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Chemical strategies for the stereoselective construction of 1,2-*cis*-galacturonic and aminogalacturonic acid glycosides

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ABSTRACT

The stereoselective synthesis of 1,2-*cis*-galacturonic acid and 2-amino-2-deoxy-galacturonic acid glycosides remains a critical challenge in carbohydrate chemistry owing to the electronic and steric effects imposed by the C5-carboxyl group and C2 substituents. The available synthetic strategies can be divided into two divergent pathways: the construction of the glycan backbone before introducing the carboxyl group and the use of pre-formed uronic acid donors during glycosylation. Key advances include the use of remotely participating acyl groups, conformational control *via* 3,6-lactone intermediates, chelation-directed anomerisation and steric shielding by bulky protecting groups such as 4,6-*O*-di-*tert*-butylsilylene and 4,6-*O*-benzylidene. This review comprehensively overviews the current strategies that overcome stereochemical challenges in the synthesis of 1,2-*cis*-galacturonic and aminogalacturonic acid–containing glycans. In addition, the application of these methodologies to the synthesis of biologically relevant carbohydrates is examined.

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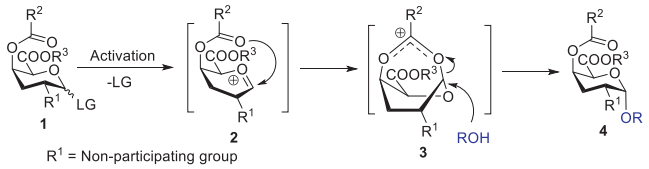
1. Introduction

Carbohydrates are crucial for several biological processes, including cell–cell recognition, immune responses and pathogen–host interactions [1–3]. These glycans often exhibit unique biological activities, rendering them attractive targets for vaccine development [4], antimicrobial agents [3] and biomaterials [5]. In particular, 1,2-*cis*-glycosidic linkages, especially those involving galacturonic acid (GalA) and its amino derivatives, *e.g.*, 2-amino-2-deoxy-galacturonic acid (GalNAcA), are structurally and functionally relevant [6–8], influencing molecular recognition and biochemical stability in bacterial polysaccharides [9], plant pectins [10], and glycosaminoglycans [11]. However, the paucity of structurally homogeneous oligosaccharides in quantities sufficient for biological studies remains a fundamental challenge in glycobiology research [12]. Although certain carbohydrates can be isolated from natural sources, the isolation of chemically pure and structurally well-defined samples of biologically relevant carbohydrates is impractical [13]. Therefore, the development of synthetic approaches for the precise construction of carbohydrates and their mimetics is indispensable for advancing glycobiology research [14–17]. Glycosylation reactions are vital for the synthesis of complex carbohydrates. Various parameters affect the glycosylation reaction selectivity and yield, such as the reaction temperature, solvent conditions, and activation strategy as well as the nature of protecting groups on the glycosyl donor and acceptor [18]. Unfortunately, current glycosylation methodologies remain limited in scope; in fact, there is no universal approach for efficiently constructing all glycosidic linkage types [13].

The stereoselective construction of 1,2-*cis*-GalA/GalNAcA glycosides remains a formidable challenge in synthetic carbohydrate chemistry owing to the interplay of electronic, steric and conformational factors [19]. Specifically, the C-5 carboxyl group in GalA/GalNAcA alters the reactivity of the glycosyl donor compared with neutral sugars, typically leading to competitive side reactions or poor stereocontrol [7]. Similarly, the electron-withdrawing properties of the C-5 carboxylate group deactivate neighbouring hydroxyl groups, endowing the C-4 hydroxyl moiety of GalA with poor nucleophilic behaviour [19]. In addition, the presence of a C-2-*N*-acyl or *N*-protecting group in aminogalacturonic acid derivatives further complicates the glycosylation by affecting neighbouring-group participation or introducing steric hindrance.

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Scheme 1. Proposed mechanism of *O*-4-acyl-mediated α-galacturonic acid glycosylation.

For example, neighbouring-group participation at C-2 is essential for the highly stereoselective formation of 1,2-*trans*-glycosides *via* intermediate dioxolenium-ion formation because it effectively shields the α-face of the glycosyl donor [18]. In contrast, the synthesis of 1,2-*cis*-glycosides requires C-2-protecting groups without neighbouring-group participation (*e.g.*, azide or benzyl ether) [20]. Although axial glycosylation products are typically thermodynamically preferred owing to the anomeric effect, these reactions frequently yield anomeric mixtures [20].

Multiple synthetic strategies have been developed for incorporating uronic acid moieties into oligosaccharide structures [6,20–23]. Two main methodologies can be adopted for uronic acid incorporation: pre-glycosylation, employing pre-formed glycuronic acid building blocks during oligosaccharide assembly (discussed in Section 2), and post-glycosylation, involving the oxidation of hydroxyl groups into carboxylates after oligomer construction (discussed in Section 3). This review summarises representative examples of both synthetic approaches, systematically and comparatively analysing their respective merits and limitations. By integrating theoretical and experimental perspectives, a comprehensive framework for the targeted assembly of these biologically critical glycoconjugates is provided.

2. Pre-glycosidation oxidation strategies

In pre-glycosylation oxidation approaches, acidic oligosaccharides are assembled using appropriately protected glycuronic acid donors. Pre-glycosylation oxidation strategies enable the efficient assembly of α-GalA oligosaccharides by leveraging stereocontrolling elements, including remote participation effects, 4-*O*-glycosylated galacturonate donors, lactone-based donors and privileged donor architectures.

2.1. Stereocontrol via remote O-4-acyl participation in α-galacturonic acid glycosylation

Although traditionally overshadowed by the dominant effects of neighbouring groups at C-2, remote substituent participation has emerged as a notable factor for stereocontrol [18]. Reportedly, the effectiveness of D-GalA derivatives in α-GalA synthesis was considerably improved when a participating functional group was introduced at C-4 [24]. The main step towards product formation is the stabilisation of the reactive oxacarbenium ion *via* the formation of the bicyclic acyloxonium intermediate **3** (Scheme 1). Subsequent nucleophilic attack by the glycosyl acceptor selectively occurs from the bottom face owing to top-face steric obstruction.

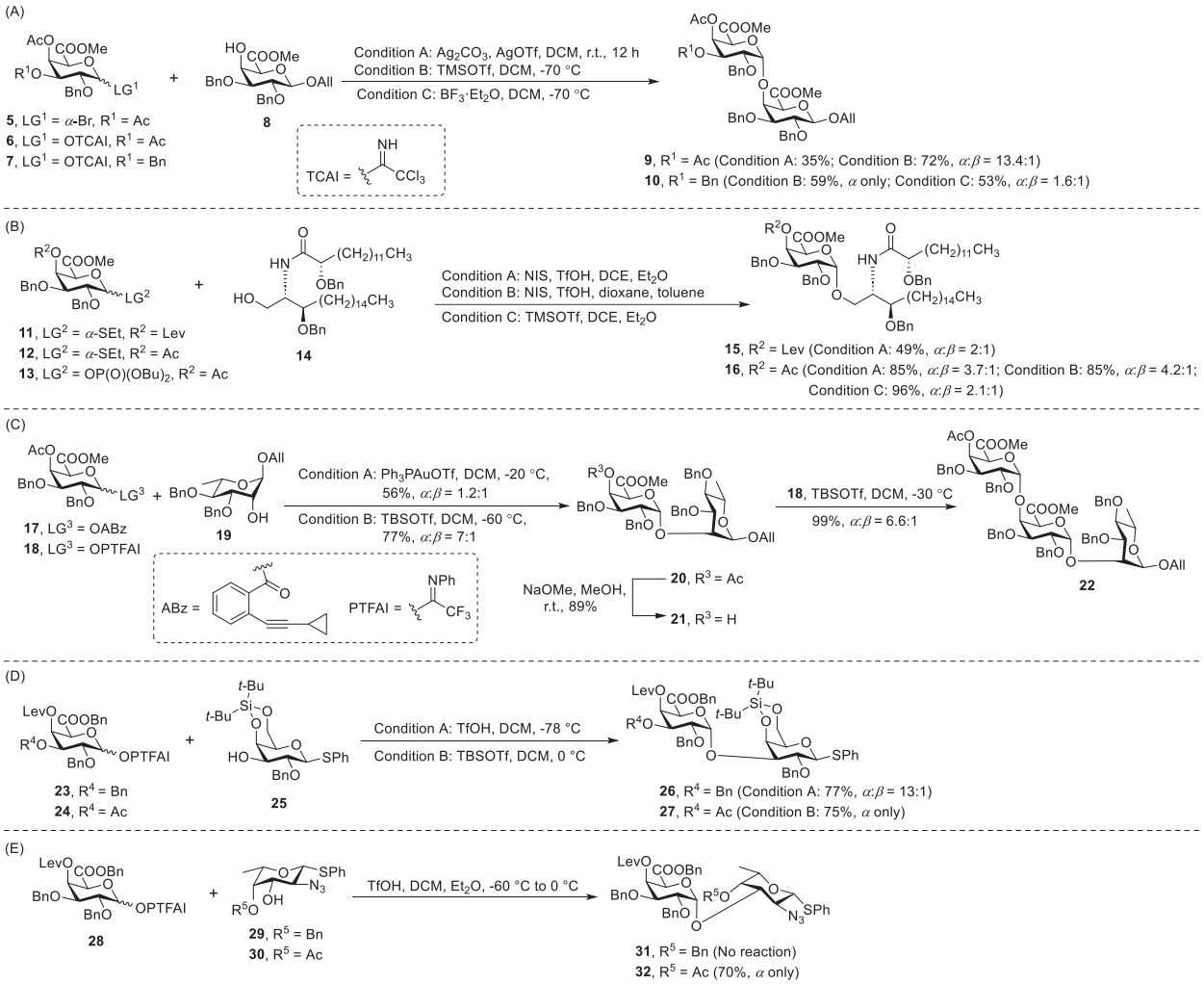
Vogel *et al.* reported the synthesis of homogalacturonan fragments using 4-*O*-acetyl-protected GalA donors [25,26]. Treatment of galacturonate bromide **5** with glycosyl acceptor **8** in the presence of silver triflate (AgOTf) and silver carbonate afforded disaccharide **9** in 35 % yield (Scheme 2A). Subsequently, the effect of C-3 and C-4 substituents in trichloroacetimidate (TCAI) galacturonate donors **6** and **7** on the glycosylation stereoselectivity was assessed. The glycosylation of 3,4-di-*O*-acetyl derivative **6** with acceptor **8** *via* trimethylsilyl trifluoromethanesulfonate (TMSOTf) activation afforded disaccharide **9** in 72 % yield and with good selectivity (α:β = 13.4:1). Contrary to previous cases, the more reactive glycosyl donor **7** reacted with acceptor **8** to afford disaccharide **10** in 59 % yield with exclusive α-selectivity. Finally, the glycosylation of **8** using donor **7** under activation with boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$) afforded disaccharide **10** in 53 % combined yield but with unsatisfactory stereocontrol (α:β = 1.6:1).

