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Zirconocene-Mediated Route to Enantiopure 9-Oxabicyclononanes Functionalized on Both Carbon Bridges

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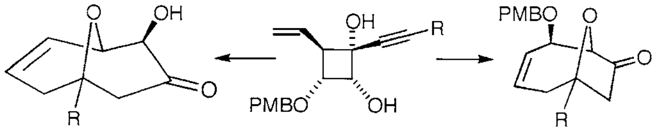
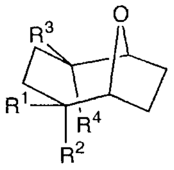
ABSTRACT



A zirconocene-mediated ring contraction of 4-vinylfuranosides generated either from D-arabinose or D-glucose is followed by sequential oxidation to the ketone and alkynyl Grignard addition. The resulting *cis*-cyclobutanediols are subjected in turn to thermal rearrangement and intramolecular oxymercuration-demercuration. The regiochemistry of the final ring closure is controlled by the nature of R.

The unique structural features of oxa-bridged cyclooctanes have caused them to serve as favored building blocks for many types of applications. During the past 35 years, the most commonly applied synthetic route to **1** and **2** has been via electrophilic addition to (*Z*,*Z*)-1,5-cyclooctadiene.[1] If water is present or an oxygenated nucleophile is involved, the incorporation of an oxa bridge results. The process leading to **1** is customarily favored kinetically[2] and somewhat advantaged over that which delivers the bicyclo[3.3.1]nonane alternative **2**. Equilibration between these isomers is possible.[3] 4-Cycloocten-1-ol,[4] its 5-isomer,[1e] 9-oxabicyclo[6.1.0]nonenes,[5] 5-alkoxycyclooct-1-enes,[1e,3c] and cyclooctanol itself[6] have also proven to be suitable precursors.



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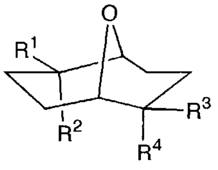

2

Although newer and more elegant routes to this class of heterocycles have been reported recently,[7,8] synthetic undertakings that involve enantioenriched 9-oxabicyclononanes have been very few in number.[9] The present contribution constitutes an attempt to offset this void to some degree. Our entirely new route to compounds of type **1** and **2** is founded on carbohydrates as starting materials. Specifically, advantage is taken of the highly diastereoselective ring contraction that operates upon exposure of 4-vinylfuranosides to zirconocene[10,11] in tandem with a notably facile oxy-Cope

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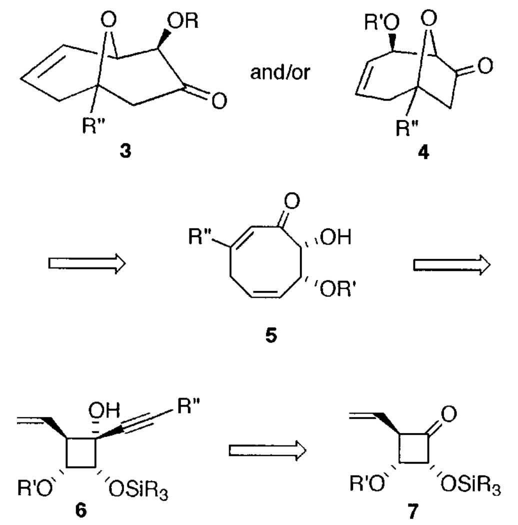
rearrangement and transannular oxymercuration. Most importantly, the absolute stereochemistry resident in the sugar is transformed efficiently and specifically into the heterocyclic product.

