RSC Advances

REVIEW

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Cite this: *RSC Adv.*, 2023, **13**, 19898

C-Glycopyranosyl aldehydes: emerging chiral synthons in organic synthesis

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Herein, we have summarized the vast array of synthetic processes that have been developed for the synthesis of *C*-glycopyranosyl aldehydes and diverse *C*-glycoconjugates derived from them by covering the literature reported from 1979 to 2023. Notwithstanding its challenging chemistry, *C*-glycosides are considered stable pharmacophores and are used as important bioactive molecules. The discussed synthetic methodologies to access *C*-glycopyranosyl aldehydes take advantage of seven key intermediates, *viz.* allene, thiazole, dithiane, cyanide, alkene, and nitromethane. Furthermore, the integration of complex *C*-glycoconjugates derived from varied *C*-glycopyranosyl aldehydes involves nucleophilic addition/substitution, reduction, condensation, oxidation, cyclo condensation, coupling, and Wittig reactions. In this review, we have categorized the synthesis of *C*-glycopyranosyl aldehydes and *C*-glycoconjugates on the basis of the methodology used for their synthesis and on types of *C*-glycoconjugates, respectively.

Received 31st March 2023
Accepted 16th May 2023

DOI: 10.1039/d3ra02122j

rsc.li/rsc-advances

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1. Introduction

C-Glycosides constitute an important and useful class of organic molecules, in which anomeric carbon of a sugar is attached to an aglycon through C–C bonds. Molecules of this class are mimics of *O*-glycosides, where the sugar moiety is attached with aglycon through C-atom instead of O-atom at the anomeric position.[1] Glycosides have made their presence felt in foodstuffs to the components of nucleic acids and cell surface glycoconjugates. The structural alteration resulting from the transformation of the anomeric centre from C–O acetal to a strong C–C bond in *C*-glycosides stimulates the resistance towards chemical/enzymatic hydrolysis and metabolic processes.[2] As a consequence, the dominance of *C*-glycosides to personate native *O*-glycosides as

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Late Professor Ashok K. Prasad (1961–2023): Professor Prasad obtained his PhD from the Department of Chemistry, University of Delhi, in 1990 in the area of synthesis of bioactive polyphenolic natural products. After spending about a decade as a post-doctoral fellow/visiting scientist at the University of Southern Denmark, the Max Planck-Institute for Molecular Physiology (Germany), Sapienza University Rome (Italy), and the University of Massachusetts Lowell (USA), Professor Prasad joined the Department of Chemistry, University of Delhi, as Reader in 2001 and subsequently became Professor in 2009. He was the Head of the Chemistry Department and Dean of Science Faculty, University of Delhi. He had published more than 300 research papers in journals of international repute. His research interests were in the areas of nucleic acid chemistry, biotransformations, natural product chemistry, and synthesis of bioactive heterocyclic compounds. We dedicate this review to the fond memory of Late Professor Ashok K. Prasad.

potential therapeutic candidates has become undoubtedly apparent. Moreover, the occurrence of *C*-glycosidic linkage is common in natural products obtained from plants and microorganisms, such as saptomycin B,[3] mangiferin,[4] aspalathin,[5] tunicamycin V,[6] and aureonuclemycin,[7] which have shown significant biological activities[8] (Fig. 1).

Remarkable structural diversity in naturally occurring *C*-glycosides has drawn considerable attention to chemically synthesized complex *C*-glycosides. The successful examples of the chemical evolution of *C*-glycosides include pro-xylene as anti-aging cosmetic agent,[9] dapagliflozin, canagliflozin and empagliflozin as SGLT2 inhibitors for the treatment of type II diabetes,[10–12] metabolically stable *C*-analogue of KRN7000 as anticancer agent,[13] *C*-mannosyl-Trp for post-transitional modification affecting folding, stability and other functions of proteins,[14] *etc.* (Fig. 2).

A literature survey on *C*-glycosides illustrates that earlier reported review articles have mainly been on *exo*-glycals,[15] *C*-mannopyranosides,[16] *C*-nucleosides,[17] *C*-glycoconjugates,[18] *C*-arylglycosides,[19,20] and on chemical synthesis of *C*-glycosides.[21,22] Although α- and β-*C*-glycopyranosyl aldehydes constitute an important class of precursor molecules for the formation of complex *C*-glycosides, it has been overlooked to make their explicit presence in any review article. About two decades ago, Dondoni presented a review that mainly referred to sugar thiazole as a key synthetic intermediate for the synthesis of *C*-glycopyranosyl aldehyde and explained its role as a precursor for the formation of *C*-disaccharide and *C*-amino acids.[23] Consequently, these facts encouraged us to compile the literature on the synthesis of α- and β-*C*-glycopyranosyl aldehydes and their applications in the synthesis of diverse biologically relevant *C*-glycoconjugates in this review article.

2. Synthesis of *C*-glycopyranosyl aldehydes

Generally, syntheses of *C*-glycosides involve the nucleophilic addition of aglycon part on sugar moiety followed by treatments

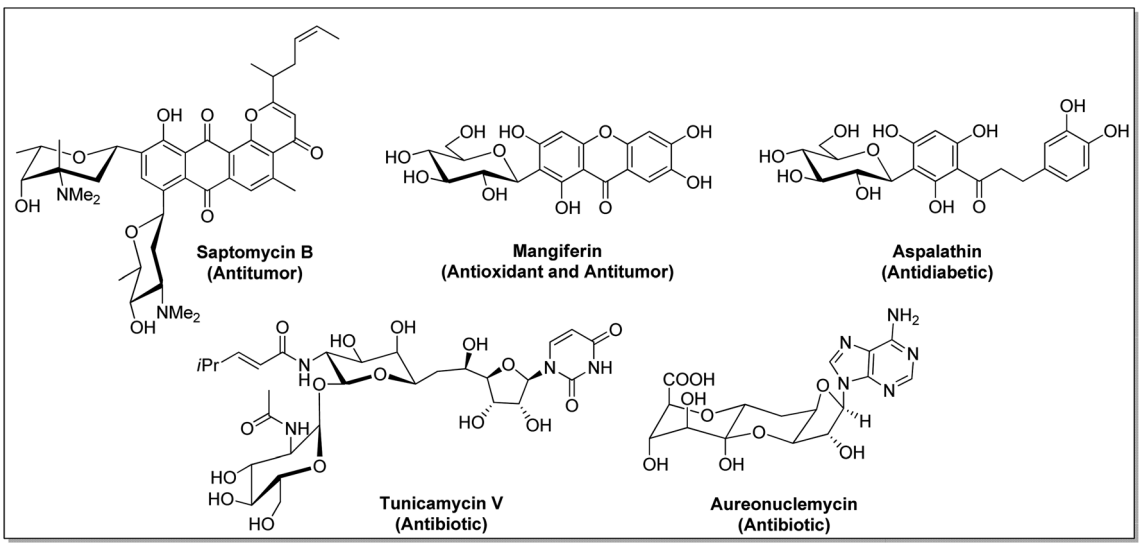


Fig. 1 Structures of some selected naturally occurring bioactive *C*-glycosides.

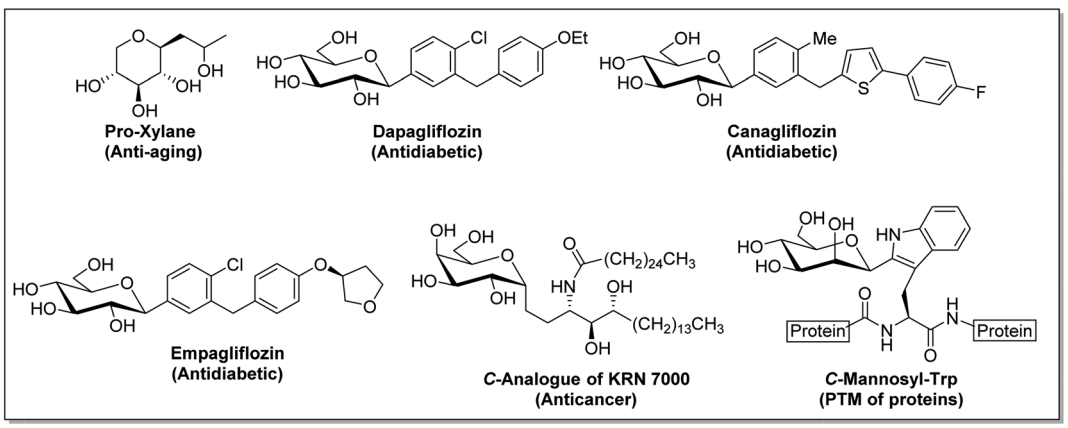


Fig. 2 Structures of some bioactive synthetic *C*-glycosides.

using dehydration, oxidation, reduction, and reductive hydrolysis reactions to obtain targeted *C*-glycopyranosyl aldehydes. In comparison to the syntheses of α-*C*-glycopyranosyl aldehydes, more methodologies have been reported on the synthesis of β-*C*-glycopyranosyl aldehydes. Further, it has been observed that α-*C*-glycopyranosyl aldehydes can be easily converted into β-*C*-glycopyranosyl aldehydes in the presence of organic bases. Seven key intermediates have been used for the preparation of α- and β-*C*-glycopyranosyl aldehydes, which have been described below (Fig. 3).

2.1 Allene approach

Kobertz *et al.*[24] reported the use of α-*C*-glycopyranosyl allenes **2a–c** as key synthetic intermediates for the synthesis of *C*-glycopyranosyl aldehydes, which in turn can be synthesized from methyl tetra-*O*-benzyl-α-D-glycopyranosides **1a–c** with high

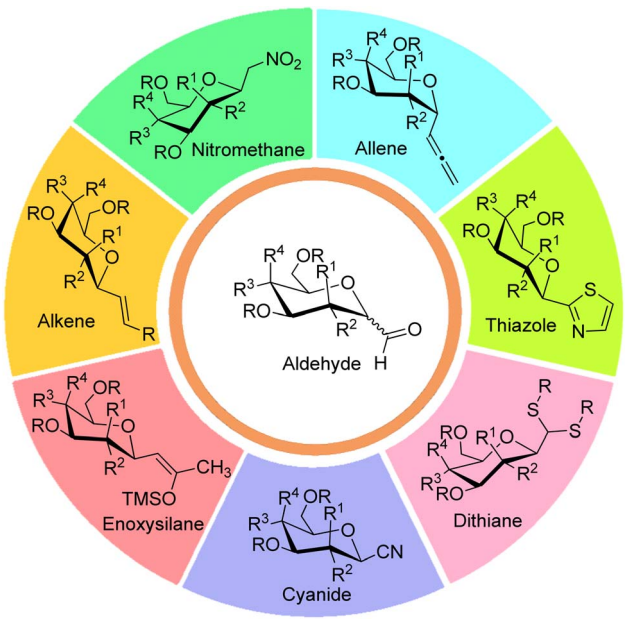


Fig. 3 Key intermediates for the synthesis of *C*-glycopyranosyl aldehydes.

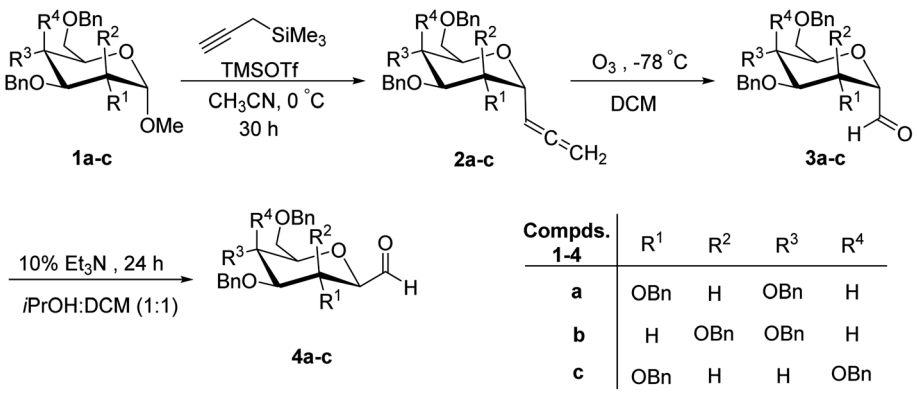
Table 1 Overall yields and equilibrium ratio of β/α for the conversion of **2a–c** into **4a–c**

Reactant	β-linked products	β : α	Yield (%)
2a	**4a**	>20 : 1	41
2b	**4b**	8 : 1	42
2c	**4c**	10 : 1	49

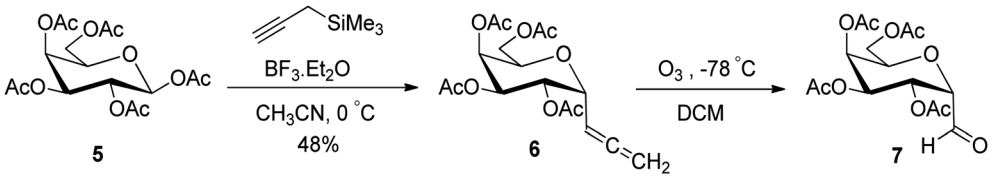
diastereoselectivity (>20 : 1) *via* Lewis acid catalysed nucleophilic substitution reaction using propargyl trimethylsilane in the presence of trimethylsilyl triflate (TMSOTf) in acetonitrile. Furthermore, ozonolysis of allenes **2a–c** in dichloromethane at −78 °C provided α-*C*-glycopyranosyl aldehydes **3a–c**, which on treatment with 10% triethylamine in isopropanol : DCM (1 : 1) at 25 °C for 24 h yielded β-*C*-glycopyranosyl aldehydes **4a–c** (Scheme 1). The overall yields and equilibrium ratio of β/α for the conversion of *C*-glycopyranosyl allenes **2a–c** into β-linked *C*-glycopyranosyl aldehydes **4a–c** are shown in Table 1.

In another synthetic approach reported by Kroger *et al.*[25] peracetylated D-galactose **5** was used as a starting material to access the sugar allene precursor (Scheme 2). 1,2,3,4,6-Penta-*O*-acetyl-β-D-galactopyranose (**5**) was converted into the corresponding α-*C*-glycosidic allene **6** using propargyl trimethylsilane in the presence of Lewis acid ($BF_3 \cdot Et_2O$) in acetonitrile at 0 °C in 48% yield. Further, compound **6** on ozonolysis afforded acetylated α-*C*-galactopyranosyl aldehyde **7**, which was found to be very labile and further used without isolation for the synthesis of *O*-glycosyl amino acid mimetics. The details of synthetic methods for these *O*-glycosyl amino acid mimetics are described in Section 3.4 (Scheme 50).

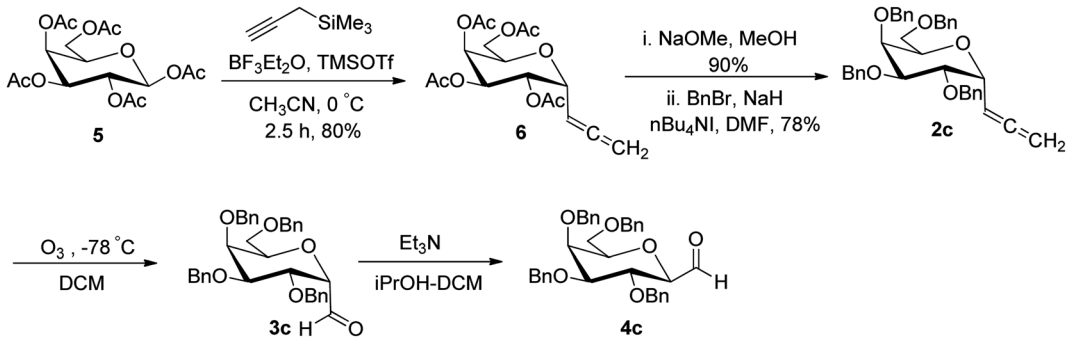
Alternatively, Kolympadi *et al.*[26] synthesized both α- and β-linked glycopyranosyl aldehydes using allene as the key precursor, which was obtained from peracetylated D-galactose **5** following the method of Kroger *et al.*[25] (Scheme 3). However, here combination of Lewis acids BF_3–Et_2O–TMSOTf produced allene **6** in 80% yield. Since Kroger observed that the acetyl-protected glycopyranosyl aldehyde **7** was very labile, here, acetylated allene **6** was converted into the perbenzylated α-*C*-glycosyl allene **2c** by deprotection of acetyl group with sodium



Scheme 1 Synthesis of β-*C*-glycopyranosyl aldehydes **4a–c**.



Scheme 2 Synthesis of α-*C*-galactopyranosyl aldehyde 7.



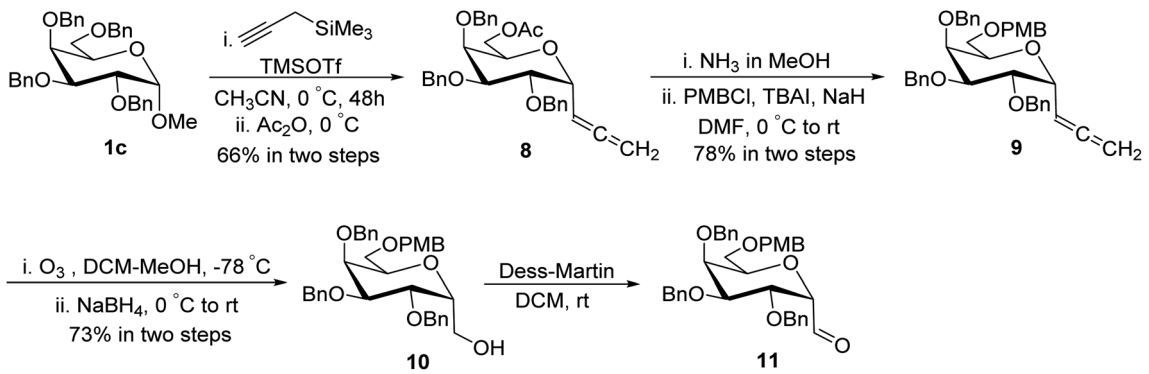
Scheme 3 Synthesis of β-*C*-galactopyranosyl aldehyde 4c.

methoxide (NaOMe)/methanol followed by the protection of generated hydroxyl groups with benzyl bromide in the presence of sodium hydride in DMF. Further, compound **2c** was converted into β-*C*-galactopyranosyl aldehyde **4c** by following the methodology developed by Kobertz *et al.*[24]

Guillaume *et al.*[27] designed a route for the synthesis of *C*-glycopyranosyl aldehyde **11** initiating from perbenzylated α-methyl galactoside **1c**. The aim for the synthesis of orthogonally protected *C*-glycopyranosyl aldehyde **11** was to be utilized for the synthesis of C6-modified α-*C*-GalCer analogues (Section 3.1, Scheme 32a). Thus, treatment of galactoside **1c** with propargyl trimethylsilane and trimethylsilyl triflate in acetonitrile at 0 °C for 48 hours followed by acetylation using acetic anhydride yielded sugar allene **8** in 66% yield. Deprotection of the C6-OBn group in **1c** under condition propargyl trimethylsilane and trimethylsilyl triflate in acetonitrile at 0 °C for 48 was due to the excess use of Lewis acid, *i.e.* trimethylsilyl triflate and longer reaction time. Acetyl protection of compound **8** was replaced with PMB on treatment with ammonia in methanol followed by protection of alcohol with PMBCl resulting in allene **9** in 78% yield, which upon ozonolysis and *in situ* reduction with sodium borohydride afforded primary alcohol **10** in 73% yield. The α-*C*-galactopyranosyl aldehyde **11** was obtained by re-oxidation of alcohol **10** *via* the Dess–Martin reaction. α-*C*-Galactopyranosyl aldehyde **11** was also found labile and further used without isolation (Scheme 4).

2.2 Thiazole approach

Thus, the allene approach carried out by these researchers concluded that the use of both Lewis acids BF_3–Et_2O–TMSOTf produced allene in good yield from sugar precursors. Excess use of Lewis acids furnished deprotection of the C6-OBn group and it was also observed that α-*C*-glycopyranosyl aldehydes are less stable than β-*C*-glycopyranosyl aldehydes and the earlier one could be easily converted into later on treatment with base triethylamine in *i*PrOH-DCM. However, the synthesis of *C*-



Scheme 4 Synthesis of α-*C*-galactopyranosyl aldehyde 11.

