Pergamon

Tetrahedron Letters, Vol. 38, No. 12, pp. 2057-2060, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00284-0

A Novel Approach to Oligocyclopropane Structural Units.

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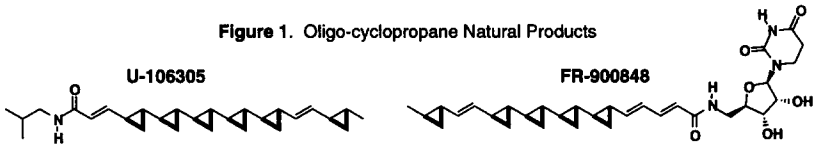
Abstract: A fundamentally novel approach to the synthesis of oligocyclopropane structural units based on the iterative formation and trapping of homo-allyl cationic intermediates has been accomplished. This methodology provides practical access to the diastereomically related trans-*syn*-trans and trans-*anti*-trans bis-cyclopropanes and higher homologues.

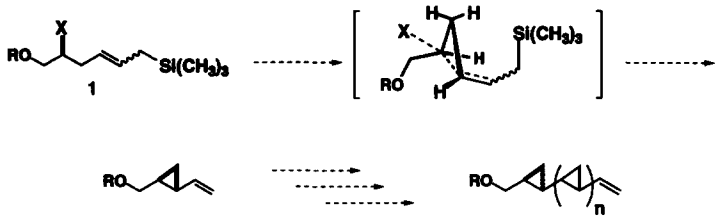
Recently, two biologically active natural products (Figure 1) have been isolated which contain remarkable contiguous cyclopropane units. FR-900848 is a nucleoside isolated from the fermentation broth of *Streptoverticillium fervens* which shows potent, selective activity against filamentous fungi.[2a] More recently, a cholesteryl ester transfer protein inhibitor, U-106305, was isolated which has a similar oligocyclopropane lipid sidechain.[2b] Their unusual structures and potent biological activities make FR-900848, U-106305 and their stereoisomeric analogues attractive synthetic targets. Several groups have approached the synthesis of these novel targets by developing strategies for the stereospecific cyclopropanation of olefins using modified Simmons-Smith type methodology.[3,4] Herein we wish to present a preliminary account of our approach to these interesting structural units based on the iterative generation, and trapping of homo-allyl cationic intermediates.

Figure 1. Oligo-cyclopropane Natural Products



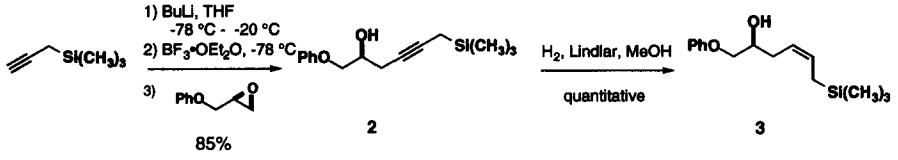
In addition to being a part of the classic discussions of carbonium ions,[5] the homo-allylic cation has been postulated as a reactive intermediate in the biosynthetic pathway to a number of cyclopropane-containing natural products.[6] However, it has only been recently that this intermediate has been utilized by synthetic chemists.[7,8] In order to exploit a homo-allyl cationic intermediate for the preparation of oligo-cyclopropanes it would be necessary to trap the cyclopropyl carbinyl and subsequently provide functionality capable of regeneration of the reactive intermediate in as few steps as possible. Our initial system is described below, Scheme I. Allylsilane **1** is our choice as the direct precursor to the cyclopropyl carbinyl cation. The leaving group ability of X could be attenuated to insure efficient stereospecific cyclization with inversion, while the presence of the silicon trap should stabilize the cyclopropyl carbinyl through hyperconjugation (β-silicon effect) and subsequently eliminate to provide a terminal olefin. The cyclization should provide exclusively the *trans*-isomer through a transition state that minimizes repulsive interactions of the carbon backbone. Moreover, elaboration of the resulting terminal olefin would provide the opportunity to reiterate the cyclization step and allow for the preparation of oligo-cyclopropane structural units.

