ORGANIC LETTERS

2012
Vol. 14, No. 21
5614–5617

# Cyclopropane Compatibility with Oxidative Carbocation Formation: Total Synthesis of Clavosolide A

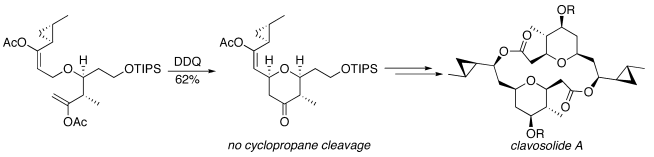
**GuangRong Peh and Paul E. Floreancig***

*Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

*florean@pitt.edu*

**Received October 4, 2012**

## ABSTRACT

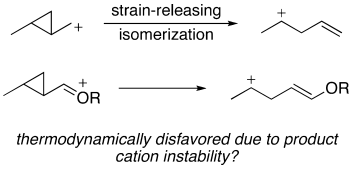



**Cyclopropane-substituted allylic ethers react with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to form oxocarbenium ions with no competitive ring cleavage. This reaction can be used for the preparation of cyclopropane-substituted tetrahydropyrans. The protocol was used as a key step in the total synthesis of the sponge-derived macrolide clavosolide A.**

The strain energy of approximately 27 kcal/mol in cyclopropanes provides a driving force for several ring-opening reactions that are not observed in less strained cycloalkanes.[1] Cyclopropane cleavage is commonly encountered when a reactive intermediate such as a carbenium ion is introduced on an adjacent atom.[2] These ring cleavage processes limit the reaction conditions that can be utilized in the presence of cyclopropanes and often mandate that the synthesis of cyclopropane-containing products employ cyclopropanation reactions at a late stage in the sequence.

Cationic cyclopropane-opening reactions can be suppressed by sufficiently stabilizing the reactive intermediate to counterbalance the energetic benefit of strain release.[3] This is illustrated in Scheme 1, whereby the cleavage of a cyclopropane with an adjacent oxocarbenium ion is postulated to be disfavored because the product contains a far less stabilized cation in comparison to the starting material. Indeed Taylor and co-workers have demonstrated[4] that cyclopropanes can be formed from intramolecular additions of electron-rich alkenes into cationic intermediates, a process that is the microscopic reverse of cation-induced cyclopropane opening.

**Scheme 1.** Energetics of Cyclopropyl Carbinyl Cation Ring Opening




*thermodynamically disfavored due to product cation instability?*

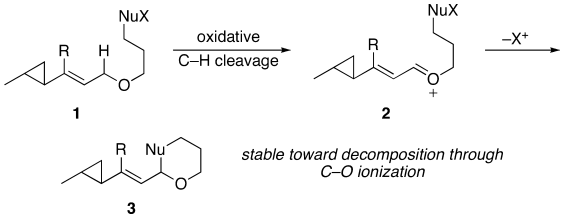
The stability of cyclopropane-substituted oxocarbenium ions creates opportunities for functionalization through nucleophilic addition reactions. The products of these additions, however, would still be susceptible to cyclopropane opening through ionization of the product alkoxy group if classical Lewis acid mediated protocols are employed for oxocarbenium ion generation. This suggests that electrophile formation under nonacidic conditions would provide strategic benefits for the functionalization of cyclopropane-containing molecules. Oxidative carbocation

(1) de Meijere, A. *Angew. Chem., Int. Ed.* **1979**, *18*, 809.
(2) (a) Hanack, M.; Schneider, H.-J. *Angew. Chem., Int. Ed.* **1967**, *6*, 666. (b) Olah, G. A.; Jeull, C. L.; Kelly, D. P.; Porter, R. D. *J. Am. Chem. Soc.* **1972**, *94*, 146. (c) Saunders, M.; Laidig, K. E.; Wiberg, K. B.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1988**, *110*, 7652.
(3) Olah, G. A.; Reddy, V. P.; Prakash, G. K. S. *Chem. Rev.* **1992**, *92*, 69.
(4) (a) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yuan, H. *J. Am. Chem. Soc.* **2001**, *123*, 2964. (b) Risatti, C. A.; Taylor, R. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6671.

