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Oligocyclopropane Structural Units from Cationic Intermediates

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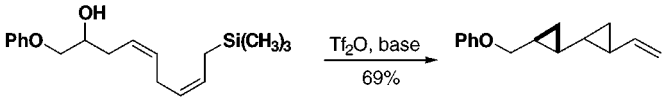
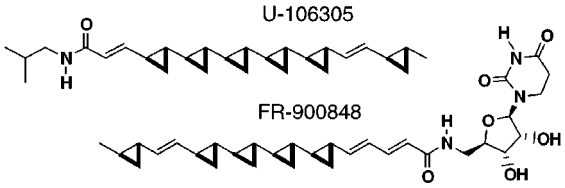
ABSTRACT



***syn*- and *anti*-bis-cyclopropanes have been efficiently prepared through two distinct routes via the trapping of cyclopropylcarbinyl cationic intermediates. A ring-closing olefin metathesis for the formation of the necessary allylsilane precursors highlights the initial route. The cyclopropanation step proceeds in good yield to provide exclusively *trans*-vinylcyclopropanes. Iteration of the sequence has provided an efficient route to bis-cyclopropanes. The stereospecificity of the second cyclization was shown to be dependent on distal functionality. An alternative approach produces these interesting structural units from skipped dienes in a single step.**

Two natural products have recently been isolated which contain remarkable contiguous cyclopropane structural units. FR-900848 is a nucleoside analogue isolated from the fermentation broth *Streptoverticillium fervens*.[1] This interesting compound has shown potent selective activity against filamentous fungi, but is surprisingly inactive against bacteria and nonfilamentous fungi. More recently U-106305, a cholesteryl ester transfer protein inhibitor, was reported containing a structurally related lipid side chain.[2] The



combination of their interesting biological activity, novel structural and conformational properties, and their potential utility as scaffolds for combinatorial chemistry, molecular recognition, catalysis design, and nanotechnology make oligocyclopropanes ideal targets for synthetic methodological development. Several groups have reported synthetic efforts for the preparation of these novel compounds[3−6] with strategies largely based on the stereoselective cyclopropanation of cyclopropyl-substituted olefins using modified Simmons−Smith methodology. In contrast, we have been investigating an approach based on the iterative generation, stabilization, and trapping of cyclopropylcarbinyl cationic intermediates.[7,8]

(1) Yoshida, M.; Ezaki, M.; Hashimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. *J. Antibiot.* **1990**, *43*, 748−754.

(2) Kuo, M. S.; Zielinski, R. J.; Cialdella, J. I.; Marschke, C. K.; Dupuis, M. J.; Li, G. P.; Kloosterman, D. A.; Spilmann, C. H.; Marshall, V. P. *J. Am. Chem. Soc.* **1995**, *117*, 10629−10634.

(3) For papers describing the total synthesis of FR-900848, see: (a) Barrett A. G. M.; Kasdorf, K. *J. Chem. Soc. Chem. Commun.* **1996**, 325−326. (b) Barrett A. G. M.; Kasdorf, K. *J. Am. Chem. Soc.* **1996**, *118*, 11030−11037. (c) Falck, J. R.; Mekonnen, B.; Yu, J.; Lai, J.-Y. *J. Am. Chem. Soc.* **1996**, *118*, 6096−6097.

(4) For the total synthesis of U-106305, see: (a) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 7863−7864. (b) Barrett, A. G. M.; Hamprecht, D.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 8608−8615. (c) Charette, A. B.; Lebel, H. *J. Am. Chem. Soc.* **1996**, *118*, 10327−10328.

(5) For alternative approaches to oligocyclopropane structural units using modified Simmons−Smith technology on cyclopropyl-substituted alkenes, see: (a) McDonald, W. S.; Verbicky, C. A.; Zercher, C. K. *J. Org. Chem.* **1997**, *63*, 1215−1222. (b) Therberge, C. R.; Verbicky, C. A.; Zercher, C. K. *J. Org. Chem.* **1996**, *62*, 8792−8798. (c) Theberge, C. R.; Zercher, C. K. *Tetrahedron Lett.* **1995**, *36*, 5495−5498. (d) Armstrong, R. W.; Maurer, K. W. *Tetrahedron Lett.* **1995**, *36*, 357−360. (e) Theberge, C. R.; Zercher, C. K. *Tetrahedron Lett.* **1994**, *35*, 9181.