The synthesis of glycosphingolipids presents substantial synthetic challenges [21]. Seeberger *et al.* reported a streamlined synthesis of orthogonally protected D-GalA thioglycoside donors, and their application in assembling glycosphingolipids (Scheme 2B) [24]. Glycosylation using thioglycoside donors **11** and **12** with ceramide **14** in dichloroethane (DCE) and diethyl ether (Et_2O) containing *N*-iodosuccinimide (NIS) and trifluoromethanesulfonic acid (TfOH) gave the corresponding products **15** (49 %, α:β = 2:1) and **16** (85 %, α:β = 3.7:1), respectively. Furthermore, employing phosphate donor **13** enhanced the glycosylation yield but reduced the anomeric selectivity (96 %, α:β = 2.1:1). The low solubility of ceramide **14** in most solvents under cryogenic conditions limited these transformations. Systematic optimisation enabled an optimal balance between yield and stereoselectivity when using 4-*O*-acetyl protected thioglycoside **12** with NIS and TfOH activation in a dioxane–toluene (3:1) solvent mixture. This protocol afforded product **16** in 85 % yield with good selectivity (α:β = 4.2:1). These studies confirmed the advantageous effects of ether solvents and the stereodirecting influence of C-4 esters in galacto-configured systems for achieving high α-selectivity.

In the chemical synthesis of pectin-derived oligosaccharides, the incorporation of α-GalA linkages is challenging [7,27]. Yu *et al.* demonstrated the synthesis of *Nerium indicum* rhamnogalacturonan oligosaccharides *via* direct α-GalA coupling using their glycosyl donors under various activation conditions (Scheme 2C) [28]. Coupling attempts between *ortho*-alkynylbenzoate donor **17** and acceptor **19** using triphenylphosphine gold(I) triflate ($Ph_3PAuOTf$) as a catalyst produced disaccharide **20** in a moderate yield (56 %) at −20 °C but with minimal stereocontrol (α:β = 1.2:1). Notably, the glycosylation efficiency considerably decreased at temperatures below −20 °C owing to the insufficient activation of donor **17**. Under *tert*-butyldimethylsilyl triflate (TBSOTf) catalysis in dichloromethane (DCM), *N*-phenyl-2,2,2-trifluoroacetimidate (PTFAI) donor **18** reacted with acceptors **19** and **21** to afford disaccharide **20** (77 %, α:β = 7:1) and trisaccharide **22** (99 %, α:β = 6.6:1), respectively, with excellent yields and stereoselectivity.

The synthesis of *Streptococcus pneumoniae* serotype 1 (Sp1) polysaccharides encounters three principal obstacles: the incorporation of the rare 2-acetamido-4-amino-2,4,6-trideoxy-D-galactose, inherently poor reactivity of GalA donors in glycosylation reactions relative to their galactose analogues and stereochemical demand for establishing *cis*-glycosidic bonds throughout the oligosaccharide chain [29]. Codée *et al.* optimised a synthetic route for Sp1 oligosaccharides, achieving the stereocontrolled assembly from the trisaccharide to dodecasaccharide length (1–4 repeating units) [29,30]. The synthesis commenced with the challenging glycosylation of GalA **23** with galactose acceptor **25** (Scheme 2D). After an extensive condition screening, disaccharide **26** was obtained in 77 % yield with outstanding α-selectivity (13:1), demonstrating scalability to multi-gram quantities. Next, under TBSOTf activation, the coupling of 3,4-di-*O*-acyl-GalA donor **24** and galactose acceptor **25** afforded disaccharide **27** in 75 % yield and with complete α-selectivity.

Kuikarni *et al.* achieved the total synthesis of the tetrasaccharide repeating unit of *Shewanella japonica* type strain KMM 3299^T [31]. The tetrasaccharide synthesis process was particularly challenging because it required three consecutive *cis*-linkages bridging unusual amino sugars and D-GalA units. Attempts to achieve the glycosylation by employing known trifluoroacetamidate donor **28** and L-fucosamine acceptor **29** using TfOH in DCM and Et_2O at



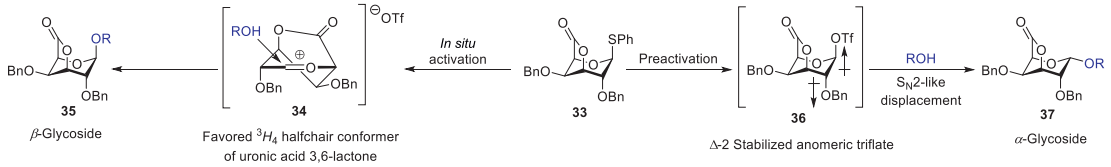
Scheme 2. Synthesis of 1,2-*cis*-glycosides using *O*-4-actyl-protected galactouronates donors.

temperatures ranging from −60 °C to 0 °C, failed to produce the desired disaccharide **31** (Scheme 2E). An aglycon transfer process occurred under the TfOH-catalyzed glycosylation conditions because of unmatched reactivities between the glycosyl donor and acceptor. Inspired by these observations, they employed a disarmed acceptor strategy comprising the coupling of donor **28** with L-fucosamine **30** under TfOH activation in DCM and Et_2O as a cosolvent, successfully obtaining disaccharide **32** in 70% isolated yield with exclusive α-selectivity.

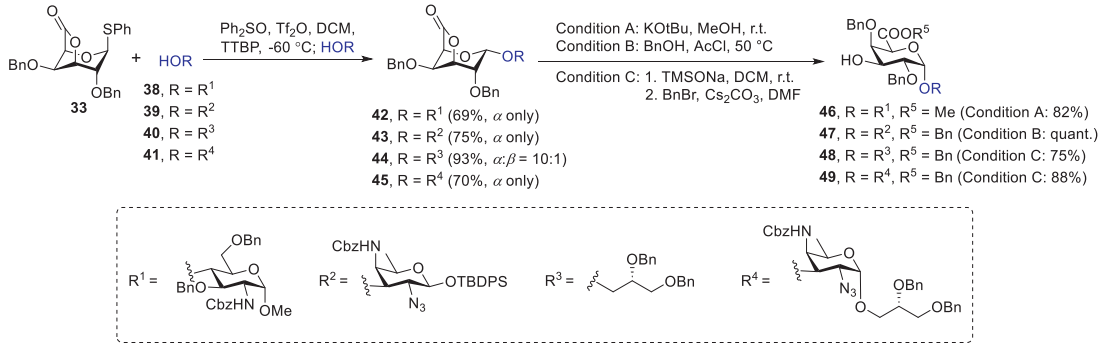
2.2. Stereoselective α-glycosylation using galacturonic acid 3,6-lactone thioglycosyl donors

Uronic acid 3,6-lactones are valuable building blocks for oligosaccharide synthesis, exhibiting conformational rigidity, distinctive reactivity patterns, and enhanced stereocontrol in glycosylation reactions [32–34]. Glycosylation stereocontrol is particularly challenging because of the concurrent operation of competing S_N1-like and S_N2-like mechanisms generating opposite diastereomers and the inherent lack of stereoselectivity in the S_N1-type pathway [35]. The pre-activation of GalA 3,6-lactone thioglycoside donor **33** generates reactive anomeric β-triflate intermediate **36**, which has been characterised *via* low-temperature NMR spectroscopy (Scheme 3) [34]. This intermediate can be displaced in an S_N2-like process to afford α-linked product **37**. In the *in situ* activation process, β-linked product **35** is obtained *via* a reactive intermediate resembling a $^3H_4$ oxocarbenium ion.

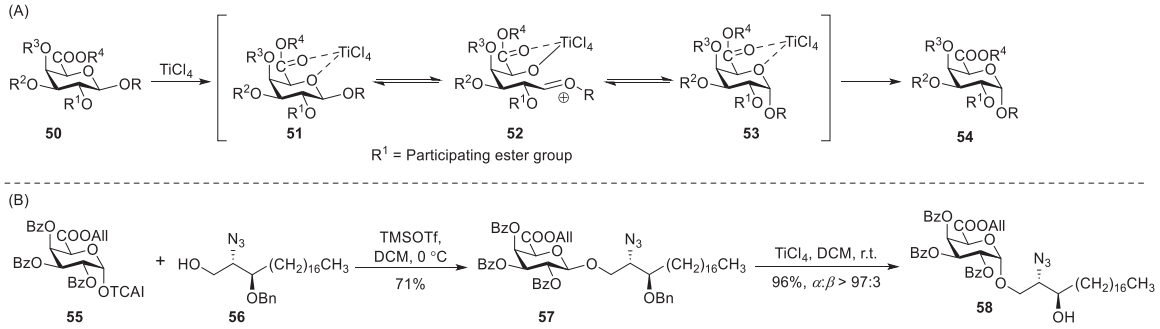
In 2005, Van der Marel *et al.* reported the synthesis of disaccharide **42** in 69% yield with complete α-selectivity *via* the pre-activation of donor **33** with diphenyl sulfoxide (Ph_2SO) and trifluoromethanesulfonic anhydride (Tf_2O) in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP) at −60 °C followed by glycosylation with acceptor **38** (Scheme 4). The selective opening of benzylated lactone **42** using potassium *tert*-butoxide (KO*t*Bu) in anhydrous methanol (MeOH) gave disaccharide acceptor **46** in 82% isolated yield [32]. Codée *et al.* successfully prepared all three frame-shifted trisaccharide repeats of the zwitterionic polysaccharide Sp1 using 1-thiogalacturonic acid lactones as crucial glycosyl donors and acceptors [19]. The pre-activation of donor **33** with *in situ* formed β-triflate followed by coupling with acceptors **39**, **40** and **41** afforded disaccharides **43** (75%, α only), **44** (93%, $\alpha:\beta = 10:1$) and **45** (70%, α only), respectively. Treatment of lactone **43** with benzyl alcohol under acidic conditions provided disaccharide acceptor **47** in a quantitative yield. Unexpectedly, attempts to open lactone **44** and **45** using benzyl alcohol under acidic conditions did not yield the desired product. The lactone rings of **44** and **45** were cleaved using sodium trimethylsilanolate (TMSONa) to generate the free acid intermediates, which were benzylated with benzyl bromide (BnBr) and caesium carbonate (Cs_2CO_3) to yield disaccharide acceptors **48** (75%) and **49** (88%); these disaccharide acceptors function as piv-



Scheme 3. Proposed glycosylation intermediates of uronic acid 3,6-lactone glycosyl donor **33**.



Scheme 4. Proposed glycosylation intermediates of uronic acid 3,6-lactone glycosyl donor.



Scheme 5. Synthesis of α-linked galacturonic acid glycolipids *via* $TiCl_4$-induced anomerisation.

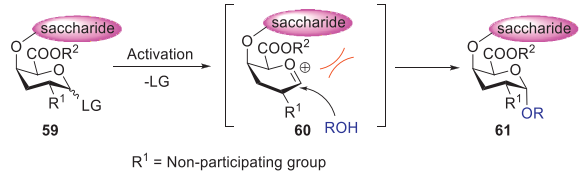
otal synthetic intermediates for assembling the desired trisaccharide repeating motifs.

2.3. Stereoselective anomerisation promoted by titanium tetrachloride ($TiCl_4$)

Murphy *et al.* circumvented the challenging direct α-glycosylation of GalA by developing innovative indirect synthetic strategies [36–38]. The synthesis involved two key steps: establishing 1,2-*trans*-β-glycosidic linkages *via* neighbouring 2-acyl group participation and subsequent construction of α-linked uronic acid glycolipids through $TiCl_4$-mediated chelation-controlled anomerisation (Scheme 5A) [36]. The coupling of TCAI donor **55** and acceptor **56** using TMSOTf activation proceeded with exclusive β-selectivity to produce **57** in 71 % yield (Scheme 5B). Subsequent $TiCl_4$-mediated anomerisation efficiently converted β-glycoside precursor **57** to α-anomer **58** with excellent selectivity (α:β > 97:3). Notably, although $TiCl_4$ cleaved the sphinganine benzyl group, anomerisation occurred faster, enabling the isolation of benzyl-protected α-anomers [38].

