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Formation of Chiral Quaternary Carbon Stereocenters Using Silylene Transfer Reactions: Enantioselective Synthesis of (+)-5-*epi*-Acetomycin

Stacie A. Calad and K. A. Woerpel*

Department of Chemistry, University of California, Irvine, California 92627-2025

kwoerpel@uci.edu

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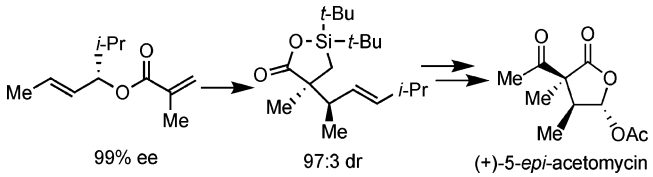
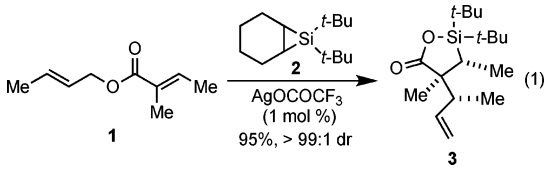
ABSTRACT



Chiral quaternary carbon stereocenters can be established with high diastereoselectivity by a silylene transfer/Ireland–Claisen rearrangement. The utility of this method was demonstrated by application to a synthesis of (+)-5-*epi*-acetomycin.

The construction of chiral molecules with all-carbon quaternary stereocenters remains a significant challenge in organic synthesis.[1] Steric repulsions develop upon bringing four alkyl groups together, which limit the number of transformations that can be used to form these sterically congested products. Controlling the absolute stereochemistry of asymmetric quaternary carbon centers presents an even further challenge.

We recently reported a method for the diastereoselective construction of quaternary carbon stereocenters (eq 1).[2] This method involves silylene transfer to an α,β-unsaturated ester, providing a silyl ketene acetal with complete regio- and stereoselectivity. When transfer to an α,β-unsaturated allylic ester occurs, the resulting silyl ketene acetal can undergo a stereospecific Ireland−Claisen rearrangement[3,4] with high facial selectivity[5] to provide silalactone products possessing a quaternary carbon stereocenter (eq 1).



In this paper, we describe silylene transfer/Ireland−Claisen reactions of enantiomerically pure esters to control the absolute configuration of compounds with quaternary carbon stereocenters. The utility of this methodology was demonstrated by the synthesis of (+)-5-*epi*-acetomycin.[6]

The formation of new stereocenters in the silylene transfer/Ireland−Claisen rearrangement can be controlled by a stereocenter at the allylic position of an α,β-unsaturated allylic ester.[7,8] Metal-catalyzed silylene transfer to ester **4**

(1) For recent reviews, see: (a) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5363−5367. (c) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369−396.

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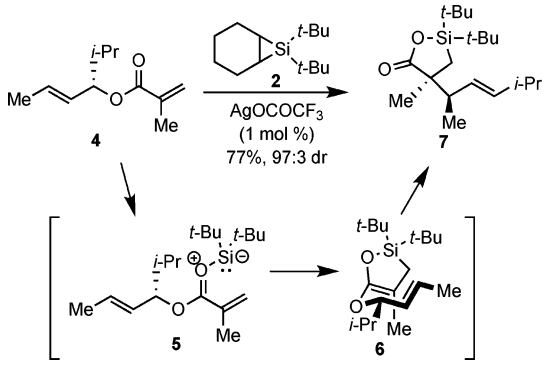
likely occurred by formation of a silacarbonyl ylide (**5**), which then underwent a 6π electrocyclization to provide oxasilacyclopentene **6** (Scheme 1). This intermediate contains

Scheme 1. Controlling Quaternary Carbon Stereochemistry

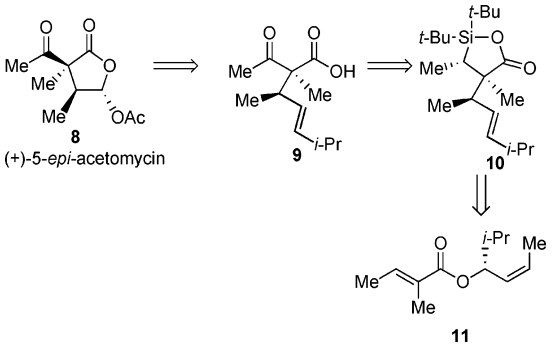


a tetrasubstituted silyl ketene acetal moiety embedded within the ring. At ambient temperature, oxasilacyclopentene **6** underwent an Ireland−Claisen rearrangement to afford silalactone **7** with high diastereoselectivity and the formation of an all-carbon quaternary center. The stereochemistry of the product can be explained by a chairlike transition state in which the isopropyl substituent adopts an equatorial position.[9]

