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PERSPECTIVE

Recent advances in the stereoselective synthesis of carbohydrate 2-*C*-analogs†

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C-branched carbohydrates are of current interest for glycochemistry, are widely found in nature and serve as important subunits in many antibiotics, bacterial polysaccharides and macrolides. Among *C*-functionalized saccharides, 2-*C*-branched carbohydrates represent challenging structures for synthetic chemists, since in contrast to *C*-glycosides they are not easily accessible from glycosyl bromides or other simple precursors. In this perspective we want to summarize recent approaches to 2-*C*-branched carbohydrates over the past fifteen years. The two main strategies are based on ring-opening of 1,2-cyclopropanated carbohydrates by various reagents, as well as radical additions to glycals and further transformations, developed in our group. Both methods are characterized by high stereoselectivities and good yields and give access to a broad variety of functionalized carbohydrate 2-*C*-analogs.

Introduction

A wide diversity of synthetic carbohydrates and related analogs is an urgent need in the development of current glycochemistry and glycobiology.[1] Multitudinous synthetic strategies have been explored,[2] and numerous carbohydrate mimetics were synthesized during recent decades. *C*-branched carbohydrates (Fig. 1), being considered as potential antibiotics, are especially attractive for synthetic organic chemists.[3] Recently, much work has been done regarding unnatural 2-*C*-branched carbohydrates, since they represent mimics of 2-*N*-acetylsugars for cell surface

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† This perspective is dedicated to Prof. Waldemar Adam on the occasion of his 75th birthday.

Jian Yin

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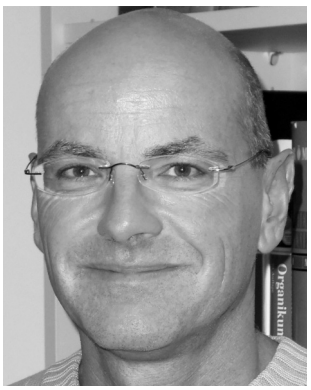


Torsten Linker

Torsten Linker was born in Germany in 1963. He received his PhD from the University of Basel, Switzerland, under the supervision of Bernd Giese in 1991. After a postdoctoral stay at the University of Alberta, Canada, with Ole Hindsgaul (1992) he received his habilitation from the University of Würzburg in 1997. From 1997–1998 he held a Heisenberg Professorship at the same University and moved to the University of Stuttgart as an Associate Professor in 1998. Since 2000 he is Full Professor of Organic Chemistry at the University of Potsdam, Germany. His research interests include radical reactions in carbohydrate chemistry, oxidations with $^1O_2$, molecular rotors and surface modifications.

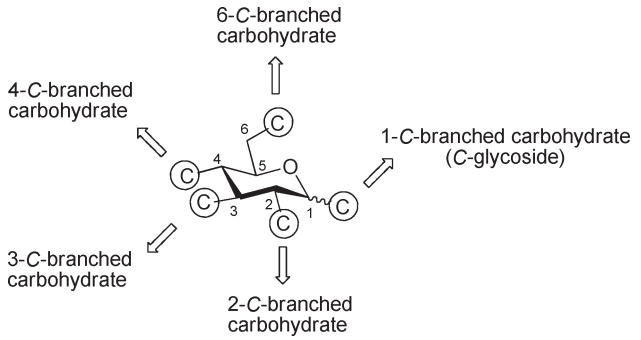


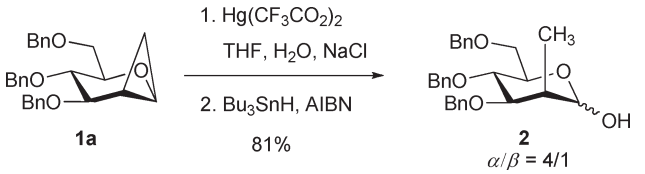
Fig. 1 General structures of *C*-branched carbohydrates.

engineering and inhibitors of the biosynthesis of lipids.[4] Although *C*-glycosides are easily available,[5] *C*-functionalizations at other positions of the sugar ring generally require many steps. Since the initial results of introducing carbon chains at the 2-position of carbohydrates by epoxide-opening reported by Kochetkov in 1962,[6] various new reagents and creative methodologies have been developed for the stereoselective synthesis of 2-*C*-branched carbohydrates.

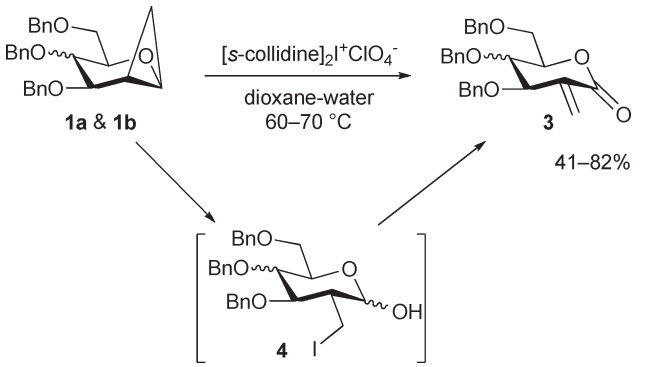
The scope of this perspective covers the period of the past fifteen years, because efficient and systematic synthetic strategies only came up starting from the middle of 1990s. Indeed, epoxide-opening, as the first valuable entry, led to a diversity of carbohydrate 2-*C*-analogs between the 1970s and 1990s, by using different Grignard reagents,[7] alkyl (or aryl) lithium reagents[8] or other matters[9] that induce the reaction of oxiranes selectively. However, fewer and fewer examples of epoxide-openings were published after 1990. This perspective doesn't give a whole overview of all independent discoveries in this area, and only highlights recent outstanding advances of stereoselective syntheses of 2-*C*-branched carbohydrates. The two main strategies are based on ring-opening of 1,2-cyclopropanated sugars in different media,[10] and radical additions to various glycals and further transformations, developed in our group.[11] Both methodologies are characterized by mild conditions, high stereoselectivities and good yields, leading to a set of diverse carbohydrate 2-*C*-analogs.

Cyclopropane openings

Since the first synthesis of a cyclopropane derivative by August Freund in 1881, the cyclopropane subunits have always been attractive for organic chemists.[12] Cyclopropanes are a class of organic compounds sharing the common cyclopropane ring, where one or more hydrogen atoms may be substituted. Cyclopropanes have been widely used as versatile synthetic intermediates in the synthesis of more functionalized chemical structures.[13] Many strategies have been developed for the construction of this three-membered ring, which was classified with donor cyclopropane (DC), acceptor cyclopropane (AC) and donor–acceptor cyclopropane (DAC).[14] The DC molecules can be cleaved by various electrophiles to afford cation equivalents for further transformations, and the AC molecules are easily opened by nucleophilic attack. In addition, the DAC structures are especially important to develop diverse transformations, since the reactivity of such molecules is enhanced by a synergistic electron 'push–pull' relationship.

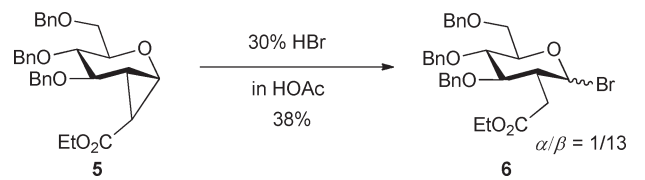


Scheme 1 Mercury-mediated opening of 1,2-cyclopropanated sugar **1a**.

