O was heated at 195 °C in the presence of 10 mol-% of MeLi for just 1h, followed by acidic work-up, solvent removal and column chromatography (Scheme 3). Loss of the trimethysilyl group occurred during aqueous workup; indeed, the principal product of the cyclization/rearrangement sequence prior to hydrolysis is the silyl enol ether **9** which can be isolated provided that the reaction is worked up under strictly non-acidic conditions. This interesting result is consistent with intramolecular migration of silicon from the α position to the carbonyl oxygen via a mechanism that is similar to the Peterson fragmentation reaction involving α-hydroxy silanes.[8]

The corresponding TBDMS derivative behaved analogously, affording a hydrolytically stable silyl enol ether in 78 % isolated yield (Table 1, entry 2), and the corresponding phenyl analogue provided the expected tricyclic α-Ph substituted ketone directly as a mixture of diastereomers (Table 1, entry 3). The formation of silyl enol ethers in these reactions is particularly

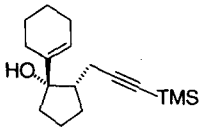
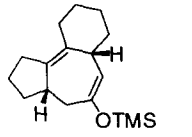
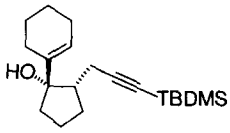
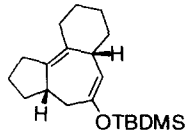
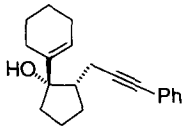
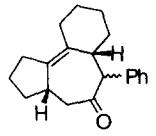
significant as it provides opportunities for further regioselective functionalization of the polycycles through standard enolate chemistry involving silyl enol ethers.[9]



Scheme 3

The exclusive formation of products having a cis relationship between the two bridgehead hydrogens was confirmed by obtaining a single-crystal X-ray structure of the tosylhydrazone derivative prepared from **10** (Figure 1).[10] It is of interest to note that the observed stereochemistry corresponds to that found in several structurally related natural products, including the tumor-promoting phorbol and its derivatives.[11]

Table 1. One-pot 5-exo-dig Cyclization/Claisen Rearrangement Sequence as a Route to Tricyclic 5-7-6 Ring Systems.

Entry	Substrate	Conditions[a] (time, temp)	Product	Yield
1		1 h, 195 °C		85 %[b]
2		3 h, 195 °C		78 %
3		3 h, 195 °C		50 %[c]

[a] All reactions were conducted in Ph_2O as the solvent and in the presence of 10–15 mol-% of MeLi.
[b] Yield reflects that of the hydrolysis product, **10**. [c]Formed as a 2:3 ratio of diastereomers.

Experiments aimed at the preparation of more functionally diverse polycycles through the consecutive cyclization/Claisen rearrangement strategy are currently ongoing, and we plan to apply

this methodology to the construction of the complete 5-7-6-3 tetracyclic core structure of phorbol. The results from these investigations will be communicated in due course.

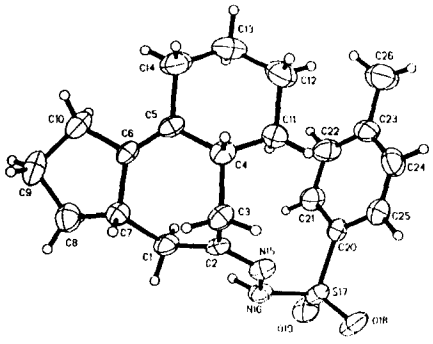


Figure 1. Single-crystal X-ray structure of the tosylhydrazone derivative of **10**.

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References and Notes

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10. Crystallographic data for the tosylhydrazone derivative of **10**: a=8.452(1) Å, b=10.841(1) Å, c=11.468(2) Å, α=88.93(1)°, β=74.83(1)°, γ=77.60(1)°, V=989.7(2)Å^3, space group=P1bar, d(calcd)=1.250 g cm^{-3}, linear absorption factor = 1.582 mm^{-1}, R-index=5.10%. Further details are provided as supplementary material.
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