



Cyclopentannulation : novel ring formation mediated by allylsilane functionality
by Kendal Troy Ryter

A thesis submitted in partial fulfillment Of the requirements for the degree of Doctor of Philosophy in
Chemistry

Montana State University

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Abstract:

Synthetic methods designed for the production of natural products composed of or containing five-membered rings selectively and efficiently are lacking in that few are general or applicable to practical synthetic strategies. 2-(Trimethylsilylmethyl)prop-2-enyllithium has proven to be a very effective reagent for the introduction of 2-(trimethylsilylmethyl)prop-2-en functionality to a wide variety of electrophilic organic substrates. Copper and chlorotrimethylsilane mediated conjugate addition of 2-(Trimethylsilylmethyl)prop-2-enyllithium to enones followed by efficient oxidative ring closure utilizing a new reagent, dichloro(2,2,2-trifluoroethoxy)oxovanadium (V) provided cyclopentenannulated products. The two step ring formation process proved to be general and selective for various enones bearing functionality and substitution.. The new oxovanadium ester was also shown much more selective in the synthesis of symmetrical and unsymmetrical 1,4-diketones.. A new synthetic strategy directed toward the total synthesis of the natural products pentalene, pentalenic acid and deoxypentalenic acid based on allyl bis(silane) functionality was investigated.

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APPROVAL

Of a thesis submitted by

Kendal Troy Ryter

The thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style and consistency, and is ready for submission to the College of Graduate studies.

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Approved for the Major Department

May 4, 1998
Date

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5/6/98
Date

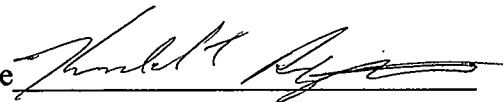
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Donald H. RyanMay 4, 1998

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ABSTRACT

Synthetic methods designed for the production of natural products composed of or containing five-membered rings selectively and efficiently are lacking in that few are general or applicable to practical synthetic strategies. 2-(Trimethylsilylmethyl)prop-2-enyllithium has proven to be a very effective reagent for the introduction of 2-(trimethylsilylmethyl)prop-2-en functionality to a wide variety of electrophilic organic substrates. Copper and chlorotrimethylsilane mediated conjugate addition of 2-(Trimethylsilylmethyl)prop-2-enyllithium to enones followed by efficient oxidative ring closure utilizing a new reagent, dichloro(2,2,2-trifluoroethoxy)oxovanadium (V) provided cyclopentenannulated products. The two step ring formation process proved to be general and selective for various enones bearing functionality and substitution. The new oxovanadium ester was also shown much more selective in the synthesis of symmetrical and unsymmetrical 1,4-diketones. A new synthetic strategy directed toward the total synthesis of the natural products pentalene, pentalenic acid and deoxypentalenic acid based on allyl bis(silane) functionality was investigated.

INTRODUCTION

Interest in synthetic methodology applicable to the preparation of cyclopentanoid natural products has been intense since the discovery of monocyclic structures comprising the prostaglandins¹ and polyquinane natural products. Polyquinane skeleta have been found in plant, marine and microbial sources and are composed of rigid and compact fused five-membered ring systems having four basic structures (Figure 1).²

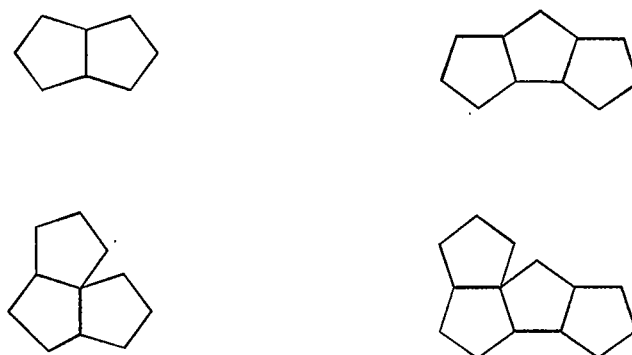
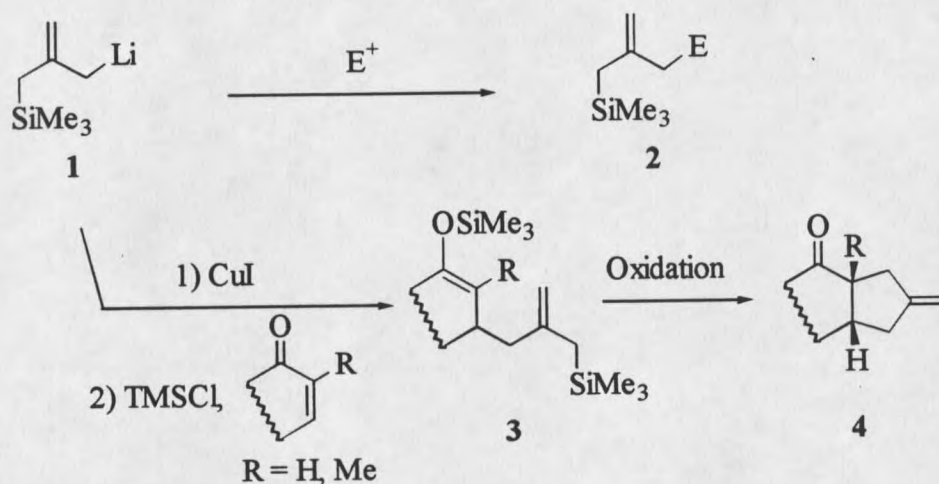


Figure 1. Characteristic carbocyclic skeleta of polyquinane natural products.

