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Review

Zirconocene-mediated deoxygenative ring contractions of vinyl-substituted carbohydrates: An expedient route to enantiomerically pure, densely functionalized 4-to-8-membered carbocycles

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Abstract

The recent finding that the powerfully electrophilic zirconocene equivalent known as "Cp_2Zr" is capable of transforming vinyl furanosides and pyranosides into enantiomerically pure, highly functionalized *cis*-2-vinyl cyclobutanols and cyclopentanols has been extended in a number of directions. The synthetic potential of this methodology is illustrated by the variety of carbocycles that can be produced, ranging from cyclobutanones, a carbacyclic nucleoside, cyclooctane polyols, and medium-ring carbohydrate mimics. Many of the key transformations are evaluated in terms of transition state energetics.

Keywords: Zirconocene dichloride; Cyclobutanes; Diastereoselectivity control; Carba sugars; (−)-Neplanocin A

Contents

1. Introduction

Once the classical isolationist practices of those chemists specializing in carbohydrate chemistry began to make room for more diverse chemical insight, remarkable growth was experienced. At the present time, the once pronounced demarcation line that sought to represent carbohydrate chemistry as a field unto itself is barely recognizable. It comes as no surprise therefore that preparative advances involving the utilization of organometallic reagents were to herald the advent of exciting new developments.

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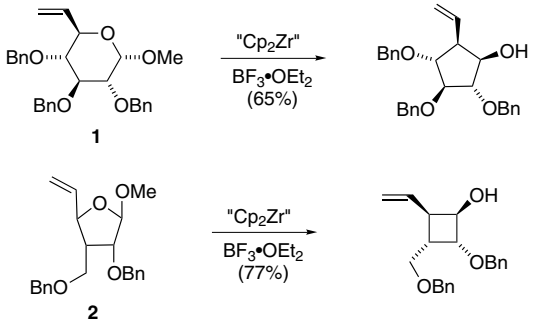
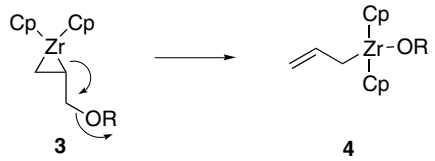
Inevitably, the reaction of carbohydrates with transition metal-based reagents would surface and contribute in a meaningful way to new directions in synthesis. A particularly notable example is the discovery by the Taguchi–Hanzawa team [1] that the action of the zirconocene reagent ("Cp_2Zr") originally developed by Negishi [2] in the presence of boron trifluoride etherate results in a most unusual ring contraction [3]. The response of vinyl pyranoside **1** and the unsaturated furanoside **2** to these conditions is to produce highly functionalized carbocycles in a single operation, most often in good yield, and, as will be outlined below, with predictable diastereoselectivity.

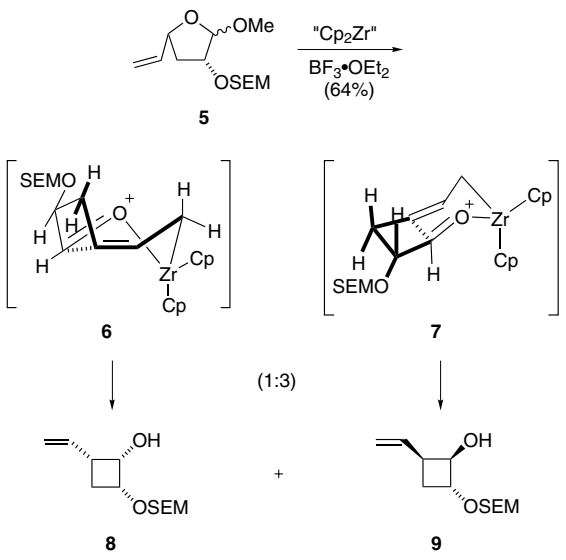


The discovery of these transformations was inspired by knowledge of the high oxophilicity of zirconium, the efficiency with which allylic ethers enter into zirconacycle formation (e.g., **3**) via ligand exchange, and the facility with which elimination of an alkoxy group operates to deliver an allylzirconium species typified by **4** [4–6]. The latter step is mild, proceeds cleanly with 1,3-elimination, and delivers a thermodynamically more stable product. The resulting σ-allylic zirconocene derivatives are capable of reacting smoothly with aldehydes and acetals, particularly in intramolecular examples. While the presence of a Lewis acid is not always mandated in the first instance, one must be present to bring about the ionization of acetal reactants [7].