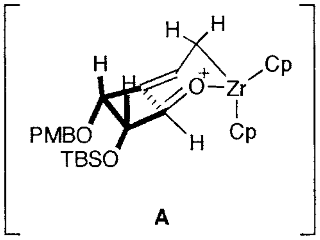
The highly reactive complex generated in situ by treating solutions of Cp_2ZrCl_2 with *n*-BuLi in toluene or THF[12] is often referred to as "zirconocene" and depicted simply as "Cp_2Zr".[13] One of the key properties of this reagent is its ability to enter into ligand exchange with unsaturated compounds. If the substrate is an allylic ether, the high oxophilicity of the zirconium atom subsequently manifests itself via β-elimination of the alkoxy group.[14] Reaction of Cp_2Zr with vinyl sugars in the presence of boron trifluoride etherate results in extrusion of the oxygen atom and formation of a highly functionalized carbocyclic ring, often with high levels of diastereodifferentiation.[10,11] For the present purposes, the goal was to generate 2,3,4-trisubstituted cyclobutanones such as **7** in advance of the stereocontrolled 1,2-addition of an acetylide anion, thermal activation of **6** so produced to deliver **5**, and ultimate conversion to **3** and/or **4** via intramolecular Hg(II)-promoted cyclization[15] (Scheme 1). Indeed, highly functionalized oxabicyclics of type **3** and **4** are attainable from D-arabinose and D-glucose via this protocol.

The *tert*-butylsiloxy substituent in **11** must be α-oriented in the vinyl group. An assessment of this requirement demands that carbinol **8**, which is readily available from D-arabinose,[11,16] be initially subjected to sequential Dess−Martin oxidation[17] and $NaBH_4$ reduction.[18] The ketone intermediate is attacked exclusively syn to the vinyl group, such that **9a** is obtained in 88% overall yield (Scheme 2). After hydroxyl protection, pursuit of the deoxygenative ring contraction of **9b** by Cp_2Zr was examined and found to proceed too slowly to be preparatively useful. Consequently, anomer **10** was prepared and integrated into the synthetic pathway. In an alternative route to **10** developed simultaneously, D-glucose diacetonide was converted to **12a** via the Horton protocol,[19] protected as the *p*-methoxybenzyl ether, and selectively hydrolyzed to give the exocyclic vicinal diol. Advancement to **13** took advantage of the reliability associated with the capability of zinc dust and NaI in hot DMF to induce reductive elimination of the ditosylate.[20−22]

Scheme 1



Exposure of **10** to Cp_2Zr and $BF_3{\cdot}OEt_2$ in toluene resulted in forward progress to deliver **11** as the only characterizable product in 65% yield. The success of this transformation is consistent with adoption of transition state **A**. The manner in which all four cyclobutane substituents are set in a well-defined absolute configurational sense introduces a minimum of nonbonded steric interactions along this reaction trajectory.



A

Oxidation of **11** with the Dess−Martin reagent[17] resulted in formation of the cyclobutanone without loss of stereochemical integrity. As hoped for,[23−25] the double bond does not migrate into conjugation with the carbonyl provided that the use of silica gel chromatography is skirted. The appropriate tactic was to add the acetylenic Grignard directly, in which case 1,2-addition to produce **14a** occurred with complete diastereocontrol (Scheme 3).

This intermediate was, in turn transformed into diol **14b** via mild acid hydrolysis. The platform established in **14b** was responsive to ring strain effects,[26,27] heating in benzene leading smoothly to **15** in quantitative yield. The oxygen