10.1021/ol302744t 
**Published on Web 10/24/2012**

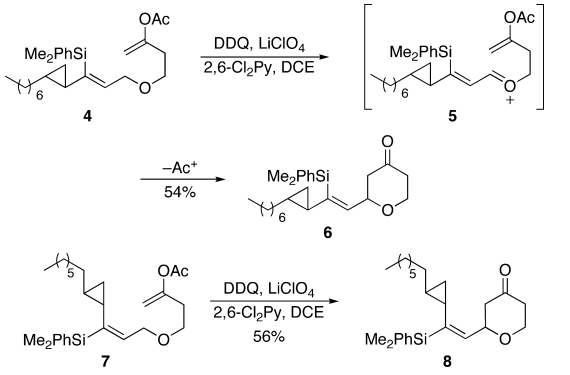
formation provides an alternative to Lewis acid mediated ionization and has been used in the synthesis of complex structures that contain sensitive groups such as acetals and epoxides.[5] We have been engaged in developing oxidative carbon−hydrogen bond cleavage reactions to generate stabilized carbocations under nonacidic conditions.[6] These processes proceed through reactions of allylic, benzylic, and vinylic ethers, amides, and sulfides with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). In this manuscript we report that cyclopropane-substituted α,β-unsaturated oxocarbenium ions can be prepared through allylic ether oxidation and that the resulting intermediates can be trapped to form tetrahydropyrans with no evidence of ring opening, as shown in the generic conversion of **1** to **2** to **3** in Scheme 2. This process is used as the key step in a convergent synthesis of the macrodiolide clavosolide A.

**Scheme 2.** Oxidative Synthesis of Cyclopropane-Containing Tetrahydropyrans




The initial demonstrations of this transformation are shown in Scheme 3. Vinylsilanes were selected as substrates because they can be converted stereoselectively to secondary alcohols through a short sequence[6d] and they are readily accessed with high geometric control from alkynes through hydrosilylation reactions[7] with ruthenium or platinum catalysts. Enol acetates were used as the nucleophiles because they are oxidatively stable enolate surrogates. Exposing *Z*-vinylsilane **4** to DDQ at 45 °C provided oxocarbenium ion **5** en route to the formation of tetrahydropyrone **6**. While many DDQ-mediated oxocarbenium ion formations proceed at ambient temperature or below, the vinylsilanes generally require higher temperatures because steric bulk interferes with their association with the oxidant.[6d] The oxidation of (*E*)-isomer **7** proceeds with similar efficiency to form **8**. These reactions provided inseparable diastereomeric mixtures of products, showing that the cyclopropyl group does not promote remote stereoinduction. While the yields of these reactions were not quantitative, the remainder of the mass can be attributed to nonspecific decomposition pathways rather than cyclopropane ring opening. These results provided a suitable precedent for the application of the protocol in a more complex setting.

**Scheme 3.** Oxidative Cyclization of Cyclopropane-Containing Substrates




We chose clavosolide A, **9** (Scheme 4), as a target to highlight the utility of the protocol. The Faulkner group isolated clavosolide A from a sponge off the coast of the Phillipines,[8] but limited quantities have precluded a thorough examination of its biological activity. A revision of the stereostructure was proposed by Willis[9] and was confirmed through a total synthesis from the Lee group.[10] Several total and formal syntheses of clavosolide A have subsequently been reported,[11] with the majority employing a late stage introduction of the cyclopropyl group to avoid the potential for ring opening. Smith and co-workers introduced the cyclopropane at an early stage but noted the Lewis acid sensitivity of the group and cautioned against prolonged reaction times and the use of strong acids.[11b] Our objective was to demonstrate that the oxidative cyclization conditions allow the cyclopropane unit of clavosolide A to be introduced at an early stage in the synthesis, thereby providing an attractive strategy for a convergent synthesis. We envisioned **9** as arising from cyclopropyl tetrahydropyran **10**, which can be accessed from ether **11** through an oxidative cyclization. This ether can arise from the union of subunits **12** and **13**.

The synthesis of the cyclopropane-containing subunit (Scheme 5) employed Feringa's elegant asymmetric 1,4-addition protocol[12] as the key step. Conjugate addition of MeMgBr to chloro enone **14**, prepared in one step from

(5) (a) Wan, S.; Gunaydin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 7915. (b) Green, M. E.; Rech, J. C.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 7317. (c) Clausen, D. J.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 5178.