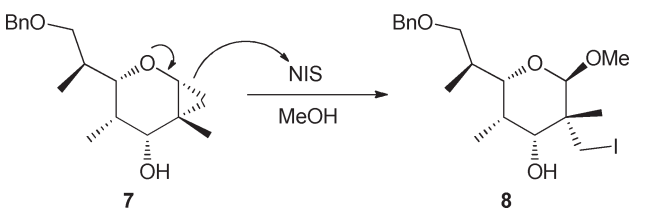


Scheme 2 Nagarajan's ring-opening of 1,2-cyclopropanated sugars **1a** and **1b**.

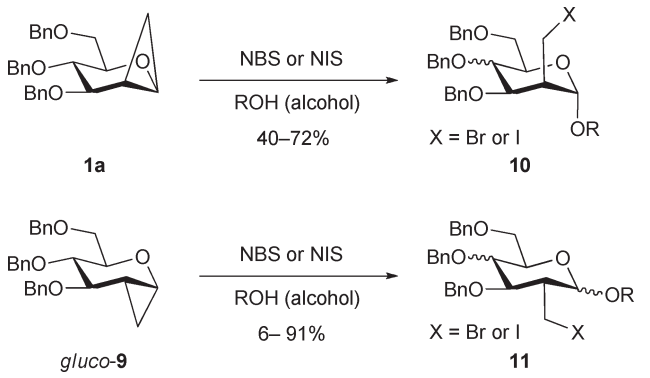
Carbohydrates, where the cyclopropane ring substitutes two hydroxyl groups at the 1- and 2-positions, have frequently been studied during the past decade.[15] Various methods were developed to synthesize these compounds, such as the zinc/copper mediated Simmons–Smith reaction,[16] cycloaddition of diazo compounds[17] or dihalocarbenes,[18] and a few other routes.[19] Furthermore, cyclopropanated carbohydrates are ideal precursors for electrophilic ring-opening, which allowed the convenient syntheses of carbohydrate 2-*C*-analogs as discussed below. Heathcock reported a strategy in which the mercury(II) ion was employed for the opening of various sugar cyclopropanes, affording 2-deoxy-2-*C*-methyl mannose (Scheme 1).[10] Treatment of sugar **1a** with mercury trifluoroacetate in the presence of water provides a organomercurial intermediate as a mixture of anomers.



Scheme 3 Opening of 1,2-cyclopropanated sugar **5** under strongly acidic conditions.



Scheme 4 NIS-mediated opening of a 1,2-cyclopropanated dihydropyrane **7**.



Scheme 5 Initial NIS-mediated openings of 1,2-cyclopropanated sugars **1a** and *gluco*-**9**.

Radical cleavage with Bu_3SnH afforded the carbohydrate 2-*C*-analog **2** in good overall yield.

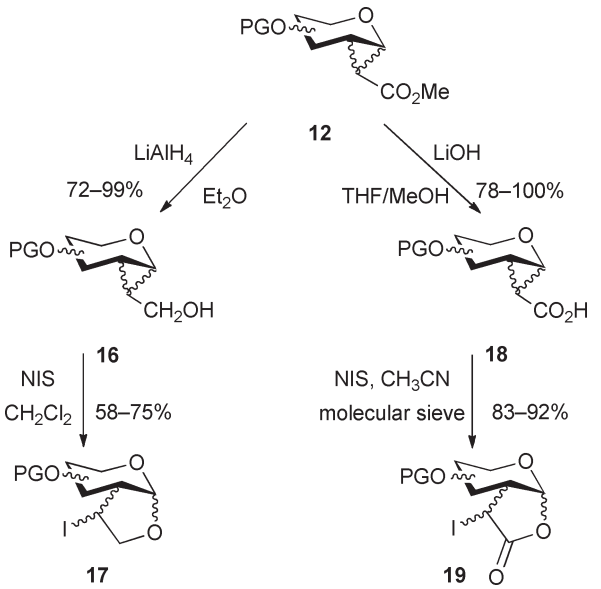
In addition, Nagarajan and co-workers reported the ring-opening of the cyclopropanated sugars **1a** and **1b** by using iodonium di(*s*-collidine)perchlorate in dioxane–water (Scheme 2),[20] which led to synthesizing the α-methylidene valerolactones **3** in moderate to good yields. This transformation was presented to proceed through an intermediate iodide **4**, followed by elimination and oxidation. *p*-TsOH was employed by Boeckman and co-workers during their study on the synthesis of Calimycin[21] to drive the successful ring opening, followed by an intramolecular attack to furnish the spiroacetal.

Such reactions demonstrated that acids can induce the ring-opening of sugar cyclopropanes, and Hoberg was able to employ HBr/HOAc to open carbohydrate **5** selectively, but the low yield of glycosyl bromide **6** was only 38% (Scheme 3).[22]

Thus, although several methods were developed to cleave cyclopropanated carbohydrates with acids, the drastic conditions resulted in low yields and did not allow a broad applicability. Thus, milder reagents were highly needed to provide general access to carbohydrate 2-*C*-analogs and to obtain a diverse set of sugar mimetics.

Halonium ion-mediated ring-opening

During the course of Danishefsky's studies on the synthesis of epothilones A and B, they developed a new strategy for the

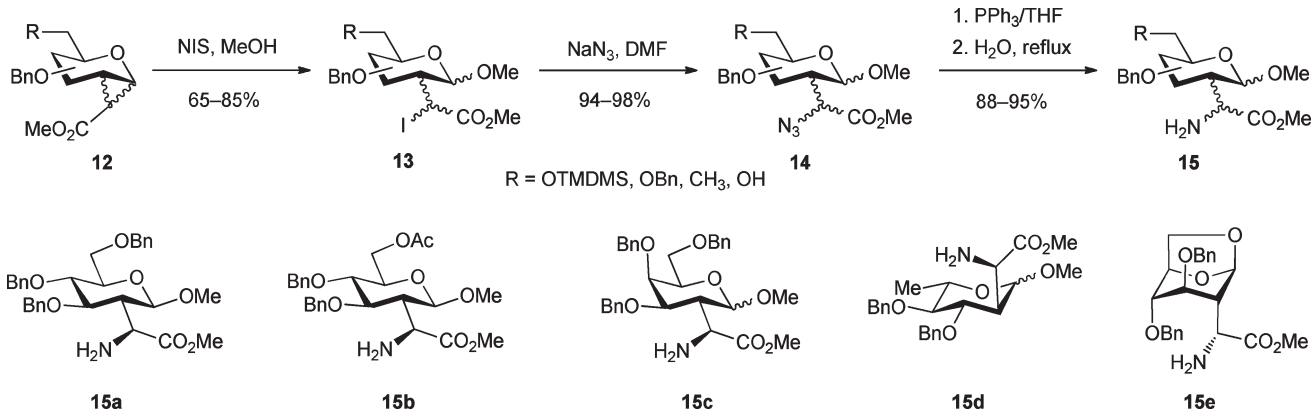


Scheme 7 NIS-mediated synthesis of iodoether **17** and iodolactone **19**.

