Review

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Posted Date: 12 November 2024

doi: 10.20944/preprints202411.0805.v1

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Advancements in Carbohydrate Scaffold Synthesis: Exploring Prins Cyclization Methodology

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Abstract: The synthesis of natural and unconventional compounds with carbohydrate structures is of great interest to glycochemists due to their vital biological roles. In recent years, there has been significant progress in developing direct and indirect synthetic strategies for constructing sugar moieties. Among these methods, the Prins reaction, employing homoallylic alcohols and carbonyl compounds, has proven invaluable for directly creating sugar skeletons. This review discusses approaches for crafting carbohydrate frameworks using the Prins reaction, utilizing both carbohydrate and non-carbohydrate starting materials.

Keywords: carbohydrates; prins reaction; 2-deoxysuagrs; homoallylic alcohols; rare sugars

1. Introduction

Common sugars like glucose and galactose, along with rare sugars such as altrose and allose found in bacteria, possess distinctive characteristics like deoxygenation, amino groups, and branched carbon structures. Developing synthesis methods for these rare sugars is essential to harness their biological potential in natural products.[1] The Prins reaction has (Figure 1) seen a renewed interest in recent years for synthesizing various tetrahydrofurans and pyrans and they lead to carbohydrate scaffolds.[2] Although there may be slight variations in reaction mechanisms due to different conditions, a Scheme 1 can be outlined. The Prins reaction involves homoallylic alcohols **1** and carbonyl compounds **2** in the presence of an acid catalyst, resulting in the formation of the oxocarbenium ion **3** intermediate. This intermediate then undergoes π-cation cyclization, followed by the addition of nucleophiles, leading to the formation of highly reactive tetrahydropyran intermediate and the synthesis of multifunctionalized tetrahydropyran **4**. The high stereoselectivity of the product is attributed to axial-axial interactions of the tetrahydropyran cation intermediate with incoming nucleophiles. Alternatively, oxocarbenium ion **3** can participate in a pinacol-type rearrangement, yielding tetrahydrofuran **5** or even directly producing product **6**.

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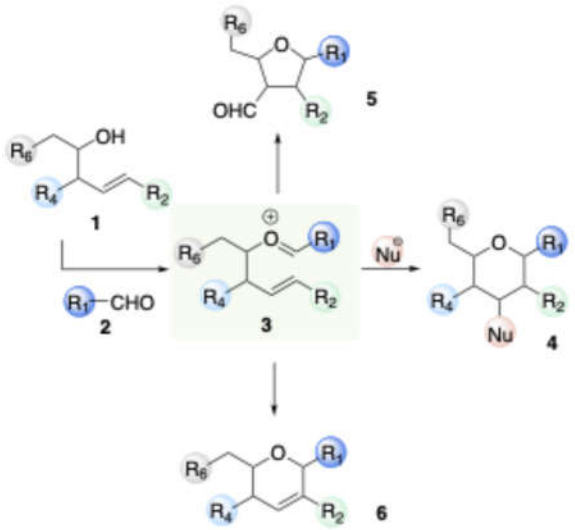

Scheme 1. General mechanism for the synthesis of carbohydrate skeleton through Prins reaction.

This review aims to provide an overview of the main strategies for accessing carbohydrate moieties. It is organized into several sections based on how the extended carbohydrate core is constructed and the number of bonds created during the critical construction step.

2. Result and Discussion

There is currently a wealth of inter and intra molecular Prins reactions are available within the modern synthetic chemist's 'toolbox'. However, among the most prevalent Prins reaction types is the addition of a nucleophiles to a secondary carbocation (typically alkenes or alkynes), Pinacol type rearrangement, Sakurai Prins reaction and

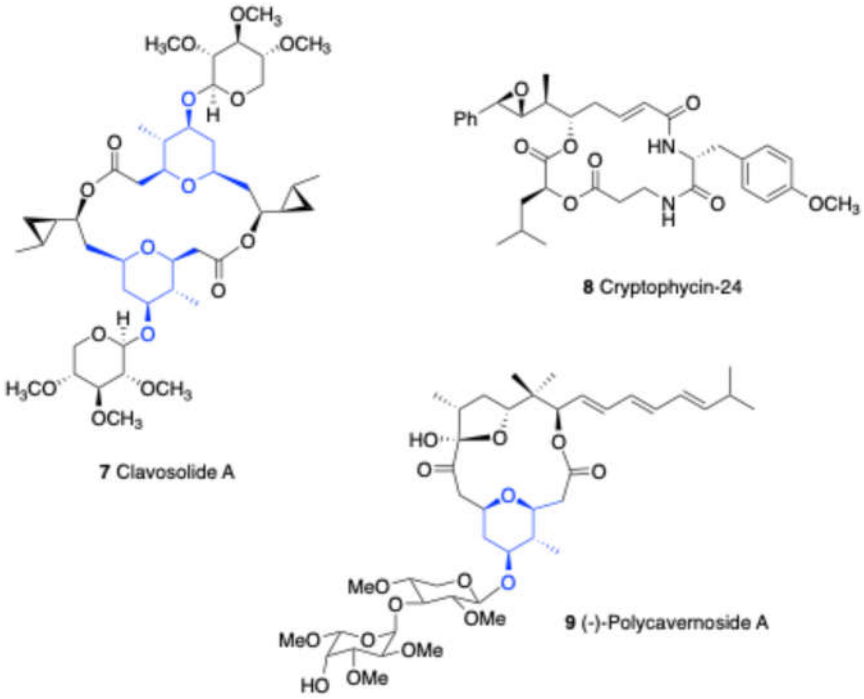

Figure 1. Synthesis of natural products by using Prins reaction.

Ritter Prins reaction. Within the context of sugar moiety synthesis via Prins cyclization and based on the origin synthon of homoallylic alocohols, these reactions are divided into two distinct

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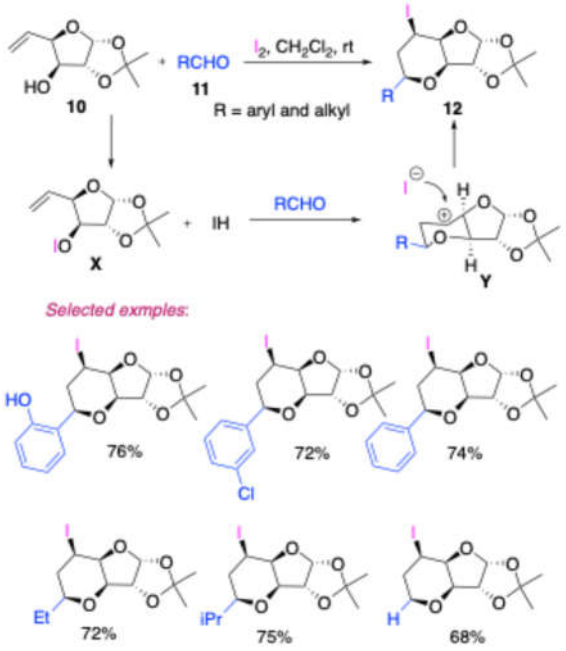
subclasses: those in which a synthesis of carbohydrate scaffolds from carbohydrate synthons (1.1) and those in which a carbohydrate scaffolds from non-carbohydrate synthons (2.2).