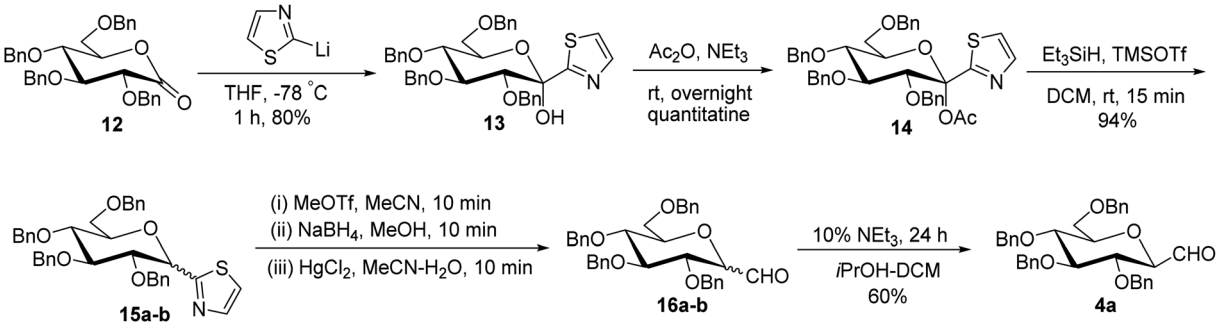
glycopyranosyl aldehydes *via* the allene approach has posed the limitation of using expensive reagents such as propargyl trimethylsilane, troublesome cleavage by ozonolysis and a long reaction time. So, a more convenient approach was developed by Dondoni *et al.*[28] in which *C*-glycopyranosyl aldehyde was synthesized using sugar thiazole as a key synthetic intermediate.

In this approach, the sugar thiazole was synthesized *via* the nucleophilic addition reaction followed by reductive dehydroxylation. The nucleophilic addition of 2-lithiothiazole (2-LTT, prepared *in situ* by the reaction of 2-bromothiazole and butyl lithium) on 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone **12** at −78 °C in THF yielded 2,3,4,6-tetra-*O*-benzyl-β-1-*C*-(2-thiazolyl)-D-glucopyranose (**13**) in 80% yield. On acetylation, compound **13** yielded anomerically activated compound **14**, which on further reduction with triethylsilane in trimethylsilyl triflate (TMSOTf) at room temperature for 15 minutes gave an anomeric mixture of α- and β-linked 2-thiazolyl-*C*-glucopyranosides **15a–b** in 1 : 1 ratio. The anomeric mixture **15a–b** when subjected to *N*-methylation followed by reduction and then hydrolysis in the presence of corresponding reagents produced α- and β-linked *C*-glucopyranosyl aldehydes **16a–b** in the ratio of 1 : 1. Treatment of **16a–b** with 10% triethylamine afforded β-*C*-glucopyranosyl aldehyde **4a** in 60% yield (Scheme 5).

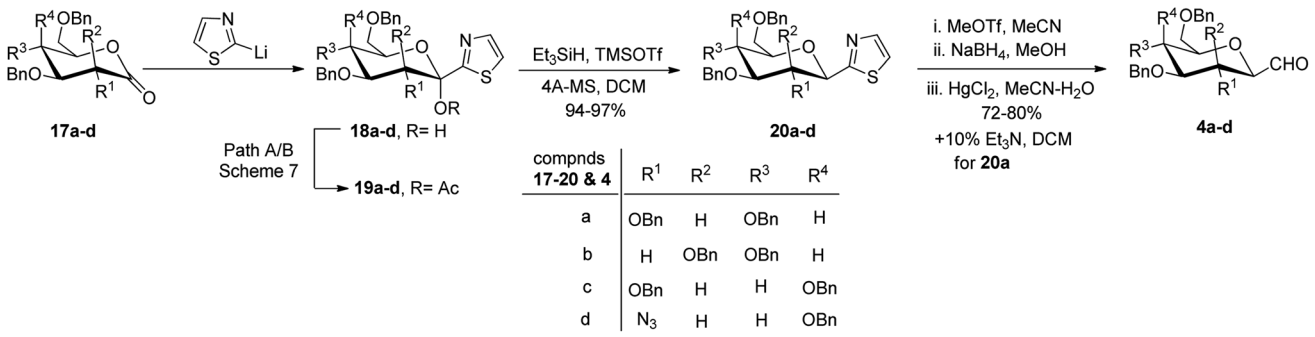
Further, Dondoni *et al.*[29] applied the same approach to other sugar precursors to study the kinetic and thermodynamic aspects of improving the stereochemical control and chemical efficacy (Scheme 6). Different sugar precursors such as 2,3,4,6-tetra-*O*-benzyl-glucose/-mannose/-galactose and 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-galactose **17a–d** were examined for the given approach where thiazole was used as a formyl group equivalent to synthesise *C*-glycopyranosyl aldehyde **4a–d**. A mixture of α- and β-isomers of *C*-glucopyranosyl aldehyde **4a** was obtained in a 1 : 1 ratio, while, on the other hand, remaining *C*-glycopyranosyl aldehydes **4b–d** were formed preferentially in β-configuration.

Ketol acetates **19a–d** were synthesised by stereoselective addition of 2-lithiothiazole to sugar lactones **17a–d**, resulting in ketol molecules and further acetylation of the corresponding hydroxy group *in situ* or after isolation. Two pathways have been studied for the conversion of **17a–d** into **19a–d** (Scheme 7). These two pathways produced an anomeric mixture in different yields along with different ratios as shown in Table 2.

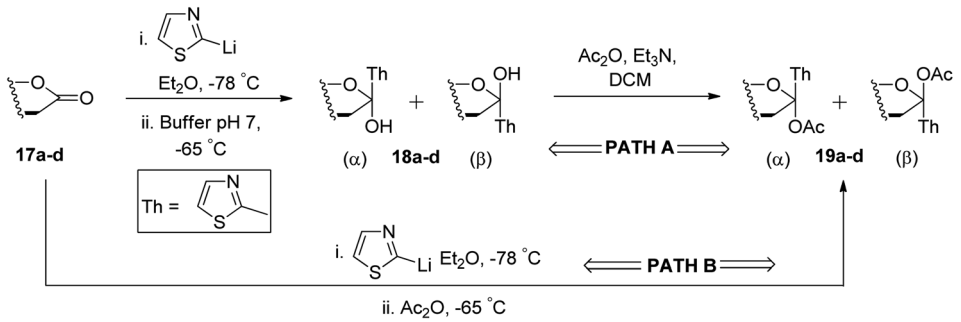
Thus, ketols **18a–d** were found as a mixture of kinetically and thermodynamically controlled products where the kinetic products were attributed to the steric effect of substituent and the thermodynamic products to the electronic effect of ring oxygen. On the further reaction of compounds **19a–d** with triethylsilane and trimethylsilyl triflate (TMSOTf), the acetate group was reduced yielding thiazolyl *C*-glycoside **20a–d** in excellent yield, which is independent of stereochemistry at *C*-1 position of glycosyls **19a–d**. Further, a reaction sequence of *N*-methylation followed by reduction of hydride and hydrolysis gave β-linked *C*-glycopyranosyl aldehydes **4a–d** in 72–80% yields. The use of thiazole ring as a masked formyl group has been proven to be very efficient and flexible as it worked well on four different substrates, which is further supported by good overall yields (52–65%) of the isolated products. Also, the



Scheme 5 Synthesis of β-*C*-glucopyranosyl aldehyde **4a**.



Scheme 6 Synthesis of *C*-glycopyranosyl aldehydes **4a–d**.



Scheme 7 The conversion process of **17a–d** into **19a–d** *via* two pathways, A and B.

Table 2 Conversion of **17a–d** into **19a–d** *via* pathways A and B

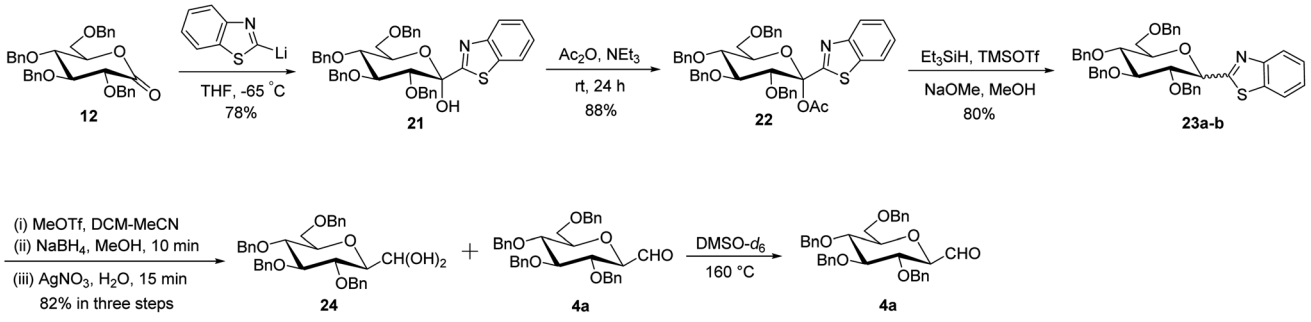
Lactone	Ketol acetate	Condition (path)	$\alpha:\beta$	Yield (%)
17a	**19a**	A	1 : 0	80
		B	1 : 7	87
17b	**19b**	A	1 : 0	73
		B	0 : 1	78
17c	**19c**	A	1 : 0	78
		B	1 : 10	75
17d	**19d**	A	1 : 0	77
		B	0 : 1	80

thiazolyl-masked precursor was indefinitely stable and tolerated the synthetic elaboration of the product to yield delicate sugar aldehydes.

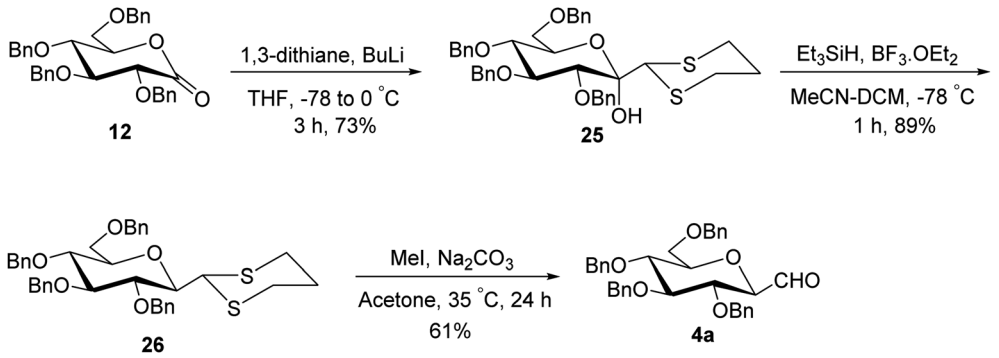
Later, Dondoni *et al.*[30] reported a multigram scale synthesis of *C*-glucopyranosyl aldehyde, where benzothiazole was used in place of thiazole as a formyl group equivalent. The precursor ketose **21** was prepared as a single anomer by the reaction of 2-lithiobenzothiazole (prepared *in situ* by the reaction of butyl lithium and benzothiazole) with 2,3,4,6-tetra-*O*-benzyl-D-glucopyrano-1,5-lactone **12** in 78% yield. The anomeric position was activated by *O*-acetylation with acetic anhydride in triethylamine to afford compound **22** in 88% yield. Next, compound **22** was reacted with triethylsilane in the presence of trimethylsilyl triflate (TMSOTf) underwent silane-based deoxygenation, and afforded benzothiazolyl α- and β-*C*-glucosides **23a–b** in 4 : 6 ratio in 80% yield. After the recovery of β-*C*-glucoside, the benzothiazole ring was converted to a formyl group by a multistep sequence starting with *N*-methylation, followed by hydride reduction and then hydrolysis to give hydrated *gem*-diol compound **24** along with formyl *C*-glucopyranosyl aldehyde **4a** in 82% yield. A mixture of compounds **24** and **4a**, when heated with DMSO-d_6 at 160 °C produced almost pure β-linked *C*-glucopyranosyl aldehyde **4a** (Scheme 8).

2.3 Dithiane approach

Although the above-described thiazole approach proved efficient in respect of the overall yield obtained, the lack of diastereofacial selectivity arises during the addition of 2-lithiothiazole to sugar lactones and the formation of the anomeric mixture of *C*-glycopyranosyl aldehyde has been the major limitation. However, it has been observed that kinetic and thermodynamic conditions control the diastereoselectivity of thiazole attack on sugar lactones. Hence, for stereoselective formylation, Sanchez *et al.*[31] introduced the sugar dithiane as the key intermediate and synthesized single β-anomer of *C*-glycopyranosyl aldehyde using anucleophilic addition reaction followed by Lewis acid-catalysed stereospecific reductive dehydroxylation. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyrano-1,5-lactone (**12**) on reaction with 2-lithio-1,3-dithiane gave a single diastereoisomer, sugar lactol **25** in 73% yield. This transformation indicated an equatorial attack on carbonyl to generate corresponding equatorial dithiane substituted sugar and hence compound **25** was assumed to be β-*C*-glucopyranosyl dithiane. Further, in the presence of boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$) at −40 °C, the hydroxyl group was stereoselectively removed by triethylsilane yielding 2,3,4,6-tetra-*O*-benzyl-β-1-*C*-



Scheme 8 Synthesis of *C*-glucopyranosyl aldehyde **4a**.

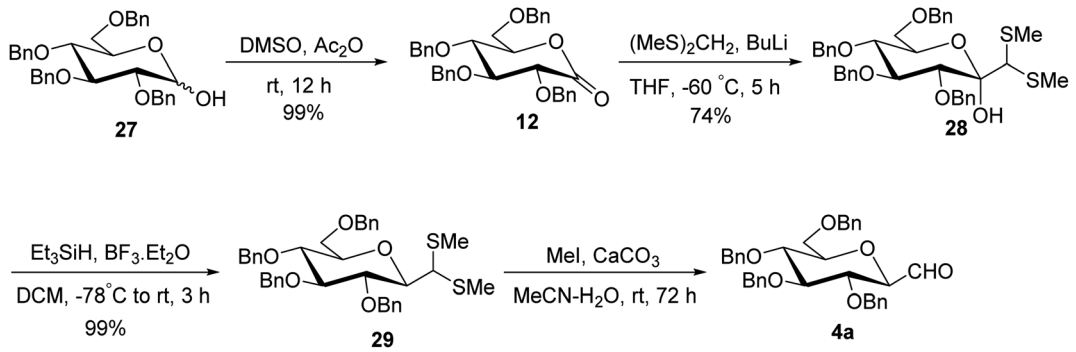


Scheme 9 Synthesis of β-*C*-glucopyranosyl aldehyde **4a**.

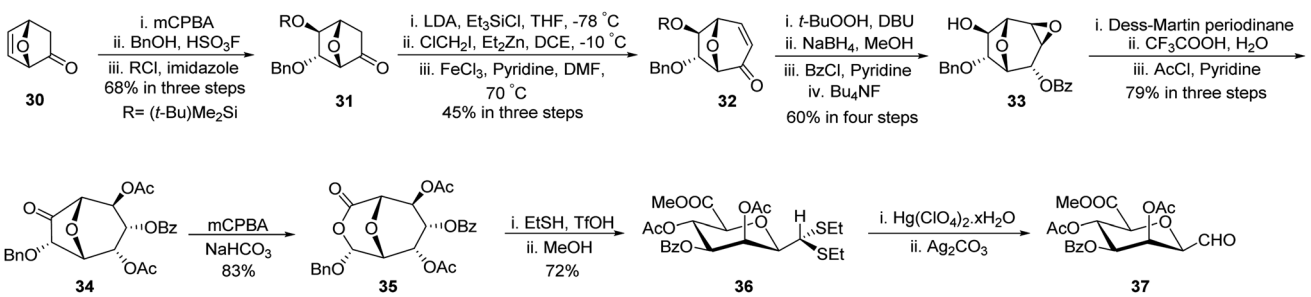
(2-dithianyl)-D-glucopyranose (**26**) in 89% yield. Subsequently, compound **26** was hydrolysed to give β-*C*-glucopyranosyl aldehyde **4a** in the presence of sodium carbonate (Na_2CO_3) and methyl iodide (MeI) in acetone at 35 °C in 61% yield along-with 20% of unreacted starting material (Scheme 9).

Later on, Labeguere *et al.*[32] reported another route for the highly diastereoselective synthesis of β-*C*-glucopyranosyl aldehyde with improved overall yield. The commercially available precursor 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**27**) underwent oxidation in the presence of dimethyl sulfoxide (DMSO) in acetic anhydride to produce2,3,4,6-tetra-*O*-benzyl-D-gluconо-1,5-lactone **12** in 99% yield. Under Umpolung Seebach reaction condition, compound **12** was transformed into 1-*C*-[bis(-methylthio)methyl]-α-D-glucopyranose (**28**) in 74% yield *via in situ* formation of bis(methylthio)methyl carbanion. In the presence of $BF_3 \cdot Et_2O$ and triethylsilane (Et_3SiH) in DCM at −78 °C, the anomeric hydroxyl group of **28** was reduced to obtain the single β-anomer, *i.e.* β-1-bis(methylthio)methyl-tetra-*O*-benzyl-D-glucopyranoside (**29**) with 99% yield. Finally, treatment with methyl iodide and calcium carbonate in a solvent mixture of acetonitrile-water afforded single β-linked glucopyranosyl aldehyde **4a** (Scheme 10).

Gerber *et al.*[33] developed a unique protocol for the stereoselective synthesis of β-*C*-*manno*-pyranosyl aldehyde (Scheme 11). Here, 7-oxabicyclo[2.2.1]hept-5-en-2-one (**30**) was converted into (−)-6-*endo*-(benzyloxy)-5-*exo*-hydroxy-7-oxabicyclo[2.2.1]heptane-2-one (**31**) in 68% yield using epoxidation by mCPBA followed by nucleophilic attack on the epoxide ring by BnOH



Scheme 10 Synthesis of β-*C*-glucopyranosyl aldehyde **4a**.



Scheme 11 Synthesis of β-*C*-glycopyranosyl aldehyde **37**.

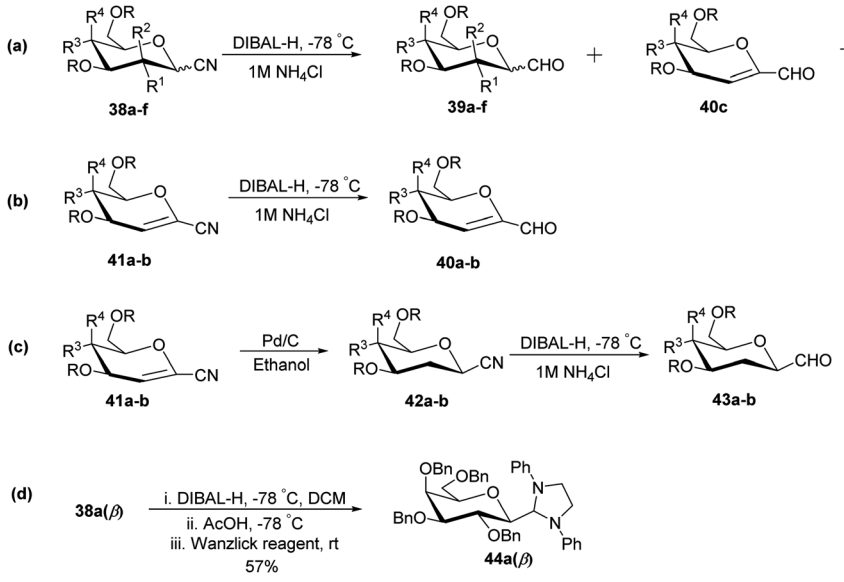
and hydroxy group protection using *tert*-butyldimethylsilyl chloride. Further, treatment with triethylsilyl chloride followed by $ClCH_2I/Et_2Zn$ in DCE and subsequent oxidation with $FeCl_3$/pyridine afforded enone **32** in 45% yield. Epoxidation using *t*-BuOOH, DBU followed by reduction with sodium borohydride after that protection with benzoyl chloride and deprotection of the silyl group using fluoride donor Bu_4NF afforded **33** in 60% yield. Dess–Martin Periodinane oxidation and epoxide ring opening using $CF_3COOH–H_2O$ and acetyl protection produced **34** in 79% yield, which on Baeyer–Villiger treatment using mCPBA furnished lactone **35** in 83% yield. Further, treatment with ethanethiol in acidic media (EtSH–TfOH) and then with methanol produced dithioacetal **36**, which on hydrolysis using $Hg(ClO_4)_2 \cdot xH_2O$ and then Ag_2CO_3 liberated unstable *C*-glycopyranosyl aldehyde **37**.