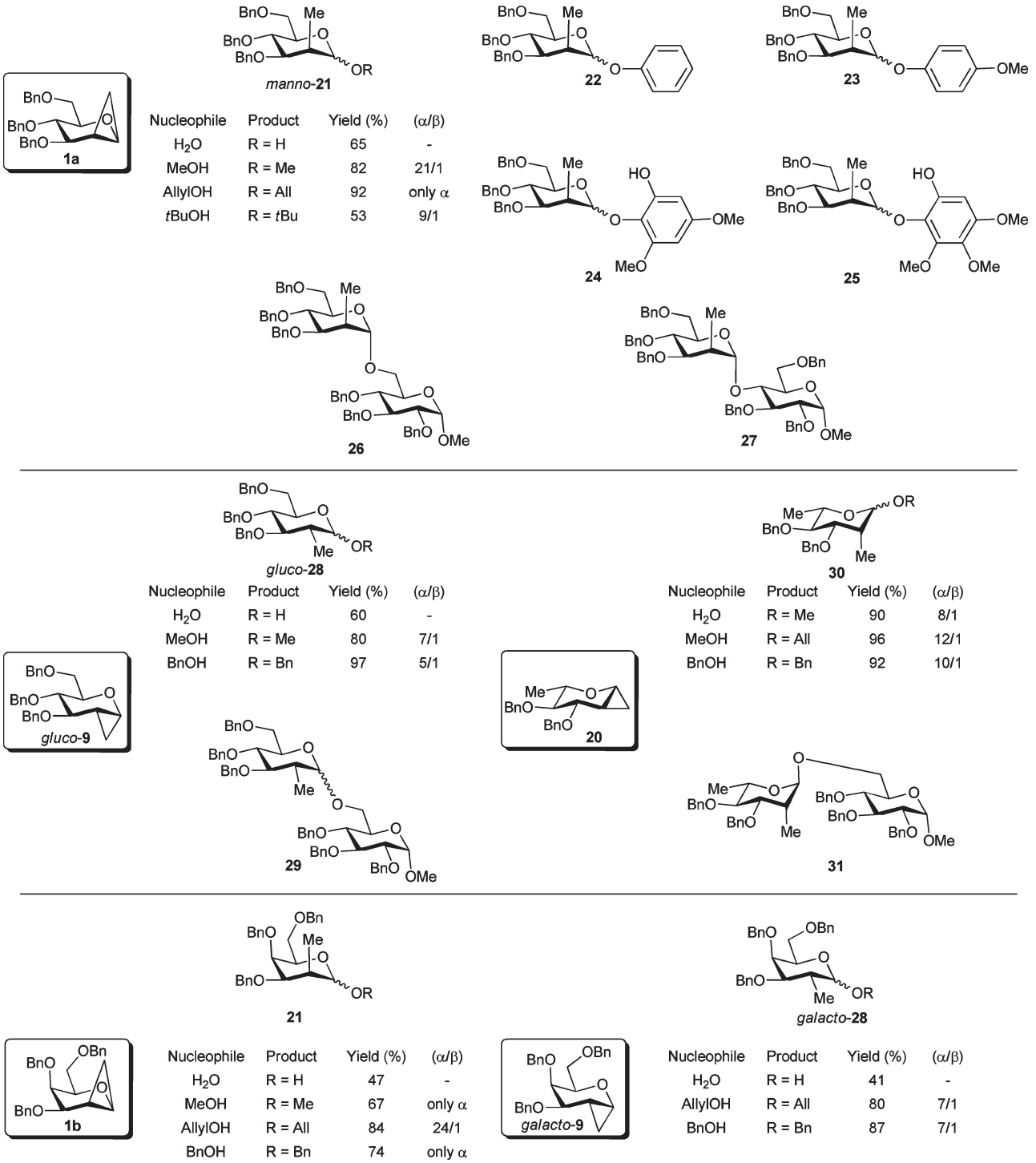
ring-opening of cyclopropanes in the presence of *N*-iodosuccinimide (NIS).[16d,23] Treatment of the dihydropyrane **7** with excess NIS in methanol afforded the acetal **8**, which was efficiently reduced with Bu_3SnH to give a good overall yield of 80% (Scheme 4).

Several groups applied this strategy for valuable chemical transformations in the late 90s. Thus, Ley[24] and Nagarajan[18c] reported independently on the opening of the diastereomeric cyclopropanes **1a** and *gluco*-**9** with NBS or NIS (Scheme 5). Interestingly, the formation of **10** proceeds slowly in moderate to good yields, and the α-anomer was isolated as sole product. On the other hand, cyclopropane *gluco*-**9** reacted fast but gave an anomeric mixture of glycosides **11**. This remarkably different behaviour was rationalized by a S_N2-type ring-opening of the sterically hindered cyclopropane **1a**, whereas a S_N1 reaction was proposed during the formation of the anomers **11**. Additionally, Nagarajan succeeded in the formation of halogenated 2-*C*-disaccharides in 60% yield.[25]

In 2004, Chandrasekaran applied such NIS-mediated ring-openings in the synthesis of 2-*C*-branched glyco-amino acids



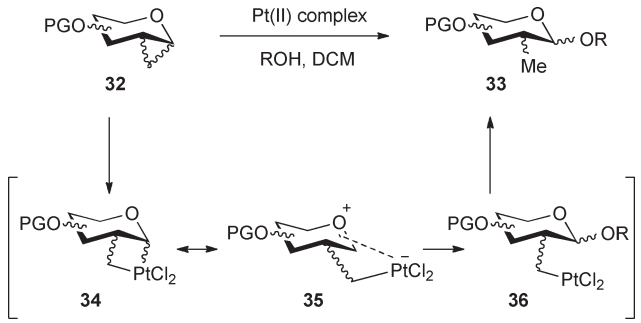
Scheme 6 NIS-mediated opening of 1,2-cyclopropanated sugars **12** and further transformations to afford various 2-*C*-branched glyco-amino acids **15a–e**.



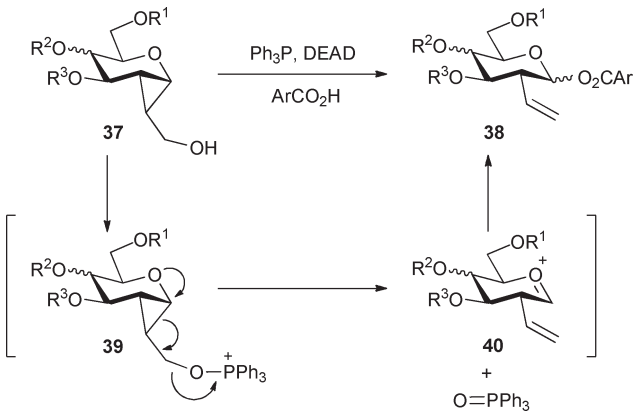
Scheme 8 Diverse syntheses of carbohydrate 2-*C*-analogs and disaccharides through platinum-catalyzed ring-opening of 1,2-cyclopropanated sugars **1a**, **1b**, *gluco*-**9**, *galacto*-**9** and **20**.