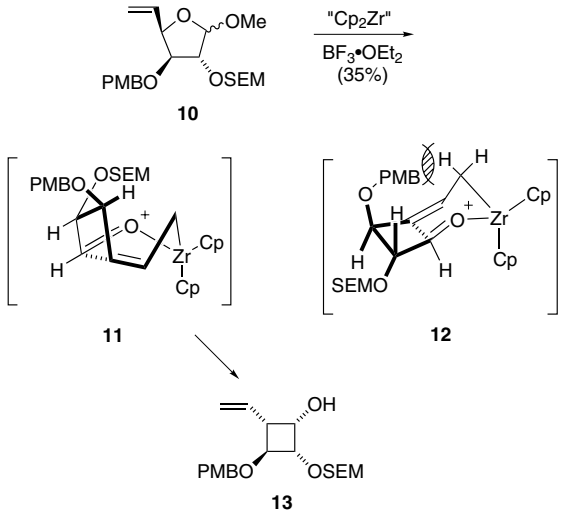


2. Diastereoselectivity control

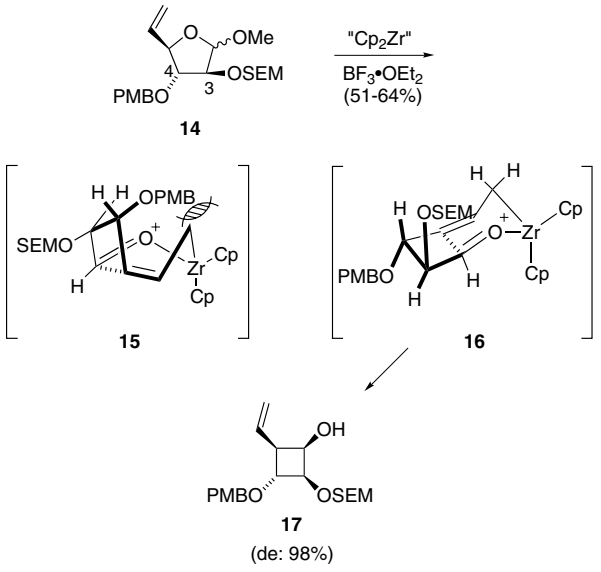
The conditions associated with the protocol outlined above have come to be regarded as relatively mild. The stereochemical course of the ring closure is such that the vinyl and hydroxyl substituents are invariably *cis* related. In addition, these groups are most often oriented *trans* to neighboring functionality when such is present. The specific events can often be controlled by the proper adjustment of the number of substituents and their stereochemistry [8]. When only one additional group is present as in **5**, the level of diastereoselectivity is only modest. Noteworthy, however, is the preferred formation of **9**, which is consistent with an expectedly faster rate of cyclization within transition state **7** relative to that represented by **6**.