We chose to highlight the synthetic utility of the silylene transfer/Ireland−Claisen rearrangement in the enantioselective synthesis of (+)-5-*epi*-acetomycin (**8**). This compound is an anologue of (−)-acetomycin because the two compounds differ only in the configuration at the acetal stereocenter. Acetomycin is an antibiotic that was isolated from *Streptomyces ramulosus* by Prelog and co-workers in 1958.[10] The structure and the relative and absolute configurations were later determined by X-ray crystallography.[11,12] In addition to showing antibacterial properties, this compound has also demonstrated in vitro antitumor activity.[13−15] Several syntheses of acetomycin and its analogues have been undertaken.[6,15−22]

The key step in our initial synthetic plan involved a silylene transfer/Ireland−Claisen rearrangement with all of the stereochemistry of the target controlled by the allylic stereocenter (Scheme 2). Disconnection of (+)-5-*epi*-acetomycin

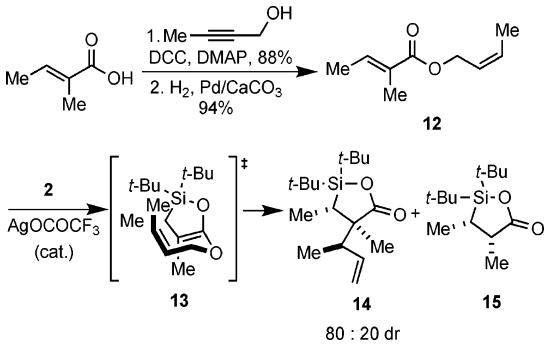
Scheme 2. Acetomycin Retrosynthesis



at the acetal center provides an aldehyde, which would be formed by ozonolysis of keto acid **9**. The acetyl group of keto acid **9** could arise by oxidation of silalactone **10**, which could be obtained from silylene transfer/Ireland−Claisen rearrangement of ester **11** through a chairlike transition state. Because the Ireland−Claisen rearrangement of *trans*-allylic ester **1** provided compound **3**, the *cis*-ester **11** should provide the opposite stereochemistry at the new allylic center in silalactone **10**.[8b]

The silylene transfer/Ireland−Claisen rearrangement of a cis-substituted α,β-unsaturated allylic ester was slow and occurred with low stereoselectivity. Treatment of ester **12**, formed in two steps from tiglic acid, under the silylene transfer conditions afforded an inseparable mixture of silalactones **14** and **15** (Scheme 3). Silalactone **15** resulted

Scheme 3. Lack of Reactivity and Diastereoselectivity



from hydrolysis of intermediate silyl ketene acetal **13** before the Ireland−Claisen rearrangement occurred. Upon prolonged standing at ambient temperature, the yield of desired

(8) For examples of chirality transfer from secondary allylic alcohols in the Claisen rearrangement, see: (a) Hill, R. K.; Edwards, A. G. *Tetrahedron Lett.* **1964**, *5*, 3239−3243. (b) Chan, K.-K.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497−3505. (c) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423−1452.

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(17) Echavarren, A. M.; de Mendoza, J.; Prados, P.; Zapata, A. *Tetrahedron Lett.* **1991**, *32*, 6421−6424.

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(19) Ziegler, F. E.; Kim, H. *Tetrahedron Lett.* **1993**, *34*, 7669−7672.

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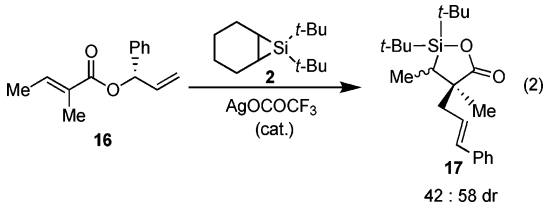
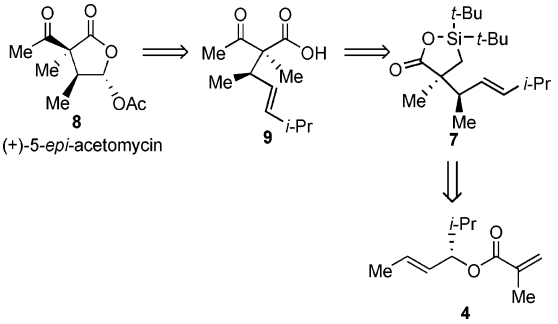
product **14** did not increase. The low reactivity observed for substrate **12** is likely the result of increased steric congestion and developing 1,3-diaxial interactions in the transition state for rearrangement.

