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Perspective

The use of levoglucosenone and isolevoglucosenone as templates for the construction of C-linked disaccharides

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Abstract—Because of their functionalities (enone, ketone, and acetal) and their bicyclic structure (steric factors), levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyran-2-ulose) and isolevoglucosenone (1,6-anhydro-2,3-dideoxy-β-D-*glycero*-hex-3-enopyran-4-ulose) are useful templates for the convergent and combinatorial synthesis of (1→2), (1→3), and (1→4)-linked C-disaccharides in reactions combining them with sugar-derived carbaldehydes. Synthetic methods relying on conjugate nucleophilic additions of these enones, their combination with aluminum reagents and aldehydes (Baylis–Hillman reaction) and modified Takai–Hiyama–Nozaki–Kishi couplings of enol triflates derived from them with sugar-derived aldehydes are reviewed. Highly stereoselective methods have thus been developed. These allow the generation of disaccharide mimetics with a high molecular diversity.

Keywords: Aluminum aldolate; Carbonylative Stille coupling; Combinatorial synthesis; Core-B structure; Fluoro-C-linked disaccharides; C-Glycosyl donor; Lemieux azidation; Takai–Hiyama–Nozaki–Kishi coupling; Thomsen–Friedenreich epitope; Oshima–Nozaki three-component condensation

1. Introduction

Carbohydrates regulate the cell/cell[1] and cell/invader[2] interactions and play a crucial role in the construction of multicellular organs and organisms. With a growing understanding of the precise function that cell-surface carbohydrates play in disorders such as inflammation, viral and bacterial infections and cancer, numerous carbohydrate analogues have now been developed and entered into clinical studies.[3] Disaccharide mimetics such as C-linked disaccharides and oligosaccharides containing them offer the advantage of being resistant to acidic and enzymatic hydrolysis. They are potential inhibitors of glycosidases[4] and glycosyltransferases.[5] Since the first synthesis of β-D-Glc*p*-CH_2-(1→6)-D-Glc*p* by Rouzaud and Sinaÿ[6] in 1983, several approaches to C-disaccharides and C-linked oligosaccharides have been reported.[7]

In this review, we shall concentrate on the use of levoglucosenone[8] and isolevoglucosenone[9] as templates for the quick construction of all kinds of C-linked disaccharides and analogues.[10] Levoglucosenone (**1**) and isolevoglucosenone (**2**) undergo stereoselective conjugate additions with nucleophiles (NuM) generating enolate **3** and **4**, respectively (Scheme 1). The latter react with aldehydes **5** giving aldols **6** and **7**, respectively, which are precursors of (1→3)-disaccharides and analogues. The intermediate enolates **3** and **4** can be quenched as triflates **8** and **9**, respectively, and reacted with the same aldehydes **5** under Takai–Hiyama–Nozaki–Kishi conditions[11] giving the corresponding allylic alcohols **10** and **11** that are precursors of (1→2)- and (1→4)-disaccharides, respectively. Examples, as well as limitations of these general (combinatorial) and convergent approaches to the synthesis of C-linked disaccharides will be given.

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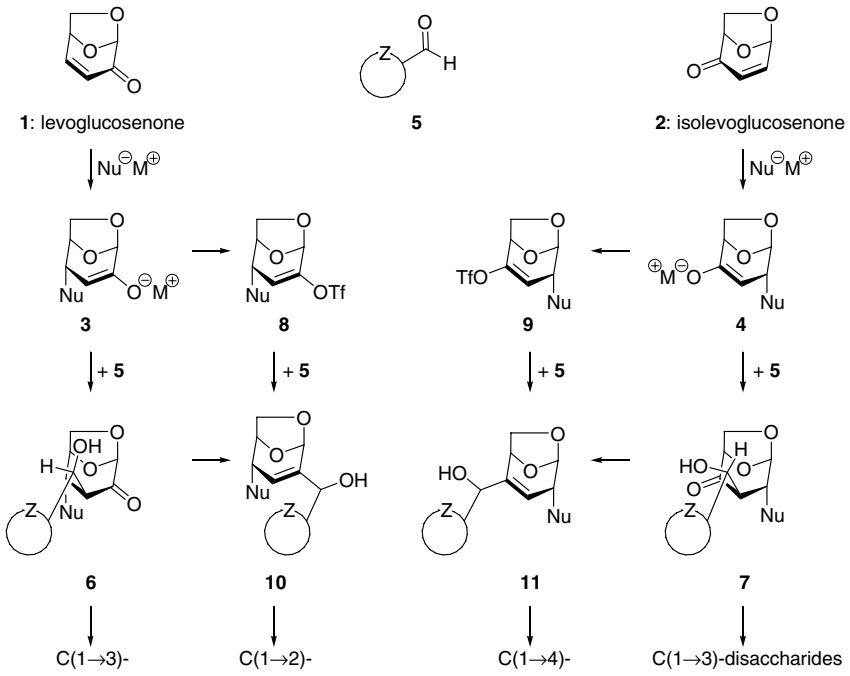


Scheme 1. Combinatorial and convergent syntheses of C-linked disaccharides and analogues.

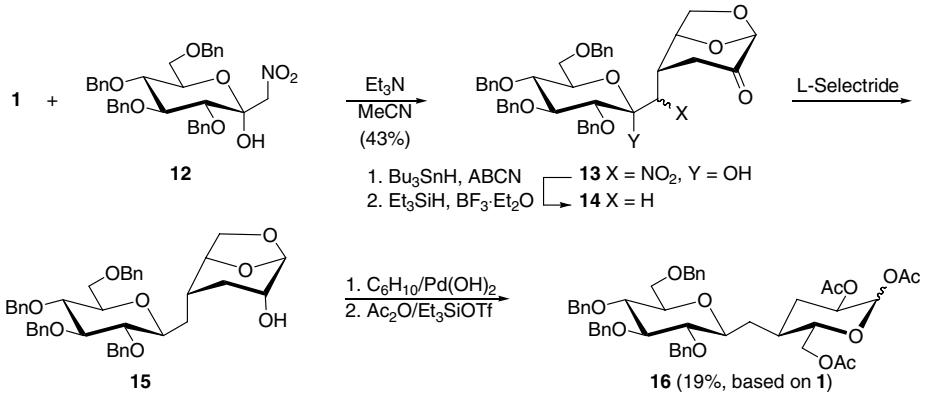
The readily available levoglucosenone (**1**)[8] has been used as homochiral starting material for the synthesis of several compounds of biological interest such as (3*S*,6*S*,7*S*)-serricornin, the sex pheromone from cigarette beetle,[12] (−)-δ-multistriatin and (+)-Prelog-Djerassi lactonic acid,[13] indole alkaloid reserpine,[14] herbicidal hexopyranose derivatives,[15] whisky lactones (+)-grandisol and methyl dihydroepijasmonate,[16] rare hexoses and nucleosides,[17] amino-sugars,[18] phytosphingosine,[19] (−)-hongconin,[20] segment C of tautomycin,[21] (−)-tetradotoxin and analogues,[22] and (+)-γ-pelargonolactone.[23] These syntheses exploit the stereoselectivity of the conjugate additions and cycloadditions of the enone moiety of **1** and of the nucleophilic additions of its keto group and that of the derivatives of **1**.[24] Isolevoglucosenone (**2**), obtained in four steps from glucose,[9d] has been used much less than **1** in total synthesis. It also shows high stereoselectivity in conjugate additions and cycloadditions.[9a,b,d,f,25]

2. Synthesis of (1→4)-C-disaccharides from levoglucosenone

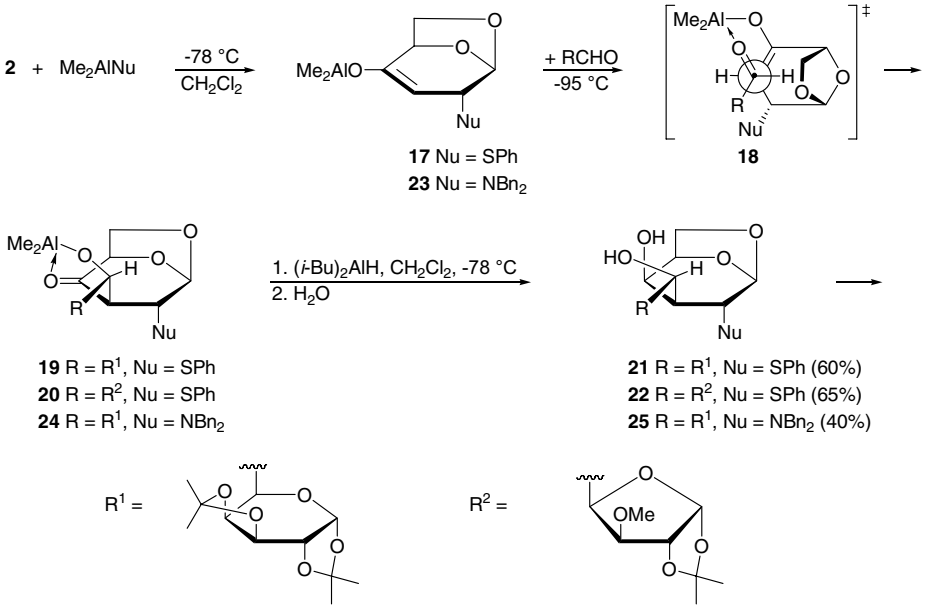
In their pioneering work, Witczak and co-workers[26] have exploited the highly α-face selective Michael addition of **1** with the nitromethane derivative **12** that gives a mixture of diastereomeric adducts **13** in 43% yield. Reductive elimination of the nitro group of **13** with Bu_3SnH in the presence of ABCN (1,1′-azobis(cyclohexane)carbonitrile) and subsequent cationic reduction of the hemiacetal with $Et_3SiH/BF_3{\cdot}Et_2O$ gave **14**. With L-Selectride, the keto group of **14** was attacked from its β-face due to the α-C-linker at C-4, giving alcohol **15**. Subsequent debenzylation and peracetylation generated the C-linked disaccharide derivative **16** in 19% overall yield based on **1** (Scheme 2). Similar methodology has been applied to the synthesis of β-(1→4)-3-deoxy-thiodisaccharides.[27]

