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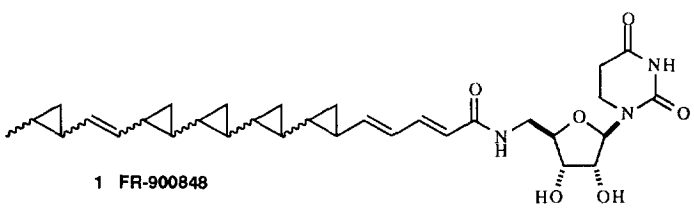
Synthesis of Vicinal Cyclopropanes

Robert W. Armstrong* and Karl W. Maurer

Department of Chemistry and Biochemistry,
University of California at Los Angeles,
Los Angeles, CA 90024

Abstract: An iterative strategy for the synthesis of conjugated cyclopropanes was developed, resulting in the generation of the trans,trans dicyclopropane derivative **16** in high enantiomeric excess.

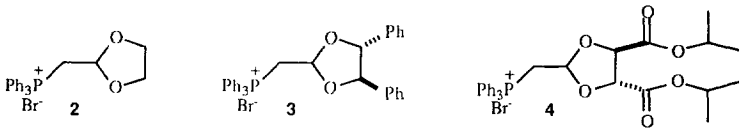
We have evaluated two routes to the synthesis of vicinal cylclopropanes with the goal of generating conjugated di-, tri- and tetracyclopropanes of defined absolute and relative stereochemistry. These compounds are related to the natural product FR-900848 (**1**), whose proposed planar structure contains a total of five cyclopropane rings, four of them conjugated.[1] FR-900848 was isolated from *Streptoverticullum fervens* HP-891 and is active against filamentous fungi but not yeast, Gram-negative or -positive bacteria. The conformationally diverse ground states available from the various cyclopropyl side-chain diastereomers, their relationship (if any) to biological activity, and their unique synthetic challange led us to analyze several synthetic routes. Described herein is the synthesis of trans, trans dicyclopropane **16**, obtained in high enantiomeric excess via a route amenable with the generation of all possible diastereomers.



1 FR-900848

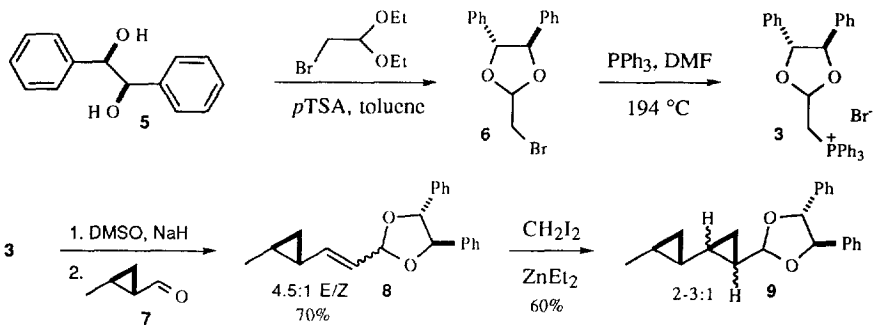
Several groups have developed strategies for stereospecific cyclopropanations using azaesters in the presence of asymmetric catalysts.[2] Catalytic cyclopropanations using the Simmons-Smith reagent show some promise, but the enantiomeric excess is insufficient for a multi-cycle linear synthesis.[3] Work by Yamamoto [4] and Mash [5] with C_2 symmetrical chiral auxiliaries attached to achiral unsaturated aldehydes and ketones by the formation of acetals and ketals appeared most promising.[6] Yamamoto reports high

yields and high enantiomeric excess (>90 %) with the readily available diisopropyl tartarate auxiliary. We hoped to use a similar chiral auxiliary in an iterative process, generating ylids described by structure **2**[7] to afford the unsaturated acetal substrates for the cyclopropanation reaction directly from the precursor aldehydes.



A mixture of (R, R)-dihydrobenzoin **5** (Scheme 1) and bromoacetaldehyde diethyl acetal in the presence of *p*-TSA were subjected to toluene azeotrope thereby affording **6**.[8] Arbuzov reaction with triphenylphosphine generated ylid **3**. On deprotonation with sodium dimsolate, the ylid reacted with aldehyde **7**[9] affording a mixture of **8** which was marginally separable by chromatography.

