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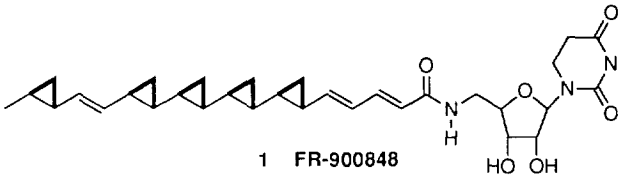
Ylide-Mediated Bis-Cyclopropane Formation: A Reversal in Substrate-Mediated Facial Selectivity

Regina E. J. Cebula, Morgan R. Hanna, Cory R. Theberge, Christopher A. Verbicky, and Charles K. Zercher*

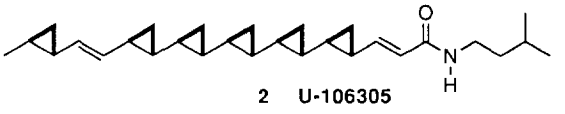
Department of Chemistry, University of New Hampshire, Durham, NH 03824

Abstract: The substrate-based stereocontrol observed in the sulfur ylide mediated cyclopropanation of *cis*-β-cyclopropyl-α,β-unsaturated esters is complementary to that observed with zinc-carbenoids. The selectivity for preparation of the *cis*-syn-*trans*-bis-cyclopropane, although modest, is superior to previous substrate and reagent-mediated processes.

The recent identification of two novel polycyclopropanated natural products, FR-900848 (**1**) and U-106305 (**2**), has stimulated interest in methods for the stereoselective preparation of polycyclopropanated fatty amides. The first of these two compounds, FR-900848 (**1**),[1] has attracted a great deal of attention due to its unusually specific biological activity and unprecedented structure.[2,3,4] The more recent discovery of a cholesteryl ester transfer protein (CETP) inhibitor, U-106305 (**2**), provided a second member of this family of natural products.[5] Stereochemical assignments for the multiple stereocenters in both FR-900848 and U-106305 have been established through the successful total syntheses of the two natural products.[4, 5b]



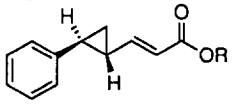
1 FR-900848



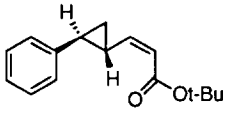
2 U-106305

Our desire to develop an iterative method suitable for the stereoselective preparation of every stereoisomeric polycyclopropane[3] has encouraged us to consider a variety of cyclopropanation methodologies. Sulfur ylides have been used for the cyclopropanation of electron-deficient olefins for many years[6] and are quite attractive for the synthesis of polycyclopropanes. Addition of the sulfur ylide through nucleophilic attack at the β-position of compounds **3-7** would establish the syn- or anti-stereochemical relationship of the two cyclopropanes. Since this bond formation occurs adjacent to the γ-stereocenter, the substrate-controlled stereoselectivity of the process may be enhanced.[7] Furthermore,

application of a one-pot transformation of carboxylate esters to chain-extended α,β-unsaturated esters[8] coupled with sulfur ylide-mediated polycyclopropane formation results in a two-pot iterative process.



3a R = Me
3b R = Et
3c R = t-Bu



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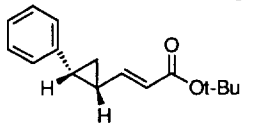

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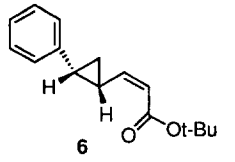

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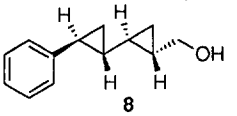
Three different esters of the *trans*-E vinylcyclopropane were initially prepared. Compounds **3a** and **3b** was generated by DIBAL-H reduction of a *trans*-cyclopropyl ester[3] and immediate treatment of the aldehyde equivalent with an appropriate preformed Horner-Emmons reagent. The α,β-unsaturated ester **3c** was prepared by treating the *trans*-carboxaldehyde with the salt of t-butyl diethylphosphonoacetate.[9] The three substrates **3a-c** were exposed to sulfoxonium methylide with the most efficient conversion to bis-cyclopropanes occurring with **3c**.[10] Due to the enhanced efficiency of the t-butyl ester, subsequent studies of isomeric vinyl-cyclopropanes **4**, **5**, and **6** were restricted to the t-butyl esters.

The other three vinyl cyclopropanes **4**, **5**, and **6** were prepared from the corresponding cyclopropane carboxaldehydes. Compound **5** was prepared by treating the *cis*-carboxaldehyde with the salt of *t*-butyl diethylphosphonoacetate.[10] Formation of the Z-isomers through the Still modification of the Horner-Emmons reaction[11] required preparation of *t*-butyl bis(trifluoroethyl)phosphonoacetate **7** which we were able to prepare through the sodium hydride induced acylation of bis(trifluoroethyl) methylphosphite with t-butylpyrocarbonate.[12] Exposure of the *trans*- and *cis*-cyclopropane carboxaldehydes to **7** provided access to both **4** and **6** with impressive Z-selectivity.