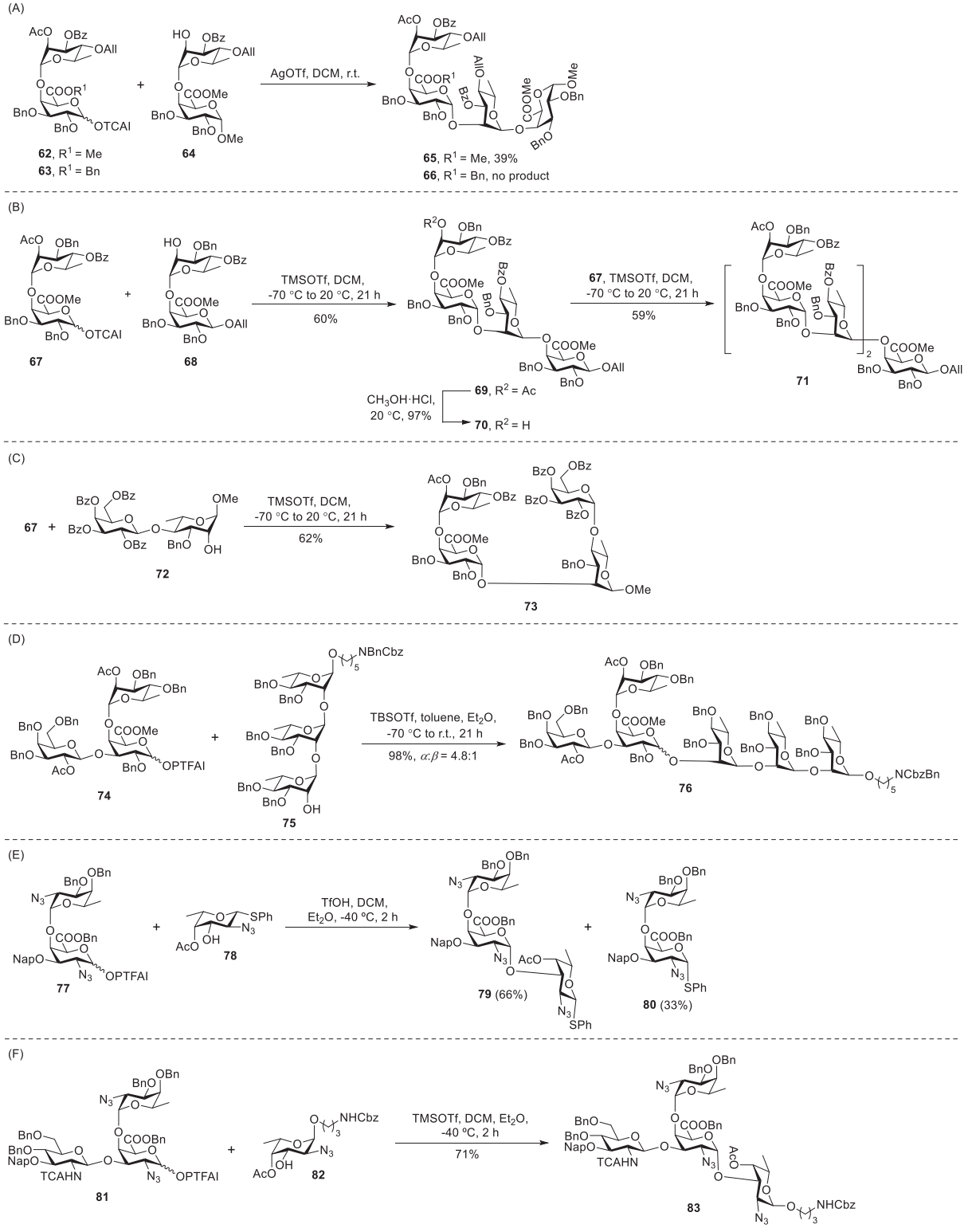
2.4. Stereoselective α-glycosylation using 4-O-glycosylated galacturonate donors

Numerous efficient synthetic routes enabling 1,2-*cis*-glycosidic bond formation have been reported. To modulate the stereochemical outcome of glycosylation reactions, steric hindrance can be introduced by attaching protecting groups to the donor [20]. For instance, the high steric hindrance effect of protecting groups at the C-4 position of completely protected oligogalacturonate donors can influence glycosylation stereoselectivity by hindering access to the β-face of the oxacarbenium ion, further promoting nucleophilic attack from the opposite, less hindered side (Scheme 6). Thus, glycosylation using galactonic acid donors containing C-4-attached oligosaccharides preferentially yields α-configured products.



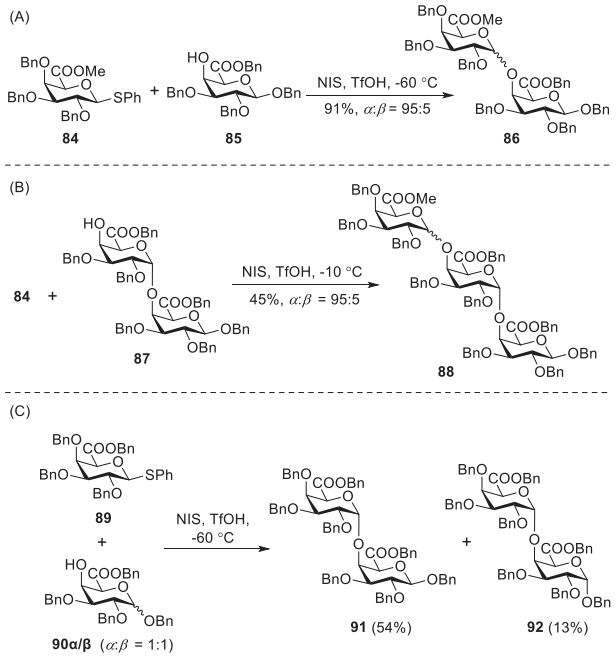
Scheme 6. Stereoselective α-glycosylation enabled by bulky *O*-4 substituents.

Oligosaccharide fragments of rhamnogalacturonan I (RG-I) can be prepared *via* various synthetic approaches [7]. For instance, Reimer *et al.* developed a synthetic route to the tetrasaccharide fragment of the RG-I backbone (Scheme 7A) [39]. The glycosylation step that converted disaccharide acceptor **64** into the target tetrasaccharide structure presented substantial challenges. By employing silver triflate (AgOTf) as a promoter, acceptor **64** was glycosylated with imidate donors **62** and **63** to form the target tetrasaccharide. The reaction, however, achieved low yields, providing **65**



Scheme 7. Synthesis of α-linked oligosaccharides using 4-*O*-glycosylated galacturonate donors.

in 39% yield and **66** in the impure form. Further, multiple purification steps required for the removal of unreacted acceptor **64** from the desired tetrasaccharide **65** led to low yields. Despite numerous efforts to optimise the synthetic strategies, the efficiency of glycosyl acceptors conversion into tetrasaccharide products remains unsatisfactory. Vogel *et al.* utilised an analogous synthetic strategy to produce RG-I oligosaccharide fragments [40]. TMSOTf-promoted glycosylation of acceptor **68** with an equimolar amount of donor **67** afforded tetrasaccharide **69** in 60% isolated yield after chromatographic purification (Scheme 7B). Meanwhile, glycosylation of acceptor **70** with donor **67** afforded hexasaccharide **71** in 59% isolated yield following HPLC purification. The β-anomers were detected (<5% NMR yield) in crude glycosylation mixtures, but the low isolated yields prevented their full characterisation. Glycosyla-



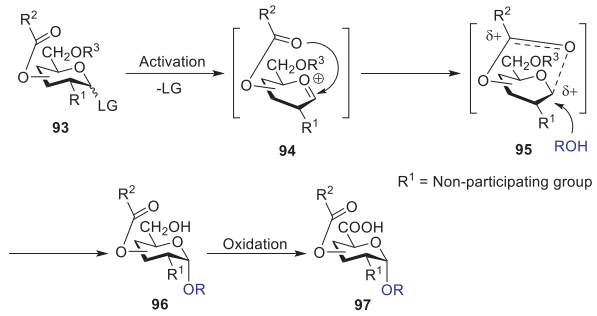
Scheme 8. Synthesis of α-linked oligosaccharides using thioglycoside as donors.

tion of acceptor **72** with rhamnogalacturonate donor **67** afforded tetrasaccharide **73** in 62 % yield (Scheme 7C). A minor amount of β-linked isomer (<5 %) was detected in the crude mixture by NMR spectroscopy.

The PTFAI donors are the most extensively investigated for glycosylation reactions in contemporary carbohydrate chemistry [13,41]. Seeberger *et al.* reported a convergent [3 + 3] glycosylation strategy for assembling the hexasaccharide repeating unit of *Klebsiella pneumoniae* using a trisaccharide PTFAI donor (Scheme 7D) [42]. After optimisation, PTFAI donor **74** and acceptor **75** efficiently underwent glycosylation in toluene and Et_2O at −70 °C to afford hexasaccharide **76** in 98 % yield with good stereocontrol (α:β = 4.8:1). Kulkarni *et al.* reported the first chemical synthesis of *Acinetobacter baumannii* strains **34** and O5 tetrasaccharide units in a conjugation-ready form using oligosaccharide PTFAI donors to establish challenging 1,2-*cis*-linkages [43]. TfOH-promoted glycosylation of PTFAI donor **77** with L-fucosamine acceptor **78** in DCM and Et_2O at 0 °C afforded trisaccharide **79** (50 %) and aglycone-transfer product **80** (50 %) (Scheme 7E). Notably, disaccharide side-product **80** could be successfully reutilised to prepare imidate **77**. When the temperature was reduced to −40 °C as per established protocols, the yield of **79** increased to 66 % and that of **80** decreased to 33 %. PTFAI donor **81** underwent TMSOTf-promoted coupling with acceptor **82** at −40 °C to yield branched tetrasaccharide **83** with full functionality (Scheme 7F).

2.5. Effect of the anomeric configuration of the galacturonic acid acceptor on α-glycosidation

Literature reports indicate that glycosyl acceptors also play a critical role in determining glycosylation stereoselectivity [18]. Doutheau *et al.* demonstrated the highly stereoselective $\alpha(1\rightarrow4)$ coupling of D-GalA esters using phenylthioglycoside donors, thereby achieving good yields [44,45]. The NIS–TfOH-promoted glycosylation of thioglycoside donor **84** with acceptor **85** at −60 °C afforded product **86** (91 %, α:β = 95:5) with excellent stereoselectivity and high yield (Scheme 8A). TLC monitoring revealed that the reaction of disaccharide acceptor **87** with 2 equiv. of glycosyl donor **84** was sluggish at −60 °C, whereas increasing the temperature to −10 °C afforded target trimer **88** (45 %) along with **87** (50 %) (Scheme 8B) [44]. Doutheau demonstrated that the reactivity of galactosiduronic acid acceptors bearing a free C-4 hydroxyl group is strongly influenced by their anomeric configuration (Scheme 8C) [46]. TLC monitoring showed faster consumption of **90*β*** during the competitive glycosylation of acceptor mixture **90*α*/*β*** (α:β, 0.5:0.5 equiv.) with donor **89** (0.6 equiv.) under standard conditions. The isolated product mixture contained **91** (54 %) and **92** (13 %). Theoretical calculations indicated that the higher reactivity of the β-anomer than that of the α-form could be attributed to the more robust hydrogen bond between the C-4 hydroxyl group and the ring oxygen.