(Scheme 6).[26] Thus, ester-substituted cyclopropanes **12** afforded iodides **13** in moderate to good yields. Finally, *C*-glycosylated glycine derivatives **15a–e** were isolated in high yields and stereoselectivities by reaction with NaN_3 and subsequent reduction. Interestingly, similar products were obtained in our group by radical addition and further transformations.[27,28,29]

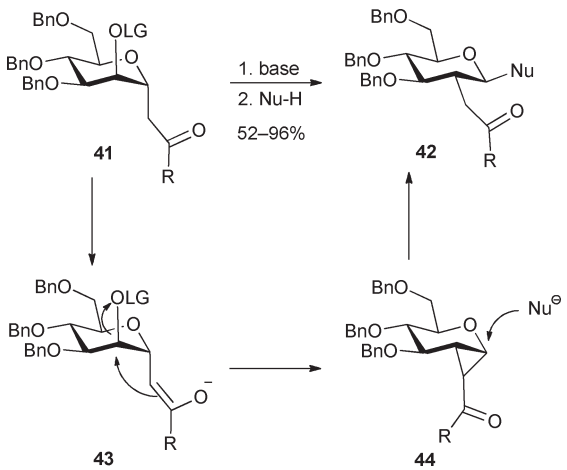
In 2007, Chandrasekaran extended his methodology for the stereoselective construction of linear-fused perhydrofuro[2,3-*b*]pyran motifs (Scheme 7).[30] Thus, reduction to alcohols **16** in combination with subsequent NIS-mediated ring-opening afforded iodoethers **17** in moderate to good yields and with high stereoselectivies. On the other hand, saponification gave the free acids **18**, which reacted under similar conditions to iodolactones **19** in high yields. Finally, Sridhar extended NIS-catalyzed ring-openings of cyclopropanated sugars for the synthesis of various disaccharides in 2009.[31]



Scheme 9 Suggested mechanism of the Pt(II)-catalyzed ring-opening.



Scheme 10 A cyclopropylcarbinyl-homoallyl rearrangement.



Scheme 11 A tandem S_N2–S_N2 reaction.

Platinum-catalyzed ring-opening

Between 1998 and 2000, Madsen realized the first openings of cyclopropanated carbohydrates with Zeise's dimer, a reactive platinum complex.[32,33] The reactions proceeded smoothly in the presence of various nucleophiles like water, alcohols or phenols, affording 2-methyl glycosides **21**–**25**, **28** and **30** as a mixture of α and β isomers in high yields (Scheme 8).

Depending on the configurations of the 1,2-cyclopropanated sugars, sometimes high α-selectivities were observed as well. Furthermore, the reactions were successfully applied for the synthesis of various *O*-disaccharides **26**, **27**, **29** and **31**. Thus, a wide variety of cyclopropanated sugars were transformed into several carbohydrate 2-*C*-analogs.

The proposed mechanism proceeds by oxidative insertion of the platinum complex into the cyclopropane ring, affording a platinacyclobutane **34**. Polarization of the carbon–platinum bond results in a stabilized oxonium ion **35**, which is attacked by the nucleophiles. Subsequent reductive cleavage of the Pt–C bond gives the final 2-methyl glycoside **33** and completes the catalytic cycle (Scheme 9).[33] This mechanistic rational was supported by detailed deuterium labelling experiments. Overall, platinum-catalyzed ring-opening of cyclopropanated sugars offers an attractive entry to a wide variety of carbohydrate 2-*C*-analogs.

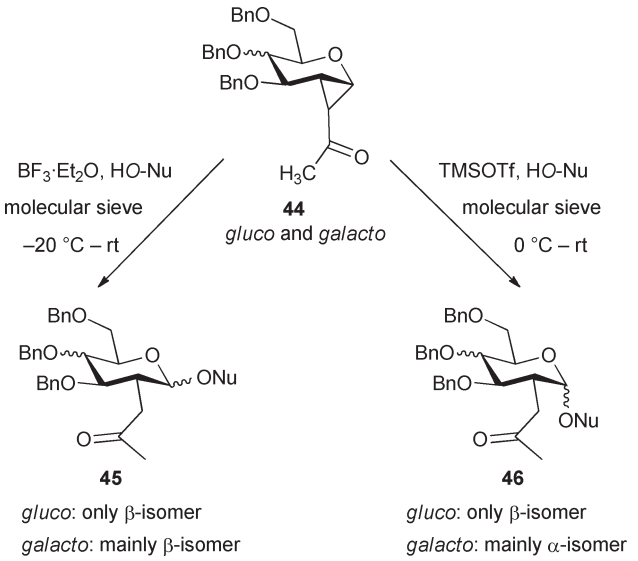
Miscellaneous rearrangements

In addition to the methodologies above, rearrangements were utilized in the synthesis of carbohydrate 2-*C*-analogs as well. The first example in the presence of silver acetate was reported by Weber and Hall in 1979.[18b] An interesting radical rearrangement of 2,3-cyclopropanated sugars, affording 2-*C*-branched carbohydrates in good to high yields, was realized by Clive and Daigneault in 1991.[34] Besides, Henry and Fraser-Reid developed a cyclopropylcarbinyl–homoallyl rearrangement (from **39** to **40**), which presumably proceeds through an S_N1-type pathway, resulting in a mixture of anomers **38** in combined 90% yield (Scheme 10).[17b]

However, these three miscellaneous rearrangements were not applied for the synthesis of more diverse sugar analogs. A general entry to nearly twenty 2-*C*-branched β-glycosides, which are functionalized by various nucleophiles at the anomeric center, was developed by Zou and co-workers (Scheme 11).[35] In this case, a 1,2-migration of the 2′-oxoalkyl group *via* 1,2-cyclopropanated sugars occurs under basic conditions with Ms or Ts as good leaving groups (LG in Scheme 11). Various nucleophiles (alcohols, thiols and azide) were employed in the subsequent ring-opening to afford a broad variety of 2-*C*-branched *O*-, *S*-glycosides and glycosyl azides.[36] Their further mechanism investigations showed that the 1,2-cyclopropanation required a 1,2-*transdiaxial* configuration, otherwise β-elimination occurred dominantly. Accordingly, this rearrangement provided an attractive methodology for the synthesis of diverse carbohydrate 2-*C*-analogs.

Lewis acid-catalyzed ring-opening

Very recently, Hu and Shao realized the opening of suitably substituted 1,2-cyclopropanated sugars **44** in the presence of different Lewis acids (Scheme 12).[37] Their strategy afforded carbohydrate 2-*C*-analogs **45** and **46** in high yields. Interestingly, TMSOTf as catalyst gave high α-selectivities with the *galacto*-isomer, whereas the *gluco*-configured starting material yielded β-anomers as sole products under the same conditions. On the other hand, $BF_3{\cdot}Et_2O$ afforded selectively β-anomers with both carbohydrates, and no influence of the configuration was observed. This behaviour was rationalized by a S_N1 pathway with the strong Lewis acid (TMSOTf) only for the sterically hindered *galacto*-isomer, resulting in the α-product by an anomeric



Scheme 12 Lewis acid-catalyzed ring-opening of 1,2-cyclopropanated sugars **44**.

effect. Contradictorily, $BF_3{\cdot}Et_2O$ operates by a S_N2 reaction and the β-anomers are formed due to a neighboring group participation. Such Lewis acid-catalyzed ring-openings were applied for the stereoselective synthesis of di- or trisaccharides, glycosyl amino acids and other diverse 2-*C*-acetylmethylglycosides,[37] which opened a convenient entry to functionalized carbohydrate 2-*C*-analogs.