2.1. Carbohydrate Synthons to Carbohydrate Scaffolds

This section summarizes research that focuses on generating valuable carbohydrate scaffolds or structural units using carbohydrate-derived starting materials, particularly carbohydrate-derived homoallylic alcohols, through a process called Prins cyclization. In this specific study conducted by Yadav and colleagues, they reported [3] the synthesis of a sugar-annulated iodotetrahydropyran compound **12** by employing Prins cyclization. They combined a D-glucose-derived homoallylic alcohol **10** with an aldehyde **11** in their synthetic approach (Scheme 2). The researchers explored the use of a variety of aromatic and aliphatic aldehydes as reactants in their experiments. Importantly, they successfully obtained the desired products in moderate to good yields, indicating the effectiveness of their synthesis method. The authors of this study proposed a reaction mechanism that involves an intermediate **X** and a highly reactive carbocation **Y**. This carbocation **Y** is subsequently captured by an iodide ion, resulting in the formation of the sugar-annulated iodotetrahydropyran compound **12**.



Scheme 2. Synthesis of sugar annulated iodotetrahydropyrons.

In a subsequent study, the same research group[4] delved deeper into the Prins reaction of homoallylic alcohol **10**, as shown in Scheme 3. They investigated this reaction with various carbonyl compounds **11**, employing $BF_3{\cdot}OEt_2$ as a catalyst and various arene solvents. This reaction led to the formation of sugar-fused diaryl hexahydro-2*H*-furo[3,2-b]pyran **13** via intermediate **III**. Notably, the researchers examined different arene solvents, including benzene, toluene, o-xylene, and anisole. The reaction proved compatible with a variety of aryl and alkyl aldehydes as well as cyclohexanone. Interestingly, one of the product further converted into diaryl dihydroxytetrahydropyara **14** (Scheme 4).

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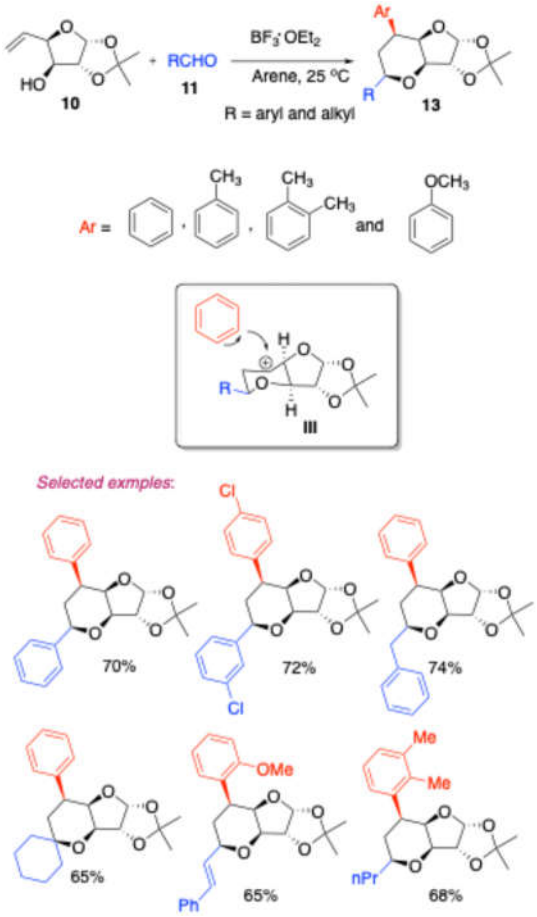
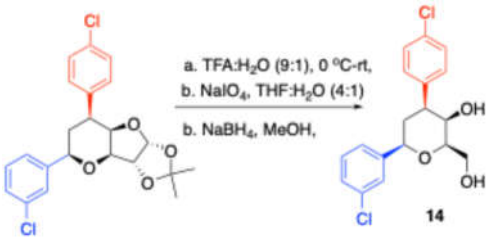


Scheme 3. Synthesis of sugar-fused diaryl hexahydro-2H-furo[3,2-b]pyran.



Scheme 4. Synthesis of sugar fused diaryl hexahydro-2*H*-furo[3,2-*b*] pyran **14**.

Reddy et al. reported[5] the synthesis of the hexahydro-2*H*-furo[3,2-*b*]pyranopyran scaffold **16** from *O*-prenyl tethered carbohydrate derived aldehyde **15** with various aldehydes in the presence of 10 mol% $Sc(OTf)_3$ in dichloromethane at 0 °C to room temperature (Scheme 5). Further, this reaction was studied with a variety of aryl and alkyl aldehydes. Eventually, this reaction was quite successful with *p*-bromobenzaldehyde and cyclohexylidene protected *O*-prenyl tethered carbohydrate derived aldehyde to furnish the product tricyclic sugar derivative **16** (Scheme 7).

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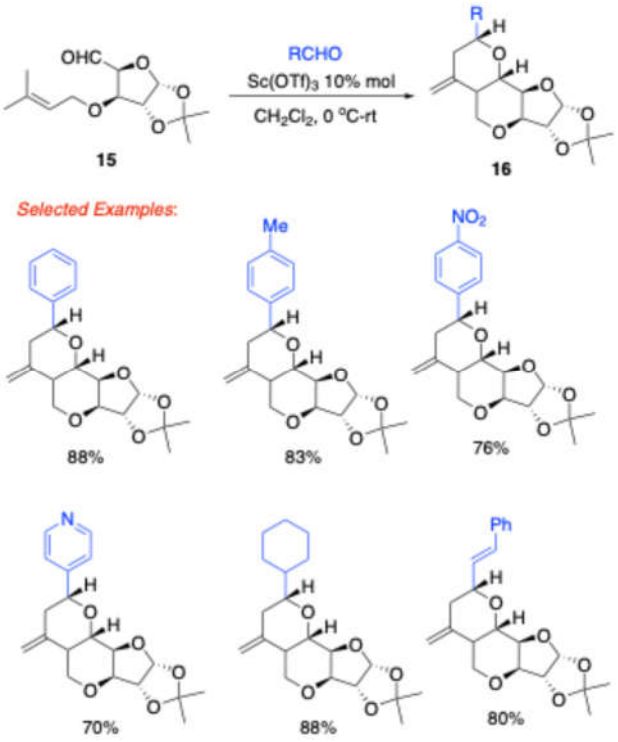
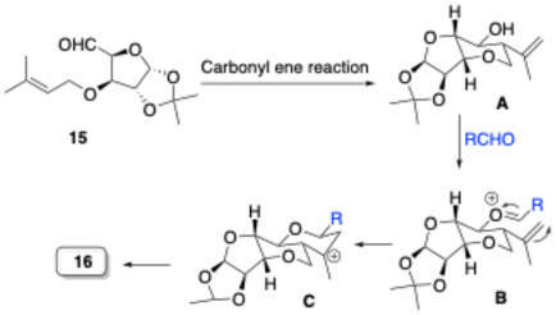


Scheme 5. Synthesis of hexahydro-2*H*-furo[3,2-*b*]pyranopyran scaffold.

First, cyclization of *O*-prenyl tethered carbohydrate derived aldehyde **15** is proposed, facilitated by carbonyl ene reaction and led to homoallylic alcohol **A**, with this being the prins reaction defining step. Then **A** condes with aldehyde in presence of $Sc(OTf)_3$ could give tertioary carbocation **C** via oxocarbonioum ion **B**. Further **C** could eliminate proton from methyl group and led to product **16**.



Scheme 6. Mechanism for the formation of hexahydro-2*H*-furo[3,2-*b*]pyranopyran.

In 2014, Lumba and Mukherjee[6] developed a practical protocol for the conversion of tri-*O*-acetyl-D-glucal derived 2-C-branched sugars **17** to the corresponding *cis*-1-oxadecalines **18**. By using $FeCl_3$ as a catalyst system at room temperature, the target molecules could be afforded [Scheme 8]. The advantages of this protocol are the use of a variety of 2-C-branched sugars.