2.4 Cyanide approach

In the dithiane approach, both cyclic and acyclic 1,3-dithiane were used, and it was observed that the acyclic dithiane could be easily removed in the last step for the synthesis of desired *C*-glycopyranosyl aldehydes. The cyclic 1,3-dithiane removal consists of a lower yield and has a longer reaction time alongwith the recovery of the starting material. Therefore, Sipos *et al.*[34] introduced a new approach to synthesise β-*C*-glycopyranosyl aldehyde by reductive hydrolysis of *C*-glycosyl cyanides. All glycosyl cyanides (**38a–f**) except **38c**(*β*) were transformed into the expected aldehydes (**39a–f**) on direct treatment with DIBAL-H in ammonium chloride at −78 °C. On the other hand, 1-*C*-formyl glycal product **40c** was formed from galactosyl cyanide (**38c**(*β*)) (Scheme 12a). Similarly, the benzylated glycalnitriles **41a–b** were reduced using DIBAL-H under the same reaction conditions to afford 2-deoxy glycopyranosyl aldehyde derivatives **40a–b**, which were observed to be very stable (Scheme 12b). The corresponding reaction was carried out by taking the same precursors **41a–b** where reduction using Pd/C in ethanol resulted in the formation of 2-deoxy-β-*C*-glycopyranosyl cyanides **42a–b**, which on further reduction with DIBAL-H in ammonium chloride at −78 °C afforded β-*C*-glycopyranosyl aldehydes **43a–b** (Scheme 12c). While compounds **40a–c** and **43a–b** were found to be very stable and could be stored, compounds **39a–f** in the case of *gluco*-, *manno*- and *galacto*-derivatives were very sensitive to the elimination of 2-alkoxy group and a one pot strategy was developed to store them (Scheme 12d). In this process, **38a**(*β*) was treated with DIBAL-H at −78 °C and excess hydride was quenched with acetic acid after 30 min followed by the addition of Wanzlick's reagent to afford **44a**(*β*) in 57% yield.

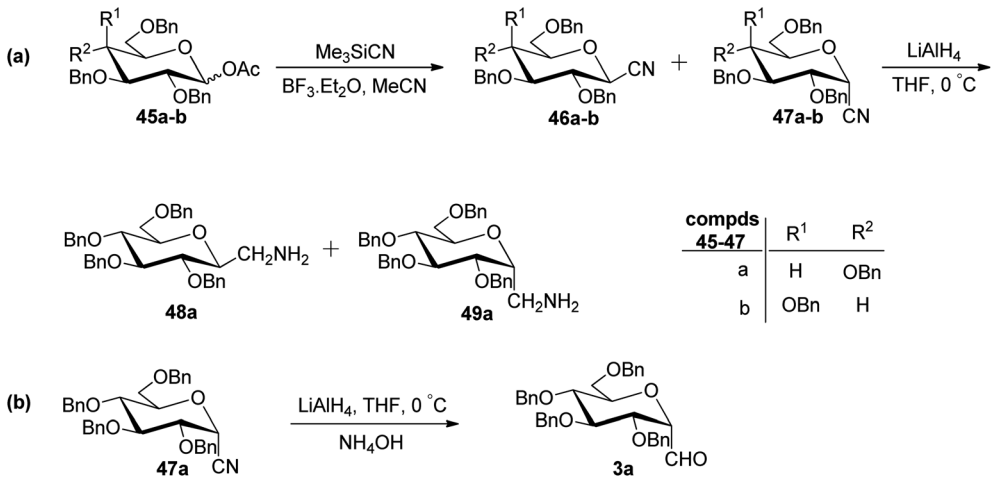
Lopez *et al.*[35] reported the synthesis of α-*C*-glucopyranosyl aldehyde *via* sugar cyanide as a key intermediate. Here, 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glycopyranose **45a–b** on reaction with trimethylsilyl cyanide and boron trifluoride etherate in acetonitrile afforded anomeric mixture of β- and α-glycopyranosyl cyanide **46a–b** and **47a–b** in 80–90% yield, which could be separated by column chromatography. Further, the reaction of glucopyranosyl cyanide **46a** and **47a** with lithium aluminium hydride in THF produced 1-amino-2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*glycero*-D-*gulo*-heptitol **48a** and 1-amino-2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-1-deoxy-D-*glycero*-D-*ido*-heptitol **49a** (Scheme 13a). *C*-Glucopyranosyl aldehyde **3a** was obtained by direct reduction of α-glucopyranosyl cyanide **47a** with lithium aluminium hydride in THF followed by hydrolysis with ammonium hydroxide (Scheme 13b).

Dettinger *et al.*[36] designed a protocol for the synthesis of β-*C*-galactopyranosyl aldehyde **50** by a series of reactions starting from 2,3,4,6-tetra-*O*-acetyl-D-galactopyranosyl cyanide **48**. Acetyl-protected cyanide **48** underwent a reduction in the presence of RANEY®-Nickel followed by protection with *N*,*N*-diphenylethylenediaminein pyridine to yield **49** in 72% yield. Subsequently, compound **49** on treatment with

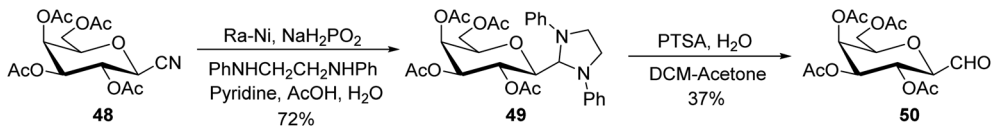


Cyanides	R^1	R^2	R^3	R^4	R	Aldehydes
38a-α	OBn	H	H	OBn	OBn	**39a**-α
38a-β	—	H	H	OBn	OBn	**39a**-β
38b-α	OMe	H	H	OMe	OMe	**39b**-α
38b-β	OMe	H	H	OMe	OMe	**39b**-β
38c-β	OAll	H	H	OAll	OAll	**40c**
38d-α	OBn	H	OBn	H	OBn	**39d**-α
38d-β	OBn	H	OBn	H	OBn	**39d**-β
38e-α	OMe	H	OMe	H	OMe	**39e**-α
38e-β	OMe	H	OMe	H	OMe	**39e**-β
38f-α	H	OMe	OMe	H	OMe	**39f**-α
38f-β	H	OMe	OMe	H	OMe	**39f**-β
41a	—	—	H	OBn	OBn	**40a**
41b	—	—	OBn	H	OBn	**40b**
42a-β	—	—	H	OBn	OBn	**43a**-β
42b-β	—	—	OBn	H	OBn	**43b**-β

Scheme 12 Synthesis of *C*-glycopyranosyl aldehydes 39a–f, 40a–c, 43a–b.



Scheme 13 Synthesis of α-*C*-glucopyranosyl aldehyde **3a**.



Scheme 14 Synthesis of β-*C*-galactopyranosyl aldehyde **50**.

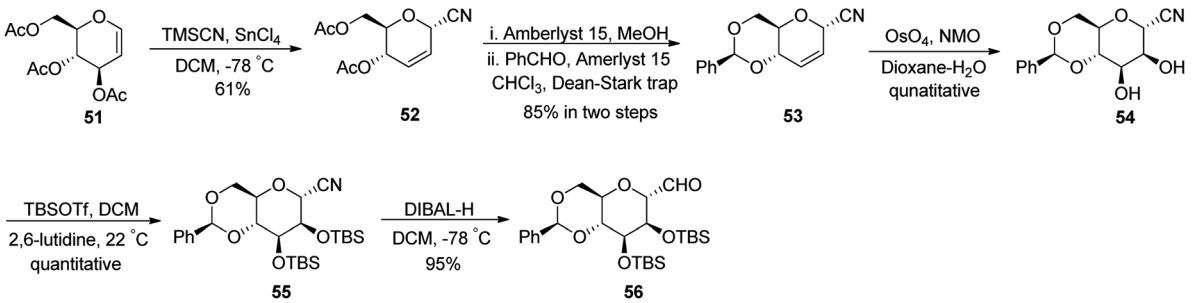
PTSA in DCM–acetone afforded β-*C*-galactopyranosyl aldehyde **50** in just 37% yield (Scheme 14).

Fujiwara *et al.*[37] synthesised β-*C*-glycopyranosyl aldehyde starting from tri-*O*-acetyl-D-glucal (Scheme 15). Acetyl-protected D-glucal **51** was converted into **52** by treatment with TMSCN, $SnCl_4$ in DCM at −78 °C in 61% yield, which transformed into benzylidene-protected compound **53** by using solid support acid (Amberlyst 15) in methanol followed by benzaldehyde in chloroform, which was refluxed using Dean–Stark apparatus to afford benzylidene protection. The yield obtained in two steps was 85%. Alkene **53** underwent dihydroxylation by treatment with osmium tetraoxide, NMO in dioxane–water to furnish diol **54** in quantitative yield. Silyl protection was carried out using TBSOTf in the presence of 2,6-lutidine in DCM to afford protected cyanide **55** quantitatively, which was further subjected to DIBAL-treatment to furnish benzylidene-protected pyranosyl aldehyde **56** in 95% yield.

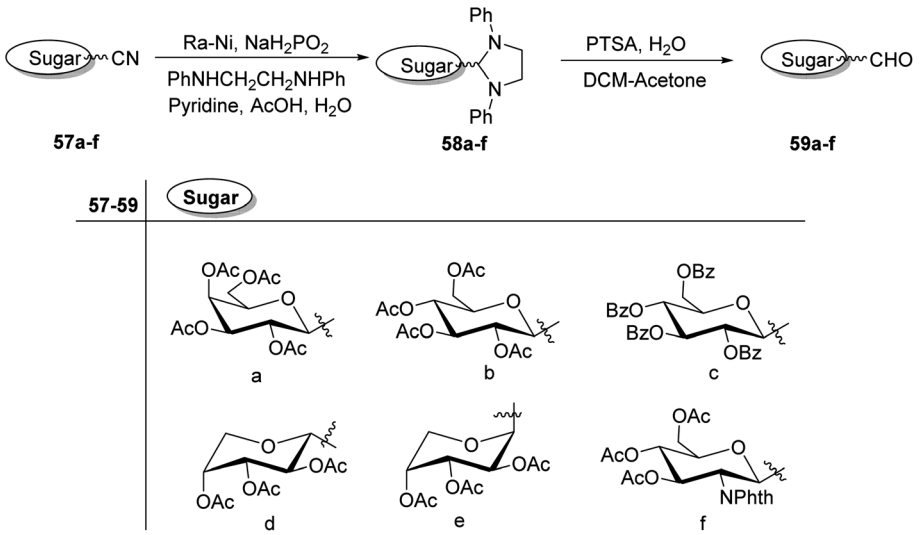
C-Glycopyranosyl aldehydes from cyanide precursors were also obtained by Toth *et al.*[38] using Dettinger *et al.*[36] protocol where reduction of glycosyl cyanides **57a–f** was achieved by RANEY® nickel and sodium hypophosphite in pyridine-aqueous acetic acid in the presence of *N*,*N*-diphenylethylenediamine to obtain imidazolidine derivatives **58a–f**. Further, by using PTSA in DCM–acetone under acidic reaction conditions *C*-glycopyranosyl aldehydes **59a–f** were obtained (Scheme 16). Further, the synthesized *C*-glycopyranosyl aldehydes **59a–f** were used for the synthesis of *exo*-glycals.

2.5 Enoxysilane approach

The cyanide approach furnished the desired *C*-glycopyranosyl aldehyde in just one step, *i.e.* protection of the cyanide group with *N*,*N*-diphenylethylenediaminein pyridine followed by treatment with PTSA and direct reduction of cyanide using reducing agents DIBAL-H or $LiAlH_4$. However, the increased

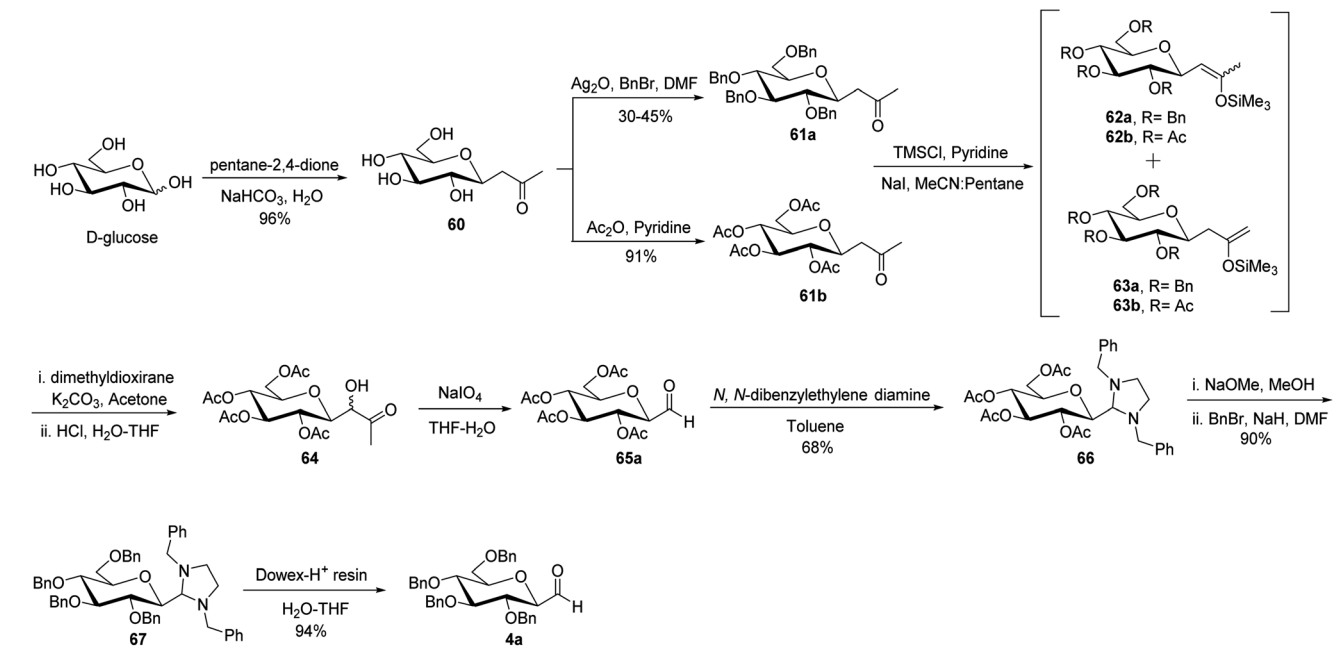


Scheme 15 Synthesis of α-*C*-glycopyranosyl aldehyde **56**.



Scheme 16 Synthesis of *C*-glycopyranosyl aldehydes **59a–f**.

interest in the synthesis of β-*C*-glycopyranosyl aldehydes due to their demanding application as intermediates in the formation of various complex *C*-glycosides led Zeitouni *et al.*[39] to introduce a new synthetic approach using enoxysilanes as a key intermediate. In this approach, the β-D-glucosidic ketone **60** was synthesised from D-glucose in 96% yield using pentane-2,4-dione. Next, compound **60** was subjected to benzylation (reagents: Ag_2O, BnBr in DMF) and acetylation (reagents: Ac_2O in pyridine) individually yielding **61a** and **61b** with a yield of 30–45% and 91%, respectively, which on enolization using TMSCl in pyridine formed structural isomers **62a** and **63a** (from **61a**) and similarly, compounds **62b** from **61b**. However, better regioselectivity was observed for compound **61b** as compared to compound **61a.** It has been observed that it was difficult to perform benzylation with the classical benzylation process (NaH, benzyl bromide, DMF) as compounds had ketone functional group present in the molecule, which further resulted in non-regioselective enolisation of compound **61a.** Subsequently, the scheme further proceeded with the reaction of enoxysilane **62b** with a freshly prepared solution of dimethyldioxirane (DMDO) to yield α-hydroxy ketone **64**, which on further treatment with sodium metaperiodate in THF–water produced desired β-*C*-glycopyranosyl aldehyde **65a.** Compound **65a** turned out to be

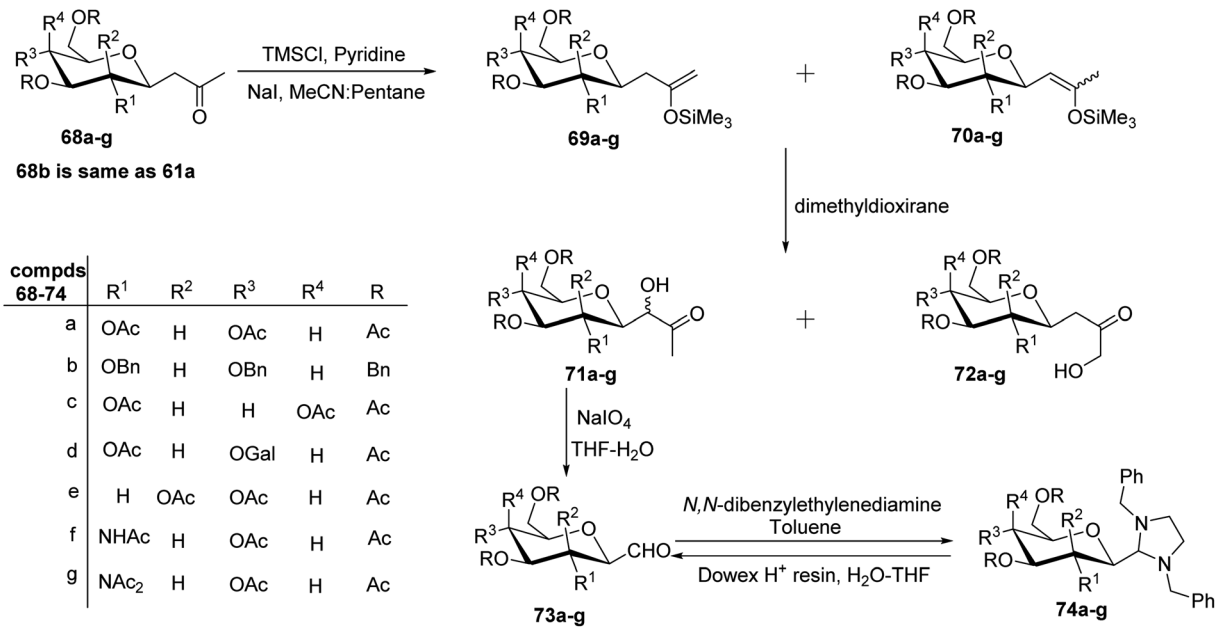


Scheme 17 Synthesis of β-*C*-glucopyranosyl aldehydes **65a** and **4a**.

unstable and less pure, so it was stored as aminal **66** using *N*,*N*-dibenzylethylene diamine in toluene. Compound 66 obtained in a yield of 68% was in turn benzylated to give **67** in a yield of 90%. On the deprotection of compound **67** with Dowex-H^+ resin quantitatively led to the formation of extremely pure β-*C*-glucopyranosyl aldehyde **4a** with a yield of 94% (Scheme 17).

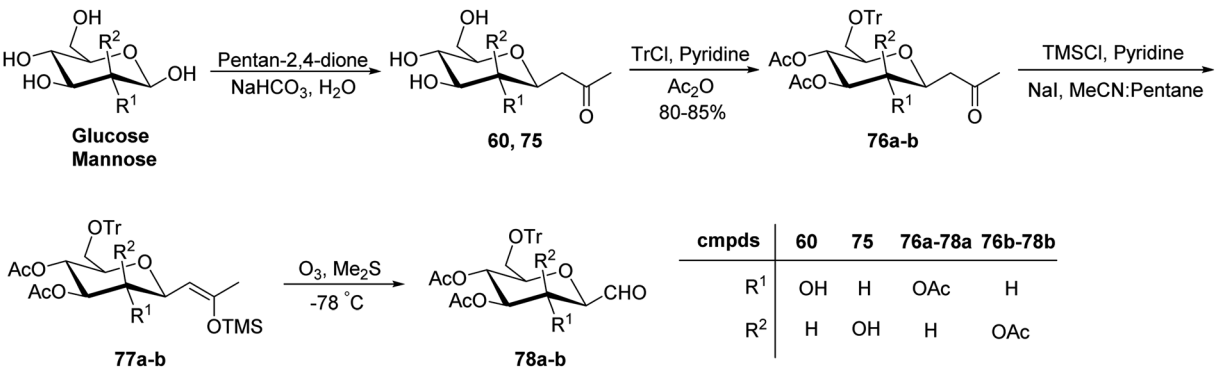
Later, Norsikian *et al.*[40] applied this effective approach to introduce the formyl group at the anomeric position of other sugar precursors and reported it to be very efficient for all sugars except D-mannose. β-*C*-Glycosyl ketones **68a–g** were treated with trimethylsilyl chloride in pyridine followed by sodium iodide in acetonitrile to afford enolized products **69a–g** and **70a–g**. The enoxysilanes thus produced were subjected to oxidation with DMDO, which produced α-hydroxy ketones **71a–g** as major products. Further, α-hydroxy ketones **71a–g** on treatment with sodium metaperiodate in THF–water gave the desired β-*C*-glycopyranosyl aldehydes **73a–g**. Due to the less stability of β-*C*-glycopyranosyl aldehydes and with an aim to achieve a more pure form of it, they were stored as aminal **74a–g**, which on deprotection with Dowex-H^+ resin yielded the purest forms of β-*C*-glycopyranosyl aldehydes **73a–g** (Scheme 18).