3. Three-component syntheses of (1→3)-C-linked disaccharides

Oshima and co-workers have shown that conjugate addition of Me_2AlSPh to simple enones, followed by reaction of the aluminum enolates with aldehydes, generates the corresponding aldols in one-pot procedures.[28] The reagent Me_2AlSPh adds to isolevoglucosenone (**2**) at low temperature giving enolate **17** that reacts with sugar-derived aldehydes RCHO affording the aluminum aldolates **19** and **20**, which are reduced in situ with $(i\text{-Bu})_2AlH$ into the C-disaccharides **21** (60%) and **22** (65% yield), respectively (Scheme 3). The high diastereoselectivity of these reactions can be interpreted in terms of steric factors. Nucleophilic additions to **2** prefer the α-face of the enone. The bulk of the α-Nu group at C-2 of the enolates so obtained leaves only the β-face available for the aldol reactions that go through 'closed transition states' **18** (Zimmerman–Traxler model[29]). The high diastereoselectivity of reductions **19**→**21** and **20**→**22** can also be interpreted in terms of steric factors, the α-faces of the aldolates **19**, **20** being less sterically hindered than their β-faces.



Scheme 2. Witczak's synthesis of a D-Glc-β-(1→4)-CH_2-3-deoxy-D-*ribo*-hexopyranose derivative.

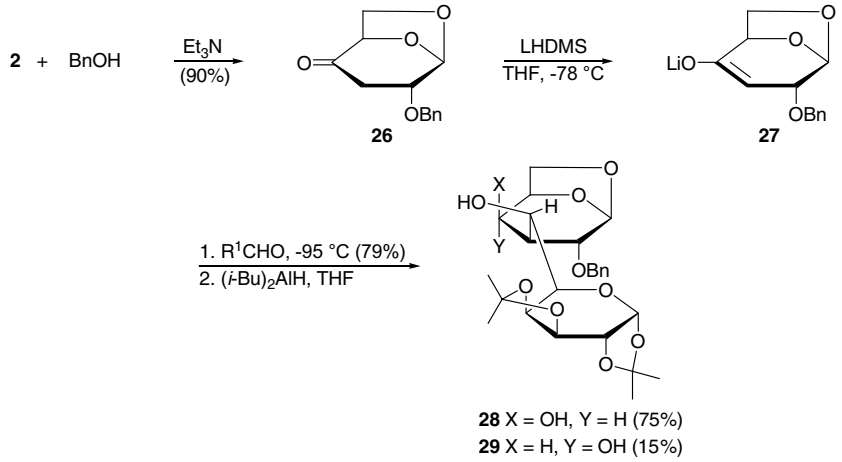


Scheme 3. One-pot syntheses of advanced (1→3)-linked C-disaccharide precursors with (*R*)-hydroxymethano linker.

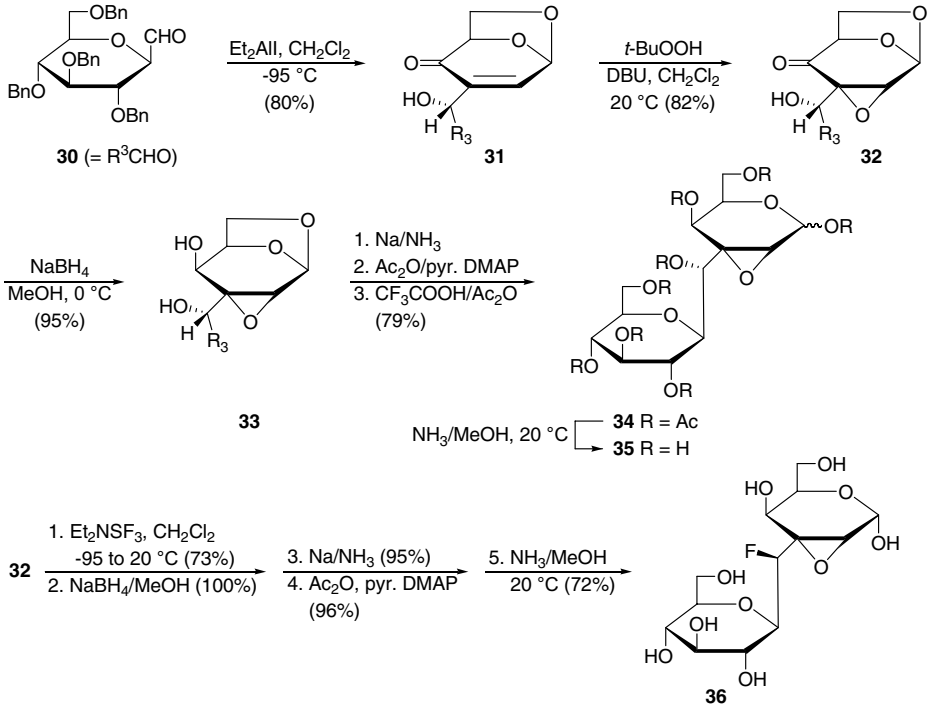
Using Me_2AlNBn_2 for the conjugate addition of enone **2** led to enolate **23**, which was reacted with R′CHO to give, after treatment with $(i\text{-Bu})_2AlH$, the protected D-galactosamine derivative **25** in 40% overall yield. When using Et_2AlNBn_2[30] instead of Me_2AlNBn_2, the yield of **25** dropped to 24%. With $Me_2AlN(Ac)Bn$, no C-disaccharide was obtained.

The addition of Me_2AlOBn to **2**, followed by addition of R′CHO and reduction with $(i\text{-Bu}_2)AlH$ did not produce the expected D-galactose derivative **28** (Scheme 4). As this one-pot three-component synthesis failed, we opened a two-pot, three-component approach. Adduct **26** (of benzyl alcohol to **2**) was deprotonated with $(Me_3Si)_2NLi$ (THF, −78 °C) without elimination of lithium benzylate. The lithium enolate **27** so obtained reacted at −97 °C with aldehydes giving the corresponding lithium aldolates that were reduced in situ with $(i\text{-Bu})_2AlH$ producing the expected diols. Using aldehyde R^1CHO (see Scheme 3), the process generated a 5:1 mixture of **28** and **29** that were separated and isolated in 75% and 15% yield, respectively.[31]

Under the same conditions of Scheme 4, the cross-aldolization of the lithium enolate **27** with β-D-glucopyranose-derived carbaldehyde **30**[32] led to a mixture of products that was reduced with $(i\text{-Bu})_2AlH$ affording less than 7% of the desired C-disaccharide. No better success was attained with the one-pot procedure of Scheme 3 using Me_2AlSPh with **2** and **30**. Nevertheless, when Et_2AlI[28] was added to a mixture **2** and **30** in dichloromethane at −95 °C the product of Baylis–Hillmann[33] coupling **31** was obtained in 80% yield. Treatment of enone **31** with *t*-BuOOH in dichloromethane and DBU afforded epoxide **32** as single product in 82% yield. Reduction of the ketone **32** with $NaBH_4$ in methanol at 0 °C provided a single diol **33** (95%). Debenzylation of **33**, subsequent acetylation and treatment



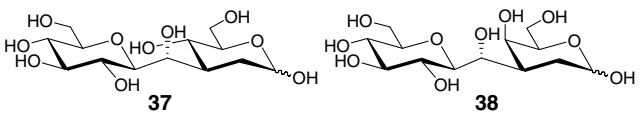
Scheme 4. Two-pot synthesis of (1→3)-linked C-disaccharide analogues of glycosides of D-galactopyranose and D-glucopyranose.



Scheme 5. Synthesis of (1→3)-C-disaccharides with hydroxymethano and fluoromethano linkers.

with trifluoroacetic acid/acetic anhydride led to **34**. Methanolysis of **34** afforded the C-disaccharide **35** (single β-pyranose in 45% yield (Scheme 5)).[31]

Fluorination of alcohol **32** with DAST (Et_2NSF_4) in dichloromethane afforded the corresponding fluoride with inversion of configuration (X-ray crystallography). After reduction of the ketone with $NaBH_4$ and subsequent debenzylation, peracetylation, and acidic treatment, an 2,3-anhydro-D-glucose derivative was obtained, the ammonolysis of which in methanol liberated the (1→3)-linked C-disaccharide **36** that bears a monofluoromethano linker.[33]



4. Syntheses of β-(1→3)-linked C-glycopyranosides of 2- and 4-deoxy-D-hexoses

The oligosaccharide components of the glycolipid-type antigens isolated from *Mycobacterium smegmatis* contain the β-D-Glc*p*-(1→3)-β-D-2-deoxy-D-arabino-Hex*p* moiety.[34] This motif, for which the C-disaccharide **37**

is a mimetic, is also found in the glucan fragment responsible for triggering the defense of the soybean to infections by the mould *Phytophthora megasperma*.[35] The lipopolysaccharide *O*-antigens of *Actinobacillus pleuropneumania* serotype 8 contains the β-D-Glc*p*-(1→3)-β-D-2-deoxy-D-lyxo-Hex*p* motif[36] for which **38** is a mimetic.[37] Deoxy-saccharides play many important roles in biology.[38]