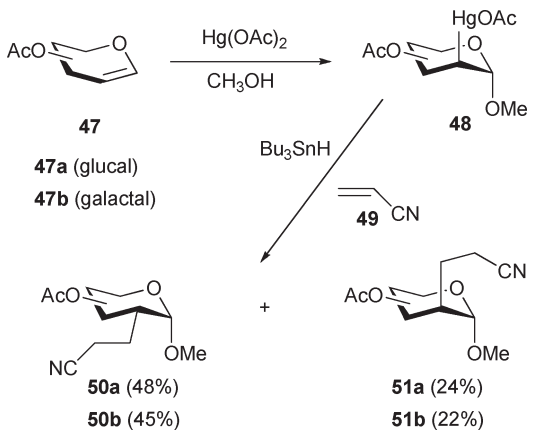
Radical additions and further transformations

Radical reactions have become an important and versatile tool for the selective formation of carbon–carbon bonds in highly functionalized molecules and have found many applications in natural product chemistry.[38] The first synthesis of carbohydrate 2-*C*-analogs by this methodology was reported by Giese in 1984.[39] Mercury compounds **48**, available from glycals **47**, served as radical precursors. Intermolecular addition to acrylonitrile **49** or other alkenes in the presence of tributyltin hydride afforded products **50** and **51** in moderate yields (Scheme 13). Furthermore, the stereoselectivity of the C–C bond formation was low. This method was applied to glucal **47a** and galactal **47b** and allowed the synthesis of six different carbohydrate 2-*C*-analogs. Later on, other inter- and intramolecular additions have also been reported, but the carbohydrate always served as the radical precursor.[40] Additionally, the tedious synthesis of the starting materials, the high toxicity of the reagents, and the often moderate stereoselectivities are disadvantageous. Thus, we became interested in a new radical strategy to install the carbon side chain at the 2-position, with carbohydrates as radical acceptors.

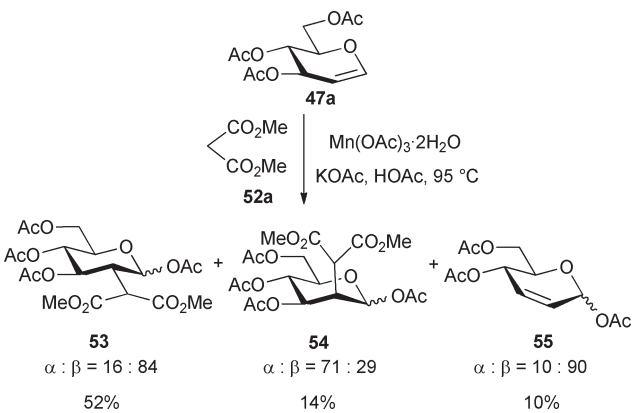
Initial studies in our group

A convenient and general entry to carbohydrate 2-*C*-analogs didn't appear until the middle of 1990s, when we applied C–C bond formations by transition-metal-mediated radical reactions for the first time in carbohydrate chemistry,[11] where glucal **47a** was employed as radical acceptor (Scheme 14). Dimethyl malonate **52a** served as CH-acidic radical precursor in the presence of manganese(III) acetate, affording two C–C bond-formation products **53** and **54** in combined moderate yields. The elimination product **55** was isolated in 10% yield, which was rationalized by a fast Ferrier rearrangement.[41] Due to the electrophilic nature of malonyl radicals, the addition is highly regioselective at the 2-position in an orbital-controlled reaction. The preferred formation of *gluco*-configured products can be rationalized by a *trans* attack to the 3-*O*-acetyl group, which is in accordance with cycloadditions to glucals.

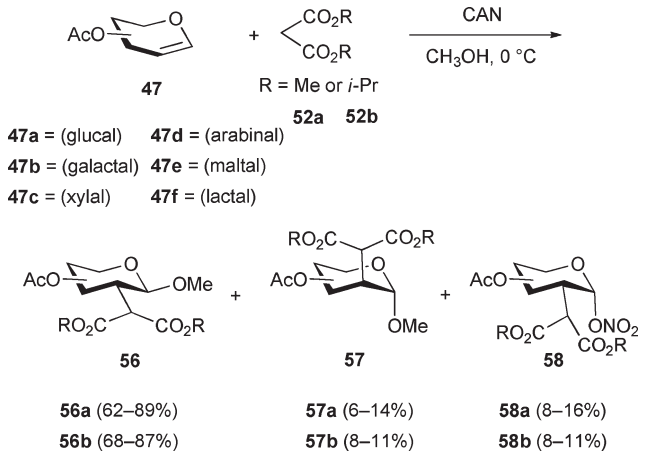
To suppress the undesired product **55**, we became interested in ceric(IV) ammonium nitrate (CAN) as a reagent to mediate radical reactions, which is superior due to the mild reaction conditions.[42] Indeed, the reaction proceeded smoothly at 0 °C and the carbohydrate 2-*C*-analogs **56** and **57** were isolated in higher yields and stereoselectivities (Scheme 15).[11,43] To compare and study the stereoselectivities, we investigated the addition of dimethyl **52a** and diisopropyl **52b** malonate, but only a moderate influence of the steric demand of those two CH-acidic substrates was observed, since the ester groups are too far away from the reaction center. Mechanistically, the formation of products **56** and **57** can be explained by an electron transfer from the



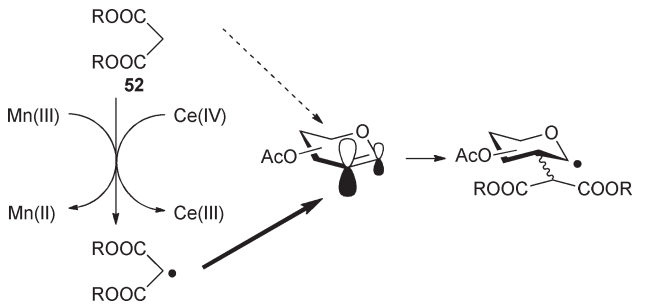
Scheme 13 Synthesis of carbohydrate 2-*C*-analogs **50** and **51** *via* Giese's radical approach.



Scheme 14 First example of a radical addition of malonate **52a** to glucal **47a**.



Scheme 15 CAN-mediated radical additions of malonates **52** to glycals **47**.



Scheme 16 Mechanism of the radical addition by favourable orbital interactions.

anomeric radical to CAN and subsequent trapping of the cation by the solvent methanol. The nitrates **58** were isolated in lower yields as by-products. In our more recent optimization, the formation of such nitrates **58** was completely suppressed by using anhydrous ceric(IV) ammonium nitrate. This can be explained by the presence of nitric acid in wet CAN and its reaction with the anomeric carbenium ion.[44] Thus, the addition of malonates to glycals provides a general and convenient entry to carbohydrate 2-*C*-analogs and is characterized by easily available precursors. Our methodology is applicable to glycals derived from hexoses, pentoses and disaccharides. Overall, the generation of malonyl radicals by ceric(IV) ammonium nitrate is superior to manganese (III) acetate in terms of milder reaction conditions and higher yields.

