Conference paper

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Reactions of 1,2-cyclopropyl carbohydrates

Abstract: Addition of a carbene to a glycal is the prominent method for the synthesis of 1,2-cyclopropyl carbohydrates. This incorporation of a cyclopropane into a carbohydrate scaffold enables divergent reactivity, with the two main classes being ring expansion and cleavage to 2-*C*-branched carbohydrates. A wide variety of products are obtained depending on the functionality attached to the cyclopropane (none or ester or halogens) and the promoter (Lewis acid, Brønsted acid, halophile or base) used in the reaction. This article reviews progress in the synthesis and reactions of 1,2-cyclopropyl carbohydrates since 2000 and discloses efforts by our group in the area.

Keywords: cyclopropane; C-branched sugar; carbohydrates; ICS-27; rearrangements; reaction mechanisms; oxepine.

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Introduction

Cyclopropyl carbohydrates marry the high reactivity of cyclopropanes [1–9] with the rich functionality and unambiguous stereochemistry of carbohydrate chiral pool reagents [10–13]. A range of product structures are preparable through ring opening reactions of the cyclopropanes (vide infra). Products derived from reactions of cyclopropyl carbohydrates represent glycosyl mimetics [14–20], with potential as therapeutics [21–23]. Therefore the pursuit of new target structures in this way has gained much recent attention [24–27].

The ready availability of glycals facilitates the synthesis of cyclopropyl carbohydrates derived from these 1,2-unsaturated sugars; additionally, the resulting 1,2-cyclopropyl sugars undergo highly regioselective ring opening due to electronic participation by the endocyclic oxygen.

A great diversity of ring opening modalities is observed with glycal-derived cyclopropanes under different conditions (Scheme 1). For example, cleavage of the fused 1,2-bond can lead to ring expanded products: oxepines from pyranoses and dihydropyrans from furanoses. Alternatively, breakage of the non-shared 1,1′-cyclopropane bond provides 2-*C*-branched products. Due to stabilization of the cationic (or radical) intermediates through oxonium intermediates, these products dominate greatly over their regioisomers. However, rare cases of cleavage at the 1′,2-bond are known and lead to *C*-glycosides.

The synthesis and reactions of cyclopropyl carbohydrates were reviewed by Cousins and Hoberg in 2000 [28]. The focus of the present article is on work published subsequently, particularly as it relates to the diversity of products obtainable by ring opening of glycal-derived cyclopropanes.

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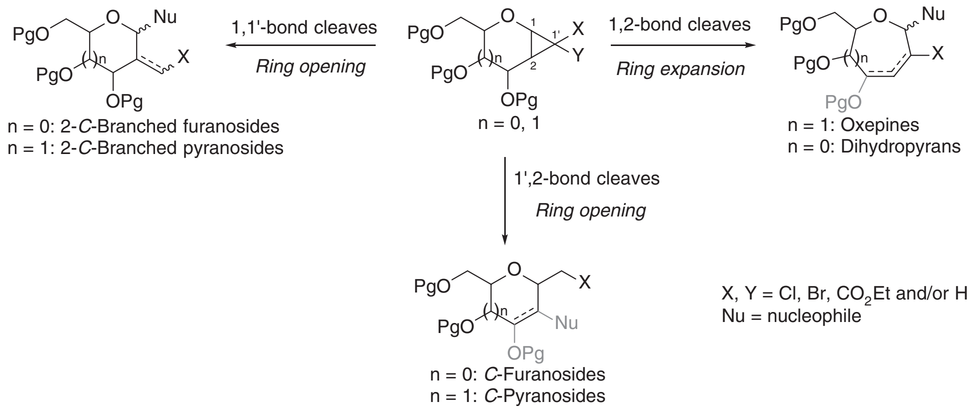
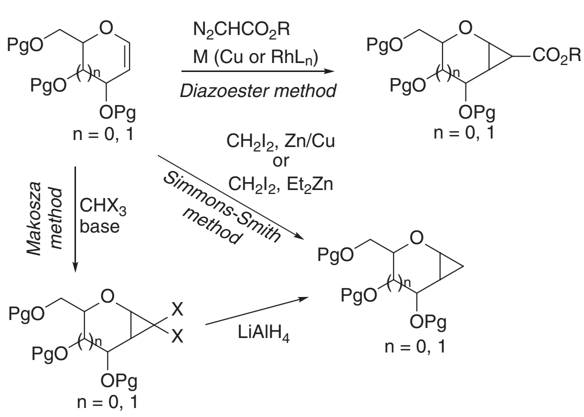


Scheme 1 Diverse ring opening reactions of glycal-derived cyclopropanes.

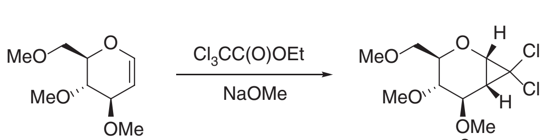
Synthesis of 1,2-cyclopropyl carbohydrates

The synthesis of 1,2-cyclopropyl carbohydrates is most often achieved by reaction of the corresponding glycal with a carbene under Simmons-Smith conditions (for cyclopropanes with an unsubstituted external methylene group) [29–31], with the Mąkosza two-phase method (for *gem*-dihalocyclopropanes) [32, 33] or with diazoesters (for ester substituted cyclopropanes) [34] (Scheme 2). Examples of cyclopropane formation by non-carbene methods, including through substitution of a leaving group attached to a carbohydrate scaffold with a carbon nucleophile, are also known [35–37].

The first cyclopropyl carbohydrate synthesized was the dichlorocyclopropane **2** (Scheme 3) [38]. The method involved formation of dichlorocarbene under anhydrous conditions, using ethyl trichloroacetate and sodium methoxide, and its trapping by glucal **1**.



Scheme 2 Synthesis of 1,2-cyclopropyl carbohydrates by carbene addition to glycals.

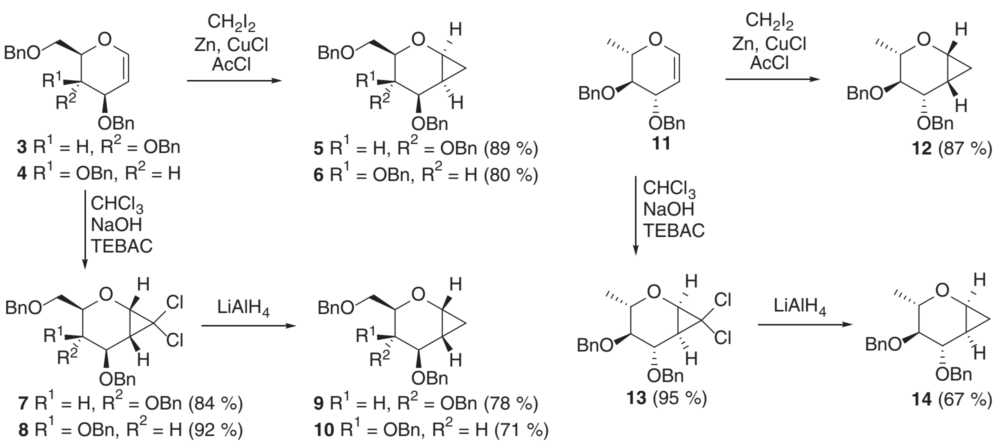


Scheme 3 First reported synthesis of a cyclopropyl carbohydrate [38].

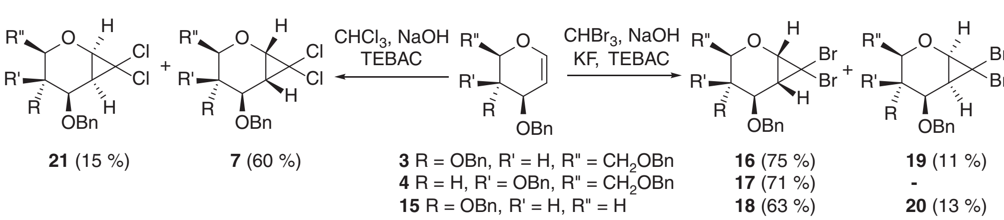
The Simmons-Smith protocol typically delivers the carbene to the same face of the alkene as the nearest oxygen substituent due to complexation to such donor groups. In contrast, the major diastereomer resulting from Mąkosza or diazoester cyclopropanation usually results from carbene addition to the sterically less hindered face of the glycal. Selective access to either diastereomer of the methylene cyclopropanes may be obtained by the Simmons-Smith method or by Mąkosza cyclopropanation followed by reductive removal of the halogens with lithium aluminum hydride (see Scheme 2) [38, 39]. The selective synthesis of both stereoisomeric cyclopropanes from each of D-glucal, D-galactal and L-rhamnal (viz. **5** and **9**, **6** and **10**, **12** and **14**) has been achieved via these pathways (Scheme 4) [40].

In preparation for our research in this area, we synthesized the *gem*-dibromocyclopropanes from D-glucal, D-galactal and D-xylal, **16**–**18**, and the D-glucal-derived *gem*-dichlorocyclopropane **7** that had been previously reported [40]. In addition, we isolated the previously unknown minor diastereomers **19**, **20** and **21** from these reactions (Scheme 5) [41]. In the D-galactal case, **4**, only one cyclopropane isomer, **17**, was formed. Presumably, the β-face of **4** is sufficiently crowded to prevent carbene attack from that side (Fig. 1). In contrast, the D-glucal **3** and D-xylal **15** have substituents shielding both faces to some extent, so a mixture is seen.

The synthesis of cyclopropanes has been thoroughly reviewed [1–9, 28] so no further analysis will be attempted here. Instead, the synthesis of cyclopropyl substrates will be mentioned in the subsequent sections where pertinent to the discussion of their reactions.



Scheme 4 Synthesis of stereoisomeric cyclopropanes by Simmons-Smith and Mąkosza-reduction methods [40].



Scheme 5 Synthesis of stereoisomeric dichloro- and dibromocyclopropanes by Mąkosza reaction [41].

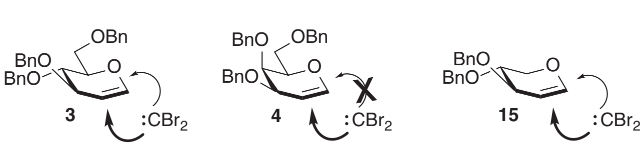


Fig. 1 Carbene approach to benzylated D-glucal **3**, D-galactal **4**, and D-xylal **15**.