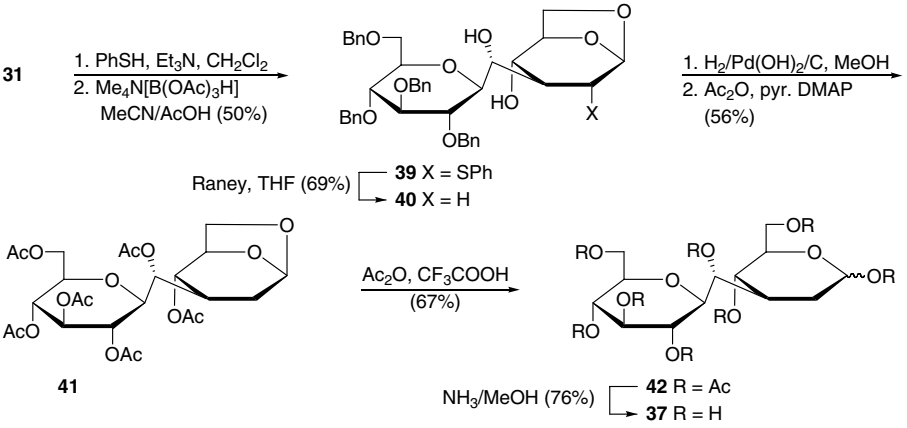
Additions of thiophenol to enone **31** (Scheme 5) in the presence of triethylamine gives a single adduct that was not isolated but treated directly with $Me_4N[B(OAc)_3H]$ in CH_3CN/acetic acid[39] to give **39**. Treatment of **39** with Raney nickel in THF afforded **40** (hydrogenation of enone **31** gave mixtures of products). As the methanolysis of the anhydro-*arabino*-hexose moiety of **40** was unsuccessful, the benzyl protective groups had to be exchanged for acetates by hydrogenolysis, followed by peracetylation. This produced **41** in 56% yield that was opened on treatment with trifluoroacetic acid/acetic anhydride giving a mixture of anomeric pyranose acetates **42**. Ammonolysis in methanol furnished pure C-disaccharide **37** in 76% yield (Scheme 6). When the addition of thiophenol to enone **31** was followed by reduction with $NaBH_4$ in methanol instead of $Me_4N[B(OAc)_3H]$, a D-*galacto* derivative was obtained, which was then converted into C-disaccharide **38** (3-*C*-[(1*R*)-2,6-anhydro-D-*glycero*-D-*gulo*-heptitol-1-*C*-yl]-2,3-dideoxy-D-*lyxo*-hexose) in a similar way as in Scheme 6.[40]

When applied to aldehyde **30** and levoglucosenone (**1**), the Oshima–Nozaki condensation induced with Et_2AlI in dichloromethane at −95 °C gave a single product **43** (30%) together with recovered aldehyde **30** (20%) and **1** (40%) (Scheme 7). No better conversion rate could be reached without concurrent decomposition on changing temperature and reaction time. This shows that levoglucosenone (**1**) is less reactive than isolevoglucosenone (**2**) in Oshima–Nozaki condensations. The (1′*R*) configuration of the alcoholic moiety of **43** has been established by ^1H NMR spectroscopy of a derivative. It is the same as that found for the product of the Oshima–Nozaki condensation of **2** + **30** which implies a 'closed transition state'[29] in the β-face of the intermediate aluminum β-iodoenolate. In the case of **1** + **30** it is assumed that the β-face attack by the aldehyde **31**, which would lead to (1′*S*) configuration, is impeded because of the C–H of the C-6 center, as noticed in related reactions.[41]

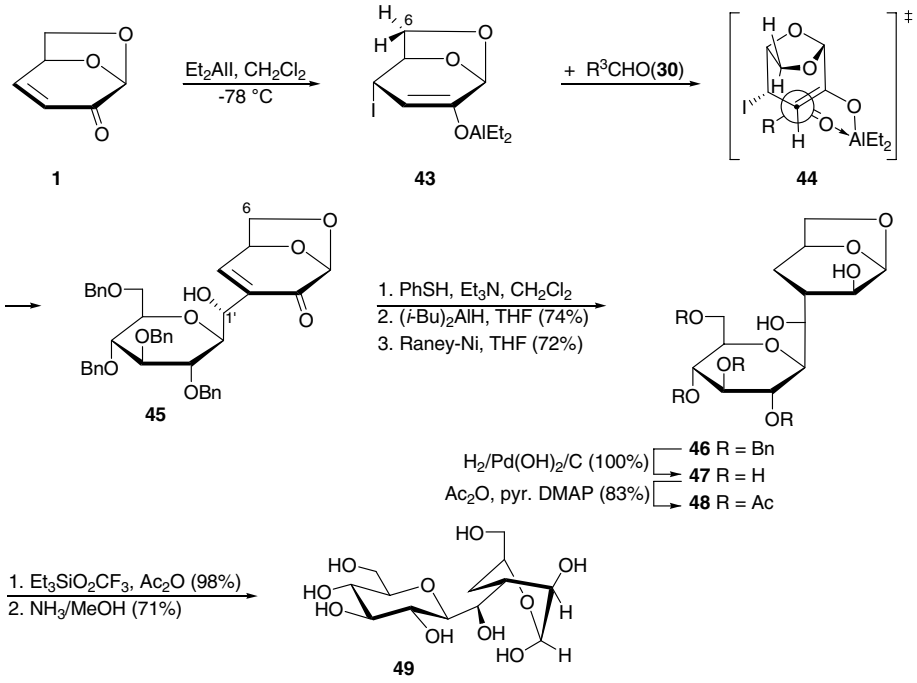
Aldehyde R^3CHO attacks thus the α-face of **43** (transition state **44**) leading to a (1′*R*)-configuration β-hydroxy-enone **45** after elimination of Et_3AlI (Scheme 7). Conjugate addition of thiophenol to **45** and subsequent ketone reduction with $(i\text{-}Bu)_2AlH$ and desulfurization with Raney nickel gave **46**. Debenzylation of **46** generated **47** that was peracetylated into **48**. Treatment of **48** with triethylsilyl trifluoromethanesulfonate in acetic anhydride produced a mixture of anomeric peracetates, the ammonolysis of which in methanol liberated the C-disaccharide **49**.[40]

5. Synthesis of C-linked analogues of β-D-galactopyranosyl-(1→3)-D-galactopyranosides and of β-D-galactopyranosyl-(1→3)-D-galactal

The β-D-galactopyranosyl-(1→3)-β-D-galactopyranosyl moiety is found as an end group in Core-B structures of a large number of proteoglycans[42] and has been isolated from a variety of other sources.[43] C-Linked disaccharides derivatives mimicking these end groups have been obtained via the Oshima–Nozaki condensation of isolevoglucosenone (**2**) with β-D-galactopyranosyl-carbaldehyde derivatives.[44] Slow addition of Et_2AlI in toluene solution to a mixture of **2** and aldehydes **50** and **51** in dichloromethane (−80 °C) produced enones **52** and **53** in 73% and 95% yield, respectively. Attempts to reduce both the C=C and C=O double bonds of **52** and **53** by direct methods led to mixtures. However, additions of thiophenol to **52** catalyzed by triethylamine generated a single adduct **54** that was treated directly with $NaBH_4$ to afford a single diol **55**. Desulfurization of **55** gave **56**. Subsequent debenzylation and peracetylation



Scheme 6. Synthesis of 3-*C*-[(1*R*)-2,6-anhydro-D-*glycero*-D-*gulo*-heptitol-1-*C*-yl]-2,3-dideoxy-D-*arabino*-hexose.



Scheme 7. Synthesis of 3-*C*-[(1*R*)-2,6-anhydro-D-*glycero*-D-*gulo*-heptitol-1-*C*-yl]-3,4-dideoxy-α-D-*arabino*-hexopyranose.