(6) (a) Tu, W.; Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4184. (b) Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567. (c) Liu, L.; Floreancig, P. E. *Org. Lett.* **2009**, *11*, 3152. (d) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 3069. (e) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 5894. (f) Brizgys, G. J.; Jung, H. H.; Floreancig, P. E. *Chem. Sci.* **2012**, *3*, 438. (g) Cui, Y.; Floreancig, P. E. *Org. Lett.* **2012**, *14*, 1720. (h) Han, X.; Floreancig, P. E. *Org. Lett.* **2012**, *14*, 3808. (i) Clausen, D. J.; Floreancig, P. E. *J. Org. Chem.* **2012**, *77*, 6574.

(7) Lim, D. S. W.; Anderson, E. A. *Synthesis* **2012**, *44*, 983.

(8) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2002**, *65*, 386.

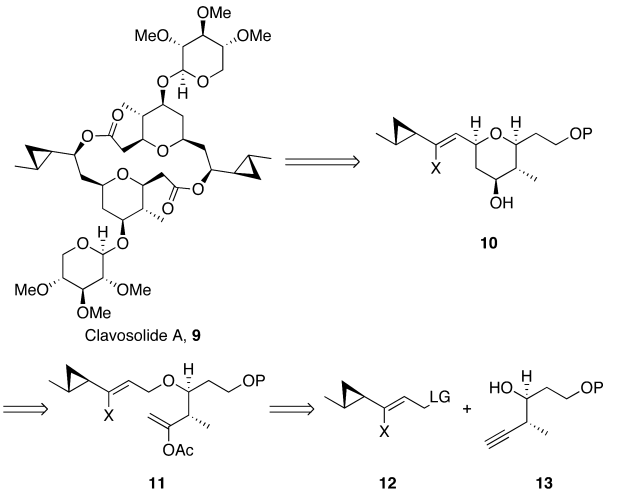
(9) Barry, C. S.; Bushby, N.; Charmant, J. P. H.; Elsworth, J. D.; Harding, J. R.; Willis, C. L. *Chem. Commun.* **2005**, 5097.

(10) Son, J. B.; Kim, S. N.; Kim, N. Y.; Lee, D. H. *Org. Lett.* **2006**, *8*, 661.

(11) (a) Barry, C. S.; Elsworth, J. D.; Seden, P. T.; Bushby, N.; Harding, J. R.; Alder, R. W.; Willis, C. L. *Org. Lett.* **2006**, *8*, 3319. (b) Smith, A. B., III; Simov, V. *Org. Lett.* **2006**, *8*, 3315. (c) Chakraborty, T. K.; Reddy, V. R.; Gajula, P. K *Tetrahedron* **2008**, *64*, 5162. (d) Carrick, J. D.; Jennings, M. P. *Org. Lett.* **2009**, *11*, 769.

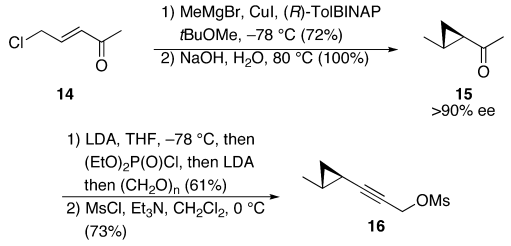
(12) den Hartog, T.; Rudolph, A.; Maciá, B.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2010**, *132*, 14349.

**Scheme 4.** Retrosynthetic Analysis of Clavosolide A




allyl chloride and acetyl chloride,[13] in the presence of CuI and (*R*)-tolylBINAP provided a chloro enolate that could either be warmed to generate cyclopropane **15** directly or quenched at low temperature and subjected to base to effect the cyclopropanation in >90% ee.[14] We found that the yield and reproducibility were superior for the two-step protocol.

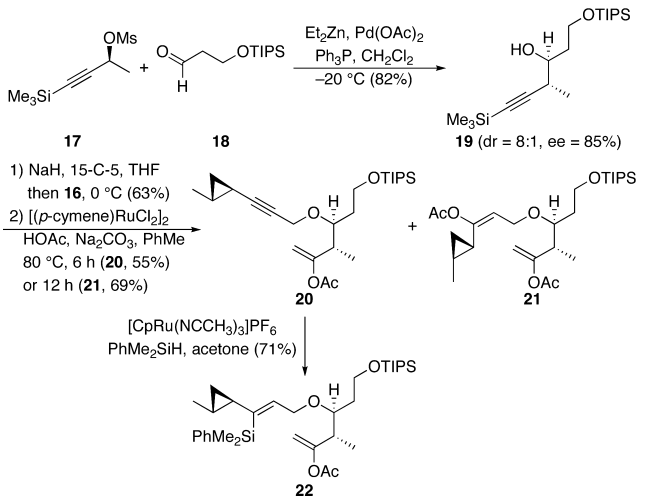
**Scheme 5.** Synthesis of the Cyclopropane-Containing Subunit