Ring expansion of glycal-derived cyclopropanes

The ring expansion of cyclopropane-fused ring systems involves cleavage of the internal, shared bond. For glycal-derived cyclopropanes, the adjacent endocyclic oxygen provides stabilization of the cation intermediate, which results in attack of a nucleophile predominately at the anomeric center.

Ring expansion of unfunctionalized 1,2-cyclopropyl carbohydrates

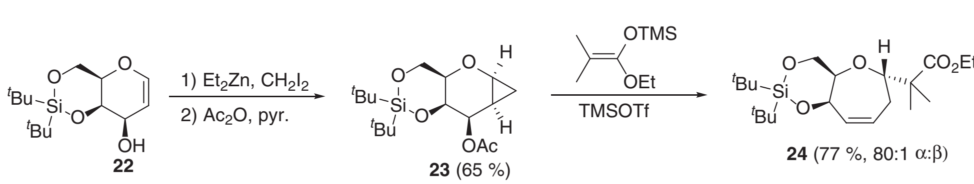
Hoberg has extensively demonstrated the ring expansion of Simmons-Smith cyclopropanes that possess a leaving group at the neighboring carbon [42–44]. A great variety of nucleophiles (Nu) are able to quench the resulting glycosyl cation, including triethylsilane (Nu = H), allyltrimethylsilane (Nu = allyl), trimethylsilyl azide (Nu = N_3), trimethylthiophenylsilane (Nu = SPh), trimethylsilyl allyloxide (Nu = OAllyl), trimethylpropargylsilane (Nu = propargyl) and silyl enol acetals (Nu = $-CR_2CO_2R'$), and provide diverse oxepine products substituted at C1 with H, C, N, S or O. For instance, the cyclopropane **23**, with an acetate leaving group, was generated from the D-galactal **22** and reacted with a silyl enol acetal to afford oxepine **24** in high yield and stereoselectivity (Scheme 6) [42]. This process represents a cyclopropyl homolog of the Ferrier reaction [45–48]. Extension of this chemistry to hydroxyls activated by a silyl Lewis acid has also been demonstrated [49].

In a related vein, Sridhar has used cyclopropyl ketones to produce disaccharides and trisaccharides containing septanoside residues [50]. For example, cyclopropyl ketone **25** reacted with protected methyl glucoside **26** to afford coupled **27** in high yield (Scheme 7). Here, the reaction proceeds through cleavage of the shared cyclopropane bond and stabilization of the resulting negative charge by enolate formation at the adjacent ketone. Reduction and Mitsunobu inversion of **27** then provided a disaccharide glycosyl acceptor **28** that, upon reaction with cyclopropane **25**, gave the trisaccharide **29**. An alternative iterative procedure, whereby cyclopropyl ketone **30** reacted with the enone **31**, gave an unsaturated disaccharide **32**. This could be cyclopropanated (by a sequence involving Luche reduction, alcohol-directed Simmons-Smith cyclopropanation, and oxidation) to produce **33**, which was subjected to further coupling with **31** to form trisaccharide **34**. Continuation of this process would enable the preparation of oligoseptanosides.

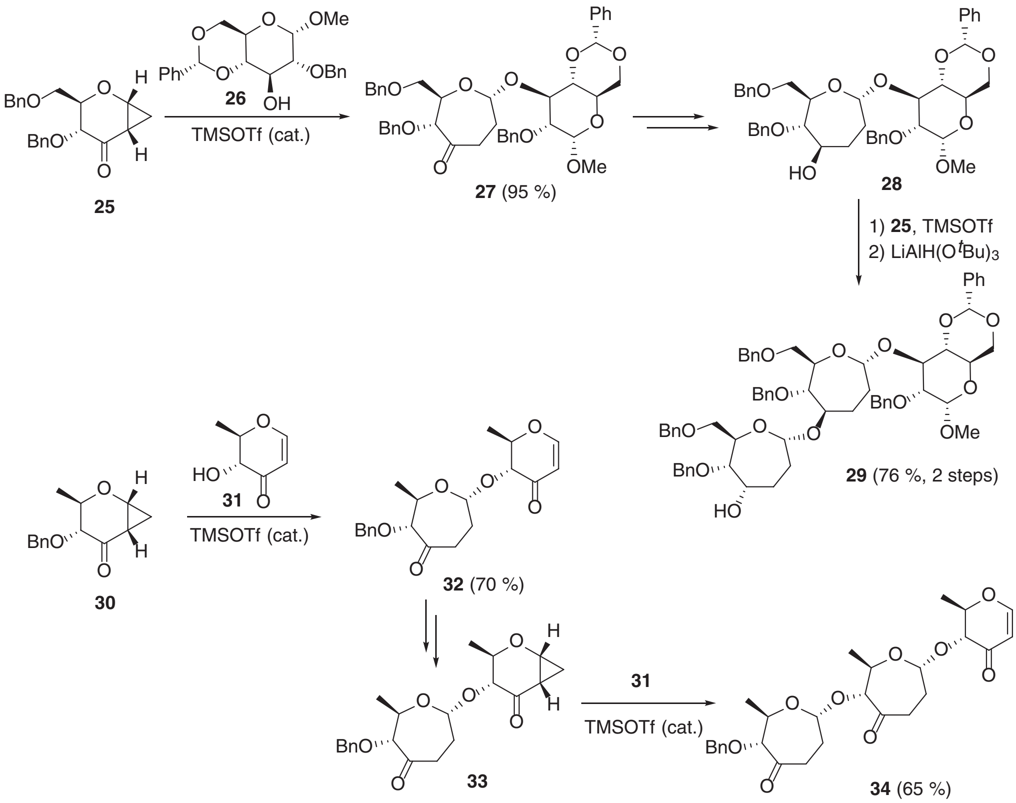
Intriguingly, treatment of cyclopropyl ketones with sulfur nucleophiles also allowed preparation of oxepine-containing disaccharides, albeit not in a single step [51]. For example, ring opening of cyclopropane **25** produced acyclic dithioacetal **35**, presumably via the thiophenol-substituted oxepine. Treatment of the dithioacetal **35** with *N*-iodosuccinimide and silver triflate in the presence of sugar alcohols afforded disaccharides such as **36** (Scheme 8).

Ring expansion of carbonyl-substituted 1,2-cyclopropyl carbohydrates

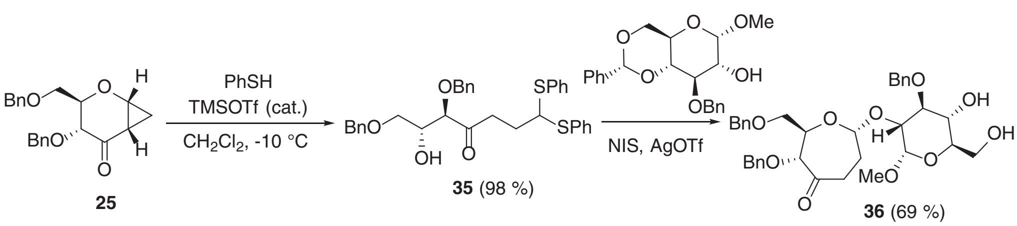
The electronics of cyclopropanes substituted with an electron-withdrawing group (most commonly esters) favor cleavage of the bonds adjacent to the carbonyl-bearing cyclopropyl carbon. Therefore, cases of cyclopropane ring expansion for such substrates are rare. Nonetheless, Yu and Pagenkopf reported the ring expansion of the donor-acceptor cyclopropane **37** that contains an acetate leaving group (Scheme 9) [52]. In this reaction, the leaving group at the 3-position provides an electron sink in formation of the oxepine **38**. Related processes have also been invoked as side reactions in other cases [53].



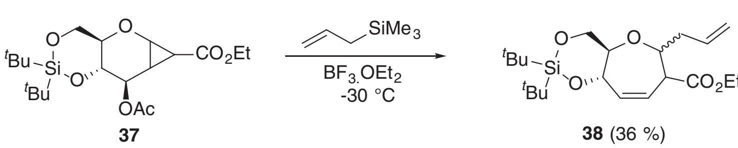
Scheme 6 Ring expansion of Simmons-Smith cyclopropyl carbohydrate **23** [42].



Scheme 7 Synthesis of di- and trisaccharides by iterative ring opening of cyclopropyl ketones [50].



Scheme 8 Two-step synthesis of disaccharides from cyclopropyl ketones [51].



Scheme 9 Ring expansion of ester-substituted cyclopropyl carbohydrate **37** [52].

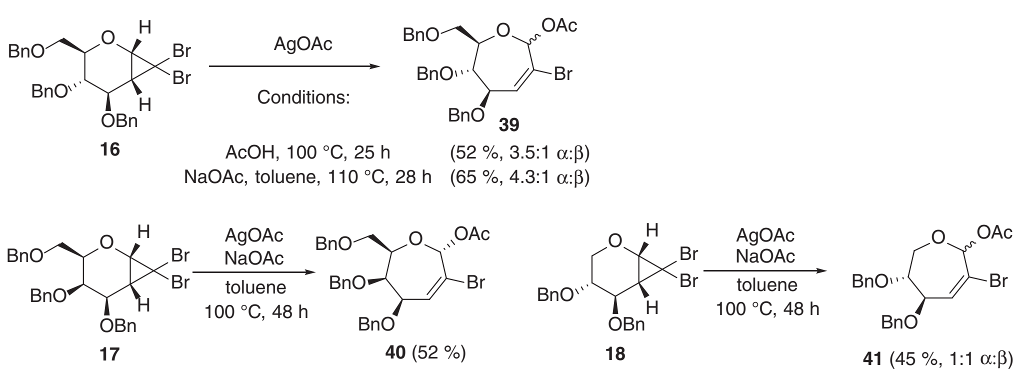
Ring expansion of *gem*-dihalogenated 1,2-cyclopropyl carbohydrates

Nagarajan and co-workers reported in 1997 that treatment of the *gem*-dibromocyclopropanes **16** and **17** with potassium carbonate in refluxing methanol provided the corresponding oxepines [40]. However, we later showed that these structures were incorrectly assigned and that the products were branched pyranosides (vide infra, see Scheme 29) [54]. In fact, the ring expansion of these 1,2-cyclopropyl carbohydrates is difficult to achieve because it is very sluggish at ambient temperatures. Nagarajan reported that attempted ring expansion using silver salts and other Lewis acids was unsuccessful: when the reaction was carried out in acetic acid at room temperature, no reaction occurred, whereas at reflux the starting material degraded [40]. With the benefit of hindsight (and the knowledge that the basic conditions did not afford the ring expanded products), we carefully re-examined the reaction of **16**. We observed the same outcomes as Nagarajan at reflux and room temperature. However, use of silver acetate in acetic acid at an intermediate temperature (100 °C) allowed sufficient reactivity whilst avoiding significant degradation, and in this way the acetate **39** was obtained in a 52 % yield and a 3.5:1 ratio of α- and β-anomers [54] (Scheme 10). These solvolytic reaction conditions were modified to ultimately replace the acetic acid with sodium acetate as the nucleophilic source (in addition to the silver counterion) and toluene as the solvent (Scheme 10). Similar reactions with the D-galactal- and D-xylal-derived cyclopropanes **17** and **18** afforded the acetates **40** (as a single diastereomer) and **41** (as a 1:1 mixture of anomers) [41]. Taken together, these results indicate that nucleophile attack is affected by steric factors operating in the intermediate cation (see Scheme 11 below). In the galactal system, the top face is significantly more crowded than the bottom face and exclusive formation of the α-anomer is observed. In comparison, nucleophilic approach to the D-glucal and D-xylal intermediates would encounter competing steric effects due to the groups on both faces of the sugar ring, and hence mixtures of product isomers are formed. It is possible that electronic factors, such as the anomeric effect, may also play a role in the selectivity.