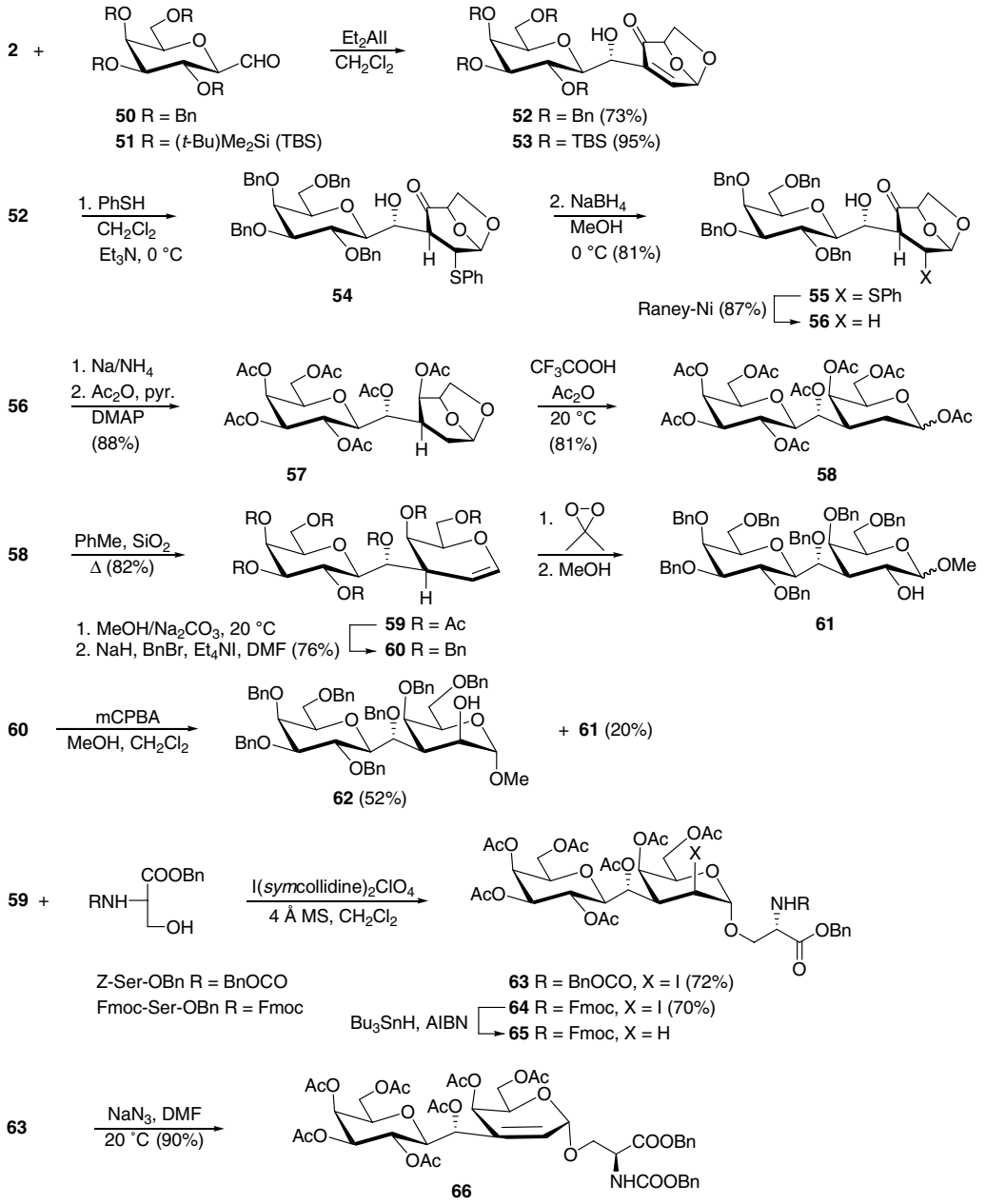
produced **57**, which was treated with CF_3COOH/acetic anhydride to give **58**. On heating **58** in toluene containing silica gel, smooth elimination of acetic acid occurred with formation of galactal **59**. Exchange of the acetate for benzyl ethers gave **60**. This galactal reacted with dimethyldioxirane in acetone giving the corresponding Brigl anhydride that was not isolated but reacted directly with methanol furnishing the C-disaccharide **61**. Interestingly, when galactal **60** was epoxidized with metachloroperbenzoic acid, the β-face was preferred (hydrogen bridging between the peracid and the 4- or 6-benzyloxy group?) and the C-linked analogue **62** of β-D-galactopyranosyl-(1→3)-(methyl α-D-talopyranoside) was obtained in 52% yield, together with 20% of **61** (Scheme 8).

The peracetylated β-*C*-galactopyranoside of galactal **59** reacted with semi-protected forms of L-serine in the presence of I(*sym*-collidine)$_2$$ClO_4$[45,46] producing 2-deoxy-2-iodo-talopyranosides **63** and **64**. Attempts to displace the iodide of **63** and **64** by all kinds of azides led to products of decomposition and/or to the α-D-*threo*-hex-2-enopyranoside **66**.

C-Disaccharides of the type β-D-galactopyranosyl-C-(1→3)-D-galactal in which there is a methano, rather than an hydroxymethano linker have also been prepared. In the presence of Raney nickel, the TBS-protected *C*-galactopyranoside **53** was reduced quantitatively into a mixture of aldols **67**. The crude mixture of **67** was treated with CH_3SO_2Cl in pyridine and a catalytic amount of 4-dimethylaminopyridine (DMAP). This led to a mixture of unstable enones **68** that were reduced directly with Raney nickel in aqueous THF producing a mixture of ketones from which pure **69** and **70** were isolated in 43% and 44% yield, respectively. Reduction of **69** with $LiBH_4$ in THF gave alcohol **71** in 79% yield. Acidic treatment of **71** gave **72**. Subsequent heating in benzene in the presence of silica gel afforded the C-linked analogue of β-D-galactopyranosyl-(1→3)-D-galactal **73** in 60% yield (Scheme 9).[44] Short and convergent syntheses of (1→3)-C-linked iminodisaccharides (aza-C-disaccharides) and homo(1→3)-C-linked iminodisaccharides have been realized following similar routes in which iminoalditol-derived carbaldehydes are condensed with levoglucosenone[41] or isolevoglucosenone.[47]

6. Synthesis of C-linked disaccharide analogue of the Thomsen–Friedenreich epitope α-O-conjugated to L-serine

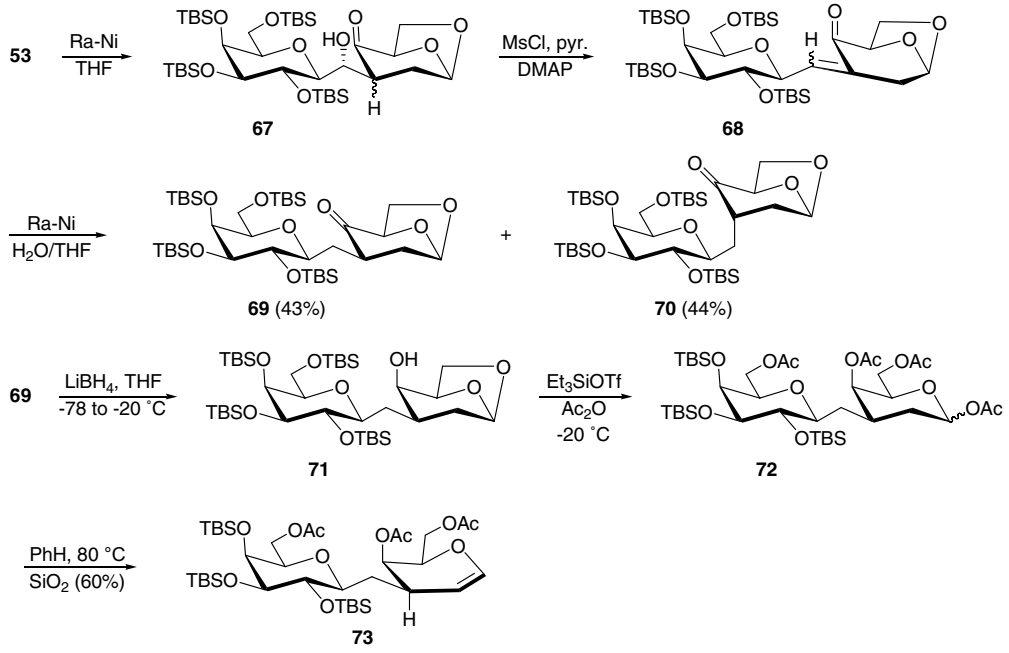
The Thomsen–Friedenreich or T epitope (β-D-Gal*p*-(1→3)-α-D-Gal*p*NAc) is a known tumor-associated antigen.[48] The presence of T antigen during an early fetal phase, its absence in noncarcinomatous post-fetal tissues and its association with carcinomas suggest that T antigen is a stage-specific oncofetal carbohydrate antigen.[49] The T antigen is also related to blood group antigens. In epithelial cells, the T epitope is carried by mucin (MUC1), which belongs to a family of highly glycosylated proteins present on the apical surface of many epithelial cells. On tumor cells MUC1 is post-translationally modified resulting in incomplete O-glycosylation and exposing the T epitope.[50] Everyone has



Scheme 8. Synthesis and reactions of *C*-(1→3)-D-galactopyranosides of D-galactal derivatives.

'preexisting' anticarcinoma anti-T antibodies, induced predominantly by the intestinal flora, while cellular immune responses to T epitopes are evoked only by carcinomas and some lymphomas.[51] The T antigens have been prepared and their immunogenicity in conjugate vaccines has been confirmed.[51,52] The clustered antigen motifs such as **74** prepared by Danishefsky and coworkers[53] have demonstrated the potential for antitumor vaccines[54] based on T antigen conjugates.

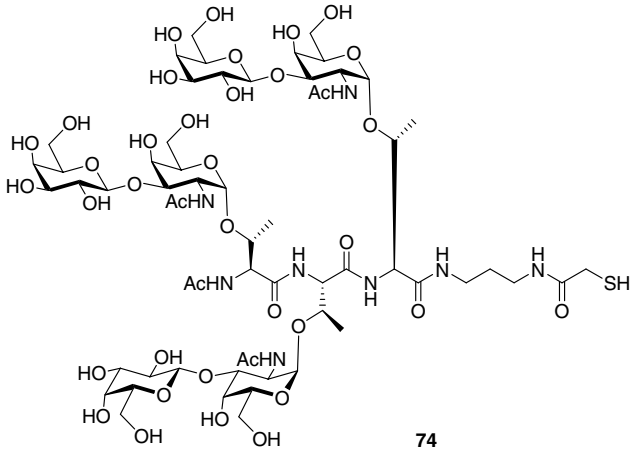
Disaccharide conjugates are relatively short-lived in the blood stream because of their hydrolysis catalyzed by ubiquitous glycosidases. Disaccharide mimetics such as C-linked disaccharide analogues offer an improved stability towards hydrolysis as required for a disaccharide-based vaccine. In a first approach to the synthesis of C-glycoside **75** analogue of epitope T disaccharide,[55] **53** was reacted with *O*-benzyl hydroxylamine to give oxime **76** in 70% yield. Control experiments showed that the initial conjugate addition of $BnONH_2$ to enone **53** giving adduct **75** is somewhat faster than the oxime formation, although the latter reaction could not be avoided. Using *N*,*O*-dibenzyl hydroxylamine enone added between −78 °C and −15 °C in the presence of Me_2AlCl giving pure adduct **77**. Reduction of ketone **77** with $LiBH_4$ in THF provided **78** with high diastereoselectivity and good yield (70%). Reaction of **78** with



Scheme 9. Synthesis of a β-D-galactopyranosyl-(1→3)-CH_2-D-galactal derivative.

