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# Diastereoselective Synthesis of Bicyclopropanes

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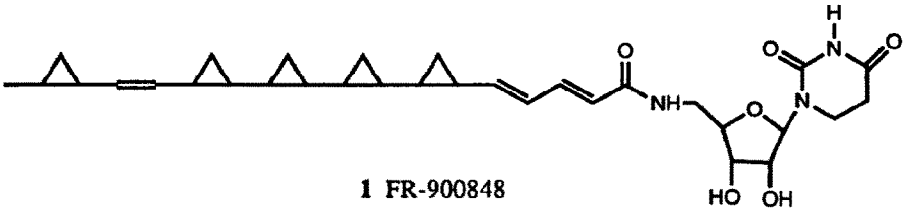
**Abstract:** Diastereoselective cyclopropanation of a trans-substituted vinyl cyclopropane was studied. The stereochemistry of the major and minor isomers was assigned by diastereoselective synthesis of the two isomers.

A recent report on the isolation of a fascinating fatty acid nucleoside stimulated our interest in the synthesis and properties of multiple-cyclopropanated fatty acids.[2] The antifungal compound FR-900848 (**1**) contains an unprecedented five cyclopropane rings on a single fatty acid backbone, four of which are located consecutively. Compound (**1**) appears to be the only naturally occurring fatty acid derivative containing more than a single cyclopropane. FR-900848 **1** demonstrates good *in vitro* antifungal activity for filamentous fungi including *Aspergillus niger* and *Mucor rouxianus* with MIC values as low as 0.05 mg/ml, although yeasts are apparently unaffected.[2] To this point no stereochemical assignments have been made for the multiple stereogenic centers on this fatty acid, contributing to questions regarding biosynthesis, mechanism of action, and the secondary structure of this intriguing molecule. The potent biological activity of FR-900848, the relationships between conformational and configurational isomers, and the synthetic challenge makes multiple-cyclopropanated fatty acids attractive synthetic targets.

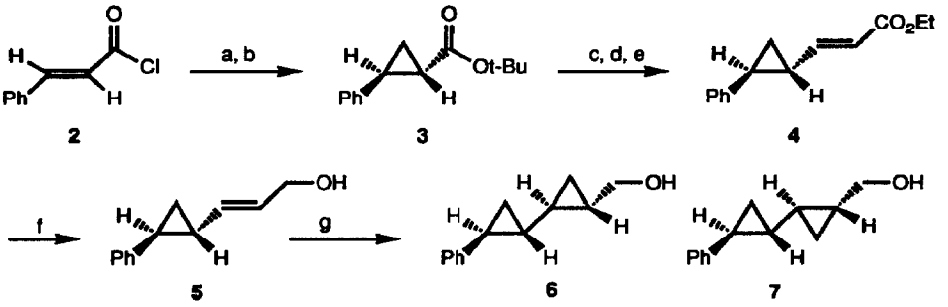



**1** FR-900848

Synthetic approaches to acyclic chains containing more than a single cyclopropane are quite rare. Until recently, all synthetic efforts were limited to the preparation of relatively simple or achiral bicyclopropanes and the *cis*- and *trans*- tricyclopropanes, both of which required the control of only two stereocenters.[3] The challenge of synthesizing a bi- or tricyclopropane in which each individual cyclopropane contains two stereocenters is formidable. While *cis*- or *trans*- cyclopropane stereochemistry can often be established through the selection of an appropriate starting material, control of the *syn*- or

*anti*- relationship between adjacent cyclopropanes will require a highly diastereoselective reaction. A recent report in the literature has prompted us to report our initial results on the diastereoselective preparation of trans-disubstituted bicyclopropanes.[4]

One of the most widely used methods for the preparation of cyclopropanes is the addition of a carbenoid methylene to an olefin, often facilitated by a neighboring heteroatom. We felt that preparation of a vinyl cyclopropane which contains a primary allylic alcohol would give not only a reactive bicyclopropane precursor, but would provide an attractive functional group handle from which to build additional cyclopropanes. The question to be answered is what influence, if any, the stereogenic centers on the existing cyclopropane have on olefin facial selectivity. We selected vinylcyclopropane **5** as a model compound from which to study the syn/anti selectivity of bicyclopropane formation.



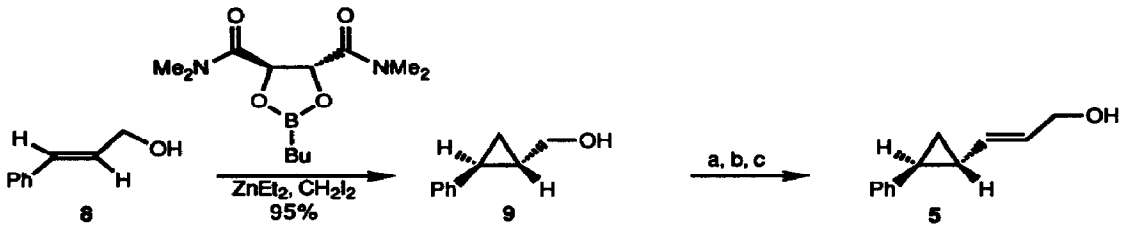

a) KOt-Bu, t-BuOH, 0° C, 79%; b) $(CH_3)_2S(O)CH_3^+ I^-$, NaH, DMSO, 55° C, 70%; c) $LiAlH_4$, THF, 0°, 97%; d) PCC, $CH_2Cl_2$, 25° C, 68%; e) $(EtO)_2P(O)CH_2CO_2Et$, n-BuLi, 0° C, 74%; f) DIBAL-H, THF, -78° C to room temp, 91%, g) $Et_2Zn$, $CH_2I_2$, 0° to room temp, 78%.