The methyl ketone was converted to a propargyl alcohol through Negishi's method[15] in which the enolate was quenched with diethylphosphoryl chloride and the resulting phosphonate was subjected to excess LDA to generate the alkynyl anion. Quenching the alkynyl anion with paraformaldehyde completed the construction of the propargyl alcohol. Converting the hydroxy group to a leaving group proved to be challenging due to cyclopropane opening upon exposure to common halogenating agents. However mesylation under standard conditions could be achieved to form **16**. This species should be prepared shortly before the subsequent step due to its propensity for ionization and decomposition.

The synthesis of the cyclization precursor is shown in Scheme 6. Coupling mesylate **17**, in which the stereocenter can be conveniently prepared through a Noyori reduction,[16] with aldehyde **18** under Marshall's conditions[17] provided homopropargylic alcohol **19** with good enantio- and diastereocontrol. Deprotonation followed by the addition of mesylate **16** under modified Williamson conditions[18] provided the expected ether with concomitant cleavage of the alkynylsilane group. The addition of HOAc through standard ruthenium-catalyzed conditions[19] provided a mixture of the expected enol acetate **20** (55%) and dienol acetate **21** (27%). This procedure is generally quite selective for terminal alkynes in preference to internal

**Scheme 6.** Synthesis of the Cyclization Substrates




alkynes,[6d,h] indicating that the cyclopropane group plays an activating role. The *cis*-addition across the internal alkyne was confirmed through NOESY experiments on a subsequent intermediate. Subjecting **20** to hydrosilylation under Trost's conditions[20] provided vinylsilane **22** in 71% yield. Since **21** could in principle also suffice for our synthetic objectives, we exposed the diyne to a higher catalyst loading and a longer reaction time to provide the diaddition product in 69% yield.

The oxidative cyclization reactions are shown in Scheme 7. Exposing **21** to DDQ at rt for 1.5 h provided **23** as a single stereoisomer in 62% yield. The cyclization of **22** required heating to 40 °C for 6 h to provide a 51% yield of **24**. No attempt was made to optimize the yield for the cyclization of **22** in consideration of material accessibility and the superiority of **21** as a substrate. The cyclization of **21** is significant in that it highlights the utility of enol

(13) Kulinkovich, O. G.; Tischenko, I. G.; Sorokin, V. L. *Synthesis* **1985**, 1058.

(14) An exact value for the ee could not be obtained because of overlapping peaks in the HPLC trace. Please see the Supporting Information for details.

(15) Negishi, E.; King, A. O.; Klima, W. L.; Patterson, W.; Silveira, A., Jr. *J. Org. Chem.* **1980**, *45*, 2526.

(16) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

(17) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1998**, *63*, 3812.

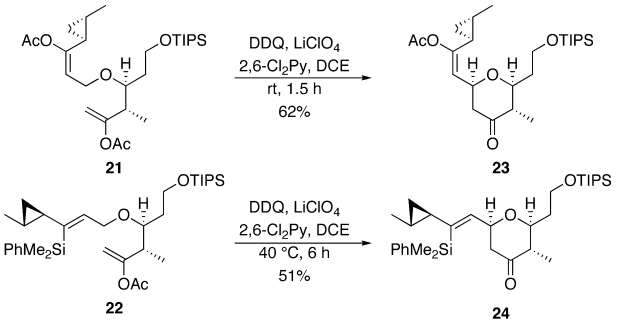
(18) Aspinall, H. C.; Greeves, N.; Lee, W.-M.; McGiver, E. G.; Smith, P. M. *Tetrahedron Lett.* **1997**, *38*, 4679.

(19) Goossen, L. J.; Paetzold, J.; Koley, D. *Chem. Commun.* **2003**, 706.

(20) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644.

acetates as stabilizing groups for oxidative carbocation formation, thereby providing an additional option for the formation of functionalized alkenyl tetrahydropyrans that can be used for subsequent diversification studies.