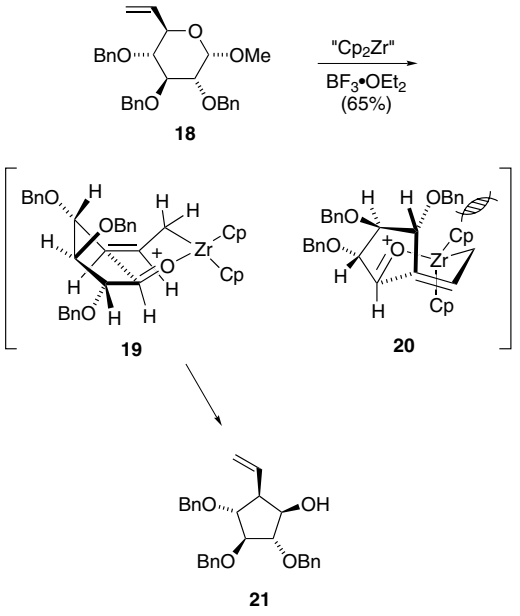
Vinylfuranoside **10** constitutes a more informative example. Its reaction with zirconocene brings into focus the fact that transition states **11** and **12** are not closely balanced energetically as in the prior example. The adoption of **12** is now strongly disfavored as a consequence of the significant steric compression that develops between the OPMB substituent and the allylic methylene group situated α to the zirconium center. Relevantly, the effect of the added 3β-oxy group is to promote the exclusive generation of **13** via **11**.



Reversal of the absolute configuration at C-3 and C-4 as in **14** results in a crossover in the transition state operational for cyclobutane formation. Under these circumstances, option **15** is sufficiently disadvantaged sterically that it is not accessible. As a consequence, **14** is transformed by way of **16** exclusively to **17**, which is isolated in enantiomerically pure form at the 64% level.

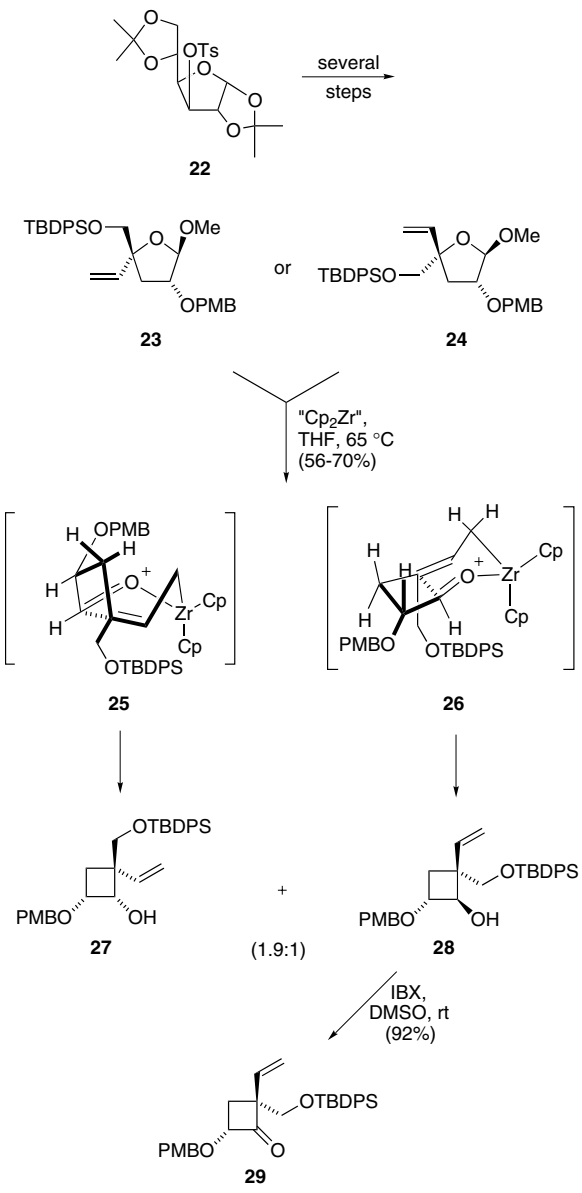


An entirely comparable mechanistic analysis can be applied to 5-vinylpyranosides [3]. For **18**, the stereochemical course that is followed projects all three protected hydroxyls in the manner defined by **19**. The alternative transition state arrangement **20** is disfavored as a direct consequence of the indicated nonbonded steric compression.