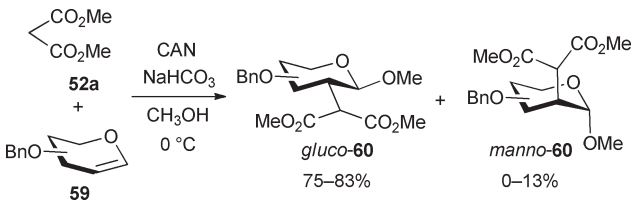
Interestingly, all additions exhibit a very high degree of regioselectivity, since only 2-*C*-branched sugars were obtained. This result can be best rationalized by favourable orbital interactions between the SOMO of the malonyl radical and the HOMO of the double bond (Scheme 16).[43,45]

Further developments and optimizations

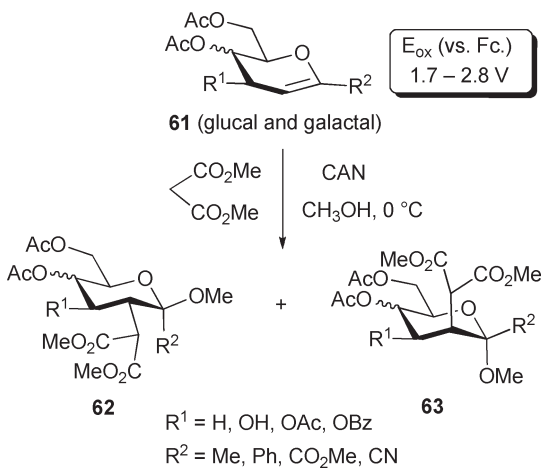
In our initial studies the lability of the acetyl protecting groups under basic conditions was disadvantageous for further transformations such as reductions or deprotonations. Therefore, we selected benzyl-protected glycals **59** as acceptors for transition-metal-mediated radical reactions. Due to the propensity of glycals to undergo a Ferrier rearrangement we had to carefully optimize the reaction conditions. Finally, $NaHCO_3$ was employed as a suitable base during the addition of dimethyl malonate **52a** and the reaction proceeded smoothly to afford the products *gluco*-**60** and *manno*-**60** in combined good yields (Scheme 17).[44,46] The high *gluco*-selectivity was again rationalized by steric interactions with the 3-*O*-benzyl group.

Additionally, we became interested in the oxidation stability of glycals **61**, which is an important issue to develop new strategies for the synthesis of carbohydrate 2-*C*-analogs **62** and **63** (Scheme 18).[47] Different donors (R^2 = Me, Ph) and acceptors (R^2 = $CONH_2$, CO_2Me and CN) were introduced at the 1-position, in order to alter the electronic nature of the double bond.[48] Indeed, a strong influence on the oxidation stability of the whole glycal was established.[47] More importantly, even variation of substituents R^1 (H, OH, OAc, OBz) altered the oxidation potential of the double bond, measured by cyclic voltammetry. Thus, unsaturated carbohydrates exhibit remarkable oxidation stabilities, making them ideal substrates for oxidative radical reactions. This allowed the total synthesis of 3-deoxy-D-oct-2-ulosonic acids (KDO) in the presence of various transition-metals.[49,50]

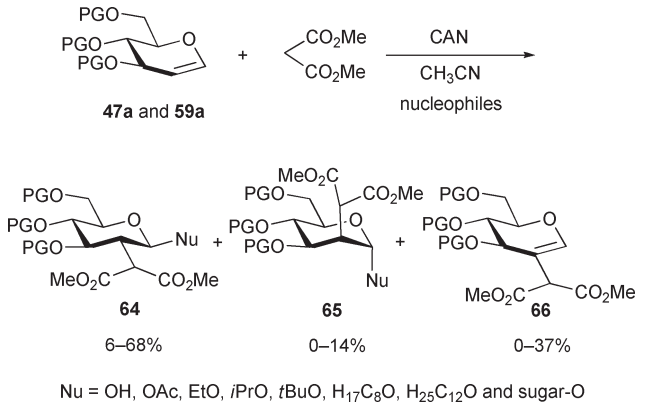
In another project we were interested in CAN-mediated additions to glycals in the presence of various nucleophiles. Acetonitrile as solvent allowed the trapping of the intermediary formed carbenium ion at the anomeric center, affording diverse glycosides **64** and **65** in combined moderate yields with high stereoselectivities (Scheme 19).[51] Even disaccharides are available by this method (sugar donors are diacetyl-glucose and



Scheme 17 Radical addition of dimethyl malonate **52a** to benzyl-protected glycals **59**.



Scheme 18 Oxidation stability of glycals **61**.



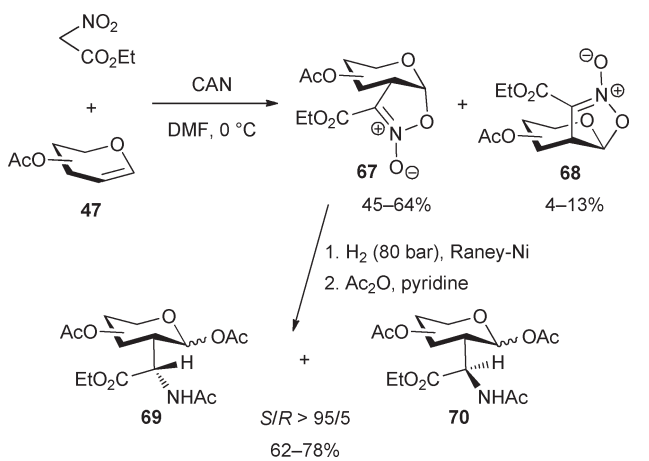
Scheme 19 Addition of dimethyl malonate to glucals **47a** and **59a** in the presence of different nucleophiles.

diacetyl-galactose), although yields are lower due to steric hindrance and competitive elimination to alkene **66**.

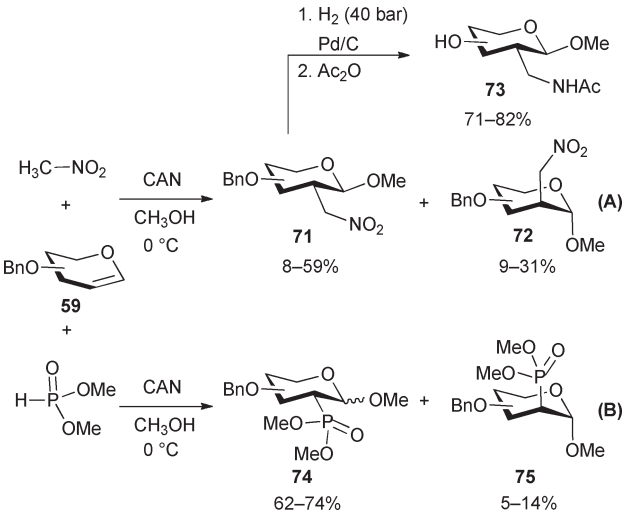
Radical additions of other CH-acidic substrates

To extend the scope of transition-metal-mediated additions to glycals **47** for the synthesis of carbohydrate 2-*C*-analogs, we next employed ethyl nitroacetate as the radical precursor, since it is very reactive due to its CH acidity (Scheme 20).[27] The reaction was conducted by the general method but with DMF instead of MeOH as solvent, to force the intramolecular trapping of the anomeric radical by the nitro group. Thus, isoxazoline *N*-oxides **67** and **68** were isolated as cyclization products in combined moderate yields and stereoselectivities. Subsequent hydrogenation in the presence of RANEY®-Ni at 80 bar afforded after acetylation the amino acid derivatives **69** and **70** with excellent *S*/*R* selectivities. This two-step reaction opened an easy entry to carbohydrate–peptide conjugates from glycals **47**.