We treated the individual α,β-unsaturated esters **3**, **4**, **5**, and **6** with excess dimethylsulfoxonium methylide and reduced the bis-cyclopropyl *t*-butyl ester products with DIBAL-H to provide the bis-cyclopropyl alcohols.[13] The ^{13}C NMR spectra of the resultant product mixtures were compared to those of eight previously prepared bis-cyclopropyl alcohols (including **8**, **9**, **10**, and **11**) in order to elucidate the amount of substrate-based stereocontrol.[3,14] Vinyl cyclopropane **3c** gave a 1:1.2 mixture of the *trans*-syn-*trans* biscyclopropane **8** and *trans*-anti-*trans* biscyclopropane **9**. Likewise, the *trans*-Z vinyl-cyclopropane **4** resulted in the nearly identical formation of a 1:1.3 (syn:anti) ratio of bis-cyclopropane isomers **8** and **9**. The low substrate-based stereocontrol and the slight anti-preference in these reactions were nearly identical to those observed for the zinc-carbenoid cyclopropanation of allylic alcohols.[3]



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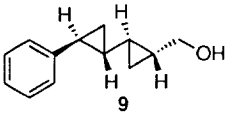

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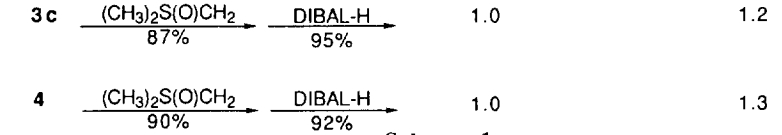
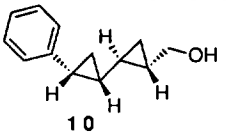


Scheme 1

Fortunately, methods which result in efficient reagent-based stereocontrol have been developed for compounds **8** and **9**.

Cyclopropanation and subsequent reduction of *cis*-E ester **5** provided a 3:1 mixture of bis-cyclopropanes **10** and **11**. A similar mixture of the bis-cyclopropanes **10** and **11** was obtained by treatment of the *cis*-Z-isomer **6**. The remarkable feature of these two reactions is the substrate-based stereocontrol. While selectivity in the zinc carbenoid-mediated cyclopropanation of the analogous allylic alcohols also testified to the influence of the *cis*-cyclopropane's stereocenters,[3b] *the substrate-based stereocontrol observed in the sulfur ylide reactions is complementary to that observed in the zinc carbenoid study.* This reversal in stereocontrol could be merely a reflection of the differences in conformational biasing between electron-rich and electron-deficient vinyl-*cis*-cyclopropanes,[15] however the mechanistic



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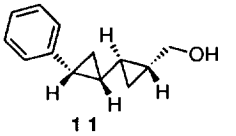

11

5	$(CH_3)_2S(O)CH_2$ 52% →	DIBAL-H 57% →	3.0	1.0
6	$(CH_3)_2S(O)CH_2$ 78% →	DIBAL-H 86% →	2.0	1.0

Scheme 2

differences between these two cyclopropanation methods cannot be ignored.[16,17] It is likely that the relative energies of conjugate addition, β-elimination, cyclopropane ring closure, and bond rotation all play a role in product determination.

The complementary substrate-based stereocontrol present in the sulfur ylide reaction takes on additional importance when determining the most efficient method to prepare specific bis-cyclopropanes. The reagent-stereocontrolled effort which uses zinc carbenoids to append a *trans*-cyclopropane adjacent to a *cis*-cyclopropane with syn-stereocontrol (as in **10**) has resulted in only modest stereocontrol.[3b] Since the inefficiency of this zinc-carbenoid strategy for the preparation of **10** appears to be due to the mismatched influences of the reagent-based and substrate-based stereodirecting elements, it appears unlikely that zinc-carbenoid strategies can be developed for the efficient preparation of *cis*-syn-*trans* bis-cyclopropanes. *However, it should be recognized that the substrate-stereocontrolled cyclopropanation of* ***5*** *with dimethylsulfoxonium methylide generates a precursor to* ***10*** *with improved stereoselectivity when compared to the reagent-stereocontrolled zinc-carbenoid method.* When these two cyclopropanation methodologies are considered, the simplicity and inexpensive nature of the substrate-stereocontrolled sulfur ylide process makes it the method of choice for the preparation of compounds which possess the *cis*-syn-*trans* stereoisomeric relationship of bis-cyclopropanes. Furthermore, it should be possible to enhance the syn-facial selectivity of the sulfur ylide with an appropriate chiral reagent.[18]

In conclusion, we have demonstrated that addition of sulfoxonium ylides to electron deficient vinyl cyclopropanes results in the efficient formation of bis-cyclopropanes. Although poor substrate-based stereocontrol was observed with *trans*-cyclopropanes, the modest substrate-based stereocontrol observed

with the *cis*-cyclopropane isomers was superior to the more expensive and synthetically challenging reagent-based method reported previously.[3b] The simplicity, inexpensive nature, and potential for iterative application makes the use of sulfur ylides attractive for polycyclopropane preparation.

Acknowledgements: We would like to thank the NIH (R15 GM51064), the Petroleum Research Fund administered by the American Chemical Society (25689-G1), and the University of New Hampshire Undergraduate Research Opportunities Program (MRH) for their support.

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13 **General procedure for the sulfur ylide-mediated cyclopropanation / DIBAL-H reduction** Into a flask was added 2.5 equiv. of a 60% dispersion of sodium hydride. A solution of 2.5 equiv. of trimethylsulfoxonium iodide in DMSO was added. After hydrogen evolution ceased, one equiv. of the requisite α,β–unsaturated ester **3-6** in DMSO was added and the solution stirred overnight. The reaction was quenched with water and extracted with diethyl ether. The combined ether extracts were washed with water, dried with $MgSO_4$, filtered, and concentrated. The crude product was stirred in THF at -78 °C while 6 equiv. of DIBAL-H in toluene was added. The reaction was quenched at room temperature by the addition of 2N NaOH, dried with $MgSO_4$, filtered, and concentrated. The crude oil was purified by chromatography on silica.

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