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Efficient and General Approach to Eremophilanes Using Siloxyalkyne−Alkene Metathesis

D. Srinivasa Reddy and Sergey A. Kozmin*

University of Chicago, Department of Chemistry, 5735 South Ellis Avenue, Chicago, Illinois 60637

skozmin@uchicago.edu

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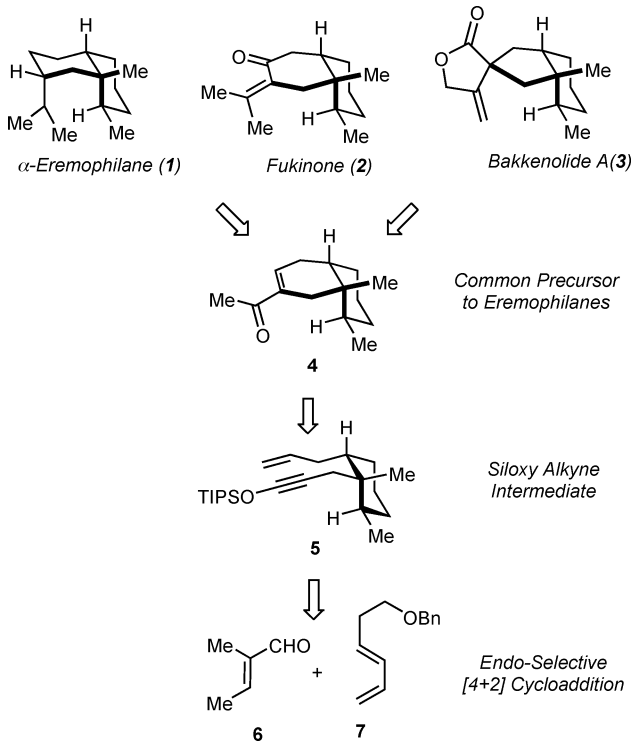
Abstract: An efficient skeletal reorganization of a terminal alkene armed with an appropriate siloxy alkyne fragment is a pivotal step in our novel and general strategy for the construction of a bicyclic core of eremophilanes with complete diastereocontrol and high synthetic efficiency. Our approach features three significant strategic elements. First, the enyne metathesis precursor is assembled via a highly endo-selective Diels−Alder reaction. Second, installation of the siloxy group at the alkyne terminus enables the regioselective assembly of the ensuing enone fragment via intramolecular enyne cyclization. Third, the common enone precursor offers the necessary flexibility of accessing several natural products of the eremophilane family.

The enyne metathesis is characterized uniquely by the formation of two new carbon−carbon bonds as a consequence of a metal-catalyzed skeletal reorganization of the appropriate enyne precursor.[1] This transformation represents a valuable and versatile method for the synthesis of cyclic and acyclic dienes.[2] In contrast to the parent olefin metathesis,[3] however, there are only a few successful applications of the enyne metathesis to the area of complex natural product synthesis.[4] In part, this disparity can be attributed to the difficulty of the subsequent regioselective functionalization of the diene products arising from simple, unfunctionalized enyne precursors. Recently, we described a highly efficient participation of siloxyalkynes in Ru-catalyzed intramolecular enyne metatheses with terminal alkenes.[5] This reaction provided a novel access to a range of cyclic silyl dienol ethers and was amenable to the construction of highly functionalized enones. Herein, we extend the scope of this method and demonstrate the utility of the siloxyalkyne−alkene metathesis in the arena of target-oriented synthesis. This communication describes an original and general strategy to several natural products, including α- and β-eremophilanes, and fukinone, which originated from a common synthetic precursor assembled via siloxyalkyne alkene metathesis.

SCHEME 1



Eremophilanes comprise a unique set of plant metabolites with more then 100 individual natural products.[6] Isolated primarily from the flowering plants of the Compositae family, this class of sesquiterpenes is characterized by the cis-fused [4.4.0] decalin architecture. The diverse biological properties of eremophilanes, combined with the unique structural and conformational challenges, have attracted considerable synthetic attention.[7] Our unique and general approach was designed to fully exploit the synthetic versatility of the enone moiety

