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The [4 + 3]-Cycloaddition/ Quasi-Favorskii Process. Synthesis of the Carbocyclic Core of Tricycloclavulone

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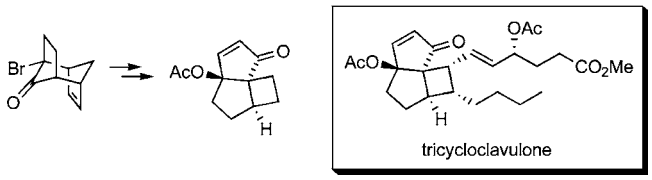
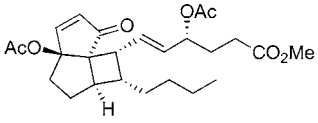
ABSTRACT

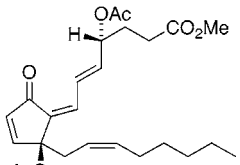


The [4 + 3]-cycloadduct derived from the reaction of 2,5-dibromocyclopentanone with cyclopentadiene was converted via a quasi-Favorskii rearrangement and ring-opening, ring-closing metathesis sequence to the carbocyclic core of the prostanoid tricycloclavulone.

Recently, Iguchi and co-workers reported the isolation of tricycloclavulone (**1**) from the Okinawan soft coral *Clavularia viridis*.[1] Soon afterward, they reported the enantioselective total synthesis of this compound.[2] While no biological activity has been reported for **1**, it is a structurally intriguing compound, related to and possibly derived from clavulone III (**2**), one of a number of marine prostanoids with diverse and important bioactivity.[3]



Tricycloclavulone, **1**



Clavulone III, **2**

Our work in the area of [4 + 3]-cycloaddition chemistry[4] has of late centered on reactions of halogenated cyclopentenyl cations with dienes and subsequent quasi-Favorskii rearrangement of the cycloadducts.[5] This process results in the generation of cyclobutane rings, though other ring sizes are available, depending on the size of the cyclic cation used in the cycloaddition process.[6] Our work to date has led to a formal total synthesis of the antitumor agent spatol and the total synthesis of sterpurene.[7]

The cyclobutane ring in **1** made this compound attractive to us as a target. As a prelude to total synthesis, we set out to prepare the carbocyclic core of the compound in order to test the viability of our design as well as specific reactions to be used in a total synthesis effort.

We thus targeted **8**, a retrosynthesis of which is shown in Scheme 1. The carbocycle **8** would be obtained from **7**,

(1) Iwashima, M.; Terada, I.; Okamoto, K.; Iguchi, K. *J. Org. Chem.* **2002**, *67*, 2977.

(2) (a) Ito, H.; Hasegawa, M.; Takenaka, Y.; Kobayashi, T.; Iguchi, K. *J. Am. Chem. Soc.* **2004**, *126*, 4520. (b) Ito, H.; Kobayashi, T.; Hasegawa, M.; Iguchi, K. *Tetrahedron Lett.* **2003**, *44*, 1259.

(3) For examples and leading references, see: (a) Rowley, A. F.; Vogan, C. L.; Taylor, G. W.; Clare, A. S. *J. Exp. Biol.* **2005**, *208*, 3. (b) Tanaka, H.; Hasegawa, T.; Iwashima, M.; Iguchi, K.; Takahashi, T. *Org. Lett.* **2004**, *6*, 1103. (c) Shen, Y,-C.; Cheng, Y.-B.; Lin, Y.-C.; Guh, J.-H.; Teng, C.-M.; Ko, C.-L. *J. Nat. Prod.* **2004**, *67*, 542.

(4) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595.

(5) (a) Harmata, M.; Shao, L. *Synthesis* **1999**, 1534. (b) Harmata, M.; Shao, L.; Kürti, L.; Abeywardane, A. *Tetrahedron Lett.* **1999**, *40*, 1075.

(6) Harmata, M.; Bohnert, G.; Kürti, L.; Barnes, C. L. *Tetrahedron Lett.* **2002**, *43*, 2347.

(7) (a) Harmata, M.; Bohnert, G. J. *Org. Lett.* **2003**, *5*, 59. (b) Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2001**, *3*, 2533. (c) Harmata, M.; Rashatasakhon, P. *Tetrahedron Lett.* **2001**, *42*, 5593.