Xia *et al.*[41] reported synthesis of L-glucose and L-galactose starting from D-glucose and D-mannose, respectively. In this synthesis, *C*-glycopyranosyl aldehyde was achieved as an intermediate, which was further converted into L-glucose and L-galactose sugars (Section 3.8, Scheme 81). Thus, both sugars, *i.e.* D-glucose and D-mannose were treated with pentan-2,4-dione, sodium bicarbonate in water to afford ketones **60** and **75**, respectively. The primary hydroxyl group was selectively protected with trityl chloride followed by acetylation of the secondary hydroxyl group to afford **76a–b** in 80–85% yield. Further, the Norsikian[40] condition was applied on ketone **76a–b** to produce silyl enol ether **77a–b**, which upon ozonolysis furnished *C*-glycopyranosyl aldehyde **78a–b** (Scheme 19).



compds 68-74	R^1	R^2	R^3	R^4	R
a	OAc	H	OAc	H	Ac
b	OBn	H	OBn	H	Bn
c	OAc	H	H	OAc	Ac
d	OAc	H	OGal	H	Ac
e	H	OAc	OAc	H	Ac
f	NHAc	H	OAc	H	Ac
g	NAc_2	H	OAc	H	Ac

Scheme 18 Synthesis of β-*C*-glycopyranosyl aldehydes **73a–g**.



cmpds	60	75	76a-78a	76b-78b
R^1	OH	H	OAc	H
R^2	H	OH	H	OAc

Scheme 19 Synthesis of *C*-glycopyranosyl aldehydes **78a–b**.

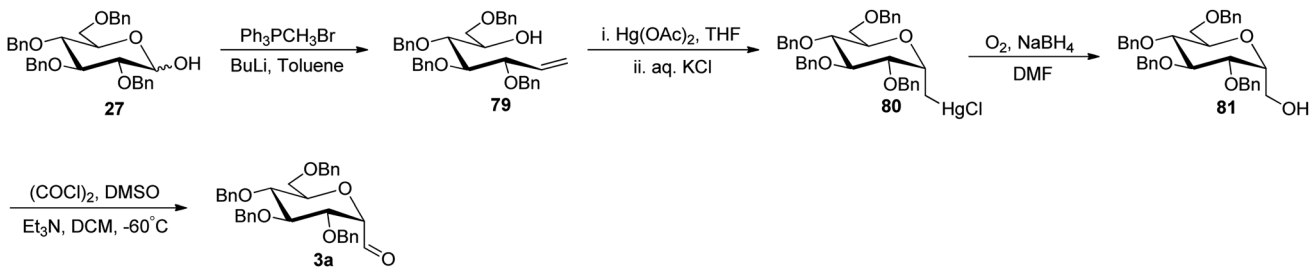
2.6. Alkene approach

The approaches using allene and thiazole ring as a masked formyl group were low yielding and in addition, the thiazole deprotection involved a lengthy process. Besides, enoxysilane approach incriminated difficult synthesis of benzylated glycopyranosyl aldehydes due to by-product formation during DMDO treatment and the use of DMDO, which made this synthetic procedure cumbersome. Dietrich *et al.*[42] utilized Wittig reaction conditions to carry out a reaction between commercially available 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**27**) and methylenetriphenylphosphorane to afford alkene **79** following the reported procedure.[43] Further, mercury-mediated cyclisation of compound **79** afforded oxymercuration product **80** with the known procedure.[44] Then, oxidative demercuration of **80** using O_2–$NaBH_4$ produced alcohol **81**,[45] which was subjected to Swern oxidation to afford α-*C*-glucopyranosyl aldehyde **3a** (Scheme 20). The obtained compound **3a** was found to be very labile and immediately used for the synthesis of benzyl-α-*C*-glucosides and anilinomethyl-α-*C*-glucosides, which act as α-glucosidase inhibitors (Section 3.5, Scheme 62).

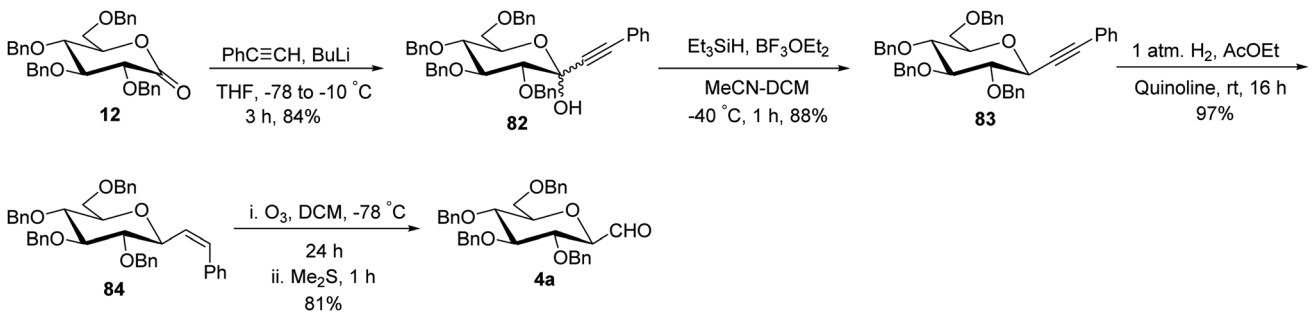
Sanchez *et al.*[31] introduced the sugar alkene as a key synthetic intermediate, which was obtained *via* nucleophilic addition and reductive dehydroxylation. This approach provided the stereochemical control during reductive dehydroxylation, before unmasking of the formyl group, unlike allene and thiazole approaches where both α- and β-isomer were formed. Sugar lactone **12** on treatment with phenylacetylyllithium at −78 °C gave a diastereomeric mixture (1 : 1) of lactol **82** in 84% yield, which furnished single isomer β-*C*-glycoside **83** in 88% yield after stereoselective removal of the hydroxyl group by triethylsilane in the presence of Lewis acid. After the stereoselectivity was achieved, Lindlar's catalyst was used in the presence of quinoline for hydrogenation, resulting in *cis*-alkene **84** in 97% yield. Further, alkene **84** was subjected to ozonolysis to afford exclusively β-*C*-glucopyranosyl aldehyde **4a** in 81% yield (Scheme 21).

Leclere *et al.*[46] prepared the α-*C*-glycopyranosyl aldehyde **90** from easily available galactosyl bromide **85.** Galactosyl bromide **85** undergoes allylation in the presence of allyltributylstannane and Et_3B/air and yielded α-*C*-allyl galactose derivative **86** in 70% yield and a trace amount, *i.e.* 6% of compound **87** resulting from *in situ* acyl migration. Terminal alkene **86** in the presence of a catalyst $(Ph_2MeP)_2Ir(COD)PF_6$ isomerised into internal alkene 2-propenyl derivative **88** using the designed protocol.[47] Initial attempts to produce desired *C*-glycopyranosyl aldehyde from acetyl-protected alkene **88** failed, so deprotection of acetate of compound **88** with K_2CO_3 in methanol followed by protection with iso-propylidenes using 2-methoxypropane, TsOH in DMF afforded compound **89** in 75% yield, which on ozonolysis yielded α-*C*-glycopyranosyl aldehyde **90** in good yield (Scheme 22).

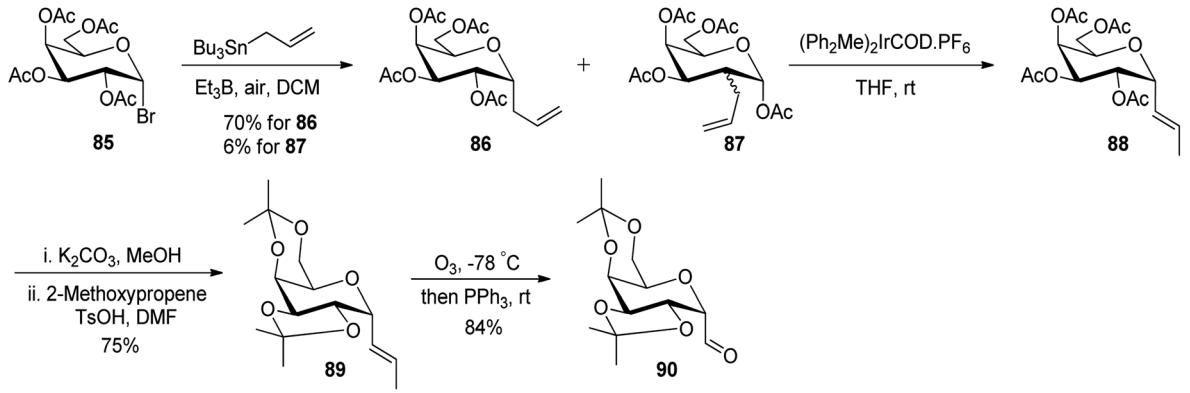
Chen *et al.*[48] incorporated easily and readily available starting material galactosyl pentaacetate **5.** The galactosyl pentaacetate **5** was subjected to allylation at the anomeric position in the presence of allyl trimethylsilane in $BF_3{\cdot}Et_2O$ to afford compound **86** in 77% yield, which next underwent de-protection in the presence of sodium methoxide in methanol followed by benzyl protection in the presence of BnBr led to the formation of compound **91** in 93% yield. Palladium-mediated isomerisation of the terminal alkene of compound **91** was performed into internal sugar alkene **92** with a 90% yield. Subsequently, compound **92** on ozonolysis followed by *in situ* reduction and



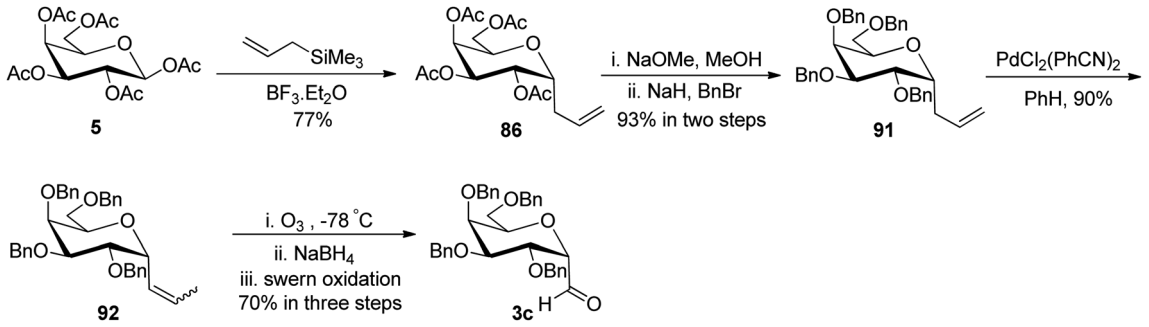
Scheme 20 Synthesis of α-*C*-glycopyranosyl aldehyde **3a**.



Scheme 21 Synthesis of α-*C*-glycopyranosyl aldehyde **4a**.



Scheme 22 Synthesis of α-*C*-glycopyranosyl aldehyde **90**.

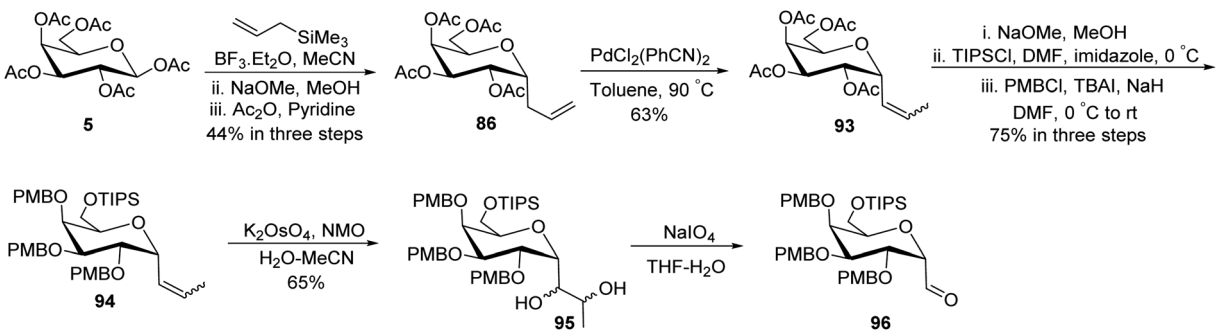


Scheme 23 Synthesis of α-*C*-galactopyranosyl aldehyde **3c**.

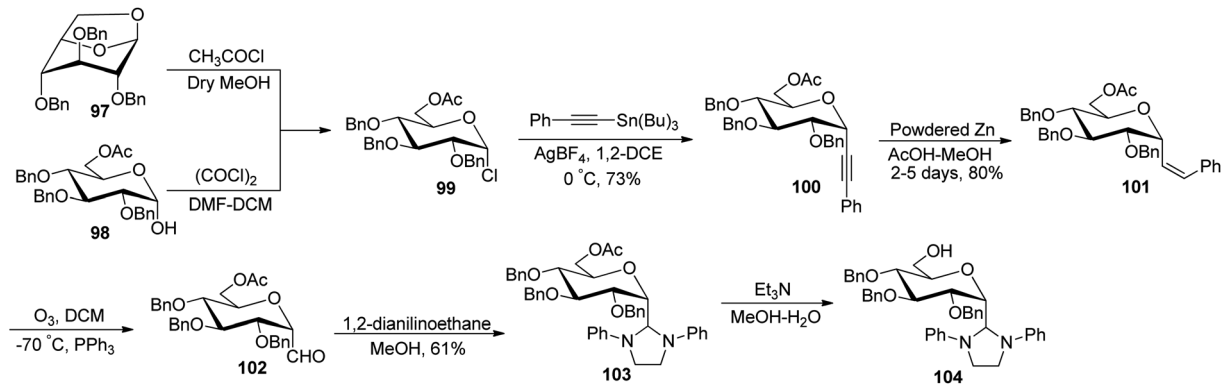
further treatment with Swern oxidation resulted in the formation of α-*C*-galactopyranosyl aldehyde (Scheme 23).

Guillaume *et al.*[27] designed a strategy to synthesise α-*C*-galactopyranosyl aldehyde **96** using galactosyl pentaacetate **5**, which is a readily available starting material. The *C*-glycosylation of compound **5** was performed with allyl trimethylsilane using conditions of Chen *et al.*[48] to afford terminal sugar alkene **86** in 44% yield, which on palladium catalysed double bond isomerisation resulted in propene **93** in 63% yield. Compound **93** upon Zemplen deacetylation with sodium methoxide in methanol followed by selective protection of primary alcohol with tri-isopropylsilyl ether and secondary alcohol were masked in the presence of PMBCl to obtain compound **94** in 75% yield. Alkene **94** on osmium-catalysed dihydroxylation resulted in vicinal diol **95**, which underwent further reaction with sodium-periodate resulting α-*C*-galactopyranosyl aldehyde **96** (Scheme 24), which was further utilized for the synthesis of C6-modified α-*C*-GalCer analogues.

Desire *et al.*[49] reported synthesis of α-*C*-glucopyranosyl aldehyde *via* alkene as a key intermediate (Scheme 25). 6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl chloride (**99**) was synthesised by ring opening of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (**97**) or from 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose (**98**) by following reported literature.[50] Further treatment of compound **99** with tributyl(phenylethynyl)tin in the presence of silver tetrafluoroborate in 1,2-dichloroethane at



Scheme 24 Synthesis of α-*C*-galactopyranosyl aldehyde **96**.



Scheme 25 Synthesis of α-*C*-glucopyranosyl aldehyde **102**.

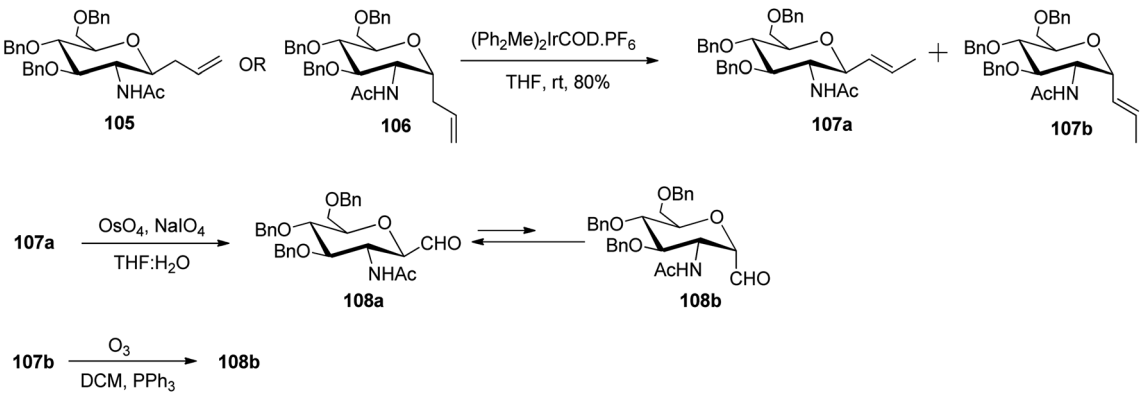
0 °C produced selectively (α-D-glucopyranosyl) phenylacetylene **100** in 73% yield. Hydrogenation of compound **100** was carried out by using powdered zinc in AcOH–MeOH for a long time of 2–5 days to give *Z*-alkene **101** in 80% yield, which underwent ozonolysis to afford α-*C*-glucopyranosyl aldehyde **102**, which was found to be prone to decomposition; therefore, it was masked by *N*,*N*′-diphenylethylenediamine as stable 1,3-diphenylimidazolidines **103** with 61% yield and could be regenerated by mild acidic treatment. Deacetylation was achieved using triethylamine in methanol–water to afford **104**.

Among the other alkene approaches, the metal-catalysed isomerisation of allyl species was also achieved by McGarvey *et al.*[51] where the benzyl protected β-isomer, **105** and the α-isomer, **106** on exposure to iridium catalyst, $(Ph_2Me)_2$-IrCOD·PF_6 (10 mol%) yielded isomeric vinyl glycosides **107a** and **107b** in 80% yield. These isomeric vinyl glycosides further gave β- and α-linked *C*-glycopyranosyl aldehydes, where the β-linked isomer was the major product. Substrate **107b** upon ozonolysis gave the desired **108b** isomer with >90% yield. Similarly, compound **107a** underwent oxidative cleavage using Lemieux reaction conditions yielding **108a** analogue. The aldehydes **108a** and **108b** thus obtained acted as intermediates for various further syntheses (Scheme 26).