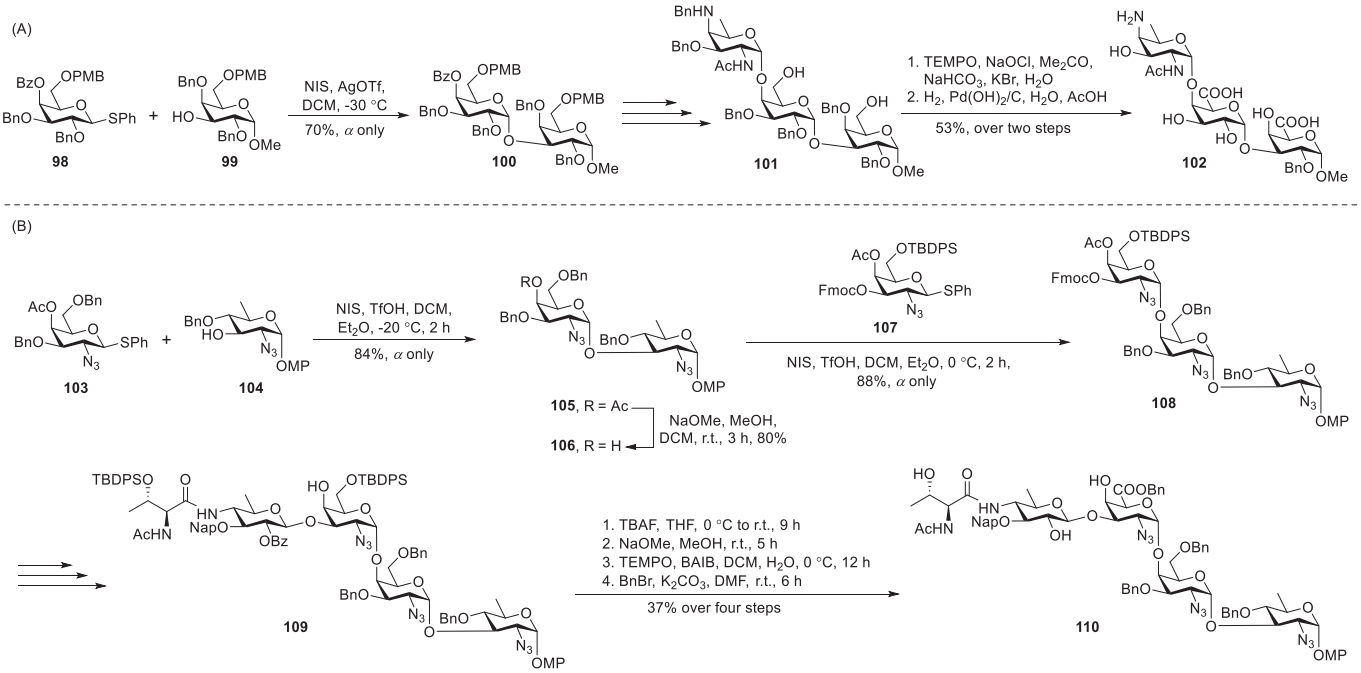


Scheme 9. Preparation of α-galacturonic acid glycosides *via* the remote participation effect using a galactose donor.

3. Post-glycosylation oxidation strategies

3.1. Stereoselective synthesis of α-galacturonic acid glycosides via the remote participation effect

The development of efficient glycosylation methodologies represents a critical challenge in α-GalA synthesis owing to the low reactivity of uronic acid derivatives, which typically leads to suboptimal coupling yields. The predominant indirect synthetic strategy for α-GalA oligosaccharides involves assembling the galactose oligosaccharide backbone followed by elective oxidation of specific primary hydroxyl groups to carboxylic acids. Protecting groups profoundly influence the reactivity and stereoselectivity; therefore, a comprehensive understanding of their effects is essential for rationalising and controlling the glycosylation outcome [20]. Numerous studies have reported stereoselective α-galactosylation reactions directed by remotely participating protecting groups at the C-3, C-4 and/or C-6 positions [47–51]. This through-space interaction leads to the stabilisation of the reactive intermediate and achieves stereochemical control, with acetyl groups shielding the β-face and promoting α-face selectivity in the glycosylation (Scheme 9) [52]. Notably, the C-4 substituent exerts greater stereocontrol than that the C-6 substituent in these glycosylation reactions [50]. Three effective approaches have been proposed for boosting 1,2-*cis* selectivity: (i) Supplementing donors having one remotely participating group with a second acyl substituent, (ii) tuning remotely acyl groups to increase the nucleophilicity of the carbonyl oxygen and (iii) appending sterically hindered side chains to participating acyl moieties [52]. However, the over-introduction of remotely participating acyl groups may reduce the 1,2-*cis* selectivity by stabilising the α-triflate intermediate, subsequently favouring β-product formation *via* nucleophilic substitution [52]. Primary alcohols can be oxidised to carboxylic acids using diverse methods, including the Dess–Martin/$NaClO_2$ system, Swern–$NaClO_2$ protocol, strongly acidic Jones reagent, milder pyridinium dichromate and pyridinium chlorochromate reagents or 2,2,6,6-



Scheme 10. Synthesis of α-linked galacturonic acid oligosaccharides using 4-*O*-acyl-protected galactose donors.

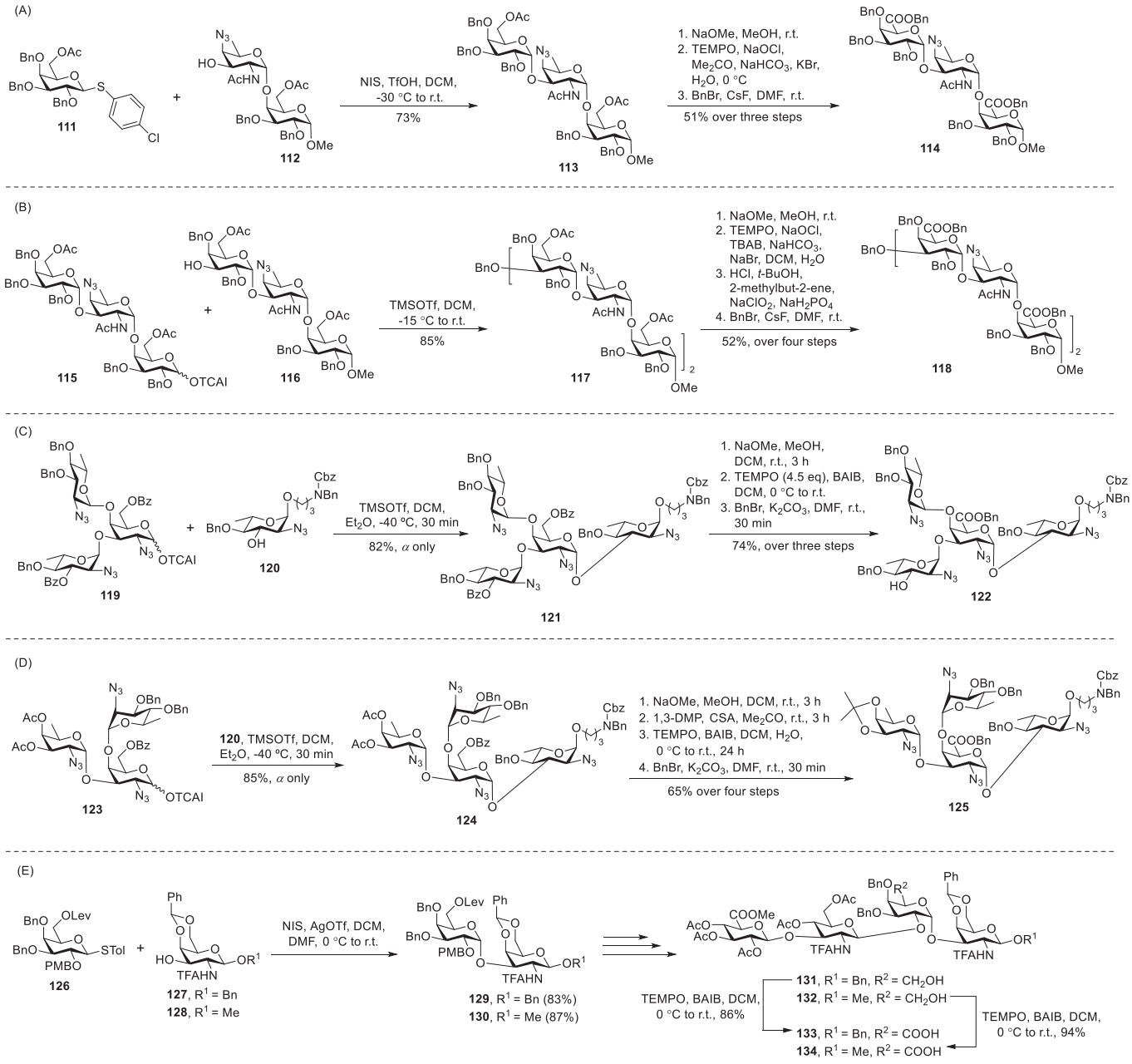
tetramethylpiperidinooxy (TEMPO)-mediated catalysis, which offer distinct selectivity and compatibility [6].

4-*O*-Acylated galacto-configured donors can be used to produce complex GalA oligosaccharides, demonstrating their utility in natural product synthesis. Bundle *et al.* developed an indirect synthesis method of the trisaccharide repeat of a zwitterionic Sp1 capsular polysaccharide (Scheme 10A) [53]. The glycosylation between donor **98** and acceptor **99** was systematically evaluated under multiple activation conditions. Initial attempts using Ph_2SO–Tf_2O as the activator system afforded disaccharide **100** in suboptimal yields ($\leq$30%), prompting investigation of alternative conditions. Although NIS–TfOH activation at −30 °C improved the yield to 57%, the optimal result was achieved using NIS–AgOTf, which afforded disaccharide **100** in 70% yield. Next, target trisaccharide **101** was isolated after sequential coupling reactions. Oxidation of diol **101** under TEMPO conditions generated the corresponding diacid, which was totally de-protected *via* hydrogenolysis to obtain **102** in 53% overall yield.

Kulkarni *et al.* reported the comprehensive total synthesis of the *Vibrio cholerae* O43 tetrasaccharide repeating unit using a 4-*O*-acetyl-protected galacturonate donor (Scheme 10B) [54]. Glycosylation of D-quinosamine acceptor **104** with D-galactosamine thioglycoside **103** using NIS and TfOH in DCM and Et_2O (1:1) at −20 °C afforded α-linked disaccharide **105** in 84% yield as a single stereoisomer. Treatment of **105** with NaOMe in DCM and MeOH at room temperature afforded deacetylated acceptor **106** in 80% yield. Glycosylation of acceptor **106** with D-galactosamine thioglycoside **107** under NIS–TfOH activation at 0 °C exclusively provided α-linked trisaccharide **108** in 88% yield. The stereocontrol originated from the participation of the Et_2O solvent in the reaction at low temperatures combined with 4-*O*-acetyl neighbouring-group assistance, guiding the acceptor to approach the α-face of the oxocarbenium ion. After the controlled regio- and stereoselective synthesis of tetrasaccharide **109**, subsequent transformation into target derivative **110** was achieved. Selective removal of the *tert*-butyldiphenylsilyl (TBDPS) and benzyl protecting groups cleanly afforded the intended *tetra*-hydroxylated product. Furthermore, the primary alcohol was selectively oxidised using TEMPO–(diacetoxyiodo)benzene (BAIB) in a DCM–H_2O system, followed by esterification with BnBr and sodium bicarbonate ($NaHCO_3$) in *N*,*N*-dimethylformamide (DMF) to afford benzyl-protected derivative **110**.

