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Diastereoselectivity Control in the Zirconocene-Mediated Ring Contraction of 4-Vinylfuranosides to Enantiopure Multiply Functionalized Cyclobutanes

Leo A. Paquette* and Nicolas Cunière

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

paquette.1@osu.edu

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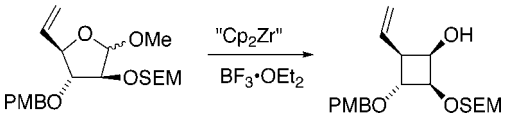
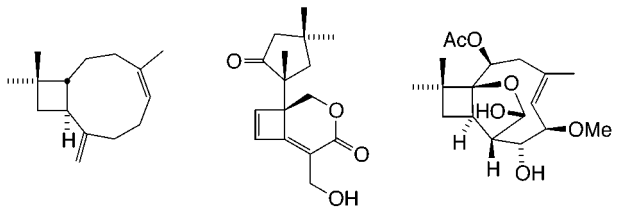
ABSTRACT



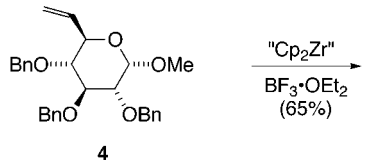
The ring contraction induced by treatment of 4-vinylfuranosides with zirconocene in the presence of boron trifluoride etherate can be rendered highly diastereoselective by proper adjustment of substituent stereochemistry. The two competing transition states that are seemingly involved appear to be usefully sensitive to nonbonded steric interactions.

Enantiomerically pure cyclobutane derivatives have found minimal use in organic synthesis, chiefly because of their general unavailability. The fact that a significant group of structurally diverse cyclobutane-containing natural products represented by γ-caryophyllene (**1**),[1] fommanosin (**2**),[2] and pestalotiopsin A (**3**)[3] has been identified raises the prospect of their asymmetric synthesis from this direction. In this



1 **2** **3**

connection, the readily generated "zirconocene" reagent,[4] often simply depicted as Cp_2Zr, is known to react with allylic ethers with formation of a nucleophilic allylzirconium reagent.[5] In a clever extrapolation of this reaction, Taguchi and co-workers demonstrated that 5-vinylpyranosides exemplified by **4** are transformed cleanly and efficiently under the influence of Cp_2Zr and boron trifluoride etherate into *cis*-2-vinylcyclopentanols such as **6**.[6] The elevated stereoselectivity profile of this ring closure is apparently dictated by nonbonded interactions that favor **5**. In contrast, the use of samarium iodide and palladium(0) eventuates in the generation of a trans relationship between the vinyl and hydroxyl groups.[7]



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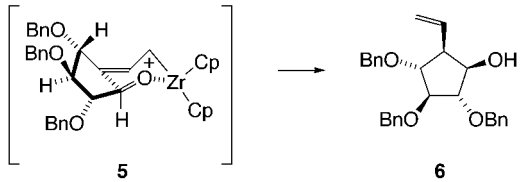

5 **6**

The capacity of this process to transform 4-vinylfuranosides into vinylcyclobutanols is of parallel interest to us in

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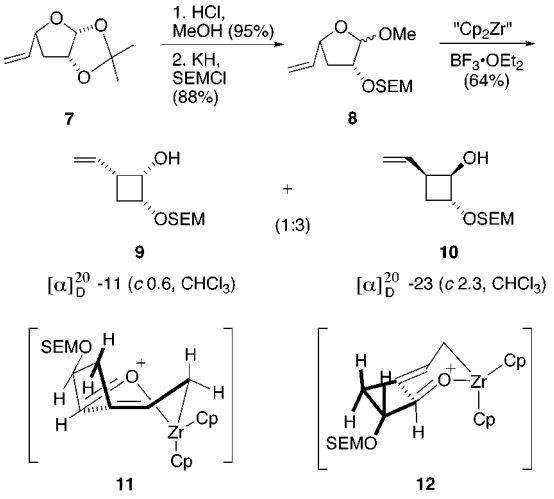
the present context. The low yields and modest stereocontrol sometimes seen in the few examples heretofore reported[6] must obviously be upgraded if applications to targeted synthesis are to be projected. The present report documents those steric factors that gain importance in the diastereomeric transition states. In addition, suitable control of reaction time, temperature, and solvent are shown to enhance overall efficiency.