(6) For additional examples oligocyclopropane preparation, see: (a) Itoh, T.; Emoto, S.; Kondo, M.; *Tetrahedron* **1998**, *54*, 5225−5232. (b) Charette, A. B.; DeFreitas-Gil, R. P. *Tetrahedron Lett.* **1997**, *38*, 2809−2812. (c) Cebula, R. E. J.; Hanna, M. R.; Theberge, C. R.; Verbicky, C. A.; Zercher, C. K. *Tetrahedron Lett.* **1996**, *37*, 8341. (d) O'Bannon, P. E.; Dailey, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 9244−9245.

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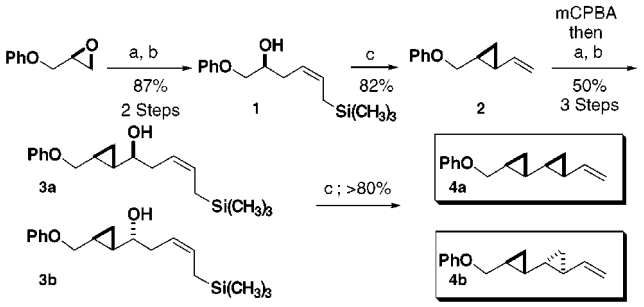
Recently, we reported a route to *trans-syn-trans* and *trans-anti-trans* bis-cyclopropanes through an efficient sequence of steps as outlined in Scheme 1.[7,9] The cyclopropanation

Scheme 1[a]

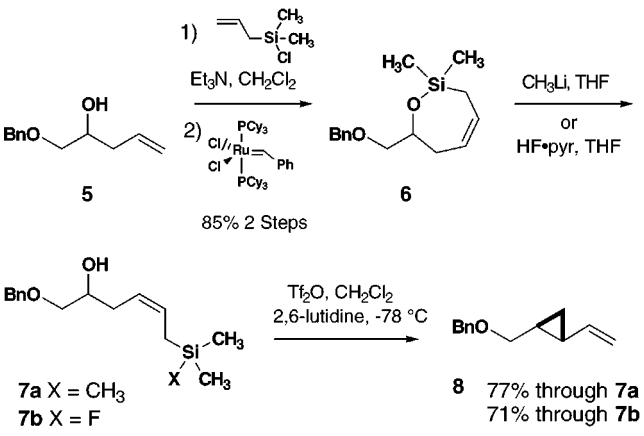


[a] (a) Propargyl-TMS, BuLi, THF, −78 °C; BF_3·OEt_2; then epoxide; (b) H_2, Lindlar; (c) Tf_2O, CH_2Cl_2, 2,6-lutidine.

was achieved by the activation of a homoallylic alcohol **1** with triflic anhydride. Rapid cyclization occurred to form an intermediate cyclopropylcarbinyl cation, which was stabilized and trapped by the presence of a β-trimethylsilyl group. The ring closure proceeded in excellent yield and provided exclusively *trans*-vinylcyclopropane **2**. Epoxidation followed by reiteration of the methodology provided efficient access to diastereomerically pure *syn*- and *anti*-bis-cyclopropanes **4**.

Since this preliminary report we have developed an alternative, more versatile route to similar cyclization precursors. The new sequence begins with an easily accessible starting material, homoallylic alcohol **5**, Scheme 2. While a