Many polyquinanes, and/or their metabolites possess potent and diverse biological activity.³ The combination of structurally alluring molecules and the potential for drug discovery has fueled interest in polyquinane natural product synthesis and the subsequent development of synthetic strategies for cyclopentannulation. The difficult task of selective formation of functionalized cyclopentane rings is evident from the number of

general procedures available for this transformation. Recent work in this area includes improved versions of the Nazarov cyclization,^{4,5,6} the Pauson-Khand reaction⁷ and formal [4 + 1] and [3 + 2] cycloadditions.¹⁰⁻¹¹ In addition, the use of organosilicon reagents and synthons in the synthesis of natural products has received considerable attention.^{14b}

Presented herein is an outline of work completed detailing a new, highly efficient and selective synthetic method whereupon allylsilane functionality may be introduced to various electrophilic substrates through the use of the bifunctional reagent [2-(trimethylsilylmethyl)prop-2-enyl]lithium, **1** (Scheme 1). This new reagent has also been



Scheme 1

shown to undergo transmetalation with copper salts allowing for silylative 1,4-addition to enones to give silyl enol ethers in excellent yield and a high state of purity. Oxidative

cyclization of the silyl enol ether is accomplished through the use of a novel oxovanadium reagent. The overall process has proven to be a highly efficient and useful method of effecting methylenecyclopentannulation.

The knowledge gained in the process of these investigations and the accomplishments of co-workers in the area of allyl bis(silane) chemistry¹⁹ is currently being applied to the synthesis of (\pm)-Pentalenic acid, 5.

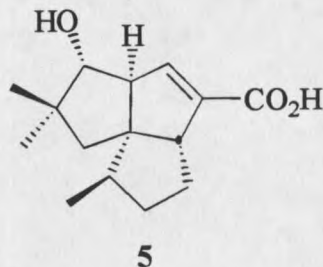


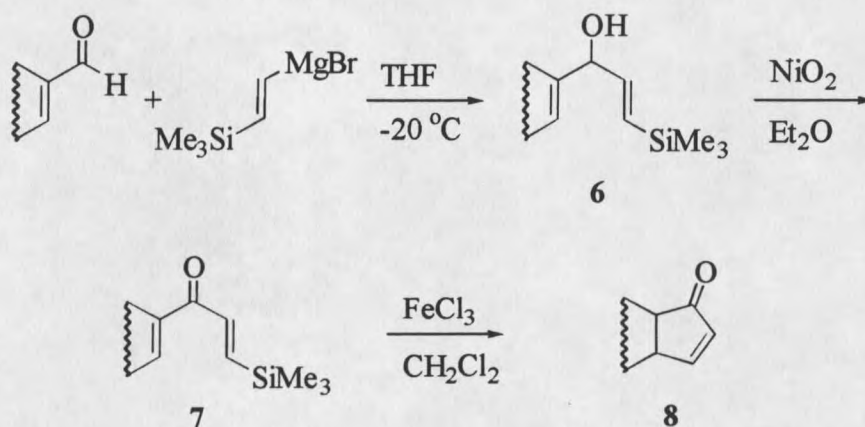
Figure 2. (\pm)-Pentalenic acid.

BACKGROUND

Cyclopentanulation

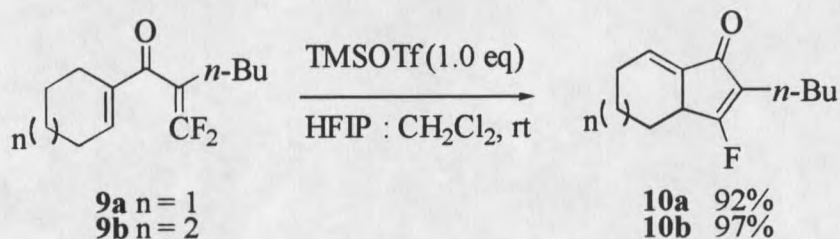
Cyclopentanoid and polyquinane natural products have stimulated the implementation of new methods for the synthesis of five-membered rings. The design and development of flexible routes using simple reagents under mild conditions is of central importance. Described herein are procedures that have been shown to be selective and versatile for the formation of cyclopentanoid structures.