Scheme I



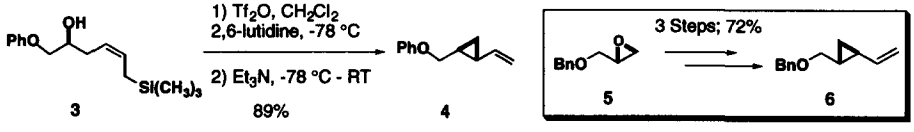
Protected glycidols have been chosen as our starting material because these epoxides of allylic alcohols are excellent sources of chirality. Several derivatives are commercially available with high enantiomeric purity, while more functionalized substrates are readily available using the Sharpless asymmetric epoxidation method.[9] The homopropargylic alcohols have been prepared easily from glycidol derivatives through oxirane ring cleavage by the boron acetylide[10] derived from commercially available propargyltrimethylsilane, Scheme II. Propargyltrimethylsilane was metallated with n-butyllithium at -78 °C. However, it was determined to be necessary to allow the mixture to warm to -20 °C in order to achieve high levels of deprotonation. After cooling back to -78 °C, an equivalent of boron trifluoride-diethyl etherate was added followed by 1,2-epoxy-3-phenoxypropane. After 30 minutes at -78 °C the reaction was quenched with saturated ammonium chloride solution and allowed to warm to room temperature. Alcohol **2** was isolated via flash chromatography in 85% yield. Reduction of the alkyne was accomplished with Lindlar catalyst under an atmosphere of hydrogen to provide the allylsilane **3** in quantitative yield.

Scheme II



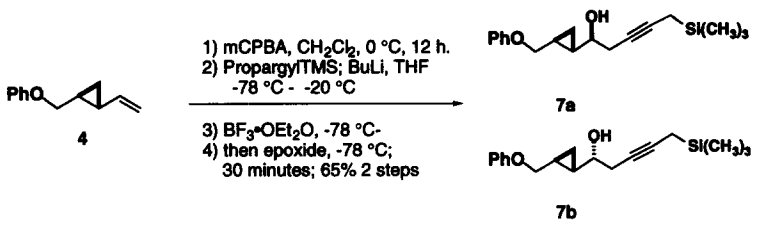
Exposure of alcohol **3** to triflouromethansulfonic anhydride in methylene chloride and 2,6-lutidine followed by a triethylamine quench provided exclusively the *trans*- vinylcyclopropane **4** in 89% yield, Scheme III. No other by-products were observed in the ^1H NMR spectrum of the crude reaction mixture. Using this three step protocol, several protected glycidols have been converted to their corresponding vinyl cyclopropane in excellent yield. In addition, enantiomerically pure benzyl-(S)-glycidyl ether, which is commercially available, provides access to *non-racemic* vinyl cyclopropane **6** in 72% yield. Loss of enantiomeric purity under the reaction conditions was potentially a concern but has been precluded by the evidence presented below.

Scheme III



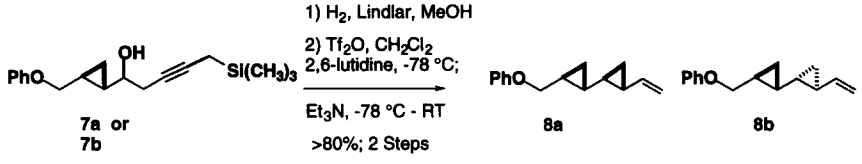
At this point we can exploit the synthetic potential of this strategy by iteration of the sequence already developed. Epoxidation of vinylcyclopropane **4** was accomplished with *m*-chloroperbenzoic acid providing a 1:1 mixture of diastereomeric cyclopropyl epoxides in good yield, Scheme IV. The crude epoxides were immediately subjected to the boron acetylide of propargyltrimethyl silane as previously described which cleanly provided the diastereomeric alcohols **7a** and **7b**. In this particular case, (protecting group = Ph) the diastereomeric alcohols were separable by flash chromatography and the combined yield for the two step sequence, epoxidation and fragmentation, was 65 %. The lack of diastereoselectivity in the epoxidation is disappointing but may be circumvented by other catalytic epoxidation (or dihydroxylation) methods. In fact, Jacobsen has reported[11] the epoxidation of a simple vinylcyclopropane with *racemic* manganese salen complex to provide exclusively one diastereomer. However, the relative stereochemistry of the product was not reported.

Scheme IV



Hydrogenation of the propargylic alcohols **7a** and **7b** proceeded without difficulty to provide in each case the Z-allylsilane quantitately, Scheme V. Individual activation of each homo-allylic alcohol with triflic anhydride under the conditions discussed above cleanly produced exclusively a single diastereomeric dicyclopropane (**8a/8b**) in excellent yield.[12] Proton NMR spectra of the crude reaction mixture showed no fragmentation of the initial cyclopropane ring suggesting an S_N2 type mechanism and precluding a cyclopropyl carbinyl intermediate. Moreover, this information fully supports the conservation of enantiomeric purity in the three step conversion of epoxide **5** to vinyl cyclopropane **6** discussed above.