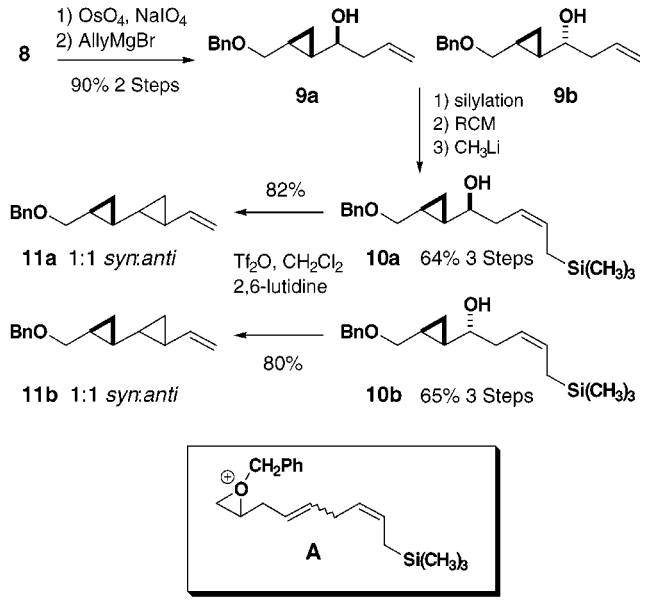
Scheme 2



diverse range of homoallylic alcohols are available from the allylation of aldehydes, **5** was prepared in a single step (vinylMgBr, CuI) from commercially available benzyl glycidyl ether. Protection of the secondary alcohol was accomplished with allylchlorodimethylsilane. The resulting bis-olefin was subjected to Grubbs' ruthenium alkylidene catalyst, providing silyoxycycloheptene **6** in excellent yield.[10] Exposure of the cyclic silyl ether **6** to methyllithium provided the allylsilane derivative **7a**, qualitatively identical to compound **1** prepared by our previously reported acetylene sequence. Not surprisingly, activation of alcohol **7a**, with trifluoromethanesulfonic anhydride provides the *trans*-vinylcyclopropane **8** in 77% yield for the two steps. Alternatively, silyl ether **6** could be fragmented by exposure to HF·pyr, providing **7b**, which upon subsequent activation yielded **8** in 71% yield for the two-step sequence. These complementary cleavage conditions provide opportunities to prepare more functionalized cyclopropane derivatives. The general sequence allows for the efficient conversion of easily accessible homoallylic alcohols to corresponding *trans*-vinylcyclopropanes.

At this point we can exploit the potential of the strategy by iteration of the synthetic sequence. Vinylcyclopropane **8** underwent clean oxidative cleavage to the corresponding aldehyde by treatment with OsO_4/$NaIO_4$, Scheme 3. The

Scheme 3



necessary homoallylic alcohol was prepared by exposure to allylmagnesium bromide at low temperature. The homoallylic

(7) Taylor, R. E.; Ameriks, M. K.; LaMarche, M. J. *Tetrahedron Lett.* **1997**, *38*, 2057−2060.

(8) For examples of chemical approaches to cyclopropanes via cyclopropylcarbinyl cationic intermediates, see: (a) Krief, A.; Provins, L. *Synlett* **1997**, 505−507. (b) Hannesian, S.; Reinhold, U.; Ninkovic, S. *Tetrahedron Lett.* **1996**, *37*, 8971−8974. (c) White, J. D.; Jensen, M. S *Synlett* **1996**, 31. (d) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 6224. (e) Nagasawa, T.; Hana, Y.; Onoguchi, Y.; Ohba, S.; Suzuki, S. *Synlett* **1995**, 739. (f) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 2970.

(9) Schaumann has previously reported the preparation of vinylcyclopropanes from similar starting materials through an allylic anion-mediated process. For a lead reference, see: Schaumann, E.; Kirschning, A.; Narjes, F. *J. Org. Chem.* **1991**, *56*, 717−723.

alcohol **9a,b** was obtained as a mixture of diastereomers (1:1) in >90% yield from **8**. While the separation of these alcohols was fairly tedious, each diastereomer could be obtained with >95% stereoisomeric purity through the use of flash chromatography. While it is expected that stereoselective allylation of the cyclopropylaldehyde could be accomplished using reagent-based methods,[11] a stereorandom allylation enabled us to test the stereospecificity of a second ring closure.

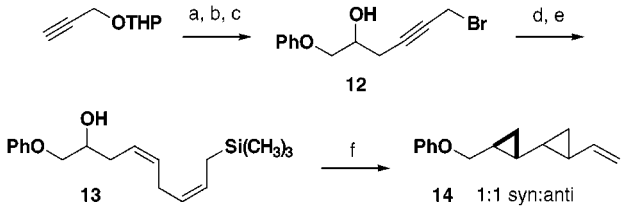
The final sequence of steps is presented for each diastereomer in Scheme 3. After silylation and ring-closing metathesis, the fragmentation proceeded smoothly for each isomer, yielding the cyclopropanation precursors **10a** and **10b**. Activation of either diastereomeric homoallylic alcohol under our standard conditions provided high yields of the bis-cyclopropane products. The only byproduct of this reaction is the trimethylsilyl ether of **10a** and **10b**, which can be isolated in as high as 20% yield. Apparently, the cyclization step, which generates an equivalent of TMSOTf is extremely fast relative to the generation of the triflate.

Although the formation of the bis-cyclopropanes was extremely efficient, we were surprised to isolate an identical 1:1 (*syn*:*anti*) mixture of diastereomers from the reaction of each precursor, **10a** and **10b**.[12] This suggests that the second ring closure is slower than ionization of the intermediate triflate, formation of a cyclopropylcarbinyl cation, and loss of the stereochemical integrity of the starting homoallylic alcohol stereogenic center.