In addition, other acidic substrates like nitromethane (Scheme 21, **A**)[51,52] or dimethyl phosphite (Scheme 21, **B**)[53] are suitable radical precursors for CAN-mediated additions to glycals **59** as well. Thus, we obtained 2-deoxy-2-*C*-nitromethyl-pyranosides **71** and **72** in combined moderate yields with high



Scheme 20 Synthesis of *C*-glycosylated glycine derivatives **69** and **70** from glycals **47** by radical addition and reduction.

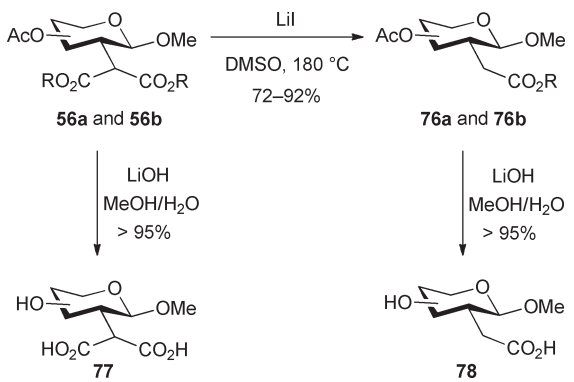


Scheme 21 Radical additions of two different CH-acidic substrates, nitromethane and dimethyl phosphite, to glycals **59**.

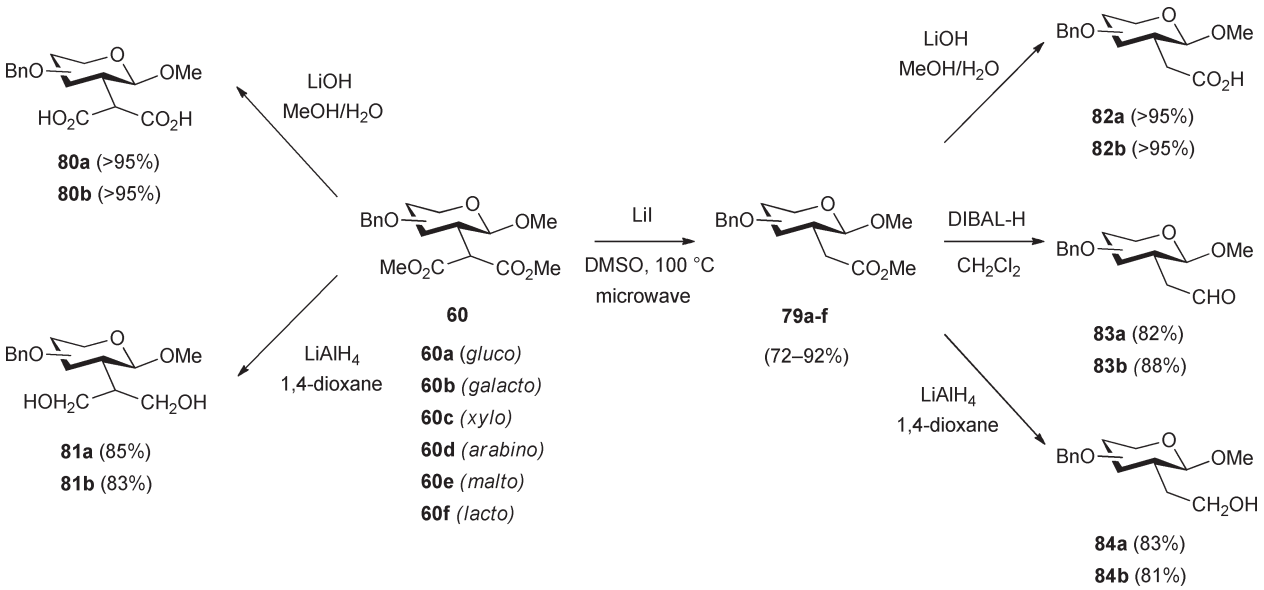
stereoselectivities for the first time.[51,52] The method is applicable to hexoses, pentoses, and disaccharides and the addition products are valuable precursors for the synthesis of *C*-2 branched disaccharides. Reduction of the nitro group afforded branched-chain glycosamines **73** in good yields.[51] The addition of dimethyl phosphite (Scheme 21, **B**) proceeded smoothly to introduce a C–P bond at the 2-position of carbohydrates. 2-Deoxy-2-phosphonates **74** and **75** were isolated also in combined moderate yields with high stereoselectivities. Furthermore, a subsequent Horner–Emmons reaction formed a C–C bond at C-2, offering another convenient entry to carbohydrate 2-*C*-analogs.[53]

Further transformations and applications

The malonate moiety is a valuable functional group for many interesting transformations in organic synthesis. First of all, we investigated the decarboxylation of addition products **56a** and **56b**. Indeed, heating in DMSO in the presence of lithium iodide gave full conversion after 4–6 h, and the esters **76a** and **76b** were isolated in good yields.[44,46] Further saponification afforded the free acids **77** and **78** almost quantitatively (Scheme 22). This



Scheme 22 Decarboxylation and subsequent saponification of malonate addition products **56a** and **56b**.

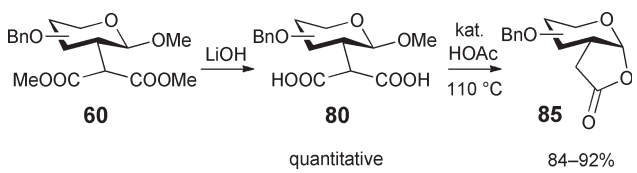


Scheme 23 Valuable transformations starting from malonates **60**.

is the first time that a decarboxylation was realized at the 2-position of sugars, which opened a possibility to introduce more functionality in carbohydrates.

More recently, we investigated decarboxylations and reductions of the benzyl-protected malonates **60** to build up more diversity at the 2-position of carbohydrates (Scheme 23).[44] This time, we optimized the decarboxylation by microwave irradiation at 100 °C to lead to the acetates **79** in good yields, which allowed further transformations under different conditions. *Gluco* and *galacto* isomers (**60a,b** and **79a,b**), which represent common configurations of hexoses in nature, were used to provide an easy entry to malonic (**80a,b**) and acetic (**82a,b**) acids after saponification. Subsequent reduction of malonates **60a,b** with lithium aluminium hydride afforded diols **81a,b**, which might be used to build up dendrimeric structures. The same reductions with the acetates **79a,b** gave access to 2-*C*-ethanol carbohydrates **84a,b**. Selective syntheses of aldehydes **83a,b**, which represent suitable precursors for *C*-disaccharides, were easily realized in the presence of diisobutylaluminium hydride in good yields. Thus, we developed a general and convenient entry to carbohydrate 2-*C*-analogs with various functional groups.