3. From D-glucose to a 2,2,4-trisubstituted cyclobutanone

An early opportunity to utilize the title reaction for preparing a 2,2,4-trisubstituted (2*S*,4*R*)-cyclobutanone as defined by **29** soon presented itself [9]. The path selected for arrival at this target involved the D-glucose-derived tosylate **22** [10,11] as starting material. Suitable chemical modification of this building block gave rise independently to the epimeric vinyl furanosides **23** and **24**. The availability of these two advanced intermediates served to bring into focus several yet unexplored mechanistic facets of the ring contraction. Their reactivity toward the zirconocene reagent was independently probed and observed to generate the cyclobutanols **27** and **28** in an identical 1.9:1 ratio (56–70%). Lower yields resulted when boron trifluoride was utilized as the promoter. Magnesium bromide was also tested and found to produce more complex reaction mixtures.

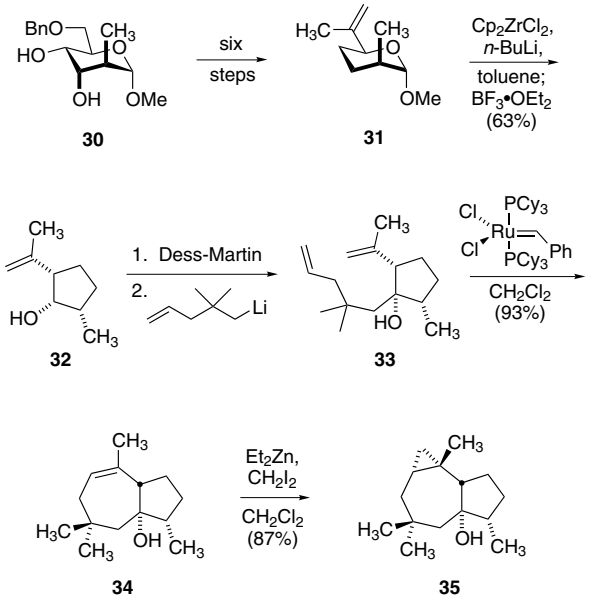


The preceding results show that the stereochemical predisposition of the OPMB group at C-2 exerts a low-level effect on the distribution of **27** and **28** as foreshadowed by the less substituted examples studied earlier. More significantly, the π-facial selectivity associated with complexation of the vinylic double bond to the zirconocene reagent has no obvious product-determining consequences. The *cis* orientation of the vinyl and hydroxyl groups in **27** and **28** most plausibly derives from operation of transition states **25** and **26**, respectively. Also, the quite good efficiency that accompanies the formation of **27** and **28** demonstrates that the

$CH_2OTBDPS$ group residing on the quaternary carbon is not a deterrent to four-membered ring closure, although longer reaction times are required [9].

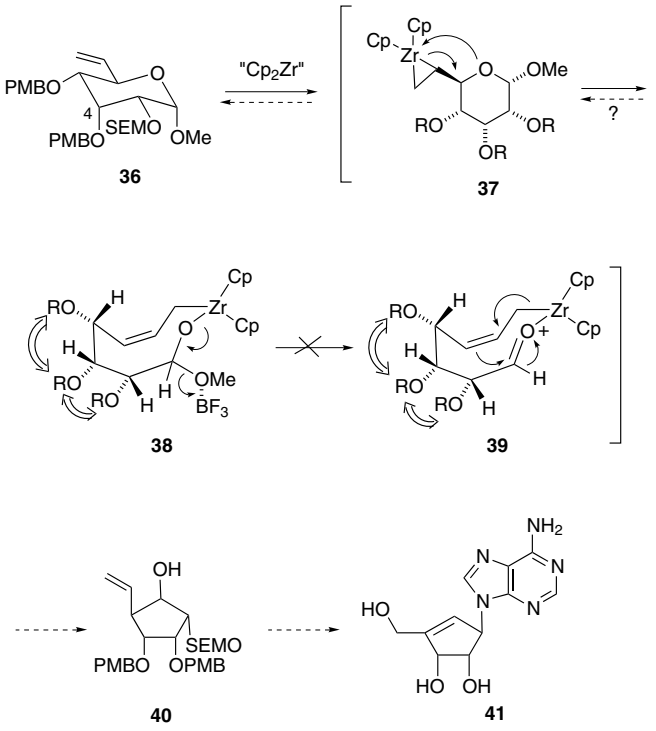
4. Synthesis of the hydroazulene sesquiterpene (+)-epiafricanol