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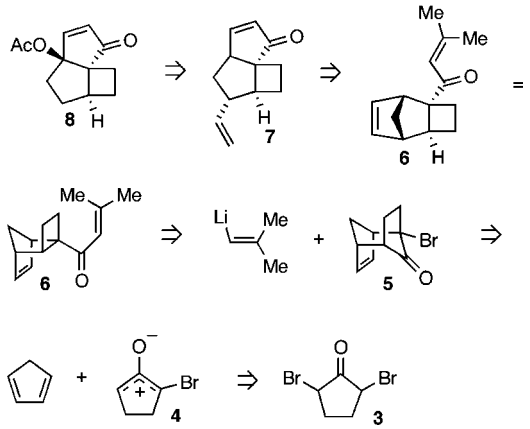
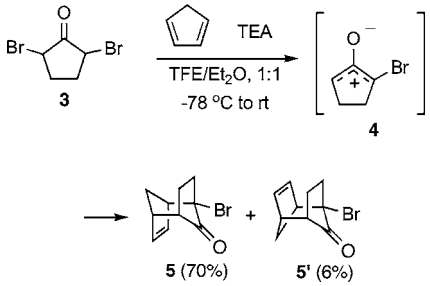
Scheme 1. Retrosynthesis of **8**



which would be formed from a ring-opening, ring-closing metathesis of **6**. This compound would be prepared from **5** via an addition of an organometallic reagent to the ketone functionality, followed by a quasi-Favorskii rearrangement. Compound **5** is a [4 + 3]-cycloadduct, derived from the reaction of **4** with cyclopentadiene. This dienophile can be easily generated from 2,5-dibromocyclopentanone (**3**).

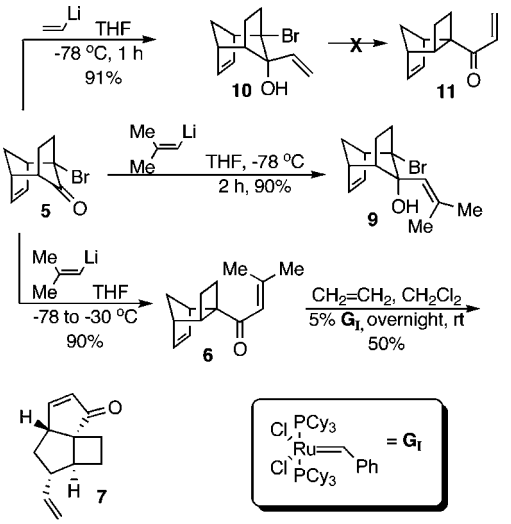
The synthesis of **5** is extremely simple. The reaction of 2,5-dibromocyclopentanone (**3**) with cyclopentadiene (10 equiv) takes place in a 1:1 mixture of trifluoroethanol and ether in the presence of 3 equiv of triethylamine at −78 °C. Warming to room temperature over 2 h gives cycloadduct **5** and the corresponding *exo*-isomer **5′** in a ratio of 11.7:1 in 76% yield (Scheme 2).[8,9]

Scheme 2. [4 + 3]-Cycloaddition of **3**



With **5** in hand, completion of the quasi-Favorskii reaction was relatively straightforward, though not as simple as we would have liked. Thus, the reaction of **5** with isobutenyllithium proceeded smoothly to give the carbonyl addition product **9** in excellent yield when the reaction was conducted and quenched at low temperature. When the reaction mixture was allowed to warm from −78 to −30 °C prior to workup, the ketone **6** was isolated in 90% yield (Scheme 3). We would have preferred to react **5** with vinyllithium. This addition reaction did in fact take place to deliver **10** in 91% yield. However, all of our attempts to date to effect the quasi-Favorskii rearrangement on the initial adduct or **10** have resulted in complex reaction mixtures. We thus chose to proceed toward our goal with **6**.

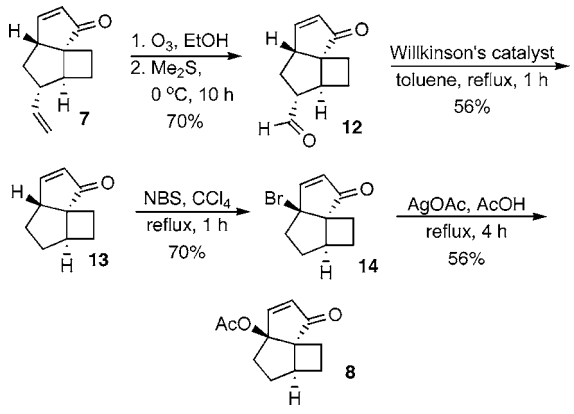
Scheme 3. Quasi-Favorskii Rearrangement and Ring-Opening, Ring-Closing Metathesis



Many attempts at a ring-closing metathesis reaction with **6** led to the result shown in Scheme 3. The reaction with the first generation Grubbs catalyst (**G**$_{\mathbf{I}}$) with **6** in the presence of ethylene afforded the tricyclic ketone **7** in 50% yield.