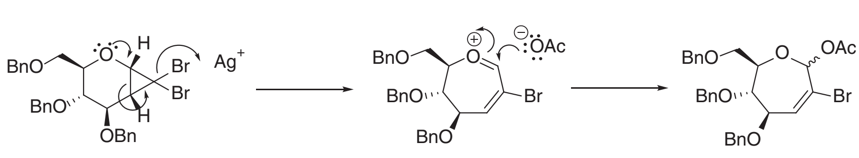
The mechanism of the ring expansion of *gem*-dibromocyclopropane **16** involves abstraction of a bromide and concomitant ring expansion, resulting in an oxonium-stabilized allylic cation **36** that is attacked by the acetate nucleophile to afford the oxepine isomers **33** (Scheme 11).

Moving on to reactions with alcohols as nucleophiles, we found the use of methanol to be unsatisfactory because its low boiling point limits the temperature at which the reaction can be performed. Nonetheless, a lengthy reaction of cyclopropane **16** with silver acetate in methanol maintained at reflux for 5 days afforded a small quantity (15 % yield) of the desired oxepine **43** as a 2.8:1 mixture of α- and β-anomers, accompanied by recovered starting material (61 %) (Scheme 12) [54].

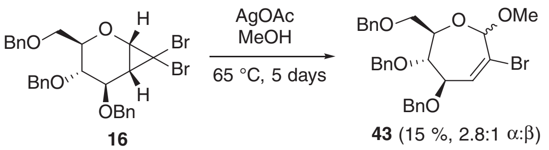
This chemistry was extended to a range of nucleophiles, including allyl alcohol, benzyl alcohol and phenol to afford oxepines **44**–**47** in moderate yields (Scheme 13) [41]. However, non-alcohol nucleophiles were less satisfactory, in that the reaction with benzylamine provided none of the anticipated aminooxepine, but instead a small quantity of the benzyloxy product **46**, which may result from loss of a benzyl protecting



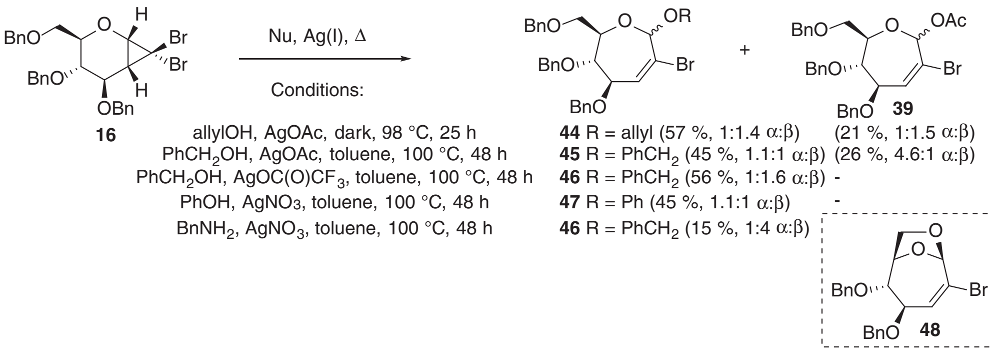
Scheme 10 Silver-promoted ring expansion of glycal-derived *gem*-dihalocyclopropane **16**–**18** with acetate [54].



Scheme 11 Mechanism of ring expansion of *gem*-dibromocyclopropane **16** and formation of acetate **39.**



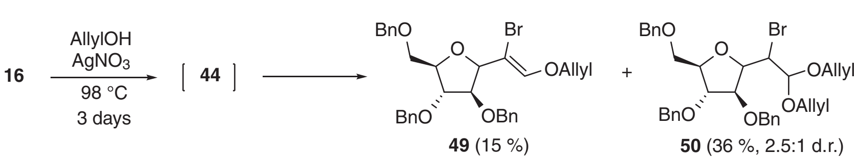
Scheme 12 Silver-promoted ring expansion of glycal-derived *gem*-dihalocyclopropane **16** with methanol [54].



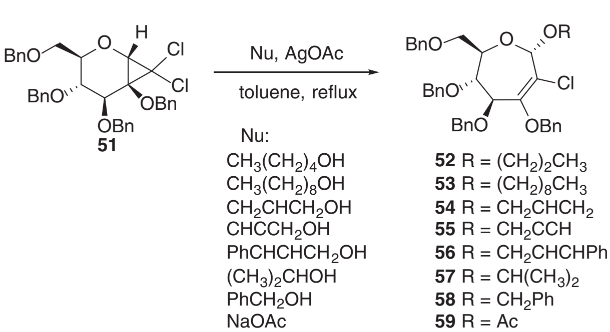
Scheme 13 Ring expansion of glucal-derived *gem*-dihalocyclopropane **16** [41].

group from some of the substrate under the reaction conditions. Furthermore, an attempted *C*-glycosidation with the anion derived from Meldrum's acid in the presence of silver acetate was unsuccessful, producing only small quantities of acetate **39** and bridged bicyclic acetal **48** [41]. The *O*-substituted oxepines showed a tendency to undergo ring contraction upon prolonged heating. For instance, performing the ring expansion of **16** with silver nitrate in allyl alcohol at reflux for 3 days afforded none of the oxepine **44**; instead the *C*-furanosides **49** and **50** were obtained (Scheme 14) [55]. Similar results were obtained by heating cyclopropane **16** in allyl alcohol in the absence of silver salt. It was demonstrated that the *C*-furanosides form via the oxepine **44** rather than through an alternative process from **16** [55]. Interestingly, no corresponding ring contraction occurred with oxyglycals (vide infra) [56].

Jayaraman's group recently demonstrated that the oxyglycal-derived cyclopropanes cleanly produce ring expanded products upon treatment with silver acetate (Scheme 15) [56]. In the presence of alcohols,



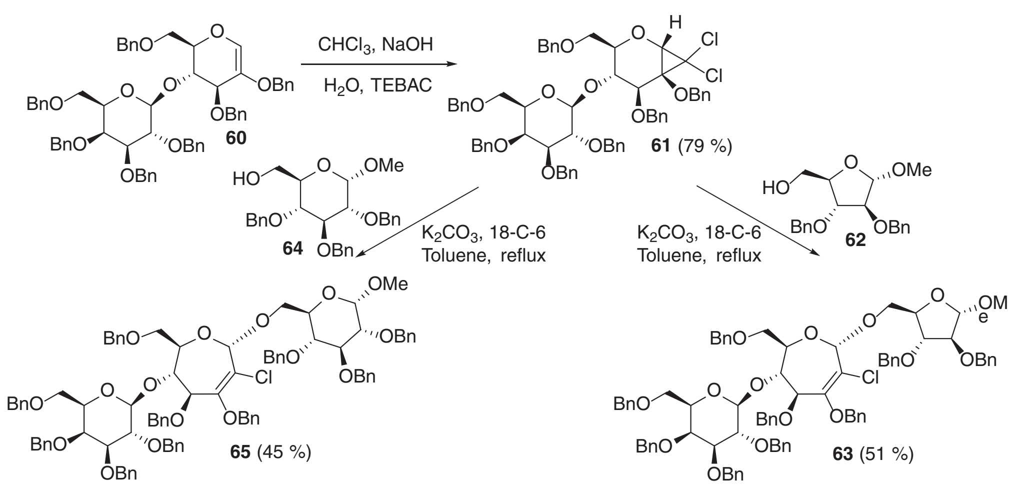
Scheme 14 Production of *C*-furanosides **49** and **50** by ring contraction of oxepine **44** [55].



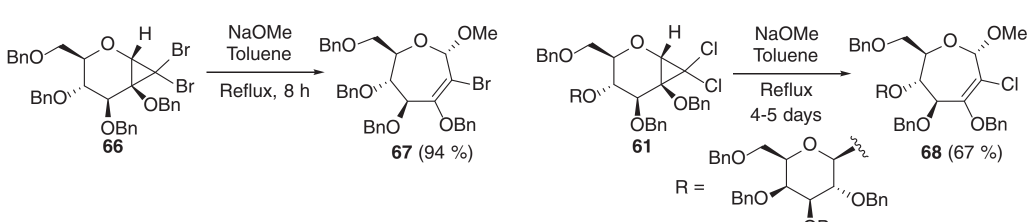
Scheme 15 Ring expansion of 2-oxyglycal-derived *gem*-dihalocyclopropanes in the presence of silver(I) [56].

the corresponding glycosides **52**–**58** were obtained from D-glucal-derived **51**, while addition of sodium acetate afforded the acetate **59**. Cyclopropanes formed from 2-oxyglycals also undergo very effective ring expansion in the presence of an alcohol and base to afford highly oxygenated oxepines [57–59]. Jayaraman and co-workers have demonstrated the efficient synthesis of alkyl [57], aryl septanosides [58], disaccharides [58, 59] and trisaccharides [59] in this way. For example, the lactose-derived 2-oxyglucal disaccharide **60** reacted with chloroform under Mąkosza conditions to afford *gem*-dichlorocyclopropane **61** (Scheme 16). Base-promoted ring expansion in the presence of 5-hydroxypentofuranoside **62** generated the trisaccharide **63**. A similar reaction with the 6-hydroxyhexopyranoside **64** provided the trisaccharide **65**. It should be noted that the 2-oxyglycal-derived cyclopropanes cleanly undergo ring expansion, even under the basic conditions that form exclusively 2-*C*-branched products in the glycal series!