Bundle *et al.* synthesised an Sp1 capsular hexasaccharide using 6-*O*-acetyl-protected galactosyl donors [55]. Under NIS–TfOH activation at −30 °C in DCM, the coupling between disaccharide acceptor **112** and thiogalactoside donor **111** efficiently proceeded to afford target trisaccharide **113** in 73% isolated yield (Scheme 11A). ^{1}H NMR analysis revealed the presence of only trace amounts of the β-anomeric galactose; this α-anomeric preference most likely resulted from the stereoelectronic influence exerted by the C-6 substituent (the acetyl group). The exposed hydroxymethyl groups, generated *via* deacetylation of **113**, underwent simultaneous oxidation using TEMPO and sodium hypochlorite (NaOCl) to form uronic acid groups. Subsequent benzylation of these acidic groups enabled an efficient purification, affording target compound **114** in 51% overall yield. Hexasaccharide **117** was obtained in 85% yield *via* the TMSOTf-mediated glycosylation of trisaccharide building blocks **115** and **116** at room temperature (Scheme 11B). This high efficiency was achieved by carefully optimising the temperature and molar equivalents of the glycosyl donor and Lewis acid.

Gao *et al.* achieved the inaugural chemical synthesis of the structurally complex tetrasaccharide motifs present in the capsular polysaccharides of *Vibrio vulnificus* strains MO6-24 and BO62316 through post-glycosylation oxidation [56]. An optimised TEMPO–BAIB oxidation system was established for the direct transformation of α-D-galactosamine into α-D-aminogalacturonic acid residues, demonstrating the successful application to di-, tri- and tetra-saccharide substrates. The TMSOTf-mediated coupling between donor **119** and acceptor **120** in a DCM–Et_2O mixture at −40 °C proceeded with unanticipated efficiency to exclusively afford tetrasaccharide **121** as the α-anomer in 82% isolated yield (Scheme 11C). Selectively oxidising specific hydroxyl moieties in complex oligosaccharide frameworks is highly challenging. Fortunately, the TEMPO-mediated oxidation (0.2 equiv.) of the 6′-hydroxyl group proceeded exceptionally well when using BAIB (4.5 equiv.) in a DCM–H_2O system, affording target carboxylate



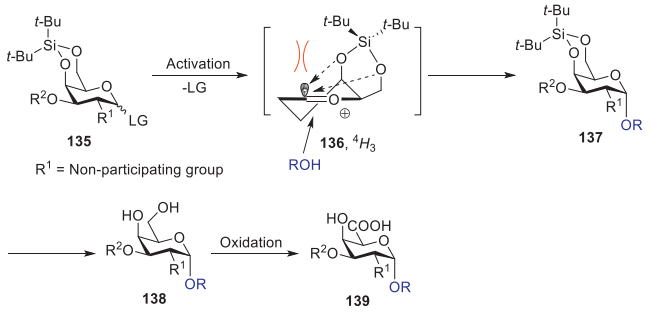
Scheme 11. Synthesis of α-linked oligosaccharides using 6-*O*-acyl-protected galactosyl donors.

122 in excellent yield. Consistent with previous results, the coupling of donor **123** and acceptor **120** proceeded with complete α-selectivity, yielding tetrasaccharide **124** in 85 % yield (Scheme 11D). After sequential acetylation and isopropylation steps, an optimised TEMPO–BAIB oxidation system efficiently generated target uronate **125** in excellent yield.

Li *et al.* established a productive semi-synthetic approach for preparing *Colwellia psychrerythraea* 34H capsular tetrasaccharide derivatives using disaccharide building blocks obtained *via* hyaluronic acid degradation [57]. The levulinoyl protecting group was strategically incorporated at C-6 to exploit its ability to stereocontrol 1,2-*cis*-linkages through remote anchimeric assistance. Donor **126** and acceptors **127** and **128** were prepared, after which established glycosylation methods were evaluated to optimise reaction yield and diastereoselectivity (Scheme 11E). The combination of NIS and AgOTf in DCM–DMF was selected as the optimal system, affording disaccharide **129** (83 %) and its counterpart **130** (87 %). From tetrasaccharides **131** and **132**, carboxyl-bearing tetrasaccharides **133** and **134** were obtained *via* TEMPO-catalysed oxidation in 86 % and 94 % isolated yields, respectively.

3.2. Stereoselective synthesis of α-galacturonic acid glycosides using 4,6-protected galactosyl donors

Sterically demanding protecting groups considerably affect the glycosylation stereochemistry and efficiency [20]. Kiso *et al.* demonstrated that the presence of the bulky 4,6-*O*-di-*tert*-butylsilylene (DTBS) group on the galactosyl donor promoted the α-selective galactosylation, overriding the influence of a participating substituent present at C-2 [58]. Notably, the DTBS moiety demonstrated exceptional and distinct stereocontrol capabilities compared with other cyclic protecting groups. A galactosyl donor featuring a six-membered cyclic protecting group between *O*-4 and *O*-6 predominantly adopts the $^4H_3$ conformation when



Scheme 12. Synthesis of α-galacturonic acid glycosides using 4,6-*O*-di-*tert*-butylsilylene-protected galactosyl donors.

converted to the oxocarbenium ion (Scheme 12) [20]. Bulky alkyl groups within the DTBS protecting framework sterically hinder nucleophilic attack from the β-direction and influence the stability of transition state **136** *via* through-space charge delocalisation.

Kováč *et al.* described the chemical synthesis of an O-antigen pentasaccharide from *Vibrio cholerae* O139 [59]. They employed post-glycosylation oxidation to establish α-GalA linkages using a 4,6-*O*-di-*tert*-butylsilylidene galactopyranosyl donor **140** for stereocontrol. Nearly complete α-selectivity was achieved in the galactosylation of **141** with donor **140** (Scheme 13A). The challenging separation of β-anomeric impurities was avoided by performing purification after removing the 4,6-*O*-protecting groups, yielding essential α-product **142** with 73% efficiency. Target tetrasaccharide **143** was obtained through multiple synthetic steps. The carboxyl group generated *via* the TEMPO-mediated oxidation of **143** was subsequently esterified using methyl iodide (MeI) and $NaHCO_3$, affording trisaccharide **144** in 90% overall yield.

Codée *et al.* prepared the capsular polysaccharide repeating unit of *Staphylococcus aureus* strain M containing α-galactosaminuronic acid residues [60]. The coupling of donor **145** with acceptors **146** and **148** in the presence of NIS and TMSOTf smoothly proceeded to exclusively afford α-configured products **147** (82%) and **149** (88%), respectively (Scheme 13B). To prevent the glycosidic bond cleavage observed during TEMPO–BAIB oxidation of a disaccharide intermediate, a sequential approach using TEMPO–BAIB–Pinnick oxidation was successfully implemented. In 2019, the researchers established an efficient synthetic strategy for constructing extended Sp1 oligosaccharide structures [29]. The condensation of silylene-protected trisaccharide donor **151** with allylcarbinol **152** efficiently proceeded to afford trisaccharide **153** in 82% yield as a single stereoisomer, demonstrating the exceptional glycosylation capability of this donor structure (Scheme 13C). Trisaccharide **151** served as a versatile precursor for assembling higher oligomers ranging from hexasaccharides to dodecasaccharides. The TEMPO–BAIB system successfully oxidised trisaccharide **153**; however, attempts to functionalise larger oligosaccharides failed, highlighting the inherent challenges in performing concurrent oxidations at multiple sites. Through systematic optimisation, alkaline conditions considerably enhanced the oxidation process. Consequently, extended oligosaccharides were successfully oxidised using TEMPO–BAIB in combination with $NaHCO_3$.

Ragains *et al.* achieved the complete chemical synthesis of an all-1,2-*cis*-configured repeating segment from a *Acinetobacter baumannii* D78 capsular polysaccharide [61]. The reaction between DTBS-protected PTFAI **155** and acceptor **156** proceeded efficiently using TfOH activation, yielding disaccharide **157** in excellent yield (83%) with complete stereocontrol (Scheme 13D). The synthetic sequence involved cleavage of the DTBS group, carboxyl-group introduction *via* oxidation and $TMSCHN_2$-mediated methylation, affording disaccharide **158** in 61% overall yield.

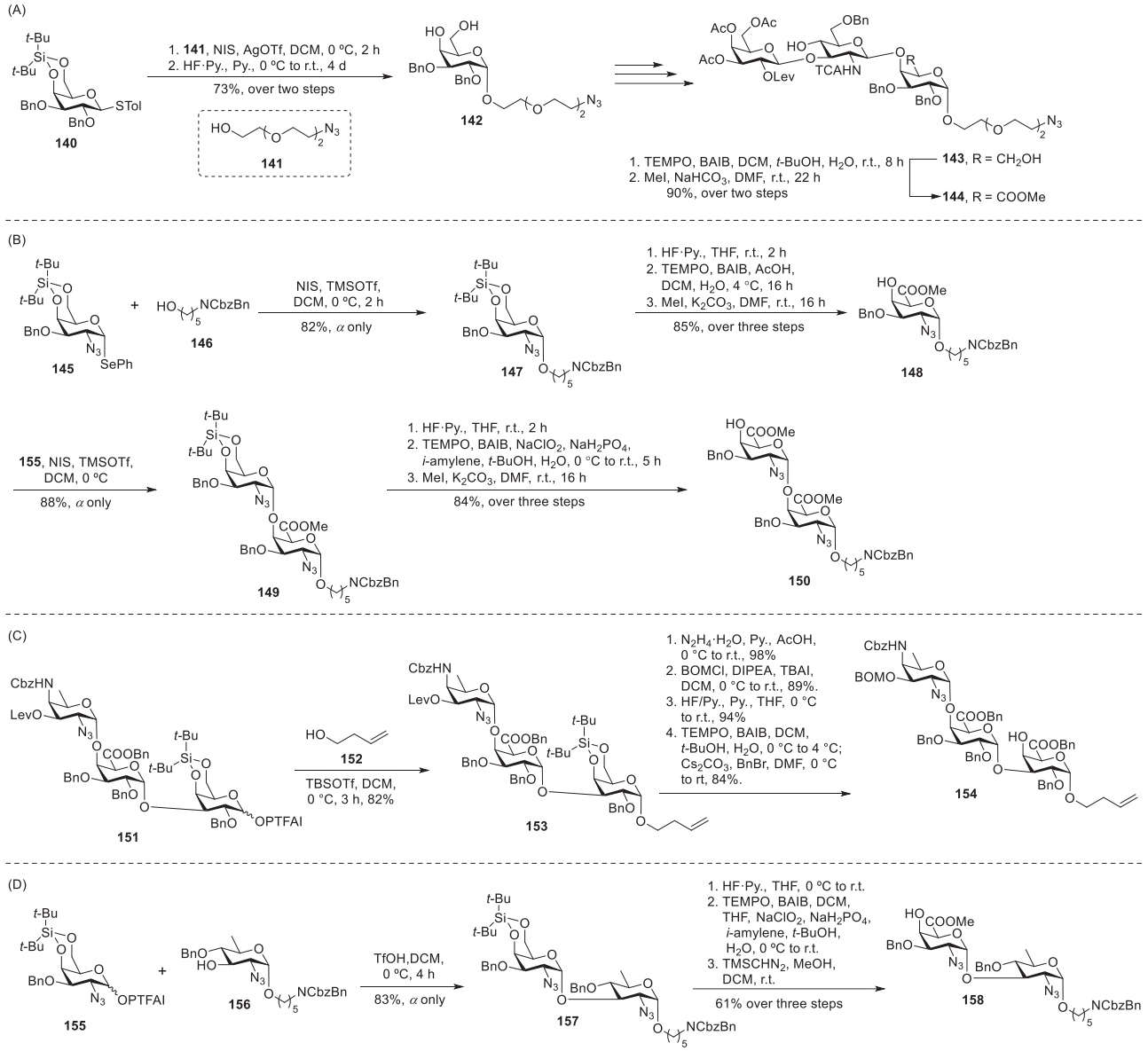
The torsional strain introduced by cyclic protecting moieties can profoundly affect anomeric selectivity during glycosylation [18]. This control is exemplified by the use of 4,6-*O*-benzylidene acetal protection to selectively generate β-mannosides [62–64], α-glucosides [65], and β-rhamnosides [66]. Furthermore, 4,6-*O*-benzylidene-protected galactosyl donors exhibit pronounced α-selectivity, as the *cis*-decalin conformation featuring an equatorially oriented phenyl group effectively blocks nucleophilic attack from the β-face [67–70]. Calenbergh *et al.* developed a synthetic strategy to access α-galacturonic-acid-modified KTHF RN7000 analogues (Scheme 14A) [71]. The Schmidt glycosidation method afforded compound **161** with excellent α-selectivity along with a small amount of β-anomeric by-products, which were easily removed *via* flash column purification [72]. Subsequently, the 6-hydroxy groups of **162** and **163** were selectively converted to carboxyl groups *via* TEMPO-mediated BAIB oxidation, furnishing galacturonates **164** and **165**, respectively [71].