Me_3SiSPh and ZnI_2 gave **79**. As the O-glycosylation of semi-protected forms of L-serine with **79** and its derivatives failed to generate the desired α-galactopyranosides (the participation by the BnNOBn moiety of **79** could not be avoided) an analogue of **79** bearing an 2-azido group was targeted.

Although isolevoglucosenone (**2**) is known to add NaN_3/acetic acid giving the corresponding β-azidoketone,[9d] enones **52** and **53** failed to react with HN_3 (−40→0 °C). With a 1:1 mixture of Me_3SiN_3 and acetic acid containing a catalytical amount of DBU,[56] **52** gave a mixture of unstable azide after aqueous treatment. The crude reaction mixture obtained at 0 °C was treated with $NaBH_4$/methanol to give a mixture of azido-diols that was not isolated, but directly converted into the corresponding acetonides under standard conditions (Scheme 11). Flash chromatography on silica gel provided the three products **80**, **81**, and **82** (52% yield, three steps) with the proportion 1:1.6:1.6. Unfortunately, none of these azides had the desired 1,6-anhydro-D-*galacto* configuration.

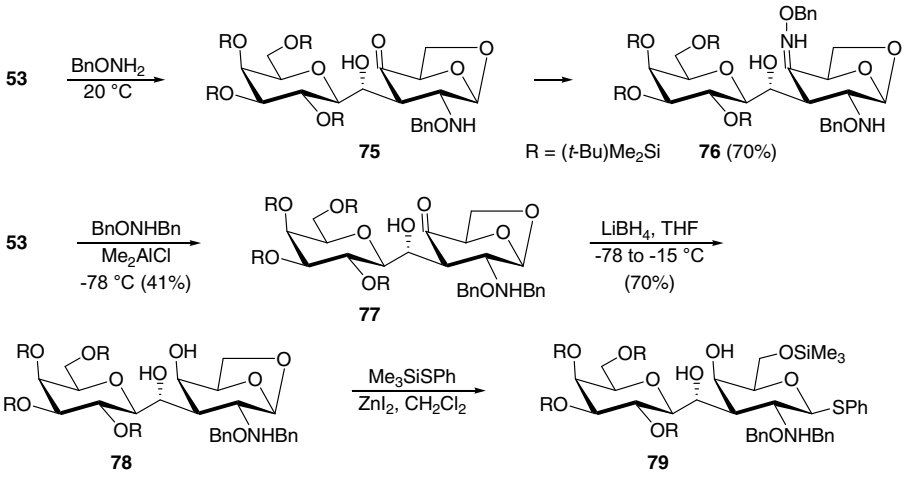


Protected D-galactals as well as peracetate of β-D-Gal*p*-(1→3)-D-galactal[57] underwent Lemieux's azidonitration (NaN_3/$Ce(NH_4)_2(NO_3)_6$)[58] giving the corresponding α- and β-D-galactopyranosyl nitrates as major products. Unfortunately, the galactopyranosyl-(1→3)-*C*-galactal derivative **59** reacted with $Ce(NH_4)_2(NO_3)_6$ and NaN_3 in CH_3CN giving a single α-nitrate **83** in 87% yield. Reaction of **83** with LiBr in acetonitrile gave α-bromide **84** (78%) which underwent Königs–Knorr glycosidation of methanol furnishing a separable 4.5:1 mixture of α- and β-talopyranosides **85α** (63%) and **85β** (14%). Triflate **86** of talopyranoside **62** has been made with the hope to displace it with an azide to reach the corresponding 2-azido-galactopyranose derivative. But this goal could not be reached as only product of elimination **87** was formed (Scheme 11).

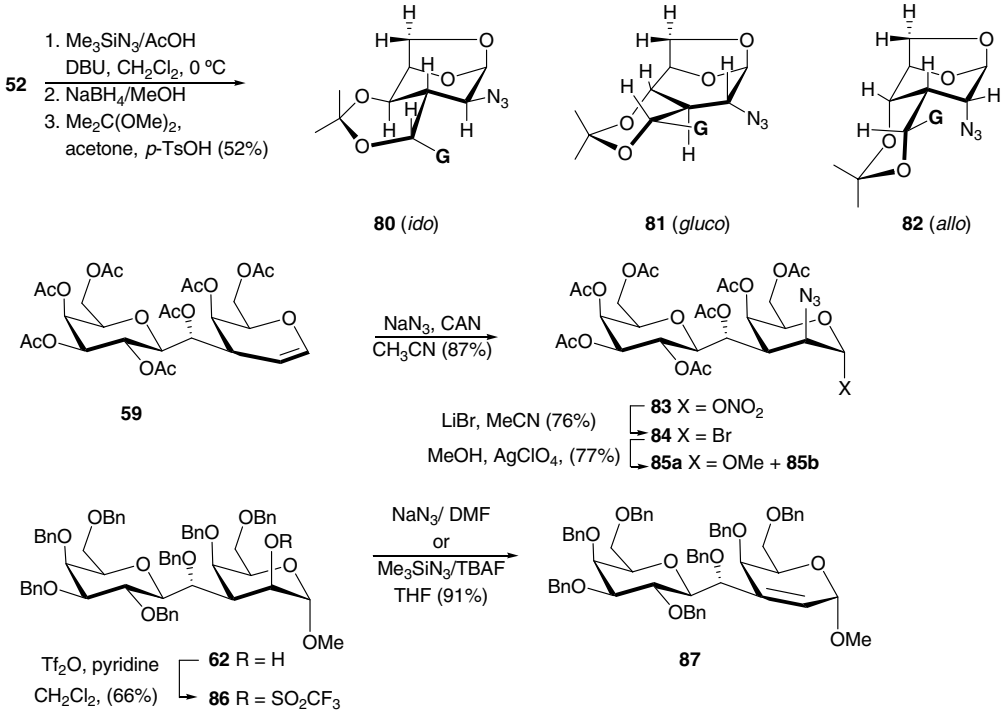
These failures are in contrast with successes encountered for similar reactions with related monosaccharide derived triflate.[59,60] Schmidt and co-workers[61a] have prepared a perbenzylated T antigen **92** by Michael-type addition of Boc-Ser-O-*t*-Bu to 2-nitro-galactal **89** derived from D-galactal **88** (Scheme 12). Applying the same reaction sequence to the perbenzylated β-Gal*p*-(1→3)-D-galactal **60** the nitro-galactal **93** (50%) was obtained. It reacted with the semi-protected L-serine **90**. Unfortunately again, only the α-talopyranoside **94** was formed. Attempts to epimerize the 2-deoxy-2-nitro-D-

talopyranoside **94** into the corresponding 2-deoxy-2-nitro-D-galactopyranoside failed (triethylamine, DBU, and DABCO).

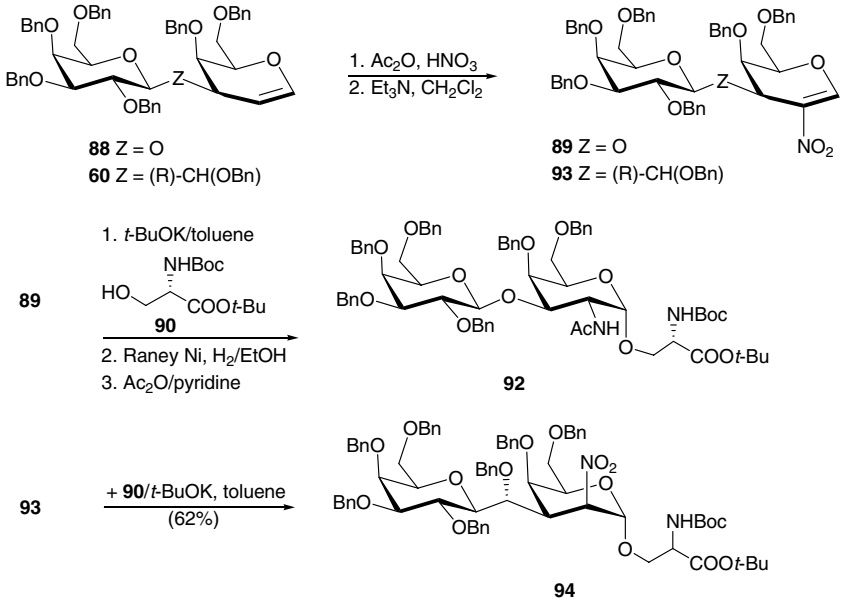
We envisioned that Lemieux's radical azidonitration of a 3-C-glycoside of D-galactal might become α-selective for the attack of N_3 radical if its 4,6-diol unit could be included in a ring such as an acetonide. As shown by several authors,[61] the stereoselectivity of this reaction depends strongly on substitution of the glycal and on its conformational mobility. We further envisioned that an acetonide involving the hydroxy groups at C-4 of the galactal moiety and at C-1′ of the hydroxymethylene linker might impede radical addition onto the β face of the galactal alkene moiety. Thus, the protected β-*C*-galactopyranosyl-(1→3)-galactal **99** was prepared as shown in Scheme 13. Its azidonitration under Lemieux's conditions gave a 1:3 mixture of 2-azido-2-deoxy-D-galactopyranosyl nitrates **100α** and **100β** in mediocre yield