As can be seen in the examples above, *gem*-dibromo- and *gem*-dichlorocyclopropanes have both been variously used in ring expansion reactions. Ring expansions of the chloro compounds are expected to be slower than those of the corresponding bromides because loss of a halide is likely to be involved in the rate-limiting step (loss of halide is known to be concerted with cyclopropane ring cleavage, such that no discrete cyclopropyl cationic intermediate forms) [60–62]. To our knowledge, there have been no systematic studies of the relative rates of 1,2-(*gem*-dibromo- and -dichlorocyclopropyl) carbohydrates in ring expansion. Nonetheless, results from Jayaraman's group provide evidence that the chlorides react significantly more slowly than the bromides: for example, the 2-oxy-D-glucal-derived *gem*-dibromocyclopropane **66** underwent ring expansion in the presence of sodium methoxide to provide the oxepine **67** in 94 % yield after 8 h at toluene reflux [57], whereas reaction of the dichlorocyclopropane **61** under the same conditions took 4–5 days to deliver **68** (Scheme 17) [59].



Scheme 16 Ring expansion of 2-oxyglycal-derived *gem*-dihalocyclopropanes to afford trisaccaharides [59].



Scheme 17 Rate differences in the ring expansion of dichloro- and dibromocyclopropanes [57, 59].

Ring opening of glycal-derived cyclopropanes to branched products

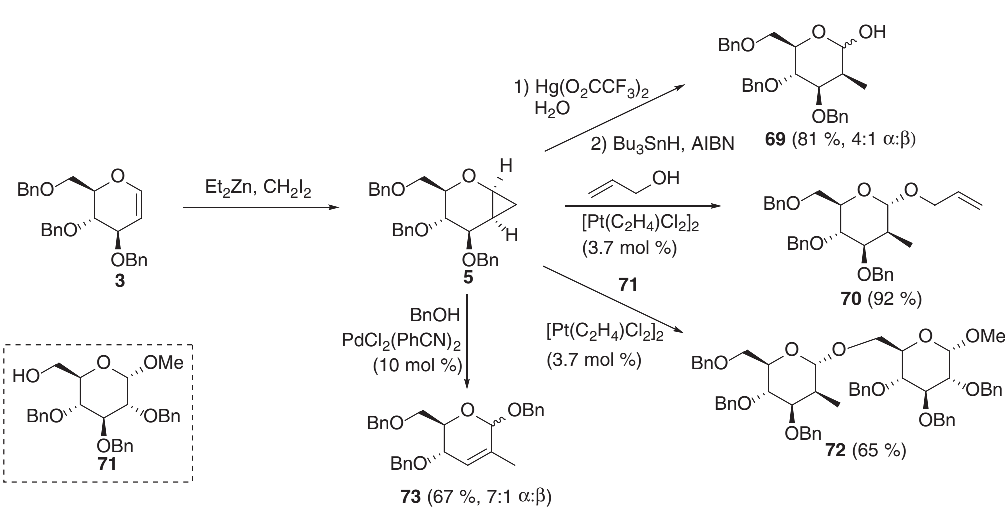
Carbon-branched carbohydrates are considered to be possible therapeutic agents [21–23] because they mimic natural cell-surface glycans. The ring opening of cyclopropyl carbohydrates by cleavage of a non-shared cyclopropane bond produces 2-*C*-branched products without ring expansion, and is one of the major strategies for synthesis of these useful compounds [24].

Non-expansive ring opening of unfunctionalized 1,2-cyclopropyl carbohydrates

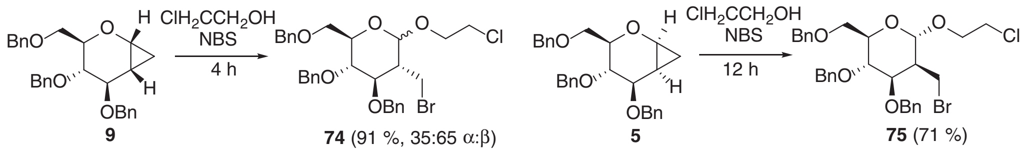
Typically, ring opening of unfunctionalized glycal-derived cyclopropanes has been achieved with an electrophile to induce cyclopropane opening and provide 2-*C*-branched products. Several formulations of this process are exemplified in Scheme 18, where Simmons-Smith cyclopropane **5** is shown to react with a Lewis acidic metal [Hg(II) or Zeise's Pt(II) dimer] in the presence of a nucleophile to afford 2-*C*-branched pyranosides **69** or **70** after demetalation [63, 64]. Heathcock further reported that the 2-*C*-branched hemiacetal **69** could be converted (Ms_2O, NEt_3) into benzyl-protected 2-methyl-D-glucal [63]. Madsen demonstrated that the reaction catalyzed by Zeise's dimer was general to cyclopropanes derived from different sugars and various nucleophiles, such that disaccharides (e.g. **72**) were obtained from reaction with a hydroxyl monosaccharide (e.g. **71**) [64].

An alternative process resulted from use of the highly electrophilic palladium(II) catalyst $PdCl_2(PhCN)_2$, producing 2-*C*-branched Ferrier rearranged products [64]. The 2-methyl-2,3-unsaturated glycoside **73** was prepared from cyclopropane **5** in this way (Scheme 18 above).

Unfunctionalized carbohydrate-fused cyclopropanes undergo a similar ring opening in the presence of electrophilic halogen. Nagarajan studied this process extensively and demonstrated that stereoisomeric cyclopropanes react with *N*-bromo- or *N*-iodosuccinimide (NBS or NIS) in various alcohols or water to afford saturated 2-*C*-branched pyranosides (Scheme 19) [40]. Interestingly, considerable rate differences were observed between ring opening reactions of the cyclopropane **9**, prepared by reduction of the dichlorocyclopropane, and Simmons-Smith-derived cyclopropane **5**. Thus, for example, the α-cyclopropane **9** reacted in 4 h with 2-chloroethanol and NBS to afford the bromomethyl branched product **74** as a mixture of anomers, whereas the β-cyclopropane **5** reacted under the same conditions much more slowly and afforded only the α-anomer **75** after 12 h. It was suggested that the differences in rates and selectivity could be due to competing S_N2 (stereospecific) and S_N1 (partially selective) processes [40]. It is mechanistically possible that the rates of electrophile-induced ring opening, which is aided by participation of the endocyclic oxygen and forms epimeric oxonium intermediates, are different for the two isomeric cyclopropanes because of conformational



Scheme 18 Cyclopropane opening to 2-*C*-branched pyranosides using metal catalysts/promoters [63, 64].

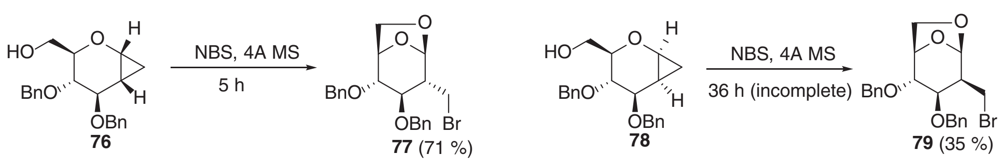


Scheme 19 Cyclopropane opening to 2-*C*-branched pyranosides using *N*-halosuccinimide [40].

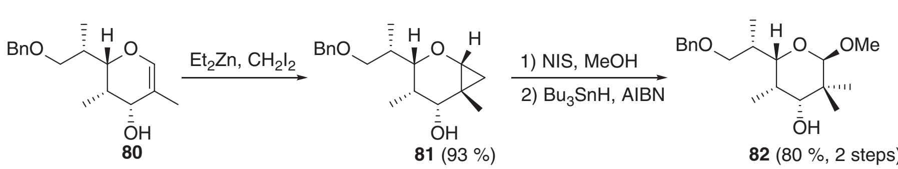
differences that alter the degree of orbital overlap between an oxygen lone pair and the adjacent antibonding orbital of the cyclopropane, thus affecting the ability of the oxygen to participate in the process. The slower ring opening of the β-cyclopropane by this S_N1-like process could allow for the intervention of a stereospecific S_N2-type mechanism. The partial selectivity of the S_N1-type process could result from the relative steric crowding of the top and bottom faces of the oxonium intermediate according to the stereochemical interplay of the adjacent bromomethyl group and the other substituents. This scenario is consistent with the results obtained from intramolecular reactions of the 6-hydroxy cyclopropylcarbohydrates **76** and **78**, which delivered bridged products **77** and **79**, respectively, with very different reaction rates (Scheme 20) [40].

A related reaction was employed in Danishefsky's synthesis of epothilone A [65]. Simmons-Smith cyclopropanation of **80** and NIS-induced ring opening of the resulting **81** in the presence of methanol, followed by reductive deiodination, delivered *gem*-dimethylpyran **82** in high yield (Scheme 21) [65]. In this way, the C3–C9 fragment of epothilone A and analogs was generated in a stereocontrolled manner.

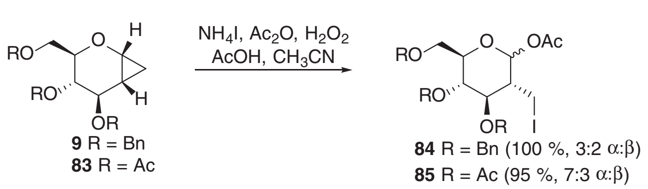
Extension of this chemistry to acetate nucleophiles would provide acetyl glycosides, useful glycosyl donors for glycosidations. Gammon et al. have reported such reactions on benzyl- and acetyl-protected cyclopropyl carbohydrates **9** and **83**, to afford 2-*C*-branched iodomethyl acetyl glycosides **84** and **85**, respectively (Scheme 22) [66]. In keeping with the hypothesis described above, the β-cyclopropyl variant of **9** (viz. **5**) was unreactive under the same conditions.



Scheme 20 Cyclopropane opening to bicyclic 2-*C*-branched pyranosides using *N*-halosuccinimide [40].



Scheme 21 Cyclopropane ring opening to *gem*-dimethyl branched product **82**, an intermediate in epothilone A synthesis [65].



Scheme 22 Cyclopropane ring opening to form 2-*C*-branched glycosides [66].

Very rarely, 1,2-cyclopropylcarbohydrates undergo ring cleavage with unusual regioselectivity, *viz.* with cleavage of the 1′,2-bond (see Scheme 1). In such cases, a highly reactive moiety must be generated at the C3 position. Balasubramanian and co-workers achieved this type of ring opening by treating the C3-xanthate **86** with AIBN and tributyltin hydride, thus forming the methyl *C*-glycoside **87** in high yield (Scheme 23) [67].