Kulkarni *et al.* developed an efficient synthetic route employing 4,6-*O*-benzylidene-protected D-galactosamine donors to access oligosaccharide repeating units of *Staphylococcus aureus* strain M [73], *Proteus penneri* 26 [74], *Proteus vulgaris* TG155 [74], *Vibrio cholerae* O43 [75] and *Vibrio vulnificus* MO6-24 [76]. Thiogalactoside donors **166** and **167** were activated with NIS–TMSOTf in DMF to generate intermediate imidates, followed by *in situ* addition of linker acceptor **168** to yield 1,2-*cis*-configured galactosamine derivatives **169** (72%) and **170** (86%), respectively, with complete stereocontrol (Scheme 14B). Acidic cleavage of the benzylidene acetal afforded diol **171**, which was subjected to TEMPO-catalysed oxidation of its primary alcohol followed by benzyl ester formation to yield **172** in 68% overall yield for the two-step sequence. Applying this methodology, disaccharide **176** and tetrasaccharides **181** and **185** were efficiently prepared with high stereoselectivity and excellent yields (Schemes 14C–E).

Notably, natural L-galactosaminuronic acid residues have been exclusively observed in the α-anomeric form among all characterised bacterial glycans [8]. Yin *et al.* developed a synthetic route to conjugation-capable trisaccharide motifs of *Pseudomonas aeruginosa* serotype O10 and O19 O-antigens, featuring α-linked L-galactosaminuronic acid residues [77]. The glycosylation between selenoglycoside donor **186** and acceptor **188** mediated by NIS–TfOH in DCM at 0 °C afforded α-linked disaccharide **189** as the sole product, albeit in modest yield (43%). The pronounced α-selectivity stemmed from the synergistic combination of the conformational constraint of the 4,6-*O*-benzylidene group and inherent anomeric stabilisation. However, using selenophenyl as the leaving group for L-$GalN_3$ donors reduced the glycosylation efficiency. Satisfactorily, the glycosylation between acceptor **188** and the more potent FTFAI donor **187** catalysed by sub-stoichiometric TMSOTf yielded α-linked product **189** in a markedly improved yield of 78%.

3.3. Stereoselective synthesis of α-galacturonic acid glycosides using 2,3-N,O-oxazolidinone-protected galactosyl donors

The 2,3-oxazolidinone protection strategy pioneered by Kerns *et al.* has enabled the highly stereoselective synthesis of diverse 1,2-*cis*-2-amino-2-deoxyglycosides [20,78]. For instance, Ye *et al.* developed an efficient method for the synthesis of α-(1→4)-linked GalNAcA repeating units characteristic of the *Salmonella typhi* capsular polysaccharide [79,80]. The combination of the 2,3-*N*,*O*-oxazolidinone protecting group strategy with pre-activation enabled glycosylations with complete α-anomeric control. Employing Ph_2SO–Tf_2O activation with sterically hindered TTBP as a base, disaccharide **193** was exclusively obtained as the α-anomer in 72% isolated yield (Scheme 15). Removal of the oxazolidinone and TBS protecting groups of **193** under basic conditions followed by

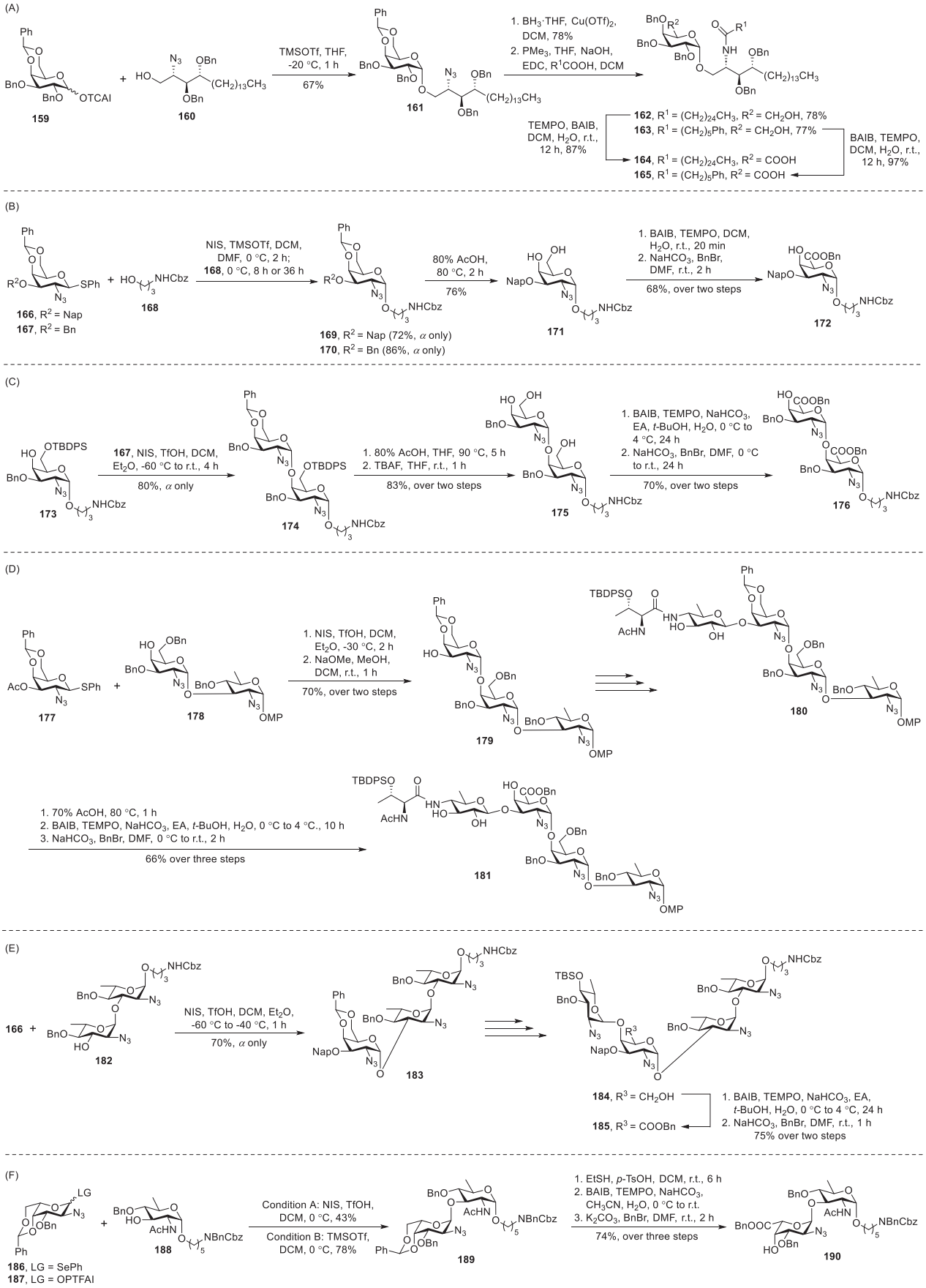


Scheme 13. Synthesis of α-galacturonic acid glycoside using DTBS-protected galactosyl donors.

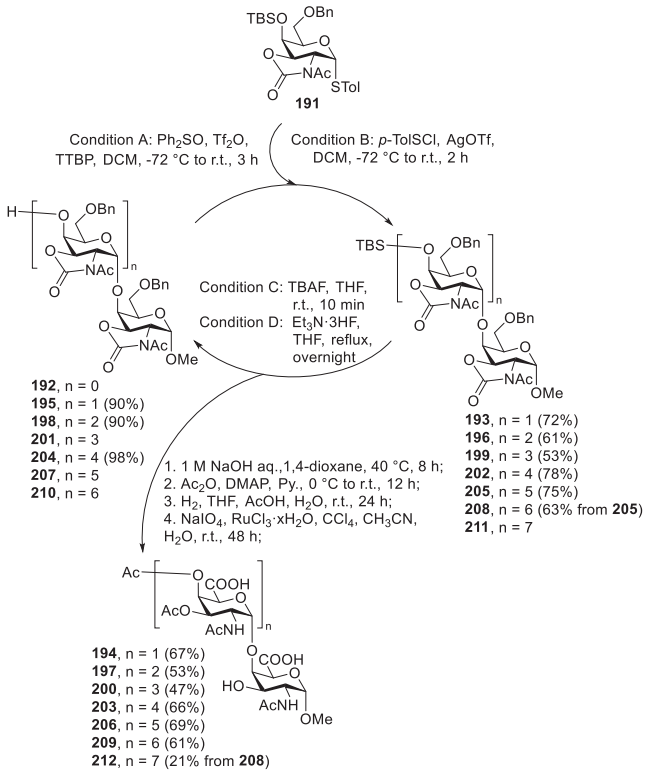
acetylation efficiently produced an intermediate compound, which was subjected to Pd/C-mediated hydrogenolysis and ruthenium chloride ($RuCl_3$)–sodium periodate ($NaIO_4$) oxidative cleavage to afford target disaccharide **194**. By performing iterative cycles of glycosylation, deprotection and oxidation, oligosaccharides ranging from tri- to octa-saccharides were successfully synthesised.

3.4. Stereoselective synthesis of α-galacturonic acid glycosides via steric hindrance at O-6

The steric effect of protecting groups on glycosyl donors can direct glycosylation stereochemistry by shielding one face of the molecule, promoting nucleophilic attack from the unhindered side [20]. One of the various α-directing galactosylation strategies includes using galactose donors containing bulky *O*-6 protecting groups such as TBDPS ethers [81]. The synthesis of glycolipid **215** was accomplished by Savage *et al.* in a moderate yield *via* glycosidic coupling followed by selective galactose oxidation to the corresponding uronic acid derivative (Scheme 16A) [82]. The synthetic sequence commenced with the Ph_2SO–Tf_2O-promoted coupling of donor **213** and acceptor **214**, followed by sequential TBDPS deprotection, TEMPO-mediated oxidation and esterification to yield target compound **215**. Bedini *et al.* developed a synthesis method for producing the capsular polysaccharide repeating unit of *Colwellia psychrerythraea* 34H using 6-*O*-TBDPS galactoside donors for controlled glycosylation [83]. Under NIS–TfOH activation, donor **216** generated intermolecular adduct **218** (74% yield from **217**) and intramolecular C-glycoside **219** (50% yield from **216**), indicating that the flexible oxonium species favoured a bimolecular reaction with the acceptor, except in the presence of excess donor (Scheme 16B). After sequential transformations, tetrasaccharide **220** was obtained. Subsequent HF–pyridine-mediated desilylation afforded an alcohol, which underwent TEMPO-catalysed oxidation to the corresponding carboxylic acid product **221**. Kulkarni *et al.* reported the pioneering total synthesis of the trisaccharide repeating elements of *Pseudomonas chlororaphis* subsp. *aureofaciens* UCM B-306 *via* a convergent one-pot assembly of the key trisaccharide framework [84]. Donor **223** and acceptor **224** were first condensed under NIS–TfOH activation in DCM–Et_2O at −20 °C, generating a disaccharide intermediate within 1 h. In the same



Scheme 14. Synthesis of α-galacturonic acid glycosides using 4,6-*O*-benzylidene-protected galactosyl donors.



