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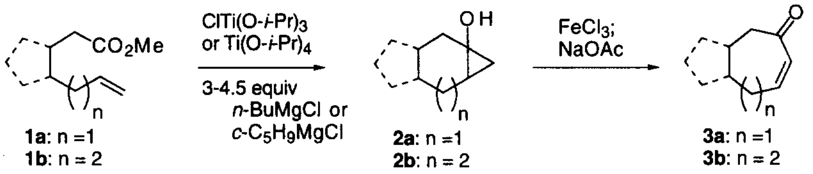
A NEW ROUTE TO SEVEN- AND EIGHT-MEMBERED CARBOCYCLES

Jong Sun U, Jinhwa Lee, and Jin Kun Cha*
Department of Chemistry, University of Alabama, Tuscaloosa, AL 35487, U.S.A.

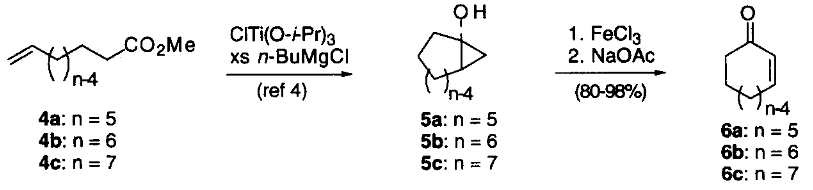
Abstract: A facile method for the construction of bicyclo[6.3.0]undecane or bicyclo-[5.3.0]decane skeleton has been developed by the tandem application of the intramolecular Kulinkovich cyclopropanation of ω-vinyl esters and oxidation of the resulting cyclopropanols.

Synthesis of structurally complex natural products often requires the formation of carbocycles or annulation onto an existing ring. Recently there has been considerable interest in the preparation of medium-sized (seven- and eight-membered) carbocyclic rings largely due to their presence in an increasing number of bioactive natural products. Among some imaginative annulations that have emerged,[1] the paucity of methods for direct cyclization of readily available acyclic precursors is striking.[2] As a preliminary study in the area of medium-sized carbocyclic natural product synthesis, we report herein a new, three-step protocol for seven- and eight-membered annulation by utilizing the tandem application of the intramolecular Kulinkovich hydroxycyclopropanation of ω-vinyl esters[3-5] and subsequent oxidative cleavage of the resulting cyclopropanols (eq 1).



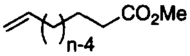
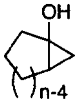
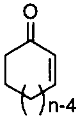
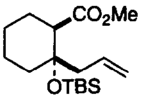
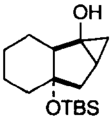
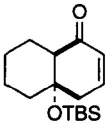
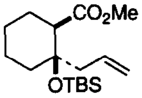
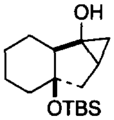
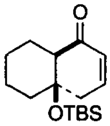
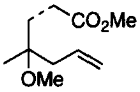
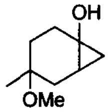
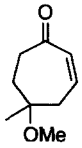
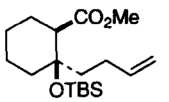
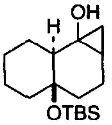
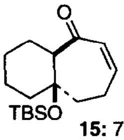
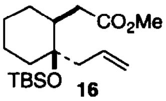
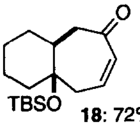
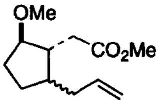
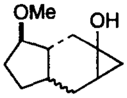
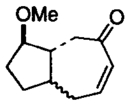
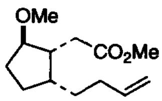
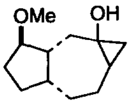
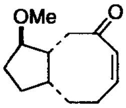
(eq 1)

Recently, we and the Sato group independently reported the intramolecular hydroxycyclopropanation of ω-vinyl esters by the olefin exchange-mediated variant of the original Kulinkovich[6] protocol (eq 2).[3,4] We anticipated that one-electron oxidation of the resultant cyclopropanols by the method of Saegusa[7] would provide a convenient preparation of 2-cycloalkenones. Indeed, mild oxidation of the cyclopropanols **5a–c** with ferric chloride smoothly produced the ring-opened β-chloro ketones. Subsequent dehydrochlorination was then achieved by treatment of sodium acetate to afford the corresponding cycloalkenones **6a–c** in good yield.[8]



(eq 2)

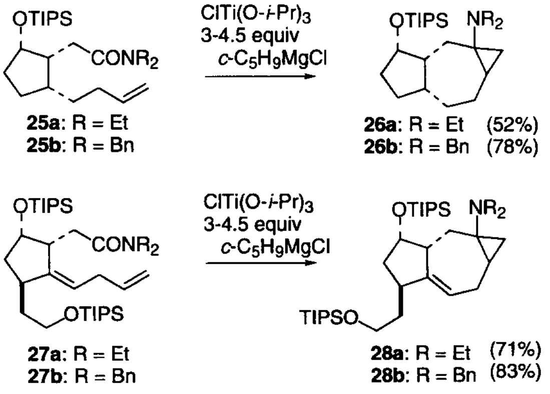
Table 1. Intramolecular Kulinkovich Cyclopropanation and Oxidative Ring Opening