The classical Nazarov cyclization⁴ has been extensively modified to incorporate synthetic handles or functional groups that facilitate the reaction and control selectivity. An improved version of the Nazarov cyclization developed by Denmark and Jones relies on the ability of silicon to control the regio- and stereochemical outcome of carbonium ion processes (Scheme 2).⁵ The three step annulation has proven to be quite general for a number of substrates giving enones, **8**, in moderate to synthetically useful yields. The iron (III) chloride mediated ring closure is dominated by the ability of the vinyl silane functionality to direct the introduction of the new double bond at the least substituted position.



Scheme 2

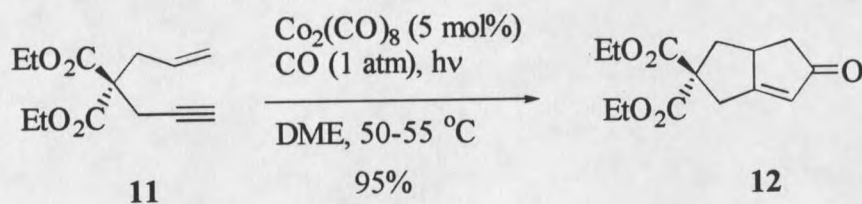
A more recent advancement in the Nazarov cyclization strategy has been developed by Ichikawa and co-workers in which the β -silane functionality has been replaced with fluorine (Scheme 3).⁶ Treatment of dienones, such as **9a** and **9b**, with trimethylsilyltriflate in a mixture of hexafluoroisopropanol (HFIP) and methylene chloride provides cyclized products in excellent yield. The β -cation destabilizing effect of fluorine atoms and the stability of the fluoride anion as a leaving group allow for the efficient formation of cyclopentenones, **10a, b**, with a high degree of selectivity.



Scheme 3

Products of the reaction possess one more double bond than previously reported Nazarov cyclization products. Further synthetic elaboration of the β -fluoro enones, **10**, can be accomplished easily by addition-elimination reactions of carbon or hetero-atom nucleophiles with the fluorine substituent.

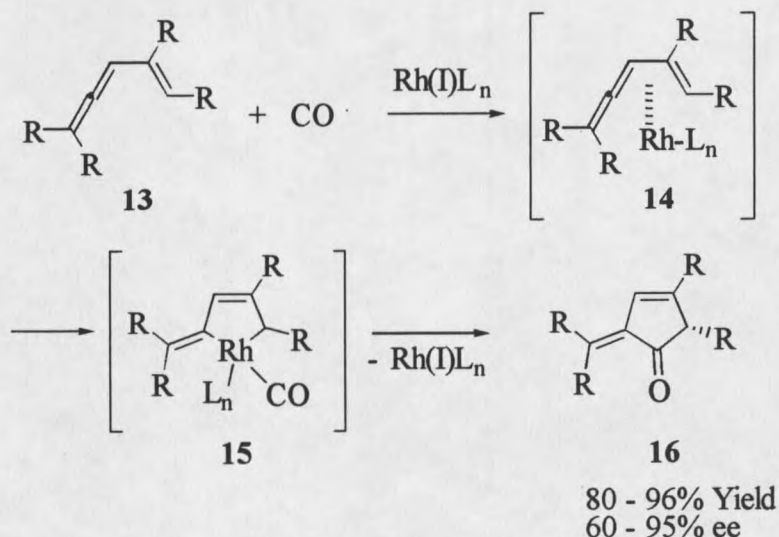
A new and highly convergent cyclopentenone synthesis has recently been developed in these laboratories, in an improved and truly catalytic version of the Pauson-Khand reaction (Scheme 4).⁷ The formal [2 + 2 + 1] cycloaddition of an alkene, alkyne and carbon monoxide has been a popular means of effecting selective organic transformations. The rate-limiting factor of the Pauson-Khand reaction has been thought to be the dissociation of carbon monoxide from the metal. The findings of Livinghouse and Pagenkopf suggest that decarbonylation of the cobalt organometallic is promoted with high-intensity visible light. Prior to this result nearly all Pauson-Khand reactions required stoichiometric amounts of $\text{Co}_2(\text{CO})_8$ in order to effect efficient transformations under mild conditions. This was a severe limitation for practical large-scale synthesis.



Scheme 4

Transition metal-catalyzed carbonylation reactions have resulted in useful methods for the formation of five-membered rings. The rhodium(I)-catalyzed [4 + 1]

cycloaddition of vinyl allenes **13** with carbon monoxide has recently been demonstrated as an effective means of forming functionalized cyclopentenones **16**.⁸ The inclusion of chiral diphosphine ligands on rhodium(I) catalyst also gives rise to very good enantioselectivity through the facially selective complexation of the ligated metal (Scheme 5).⁹



Scheme 5

Of continuing interest in cyclopentane ring formation is the development of a general procedure for the conversion of conjugated dienes, **17**, to cyclopentenones by means of a formal [4 + 1] cycloaddition. Similarities of this transformation to the Diels-Alder [4 + 2] reactions for cyclohexane ring formation would suggest that a high degree of regio- and stereoselectivity might be achieved.