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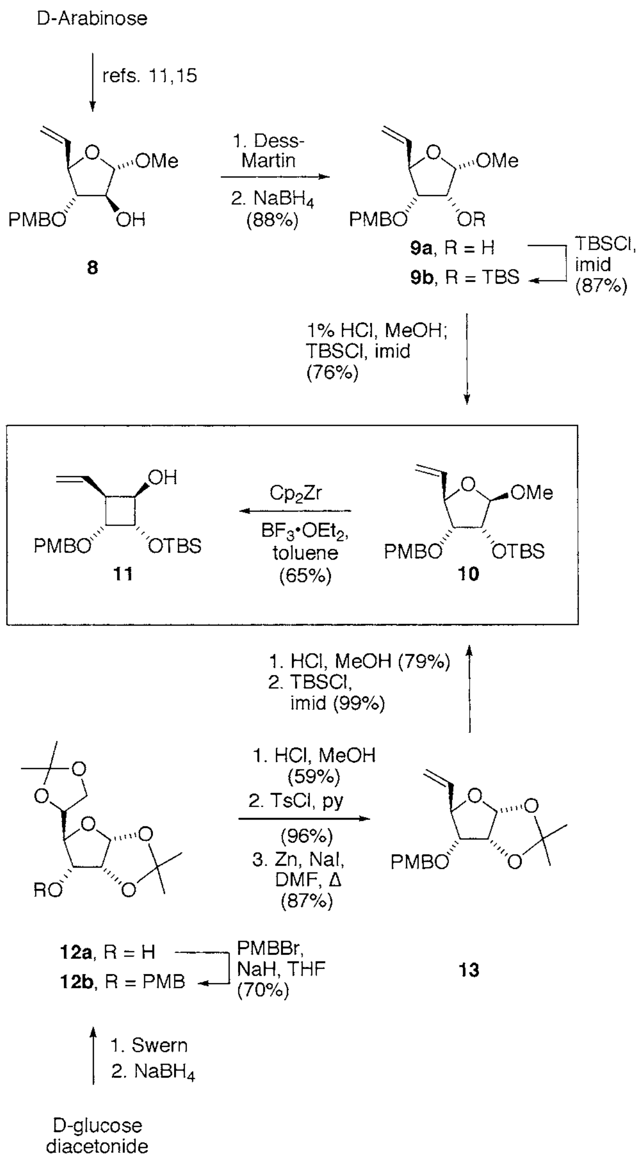
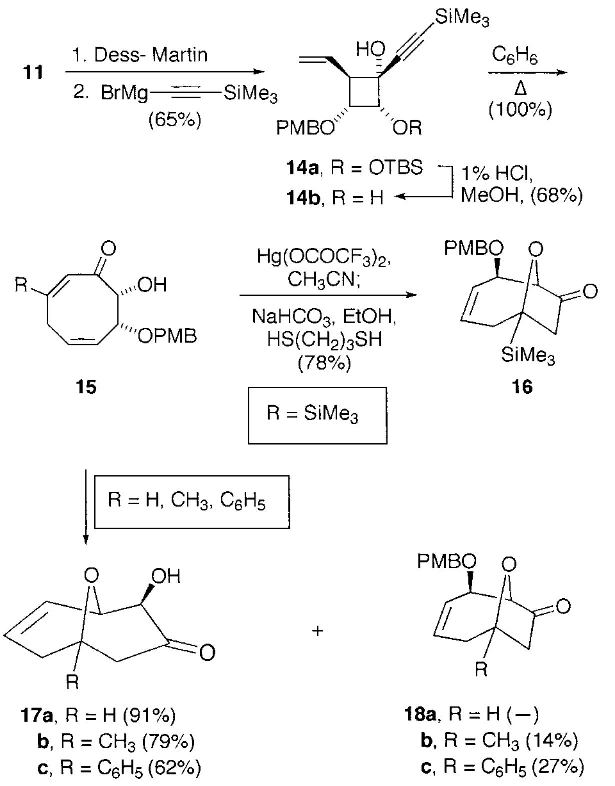
Scheme 2



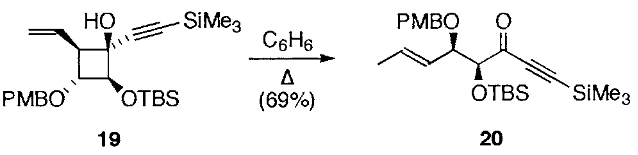
bridge was next installed by subjecting **15** (R = $SiMe_3$) to the action of mercuric trifluoroacetate,[28] with subsequent reductive cleavage of the organomercurial so formed with 1,3-propanedithiol.[29] This two-step sequence gave rise with reasonable efficiency to the [4.2.1] bicyclic ketone **16** (78%). In the case of the protio analogue **15** (R = H), only **17a** was produced in 91% yield, a result of preferred neighboring group participation by the OPMB oxygen center. Analogous treatment of **15** (R = CH_3, C_6H_5) gave rise to readily separable two-component product mixtures in which the bicyclo[3.3.1]nonane isomers **17** were more prevalent.

Scheme 3



In line with the response of 1,2-dialkenylcyclobutanols to thermal rearrangement,[30] the operative pathway adopted by their 1-alkenyl-2-alkynyl congeners is entirely dependent on the cis or trans relationship of the two unsaturated side chains. For **14**, the discharge of strain operates exclusively by oxy-Cope rearrangement.[31] When the groups are disposed trans as in **19**, ring opening occurs by way of a retro-ene process leading to **20** rather than a ring-expanded product (Scheme 4).

Scheme 4



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Supporting Information Available: Full spectral characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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