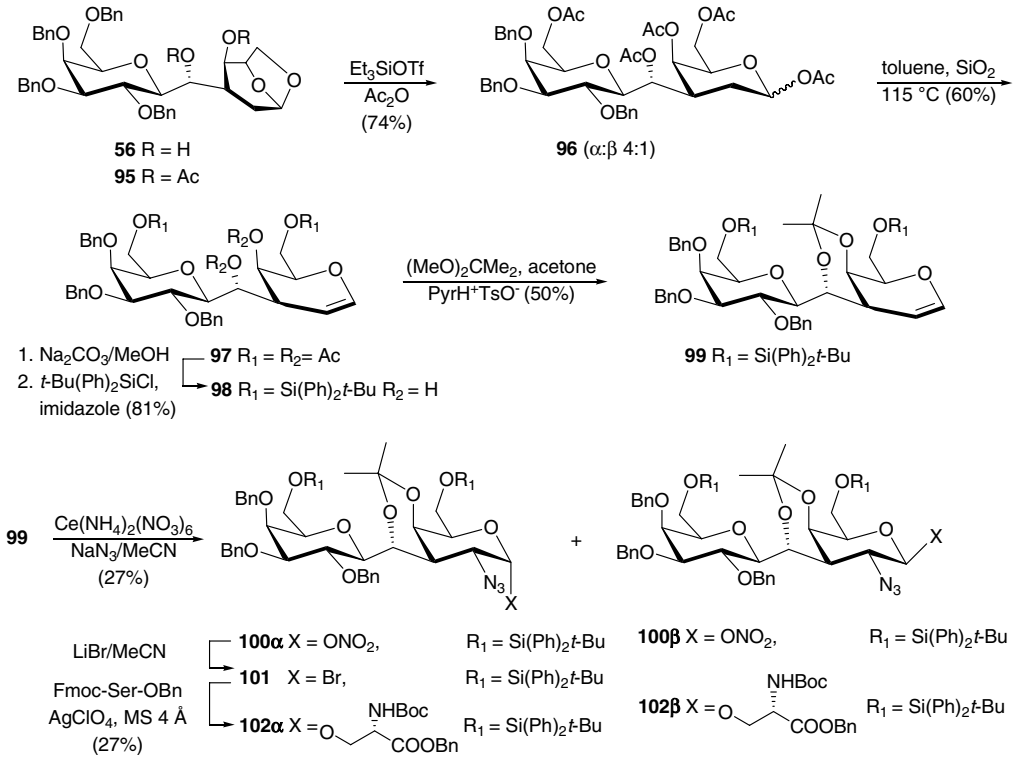
Scheme 10. Synthesis of a C-disaccharide analogue of the Thomsen–Friedenreich epitope.



Scheme 11. Attempted syntheses of galactopyranosyl-(1→3)-*C*-2-azido-2-deoxy-galactopyranose derivatives.



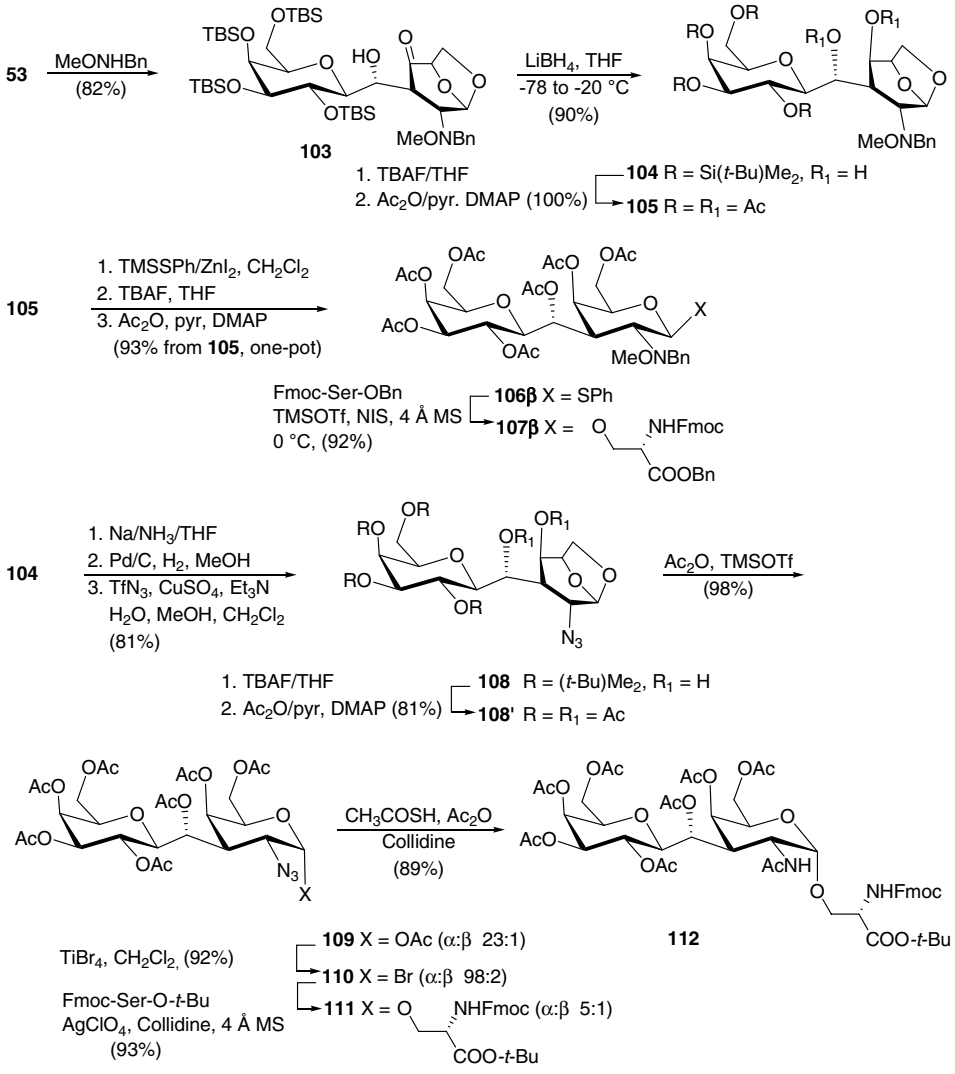
Scheme 12. Failure of the Schmidt's route to generate the α-galactopyranoside precursor.



Scheme 13. Lemieux's azidonitration is α-face selective on a conformationally constraint D-galactal derivative.

(27%). Nitrates **100α,β** was then converted into bromide **101** that was used for the Königs–Knorr glycosidation of Fmoc-Ser-OBn. This led to a 1.5:1 mixture of the desired α- and undesired β-galactopyranosides **102α** and **102β** respectively, with mediocre yield (36%, Scheme 13).

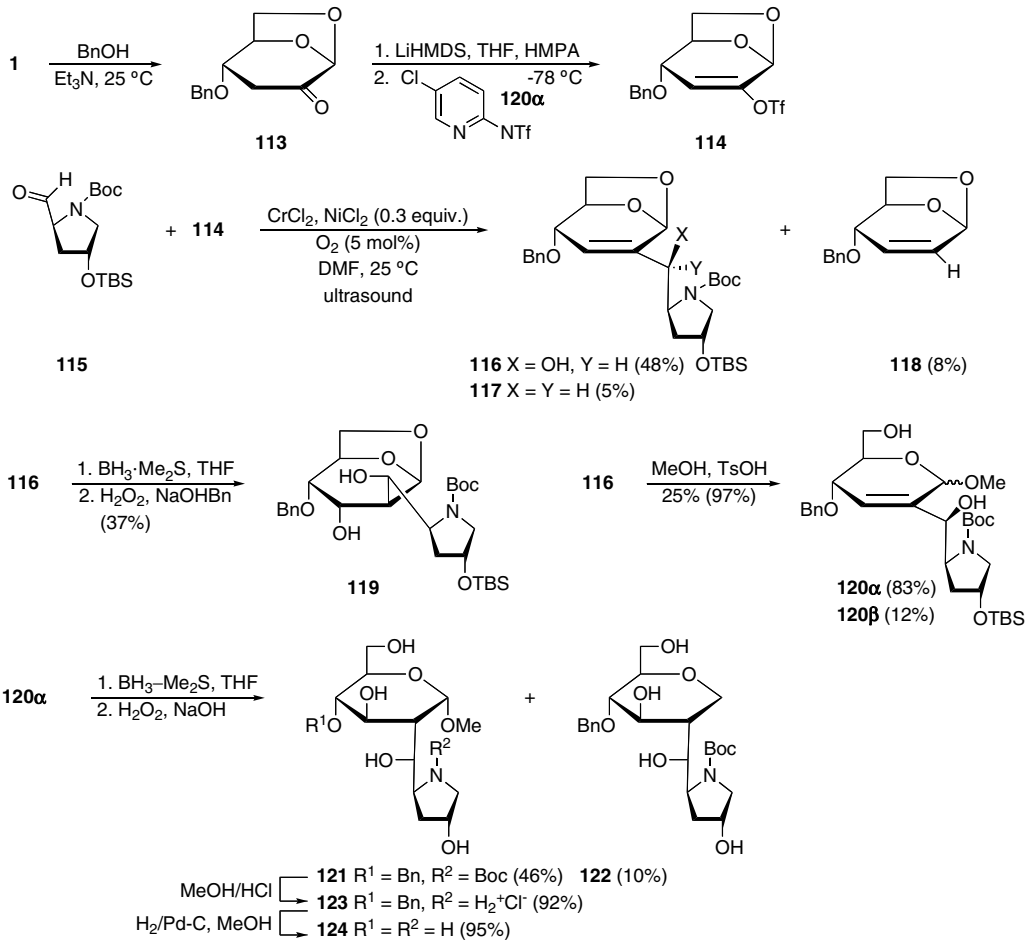
All these unsatisfactory results forced us to come back to our initial studies during which the 2-amino-2-deoxy-D-galactal moiety was obtained under the protected form of a *N*-benzyl-*O*-(benzyloxy)amino group (Scheme 10). CH_3ONHBn added to enone **53** giving mixture of



Scheme 14. Synthesis of a C-linked disaccharide analogue of the Thomsen–Friedenreich epitope α-O-conjugated to L-serine.

stereomeric adducts that are isomerized into **103** during their slow chromatography on silica gel at room temperature. Reduction of ketone **103** with $LiBH_4$ furnished diol **104** in 90% yield.