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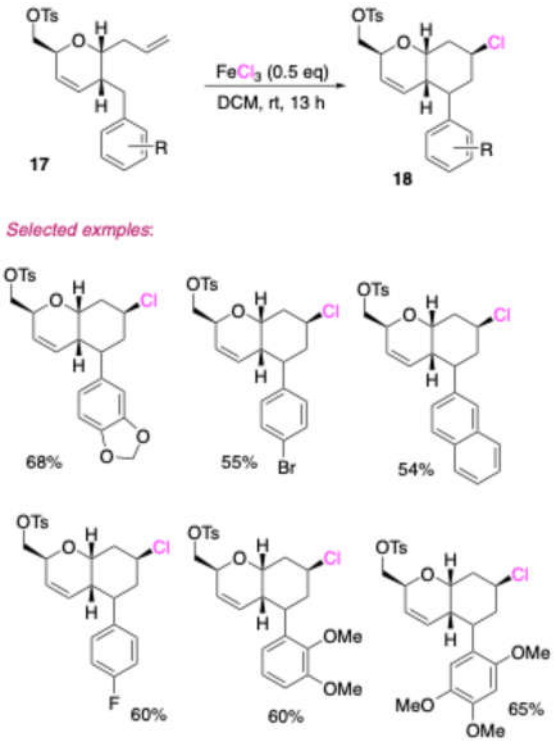
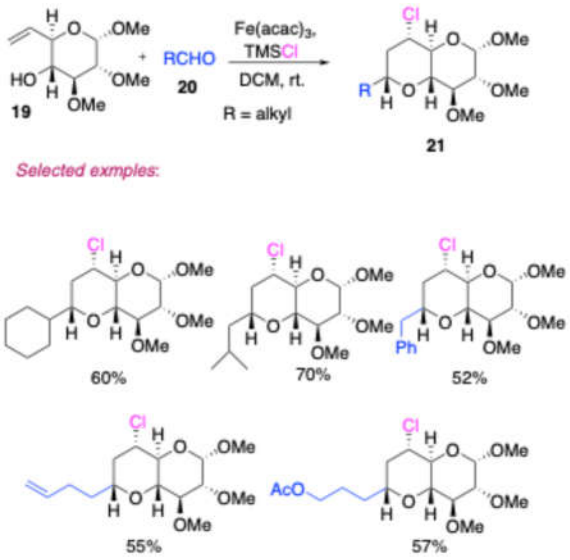


Scheme 8. Synthesis of *cis*-1-oxadecalines **17** from 2-C-branched sugar **18**.

Padrón and co-workers[7] reported a simple preparation method for *trans*-fused bicyclic tetrahydropyran **21** by a iron(lll) catalyzed tandem reaction using tri-*O*-acetyl-D-glucal derived homoallylic alcohol **16** and iso-valeraldehyde [Scheme 9]. This reaction was further studied with more complex molecule **19**, which is derived from α-methyl-D-glucopyranoside with aldehydes and led to the *trans*-fused bicyclic tetrahydropyrans **20**. Here, the features are the good substrate generality and the mild reaction conditions.



Scheme 9. Synthesis of trans-fused bicyclic tetrahydropyrans **21** from tri-*O*-acetyl-D-glucal and α-methyl-D-glucopyranoside.

Cis-fused heterobicyclic systems are very important substrates in neuronally active agents such as marine-derived dysiherbaine and their analogues IKM-159 and MC-27. Oikawa and co-workers[8] reported a $BF_3{\cdot}OEt_2$ catalyzed condensation reaction between glucose derived enetiomerically pure homoallylic alcohol **22** with aldehydes 11 and nitrile solvent **23**; the intended cis-fused 4-amidotetrahydropyrans **24** were obtained in a one-pot manner under relatively mild conditions

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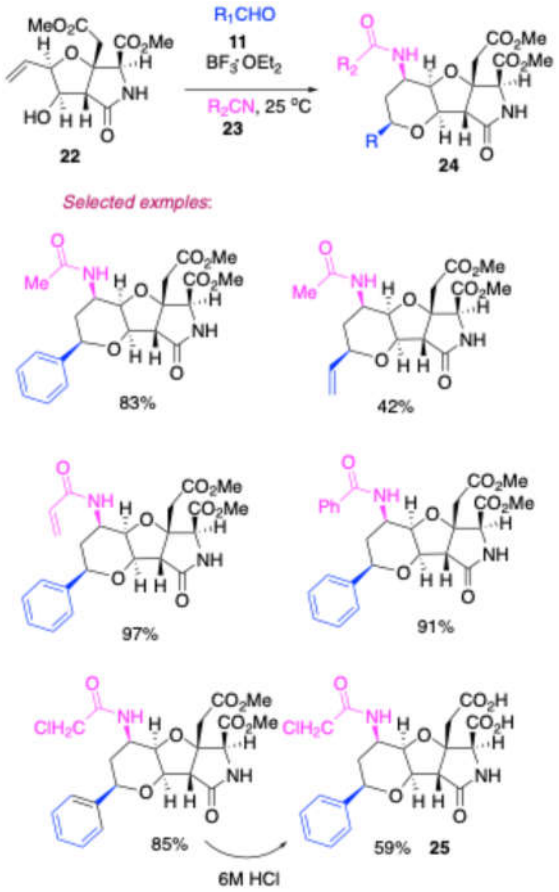
(Scheme 10). Based on these results and the scope was extended to substrate **24** with variety of aldehydes and nitrile solvent via Prins-Ritter reaction to obtained cis-fused heterobicyclics **24** which were further subjected to acid hydrolysis led to the formation for novel glutamates **25**.

Vankar and co-workers[9] developed an efficient synthesis of bridged tricyclic ketals **28/29** with good substrate generality starting from homoallylic alcohols **26**/**27** derived from 1,2-anhydro and aldehydes; they used $BF_3{\cdot}OEt_2$ as catalyst [Scheme 11]. Here, the main advantages include the stereoselectivity and good yields. They proposed the plausible mechanism for the formation of bridged tricyclic ketals **28**/**29** shown in the Scheme 12. It is presumed that after initial formation of the oxocarbenium ion **A**, it can either undergo Oxonia-Cope rearrangement to form **B**, or simply a π-cation cyclization to form C. Both of these intermediates will then undergo 7-exo trig cyclization or pinacol-type rearrangement via the transition state **D**, followed by cleavage of the C4-OBn participation resulting into to form bridged tricyclic ketals **28**/**29**. To get further insight into the proposed mechanism they tested homoallylic alcohol **26** with acetaldehyde and *p*-xylene as nucleophile observed the *p*-xylene trapped prins product **30** (Scheme 13). *p*-xylene trapped prins product was further hydrogenolysis with $Pd(OH)_2/C$ followed by benzoylation of the resulting alcohol with p-nitrobenzoylchloride/Et_3N to give the corresponding annulated sugar **32**. Later, these bridged tricyclic ketals were converted to (Scheme 14) tetrahydrofuran ring fused heptose **31** and 2C-branched heptose **32**.



Scheme 10. *Cis*-fused 4-amidotetrahydropyrans towards a precursor for possible neuronal receptor ligands via Prins-Ritter reaction.