In 2009 we started our investigations on bicyclic carbohydrate 1,2-lactones **85**,[54] which represent interesting conformationally fixed 2-*C*-analogs. At that time, only lactones with other substituents were known,[30,55] very recently manganese(III) was employed for a direct synthesis of unsubstituted lactones.[56] Our approach is again based on malonate addition products **60** which were saponified to malonic acids **80** (Scheme 24). The



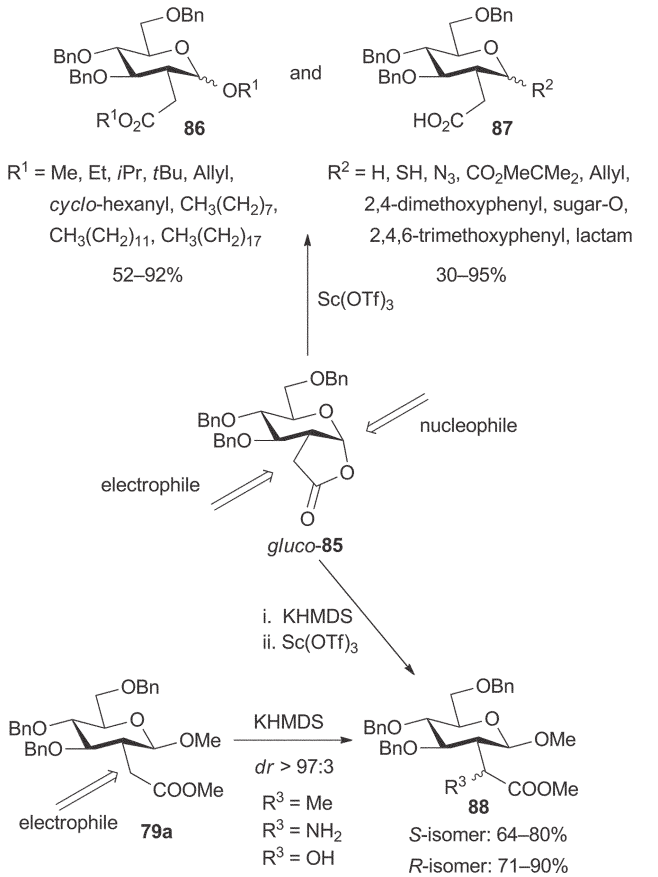
Scheme 24 Synthesis of carbohydrate 1,2-lactones **85**.

lactonization was initiated by careful adjustment of the pH value with catalytic amounts of acetic acid and heating to 110 °C in toluene. Thus, decarboxylation and elimination of methanol is the driving force for this reaction and the lactones **85** were isolated in good to high yields.[54] This method is suitable for hexoses, pentoses and disaccharides.

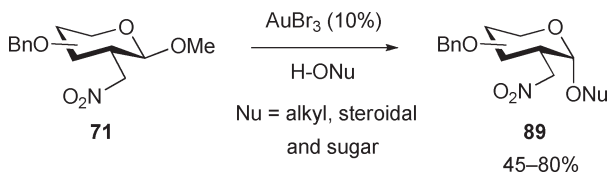
The *gluco*-configured lactone **85** served as an important precursor for diversity-oriented synthesis (DOS).[28,29] Thus, stereoselective opening with various *C*-, *O*- and *S*-nucleophiles was realized in the presence of $Sc(OTf)_3$. This method enabled the introduction of different substituents at the anomeric position, to afford a broad variety of 1-fuctionalized saccharides **86** and **87** in moderate to good yields (Scheme 25). Additionally, deprotonation of lactone **85** with KHMDS and reaction with various electrophiles (MeI, trisyl azide and Davis reagent) proceeded with excellent stereoselectivity. Subsequent ring-opening with $Sc(OTf)_3$ afforded a collection of 2-functionalized saccharides **88** (Scheme 25). Overall, more than 30 2-*C*-analogs were obtained starting from the same precursor **85**, demonstrating the potential of CAN-mediated radical reactions and further transformations in carbohydrate chemistry.

Finally, we very recently established in a collaboration with Hotha gold-catalyzed transglycosylations of carbohydrate 2-*C*-analogs. Thus, nitro compounds **71** reacted with $AuBr_3$ and various *O*-nucleophiles to the products **89** in moderate to good yields (Scheme 26).[57] Interestingly, high α-selectivities were obtained, which was rationalized by an anomerization *via* cleavage of the endocyclic C–O bond. The method was applied for simple benzyl glycosides, the introduction of menthyl or steroidal substituents, and even the synthesis of disaccharides.

In conclusion, we have established CAN-mediated C–C bond formations in carbohydrate chemistry during the past 15 years. Starting from easily available glycals and various CH-acidic precursors the reactions proceed in only one step with high selectivities in good yields. The products allow various transformations and offer a general entry to carbohydrate 2-*C*-analogs. More than 50 carbohydrate mimetics have been synthesized by our method,



Scheme 25 Stereoselective diversity-oriented syntheses (DOS) of functionalized carbohydrate 2-*C*-analogs starting from *gluco*-lactone **85** and decarboxylated product **79a**.



Scheme 26 Gold-catalyzed reactions of 2-*C*-branched carbohydrates starting from 2-*C*-nitromethyl carbohydrate **71**.

demonstrating the power of radical reactions in natural product chemistry.

Other strategies

Recently, some other examples were also presented for the synthesis of carbohydrate 2-*C*-analogs by using either old protocols or new entries, which all were not very systematic like opening of cyclopropanated sugars or our radical additions. Here, we summarize them together as follows: 1) gold-catalyzed rearrangements;[58] 2) autoxidation–Michael addition sequences;[59] 3) transformations of 2-formyl glycals;[60] 4) palladium–indium bromide-mediated carbonyl allylation;[61] 5) indium-promoted Barbier-type allylations;[62] 6) Dötz reactions;[63] 7) one-pot acylation of glycals;[64] and 8) transformations of 2-nitroglycals.[65] These methods opened more possibilities in the construction of 2-*C*-branched carbohydrates.

Conclusions

In summary, this perspective has outlined recent useful organic transformations for diverse syntheses of carbohydrate 2-*C*-analogs. The two main strategies start from easily available glycals by radical additions or cyclopropanations with subsequent transformations. During the past fifteen years, 1,2-cyclopropanated sugars, as important synthons in carbohydrate chemistry, have been opened with several reagents, such as halonium ions, platinum complexes and Lewis acids. Furthermore, novel rearrangements offer various pathways to functionalized carbohydrate 2-*C*-analogs. All ring-opening protocols are characterized by mild conditions, affording the products in good yields and with high stereoselectivities.

Besides, our transition-metal-mediated C–C bond formations in the presence of ceric(IV) ammonium nitrate (CAN) have been established as a convenient and versatile tool for the synthesis of diverse 2-*C*-branched carbohydrates. Various CH-acidic substrates are suitable radical precursors, which attack glycals highly regioselectively at the 2-position. Moreover, the procedure allows various transformations of the addition products, including reductions, saponifications, lactonizations and alkylations. The advantages of these methods are the good yields and high stereoselectivities.

Both ring opening of 1,2-cyclopropanated sugars as well as radical additions in combination with further transformations have been well developed since the middle of the 1990s. Now, a huge amount of carbohydrate 2-*C*-analogs have been efficiently prepared by these two strategies.

However, some lacking areas are still highly needed, which include more 2-*C*-branched-*C*-, *S*-, and *N*-glycosides and the construction of higher oligosaccharides. In addition, further transformations of the side-chain at the 2-position would give access to more diverse and highly functionalized carbohydrate 2-*C*-analogs. In the future, the biological potential of such carbohydrate mimetics has to be explored, offering promising prospects for applications in medical chemistry.

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