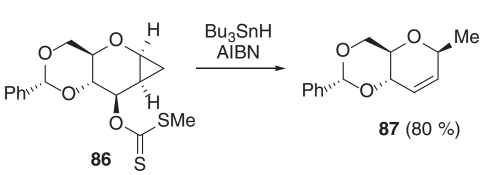
Non-expansive ring opening of carbonyl-substituted 1,2-cyclopropyl carbohydrates or their derivatives

Carbonyl-substituted glycal-derived cyclopropanes are electronically tuned for ring opening through cleavage of the bond proximal to the electron-withdrawing group and the electron-donating endocyclic oxygen. The synthesis and reactions of such *donor-acceptor* cyclopropanes have been reviewed [52, 68–70].

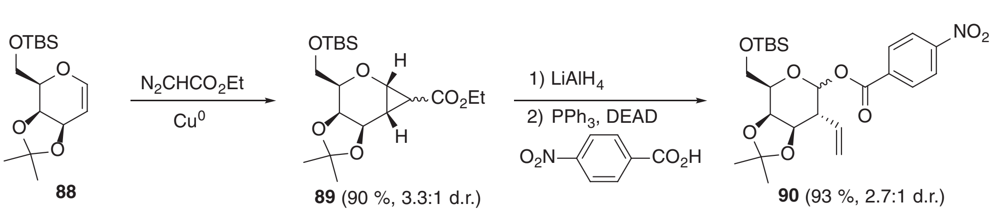
In the first systematic investigation of glycal-derived carboxylcyclopropanes, Fraser-Reid and co-workers demonstrated that several parent glycals (D-glucal, D-galactal and L-rhamnal) with varied protecting groups were amenable to high-yielding cyclopropanation with ethyl diazoacetate and copper(0) powder [53]. In the case of D-galactal-derived **88**, cyclopropane **89** was obtained in high yields as a mixture of isomers at the ester linkage. Following reduction of the ester, treatment of the corresponding alcohol under Mitsunobu reaction conditions caused a homoallylic rearrangement to the 2-vinyl-substituted glycoside **90** (Scheme 24).

This homoallylic rearrangement has been extended and made more general by the introduction of an acetate leaving group onto the cyclopropane ring [71]. Thus, for example, the ester **91** was reduced and acetylated to afford **92** (Scheme 25). This was amenable to cyclopropyl ring cleavage under the influence of Lewis acid aluminum triflate (or boron trifluoride) in the presence of oxygen, sulfur or nitrogen nucleophiles to afford the 2-vinyl-substituted glycosides **93**–**96**. The more highly substituted hexenyl compound **98** could be generated from the acetate **97** through a stereoselective homoallylic rearrangement [71].

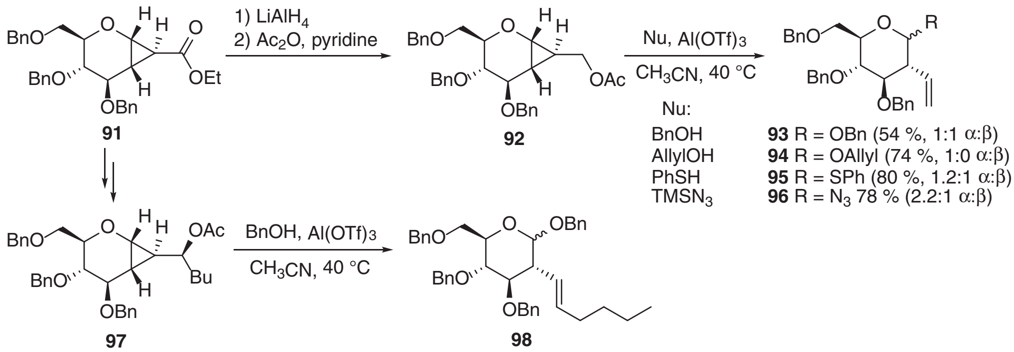
More typically, the donor-acceptor cyclopropanes themselves are subjected to the ring-opening process, without the reduction step. The reaction of ester-substituted cyclopropanes with halonium electrophiles leads to 2-*C*-ester-branched glycosides. Chandrasekaran and Sridhar have thus prepared α-iodoester-branched glycosides [72–74]. The iodide on the branch provides a synthetic handle for further functionalization, such as conversion into glycosyl amino acids. For example, donor-acceptor cyclopropane **99** reacted with NIS and alcohol **100** to produce α-iodoester **101**. Substitution of the iodide with azide afforded **102** and Staudinger reduction gave the amino ester **103** (Scheme 26) [72–74].



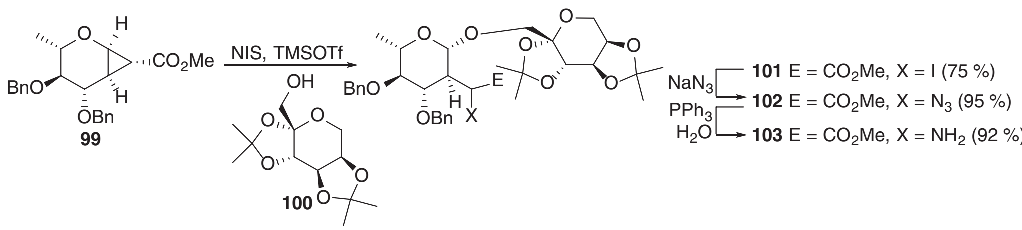
Scheme 23 Cyclopropane ring opening of xanthate **86** to *C*-glycoside **87** [67].



Scheme 24 Cyclopropane opening by Mitsunobu-type homoallylic rearrangement [53].



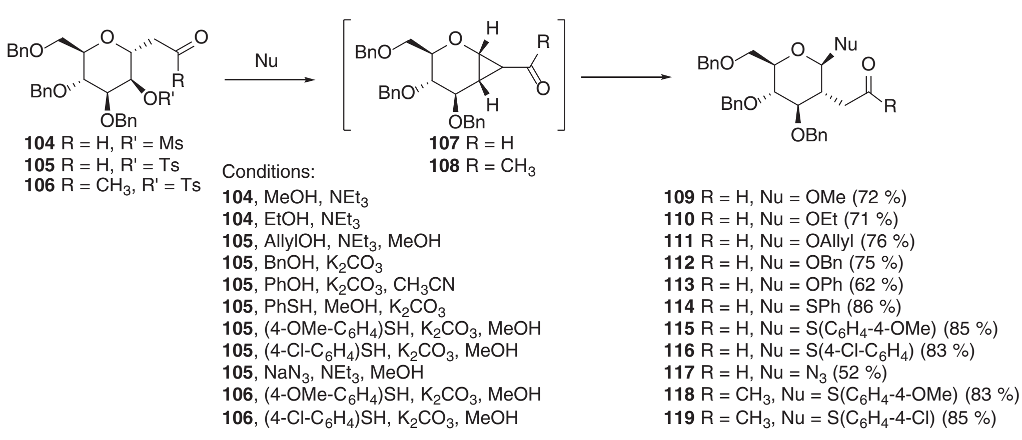
Scheme 25 Cyclopropane opening by acetate displacement and homoallylic rearrangement [71].



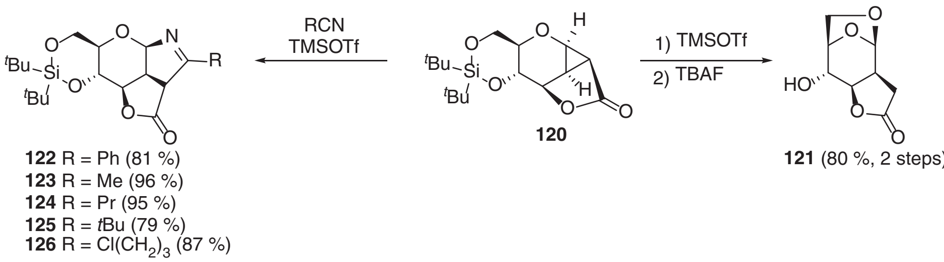
Scheme 26 Cyclopropane opening of ester-substituted cyclopropane **99** [74].

The preparation of 2-*C*-branched pyranosides by in situ formation and ring opening of formyl- and acetyl-substituted cyclopropanes has been demonstrated by Zou et al. with numerous nucleophiles (Scheme 27) [75]. The cyclopropanes **107** and **108** were generated in situ through S_N2 displacement of the mesylate or tosylate leaving group at C2 by an enolate derived from the aldehyde or ketone *C*-glycosides **104**–**106**. The branched products of the cyclopropyl ring opening, **109**–**119**, contain aldehyde or ketone functionalities that may be convenient for future transformations, and various aglycons (O-, S- or N-). Formally, the reaction represents a 1,2-migration of the aldehyde or ketone chain.

Pagenkopf and Yu have shown that the lactone cyclopropane **120**, prepared by intramolecular delivery of a diazoester-derived carbene onto the glycal, undergoes ring opening (Scheme 28) [76]. Trapping of the zwitterionic intermediate by the internal hydroxyl group at C6 gave **121**, while addition of various nitriles provided tetracyclic dihydropyrroles **122**–**126** through [3+2] cycloadditions.



Scheme 27 Cyclopropane opening of carbonyl-substituted cyclopropanes [75].



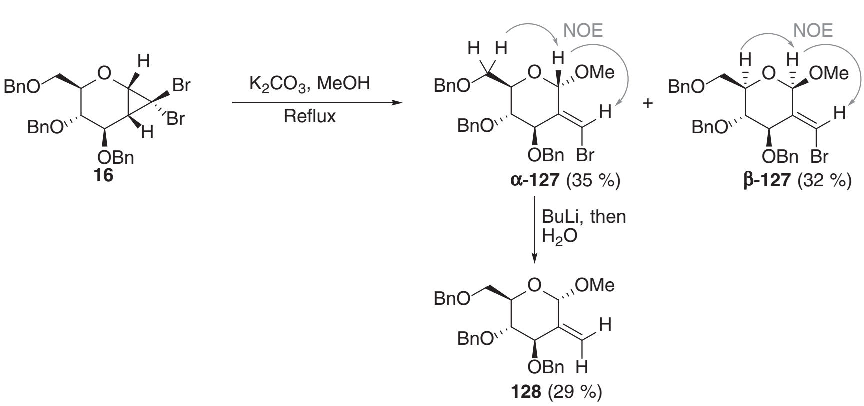
Scheme 28 Cyclopropane opening of lactone-substituted cyclopropane **120** and trapping with a hydroxyl nucleophile or nitrile dipolarophile [76].