The electrophilic "Cp_2Zr" equivalent has also made possible the transformation of D-glucose into the sesquiterpene (+)-epiafricanol (**35**) [12], thus merging these two subfields of natural products chemistry. The tricyclic alcohol target was synthesized in a series of steps that began with the generation of **30** according to known carbohydrate transformations [13–16]. An additional six steps were necessary to secure **31**. The critical ring contraction proved to be usefully diastereoselective, affording **32** in 63% isolated yield. The availability of this enantiomerically pure cyclopentanol set the stage for conversion to **33** and the transformation of this advanced intermediate into **34** via ring-closing metathesis. The final structural modification to give **35** involved a stereodirected Simmons–Smith cyclopropanation.

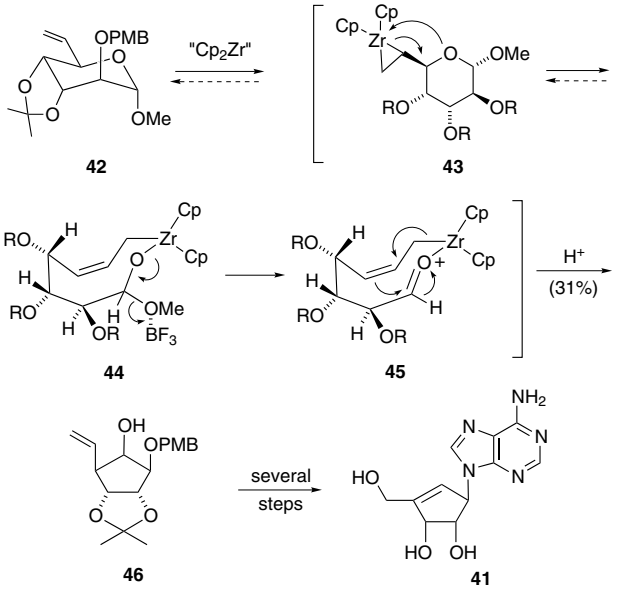


5. Zirconocene-mediated route to (−)-neplanocin A

Two approaches involving the conversion of D-glucose into the cytotoxic cyclopentyl nucleoside (−)-neplanocin A (**41**), both based on application of zirconocene-promoted ring contraction, have been evaluated [17]. In the first approach, the vinyl pyranoside precursor featured the α-D-allo configuration as in **36**. This ideal arrangement is such that ultimate introduction of the nucleobase is dependent only on a single inversion of configuration. However, none of the many conditions designed to produce **40** by zirconocene ring contraction gave evidence for the operation of this process. The only chemical change observed involved epimerization at the anomeric center. This tendency to experience anomerization suggests that **37** is possibly generated and that advancement to **38** may even occur. Further progress toward **40** is precluded because of the *cis* orientation of the three OR substituents on the periphery of the nine-membered ring in **39**. The resulting nonbonded steric repulsion provides a barrier too elevated for progression to **40**.