An additional stereochemical problem emerged with the initial synthetic plan. Attempts to control the stereoselectivity of the 6π electrocyclic reaction failed. Treatment of ester **16** to the silylene transfer/Ireland−Claisen rearrangement conditions provided silalactone **17** with low diastereoselectivity (eq 2).



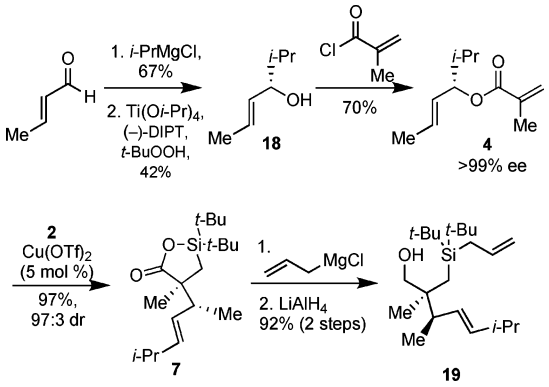
The synthetic plan was revised so that the acetyl moiety of keto acid **9** could result from the carbonyl group of silalactone **7** and the carboxylic acid moiety of acid **9** could be revealed by a carbon−silicon bond oxidation of silalactone **7** (Scheme 4).[23−25] Silalactone **7** could be obtained by silylene transfer to chiral ester **4**, as was demonstrated in Scheme 1.

Scheme 4. Redesigned Acetomycin Retrosynthesis



The initial stereocenter of ester **4** was established with complete enantioselectivity. Addition of isopropylmagnesium chloride to crotonaldehyde followed by kinetic resolution provided a single enantiomer of **18** (Scheme 5).[26−28] Esterification with methacryloyl chloride provided α,β-unsaturated allylic ester **4** in 70% yield and >99% ee.

Scheme 5. Chiral Induction and Chirality Transfer

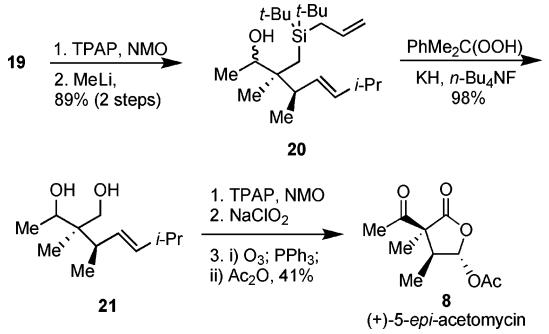


Silylene transfer to chiral ester **4** followed by an Ireland−Claisen rearrangement established two stereocenters, including the quaternary carbon center, with high diastereoselectivity (Scheme 5). Treatment of ester **4** with $Cu(OTf)_2$ and silacyclopropane **2** provided an oxasilacyclopentene, which underwent an Ireland−Claisen rearrangement in 97% yield with no apparent erosion of enantiomeric purity.[29] Copper salts proved to be optimal catalysts for this transformation because problems with product inhibition were seen upon scale-up of the silver-catalyzed reaction.

The conversion of silalactone **7** to alcohol **19** was achieved by nucleophilic additions to both the silicon atom and the carbonyl group. Phenylmagnesium bromide did not add to silalactone **7**, but addition of allylmagnesium chloride yielded a carboxylic acid (Scheme 5). Reduction of this carboxylic acid with $LiAlH_4$ afforded alcohol **19**.

Diol **21** was constructed in three high-yielding steps from alcohol **19**. Oxidation followed by addition of MeLi provided alcohol **20** (Scheme 6). Oxidation of the carbon−silicon bond

Scheme 6. Synthesis of (+)-5-*epi*-Acetomycin



of alcohol **20** with cumene hydroperoxide and potassium hydride in the presence of a fluoride source afforded diol **21** in 98% yield.[23−25]

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(29) An analysis of the chirality transfer is provided in the Supporting Information.

The synthesis of (+)-5-*epi*-acetomycin was completed in three steps from diol **21**. Stepwise oxidation of diol **21** to a 1,3-dicarbonyl compound, followed by further oxidation of the aldehyde group to the acid, provided an intermediate β-keto acid.[30] This intermediate was prone to decarboxylation at room temperature,[17] so it was handled quickly at cooler temperatures (0 to −78 °C). Immediate ozonolysis of the carbon−carbon double bond,[6,16] followed by in situ acetylation,[17] provided (+)-5-*epi*-acetomycin in 41% yield.

In conclusion, the silylene transfer/Ireland−Claisen rearrangement of chiral α,β-unsaturated allylic esters affords silalactone products containing chiral quaternary stereocenters. These reactions occur with chirality transfer and with high diastereoselectivity. Application of this methodology to the synthesis of (+)-5-*epi*-acetomycin has been accomplished in ten steps and 23% overall yield from the known chiral allylic alcohol **17**.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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