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A Divergent Diastereoselective Approach to Bicyclopropanes

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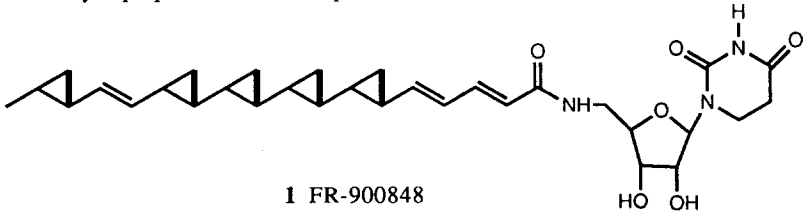
Abstract: The diastereoselective cyclopropanation of three stereoisomerically unique vinylcyclopropanes was studied. The selective preparation of six stereoisomeric bicyclopropanes was accomplished by an iterative reagent-controlled process. With the exception of the cis-syn-trans-bicyclopropane, all isomers can be prepared in a diastereomeric excess of greater than 5:1.

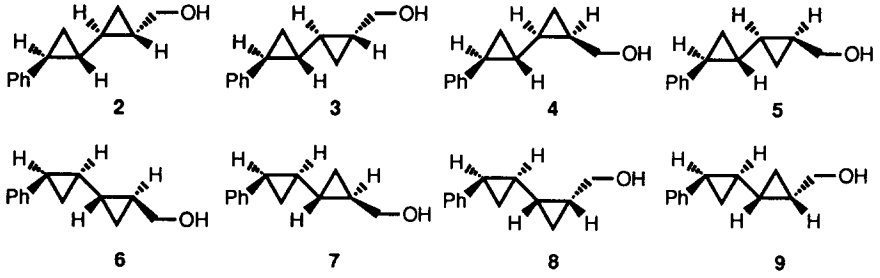
A structurally unique natural product recently isolated from a fermentation broth of *Streptoverticillium fervens* has shown remarkably selective activity toward filamentous fungi.[1] FR-900848 (**1**) is a fatty acid nucleoside which possesses an unprecedented five cyclopropanes on a single fatty acid backbone, four of which are located on consecutive two-carbon fragments. The initial literature report provided no stereochemical information for the ten cyclopropyl stereocenters on the fatty acid backbone, however a recent report by Falck has suggested that the polycyclopropane stereochemistry of the natural product is a repeating trans-syn-trans relationship.[2] The combination of the unusual structure and the selective biological activity makes FR-900848 (**1**) and its analogues attractive synthetic targets. Numerous synthetic approaches to polycyclopropanes have been described recently, however all of these efforts have been directed toward the preparation of polycyclopropanes which possess the trans-syn-trans and trans-anti-trans stereochemical relationships.[3] No synthetic efforts directed toward polycyclopropanes which include cis-cyclopropanes have been reported.



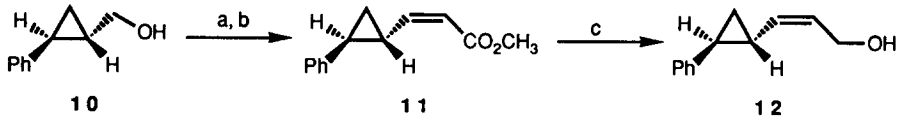
1 FR-900848

Our interest in studying the relationship of polycyclopropane configuration and conformation to the chemistry and biochemistry of polycyclopropanated fatty acids demands access to all possible stereochemical relationships. We are interested in developing a strategy by which we can prepare any bicyclopropane while efficiently controlling its diastereomeric relationship. We have previously reported a

reagent-controlled strategy in which we can incorporate adjacent to a trans-cyclopropane a second trans-cyclopropane with efficient control of the syn-(**2**) and anti-(**3**) stereochemical relationship.[3c] We report in this communication both the syn-**4** and anti-**5**-selective incorporation of a cis-cyclopropane next to an initial trans-cyclopropane. We also report the syn- and anti-selective incorporation of both cis- and trans-cyclopropanes adjacent to an initially-formed cis-cyclopropane to give the bicyclopropane isomers **6** - **9**. All of these approaches rely heavily on the enantioselective cyclopropanation methodology of Charette which utilizes tartrate-derived dioxaborolanes as the chiral-inducing agent.[4]



The allylic alcohol which serves as the precursor to the trans-syn-cis and trans-anti-cis bicyclopropanes **4** and **5** was prepared[5] (Scheme 1) from the optically active cyclopropane **10** (85% ee)[6] by TPAP/NMO oxidation[7] followed by application of the cis-selective Horner-Wadsworth-Emmons modification of Still.[8] The cis and trans isomers of the α, β-unsaturated ester (12:1 ratio) were easily separated and the cis isomer **11** reduced with DIBAL-H to provide the allylic alcohol **12**.

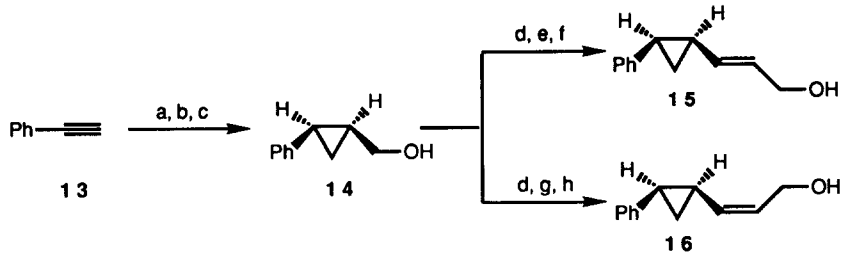


a) TPAP, N-methylmorpholine N-oxide, 0°, 90%; b) $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$, KHMDS, 18-crown-6, -78° C, 77%; c) DIBAL-H, THF, -78 to room temp, 91%.