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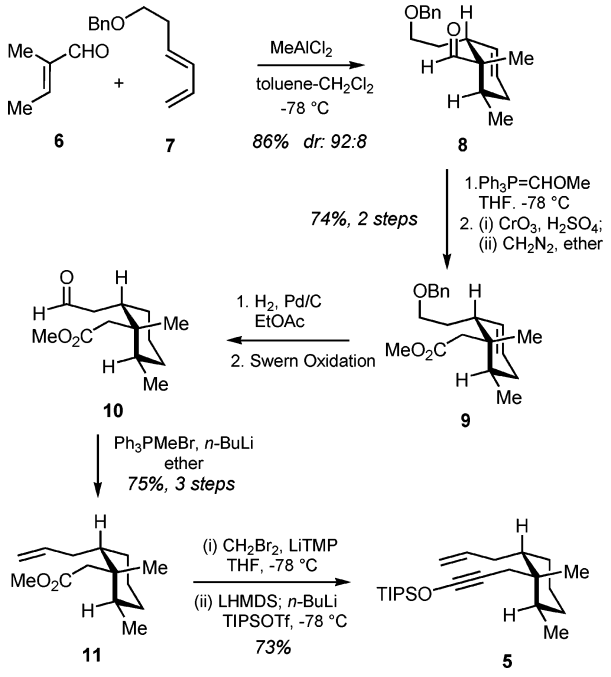
assembled via siloxyalkyne-alkene metathesis[5] for the subsequent elaboration into a range of structural motifs found in eremophilanes. To this end, we envisioned a bicyclic enone **4** (Scheme 1) to serve as a common intermediate for the assembly of several representative eremophilanes. Enone **4**, in turn, would derive from an intramolecular enyne metathesis of the appropriately functionalized siloxy alkyne **5**. Diastereoselective construction of **5** would entail an endo-selective Diels−Alder reaction of diene **7** with aldehyde **6**.

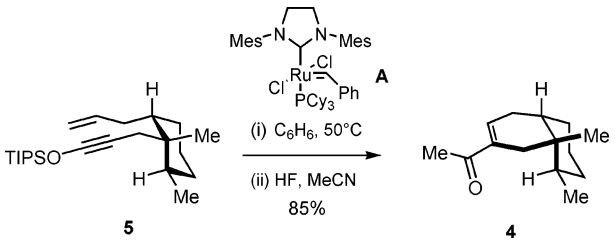
The synthesis began with a systematic evaluation of Lewis acid catalysis of the Diels−Alder reaction between diene **7** and dienophile **6**. As a result of this search, we found that this reaction can be successfully performed in the presence of $MeAlCl_2$ (Scheme 2). Gratifyingly, an excellent level of endo-selectivity was observed (dr 92:8, 86% yield). Indeed, this highly diastereoselective [4 + 2] cycloaddition provides a simple solution for fully stereocontrolled installation of the three stereogenic centers present in eremophilanes, setting the stage for efficient elaboration to the bicyclic scaffold. Conversion of aldehyde **8** to the one-carbon homologated ester **9** was efficiently accomplished via Wittig methoxymethylenation, followed by hydrolysis/oxidation of the resulting enol ether with CrO_3 and subjection of the resulting acid to ethereal diazomethane (74%, two steps). Alkene hydrogenation with concomitant removal of the benzyl ether, followed by Swern oxidation and Wittig methylenation, afforded ester **11**, setting the stage for the introduction of siloxyalkyne moiety. In the event, dibromomethyllithium addition to ester **11** and subjection of the resulting dibromomethyl ketone to LHMDS and *n*-BuLi followed by silylation of the ynolate anion furnished the requisite siloxy alkyne **5** in 73% yield.[8,9]

SCHEME 2



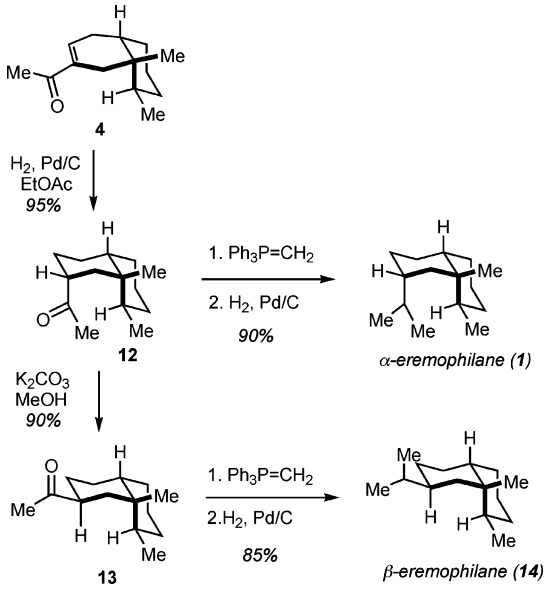
Siloxyalkyne alkene metathesis of enyne **5** represented a pivotal point in the synthesis, as the product of this transformation was envisioned to lead to several natural products. To our delight, subjection of siloxy alkyne **5** to Ru catalyst **A**[10] under our standard conditions [**A** (5 mol %), 50 °C, 30 min][5] resulted in facile and quantitative ring closure, which was evident from monitoring this process by ^1H NMR spectroscopy. Subsequent in situ exposure of the resulting siloxy diene to a solution of hydrogen fluoride in MeCN furnished bicyclic enone **4** in 85% yield after chromatographic purification (Scheme 3).