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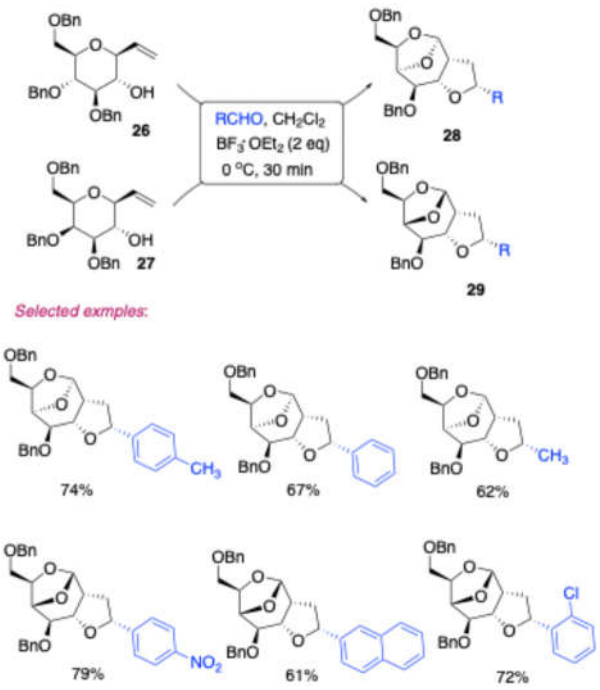
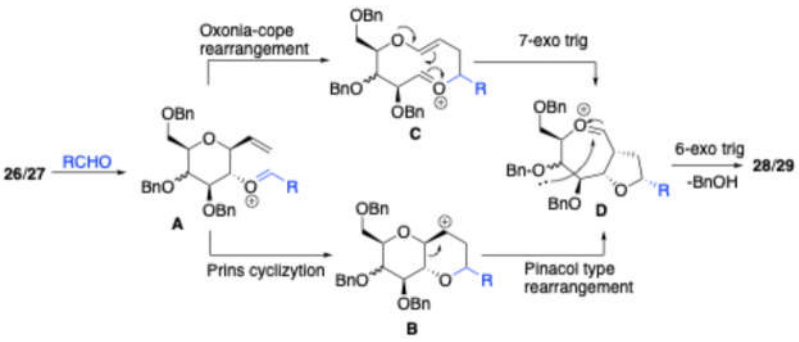
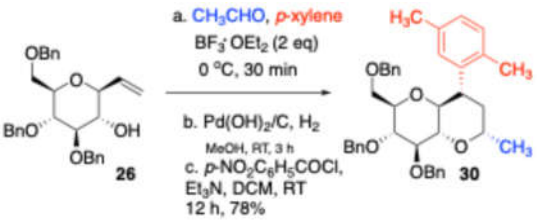


Scheme 11. Synthesis of bridged tricyclic ketals **28/29** thorugh Prins-Pinacol type rearrangement and C4-OBn participation.



Scheme 12. Mechanism for the formation of bridged tricyclic ketals **30**/**31**.



Scheme 13. Trapping with *p*-xylene.

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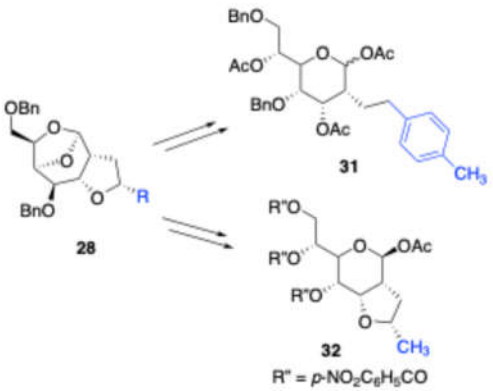
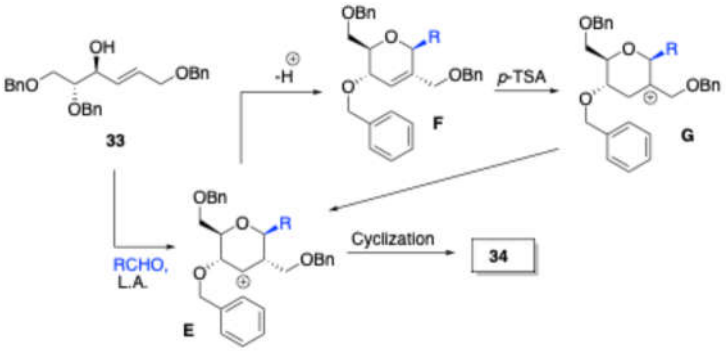


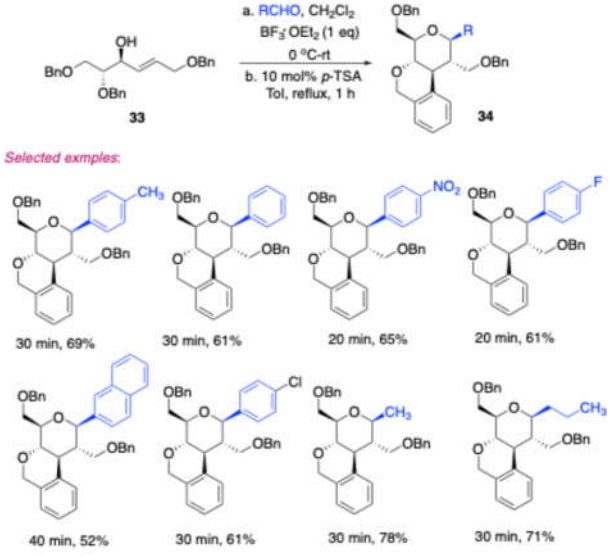
Scheme 14. Derivitization of bridged tricyclic ketal.

In 2017, Vankar et al. [10] reported a very effective synthetic route by using $BF_3{\cdot}OEt_2$ to synthesize 1C-aryl/alkyl 2C-branched sugar fused isochroman derivatives **34** from 2C-formyl glucal derived homoallylic alcohol **33** and aldehydes, in a moderate



Scheme 16. Mechanism for the formation of 1C-aryl/alkyl 2C-branched sugar fused isochroman derivatives.

Later, Dubbu and Vankar strategically synthesized[11] a series of 2-deoxy-3,4-fused-C-aryl/alkylglycosides through a cascade Prins cyclization of a D-mannitol-derived homoallylic alcohol, using $BF_3{\cdot}OEt_2$ as a catalyst. Initially, (Scheme 17) the D-mannitol-reaction time (1 h) in 60–70 % yields (Scheme 15).



Scheme 15. Synthesis of 1C-aryl/alkyl 2C-branched sugar fused isochroman derivatives.