Scheme 15. Synthesis of α-(1→4)-linked *N*-acetyl galactosaminuronic acids using 2,3-*N*,*O*-oxazolidinone-protected galactosyl donors.

pot, D-rhamnosyl donor **224** was introduced with fresh NIS–TfOH at 0 °C, affording α-trisaccharide **225** in 78% overall yield. After TBDPS cleavage, the resulting alcohol was oxidised to its carboxylate form using TEMPO–BAIB and then esterified with MeI and potassium carbonate (K_2CO_3) to yield protected trisaccharide **226** in 64% overall yield. Gao *et al.* reported the total synthesis of *Pseudomonas aeruginosa* O-antigen repeats containing α-*N*-acetyl-L-galactosaminuronic acid (α-L-GalpNAcA) units using 6-*O*-TBS-L-GalN_3 donors for controlled glycosylation [85]. After establishing reliable α-L-GalN_3 coupling conditions, they implemented this stereocontrolled glycosylation strategy in **233** and **234** synthesis. The glycosylation between **227** and **229** mediated by NIS–TfOH in DCM–Et_2O proceeded to yield only α-linked tetrasaccharide **231** with 81% efficiency. Under the established conditions, coupling acceptor **228** with donor **230** afforded trisaccharide **232** in 81% isolated yield with exclusive α-anomeric configuration. After removing TBS from **231** and **232**, the liberated primary alcohols underwent oxidation *via* the optimised TEMPO–BAIB protocol, and subsequent benzyl ester formation yielded products **233** and **234**, respectively.

3.5. Stereoselective synthesis of α-galacturonic acids using privileged galactosyl donors

The *n*-pentenyl glycoside methodology was first established by Fraser-Reid *et al.* in 1988, introducing this alkyl group as an innovative anomeric substituent for glycosyl donors [86]. Glycosylation potentially initiated *via* the electrophile-induced cyclisation of **235** to produce bromonium intermediate **236**, which was in equilibrium with oxonium cation **237** (Scheme 17A) [87]. After releasing the halomethyltetrahydrofuran by-product, the resulting oxocarbenium species **238** underwent nucleophilic capture by the alcohol acceptor to yield glycoside product **239**. Clausen employed *n*-pentenyl glycosyl donors as a versatile method for oligogalacturonate assembly [88–90]. PMP-protected galactoside **240** was subsequently glycosylated with **241** in the presence of bromine gas (Br_2) and tetrabutylammonium bromide (Et_4NBr), affording the desired α-linked product **242** in 70% yield with excellent α-selectivity (α/β > 95:5). The activation of donor **240** generated a mixture of α- and β-glycosyl bromides, where the α-anomer was the major component. Owing to its superior reactivity, the transient β-glycosyl bromide was the sole participant in the coupling reaction, resulting in the formation of an α-linked product. Coupling of disaccharide donor **243** with acceptor **242** *via* activation using NIS and triethylsilyl triflate (TESOTf) yielded target α-configured trisaccharide **244** in 71% isolated yield. The PMP groups in compound **244** underwent CAN-catalysed oxidative cleavage followed by further oxidation and esterification. The oxidation sequence employed Dess–Martin periodinane followed by sodium chlorite to afford the carboxylic acids, which were immediately esterified *in situ* with (trimethylsilyl)diazomethane ($TMSCHN_2$), thereby avoiding intermediate purification.

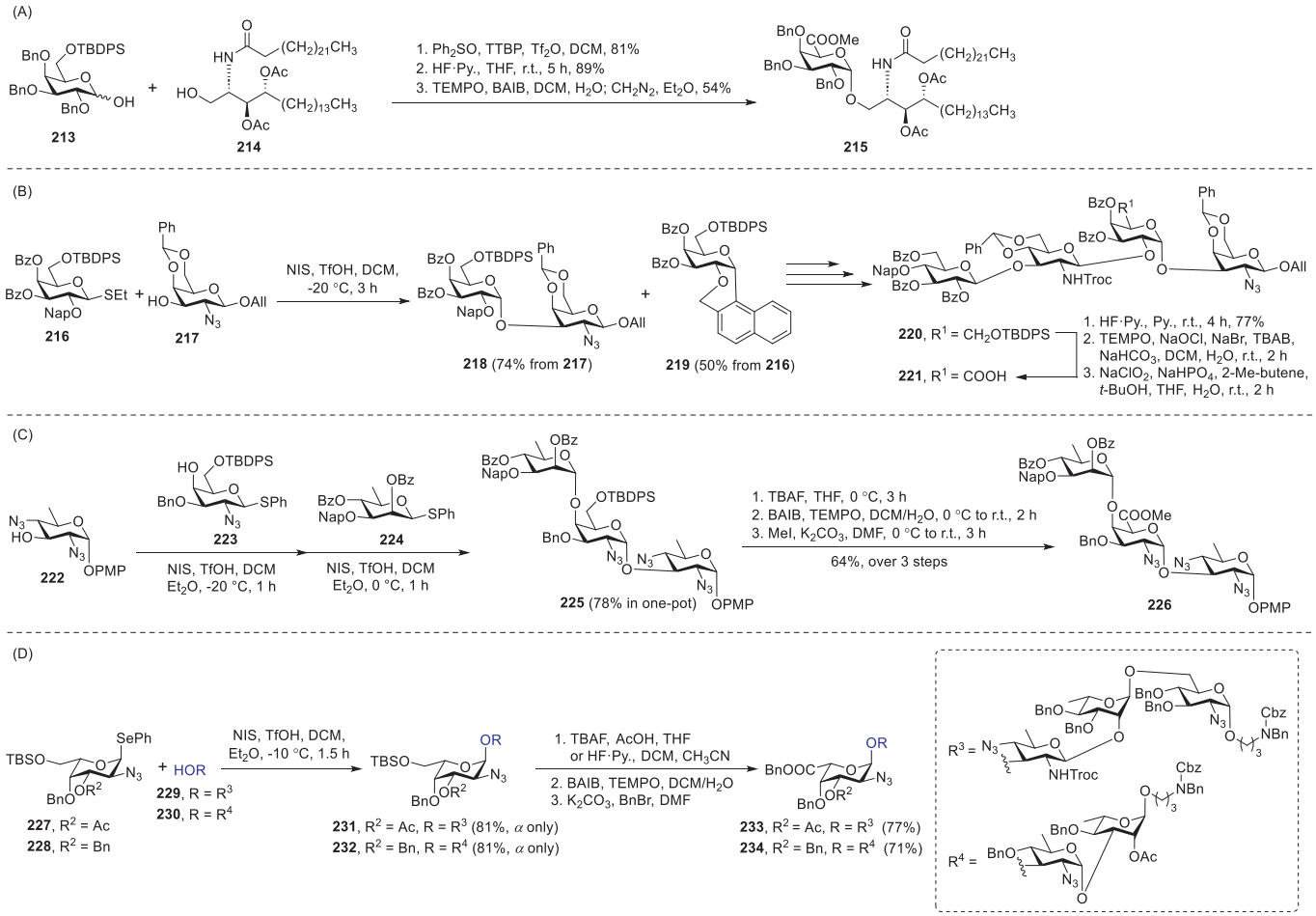
The immunodominant capsular polysaccharide of *Salmonella typhi* comprises of repeating α-(1→4)-linked *N*-acetyl-D-galactosaminuronic acid residues. Sinaÿ *et al.* demonstrated the synthesis of oligosaccharide fragments of *Salmonella typhi* containing repeating α-(1→4)-*N*-acetyl-D-galactosaminuronic acid polymers by employing 2-azido-2-deoxy-D-galactopyranosyl *S*-xanthates as key glycosyl donors (Scheme 18) [91]. The oligosaccharide construction commenced with DMTST-promoted glycosylation of acceptor **247** with donor **246**, affording trisaccharide **248** in 58% yield with good selectivity (α:β = 8.7:1). Debenzylation of **249** and **250** *via* hydrogenation, followed by Sharpless oxidation of the primary alcohols, afforded oligogalacturonates **251** (60%) and **252** (78%), respectively.

Ogawa *et al.* demonstrated the synthesis of α-(1→4)-linked GalA trisaccharides by employing D-galactopyranosyl fluoride donors in their glycosylation strategy (Scheme 19A) [92]. The stannous chloride ($SnCl_2$)–silver perchlorate ($AgClO_4$)-promoted glycosylation between **253** and **254** in Et_2O proceeded with complete selectivity, yielding galactotrioside **255** as the sole product in 77% yield (Scheme 19A). Employing 1,2-dichloroethane as the solvent decreased the stereoselectivity, affording the desired product **255** in 68% yield along with 4% of the β-linked isomer. Under $SnCl_2$–$AgClO_4$ promotion, galactobiosyl acceptor **258** reacted with donor **257** to predominantly give trisaccharide **255** (63%) along with trisaccharide **259** (12%) as a minor side product (Scheme 19B). The α-D-galactopyranosyl moiety at C-4 in donor **253** demonstrated superior α-stereoselectivity compared with benzyl-protected analogue **257**, suggesting that the bulky protecting group at C-4 considerably influences the glycosylation outcome.

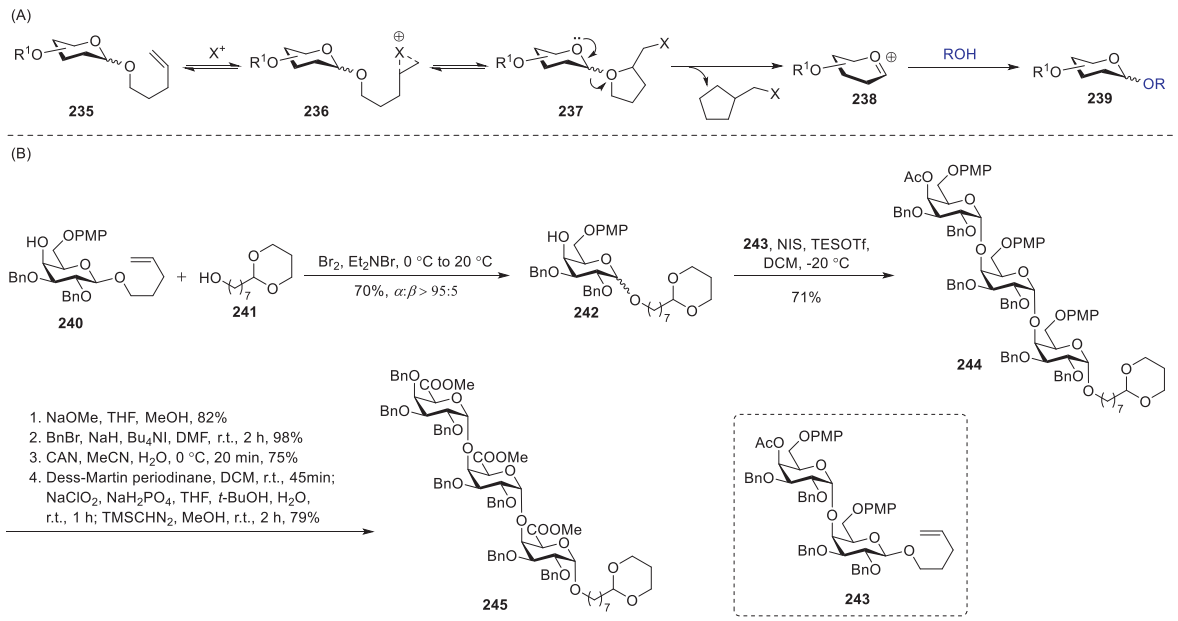
Misra *et al.* accomplished the convergent synthesis of an acidic pentasaccharide repeating unit that was structurally identical to the *O*-antigen polysaccharide of enterohemorrhagic *Escherichia coli* O113 by employing an efficient [3 + 2] block glycosylation strategy [93]. The $HClO_4$–SiO_2-promoted glycosylation of donor **261** with acceptor **262** in DCM–Et_2O (3:1) proceeded stereoselectively, affording α-linked pentasaccharide derivative **263** in 68% yield along with a small amount of the stereoisomer (~10%), which was subsequently removed using silica-gel chromatography (Scheme 20). A selective TEMPO-catalysed oxidation reaction was employed in the final synthetic steps to incorporate the D-GalA moiety, demonstrating excellent functional-group compatibility.