Treatment of **104** with *n*-Bu_4NF (TBAF) in THF (20 °C, 3 h) and then with acetic anhydride/pyridine and a catalytic amount of 4-dimethylaminopyridine (DMAP) provided peracetate **105**. Ring opening of the 1,6-anhydro-galactose moiety of **105** required suitable conditions avoiding the easy formation of furanoside rather than pyranoside derivatives. This was the case when treating **105** with anhydrous ZnI_2 and Me_3SiSPh in dichloromethane.[62] The crude product so obtained was not isolated but desilylated (TBAF and THF) and peracetylated under standard conditions producing thiogalactoside **106** in 93% yield (Scheme 14). Glycosylation[63] of Fmoc-Ser-OBn with **106** led exclusively to the β-D-galactopyranoside **107** (93% yield), as expected. Following the method of Wong and co-workers,[64] the *N*-benzyl-*N*-methoxyamino group of **104** was converted into the corresponding primary amine under Birch's conditions[65] and subsequent catalytical hydrogenation. The amine so obtained was not isolated but directly treated with trifluoromethanesulfonyl azide, cupric sulfate, triethylamine in a mixture of water/methanol/dichloromethane. Azide **108** was obtained in 81% yield (based on **104**). Smooth ring opening of the 1,6-anhydrogalactose moiety of **108** involved first peracetylation (acetic anhydride/pyridine/DMAP) and then treatment with $Me_3SiOSoxygenCF_3$ in acetic anhydride; this gave **108′** in 98% yield. Conversion of galactosyl acetate **108′** into the corresponding bromide **110** (92%) used $TiBr_4$ in dichloromethane (20 °C, 12 h). Königs–Knorr glycosidation ($AgClO_4$/dichloromethane, 2,4,6-collidine, 4 Å molecular sieves)[66] of *N*-Fmoc-serine *tert*-butyl ester gave a 5:1 mixture of α- and β-galactopyranosides in 93% yield. Flash chromatography provided pure α-galactopyranoside that reacted with thiolacetic acid,

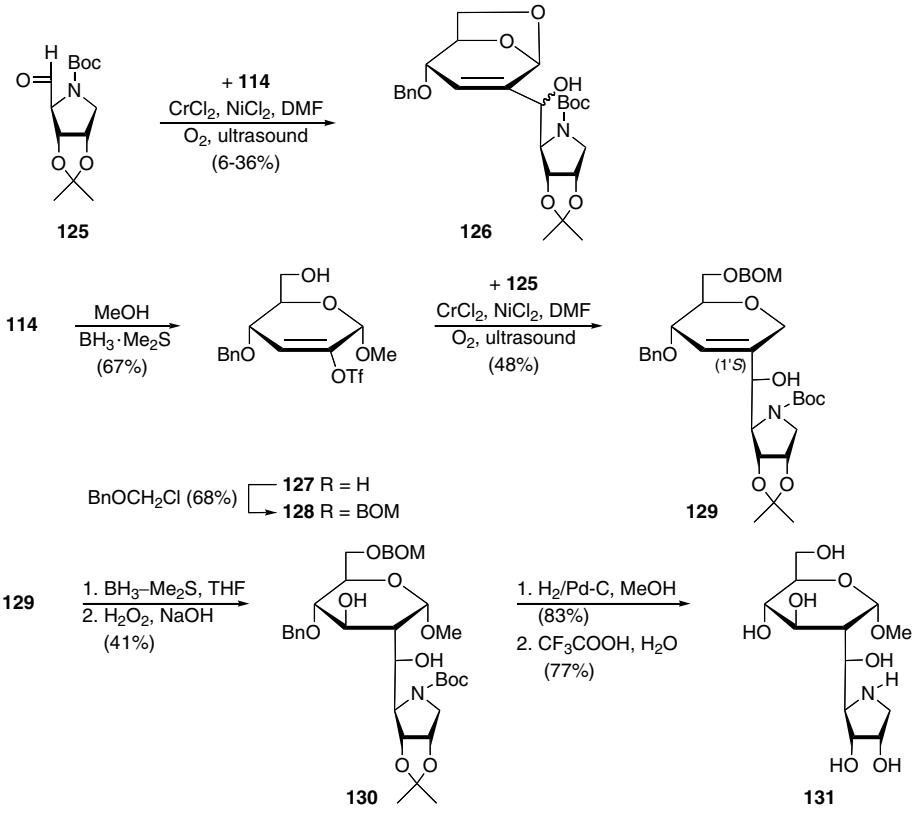


Scheme 15. Synthesis of 2-deoxy-2-{(1*R*)-2,5-imino-2,3,5-trideoxy-L-*erythro*-pentitol-1-*C*-yl}-α-D-glucopyranoside.

collidine, and acetic anhydride[67] furnishing **112** in 89% yield, a protected form of a C-linked analogue of epitope T α-O-conjugated to L-serine.[68] This form must be suitable for the construction of clusters via peptide synthesis and further conjugation to immunogenic proteins, as demonstrated by Danishefsky and co-workers[53] for an O-linked analogue of **112** that was converted into cluster **74**.

7. Convergent synthesis of (1→2)-C-linked disaccharides

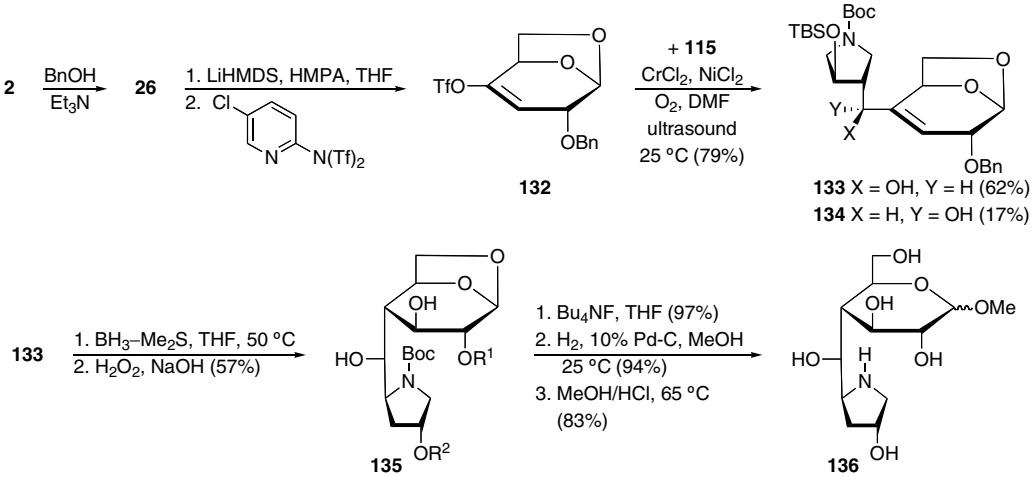
As mentioned in the introduction (Scheme 1), quenching of enolates **3**, resulting from the conjugate addition of nucleophilic agents (NuM) to levoglucosenone (**1**), as triflate **8**, and the addition of the latter of sugar-derived aldehydes, RCHO, generates advanced precursors of (1→2)-C-disaccharides and analogues. This route has been used to prepare (1→2)-C-linked iminodisaccharides **124** (Scheme 15) and **131** (Scheme 16). Benzyl alcohol adduct **113**[68] to **1** was converted into triflate **114** by lithiation with $(Me_3Si)_2NLi$ in THF/HMPA, followed by quenching of the lithium enolate by 2-[bis-(trifluoromethylsulfonyl)amino]-5-chloropyridine[69] at −78 °C. Under typical conditions for the Takai–Hiyama–Nozaki–Kishi coupling conditions ($CrCl_2$, 0.3 mol % $NiCl_2$, and DMF),[11] the reaction of triflate **114** with aldehyde **115** proceeded in low yield (2–15%). It was found[70] that this reaction could be accelerated by ultrasound and oxygen (5 mol %). Moreover, oxygen reduced the formation of products reduction of triflate **114** resulting from H_2O quenching of the alkenylchromium species. Thus, conditions were found under which the product of coupling **116** could be isolated in 48% yield together with deoxygenated product **117** (5%) and **118** (8%). Hydroboration of **116** followed by oxidative work-up provided diol **119** in modest yield (37%). Hydroboration takes places from the *exo* face of the bicyclic system probably because of steric hindrance from the *endo* C–H group at C-6. The allylic acetal **116** was readily opened by acidic methanolysis. This provided a mixture of methyl glycosides **120α** and **120β** from which the major α-anomer **120α** could be isolated pure in 85% yield. Hydroboration of **120α** gave alcohol **121** (46%) and the anhydroglucitol derivative **122** (10%). Under reflux in methanol saturated with



Scheme 16. Synthesis of methyl 2-deoxy-2-[(1*S*)-2,5-dideoxy-2,5-imino-L-ribitol-1-*C*-yl)-α-D-glucopyranoside.