To finish the synthesis of **8**, we needed to remove the vinyl group from **7** and perform an allylic oxidation (Scheme 4).

Scheme 4. Completion of the Synthesis of **8**



Ozonolysis of **7** gave aldehyde **12** in 70% yield. Decarbonylation was effected with Wilkinson's catalyst in toluene

(8) We have previously reported that the formation of **5** takes place in 95% yield. However, this result does not appear to be consistently reproducible, especially on a multigram scale. See: Harmata, M.; Kirchhoefer, P. *Synlett* **2003**, 497.

(9) We routinely made no attempt to isolate the *exo*-isomer of the cycloadduct, which appeared to be sensitive to both chromatography and storage.

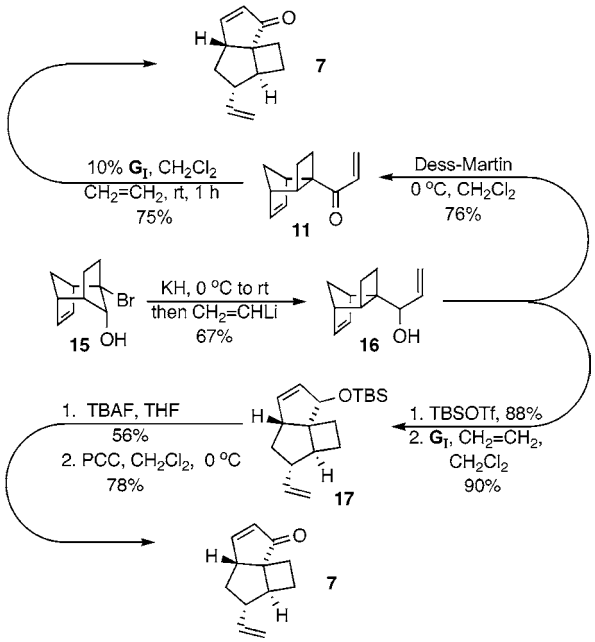
at reflux to produce ketone **13** in 56% yield.[10] Finally, allylic bromination and solvolytic displacement of the bromide afforded **8** in 39% yield over two steps.[11]

We did not try to optimize the individual steps of this synthesis to any great extent, deferring that to our anticipated total synthesis of tricycloclavulone. However, we were concerned about the ring-closing metathesis reaction and our inability to raise the yield above 50% and the fate of the remaining material (mass balance). The literature suggests that formation of a bicyclo[3.3.0] ring system such as that found in **7** via metathesis should not be difficult.[12] We surmised that the problem was the trisubstituted alkene in **6** and devised a route that avoids the formation of this compound.

The alcohol **15** is available from **5** via sodium borohydride reduction.[8] Treatment of **15** with 2 equiv of KH in THF at 0 °C and warming to room temperature, followed immediately by reaction with vinyllithium, afforded the alcohol **16** in 67% yield. This compound appeared to be a single diastereomer according to proton and carbon NMR, but no attempt was made to determine the relative stereochemistry at the hydroxy-bearing carbon. Oxidation of **16** with the Dess−Martin reagent[13] afforded the ketone **11** in 76% yield. Ring-closing metathesis proceeded to afford **7** directly in 75% yield (Scheme 5). Alternatively, protection of **16** as a TBS ether followed by reaction with the first generation Grubbs catalyst ($\mathbf{G_I}$) afforded **17** in 79% overall yield. Desilylation with TBAF and PCC oxidation led uneventfully to **7** (Scheme 5).

In summary, we have reported a short synthesis of the carbocyclic core of the prostanoid tricycloclavulone (**1**). The approach uses a [4 + 3]-cycloaddition and subsequent quasi-Favorskii rearrangement as key steps. We plan on expanding on this methodology in conjunction with other chemistry to pursue an enantioselective synthesis of **1**. Progress will be reported in due course.

Scheme 5. Alternative Routes to **7**



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Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR and other characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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