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Structural Diversity Based on Cyclopropane Scaffolds

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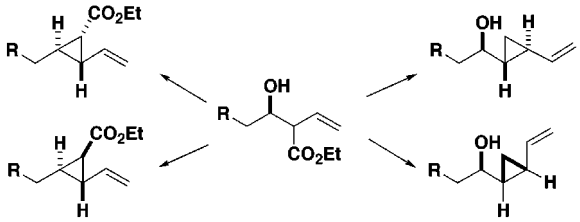
ABSTRACT

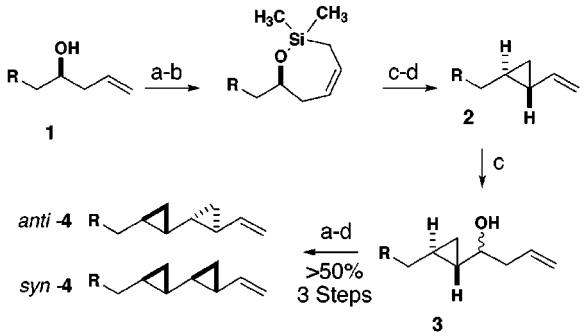


A practical and efficient route for the stereoselective conversion of easily accessible homoallylic alcohols to diastereomerically pure cis- and trans-disubstituted and 1,2,3-trisubstituted cyclopropanes has been developed. The diversity of structures that can be prepared and the simplicity of the overall sequence make this route ideal for extension to solid-phase synthesis techniques and ultimately combinatorial library generation.

Over the past decade, combinatorial chemistry has taken its place as a synthetic tool, complementary to rational design, with the power to identify compounds with beneficial biological,[1] catalytic,[2] binding,[3] sensing,[4] and material[5] properties. From a medicinal point of view, most libraries have been generated on the basis of known pharmacophores that contain aromatic or heteroaromatic scaffolds.[6] As an alternative, we have focused on the development of practical synthetic methodology for the preparation of structural units applicable to combinatorial chemistry but based on natural products.[7] Cyclopropanes and oligocyclopropanes are ideal scaffolds for the display of functionality. Each cyclopropane represents a rigid framework with six points of attachment but, in contrast to aromatic scaffolds, displays functionality in three dimensions. Additionally, oligocyclopropane structures have interesting conformational properties dependent upon the relative stereochemistry of adjacent "residues". We have been developing synthetic methodology capable of preparing a diverse range of stereoisomeric cyclopropane structural units through the stablization and trapping of cyclopropylcarbinyl cationic intermediates.[8,9]

Recently, we reported a route to trans-syn-trans and trans-anti-trans bis-cyclopropanes as outlined in Scheme 1.[8b] Readily available homoallylic alcohols **1** were chosen as practical starting materials for the route. A ring-closing olefin

Scheme 1



a) allylchlorodimethylsilane, imid.; 83%, b) $[(Cy)_3P]_2Cl_2Ru{=}CHPh$; 92%, c) CH_3Li, Et_2O; d) Tf_2O, 2,6-lutidine; 74% 2 steps

(1) Netzi, A.; Ostresh, J. M.; Houghton, R. A. *Chem. Rev.* **1997**, *97*, 449−472.
(2) Bein, T. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 323−326.
(3) Timmerman, P.; Reinhoudt, D. N. *Adv. Mater.* **1999**, *11*, 71−74.
(4) (a) Patterson, S; Smith, B. D.; Taylor, R. E. *Tetrahedron Lett.* **1998**, *39*, 3111−3114. (b) Dickinson, T. A.; Walt, D. R.; White, J.; Kauer, J. S. *Anal. Chem.* **1997**, *69*, 3413−3418.
(5) Jandeleit, D.; Shaefer, D. J.; Powers, T. S.; Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2495−2532.
(6) Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 112−113.