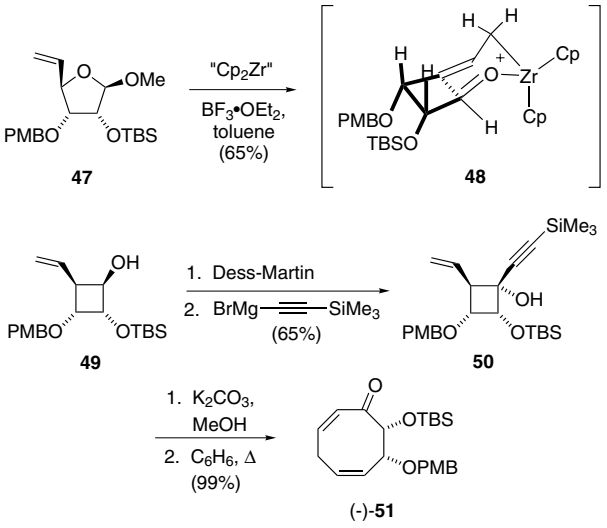


Contrariwise, the OR groups in glycoside **42** do not share in the same level of steric congestion as is present in **36** with the result that **43**, once formed, finds it possible to produce **46** via **44** and **45**. In agreement with expectation, the cyclic nature of the chair-like transition state represented by **45** delivers **46** with excellent diastereoplacement of the *cis*-oriented vinyl and hydroxyl substituents. The final conversion from **46** to (−)-neplanocin A (**41**) was conveniently achieved by way of a double-inversion sequence [17].

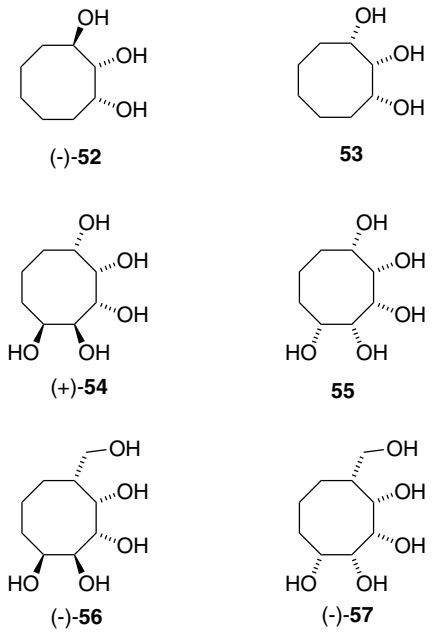


6. Carbohydrates as precursors to cyclooctene polyols and carba sugars

Carbohydrate recognition events have often been probed with polyhydroxylated carbocyclic mimetics consisting uniquely of five- and six-membered cyclitols [18,19]. More recently, attention has been accorded to eight-membered ring systems, where the endocyclic oxygen atom of a pyranoside ring is replaced by a triad of methylene groups [20–32]. Such a structural change provides for the adoption of unprecedented conformational projections while precluding degradation by carbohydrate-processing enzymes. Our efforts in this field originated with the zirconocene-mediated conversion of **47**–**49** [33]. Vinyl furanoside **47**, which is readily available from either D-arabinose or D-glycose diacetonide, delivers the cyclobutanol **49** cleanly in 65% yield. The success of this transformation is consistent with adoption of transition state **48**, where all four cyclobutane substituents are set in a well-defined absolute configurational sense that introduces minimal nonbonded steric interaction.



If the oxidation of **49** is performed with the mild Dess–Martin periodinane reagent [34], the cyclobutanone that results suffers from no loss of stereochemical integrity. In addition, the double bond does not migrate into conjugation with the carbonyl group. At this point, direct addition of the silylated acetylenic Grignard reagent results in stereocontrolled 1,2-addition to produce **50**. Subsequent to mild basic chemoselective desilylation, heating in benzene gave rise to the key cyclooctadienone intermediate **51**. The functionalization resident in **51** has been extended in a number of directions. The first of these thrusts involved conversion to the levorotatory 1,2,3-triol **52** and its meso counterpart **53**. Advancement to the pentahydroxy congeners **54** and **55** was also realized when timely use was made of osmium tetroxide [35]. An additional carbon could also be installed as in the cyclooctane carba sugars **56** and **57** by suitable deployment of a Wittig olefination followed by hydroboration [36].



7. Conclusions

This review summarizes various ways in which the zirconocene-mediated ring contraction of vinyl-substituted carbohydrates can be applied to the stereocontrolled elaboration of small and medium-sized rings. Most often, elevated levels of functionality are present, enantiomeric purity is guaranteed, and reaction efficiency is quite acceptable. Few complications have surfaced so far [37]. The use of "$CpZr_2$" provides greater diastereocontrol than diethylzinc/Pd(0) [38] and is complementary to the predominant *trans* relationship of vinyl and hydroxyl groups that materializes in the presence of samarium iodide and palladium(0) [39].

Acknowledgement

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