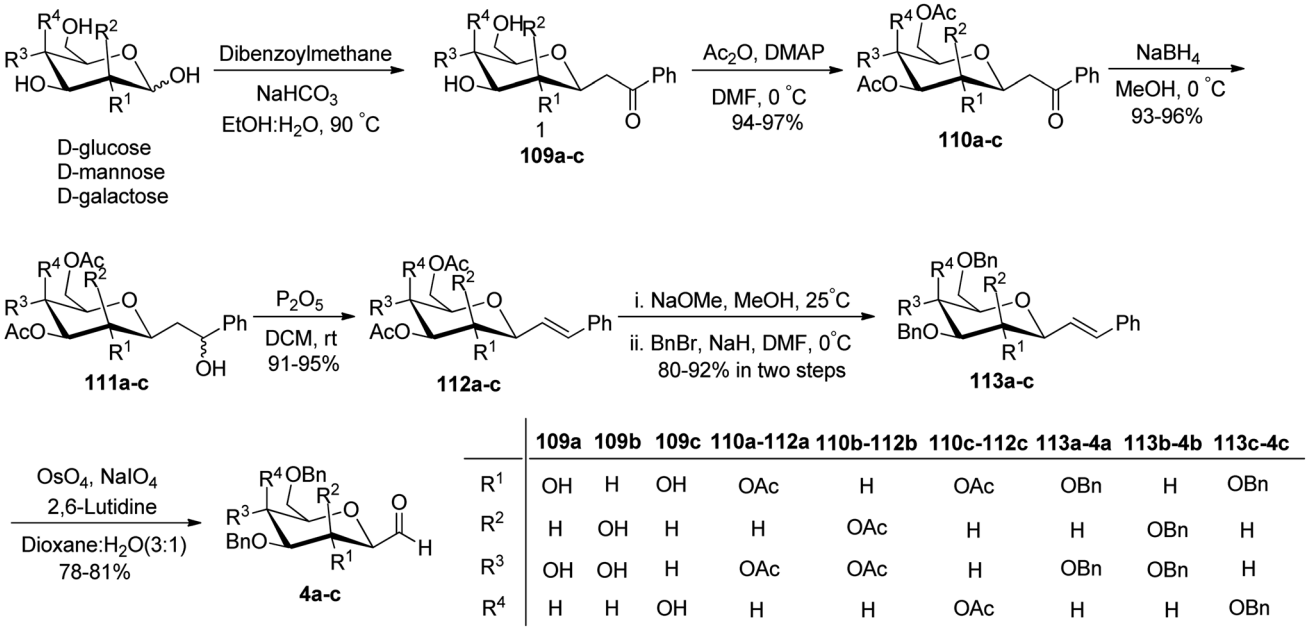
Khatri *et al.*[52] reported another synthesis of stereoselective β-linked *C*-glycopyranosyl aldehyde *via* an alkene approach using easily available precursors *i.e.*, D-galactose, D-glucose, and D-mannose. The native sugars were treated under a developed procedure,[53] *i.e.* reaction with dibenzoylmethane–sodium bicarbonate in aqueous alcoholic solution gave β-*C*-glycosyl benzoylmethane **109a–c**, which further reacted with acetic anhydride–DMAP in DMF yielding the peracetylated derivatives of β-*C*-glycosyl benzoylmethane **110a–c** in 94–97% yield. Compounds **110a–c** upon reduction with $NaBH_4$ gave corresponding alcohols **111a–c** in 93–96% yield, which was followed by dehydration reaction with dehydrating reagent P_2O_5 in dichloromethane to obtain alkene derivatives **112a–c** in 91–95% yield. The peracetylated *C*-glycosides **112a–c** were converted to the corresponding perbenzylated sugar alkene **113a–c** since the former gave very unstable products on oxidation. Hence, **112a–c** were firstly deacetylated using sodium methoxide followed by perbenzylation using benzyl bromide in NaH to obtain the perbenzylated sugar alkene **113a–c** in 80–92% yield. These perbenzylated analogues **113a–c** upon oxidation with OsO_4–$NaIO_4$ resulted in β-*C*-glycopyranosyl aldehydes **4a–c** in 78–81% yield (Scheme 27).

2.7 Nitromethane approach

In the above-discussed approaches, the alkene approach was found to be most efficient in respect of overall yield obtained and selectivity due to the formation of only one anomeric



Scheme 26 Synthesis of *C*-glycopyranosyl aldehydes **108a–b**.



	109a	109b	109c	110a-112a	110b-112b	110c-112c	113a-4a	113b-4b	113c-4c
R^1	OH	H	OH	OAc	H	OAc	OBn	H	OBn
R^2	H	OH	H	H	OAc	H	H	OBn	H
R^3	OH	OH	H	OAc	OAc	H	OBn	OBn	H
R^4	H	H	OH	H	H	OAc	H	H	OBn

Scheme 27 Synthesis of β-*C*-glycopyranosyl aldehydes **4a–c**.

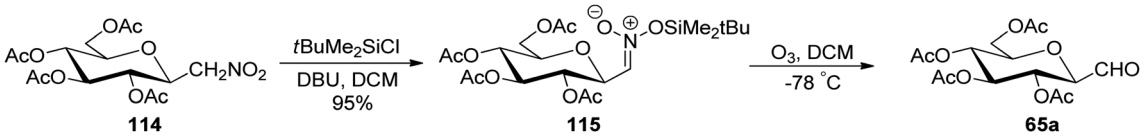
isomer of *C*-glycopyranosyl aldehydes. Moreover, the synthetic routes consisted of cheap and easily available starting materials. Now we are moving towards the end of approaches developed for the synthesis of *C*-glycopyranosyl aldehydes and at last we are discussing nitromethane as a key synthetic intermediate. So, Martin *et al.*[54] developed a synthetic route for the synthesis of the β-*C*-glucopyranosyl aldehyde **65a** starting from β-D-glucosylnitromethane **114**, which in turn can be synthesized from readily available D-glucose following two steps.[55] The β-D-glucosylnitromethane **114** on reaction with *tert*-butyldimethylsilyl chloride, DBU in DCM, yielded the silyl nitronate derivative **115** in 95% yield, which on ozonolysis afforded the 2,3,4,6-tetra-*O*-acetyl-β-*C*-glucopyranosyl aldehyde **65a** (Scheme 28).

Simo *et al.*[56] achieved the synthesis of *C*-glycopyranosyl aldehyde starting from nitromethane sugar precursor (Scheme 29). Here, *C*-(4,6-*O*-benzylidene-β-D-glucopyranosyl) nitromethane (**116**) was reduced to hydroxylamino derivative **117** using H_2, Lindlar catalyst in methanol which was difficult to isolate and directly oxidised in the air under basic condition (NH_4OH) to obtain *cis–trans* mixture of oxime **118** in 70% yield. The oxime **118** reacted with H_2 in the presence of RANEY® nickel affording the dimeric aminal **119** in 79%, which on reaction with 1,2-dianilinoethane (Wanzlick base) produced imidazolidine **120** in 90% yield. Acetylation was carried out using acetic anhydride in pyridine to afford **121**, which was hydrolysed by *p*-toluenesulfonic acid monohydrate in dry THF to furnish *C*-glycopyranosyl aldehyde **122** in 57% yield.

Petrusova *et al.*[57] designed a one-step protocol for the synthesis of β-*C*-glycopyranosyl aldehydes from β-D-glucosylnitromethane (Scheme 30). 2,6-Anhydro-7-deoxy-7-nitro-L-*glycero*-L-galacto-heptitol **123a–d** treated with an aqueous alkaline solution followed by ozonolysis at room temperature to give β-*C*-glycopyranosyl aldehydes **124a–d**. It was observed that in an aqueous solution, the compound **124a–d** exists in its hydrate form predominantly. Thus, the resulting native *C*-glycopyranosyl aldehydes **124a–d** were found very much labile and were used further for the synthesis of 2-β-D-glycopyranosyl-nitroethenes and -nitroethanes (Section 3.8, Scheme 82).

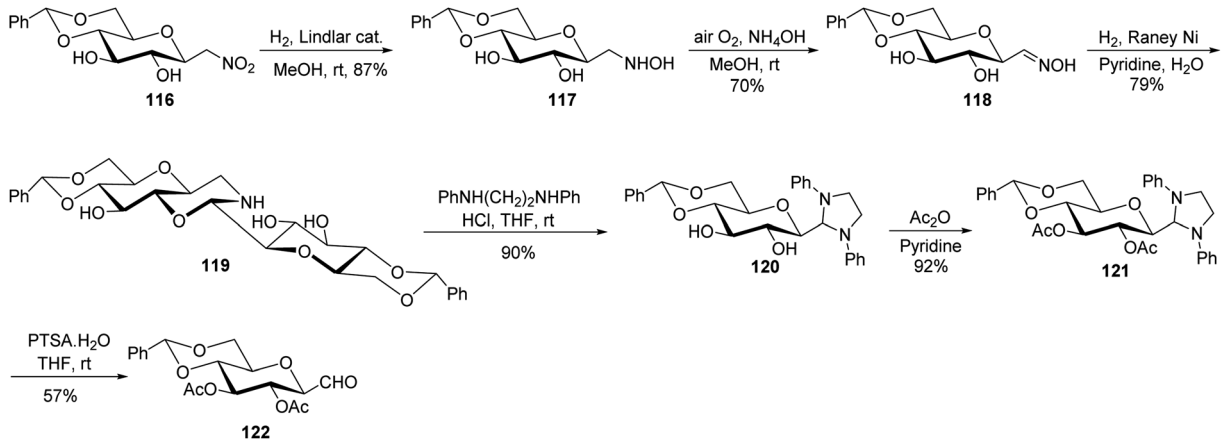
3. Synthesis of *C*-glycoconjugates

The availability of numerous methods to bring diversity in the formation of aldehyde at the anomeric position of sugar benefited the development of *C*-galactosphingo lipid analogues, *C*-glycopyranosyl disaccharides, *C*-glycopyranosyl amino acid precursors, *C*-glycopyranosyl-amino acids and dipeptides, glycopyranosyl phenyl methane and its fluoro derivatives, *C*-glycopyranosyl heterocycles, glycopyranosyl bis-amides, several natural product fragments, and many other *C*-linked glycoconjugates. Some of them play important roles in biological systems, for instance, glycoconjugate **125** is a potent inhibitor of

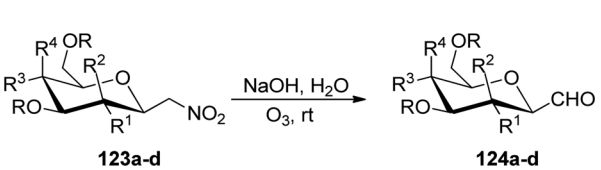


114 **115** **65a**

Scheme 28 Synthesis of β-*C*-glucopyranosyl aldehyde **65a**.



Scheme 29 Synthesis of *C*-glycopyranosyl aldehyde **122**.



compds 123-124	R^1	R^2	R^3	R^4	R
a	OH	H	H	OH	H
b	OH	H	OH	H	H
c	H	OH	OH	H	H
d	NHAc	H	OH	H	H

Scheme 30 Synthesis of β-*C*-glycopyranosyl aldehydes **2a–d**.

ice recrystallization and could protect embryonic liver cells from cryo-injury;[46] the acyl- and benzyl-*C*-β-D-glucosides (**126** and **127**) work as glucose uptake promotor;[58] *C*-mannosides analogues (**128a–b**) block uropathogenic *Escherichia coli* from colonizing the lower urinary tract;[59] *C*-glycosides **129a–c** were determined by ELISA of a blood sample obtained from mice stimulated by a 1 μg injection of glycolipid in the buffer. It was found that *E*-isomer **129b** is superior to *Z*-isomer **129c** as a ligand for CD1d/NKT immunity pathway;[48] *C*-linked galactosphingo lipid analogue (**130**) blocks the interaction of HIV-1 gp120 with GalCer;[60] *C*-linked disaccharide analogue (**131a**) of TF epitope induces a strong immune response in mice, which imparts it a possibility to be developed as a therapeutic vaccine;[61] *C*-linked disaccharide (**132a**) mimics *O*-β-D-galactopyranosyl-(1–3)-D-galactopyranosidesand proved to be a suitable agent for *O*-glycosidation and construction of glycoconjugates;[62] carbohydrate amino acids mimetic (**133**) shows *in vivo* stability towards α-galactosidase enzyme and might function as glycosidase inhibitor(Fig. 4).[25] Henceforth, we describe the following synthetic processes for the development of structurally diversified and complex *C*-glycoconjugates.

3.1 *C*-Glycolipid analogues

Bertozzi *et al.*[60] designed a range of water-soluble, *C*-linked galactosphingo lipid derivatives, which bind specifically to HIV-1 gp120, inhibiting its interaction with CD_4 of host cells. The designed compounds have β-linked galactose mimicking galactosyl ceramide (GalCer) antibodies, which inhibit the infection of two CD_4-negative neural cell lines. The synthesis of these *C*-linked galactosphingo lipids was initiated from β-*C*-galactopyranosyl aldehyde **4c**, which upon condensation with Wittig reagent **134** furnished oxazolidinone **135** in 34% yield. Next, alkene was reduced by tosyl hydrazine and sodium acetate in DME-H_2O producing compound **136** in 92% yield, which was transformed into compound **137** using the reaction condition of Boc-anhydride/triethylamine in DMF, and further calcium carbonate in methanol. Upon oxidation with Jones reagent, compound **138** was achieved in 95% yield, which was transformed to its amide derivative **139** by reaction with tetradecylamine in the presence of coupling reagent (EDC and HOBt). The deprotection of Boc and benzyloxy group was achieved on treatment with TFA and H_2 in Pd/C to afford *C*-linked galactosphingo lipid **130** quantitatively (Scheme 31). Similarly, other derivatives **140**, **141**, **142**, and **143** were also synthesized from the condensation of acid derivative **138** and different varieties of amines (Table 3). The introduction of different amines displayed different inhibition range against gp120 GalCer binding at 1 mg mL^{-1} as given in Table 3.

It was observed that compound **130** (entry 1) showed the highest affinity for recombinant gp120 at $IC_{50} = 120$ μM and slightly better than their *O*-linked glycolipid analogue **143** (entry 5). A decrease in inhibitory activity was observed with a decrease in the length of hydrocarbon.

Guillaume *et al.*[27] designed a strategy to synthesise immunogenic glycolipids due to their importance in the medical field. These have the potential to act as vaccine adjuvants to fight cancer and other microbial infections. One such glycolipid synthesised is α-GalCer analogues starting from *C*-

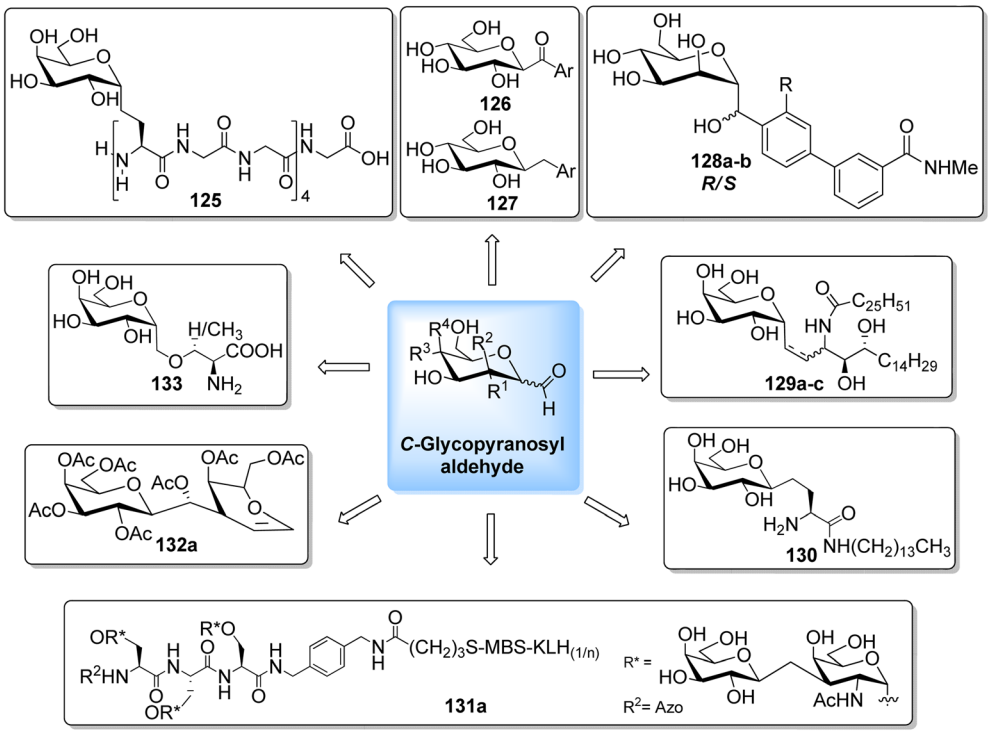
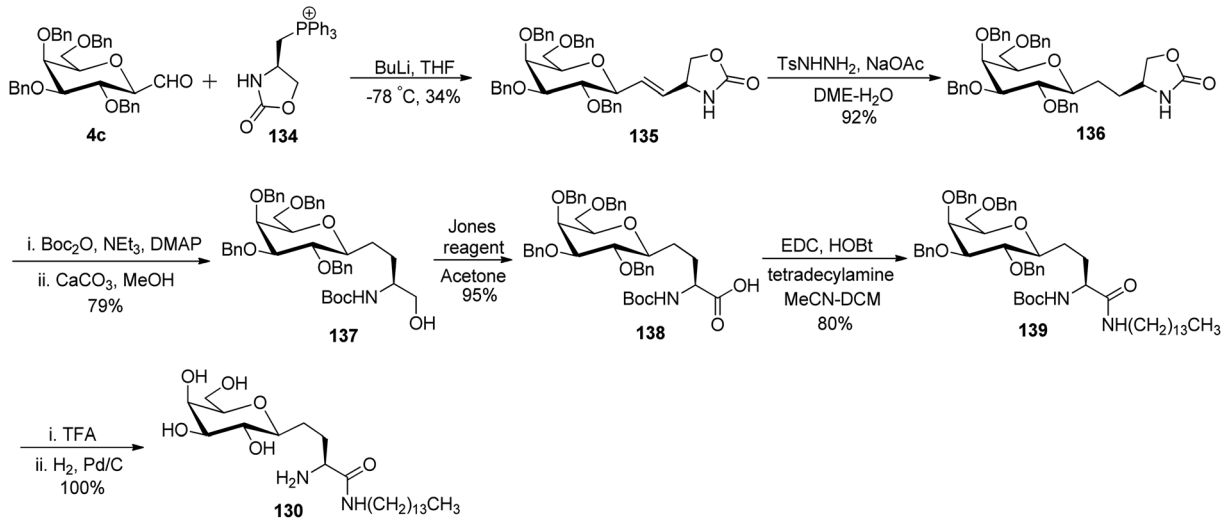


Fig. 4 Structures of various biologically important *C*-glycoconjugates derived from *C*-glycopyranosyl aldehyde.

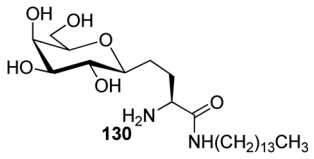
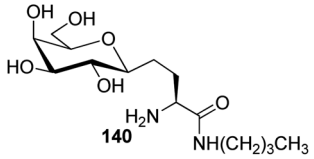
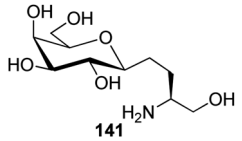
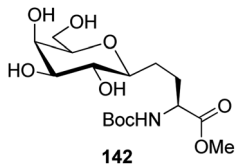
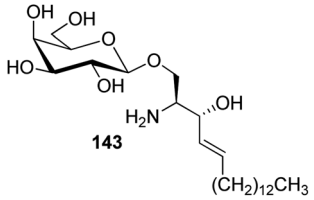


Scheme 31 Synthesis of galactosphingo lipid **130**.

galactopyranosyl aldehyde **96** (Scheme 32a). Aldehyde **96** upon Julia–Kocienski olefination with the known benzothiazole **144** yielding inseparable α–β anomers of olefin **145a–b** in just 44% yield. Olefin **145a–b** underwent deprotection of silyl ethers on treatment with tetrabutylammonium fluoride, leading to the separation of both anomers and α-anomer alcohol **146** in 65% yield was subjected to Mitsunobu reaction with phthalimide to afford compound **147** in 88% yield. This compound **147** on treatment with methylhydrazine did not reduce the double bond, while the same compound on treatment with hydrazine monohydrate reduced the alkene and liberated free ammonia. Further treatment of both analogues with 1-napthyl isocyanate furnished corresponding urea derivatives **148** and **150**, in 66% and 77% yields, respectively. Further, deprotection of compounds **148** and **150** was achieved by treatment of 4 M HCl in dioxane after that acylation with cerotoyl chloride in a biphasic mixture of THF and 1 M KOH solution gave α-*C*-GalCer derivatives **149** and **151** in 29% yield, respectively.

Further, for the synthesis of α-GalCer analogues **153** and **156**, the alcohol **146** on treatment with *p*-nitrophenyl chloroformate

Table 3 Different amines displaying different inhibition ranges

Entry	Compounds	% inhibition of 1 mg mL^{-1}
1	 **130**	86 (IC_{50} = 120 μM)
2	 **140**	34
3	 **141**	0
4	 **142**	0
5	 **143**	96 (IC_{50} = 160 μM)

followed by the addition of 4-aminopyridine resulted in the 4-pyridylcarbamate intermediate **152** in 62% yield, while the same sequence when followed after the reaction with hydrazine and 1-napthyl isocyanate afforded 4-pyridylcarbamate intermediate **155**. Both compounds **152** and **155** when treated with HCl followed by acetylation afforded the corresponding pyridinylcarbamate analogues **153** and **156** in 17% and 44% yields, respectively (Scheme 32b).