Advantage was first taken of the ease with which D-glucose can be transformed into **7**[8] (Scheme 1). Following stepwise

Scheme 1



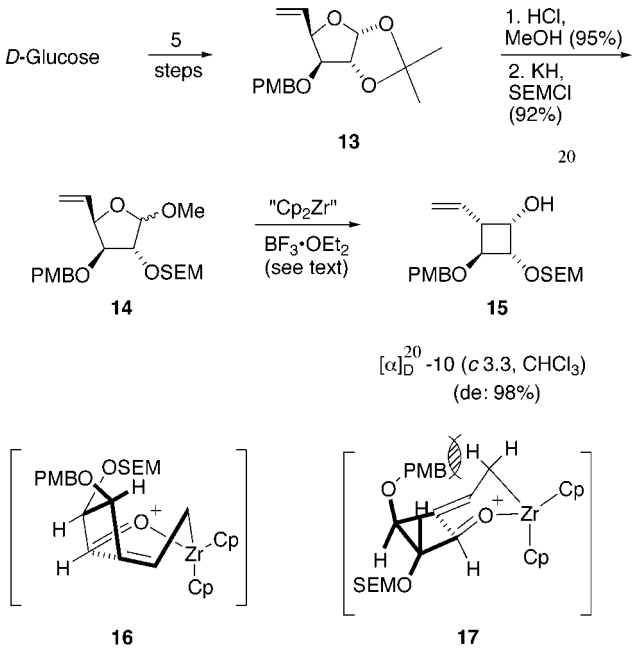
7 **8** **9** **10** **11** **12**

$[\alpha]_D^{20}$ -11 (*c* 0.6, $CHCl_3$) $[\alpha]_D^{20}$ -23 (*c* 2.3, $CHCl_3$)

introduction of the methyl acetal and SEM groups, the stage was set for the zirconocene-mediated ring contraction. In this example, a 1:3 mixture of **9** and **10** was generated in 64% combined yield. Since both anomers react, it would appear reasonable to rationalize this product composition in terms of the faster rate of cyclization within transition state **12** relative to that of **11**. The stability of the SEM protecting group to the reaction conditions holds equally special significance.

The ready conversion of D-glucose to **13**[8c] provided the opportunity to examine the consequences of a β-oriented

Scheme 2



13 **14** **15** **16** **17**

$[\alpha]_D^{20}$ -10 (*c* 3.3, $CHCl_3$) (de: 98%)

OPMB substituent at C-3 on the ring contraction stereoselectivity (Scheme 2). Two important features emerged. The first was that only the α-anomer of **14** reacted. Second, the process was highly stereoselective, giving rise to **15** (98% de) in 35% yield. Since the independent equilibration of the β-anomer of **14** with its α-form operates readily, the overall conversion to **15** after only one additional pass is quite good. These results bring into focus the fact that transition states **16** and **17** are no longer closely balanced energetically as in the case of **11** and **12**. Presumably the adoption of **17** is totally disfavored as a consequence of the steric compression that develops between the OPMB substituent and the allylic methylene group positioned α to the zirconium as illustrated. A relevant point made evident in Scheme 2 concerns the fact that a 3β-oxygenated substituent as in **14** promotes clean reaction via **16**, a transition state prototype otherwise disfavored at a lower level of functionalization (cf. **11**).

The transformation of D-arabinose into carbinol **18** in four steps[9] made possible the convenient acquisition of 4-vinylfuranoside **19** (Scheme 3). When exposed to Cp_2Zr and boron trifluoride etherate, **19** underwent smooth ring contraction to deliver only **20** in an unoptimized yield of 54%. As hoped for, a reversal in the configurations at C-2 and C-3 leads to a switchover in the operational transition state for cyclobutane bond formation. We now see that **21** is so sterically disadvantaged relative to **22** that it is inoperative at a detectable level.