The lack of stereospecificity in the second cyclization strongly contrasts our previously published work,[13] which contained a distal phenoxy group in place of the benzyl ether (Scheme 1). A potential explanation is that benzyl ether assists in the ionization of the secondary triflate and stabilization of the homoallylic carbocation[14] through proposed intermediate **A** which then undergoes sequential cyclizations to provide the mixture of diastereomeric bis-cyclopropanes. On the basis of this hypothesis, it should be possible to generate multiple cyclopropanes in a single step from an acyclic skipped diene structure.

Skipped diene **13** was efficiently prepared through the sequence shown in Scheme 4. Epoxide fragmentation with the alkynyl anion of *O*-THP-propargyl alcohol was immediately followed by acid-catalyzed deprotection. The primary alcohol underwent selective conversion to the propargylic bromide **12** in good yield. A skipped diyne was then prepared by condensation of propargyltrimethylsilane with the bromide under the conditions reported by Jeffery et al.[15] The diyne was then selectively reduced to the *Z,Z*-diene **13** via Lindlar hydrogenation in the presence of pyridine. *Exposure of the* ***13*** *to the standard activation conditions provided the bis-cyclopropane* ***14*** *as a 1:1 mixture of diastereomers in a remarkable 69% yield*. Only minor uncharacterizable byproduct formation was observed in the ^{1}H NMR of the crude reaction mixture. Presumably, the bis-cyclopropane forms via trapping of the intermediate cyclopropylcarbinyl cation.[14] This appears to be faster than trapping of the related homoallylic cation to form a thermodynamically more stable cyclohexene isomer through a six-membered ring transition state. Alternatively, both carbon−carbon bonds could be forming in a more concerted fashion without the generation of a discrete cyclopropylcarbinyl cation.

Scheme 4[a]



[a] (a) BuLi, THF, −78 °C; BF_3·OEt_2; phenylglycidyl ether, 58%, (b) pTsOH, CH_3OH; 89%; (c) CBr_4, Ph_3P, CH_2Cl_2; 98%; (d) Na_2CO_3, TBAI, CuI, DMF, propargyl-TMS; 67%; (e) H_2, Lindlar, pyr; 76%; (f) Tf_2O, CH_2Cl_2, 2,6-lutidine; 69%.

In summary, we have developed a practical method for the conversion of readily available homoallylic alcohols to *trans*-vinylcyclopropanes and oligocyclopropanes based upon novel reactive intermediates. A ring-closing olefin metathesis and an intramolecular displacement of a homoallylic triflate with an allylsilane nucleophile highlight the efficient four-step sequence. The route is general and applicable to the stereocontrolled preparation of 1,2,3-trisubstituted cyclopropanes, which will be reported in a subsequent publication. The stereospecificity of the second cyclization was shown to be dependent upon the nature of functionality distal to the cyclopropylcarbinyl triflate. The tandem cationic cyclization, reminiscent of the elegant work of W. S. Johnson[16] is extraordinarily facile. We are continuing to explore many aspects of this work and related synthetic and mechanistic challenges.

Acknowledgment. We gratefully acknowledge support from the National Science Foundation through an Early Career Award (CHE97-33253). This work is also supported

(10) For the preparation of olefinic diols via similar silyloxycycloalkenes, see: Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757−4760. For the preparation of tetrahydrofurans and pyrans via similar silyloxycycloalkenes, see: Meyer, C.; Cossy, J. *Tetrahedron Lett.* **1997**, *38*, 7861−7864.

(11) (a) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827−7828. (b) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401−404. (c) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109−4117.

(12) The relative stereochemistry of the diastereomeric homoallylic alcohols **9a** and **9b** was determined by chemical correlation to previously reported compounds. See: Mohapatra, D. K.; Datta, A. *J. Org. Chem.* **1998**, *63*, 642−646.

(13) (a) We have more recently repeated these experiments and have shown that the phenoxy series is ~80% stereospecific. (b) We do not believe that the benzyl ether has an effect on the initial cyclopropanation reaction (**7** to **8**, Scheme 2).

(14) The "classic" and "nonclassic" carbocationic behavior of homoallyl-cyclopropyl carbinyl-cyclobutyl cations has recently been reviewed: Olah, G. A.; Reddy, V. P.; Surya Prakash, G. K. *Chem. Rev.* **1992**, *92*, 69−95. For a seminal discussion of these intermediates, see: Roberts J. D.; Mazur, R. H. *J. Am. Chem. Soc.* **1951**, *73*, 2509.

(15) Jeffery, T.; Gueugnot, S.; Linstrumelle, G. *Tetrahedron Lett.* **1992**, *33*, 5757−5760.

(16) Johnson, W. S. *Acc. Chem. Res.* **1968**, *54*, 4731.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and full experimental details for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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