**Scheme 1**

Vinylcyclopropane **5** was prepared from cinnamoyl chloride in a five step procedure in which the initial cyclopropane was incorporated using a sulfur ylide (Scheme 1).[5] The t-butyl ester of **3** was reduced with $LiAlH_4$, oxidized to the aldehyde with PCC, and reacted via the Horner-Emmons protocol to give a 20:1 mixture of olefin isomers from which the major E-isomer **4** could be separated by careful chromatography on silica. Attempts to reduce **4** with $LiAlH_4$ resulted in formation of the saturated alcohol, however DIBAL-H reduction gave the allylic alcohol **5** in 91%. Cyclopropanation of the alcohol **5** via the Furukawa modification of the Simmons-Smith reaction resulted in formation of an inseparable mixture of the *syn*- and *anti*- bicyclopropanes **6** and **7**.[6] The diastereomeric ratio of these two compounds was determined to be 1.3:1 by both $^{13}C$ NMR[7] and capillary zone electrophoresis.[8]

The stereochemical assignments for the two diastereomers **6** and **7** were made through the selective synthesis of the two individual isomers. Since the existing stereocenters would not provide sufficient stereocontrol we required a stereoselective cyclopropanation method mediated by a removable chiral auxiliary. Although we initiated these studies using the covalently-bound acetal method of Yamamoto,[9] the attractiveness of a non-covalently bound chiral auxiliary which promotes the stereoselective introduction of a cyclopropane led us to adopt the recently reported method of Charette.[10] This method

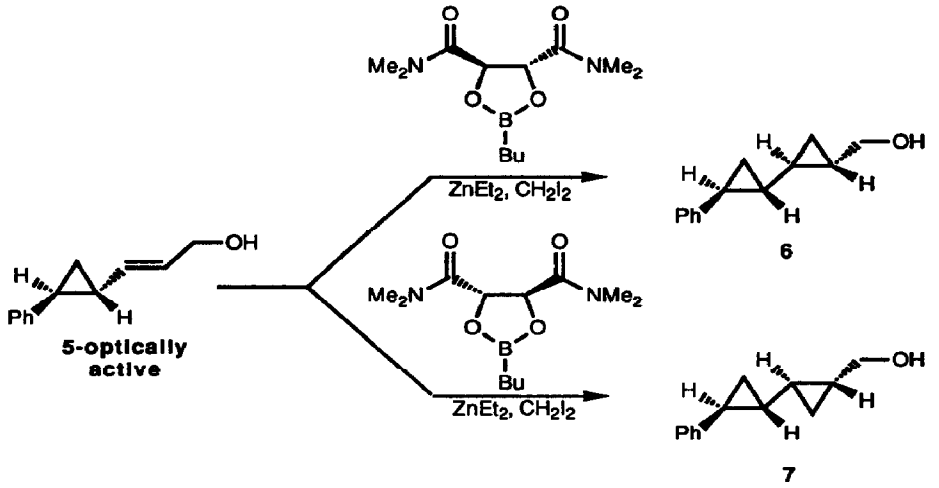
utilizes a tartrate-derived dioxaborolane as a stoichiometric additive to a diethylzinc-mediated cyclopropanation.




a) TPAP, N-methylmorpholine N-oxide, room temp, 85%; b) $(EtO)_2P(O)CH_2CO_2Et$, n-BuLi, 0° C, 80%; c) DIBAL-H, THF, -78 to room temp, 91%.

**Scheme 2**

Cinnamyl alcohol **8** was converted to an enantiomerically enriched cyclopropane **9** (92% ee)[11] by the reaction with diethylzinc, methylene iodide, and a (+)-tartrate derived dioxaborolane (Scheme 2). The alcohol **9** was oxidized with TPAP, condensed with a phosphonate anion, and subsequently reduced with DIBAL-H to give the corresponding optically active allylic alcohol **5**. The *syn*-bicyclopropane isomer **6** was produced in 67% by reaction with diethylzinc, methylene iodide, and the (+)-tartrate-derived dioxaborolane, while the *anti*-bicyclopropane isomer **7** was prepared in 72% by substituting the (-)-tartrate-derived dioxaborolane (Scheme 3). The diastereoselectivities observed in the formation of **6** and **7** have been consistently greater than 12:1, resulting in an overall diastereomer ratio of greater than 10:1 for each targeted bicyclopropane. Comparison of the $^{13}C$ NMR spectra allowed us to assign the major isomer from the initial study (Scheme 1) as the *anti*-isomer **7**.




**Scheme 3**

In conclusion, we have demonstrated a short, efficient, and highly diastereo- and enantioselective approach to both *syn-* and *anti- trans*-disubstituted bicyclopropanes. The efficient preparation of longer, stereocontrolled cyclopropane sequences should be possible by this reagent-controlled process. The use of an external chiral auxiliary to control stereochemistry is far superior to an approach which relies upon existing cyclopropane stereocenters for diastereocontrol. Studies are underway on the preparation and properties of longer cyclopropane sequences.

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7 In order to ensure complete relaxation of the carbon nuclei, a 2 minute pulse delay was used during acquisition. Each pair of the diastereotopic cyclopropane carbons was compared by integration. This provided ratios varying from 1.28:1 to 1.34:1.

8 We would like to acknowledge the assistance of Professor Sterling Tomellini and James Clothier of the University of New Hampshire for their assistance with this analysis.

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