The generality of this completely stereoselective pathway was investigated by generating **24** from the known pivalate

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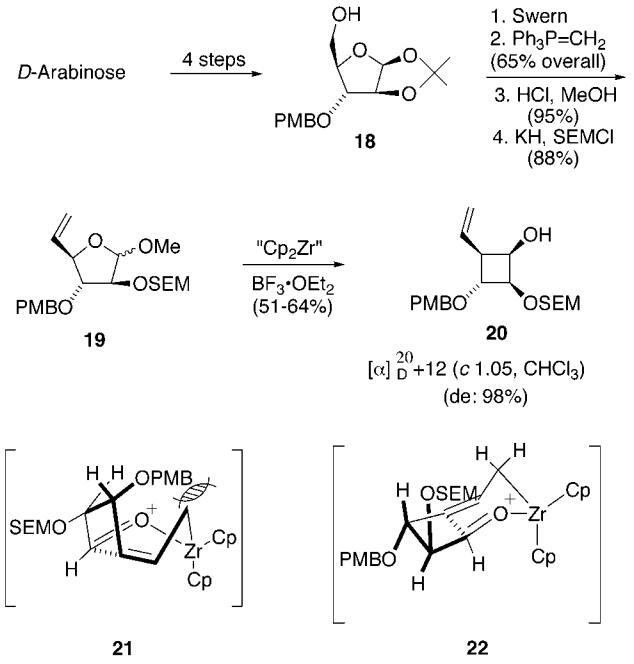
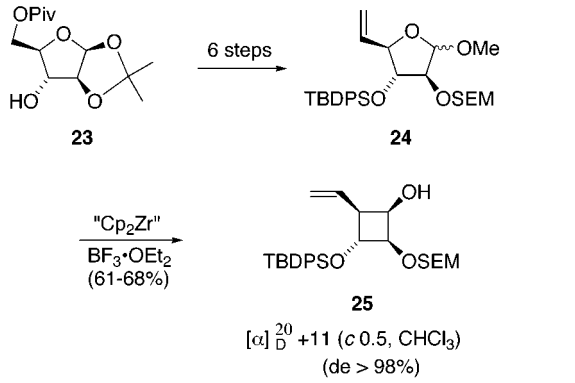
Scheme 3

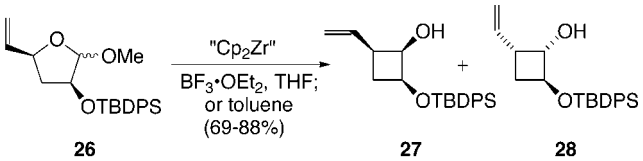


Scheme 4



23[10] (Scheme 4). Similar treatment of **24** with Cp_2Zr and $BF_3{\cdot}OEt_2$ resulted in forward progress to give **25** exclusively in 51% isolated yield. The reasonable working assumption that a transition state of type **22** is again responsible concisely rationalizes the manner in which all four cyclobutane substituents are set in their proper absolute configurational sense.

During the course of these studies, certain additional observations have been made that suggest yield optimization to not yet be in hand. For example, boron trifluoride etherate is not a necessary additive. Its absence when Lewis acid sensitive protecting groups are involved can be compensated for by carrying out the ring contraction at 45 °C for at least 3 h. As a result, the yields of **20**, **25**, and related cyclobutanes were enhanced by approximately 7−13%. Moreover, a change in the reaction medium from tetrahydrofuran to toluene in conjunction with the introduction of $BF_3{\cdot}OEt_2$ at −20 °C followed by no more than 20 min of stirring in the cold has also proven conducive to increased reaction efficiency. Vinylfuranoside **26** constitutes a useful reference substrate. When subjected to the oxygen extrusion process in THF containing $BF_3{\cdot}OEt_2$, this reactant gave rise to the diastereomeric cyclobutanols **27** and **28** in a 1:1.2 ratio (69%). Substitution of toluene as the reaction medium and omission of the Lewis acid were met with an 88% yield of the same alcohols, with **27** now favored by a factor of 2.



Our objectives in this investigation were to demonstrate the predictability of diastereoselective pathways associated with the zirconocene-promoted conversion of 4-vinylfuranosides into heavily substituted, nonracemic cyclobutanes. The direct comparison of two possible transition state options suffices for predictability purposes. The seemingly reliable nature of the nonbonded steric interactions at play during intramolecular formation of the cyclobutane carbon−carbon bond holds considerable value in synthesis design based on enantiopure four-membered ring building blocks. We hope to demonstrate soon various means for utilizing these subtargets to facilitate the synthesis of select natural products.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health for their support of our research programs.

Supporting Information Available: Experimental procedures and characterization for compounds **9**, **10**, **15**, **20**, **25**, **27**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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