4. Summary and outlook

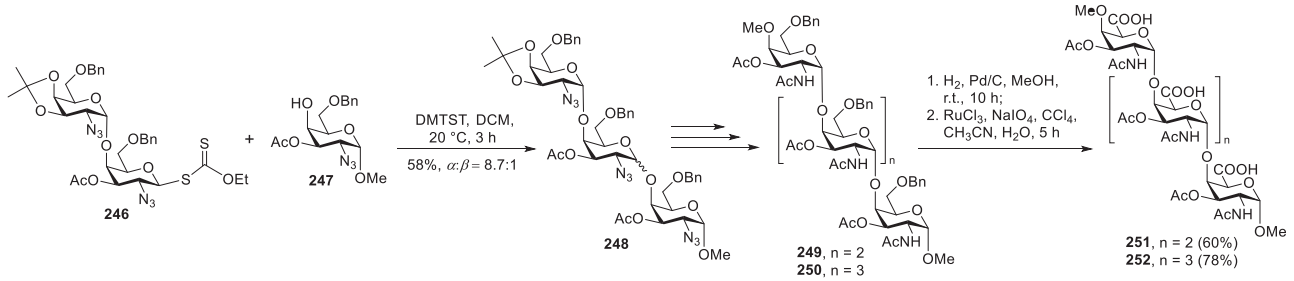
Two synthetic strategies for incorporating α-linked galacturonic acid moieties into acidic oligosaccharides, *i.e.* pre- and post-glycosylation oxidation strategies, are described herein. The pre-glycosylation oxidation strategy for α-GalA/α-GalNAcA-containing



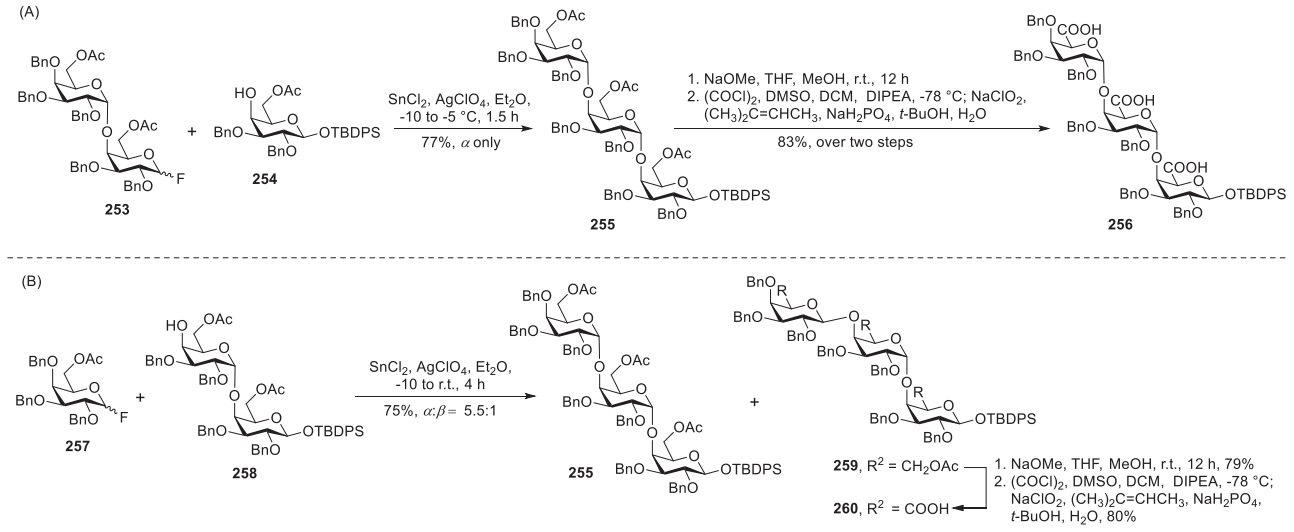
Scheme 16. Synthesis of α-galacturonic acid glycosides using galactose donors containing bulky *O*-6 protecting groups.



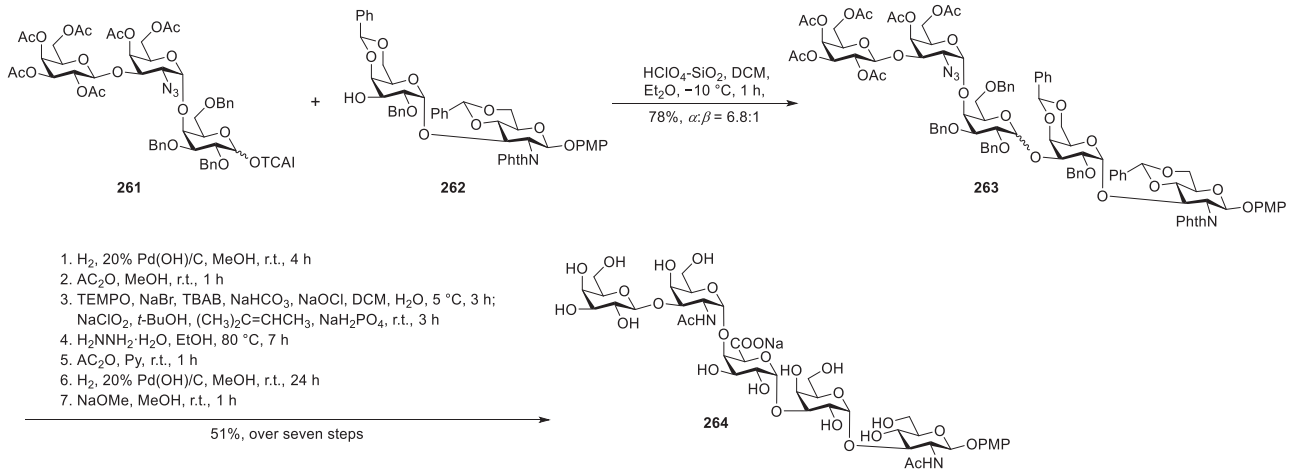
Scheme 17. Synthesis of α-linked oligogalacturonates using *n*-pentenyl galactosyl donor.



Scheme 18. Synthesis of α-linked oligogalacturonates using galactosyl *S*-xanthates.



Scheme 19. Synthesis of α-linked oligogalacturonates using D-galactosyl fluoride donors.



Scheme 20. Synthesis of α-galacturonic acid glycosides using a TCAI galactosyl donor.

oligosaccharides involves C-4 modification to control anomeric selectivity. Further, *O*-4-acyl protecting groups stabilise key intermediates, and bulky C-4 substituents direct α-selectivity *via* steric hindrance during glycosidic bond formation. Conformationally constrained 3,6-lactones enable the S_N2-like displacement of anomeric triflates, yielding exclusive α-linkages. $TiCl_4$-mediated anomerisation converts β-linked glycolipids into α-anomers *via* chelation control. Galactopyranosyl thioglycosides and phosphates are versatile donors achieving high α-selectivity after careful optimisation of the reaction conditions, while offering adjustable reactivity and selectivity for controlled oligosaccharide assembly. Premature oxidation at C-6 compromises the selectivity during protection of glycosyl donor hydroxyl groups. In addition, the electron-withdrawing character of the carboxylate ester moiety considerably reduces the reactivity of uronic acids. The challenging synthesis of 1,2-*cis*-α-GalA/α-GalNAcA derivatives can be achieved using a strategic approach involving initial glycosylation of 1,2-*cis*-Gal/α-GalNAc followed by subsequent oxidation. The presence of acyl protecting groups at C-3, C-4 and/or C-6 positions in galactopyranosyl donors facilitates the α-selective glycosylation by electronically stabilising the transient oxocarbenium ion intermediate. The 4,6-*O*-DTBS and 4,6-*O*-benzylidene protecting groups pro-

mote α-selectivity through dual mechanisms: (i) Steric shielding of the β-face and (ii) conformational locking of the galactopyranosyl intermediate. The 2,3-*N*,*O*-oxazolidinone protecting group strategy based on the pre-activation protocol ensures exclusive α-selectivity. The strategic incorporation of sterically demanding 6-*O*-TBDPS or 6-*O*-TBS groups promotes α-selectivity by effectively shielding the β-face from nucleophilic attack during galactosylation. *n*-Pentenyl glycosides, galactosyl fluorides and *S*-xanthates offer unique activation pathways for α-control. Ultimately, achieving complete selectivity in the 1,2-*cis*-glycosylation hinges on three critical factors: strategic design of the protecting group pattern on the donor, precise control of the counterion and optimisation of the reaction conditions, including the use of modulating additives. Although TEMPO oxidation enables an efficient carboxyl-group incorporation, the post-glycosylation route presents synthetic complexity through necessary protecting group strategies and inherent risks of oxidative damage to pre-assembled oligosaccharides.

Despite these advances, some limitations persist, including moderate yields, competing side reactions and the need for extensive protecting group manipulations. Further development of catalytic activation methods, mechanistic studies and streamlined synthetic routes are essential to provide access to structurally diverse α-GalA/GalNAcA-containing glycans for biological and therapeutic applications. Recent efforts have also highlighted the limitations of conventional oxidation protocols in incorporating the C-5 carboxyl group of galacturonic acid derivatives. Traditional methods often suffer from poor functional group tolerance, over-oxidation or lack of stereocontrol at C-5, complicating downstream glycosylation. Emerging strategies such as electrochemical oxidation, enzyme-mimetic catalysis and organocatalytic dehydrogenation offer milder alternatives but require further optimisation for carbohydrate substrates.

Integrating multidisciplinary tools, *e.g.*, machine-learning-guided reaction optimisation, bio-orthogonal chemistry and automated synthesis, can accelerate the development of robust protocols for these glycosides, unlocking their potential in glycoscience and materials science.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Juntao Cai: Writing – review & editing, Writing – original draft, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Qian Wang:** Investigation, Data curation. **Xu Shen:** Writing – review & editing. **Lifeng Zhu:** Writing – review & editing. **Shiqing Jiang:** Writing – review & editing, Supervision, Resources. **Jian Yin:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Chunhong Dong:** Writing – review & editing, Supervision, Resources, Project administration, Formal analysis, Conceptualization.

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