entry	substrate	cyclopropanol	cycloalkenone
	 $\xrightarrow{a}$	 $\xrightarrow{b}$	
1	**4a**: n = 5	**5a**: 55%	**6a**: 98%
2	**4b**: n = 6	**5b**: 62%	**6b**: 80%
3	**4c**: n = 7	**5c**: 11%	**6c**: 82%
4	 **7a**	 **8a**: 79% (2:1 ds)	 **9a**: 76%
5	 **7b**	 **8b**: 42% (3:2 ds)	 **9b**: 70%
6	 **10**	 **11**: 85% (1.2:1 ds)	 **12**: 60%
7	 **13**	 **14**: 86% (9:1 ds)	 **15**: 75%
8	 **16**	 **17**: 78% (1.3:1 ds)	 **18**: 72%
9	 **19**^{c}	 **20**: 60% (1:1 ds)	 **21**: 71%
10	 **22**	 **23**: 40% (1:1 ds)	 **24**: 63%

a. Conditions: ester (1 equiv), ClTi(O-*i*-Pr)$_3$ (1 equiv), *c*-C$_5$H$_9$MgCl (3-5 equiv), THF, room temperature. *b.* 1. FeCl$_3$, DMF; 2. NaOAc, MeOH, reflux. *c.* A 2:1 mixture of *cis*- and *trans*-dialkyl isomers was employed.

Additional examples, obtained under the standard reaction conditions, are summarized in Table 1. Treatment of the readily available ω-vinyl esters **7a,b**, **10**, **13**, **16**, **19**, and **22** with excess of commercially available cyclopentyl magnesium chloride in the presence of $ClTi(O\text{-}i\text{-}Pr)_3$ (1.0 equiv) at room temperature afforded the hydroxycyclopropanes **8a,b**, **11**, **14**, **17**, **20**, and **23**, respectively, in fair to good yields.[9] Not surprisingly, compared to the five- and six-membered annulation, the seven-membered ring formation of ω-vinyl esters suffers from a noticable decrease in yield (entries 3 and 10). In any event, $FeCl_3$ oxidation of these cyclopropanol adducts and subsequent dehydrochlorination (NaOAc) by the method of Saegusa[7] smoothly produced the corresponding cycloalkenones **9a,b**, **12**, **15**, **18**, **21**, and **24** in 63–76% yield.[10] While each cyclopropanation of ω-vinyl esters (entries 4–10) took place with no diastereoselectivity, both diastereomers cleanly underwent $FeCl_3$ oxidation to afford the identical ring-opened β-chloro ketones. In passing we note that esters **19** and **22** were readily available in enantiomerically pure form from commercially available Corey lactone aldehyde.[11]

Thus, the overall sequence provides a rapid, efficient construction of the bicyclo[5.3.0]decane skeleton. On the other hand, the preparation of the bicyclo[6.3.0]undecane derivatives suffers from poor efficiency in the seven-membered cyclization of ω-vinyl esters (entries 3 and 10). It is noteworthy, however, that this unfavorable trend subsides in cyclopropanation of carboxamides (eq 3). Moreover, when a bulky *N*,*N*-dialkyl group was employed, excellent yields became available. An overall efficient cyclization of carboxamides (*vis-à-vis* esters) and the beneficial effect of a bulky *N*,*N*-dialkyl moiety can be understood in terms of low reactivity of amides towards competing nucleophilic attack (by the Grignard or related reagents), thereby favoring cyclization. In light of efficient cyclization of these ω-vinyl amides, the hitherto unknown ring opening of aminocyclopropanes **26a,b** and **28a,b** is currently under investigation.[12]



25a: R = Et
25b: R = Bn

26a: R = Et (52%)
26b: R = Bn (78%)

27a: R = Et
27b: R = Bn

28a: R = Et (71%)
28b: R = Bn (83%)

(eq 3)

In summary, we have developed a facile method for seven- and eight-membered annulation by the tandem application of the intramolecular Kulinkovich cyclopropanation of ω-vinyl esters and subsequent oxidative cleavage of the resulting cyclopropanols to prepare the bicyclo[6.3.0]undecane or bicyclo[5.3.0]decane skeleton. The implementation of this annulation protocol towards a total synthesis of ophiobolines sesterterpenes is currently in progress.[13,14]

References and Footnotes

1. For general reviews, see: (a) Rigby, J. H. In *Studies in Natural Products Chemistry*; Rahman, A., Ed.; Elsevier: New York, 1988; Vol. 1, pp 545-576. (b) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.
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8. Manganese(III) 2-pyridinecarboxylate–cupric acetate can be employed in place of $FeCl_3$ for a one-step preparation of enones: Iwasawa, N.; Hayakawa, S.; Funahashi, M.; Isobe, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 819 and refereces cited therein.
9. The requisite cyclization substrates **7a,b**, **10**, **13**, **16**, **19**, and **22** were prepared by standard methods and details will be reported in a full paper.
10. (a) Unoptimized yield. (b) As **19** was prepared as a 2:1 mixture of *cis-* and *trans-* ring junction diastereomers, the bicyclic enone **21** was isolated as a 2:1 diastereomeric mixture, and each isomer was separated and fully characterized. (c) We believe that the actual yield for the oxidation-dehydrochlorination sequence is somewhat higher, since these cyclopropanols, in particular strained tricyclic compounds, are found to undergo decomposition in storage.
11. (a) Available in large quantities from Cayman Chemical, Ann Arbor, MI 48108. (b) The requisite alcoholysis of the lactone moiety was achieved by use of King's procedure: King, S. A. *J. Org. Chem.* **1994**, *59*, 2253.[9]
12. A new method for ring opening of the aminocyclopropanes has recently been developed in our laboratory: Lee, J.; U, J. S.; Cha, J. K. unpublished results.
13. Cf. For previous successful syntheses, see: (a) Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735. (b) Boeckman, R. K., Jr.; Arvanitis, A.; Voss, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 2737.
14. We are grateful to the National Institutes of Health (GM 35956) for generous financial support and a Research Career Development Award (GM00575 to J.K.C.).

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