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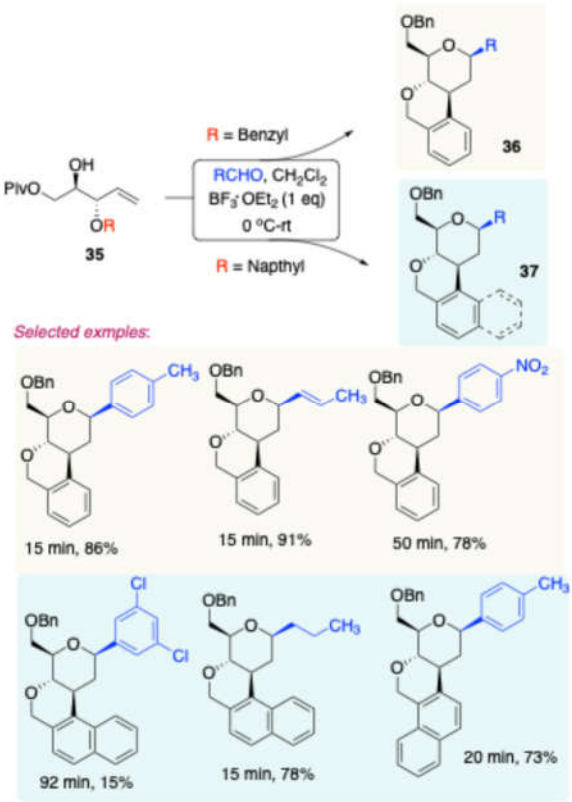
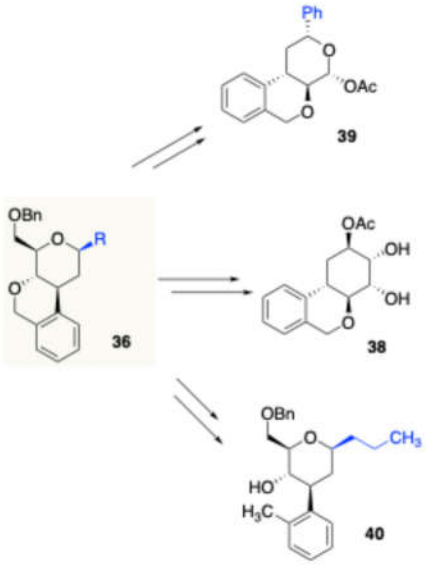
In the presence of the $BF_3{\cdot}OEt_2$, substrate **33** and aldehyde were condensed to produce intermediate **E**, which would undergo elimination of adjacent proton and generate dihydropyran **F**. This dihydropyran **F** treated with PTSA gives tertiary carbocation **G**, which is equilibrium with intermediate **E.** then intermediate **E** may directly give the product **34**.

derived homoallylic alcohol **35** was treated with various carbonyl compounds in the presence of $BF_3{\cdot}OEt_2$ in DCM, yielding 2-deoxy-3,4-fused isochroman derivatives **36/37** in good to excellent yields. The authors further modified these products to obtain potentially bioactive scaffolds 38, 39, and 40 (Scheme 18).



Scheme 17. Synthesis of 1C-aryl/alkyl fused isochroman derivatives.



Scheme 18. Derivatization of sugar fused isochroman derivatives.

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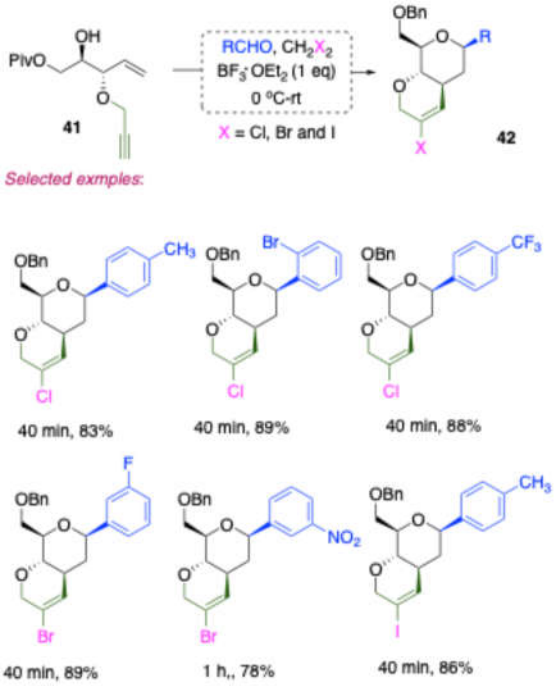
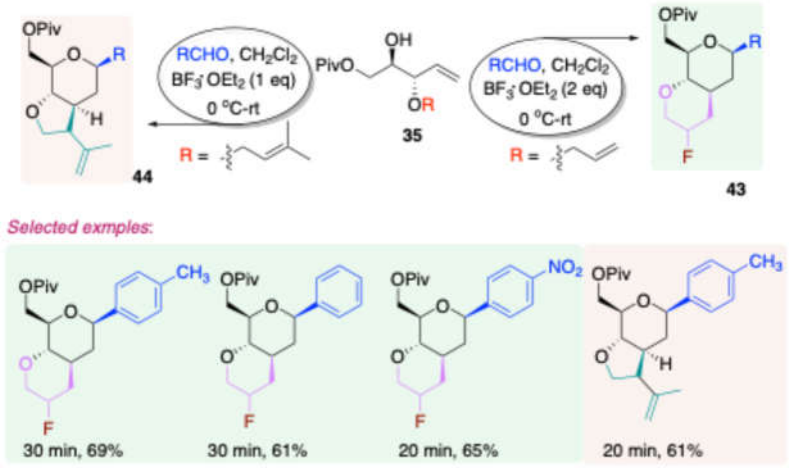
Using similar reaction conditions, but with a D-mannitol-derived homoallylic alcohol protected with a propargyl group, Dubbu and Vankar obtained [11] 1C-aryl/alkyl-fused bicyclic vinyl halide derivatives **42** in good to excellent yields x. The halogen abstraction was achieved through the use of halogenated solvents. Depending on the solvent used—CH_2Cl_2, CH_2Br_2, CH_3I, etc.—the products obtained were 1C-aryl/alkyl-fused bicyclic vinyl chloride, vinyl bromide, or vinyl iodide derivatives, respectively.



Scheme 19. Synthesis of 1C-aryl/alkyl fused bicyclic vinyl halide derivatives.

By applying similar reaction conditions, Dubbu and Vankar further transformed[11] the D-mannitol-derived homoallylic alcohol **35**, protected with allyl and substituted allyl groups, to synthesize 1C-aryl/alkyl-fused bicyclic fluorine-substituted tetrahydropyran and furan derivatives 43/44, achieving good to excellent yields (Scheme 20).

In 2019, Vankar reported the stereoselective synthesis of 3-deoxy-3C-formyl β-C-aryl/alkyl furanosides **46** (Scheme 21) through a cascade Prins reaction followed by a pinacol-type rearrangement. [12] This transformation involved an –OTBDPS-protected homoallylic alcohol **45**, derived from D-mannitol, reacting with various carbonyl compounds in the presence of $BF_3{\cdot}OEt_2$ in DCM. The reaction provided excellent yields and high selectivity.



Scheme 20. Synthesis of 1C-aryl/alkyl fused bicyclic fluorine substituted tetrahydropyrans and furan derivatives.

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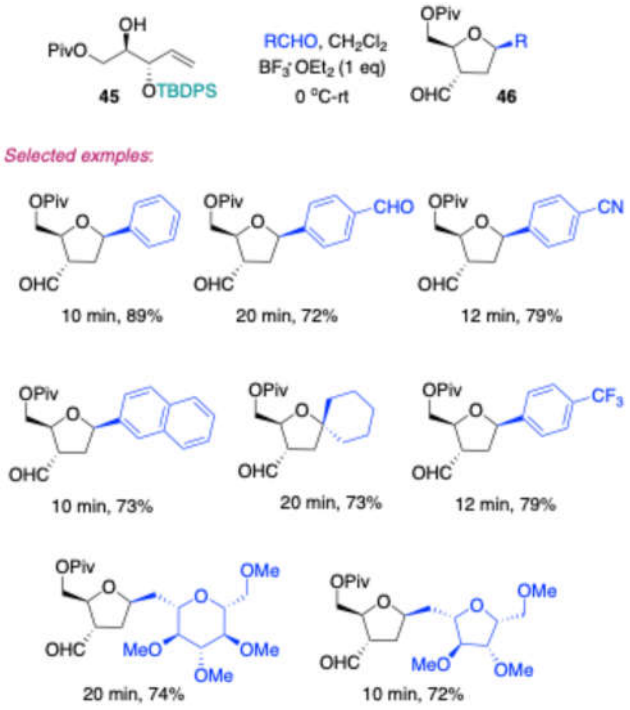
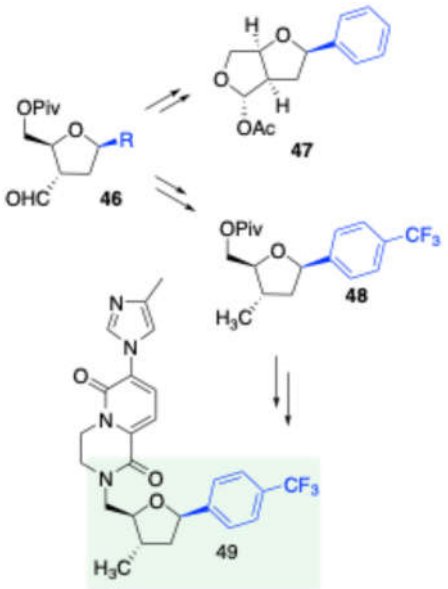