Chen *et al.*[48] reported the synthesis of *E* and *Z* α-*C*-galactosylceramides using Julia–Lythgoe–Kocienski reaction as the key step between *C*-glycopyranosyl aldehyde **3c** and sulfones **157** or **158** using lithium hexamethyldisilazide (LiHMDS) at −78 °C to afford olefin **159** along with a trace amount of 1-*C*-formyl glycal (Scheme 33a). Only an *E*-isomer was formed in the case of BT-sulfone while in the case of PYR-sulfone *E*/*Z* ratio (39 : 61) was obtained. Further, the installation of fatty amide side chain was achieved by treatment of olefin **159** with trifluoro acetic acid (TFA), triethylsilane (Et_3SiH) in DCM followed by di-isopropanyl carbodiimide (DIC), DMAP in butyl alcohol to obtain the precursor of targeted compound **160** in 80% yield. The *trans* isomer in amide **160** could be easily separated from its *cis* counterpart by flash chromatography. Finally, amide **160** was elaborated by either the retention or removal of double bonds. Hydrogenation of the double bond together with debenzylation was achieved using H_2, Pd/C to afford *C*-glycoside **129a** in 80% yield, while unsaturated compounds **129b** and **129c** were prepared in 80% and 84% yield, respectively, by Birch reduction ($Na–NH_3$).

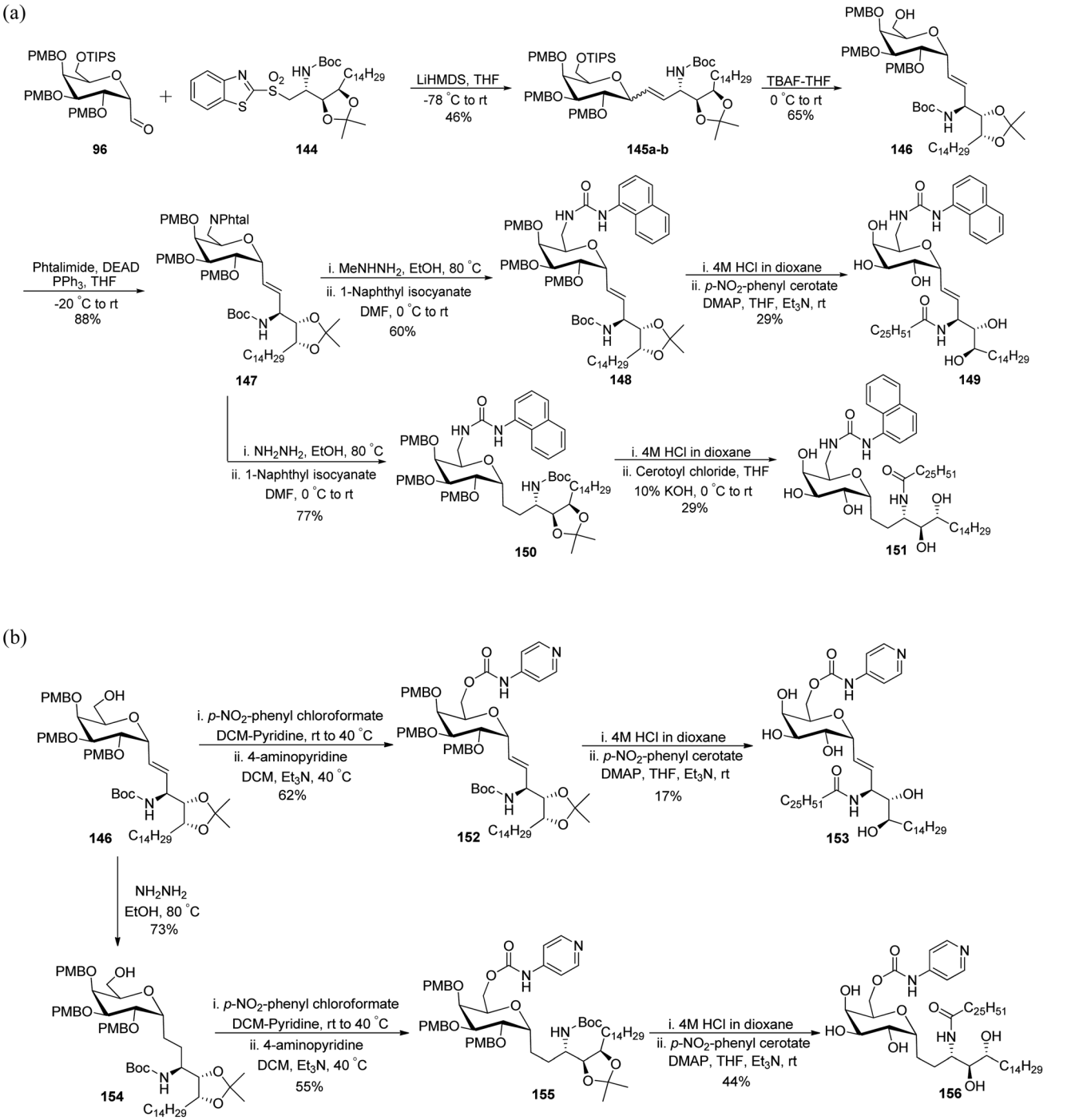
IL-12, IFN-γ and IL-4 levels of these synthetic *C*-glycosides **129a**, **129b**, and **129c** were determined by ELISA of blood samples obtained from mice stimulated by a 1 μg injection of glycolipid in the buffer. It was found that *E*-isomer **129b** is superior to *Z*-isomer **129c** as a ligand for the CD1d/NKT immunity pathway.

Both sulfones used in the above Julia–Lythgoe–Kocienski reaction were prepared from commercially available phytosphingosine (Scheme 33b). BOC protection was achieved from phytosphingosine to afford butyl carbamate **161** in 93% yield. Further, primary alcohol was temporarily blocked by the silyl protecting group (TBSCl) followed by isopropylidene protection of vicinal diol and deprotection of primary alcohol, producing precursor **162** in 87% yield. Mitsunobu transformation to thioether using PPh_3, BtSH, and DIAD followed by oxidation with *m*-CPBA afforded BT-sulfone **157** in 95% yield. Similarly, the mesylation of the hydroxyl group in **162** followed by substitution with PYRSH afforded **164**, which on oxidation with *m*-CPBA produced PYR-sulfone **158** in 92% yield.

Dondoni *et al.*[63] developed a strategy for the synthesis of β-D-galactosyl ceramide methylene isostere starting from *C*-galactopyranosyl aldehyde (Scheme 34). First, *C*-galactopyranosyl aldehyde **4c** was transformed into alkyloxazolidine **164** by a sequence of reactions.[64] Acetonide protective group removal was achieved by $AcOH–H_2O$ to afford *N*-Boc amino alcohol, which on further oxidation under Swern conditions obtained aldehyde **165** in 55% yield. Addition of lithium 1-pentadecyne in anhydrous THF produced alcohol **166** as a mixture of *S*/*R* (*syn*/*anti*) isomer in a 70 : 30 ratio. Due to the isomer formation, oxidation–reduction steps were carried out with **166**. First, Swern oxidation afforded ketone **167** followed by reduction with L-selectride in THF afforded *anti* isomer **168** as a major product with *S*/*R* (*syn*/*anti*) isomer in a 5 : 95 ratio. BOC deprotection was carried out with 4.8 M HCl in dioxane-afforded amino alcohol **169** in 90% yield. Further, stereoselective hydrogenation of triple bond using lithium aluminium hydride produced alkene **170** where installation of *N*-palmitoyl group produced benzyl protected β-D-galactosyl ceramide methylene isostere **171** in 80% yield. Switching of the protective group produced another β-D-galactosyl ceramide methylene isostere **172** in 55% yield. Isostere **172** with a 45% yield was also obtained from **169** *via* another sequence of reactions (Scheme 34).

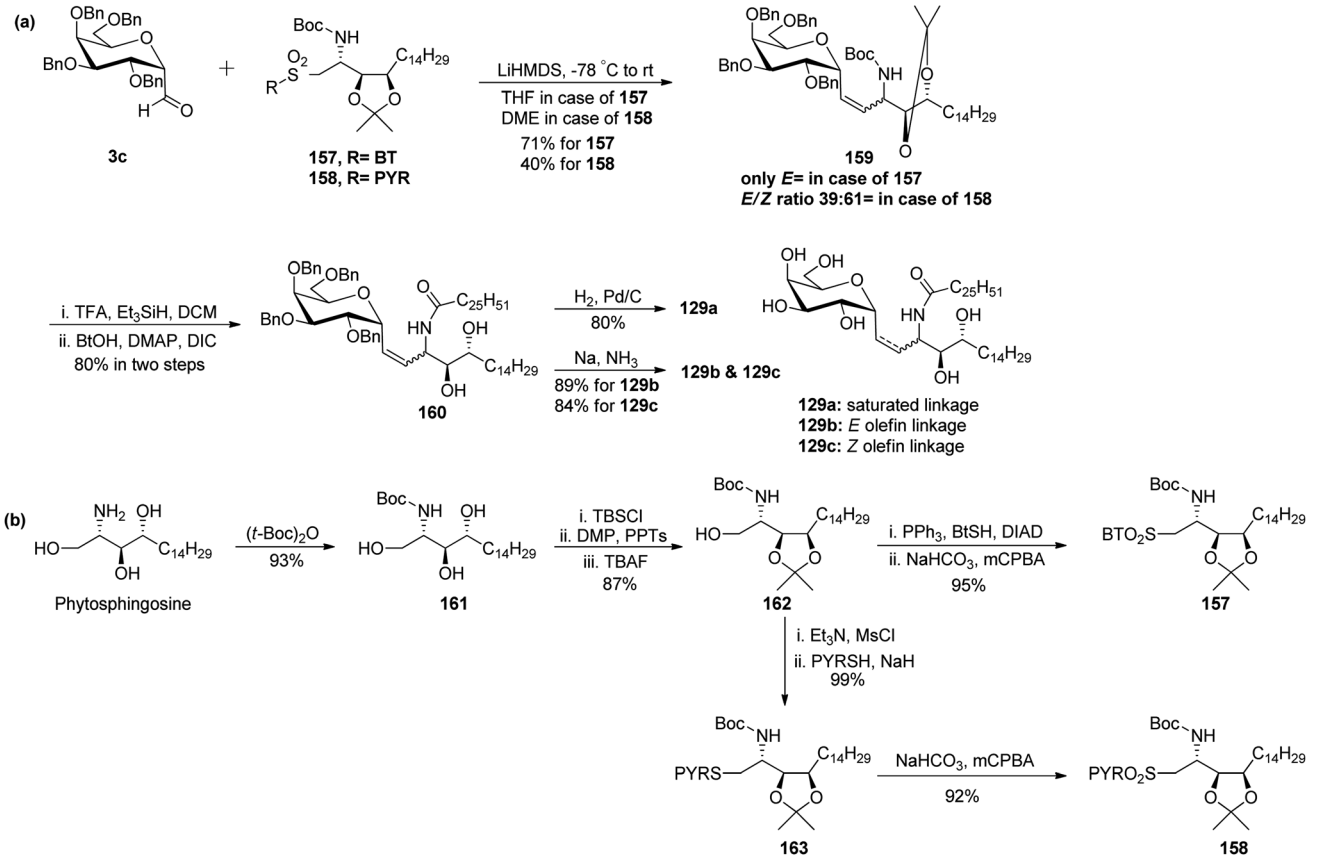
3.2 *C*-Glycopyranosyl di- and polysaccharides

Due to the presence of ubiquitous glycosidases and their ability to carry out hydrolysis, a short lifetime of the usual *O*-linked disaccharide conjugates was observed in the bloodstream whereas *C*-linked disaccharides are stable enough towards hydrolysis so that they could be utilised as a disaccharide-based vaccine. Due to the immense potential of *C*-linked disaccharides, Kobertz *et al.*[65] described the synthesis of *C*-linked disaccharide using nitro aldol condensation between *C*-

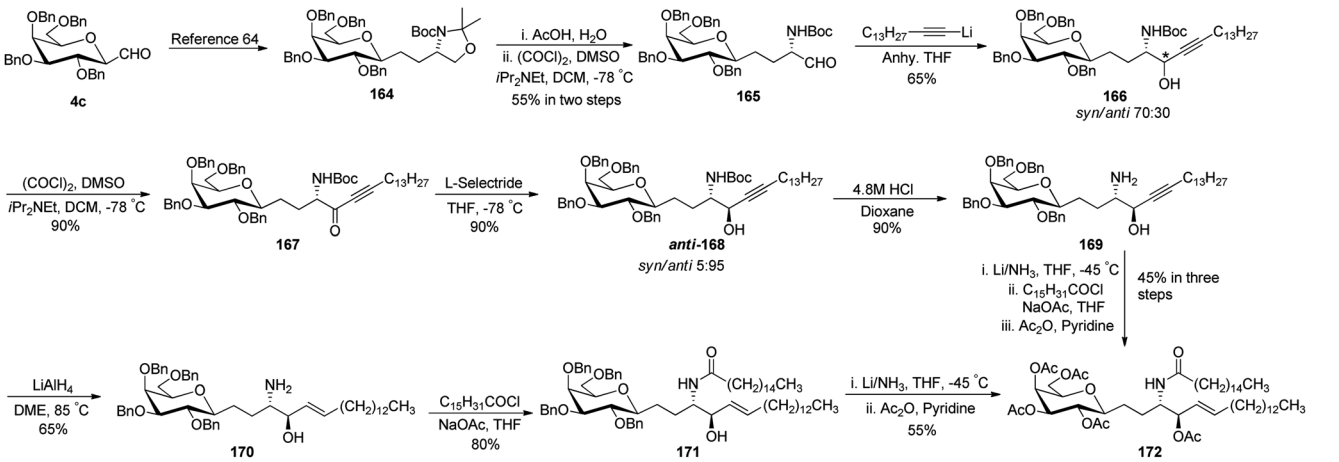


Scheme 32 (a) Synthesis of α-GalCer analogues **149** and **151**. (b) Synthesis of α-GalCer analogues **153** and **156**.

galactopyranosyl aldehyde **4c** and nitro sugar **175** in the presence of KF in acetonitrile, which afforded compound **176** as a diastereomeric mixture in 52% yield (Scheme 35). Nitro sugar derivative **175** used herein was prepared from compound **1a** by acid catalysed selective debenzylation followed by substitution with the azide group to obtain **174.** Next, compound **174** was subjected to reduction followed by oxidation to afford compound **175** in 61% yield. Compound **176** was converted into completely protected compound **177** using *n*-butyl lithium followed by phenyl chlorothionocarbonate (PTC-Cl), which was used in the next step without isolation. Further, a radical-assisted elimination reaction using Bu_3SnH-AIBN was carried out to afford alkene **178** in 10% yield calculated from compound **176.** The reduction of olefin **178** was carried out by diimide (generated in *situ* from tosyl hydrazine and sodium acetate) to obtain disaccharides **179** in 98% yield. The debenzylation of **179** was carried out by dissolving metal reduction in liquid ammonia to obtain compound **180** in quantitative yield.

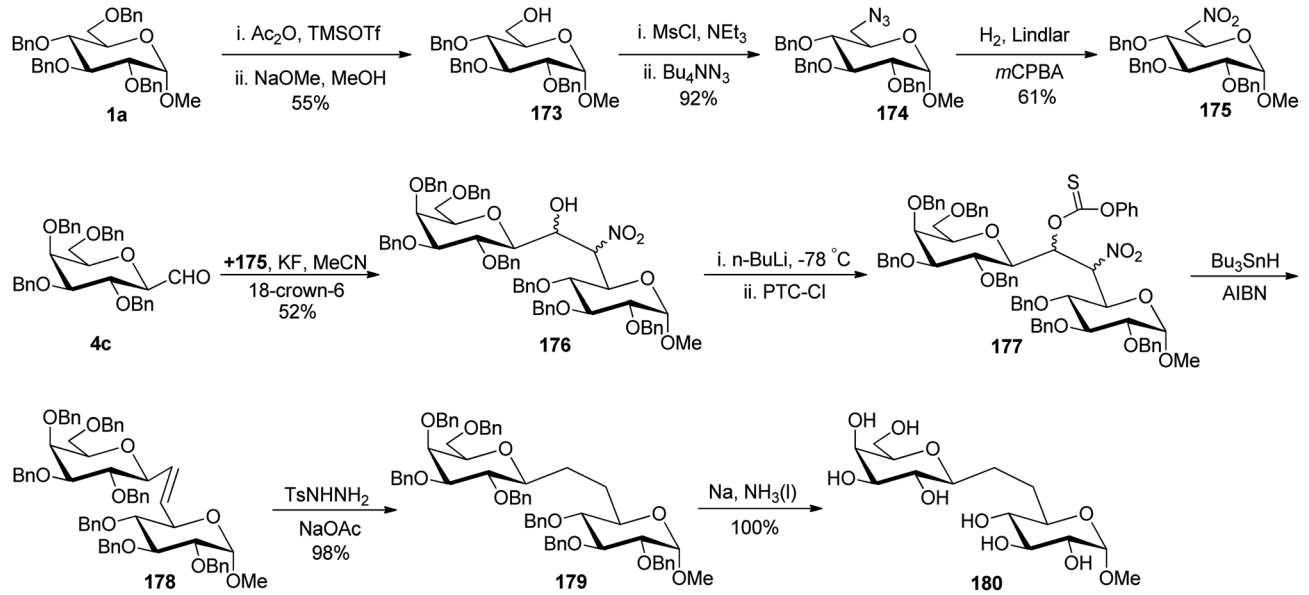


Scheme 33 Synthesis of α-*C*-galactosylceramides **129a–c**.

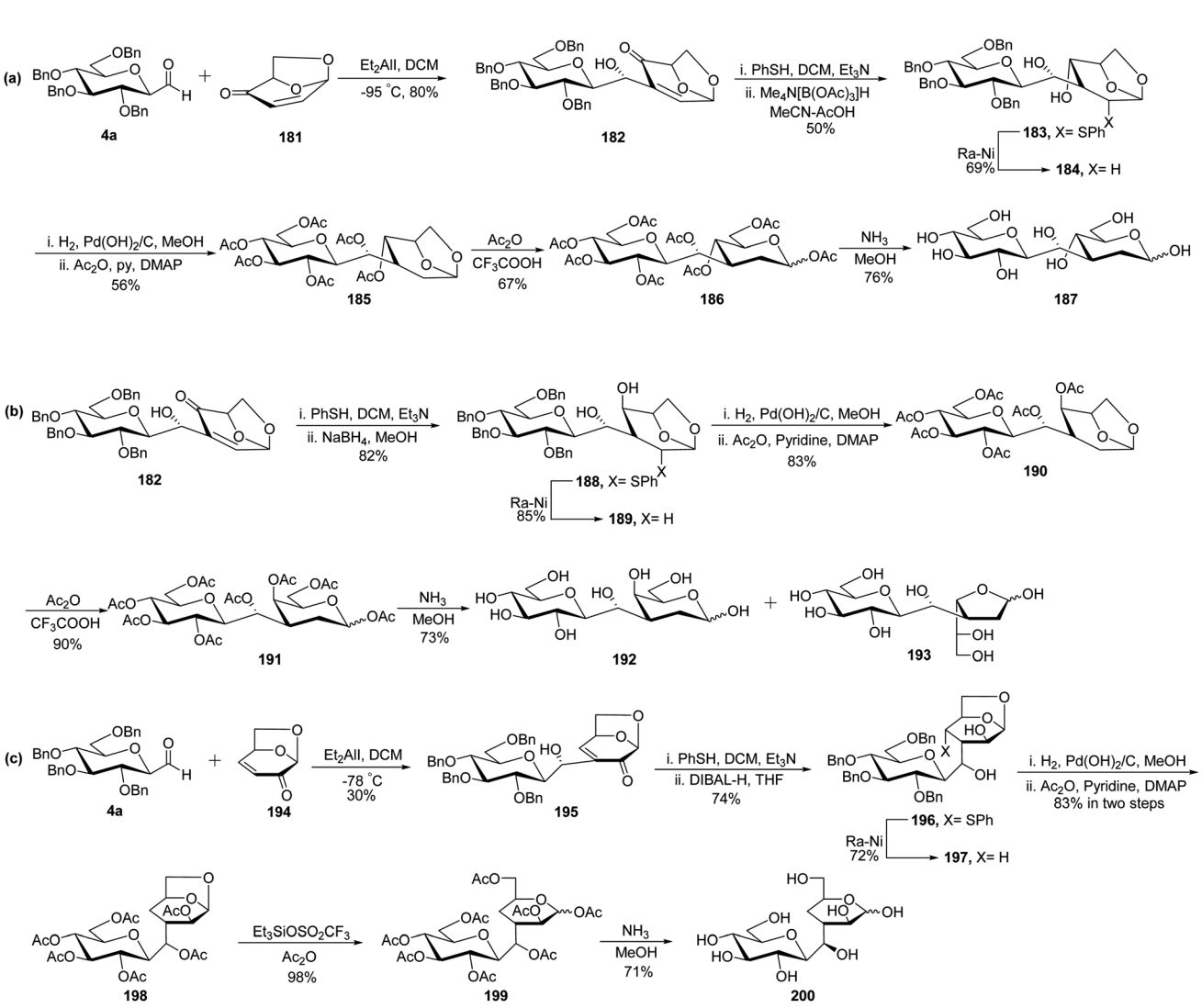


Scheme 34 Synthesis of β-D-galactosyl ceramide methylene isostere **171** and **172**.