Scheme 1

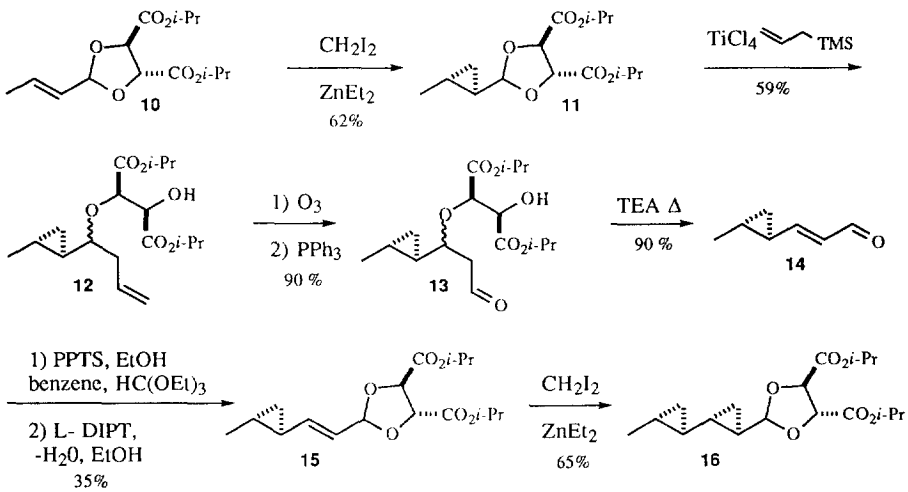


Cyclopropanation of the E diastereomer of **8** under standard Simmons-Smith conditions afforded **9** in <50 % diastereoselectivity. The absolute induction in the cycloporpanation was opposite that predicted for the tartrate analog.[10] Separation of the dicyclopropanated diastereomers proved impractical. While this route appeared promising, difficulties in generating compounds of the type represented by **4** led us to investigate a parallel iterative route.

The diisopropyl tartrate auxiliary is reported to give high selectivity for acyclic unsaturated acetals. Yamamoto showed that crotonaldehyde could be converted to its L-diisopropyl tartarate acetal **10** and cyclopropanated stereoselectively to afford **11** in 94 % e.e. (Scheme 2). We had originally envisioned hydrolysis of this acetal to the aldehyde followed by homologation and re-introduction of the tartrate auxiliary to allow for a repetitive cycle. The hydrolysis of **11** proceeds in low yield due in part to the volatility of the aldehyde. Alternatively, reaction of acetal **11** with allyltrimethylsilane and $TiCl_4$ in anhydrous CH_2Cl_2 at -78° C[11] yielded an inseparable mixture of diastereomers (**12**), corresponding to addition to the acetal. The mixture was subjected to ozonolysis leading to a high yield (90%) of a mixture

of two aldehyde diesteriomers (**13**). Treatment with triethylamine in chloroform at 35°C led to the unsaturated aldehyde **14** in 90% yield. Aldehyde **14** was then converted to its diethyl acetal by reaction with PPTS, triethylorthoformate and ethanol in benzene. This acetal was not isolated and was directly converted to its diisopropyl tartarate acetal **15** by addition of diisopropyl tartarate and azeotropic removal of ethanol. Cyclopropanation of **15** produced dicyclopropane **16** in 65% yield as a single isomer (>90% d.e.).[1,2] The relative and absolute stereochemistry in the cyclopropanation was assigned by analogy to the work of Yamamoto.

Scheme 2



In conclusion, an iterative strategy has been developed for the generation of conjugated cyclopropyl derivatives related to the natural product FR-900848. Further work on these substrates is currently underway in these laboratories.

Acknowledgement

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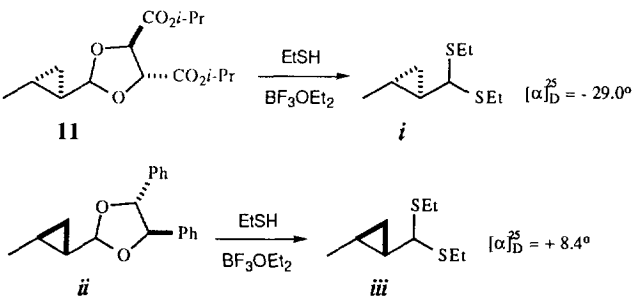
10. The absolute stereochemistry of the cylcopropanation products (*ii* and **9**) using the dihydrobenzoin-derived auxiliary was deduced by comparison of thioacetals *iii* and *i*.. The later was derived from tartrate **11**:



11. For example procedures see Denmark, S.E.; Almstead, N.G., *J. Am. Chem. Soc.* **1991**, *113*, 8089.

12. The diastereoselctivity was determined by analysis of ^{13}C and ^{1}H NMR data. A chiral shift reagent was useful in resolving the upfield region containing the eight cyclopropyl hydrogens in compound **16**.

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