Non-expansive ring opening of *gem*-dihalogenated 1,2-cyclopropyl carbohydrates

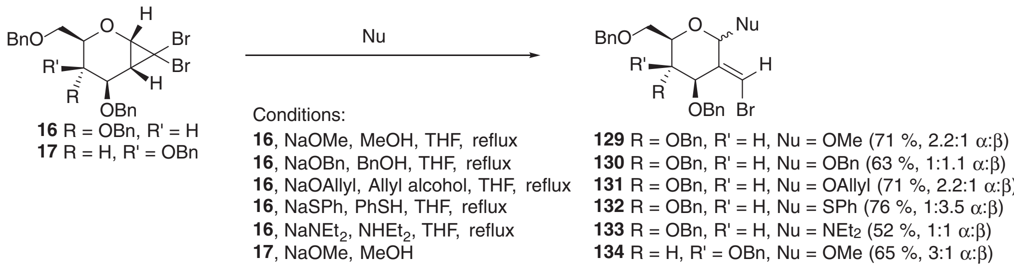
Ring opening of *gem*-dibromocyclopropane **16** with potassium carbonate in refluxing methanol was shown by us not to give the oxepines previously reported [40], but instead the 2-exobromomethylene anomers **α-127** and **β-127** [54] (Scheme 29). The structural revision was not a trivial matter. The small coupling constant and downfield chemical shift (δ ca. 6.8, $J = 0–1.7$ Hz) for the alkene proton were cause for suspicion, but not enough to disprove the assigned structure. Indeed, the 2D NMR spectra (COSY, HSQC, HMBC) were generally consistent with the oxepine structure. However, an NOE correlation between the alkene and anomeric protons did not support the oxepine structure [54]. Indeed, preparation of the oxepine **43** (with distinct spectroscopic data) from cyclopropane **16** by use of silver salts (see Scheme 12) allowed us to definitively determine that the base-induced product was not the oxepine **43**. The nature of this product was ultimately revealed by bromine-for-lithium exchange and quenching with water, which delivered the unmistakable 2-methylene-substituted compound **128** [77].

This unusual ring opening process operates with a variety of alcohols to afford glycosides **129**–**131**, as well as with thiophenol and diethylamine to produce thioglycoside **132** and aminoglycoside **133**, respectively (Scheme 30) [41]. Use of the galactal-derived substrate **17** produced the corresponding methyl glycoside **134** in a good yield. In all cases, only the *E*-bromoalkene was observed.

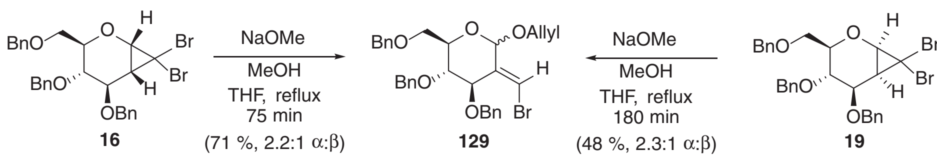
We have found that the isomeric D-glucal-derived cyclopropane **19** reacts in a similar way but significantly more slowly than the major cyclopropane isomer [41]. Thus, reaction of the α-cyclopropane with sodium methoxide and methanol provided a high yield of the methyl glycoside **129** (2.2:1 d.r.) after 75 min refluxing in THF, whereas the β-cyclopropane failed to reach completion after 3 h, at which point some of the product **129** (48 % yield, 2.3:1 d.r.) was obtained, along with recovered starting material (16 % yield) (Scheme 31) [41]. The similarity of the ratios of glycoside products from both cyclopropane isomers indicates that the mechanism



Scheme 29 Ring opening of glucal-derived *gem*-dibromocyclopropane **16** to 2-*C*-branched bromomethylene pyranoside **127** and dehalogenation [54].



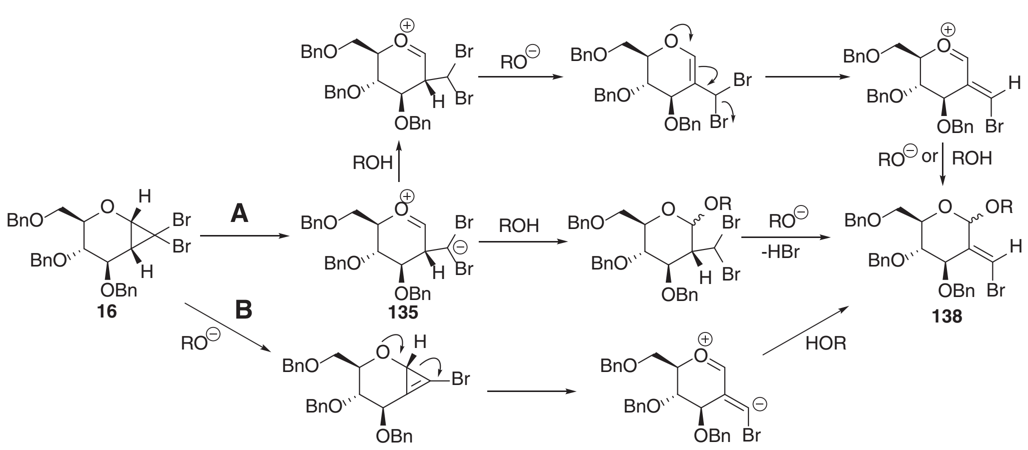
Scheme 30 Ring opening of *gem*-dibromocyclopropanes **16** and **17** to 2-*C*-branched bromomethylenes **129**–**134** [41].



Scheme 31 Comparison of ring opening of isomeric *gem*-dibromocyclopropanes **16** and **19** [41].

does not change but rather that it is significantly less favored for the β-cyclopropane (possibly due to poorer orbital overlap in the favored conformation, vide supra). A competition study was carried out on an (approximately) equimolar mixture of α- and β-cyclopropanes **16** and **19** with sodium allyloxide and allyl alcohol in THF at room temperature [41]. After 4 h, all of the α-cyclopropane but almost none of the β-cyclopropane had been consumed. The reaction was terminated after 60 h, at which point only ca. 20 % of the β-cyclopropane had reacted.

At present, the mechanism of this ring opening to form *exo*-bromomethylene pyranosides is not fully elucidated. There are two broad pathways that seem plausible and have some precedent [5, 6, 78–81]. One of these (**A**) involves an early (and probably rate determining) cyclopropane opening with participation from the endocyclic oxygen to afford the zwitterionic intermediate **135** (Scheme 32). At this point, the route diverges, according to the order of the subsequent steps, which involve addition of the alcohol and elimination of HBr. The second main mechanistic pathway (**B**) involves an initial, rate determining elimination of the elements of HBr to form a cyclopropene **136**, which may occur in a single, concerted step or by deprotonation followed



Scheme 32 Plausible mechanisms for ring opening reactions of *gem*-dibromocyclopropane **16** to 2-*C*-branched bromomethylenes **138.**

by loss of bromide ion. Ring opening of this strained intermediate would form the zwitterionic intermediate **137**, which has a carbene resonance structure (not shown), and addition of the alcohol would produce the branched product **138**. Such a mechanism has been proposed previously for the ring opening of a chlorocyclopropene [81]. The difference in reaction rates of the cyclopropane isomers could be consistent with either mechanism, as the conformation of the bicyclic precursor could influence the facility of either the rate-determining ring opening or the cyclopropene formation. The production of only the *E*-alkene isomer points towards the cyclopropene mechanism, as the stereochemical integrity could certainly be maintained in the ring opening to the zwitterionic intermediate **137**, but it is not inconsistent with the other mechanism, as a stereoselective loss of bromide at a late stage is possible. We have undertaken trapping and deuteration experiments, but these have not yet definitively discounted either mechanism [82].

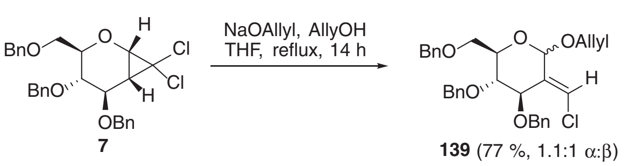
The corresponding *gem*-dichlorocyclopropane **7** was found to react in a similar manner to the bromo compound, but much more slowly. Thus, after 14 h at reflux in THF, some starting material remained, and the product **139** was isolated in 77 % yield as a 1.1:1 mixture of α- and β-anomers (Scheme 33) [41].

Synthesis and reactions of furanose glycal-derived cyclopropanes

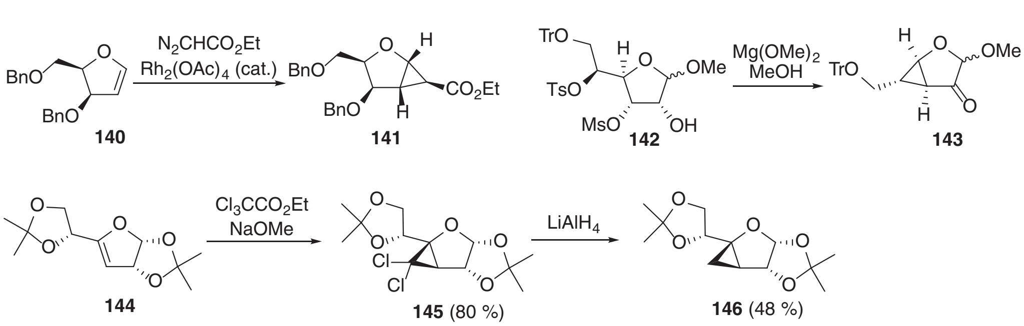
There are relatively few examples of cyclopropanes derived from five-membered ring glycals. This may be partly due to difficulties in synthesis and isolation of these highly reactive bicyclo[3.1.0]hexanes. Nonetheless, several furanose cyclopropanes are known and have been deemed worth addressing in a separate section to highlight this class of compounds and the challenges associated with their preparation.

Synthesis of furanose cyclopropanes

Several early examples of furanose cyclopropanes are shown in Scheme 34. The ester-substituted cyclopropane **141** was prepared from the furanose glycal **140**, derived from D-xylal (Scheme 34) [83]. A substitution process has been employed for the preparation of the furanose-based cyclopropane **143** from tosylate **142** [84]. The *gem*-dichlorocyclopropane **145** was available by addition of dichlorocarbene (generated from ethyl



Scheme 33 Ring opening of glucal-derived *gem*-dichlorocyclopropane **7** to 2-*C*-branched chloromethylene anomers **139** [41].



Scheme 34 Synthesis of furanose cyclopropanes **141, 143, 145** and **146** [38, 83, 84].