Scheme 1

Preparation of the cis-cyclopropane series (Scheme 2) began with the hydroxylmethylation of phenyl acetylene **13**, followed by a Lindlar reduction of the alkyne.[9] The intermediate cis-allylic alcohol was converted to the enantiomerically enriched cyclopropane **14** (75% ee)[10] by utilization of Charette's method using the L-tartrate-derived dioxaborolane.[4] The two allylic alcohols **15** and **16** were prepared in parallel by oxidation with TPAP/NMO, application of a trans- or cis-selective Horner-Wadsworth-Emmons reaction, and reduction with DIBAL-H.

We initiated our investigation of the cyclopropanation of the allylic alcohol **12** (Table 1) by probing the stereochemical influence of the existing cyclopropane. Compound **12** was cyclopropanated in the absence of chiral dioxaborolane to give nearly a 1:1 ratio of the syn-(**4**) and anti-(**5**)-bicyclopropanes.[11]

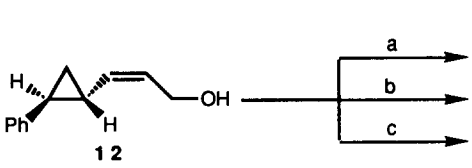


a) i) n-BuLi, ii) CH_2O, 0° C, 79%; b) Lindlar's catalyst, H_2, 70%; c) Et_2Zn, CH_2I_2, L-tartrate-derived dioxaborolane, 0°, 97%; d) TPAP, N-methylmorpholine-N-oxide, 0°, 86%; e) $(EtO)_2P(O)CH_2CO_2Et$, n-BuLi, 0° C, 65%; f) DIBAL-H, THF, -78° C to room temp, 90%, g) $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$, KHMDS, 18-crown-6, -78° C, 70%; h) DIBAL-H, THF, -78° C to room temp, 90%,

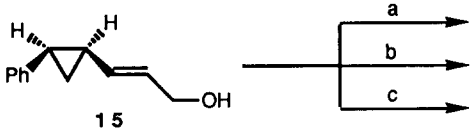
Scheme 2

This lack of selectivity is consistent with a similar observation in the study of the trans-trans bicyclopropanes.[3c] However, application of the reagent-controlled process of Charette[4] allowed the efficient preparation of the syn and anti diastereomers **4** and **5**.[12]

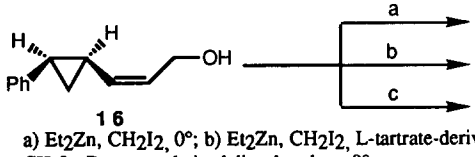
Table 1 Diastereoselectivity of Bicyclopropane Formation



	yield	ratio 4/5
a	79 %	1 : 1.3
b	78 %	1 : 6
c	81 %	10 : 1



	yield	ratio 6/7
a	82 %	1 : 9
b	81 %	2.5 : 1
c	79 %	1 : >10



	yield	ratio 8/9
a	85 %	1 : 2.8
b	80 %	1 : 5
c	79 %	5 : 1

a) Et_2Zn, CH_2I_2, 0°; b) Et_2Zn, CH_2I_2, L-tartrate-derived dioxaborolane, 0°; c) Et_2Zn, CH_2I_2, D-tartrate-derived dioxaborolane, 0°;

The series of bicyclopropanes derived from the cis-substituted cyclopropanes **15** and **16** was studied in a similar fashion. When vinylcyclopropane **15** was exposed to diethylzinc and methylene iodide in the absence of chiral dioxaborolane, a surprisingly diastereoselective reaction (9:1) was observed. The exposure of **15** to diethylzinc and methylene iodide in the presence of D-tartrate-derived dioxaborolane confirmed that the major product **7** formed in the substrate-controlled process possessed the anti-stereoisomeric relationship. Exposure of **15** to cyclopropanation conditions containing the L-tartrate-

derived dioxaborolane provided only a modest 2.5:1 syn/anti selectivity thereby demonstrating that the anti-directing influence of the substrate is competitive with the reagent-controlled selectivity.

Vinylcyclopropane **16** was exposed to the same set of reaction conditions. The syn- and anti-stereoisomers **8** and **9** were prepared with fair diastereoselectivity using the reagent-controlled process, while cyclopropanation of compound **16** in the absence of chiral dioxaborolane favored the anti bicyclopropane **9** in a modest 2.8:1 ratio.

In conclusion, we have demonstrated that syn- and anti-bicyclopropanes which incorporate both cis-and trans-cyclopropanes can be efficiently prepared. With one exception, that being the cis-syn-trans isomer **6**, the bicyclopropanes have been generated in diastereomeric ratios of greater than 5:1 using a reagent-controlled strategy. This study suggests that longer polycyclopropanated fatty acids, which contain multiple stereochemical combinations, can be approached using an iterative reagent-controlled strategy. Efforts to apply the selectivity of these reactions to the preparation of longer polycyclopropanes and to probe the nature of the substrate-controlled selectivity in formation of **7** are currently underway.

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5 All reported yields are of the isolated pure compounds. All compounds have been characterized by ^{1}H and ^{13}C NMR, optical rotation, and either mass spectral or elemental analysis.

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11 Diastereoselectivities were determined by integrating the cyclopropane ^{13}C-NMR signals. Ratios were calculated for each of the six diastereomeric pairs of signals with the average ratio reported.

12 The syn and anti stereochemistry is assigned on the basis of the expected facial selectivity reported in the cyclopropanation of cis and trans olefins by Charette (ref. 4).

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