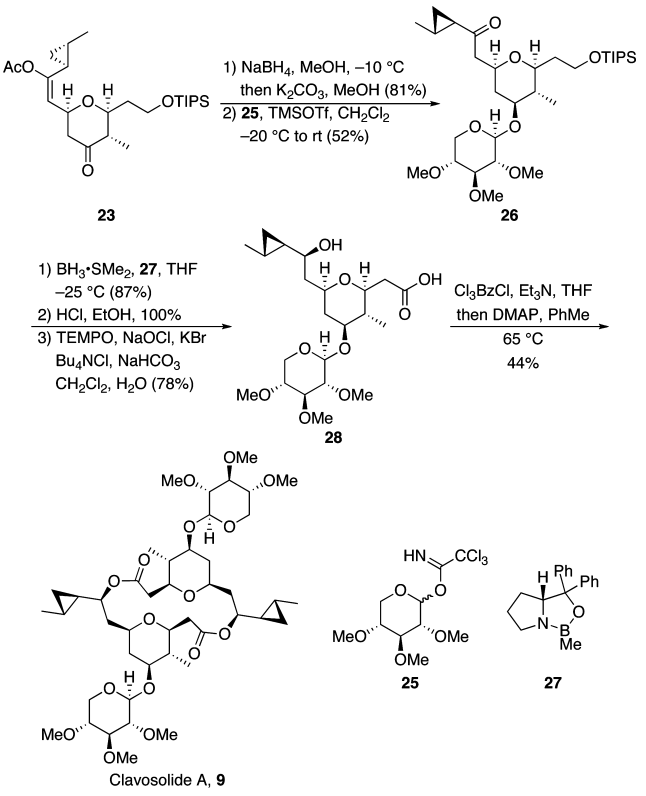
**Scheme 7.** Comparison of Oxidative Cyclization Substrates




The completion of the synthesis is shown in Scheme 8. Ketone reduction of **23** with $NaBH_4$ smoothly provided the equatorial alcohol on the tetrahydropyran. The enol acetate was then cleaved with $K_2CO_3$ and MeOH to yield the corresponding ketone. Glycosidation was conducted at this point in accord with syntheses of related structures,[10,21] because the glycosyl group can effectively serve as a hydroxyl protecting group. Additionally, three anomeric stereoisomers can form if glycosidation is conducted after macrodiolide formation, resulting in a low product yield and a significant separation problem if the glycosylation reaction shows poor selectivity. Adding the tetrahydropyranol to trichloroacetimidate **25**[9] in the presence of TMSOTf provided glycoside **26** (52%) along with significant amounts of its anomer. The reduction of a similar ketone group has been reported[11c] to proceed with useful substrate-directed stereocontrol, but we found superior results could be attained through reagent-directed stereocontrol. Exposing **26** to $BH_3$•$SMe_2$ and catalyst **27**[22] provided the desired secondary alcohol in high yield and with good diastereocontrol. Removal of the silyl protecting group was achieved with HCl in EtOH. Selective oxidation of the primary alcohol[23] yielded carboxylic acid monomer **28**. Macrodiolide formation under Yamaguchi's conditions[24] completed the synthesis of clavosolide A.

We have shown that cyclopropanes are compatible with oxocarbenium ion formation through C−H bond oxidation and have applied this result to the synthesis

**Scheme 8.** Completion of the Synthesis




of cyclopropane-substituted tetrahydropyrans. The functional group tolerance of the oxidative cyclization allowed for a convergent total synthesis of clavosolide A. Key steps in the sequence include an early stage Feringa asymmetric cyclopropanation reaction and the oxidation of of an acetoxy-substituted allylic ether as a precursor to a functionalized unsaturated oxocarbenium ion. The capacity to introduce cyclopropane groups at an early stage of a synthetic sequence that eventually proceeds through a carbocation-forming reaction adds to the unique strategic options that oxidative C−H bond functionalization offers for complex molecule synthesis.

**Acknowledgment.** We thank the National Institutes of Health (GM062924) for generous support of this work. We thank Professor T. K. Chakraborty and Dr. R. Reddy Vakiti (Central Drug institute, Lucknow, India) for helpful discussions and sharing spectra.

**Supporting Information Available.** Experimental procedures for cyclization reactions and characterization data for all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(21) (a) Kim, H.; Hong, J. *Org. Lett.* **2010**, *12*, 2880. (b) Seden, P. T.; Charmant, J. P. H.; Willis, C. L. *Org. Lett.* **2008**, *10*, 1637.

(22) (a) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(23) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.

(24) Inanaga, J.; Hirata, K.; Saeki, H.; Katzuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.