Scheme 21. Synthesis of 2,3-dideoxy-3C-formyl β-*C*-aryl/alkyl furanosides **48**.

Furthermore, (Scheme 22) this method was effectively applied to synthesize a fused-bicyclic β-C-aryl furanoside moiety **47** and a 2,3-dideoxy-3C-methyl β-C-aryl furanoside **48**, both of which are found in the core structures of bioactive molecules.



Scheme 22. Derivatization of 2,3-dideoxy-3C-formyl β-*C*-aryl/alkyl furanosides.

Later, Vankar and co-workers optimized (Scheme 23) the Sakurai-Prins reaction of a D-mannitol-derived homologated allylsilane homoallylic alcohol **48** with *p*-tolualdehyde **51** in the presence of $BF_3{\cdot}OEt_2$.[12] This reaction yielded 2-deoxy-2C-branched β-C-aryl furanosides in good yield (84%) as an inseparable diastereomeric mixture (α:β = 0.8:1 ratio) (Scheme 9). To separate the stereoisomers, compound **48** was subsequently deprotected at the –OPiv group using NaOMe/MeOH, resulting in diastereomers **53** and **54**, which were then separated by column chromatography with yields of 43% and 35%, respectively.

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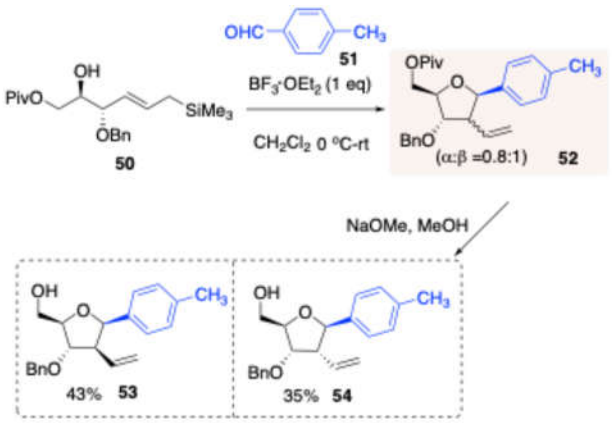
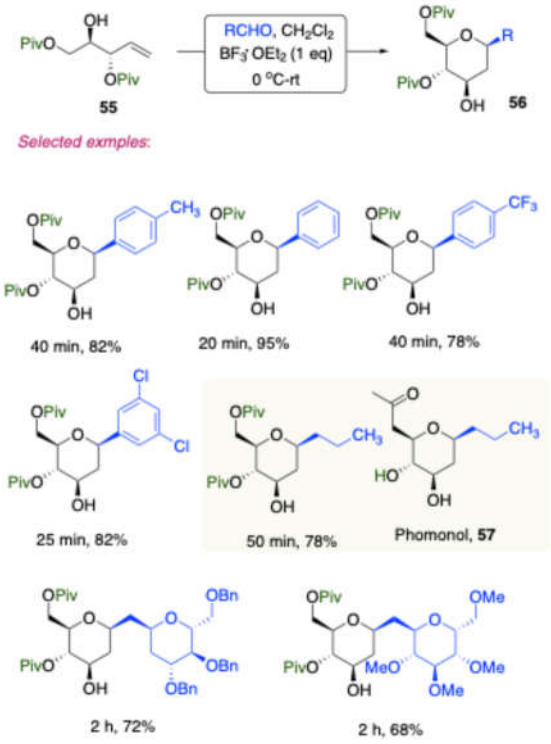


Scheme 23. Synthesis of 2-deoxy-2C-branched β-C-aryl furanosides **53** and **54**.

Vankar and co-workers further synthesized[13] a non-participating protecting group at allylic position of D-mannitol derived homoallylic alcohol **55** and



Scheme 24. Synthesis of 2-deoxy-β-C-aryl glycosides **52** from D-mannitol derived homoallylic alcohol **51**.

which was subjected to the Prins reaction with a vairy of aldehydes in the presence of $BF_3{\cdot}OEt_2$ as a catalyst and led to stereoselective 2-deoxy-C-aryl/alkyl glycosides **56** (Scheme 24). The synthetic versatility of this approach has been demonstrated in the synthesis of C-disaccharide and O-linked disaccharides **58**, and differently protected 2-deoxy-β-C-aryl glycosides **59**,**60** (Scheme 25).

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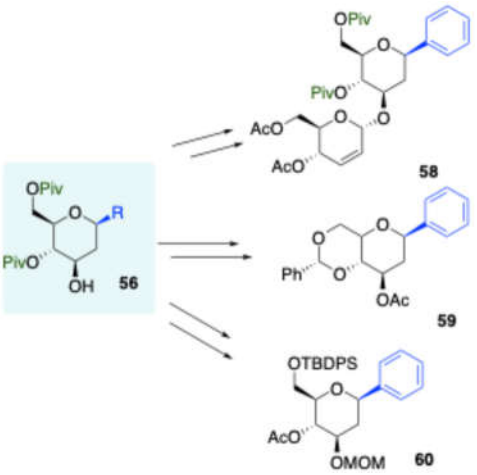
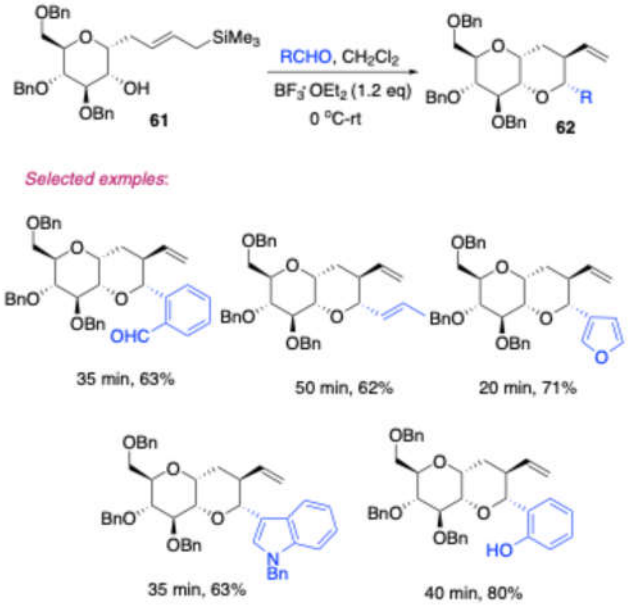