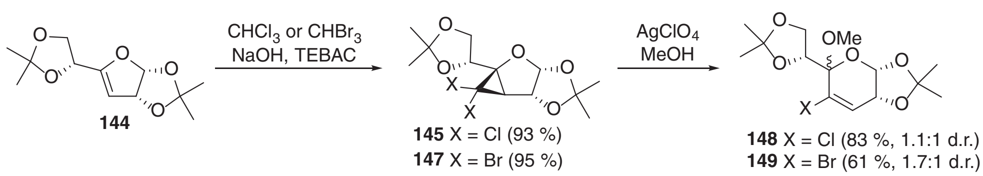
trichloroacetate by the action of sodium methoxide) to the glycal **144** and the chlorides removed reductively with lithium aluminum hydride to give **146** [38].

Ring expansion of furanose cyclopropanes

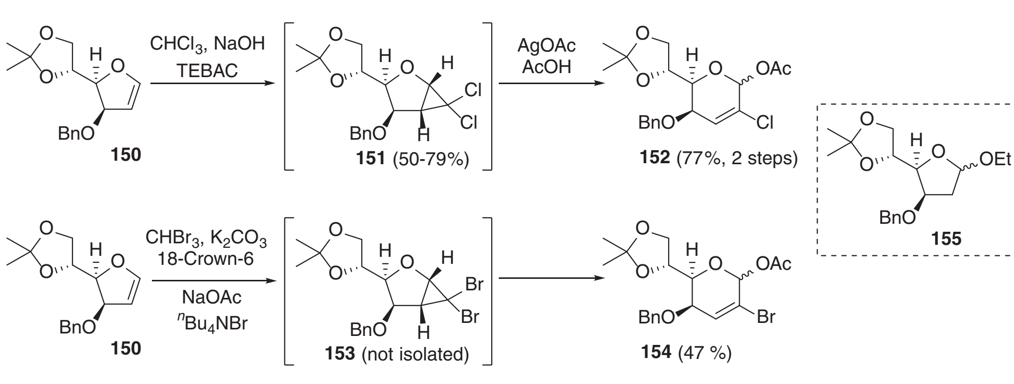
The strain in the bicyclo[3.1.0]hexane system and the donor properties of the endocyclic oxygen greatly facilitate ring opening of furanose-fused cyclopropanes. Ring expansion is typically seen in systems that develop a positive charge at the exterior carbon, such as with halogenated cyclopropanes.

Gross and co-workers found that Mąkosza conditions were also suitable for synthesis of the *gem*-dichlorocyclopropane **145** (previously prepared from ethyl trichloroacetate as described above) and that the bromine variant **147** could be made in a similar way, although the *gem*-dibromocyclopropane **147** was not stable enough to characterize (Scheme 35) [85]. These cyclopropanes underwent ring expansion to afford the dihydropyrans **148** and **149** as mixtures of diastereomers.

We have employed the ring expansion of *gem*-dichloro- and dibromocyclopropanes prepared from the D-mannose derivative **150** [86] to synthesize dihydropyrans **152** and **154** (Scheme 36) [87, 88]. Chloride **152** was used in the first synthesis of the ring system of the natural product TAN-2483B [87]. Synthesis of dichlorocyclopropane **151** was a facile, clean process, although the reactivity of the system was evident from the variable yields obtained after column chromatography. Improved results were achieved by immediate ring expansion of the crude material in the presence of silver acetate and acetic acid, to provide the dihydropyran acetate **152** as a mixture of anomers in consistently good yields. In contrast, preparation of the dibromocyclopropane **153** was fraught with difficulty, in part due to the even higher reactivity of this strained cyclopropane containing bromide leaving groups. Nonetheless, the bromide **154** was deemed to be more versatile in subsequent derivatizations (vide infra), so preparation of the dibromocyclopropane was exhaustively pursued. Reaction of glycal **150** with bromoform under Mąkosza phase-transfer conditions led to none of the desired cyclopropane, although use of undistilled bromoform, containing 1–3 % ethanol as stabilizer,



Scheme 35 Synthesis and ring expansion of furanose cyclopropanes **145** and **147** [85].



Scheme 36 Synthesis and ring expansion of furanose cyclopropanes **151** and **153** [87–89].

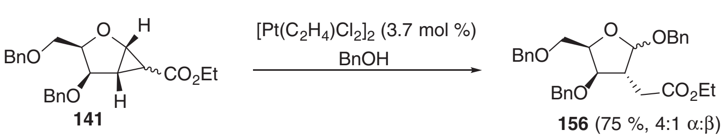
afforded small quantities of ethyl 2-deoxyhexofuranoside **155** as a mixture of isomers (26 %, 1:1.2 d.r.) [89]. Performing the reaction with distilled bromoform provided complex mixtures of unidentified products [88, 89], as did carbene formation with anhydrous potassium *tert*-butoxide [88]. Numerous other methods were attempted for the dibromocyclopropanation, to no avail. The method of Galin et al. for cyclopropanation with bromoform and potassium carbonate in the presence of methanol [90] produced the ring-expanded methyl pyranoside when applied in this setting. These conditions were adapted to incorporate an acetate nucleophile and afforded the bromoalkene-containing dihydropyran **154** in reasonable yield after recycling of the recovered starting material [88]. It should be noted that, for both dichloro- and dibromocarbene addition, only a single stereoisomeric cyclopropane was observed, which is accounted for by the high steric loading of the top face.

Ring opening of furanose cyclopropanes to branched products

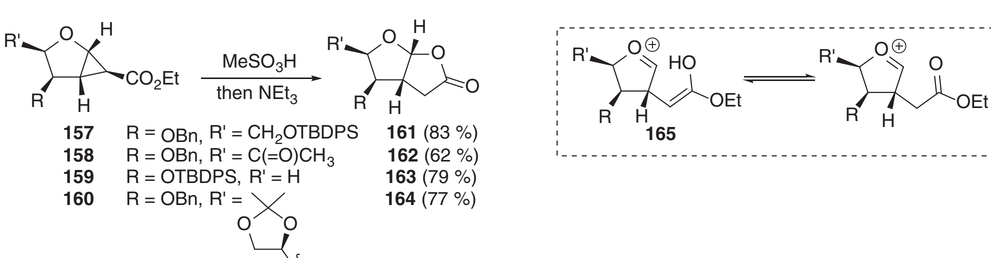
Isolated examples exist of branched furanosides formed from furanose cyclopropanes. The use of an electron-withdrawing substituent (usually an ester) generally favors non-expansive cyclopropane ring opening, because the anion derived from heterolytic cleavage of a cyclopropane bond adjacent to the ester is stabilized as the enolate.

Madsen and co-workers found that ester-substituted furanose cyclopropane **141** reacted with benzyl alcohol in the presence of Zeise's dimer as catalyst, at higher temperature (70 °C) than with the unfunctionalized cyclopropanes, to produce branched furanoside **156** as a mixture of anomers (Scheme 37) [64]. Unfortunately, this process was not entirely general. When the smaller nucleophile methanol was employed, transesterification was observed to a small degree. In a testimony to the lower reactivity of the homologous pyranose cyclopropanes, transesterification was a major problem for the ester-substituted glucal-derived cyclopropane, even with benzyl alcohol.

Conversion of a range of ester-substituted furanose cyclopropanes **157**–**160** into lactones **161**–**164** was achieved in high yields by Theodorakis and co-workers (Scheme 38) [91]. The reaction presumably proceeds through acid-promoted cyclopropane cleavage via oxonium intermediate **165**. In the absence of a better nucleophile, the ester oxygen attacks the oxonium ion to produce, after quenching with base, the furo[2,3-*b*] furanones **161**–**164**.



Scheme 37 Synthesis of branched furanoside **156** from furanose cyclopropane **141** [64].



Scheme 38 Synthesis of lactones **161**–**164** from furanose cyclopropanes **157**–**160** [91].

Further manipulations of products from cyclopropane ring opening

Functionalization of oxepines and preparation of septanosides

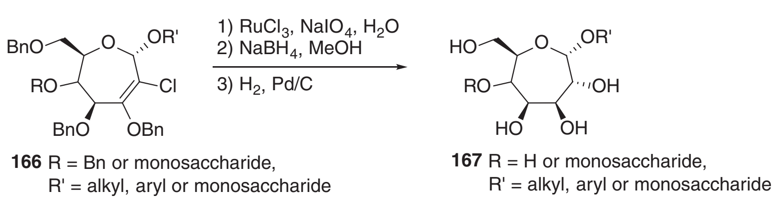
Ring expansion of pyranose cyclopropanes reveals seven-membered oxepine rings with high functional density. The presence of an alkene double bond, resulting from the ring expansion process, provides the opportunity for further functionalization. Oxygenation of the olefin leads to septanosides, seven-membered ring sugar analogs, while cross-coupling reactions of haloalkenes produce branched oxepines, amenable to further modifications.

Oxyglycal-derived oxepines **166** have been shown extensively by Jayaraman and co-workers to provide septanosides **167** by a process involving dioxygenation of the haloalkene, reduction of the resulting diketone and hydrogenolysis of the benzyl protecting groups (Scheme 39) [57–59].

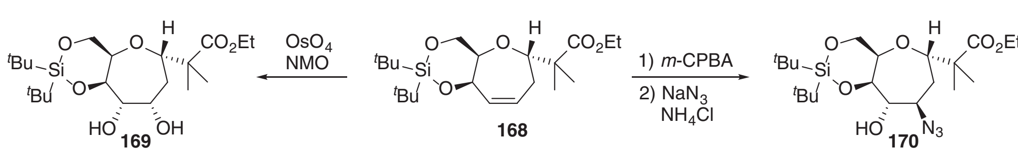
A diverse array of heteroatom-functionalized 2-deoxyseptanosides can be prepared from oxepines [92]. For example, dioxygenation of oxepine **168** affords 2-deoxyseptanoside **169**, while epoxidation and ring opening with azide provides 2,3-dideoxy-3-azidoseptanoside **170** with potential for transformation into aminosugar analogs (Scheme 40).

Dehalogenation of the haloalkenes formed by ring expansion of dihalocyclopropanes affords oxepines through halogen-for-lithium exchange and quenching. For instance, glycal-derived bromooxepine **44** reacted with butyllithium to yield oxepine **171** [89] while oxyglycal-derived **67** produced **172** in a similar manner [56] (Scheme 41). This demonstrates an alternative mode of halogen substitution with the capacity for further olefin transformations [56].