Demange *et al.*[66] designed a synthesis of *C*-(1→3)-linked disaccharides *via* the Oshima–Nozaki condensation of β-*C*-glucopyranosyl aldehyde with isolevoglucosenone and levoglucosenone (Scheme 36). In both condensations, an exclusively (1′*R*)-hydroxymethano linker was formed. β-*C*-Glucopyranosyl aldehyde **4a** was condensed with isolevoglucosenone **181** using Et_2AlI in DCM at −95 °C to generate enone **182** in 80% yield. Further, the addition of thiophenol was taken using base Et_3N followed by direct reduction with $Me_4N[B(OAc)_3]H$ in MeCN–AcOH to give **183** in 50% yield. Treatment with RANEY®-Nickel produced **184** in 69% yield, where debenzylation followed by acetylation was achieved to obtain compound **185** in 56% yield. Further, treatment with Ac_2O–CF_3COOH afforded an anomeric mixture **186** where ammonolysis was carried out to give pure *C*-disaccharide **187** in 76% yield (Scheme 36a).



Scheme 35 Synthesis of disaccharide **180**.

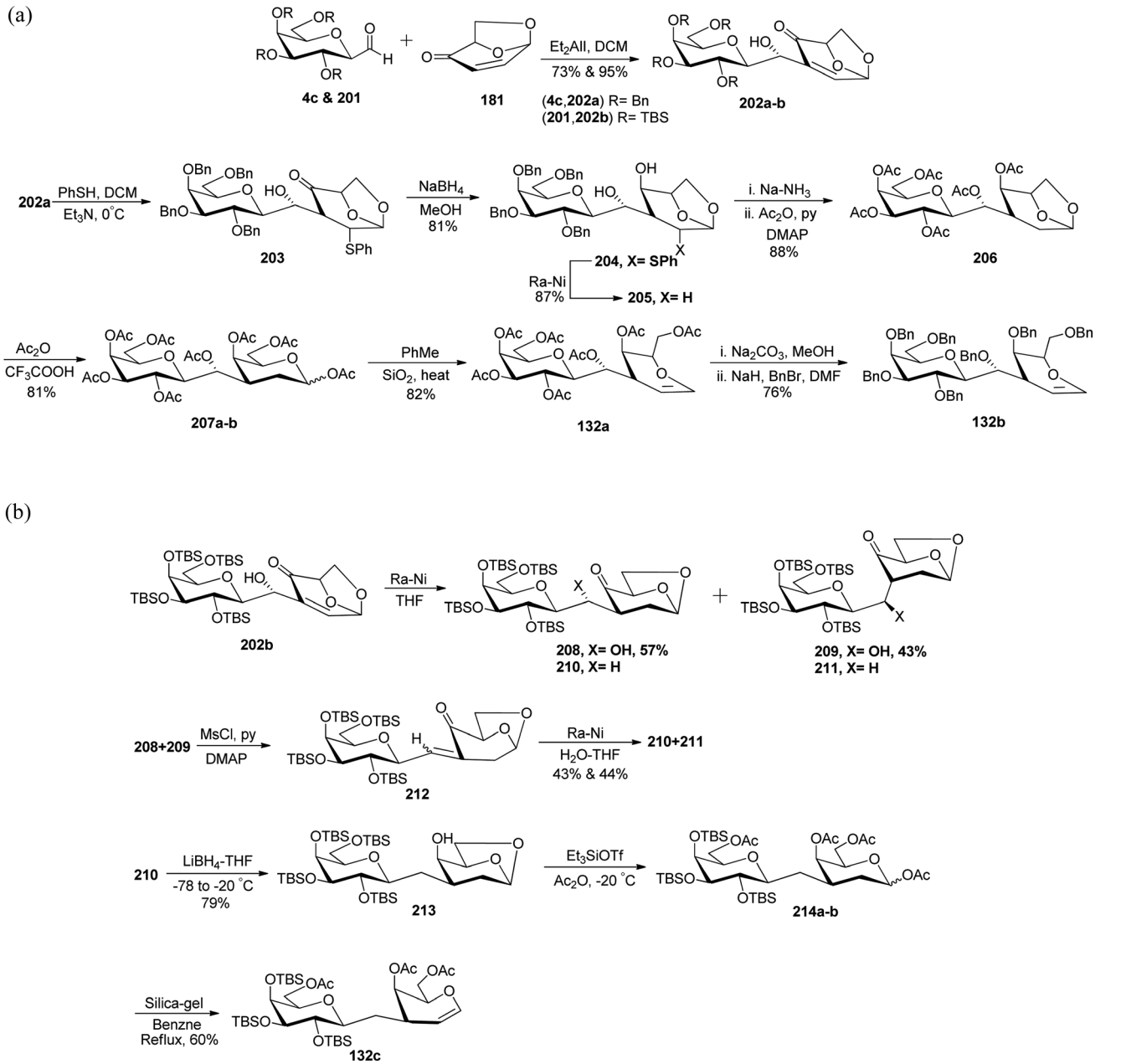


Scheme 36 Synthesis of *C*-linked disaccharides **187**, **192**, **193**, and **200**.

The addition of thiophenol to enone **182** was followed by a reduction with $NaBH_4$ instead of $Me_4N[B(OAc)_3]H$ to obtain **188** in 82% yield, which on reduction with RANEY®-Nickel afforded compound **189** in 85% yield. *C*-Disaccharides **192** and **193** were obtained by applying the same sequence of reactions as carried out for the synthesis of *C*-disaccharide **187**. Exchange of the benzyl protective group with acetyl produced **190**, which on acetolysis afforded anomer mixture **191** in 90% yield. Further, deacetylation was achieved by NH_3–MeOH to produce the mixture of **192** and **193** in 73% yield (Scheme 36b).

C-Glucopyranosyl aldehyde **4a** and levoglucosenone **194** were subjected to Oshima–Nozaki condensation, which produced enone **195** in just 30% yield. The addition of thiophenol followed by reduction with DIBAL-H afforded **196** in 74% yield, which was further treated with RANEY®-Nickel to obtain **197** in 72% yield. The debenzylation of compound **197** followed by acetylation was carried out to obtain **198** in 83% yield. Further, acetolysis was carried out using triethylsilyltrifluoromethanesulfonate in acetic anhydride to obtain an anomeric mixture **199** in 98% yield, which was deacetylated using NH_3–MeOH to give *C*-disaccharide **200** in 71% yield (Scheme 36c).

Demange *et al.*[62] reported the synthesis of *C*-linked disaccharides, which mimics *O*-β-D-galactopyranosyl-(1→3)-D-galactopyranosides starting from *C*-galactopyranosyl aldehyde. Three *C*-linked disaccharides **132a**, **132b**, and **132c** were

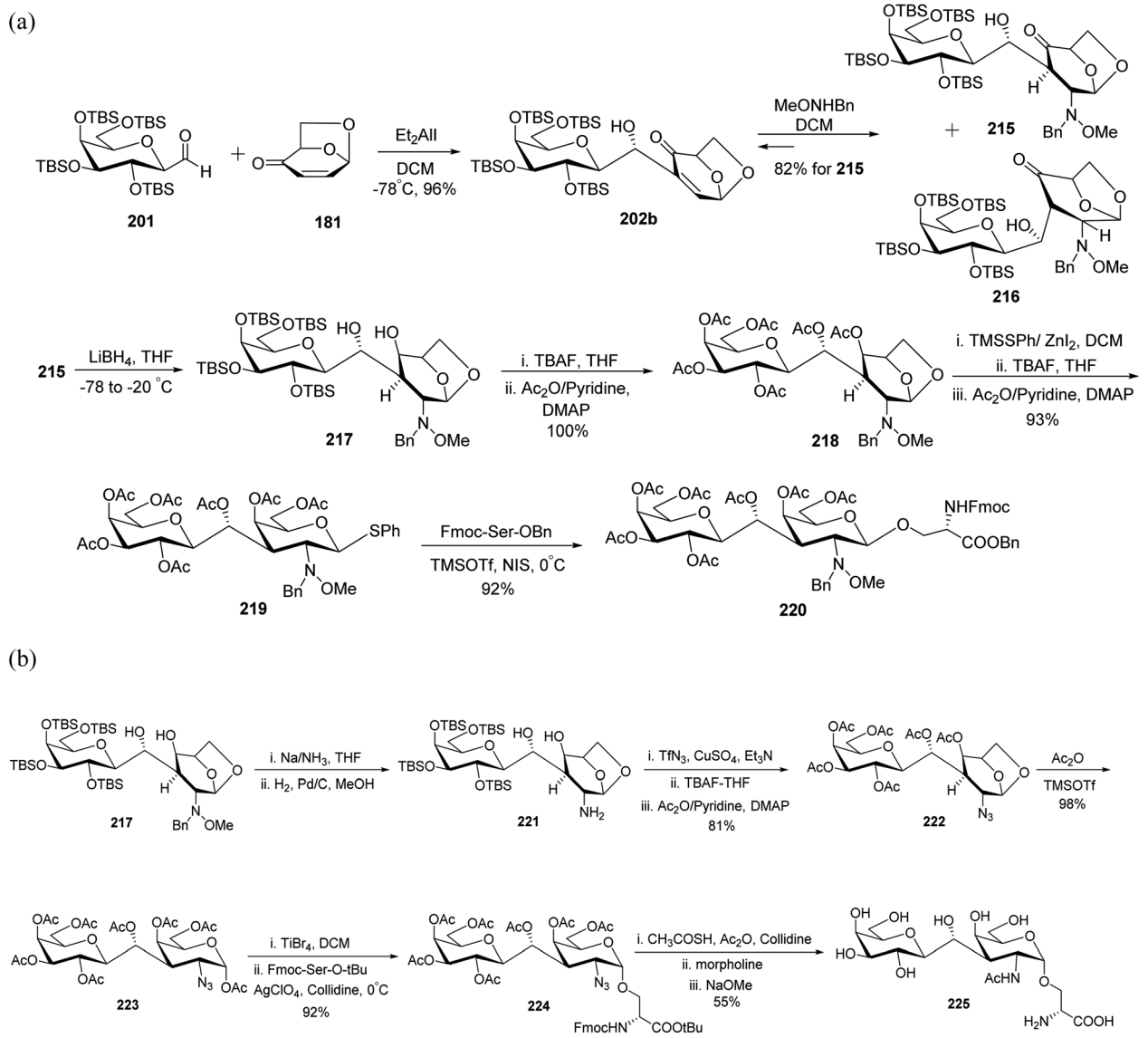


Scheme 37 (a) Synthesis of disaccharides **132a–b**. (b) Synthesis of β-D-galactopyranosyl-D-galactal **132c**.

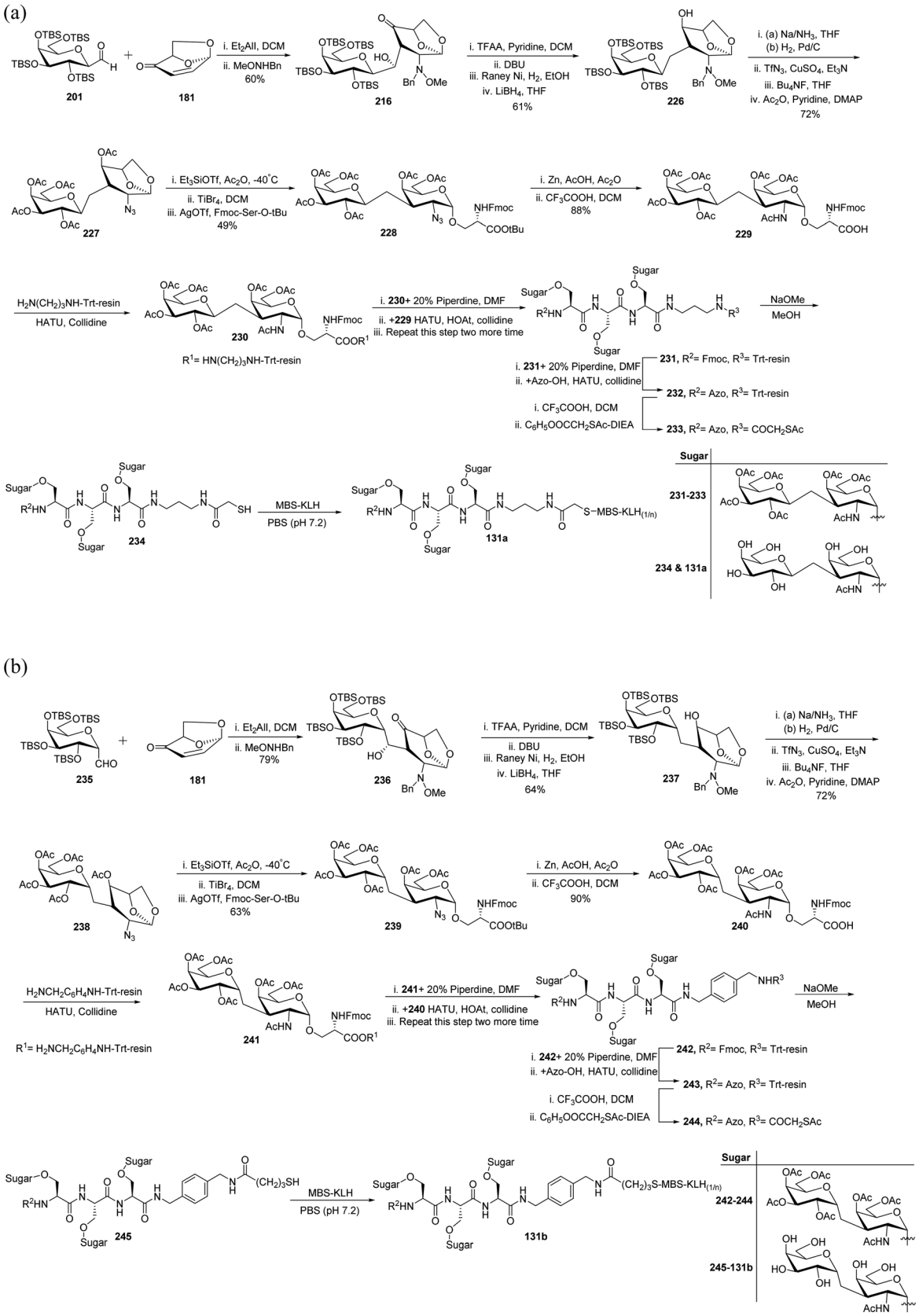
synthesized, out of which **132a** was found to be a suitable agent for *O*-glycosidation and for the construction of conjugates (Scheme 37). *C*-galatopyranosyl aldehyde **4c** and **201** reacted with **181** to prepare **202a** and **202b** in 73% and 95% yields, respectively. Michael addition of thiophenol to **202a** afforded **203**, which was directly converted into **204** with 81% yield by reduction using sodium borohydride in methanol. Treatment with RANEY®-nickel converted compound **204** into compound **205** in 87% yield, which on debenzylation following the acetylation furnished peracetylated **206** in 88% yield. Treatment of **206** with Ac_2O-TFA gave **207a–b** as a mixture of anomers ($\alpha:\beta$, 1 : 0.3) in 81% yield, which on refluxing in toluene afforded **132a** in 82% yield. Further replacement of acetyl protection with the benzyl group produced **132b** in 76% yield (Scheme 37a).

C-Galactoside **202b** on reduction with RANEY®-nickel produced a mixture of aldols **208–211** in quantitative yield. From this mixture, compounds **208** and **209** were isolated by flash chromatography in 57% and 43% yield, respectively. This mixture of aldols **208** and **209** when treated with CH_3SO_2Cl/pyridine and DMAP formed unstable enone **212**, which when reduced with Ra–Ni in aq. THF produced a mixture of ketones **210** and **211** in 43% and 44% yield, respectively. The ketone **210** thus produced when reduced with lithium borohydride in THF at low temperature formed alcohol **213** in 79% yield, which on treatment with triethylsilyltrifluoromethanesulfonate(Et_3SiOTf) and acetic anhydride underwent ring opening of 1,6-anhydro moiety followed by acylation to give a mixture of α- and β-pyranosides **214a–b.** Anomeric mixture **214a–b** was directly treated with silica gel in benzene and heated under refluxing conditions, which resulted in a *C*-linked analogue of β-D-galactopyranosyl-D-galactal **132c** in 60% yield (Scheme 37b).

In 2001, Zhu *et al.*[67] and in 2005, Awad *et al.*[68] reported the synthesis of a *C*-linked disaccharide analogue of epitope T. First, Oshima–Nozaki condensation[69] was carried out



Scheme 38 (a) Synthesis of β-*C*-galactopyranosyl disaccharide **220**. (b) Synthesis of β-*C*-glycopyranosyl disaccharide **225**.



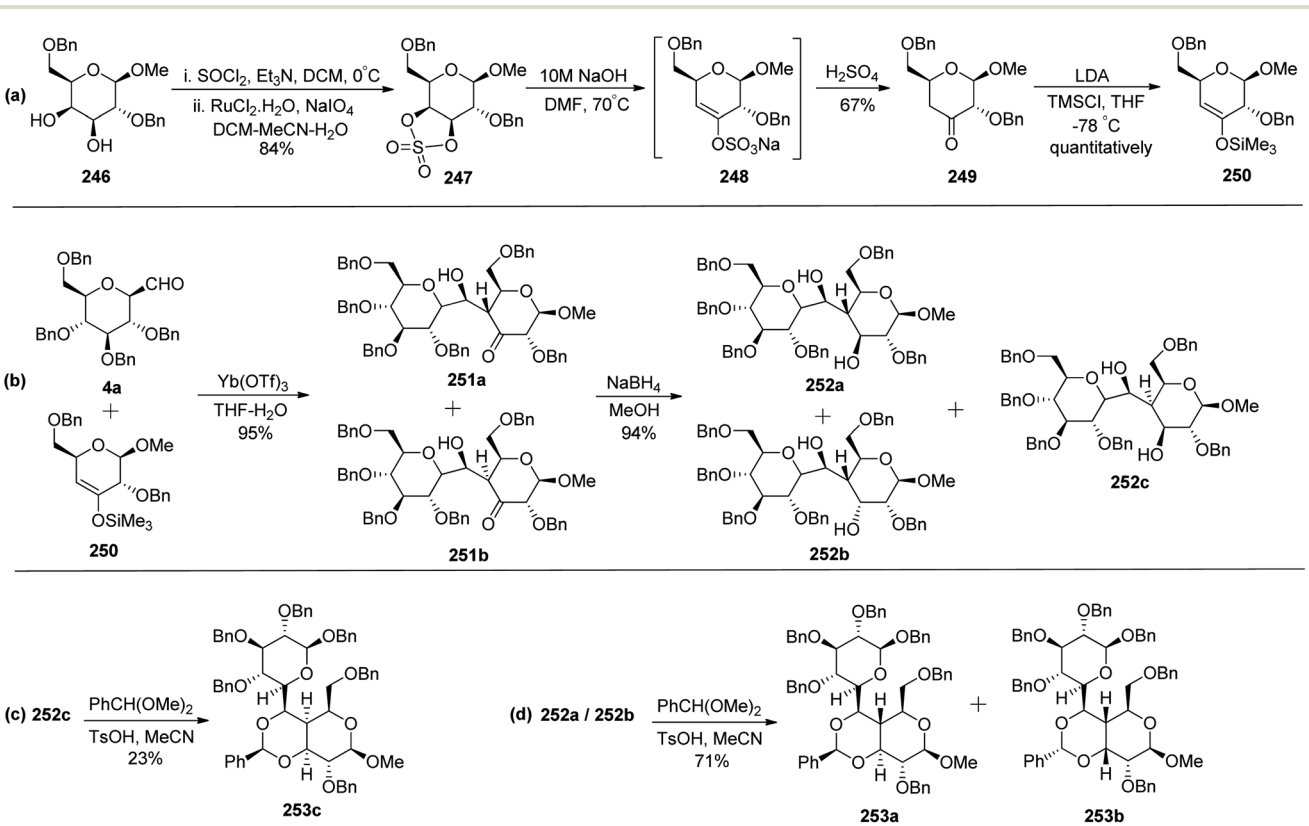
Scheme 39 (a) Synthesis of antigen **131a**. (b) Synthesis of antigen **131b**.

between *C*-glycopyranosyl aldehyde **201** and commercially available isolevoglucosenone **181** using Et_2AlI in DCM to afford **202b** in 96% yield. Further conjugate addition of MeONHBn to enone **202b** produced a stereoisomeric mixture of **215** and **216**, which were isomerised during column chromatography, and adduct **215** was recovered in 82% yield. Reduction of **215** was carried out with lithium borohydride in THF at −78 °C to afford compound **217**, which was directly treated with TBAF in THF following acetylation to furnish **218** quantitatively. Treatment of peracetylated compound **218** with TMSSPh/ZnI_2-DCM followed by TBAF and acetylation furnished **219** in 93% yield, which was reacted with protected serine to afford β-*C*-glycopyranosyl disaccharide **220** in 92% yield (Scheme 38a).