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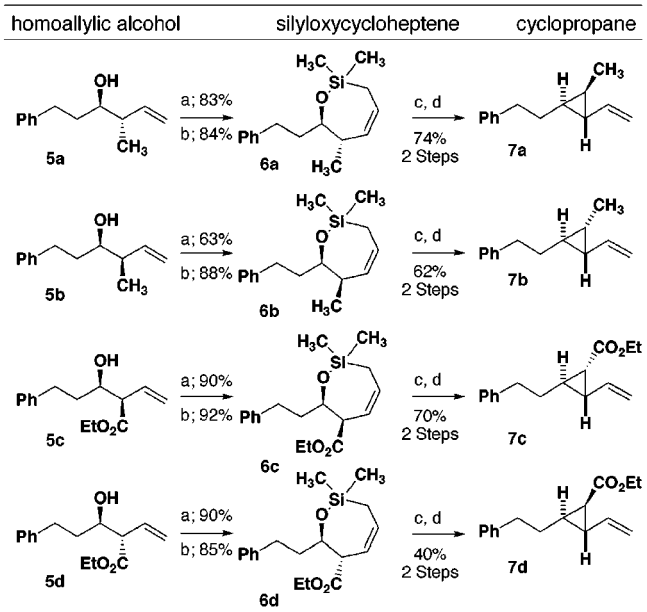
metathesis and an intramolecular displacement of a homoallylic triflate with an allylsilane nucleophile highlight this efficient four-step sequence. Moreover, oxidative cleavage and allylation followed by reiteration of the methodology provided efficient access to bis-cyclopropanes **4**.

Herein, we detail the synthetic utility of the general methodology for the efficient preparation of diastereomerically pure trans- and cis-disubstituted as well as trisubstituted cyclopropane structural units.[10] The sequence begins with an easily accessible starting material, homoallylic alcohol *anti*-**5a**, Table 1. This alcohol was prepared from hydrocinnamaldehyde using crotylbromide and Cr(II).[11] Protection of the secondary hydroxyl was accomplished with allylchlorodimethylsilane, and the resulting bis-olefin was subjected to Grubbs' ruthenium alkylidene catalyst to provide the silyloxycycloheptene **6a** in excellent yield.[12] To generate the necessary cyclization precursor, the cyclic silyl ether **6a** was treated with HF·pyr. Activation of the crude homoallylic alcohol as a trifluoromethane sulfonate provided the vinylcyclopropane **7a** in good yield. Alternatively, exposure to thionyl chloride at 0 °C provides the identical trisubstituted cyclopropane in a similar 69% yield. As shown in Table 1, the diastereomeric vinylcyclopropane **7b** was easily prepared through an identical series of transformations from *syn*-**5b**. This isomeric homoallylic alcohol was prepared from hydrocinnamaldehyde and crotyltributylstannane.[13] More functionalized cyclopropanes are readily accessible via more functionalized homoallylic alcohols. Vinylcyclopropane **7c** and **7d** were efficiently prepared through the four-step sequence. The necessary homoallylic alcohols *syn*-**5c** and *anti*-**5d** were readily available from the indium(0)-promoted coupling of ethyl bromocrotonate and hydrocinnamaldehyde.[14] The general sequence allows for the efficient conversion of easily accessible homoallylic alcohols to their corresponding diastereomerically pure vinylcyclopropanes in a short sequence of steps. It is important to note that all the stereochemical information of the cyclopropane structural unit is contained within the homoallylic alcohol starting material. While compounds in this study were prepared in racemic form, there are numerous published methods for the preparation of enantiomerically pure homoallylic alcohols.[15]

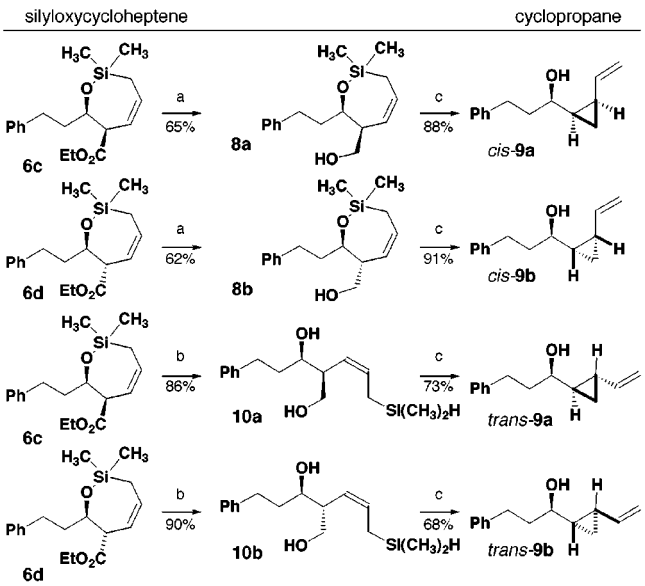
As shown in Table 2, the silyloxycycloheptene intermediates **6c** and **6d** have the potential to provide disubstituted cyclopropanes through activation and ring closure on a primary homoallylic alcohol. Exposure of **6c** to 2 equiv of DIBAL reduced the carbethoxy group as expected to provide