SCHEME 3



Our subsequent efforts centered on further elaboration of enone **4** to α- and *β*-eremophilanes (Scheme 4). To this end, convex-face hydrogenation of **4** furnished axially disposed ketone **12** (dr 80:20). Wittig methylenation and hydrogenation completed the assembly of α-eremophilane **1** (11 steps). Alternatively, base-promoted epimerization of ketone **12** furnished a thermodynamically favorable equatorial isomer **13** (dr > 95:5). Wittig methylenation of ketone **13** followed by hydrogenation afforded *β*-eremophilane **1** (12 steps). The 500 MHz ^1H NMR and 125 MHz ^{13}C NMR spectra of synthetic eremophilanes **1** and **14** were in excellent agreement with those reported in the literature.[11]

SCHEME 4



Having secured access to α- and *β*-eremophilanes, we focused our next effort on the synthesis of fukinone,

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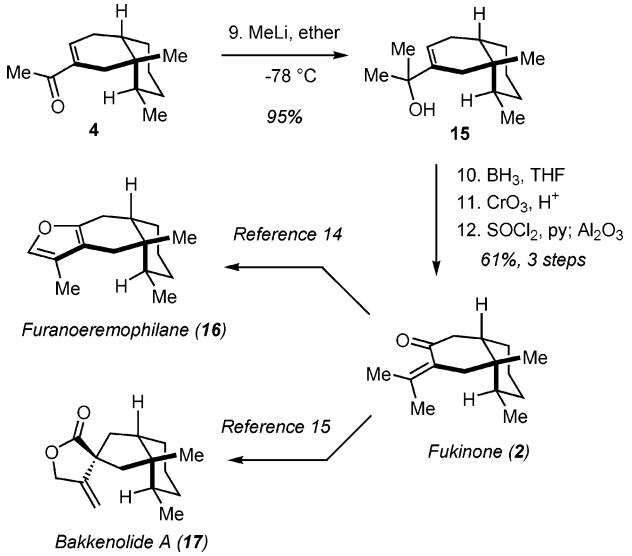
another notable member of this class of natural products.[12] Importantly, our strategy would represent a conceptually novel entry into this target and would rival the efficiency of the previously reported approaches.[13] Fukinone was envisioned to arise from the PCC-mediated transposition of enone **4** following the initial 1,2-addition (Scheme 5). Indeed, treatment of enone **4** with methyllithium (ether, −78 °C) furnished tertiary alcohol **15** in 95% yield. However, multiple attempts to induce the desired transposition of **15** using PCC proceeded without success. To circumvent this issue, we developed a three-step protocol carried out without any purification of the intermediates. This sequence entailed hydroboration, Jones oxidation and dehydration of the resulting β-hydroxy ketone to afford fukinone **2**. Comparison of the 500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR data of **2** revealed that this material was identical to the previously reported natural product.[12,13] Importantly, fukinone represents a well-established precursor to several additional members of the eremophilane family. For instance, exposure of fukinone to Ac_2O in H_2SO_4 affords furanoeremophilane (**16**) in a single operation.[14] In addition, base-promoted fragmentation followed by lactonization provides a simple two-step route to bakkenolide A (**17**).[15]

SCHEME 5



In conclusion, we have developed an efficient and highly stereocontrolled strategy to the eremophilane family of natural products. Our approach features three significant strategic elements. First, the enyne metathesis precursor is assembled via a highly endo-selective Diels−Alder reaction. Second, installation of the siloxy alkyne moiety enables a highly efficient and regioselective assembly of the ensuing enone fragment via intramolecular Ru-catalyzed enyne cyclization. Third, the resulting enone segment offers the necessary synthetic flexibility of accessing several natural products of the eremophilane family with high efficiency and diastereoselectivity. Most importantly, this work provides a clear demonstration of the general synthetic utility of the siloxyalkyne−alkene metathesis in the area of target-oriented synthesis.

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Supporting Information Available: Selected experimental procedures and spectroscopic characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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