Scheme V



In summary, we have developed a practical method for the preparation of oligocyclopropanes based upon a novel reactive intermediate.[13] These structural units should find utility in a variety of applications including precursors to new materials, ligands for asymmetric catalyst design, and conformational control elements for the preparation of analogues of biologically active natural products. In addition, we have begun investigating multiple cyclopropane generation via a tandem cationic cyclization mechanism. The results of this effort as well as further synthetic exploitation of the iterative process presented here will be reported in due course.

ACKNOWLEDGEMENT

This work has been generously supported by the Petroleum Research Fund as administered by the American Cancer Society (31817-G1). Undergraduate research support from the University of Notre Dame is gratefully acknowledged.

REFERENCE AND NOTES

1. Undergraduate Research Participant

2. a)Yoshida, M.; Ezaki, M.; Hasimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. *J. Antibiotics* **1990**, *43*, 748. b) Kuo, M. S.; Zielinski, R. J.; Cialdella, J. I.; Marschke, C. K.; Dupuis, M. J.; Li, G. P.; Klooserman, D. A. ; Spilmann, C. H.; Marshall, V. P. *J. Am. Chem. Soc.* **1995**, *117*, 10629.

3. For total synthesis: a) Charette, A.; Lebel, H. *J. Am. Chem. Soc.* **1996**, *118*, 10327. b)Barrett A. G. M.; Kasdorf, K. *J. Chem. Soc. Chem. Commun.* **1996**, 325. c) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 7863. d) Falck, J. R.; Mekonnen, B.; Yu, J.; Lai, J-Y. *J. Am. Chem. Soc.* **1996**, *118*, 16096.

4. a) Theberge, C. R.; Zercher, C. K. *Tetrahedron Lett.* **1994**, *35*, 9181. b) Theberge, C. R.; Zercher, C. K. *Tetrahedron Lett.* **1995**, *36*, 5495. c)Armstrong, R. W.; Maurer, K. W. *Tetrahedron Lett.* **1995**, *36*, 357. d) Cebula, R. E.J.; Hanna, M. R.; Theberge, C. R.; Verbicky, C. A.; Zercher, C.K. *Tetrahedron Lett.* **1996**, *37*, 8341.

5. For a seminal discussion of these intermediates, see; Roberts J. D.; Mazur, R. H. *J. Am. Chem. Soc.* **1951**, *73*, 2509 and Olah, G. A.; Reddy, P.; Parakash, G. K. S. Chem *Rev.* **1992**, *92*, 69.

6. a) Jarstfer, M. B.; Blagg, B. S. J.; Rogers, D. H.; Poulter, C. D. *J. Am. Chem. Soc.* **1996**, *118*, 13089-13090. b) Baertschi S. W.; Brash, A. R.; Harris, T. M. *J. Am. Chem. Soc.* **1951**, *73*, 2509.

7. a)White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 2970. b)White, J. D.; Jensen, M. S.*J. Am. Chem. Soc.* **1995**, *117*, 6224. c)White, J. D.; Jensen, M. S. *Synlett* **1996**, 31. d) Nagasawa, T.; Hana, Y.; Onoguchi, Y.; Ohba, S.; Suzuki, S. *Synlett* **1995**, 739. e)Shiramura, H.; Hayano, K.; Kanemoto, Y.; Misumi, S.; Ohtsuka, T.; Hashiba, N.; Furusaki, A.; Murata, S.; Noyori, R.; Matsumoto, T. *Tetrahedron Lett.* **1980**, *21*, 4835.

8. For a novel approach to α-methano hetereocycles using a destannylative cyclopropanation. Hannesian, S.; Reinhold, U.; Ninkovic, S. *Tetrahedron Lett.* **1996**, *37*, 8967-8970 and 8971-8974.

9. Katsuki, T.; Sharpless, K. B. *J. Am . Chem. Soc.* **1980**, *102*, 5974-5976.

10. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391-394.

11. Fu, H.; Look, G.; Zhang, W.; Jacobsen, E.; Wong, C-H. *J. Org. Chem.* **1991**, *56*, 6497-6500.

12. Although not unambiguously established at this time presumably **7a** provided **8a** and **7b** provided **8b**.

13. Satisfactory spectral and HRMS data have been obtained for all new molecules.

(*Received in USA* 15 *January* 1997; *revised* 31 *January* 1997; *accepted* 2 *February* 1997)