Table 1



a) allylchlorodimethylsilane, imid.; b) $[(Cy)_3P]_2Cl_2Ru{=}CHPh$; c) HF·pyr, THF; d) Tf_2O, 2,6-lutidine

Table 2



a) DIBAL (2 equiv.); b) DIBAL (4 equiv.); c) Tf_2O, 2,6-lutidine

(7) For a presentation of libraries based on "natural product-like" scaffolds, see: (a) Tan, D. S.; Foley, M. A.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 8565−8566. (b) Tan, D. S.; Foley, M. A.; Stockwell, B. R.; Shair, M. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9073−9087.

(8) (a) Taylor, R. E.; Ameriks, M. K.; LaMarche, M. J. *Tetahedron Lett.* **1997**, *38*, 2057−2060. (b) Taylor, R. E.; Engelhardt, F. C.; Yuan, H. *Org. Lett.* **1999**, *1*, 1257−1260.

(9) 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.

(10) Progress in the area of diastereo- and enantioselective methods for cyclopropane construction has been largely focused on the modification of allylic alcohols through intramolecular rhodium carbeniod intermediates or intermolecular Simmons−Smith chemistry. For leading references to the former, see: Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763−5775. For references to the latter, see: Charette, A. B.; Lemay, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1090−1092.

primary alcohol **8a**. Activation of this material under our standard conditions provided the cis-disubstituted cyclopropane **9a** in an efficient 88% yield. The presence of the silyloxepane ring at the transition state constrains the substituents in cis orientation about the forming cyclopropane, Figure 1 (transition state A). The closure is remarkably

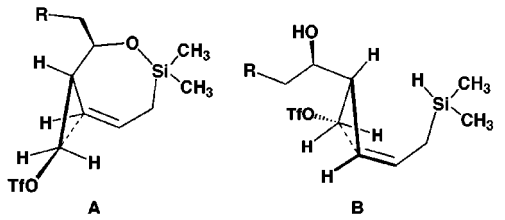


Figure 1. Transition states leading to *cis*- and *trans*-vinylcyclopropanes.

efficient considering the lack of orbital alignment between the olefinic π-system and the allylic carbon−silicon bond.[16] In addition, diastereomeric homoallylic alcohol **8b**, prepared from the reduction of **6d**, yielded the *cis*-vinylcyclopropane **9b** (91%).

Altering the reaction conditions during the reduction step provided an efficient route to trans-disubstituted vinylcyclopropanes. The silicon−oxygen bond is reduced to give the isolable intermediate silane by exposure to excess hydride reagent. Selective activation of this diol then provided *trans*-cyclopropane **9a** in 73% yield. As diagrammed in Figure 1 (transition state B), the acyclic nature of this intermediate allows the substituents to minimize steric interactions at the transition state, thus providing a trans-disubstituted cyclopropane. In a similar manner, diastereomeric silyloxycycloheptene **6d** provided access to *trans*-vinylcyclopropane **9b** (68%).

In summary, we have developed a practical method for the conversion of homoallylic alcohols to vinylcyclopropanes based upon cyclopropylcarbinyl cationic intermediates. The route is general and applicable to the stereocontrolled preparation of diastereomerically pure cis- and trans-1,2-disubstituted and 1,2,3-trisubstituted cyclopropanes. The diversity of structures that can be prepared and the simplicity of the overall sequence make this route ideal for extension to solid-phase techniques and ultimately combinatorial library generation. In addition, utilization of the methodology in an iterative fashion has the potential to prepare highly substituted oligocyclopropane structural units. Efforts toward these goals are currently being investigated in our laboratory.

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(11) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179−3181.
(12) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757−4760.
(13) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889−7896 and reference therein.
(14) Li, C. J.; Chan, C. J. *Tetrahedron Lett.* **1991**, *32*, 7017−7020.
(15) For a recent review of the reaction of aldehydes with allylic metals, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. For an alternative preparation of homoallylic alcohols using chiral crotonate enolates, see: Evans, D. A.; Sjorgren, E. B.; Bartoli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957−4960.
(16) Lambert, J. B.; Zhou, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X. Y.; So, J. H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183−190.