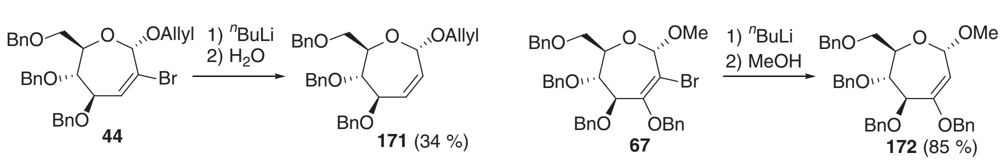
Complex oxepine derivatives can be prepared by cross coupling of the haloalkenes generated by ring expansion of *gem*-dihalocyclopropylglycals. Thus, both we and Jayaraman have recently demonstrated the potential of such a strategy for divergent formation of multiple carbohydrate mimics [41, 93].



Scheme 39 Synthesis of septanosides **167** from oxepines **166** [57–59].



Scheme 40 Synthesis of septanosides **169** and **170** from oxepine **168** [92].



Scheme 41 Dehalogenation of haloalkenes **44** and **67** to form oxepines **171** and **172** [57, 89].

A number of Suzuki, Heck and Sonogashira reactions were carried out with the bromoalkene **67** (Scheme 42) [93]. For example, Suzuki reaction of bromooxepine **67** with phenylboronic acid led to a high yield of phenyl coupled **173**, while Sonogashira reaction with phenylacetylene gave the alkyne **174**. Heck reaction of **67** with *tert*-butyl acrylate provided conjugated diene **175**, which was hydrogenated and hydrogenolyzed, and the resulting ketone reduced to afford 2-deoxy-2-branched septanoside **176**.

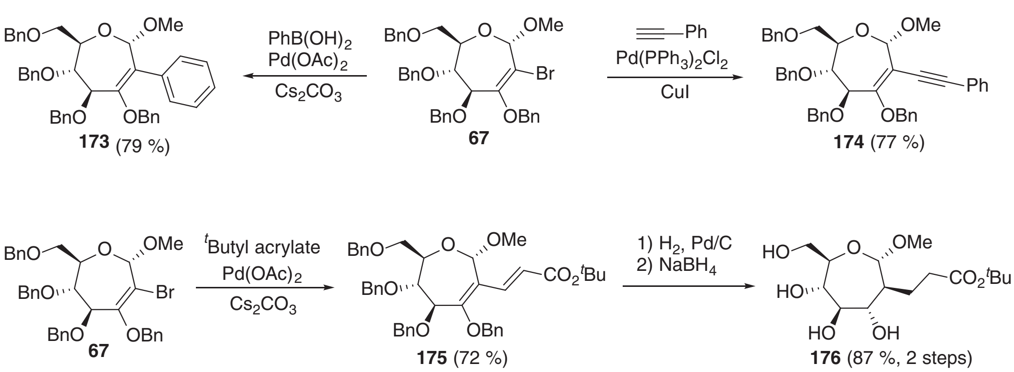
We performed Suzuki cross couplings of tetra-*O*-benzyloxepine **β-46**, prepared from the D-glucal-derived *gem*-dibromocyclopropane **16** (see Scheme 13), with several boronic acids including 4-acetylphenylboronic acid, which gave product **177** (Scheme 43) [41]. Intramolecular Heck reaction of allylated oxepine **α-44** afforded the furo[2,3-*b*]oxepine **178** [41].

Functionalization of 2-branched sugars

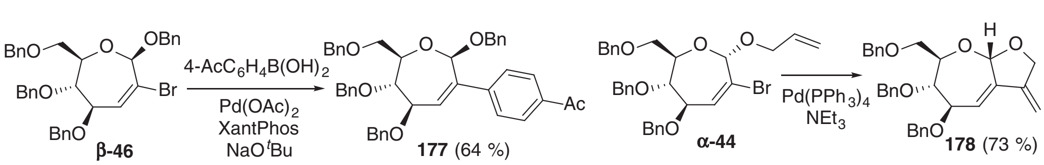
Formation of 2-*C*-branched pyranosides through the ring opening of 1,2-cyclopropyl carbohydrates provides the potential for further functionalization, due to the synthetic handles usually present on the branch. Branched pyranosides derived from dihalocyclopropanes contain a halide, those from ester-substituted cyclopropanes contain an ester group and those from unfunctionalized cyclopropanes often have a halogen installed by the electrophilic reagent. These functionalities provide the capacity for further transformation.

Such a strategy has already been discussed (see Scheme 26) in the derivatization of iodomethyl-branched pyranosides to glycosyl amino acids through substitution of the iodide by azide and then reduction to the α-aminoester [74].

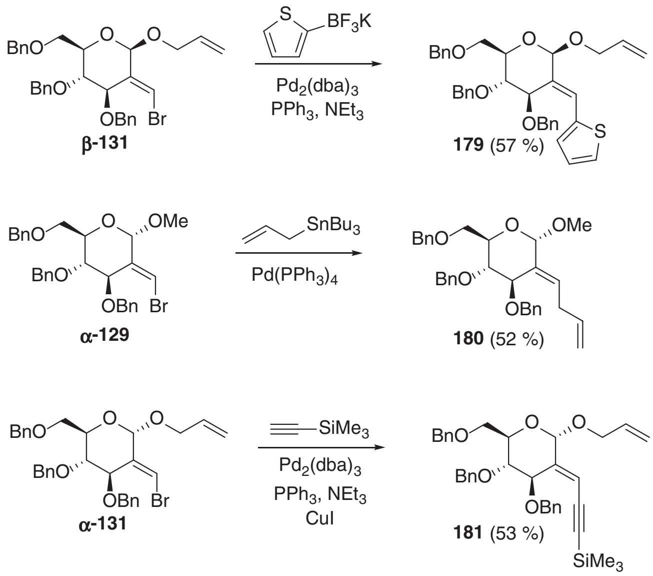
We have performed cross-coupling reactions of the bromoalkene-branched products obtained by base-promoted ring opening of *gem*-dihalocyclopropyl carbohydrates [41]. Suzuki reactions of *E*-bromoalkene **β-131** with several arylboronic acids afforded modest yields of the coupled products, while use of potassium 2-thiophenyltrifluoroboronate provided compound **179** in reasonable yield (Scheme 44). Stille reaction of methylated *E*-bromoalkene **α-129** with allyltributylstannane produced skipped diene **180**. The allylated *E*-bromoalkene **α-131** reacted in a Sonogashira reaction with trimethylsilylacetylene to give enyne **181**.



Scheme 42 Derivatization of bromoalkene **67** with Suzuki, Sonogashira and Heck reactions and formation of a 2-deoxyseptanoside **176** [93].



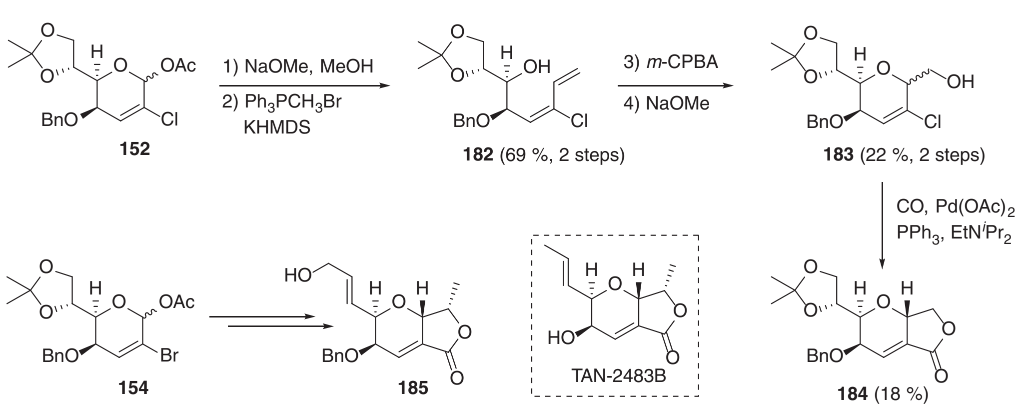
Scheme 43 Derivatization of bromoalkenes **β-46** and **α-44** with Suzuki and intramolecular Heck reactions [41].



Scheme 44 Derivatization of 2-*C*-branched bromoalkenes with Suzuki, Stille and Sonogashira reactions [41].

Functionalization of dihydropyrans from ring-expansion of furanose cyclopropanes

As mentioned earlier, we have converted the dihydropyran **152** into the core of the fungal natural product TAN-2483B [87]. The acetate **152**, prepared by ring expansion of a *gem*-dichlorocyclopropyl furanose (see Scheme 36) was saponified and the resulting hemiacetal underwent a Wittig reaction with methylene ylide to provide diene **182** (Scheme 45). Epoxidation of the terminal alkene (not stereoselective) and base-promoted attack of the alcohol on the epoxide gave *C*-glycoside **183**. Palladium-catalyzed carbonylative lactonization then afforded the furo[3,4-*b*]pyran **184**, containing the ring system of TAN-2483B with the correct stereochemistry at the ring junction. Unfortunately, poor selectivity in the epoxidation (even with Jacobsen catalyst [88, 89]) and low yields in the final steps do not recommend this route for attaining access to the natural product itself. Through use of the brominated dihydropyran **154** to facilitate the carbonylation and considerable adaptation of the synthetic strategy to install the required two-carbon substituent at the anomeric center, we have very recently achieved the synthesis of **185**, containing the full carbon skeleton of TAN-2483B [88].



Scheme 45 Derivatization of the chloro- and bromo-substituted dihydropyrans **152** and **154** to the ring system of TAN-2483B [87].

Final comments and outlook

As described in the preceding sections, there is a great diversity in the products that can be prepared through the ring opening or expansion of 1,2-cyclopropyl carbohydrates. The examples chosen have demonstrated some of the scope available for generating structural novelty through such chemistry. They have, furthermore, shown that many typical sugar protecting groups, such as ethers, acetals, silyl ethers and esters, are compatible with the conditions required for the synthesis and ring openings of cyclopropanes. In our experience, however, certain protecting groups are not ideally suited to dibromocyclopropanations by the Mąkosza method, such as acetates and PMB-ethers [89].

In recent years, reactions of cyclopropyl carbohydrates have enjoyed a surge in popularity, as indicated in this article, with several groups worldwide showing a sustained interest in such chemistry. The impetus driving such research can include the search for new bioactive materials, exploration of the diverse chemistry associated with cyclopropanes fused to a stereochemically rich scaffold, and obtaining building blocks for total synthesis. In light of these motivations, it is certain that there will continue to be many advances in this area in future years.

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