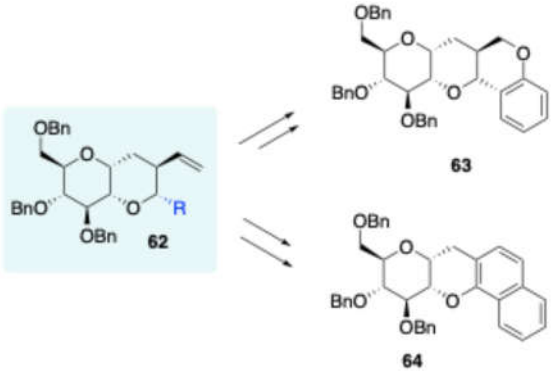
Scheme 25. Derivatization of 2-deoxy-β-C-aryl glycosides **56.**

Furthermore, Vankar and co-workers reported[14] (Scheme 26) the synthesis of 1,2-annulated



Scheme 26. Synthesis of 1,2-annulated Sugars having substituted tetrahydropyrans **62**.

tetrahydropyran fused sugar derivaties **62** by the reaction of a D-glucose derived alcohol **61** with various carbonyl compounds in the presence of $BF_3 \bullet Et_2O$, via Prins cyclization. The obtained products were converted to more useful scaffolds *cis*-sugar fused pyrano[3,2-*c*][1]benzopyran **63** and *cis*-sugar fused 4*H*-naptho [1,2-*b*] pyran **64** (Scheme 27). Further studied that in the presence of TMSOTf, 1,2-annulated tetrahydrofuran fused sugar derivatives were obtained in moderate to excellent yields from D-glucose derived homopropargyl alcohol **65** and few aldehydes (Scheme 28).



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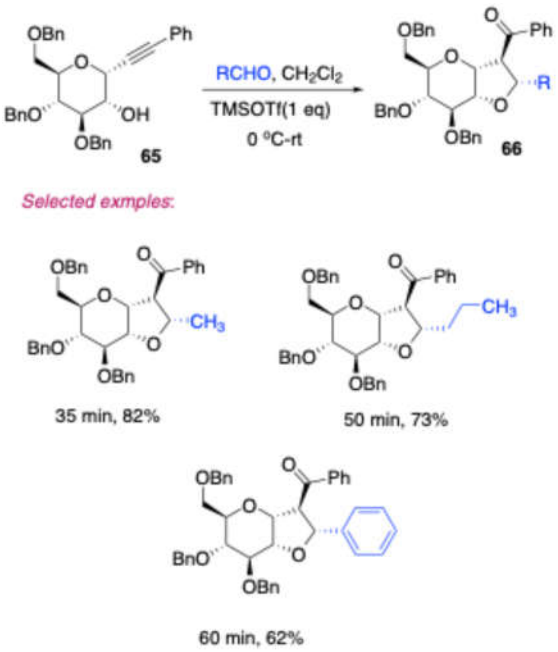
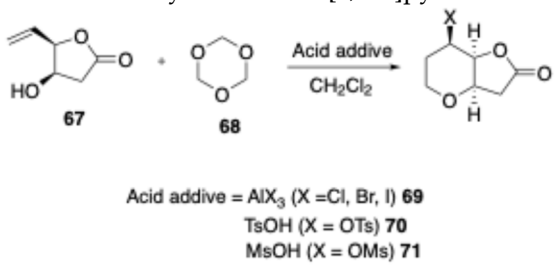
Scheme 27. Synthesis of *cis*-sugar fused pyrano[3,2-*c*][1]benzopyran **63** and *cis*-sugar fused 4*H*-naptho [1,2-*b*] pyran **64**.



Scheme 28. Synthesis of 1,2-annulated Sugars having substituted tetrahydrofurans **66**.

In 2008, Oikawa and co-workers reported[15] the Prins reaction of glucose derived enetiomerically pure homoallylic alcohol **67** with unreactive formaldehyde equivalent *i.e.,* 1,3,5-trioxane **68** to trisubstituted *cis*-fused hexahydro-2H-furo[3,2-b]pyran derivatives **69-71** (Scheme 29).



Scheme 29. Synthesis of trisubstituted *cis*-fused hexahydro-2H-furo[3,2-b]pyran derivatives **69-71**.

2.2. Non-Carbohydrate Synthons to Carbohydrate Scaffolds

Besides exhibiting excellent biological activities, the carbohydrate-derived deoxy-C-aryl glycosides were found to be versatile substrates for the synthesis of various skeletal frameworks. Deoxy-C-aryl glycoside is a common structural motif found in a number of biologically relevant compounds, such as aquayamycin Adriamycin, pluramycin A, and kidamycin. An efficiently non-carbohydrate synthons source to sugar sketons by applying Prins reaction is a topic which has seen extensive study since the midtwentieth century.[32] Within this reaction manifold, Migaud and co-workers reported [16] stereoselective synthesis of noncarbohydrate-based core sugar skeleton **73** via sakuri Prins cyclization of alcohol **72** with crotanaldehyde. The core sugar skeleton **73** further, the hydroxyl groups at C-6 and C-3 were introduced by oxidative cleavage of the alkenes in **73** followed by reduction of the dicarbonyl intermediate. Subsequent acetylation of these hydroxyls, purification, and acetyl removal then yielded the final C-nucleosides **74** and **75**. Following the same reaction sequences and protocols, the synthesis of deoxy-C-aryl glycosides **77**, **81**, **82** and **84** were achieved using alcohol **72, 78** as a building block respectively.

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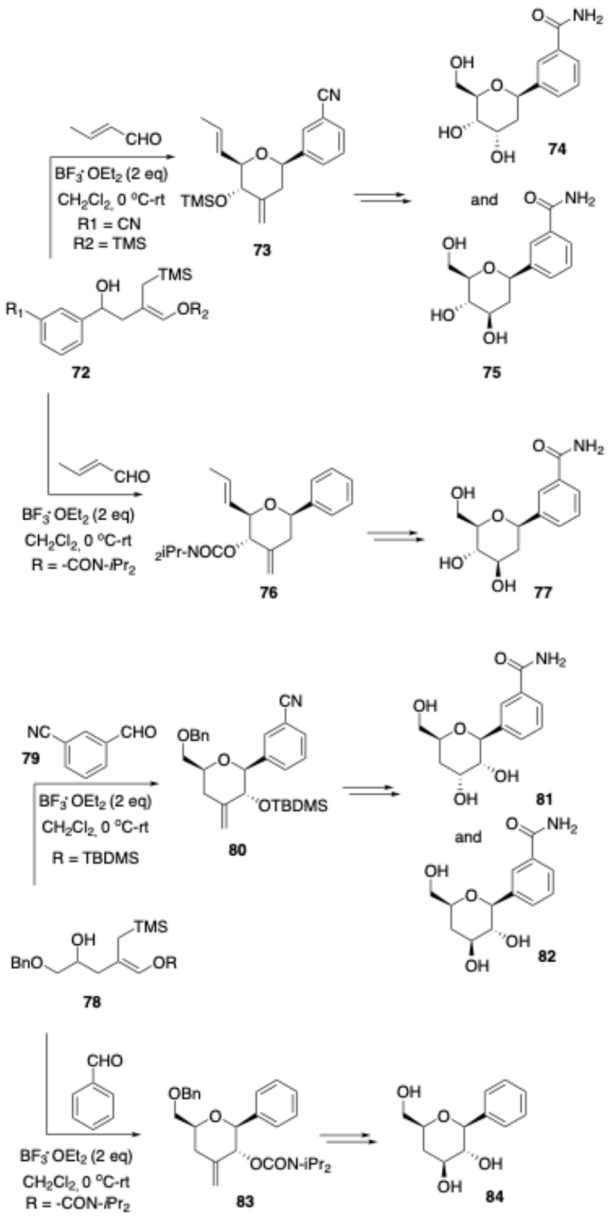

Scheme 30. Synthesis of deoxy-C-aryl glycosides from noncarbohydrate-based starting materials.