HCl, **123** was obtained in 92% yield. Hydrogenation liberated the (1→2)-C-linked imino-disaccharide **124** (Scheme 15).[70]

Under standard conditions,[11] the Takai–Hiyama–Nozaki–Kishi coupling reaction of bicyclic triflate **114** with aldehyde **125** failed completely. In the presence of 5 mol % of oxygen and under activation with ultrasound, a 1:2 mixture of allylic alcohols **126** could be obtained in modest yield (6–36%). Acidic methanolysis of **114** provided pyranoside **127**. Its primary alcoholic moiety was protected as a (benzyloxy)methyl (BOM) ether **128**. Under our modified conditions for the Takai–Hiyama–Nozaki–Kishi coupling, monocyclic triflate **128** reacted with aldehyde **125** giving a single allylic alcohol **129** isolated in 48% yield. In contrast to coupling **114** + **115** → **116** (Scheme 15) for which the (1′*R*)-alcohol was obtained as major product, the reaction **128** + **125** → **129** (Scheme 16) generated a (1*S*′)-alcohol.



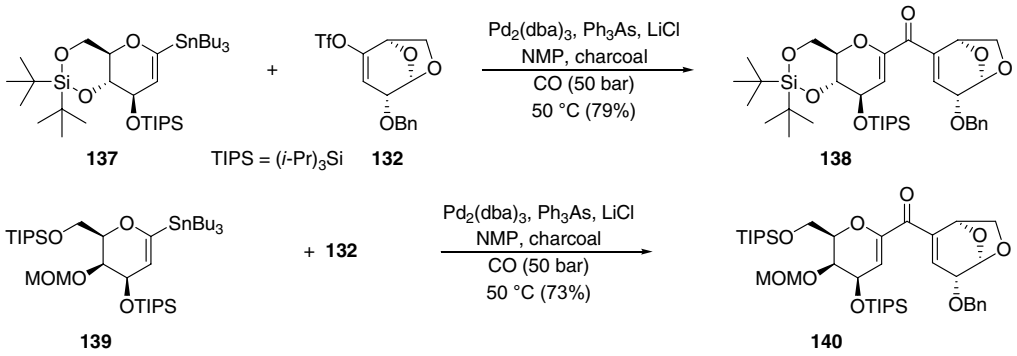
Scheme 17. Synthesis of methyl 4-methoxy 4-deoxy-4-[(1*R*)-2,5-imino-2,3,5-trideoxy-L-*erythro*-pentitol-1-*C*-yl]-α and β-D-glucopyranoside.

Hydroboration of the alkene moiety of **129** gave alcohol **130**. Debenzylation of **130**, and subsequent acidic treatment (Scheme 16) provided the methyl α-D-glucopyranoside **131**.[71]

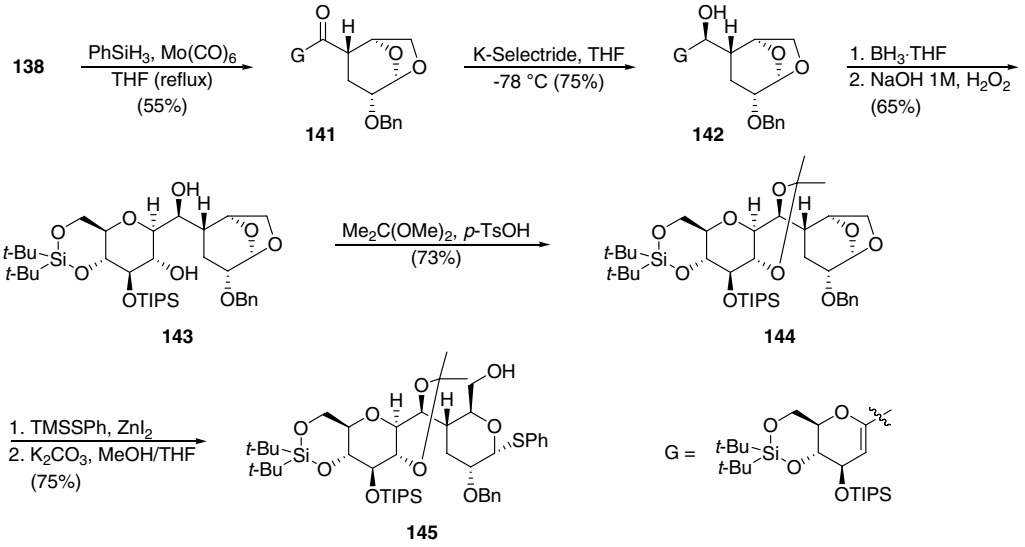
8. Convergent synthesis of (1→4)-C-linked disaccharides

As already mentioned (Scheme 2), Witczak and coworkers have opened an efficient route for the synthesis of (1→4)-C-disaccharides based on the Michael addition of nitroalkanes derived from sugars to levoglucosenone (**1**). Here we summarize two routes that have been developed in our group using C–C-coupling reactions of enol triflate **132** derived from ketone **26**, the adduct of benzyl alcohol to isolevoglucosenone (**2**). Triflate **132** was prepared in a similar way as **114**. Under our modified conditions of the Takai–Hiyama–Nozaki–Kishi coupling reaction **132** reacted with aldehyde **115** giving a mixture of allylic alcohols **133** and **134** isolated in 62% and 17% yield, respectively. Hydroboration of **133** led to the D-glucose derivative **135**. Desilylation of **135** and subsequent debenzylation and refluxing in methanol saturated with HCl furnished a 2:1 mixture of (1→4)-C-linked iminodisaccharides **136α/β** (Scheme 17).[70]

Enol triflates are good electrophilic partners in Stille and carbonylative Stille C–C coupling reactions.[72] The carbonylative Stille cross-coupling of triflate **132** with tinglucal **137** was possible using $Pd_2(dba)_3$ in the presence of Ph_3As, LiCl, powdered charcoal, and 50 bar atmosphere of CO and heating to 50 °C. At higher temperature, only direct coupling between the tinglucal **137** and **132** was observed. At low temperature no reaction took place. The yield in **138** was the best (79%) using *N*-methylpyrrolidone (NMP) as solvent. The amount of LiCl is crucial for success. With Pd/LiCl ratio 1:3 and for Pd(0)/Ph_3As the ratio must be 1:1. Replacement of Ph_3As for Ph_3P or the use of solid charcoal instead of powdered charcoal failed to give product of carbonylative coupling! This is explained by the property of pow-



Scheme 18. Carbonylative Stille coupling applied to the synthesis of (1→4)-C-disaccharide precursors.



Scheme 19. Synthesis of a (1→4)-C-linked disaccharide glycosyl donor.

dered charcoal to disperse metallic palladium and to allow for efficient resolubilization into active catalytical species. Other protected glucal (4,6-*O*-isopropylidene-3-*O*-methoxymethyl, 4,6-*O*-isopropylidene-3-*O*-tri(isopropyl), and 3-*O*-[(*t*-butyl)dimethylsilyl]tinglucal) than **137** also undergo carbonylative Stille coupling with triflate **132** under the above optimal conditions but with lower yields, and not at all under standard conditions. Triflate **132** could also be coupled with stannylated galactal **139** to give **140** in 73% yield (Scheme 18).[73]

The cross-conjugated dienone **138** has been converted into a (1→4)-C-linked disaccharide glycosyl donor (Scheme 7). Which combines β-D-glucopyranosyl unit with a 3-deoxy-D-*ribo*-hexopyranosyl moiety through a (*S*)-hydroxymethano linker. Probably because of the ring-strain of the 1,6-anhydrohexose unit of **138**, the double bond from the enol triflate is more reactive than the double bond of the glucal moiety. For instance, chemo- and stereoselective hydrogenation of the bicyclic alkene could be carried out with $PhSiH_3$ in the presence of $Mo(CO)_6$ as catalyst, giving enone **141** in 55% yield. Reduction of **141** with $(i\text{-Bu})_2AlH$ gave a 2:1 mixture of allylic alcohol **142** and its diastereomer in 85% yield. With K-Selectride only **142** was formed and isolated in 75% yield. Hydroboration (BH_3·THF) of **142** gave diol **143** (65%) with high diastereoselectivity, probably because the α-face of the glucal alkene moiety is less sterically hindered then its β-face. Protection of diol **143** as an acetonide under standard conditions ($Me_2C(OMe)_2$ and *p*-TsOH) produced **144** (73%). Although the 1,6-anhydrohexose **144** is a potential glycosyl donor, it was converted into the thioglycoside **145**, another potential glycosyl donor. Thus treatment of **144** with Me_3SiSPh and ZnI_2 provided **145** in 75% yield, after work up with K_2CO_3/methanol (Scheme 19).[73] Applying the carbonylative Stille coupling conditions described above to 1-iodoglucal and tinglucal derivatives[74] advanced precursors of (1→1)-C-linked disaccharides[75] have been prepared.[73]

9. Conclusion

Both levoglucosenone (**1**) and isolevoglucosenone (**2**) are extremely useful templates for the convergent synthesis of (1→2), (1→3), and (1→4)-C-disaccharides and analogues. Because of their bicyclic structures, their reactions show high diastereoselectivities thus allowing planning in target synthesis. The Oshima–Nozaki three-component condensation of **1** and **2** with dialkylaluminum species and sugar-derived aldehydes allows the quick assembly of advanced precursors of (1→3)-C-disaccharides. The products of conjugate addition of **1** and **2** can be trapped as enol triflates capable to react with the sub-library of sugar-derived aldehydes under modified Takai–Oshima–Nozaki–Kishi conditions ($CrCl_2$, $NiCl_2$, oxygen, ultrasound) leading to advanced precursors of (1→2)- and (1→4)-linked C-disaccharides. The same enol triflates can be used also as electrophilic partners in carbonylative Stille coupling with tinglycals, thus realizing another type of one-pot, three-component synthesis of C-linked disaccharides. The methods developed are efficient and generate a high molecular diversity for these important disaccharide mimetics.

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