In 2016, Galan and coworkers reported[17] a de novo approach for the rapid construction of orthogonally protected L- and D-deoxysugars and analogues via Prins cyclization. In this approach, homoallylic alcohol **85** was treated with aldehyde **86** in the presence of TMSOTf and TMSOAc/AcOH, resulting in the formation of silyltetrahydropyran **87** in good to excellent yield. This compound was subsequently subjected to Tamao–Fleming oxidation, leading to the formation of 2,4-dideoxysugar **88**. By applying a similar reaction, compound **89** was converted into the 2,6-dideoxysugar **91**.

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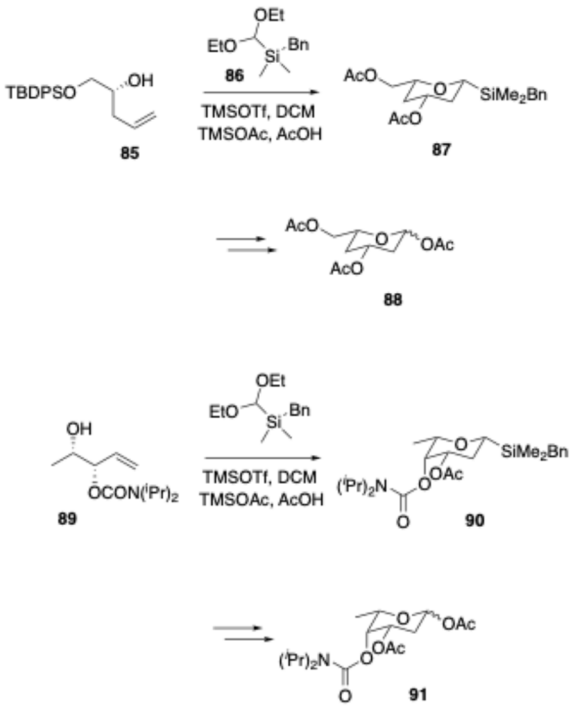
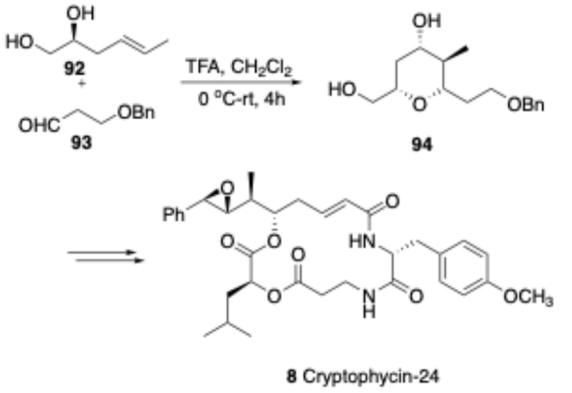


Scheme 31. Synthesis of dideoxysugars from silyltetrahydropyrans and noncarbohydrate-based starting materials via Prins reaction.

In 2016, Yadav and co-workers[18] demonstrated a diastereoselective formal synthesis of cryptophycin-24. The key step for constructing the core center involved a Prins cyclization of homoallylic alcohol **92** with aldehyde **93** in the presence of TFA in DCM, yielding core sugar skeleton **94**. Furthermore, this methodology was extended for the total synthesis of the natural product cryptophycin-24.



Scheme 32. Synthesis of cryptophycin-24 from noncarbohydrate-based starting materials via Prins reaction.

In 2012, Floreancig and Peh reported[19] a DDQ-mediated oxidative intramolecular Prins cyclization of compound **95**, yielding sugar core **96** in moderate yield (Scheme 33). This reaction proceeds via a diene-type intermediate.

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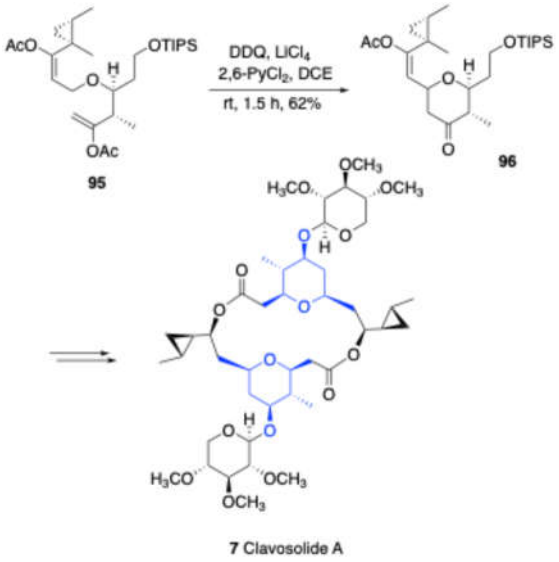
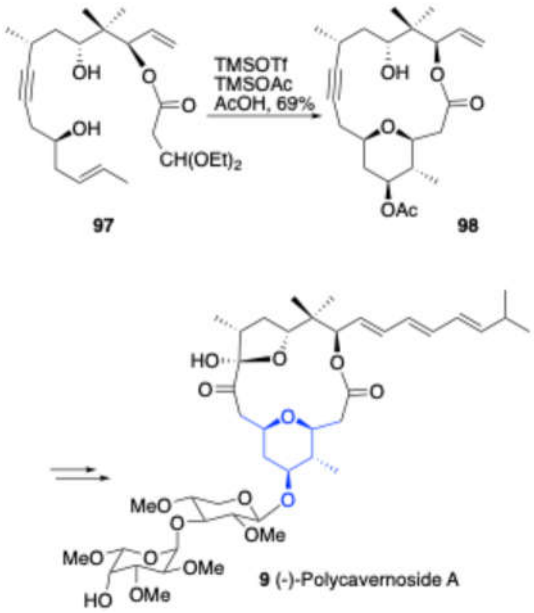


Scheme 33. Total synthesis of Clavosalidde A **7** via Prins reaction.

In 2010, Lee and Woo reported[20]a intramolecular prins reaction of **97** in the presence of TMSOTf and



Scheme 34. Total synthesis of (-)-Polycavernoside A **9** via Prins reaction.

TMSOAc/AcOH, resulting in the formation of sugar core **98** in good yield. This compound was further subsequently used for the total synthesis of (-)-Polycavernoside A **7.**

3. Conclusions

Carbohydrate-based structures are of high interest in glycochemistry due to their crucial roles in biological systems. Recent innovations have introduced both direct and indirect methods to synthesize sugar moieties effectively. Notably, the Prins reaction—a process involving homoallylic alcohols and carbonyl compounds—has become a valuable approach for constructing sugar backbones. This review delves into various Prins reaction techniques for assembling carbohydrate frameworks, highlighting the use of both traditional carbohydrate precursors and alternative non-carbohydrate starting materials.

 doi:10.20944/preprints202411.0805.v1

Author Contributions: SD Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Conceptualization. SJ Writing – review & editing, Writing – original draft.

Acknowledgments: SD gratefully acknowledge the University of Illinois Urbana-Champaign for infrastructure. SJ gratefully acknowledge The University of British Columbia.

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