The bulky 2-MeONBn group present on compound **219** enforced the reaction to undergo β-glycosylation, which afforded compound **220** (Scheme 38a). To achieve α-glycosylation, 2-MeONBn group was removed initially from compound **217** using Na/NH_3 reduction conditions followed by hydrogenation with H_2–Pd/C to afford compound **221** (Scheme 38b). Further, compound **221** was treated without isolation with TfN_3-$CuSO_4$ following treatment with TBAF in THF and acetic anhydride in pyridine to furnish **222** in 81% yield. The peracetylated compound **222** on treatment with Ac_2O-TMSOTf afforded **223**, which reacted with protected serine to afford α-glycosylated product **224** in 92% yield. The treatment of compound **224** with CH_3COSH-Ac_2O followed by further deacetylation afforded targeted compound **225** in 55% yield.

In 2012, Awad *et al.*[61] reported another interesting application of *C*-glycopyranosyl aldehyde by synthesizing *C*-linked disaccharide, which was found to induce a strong immune response in mice. The TBS-protected *C*-galactopyranosyl aldehyde **201** and isolevoglucosenone **181** were condensed followed by a reaction with MeONHBn to afford **216** in 60% yield. Compound **216** on treatment with TFA in pyridine following DBU furnished dehydration, further reduction of the double bond with RANEY®-nickel, and then by $LiBH_4$ converted the keto group to afford compound **226** in 61% yield. Compound **227** was achieved in 72% yield by reduction of the 2-MeONBn group, its conversion into azide by diazo transfer, and desilylation following acetylation of **226**. α-*O*-Galactosidation was achieved with protected serine to afford compound **228**, which on reaction with Zn–AcOH followed by treatment with TFA in DCM afforded compound **229** in 88% yield, which was coupled with trityl polymer to give **230**. Compound **231** was obtained first by removal of Fmoc protection from **230** and then by coupling it with the –COOH group of **229**.

The deprotection of Fmoc from compound **231** followed by capping with 4-(dimethylamino)-azobenzene-4′-carboxylic acid (Azo-OH) gave compound **232**. Coupling with pentaflurophenylacetylthioacetate after the liberation of protected triglycopeptides from the polymer furnished **233**, which was treated with sodium methoxide to give peptide **234**. Finally, the reaction of peptide **234** with MBS-KLH under the Michael addition reaction condition furnished antigen **131a** (Scheme 39a).



Scheme 40 Synthesis of *C*-linked disaccharide 253a–c.

A similar synthetic protocol was developed for TBS protected α-*C*-galactppyranosyl aldehyde **235** (Scheme 39b). In this strategy, trityl resin-monoprotected diamine 1,4-di(aminomethyl)benzene was coupled with compound **242**. So, following the same sequence of reactions, antigen **131b** was prepared.

Zeitouni *et al.*[70] introduced a new class of *C*-linked disaccharides **253a–c**, which were obtained by the Mukaiyama aldol[71] reaction between β-*C*-glucopyranosyl aldehyde **4a** and trimethylsilyl enol ether **250.** This enol ether was synthesised from readily available methyl-2,6-di-*O*-benzyl-β-D-galactopyranoside **246** (Scheme 40a). The diol **246** was reacted with $SOCl_2$–Et_3N followed by reaction with $RuCl_3 \cdot H_2O$–$NaIO_4$ to afford 3,4-cyclic sulfate **247** in 84% yield, which on treatment with 10 M NaOH gave unstable compound **248** and subsequent acidic hydrolysis furnished ketone **249** in 67% yield. Final enol ether **250** was obtained quantitatively by treatment with LDA-TMSCl in THF.

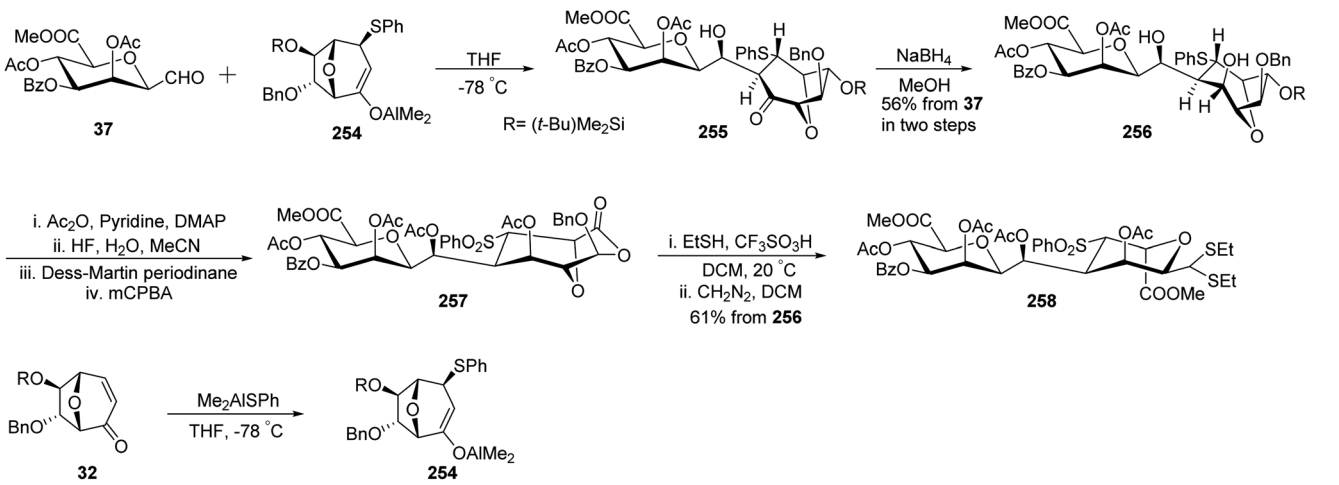
Condensation of **4a** and **250** in the presence of $Yb(OTf)_3$ in THF–H_2O furnished diastereomeric mixture **251a** and **251b** in a 59 : 41 ratio out of four possible diastereomers in 95% yield. The diastereomers could not be separated by column chromatography so they were further reduced with sodium borohydride to furnish three diol products **252a**, **252b**, and **252c** in 94% yield (Scheme 40b). Here, only **252c** could be separated by column chromatography which was reacted with benzaldehyde dimethyl acetal in acetonitrile in the presence of PTSA to give **253c** in 23% yield (Scheme 40c). The same reaction was also carried out on the **253a**/**253b** mixture to give **253a** and **253b** in 71% yield, they could be separated easily (Scheme 40d).

Gerber *et al.*[33] designed a stereoselective synthesis of *C*-linked disaccharides and oligosaccharides due to their advantage of being resistant to acidic and enzymatic hydrolysis. The enolate **254**, which in turn was synthesised from enone **32** using Me_2AlSPh was reacted with *C*-glycopyranosyl aldehyde **37** in tetrahydrofuran to furnish aldol **255**, which turned out to be unstable and hence was reduced with $NaBH_4$ in methanol to afford diol **256** with 56% yield. Diol **256** on acetylation with Ac_2O in pyridine, followed by desilylation with HF in H_2O and MeCN, and then undergoing Dess–Martin periodinane oxidation furnished a ketone, which upon Baeyer-Villiger oxidation afforded compound **257**. Compound **257** on treatment with EtSH/CF_3SO_3H/CH_2Cl_2 and with CH_2N_2 in DCM afforded β-D-*C*-*manno*-pyranoside **258** in 61% yield (Scheme 41).

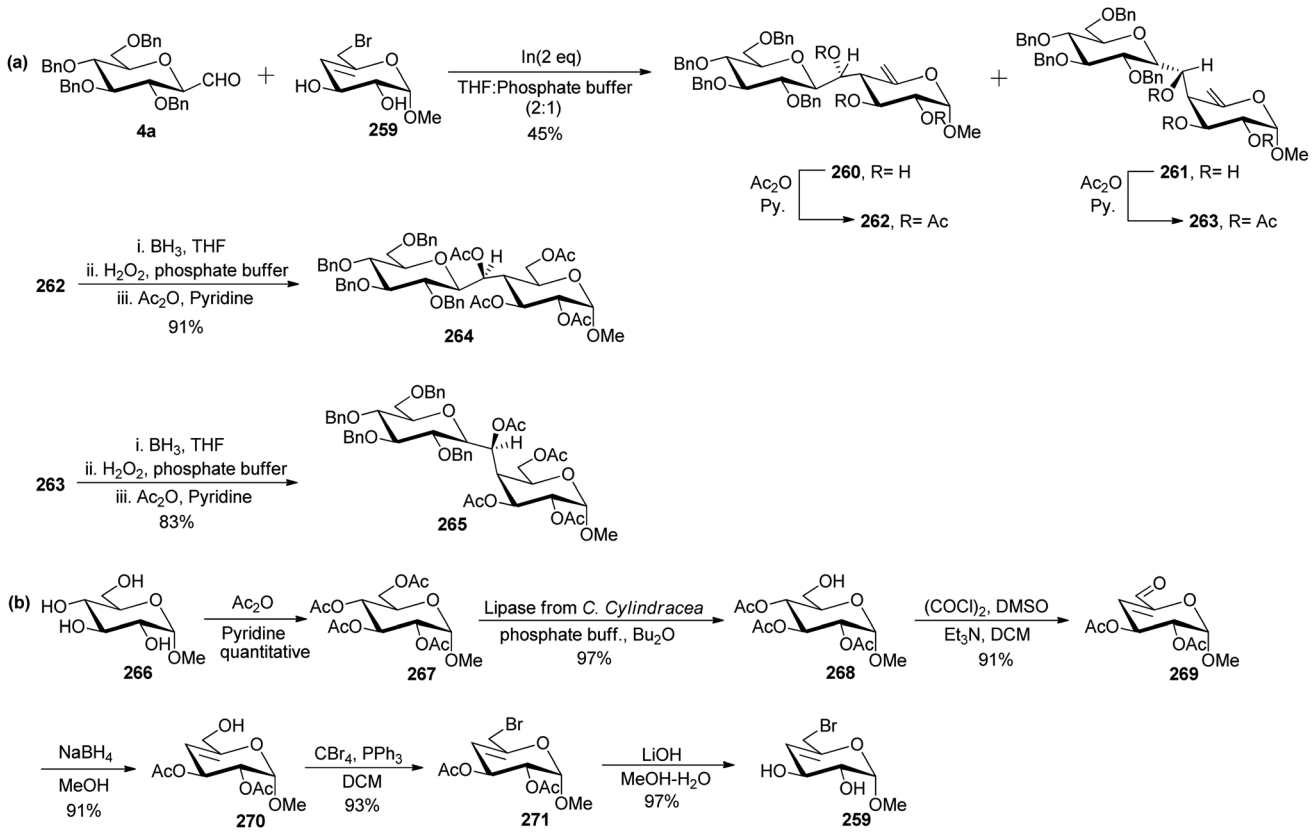
Levoirier *et al.*[72] developed a strategy for the synthesis of β-(1→4)-*C*-disaccharides using Barbier-type allylation catalysed by indium in aqueous media (Scheme 42). *C*-Glucopyranosyl aldehyde was reacted with 6-bromo-4,6-dideoxy-α-D-*threo*-4-enopyranoside **259** using indium in THF–phosphate buffer to obtain an inseparable mixture of *C*-disaccharide **260** and **261** in 45% yield, which was acetylated using acetic anhydride in pyridine affording **262** and **263**, respectively which could be separated easily. Hydroboration with diborane-tetrahydrofuran followed by oxidation with hydrogen peroxide in phosphate buffer and then acetylation was carried out on **262** and **263** to obtain protected *C*-disaccharides **264** and **265** in 91% and 83% yields, respectively (Scheme 42a).

6-Bromo-4,6-dideoxy-α-D-*threo*-4-enopyranoside **259** used in the above Barbier-type allylation was synthesised from methyl α-D-glucopyranoside **266**, which on acetylation produced peracetylated derivative **267** quantitatively. Selective deacetylation of peracetylated derivative was performed after treatment with lipase from *C. Cylindracea* in a mixture of phosphate buffer and di-*n*-butyl ether produced methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside **268** in 97% yield. Compound **268** underwent Swern oxidation to afford unsaturated aldehyde **269** in 91% yield, which on further reduction with $NaBH_4$ in MeOH produced allyl alcohol **270** in 91% yield. Treatment of allyl alcohol **270** with carbon tetrabromide and triphenylphosphine in DCM followed by deacetylation using LiOH in MeOH–H_2O afforded **259** in 97% yield (Scheme 42b).

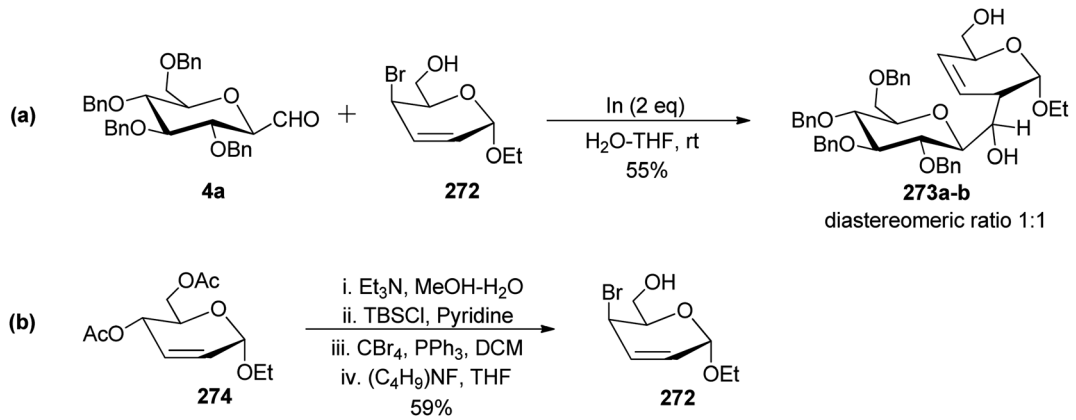
Canac *et al.*[73] designed a protocol for the synthesis of *C*-disaccharides under indium-promoted Barbier-type allylation (Scheme 43). Here, *C*-glucopyranosyl aldehyde **4a** was reacted with 4-bromo-2-enopyranoside **272** using indium in H_2O–THF.



Scheme 41 Synthesis of β-D-*C*-*manno*-pyranoside **258**.



Scheme 42 Synthesis of β-(1→4)-*C*-disaccharides **264** and **265**.

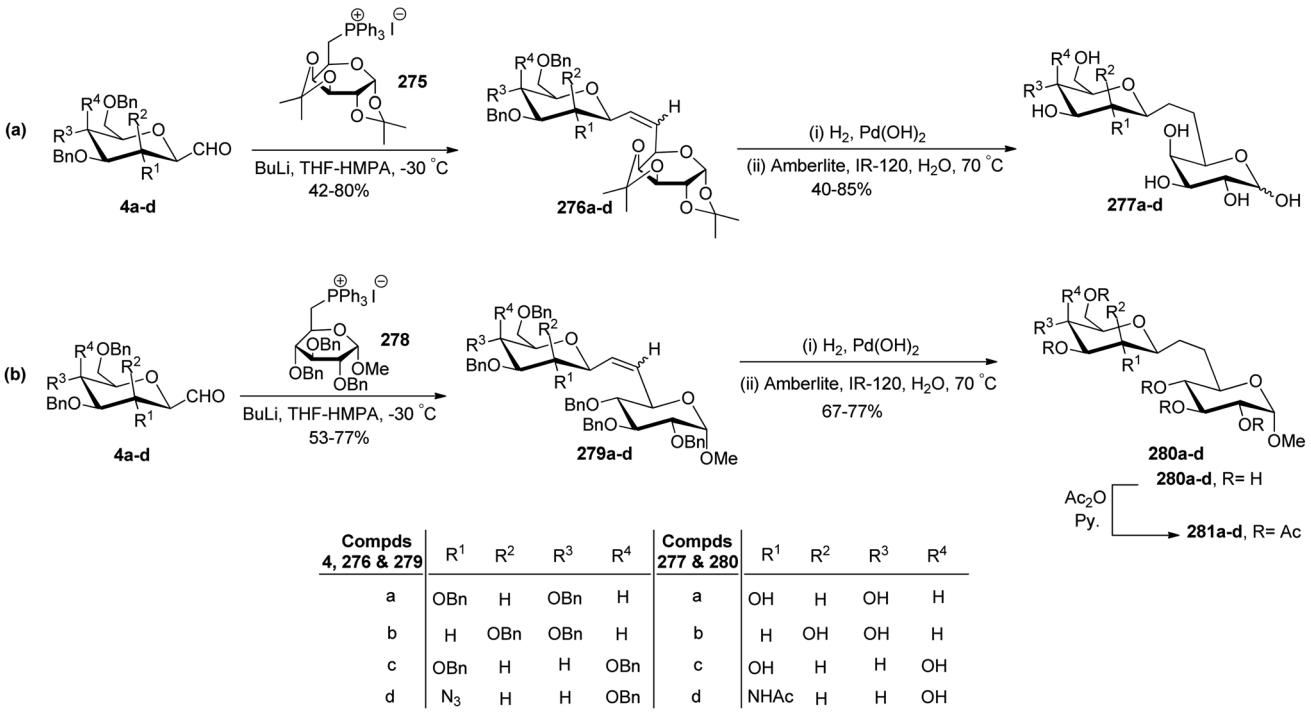


Scheme 43 Synthesis of *C*-disaccharide **273a–b**.

A mixture of diastereomers **273a–b** with a ratio (1 : 1) in 55% yield was obtained.

The key compound **272** used in the above Barbier-type allylation was synthesised from 2-enopyranoside **274** using a sequence of deprotection of the acetyl group, selective protection of the primary hydroxyl group, bromination followed by deprotection reaction (Scheme 43b).

Dondoni *et al.*[74] achieved the synthesis of (1→6)-*C*-disaccharides by Wittig olefination reaction between *C*-glycopyranosyl aldehyde and pyranose 6-phosphoranes (Scheme 44). First, *C*-glycosyl aldehydes **4a–d** were reacted with galactose 6-phosphorane **275** using *n*-butyl lithium, THF–HMPA at −30 °C to afford alkenes **276a–d** in 42–80% yield. In the case of mannopyranosyl aldehyde **4b** low yield (42%) was observed due to the formation of unexpected side products (formed by the elimination of BnOH from C1 and C2 of sugar). Further, treatment of alkenes **276a–d** with H_2, $Pd(OH)_2$ led to the debenzylation and reduction of the double bond, which on deprotection with amberlite IR-120 in water furnished β-D-(1→6)-*C*-disaccharides **277a–d** in 40–85% yield.



Compds 4, 276 & 279	R^1	R^2	R^3	R^4	Compds 277 & 280	R^1	R^2	R^3	R^4
a	OBn	H	OBn	H	a	OH	H	OH	H
b	H	OBn	OBn	H	b	H	OH	OH	H
c	OBn	H	H	OBn	c	OH	H	H	OH
d	N_3	H	H	OBn	d	NHAc	H	H	OH

Scheme 44 Synthesis of (1→6)-*C*-disaccharides **277** and **280**.

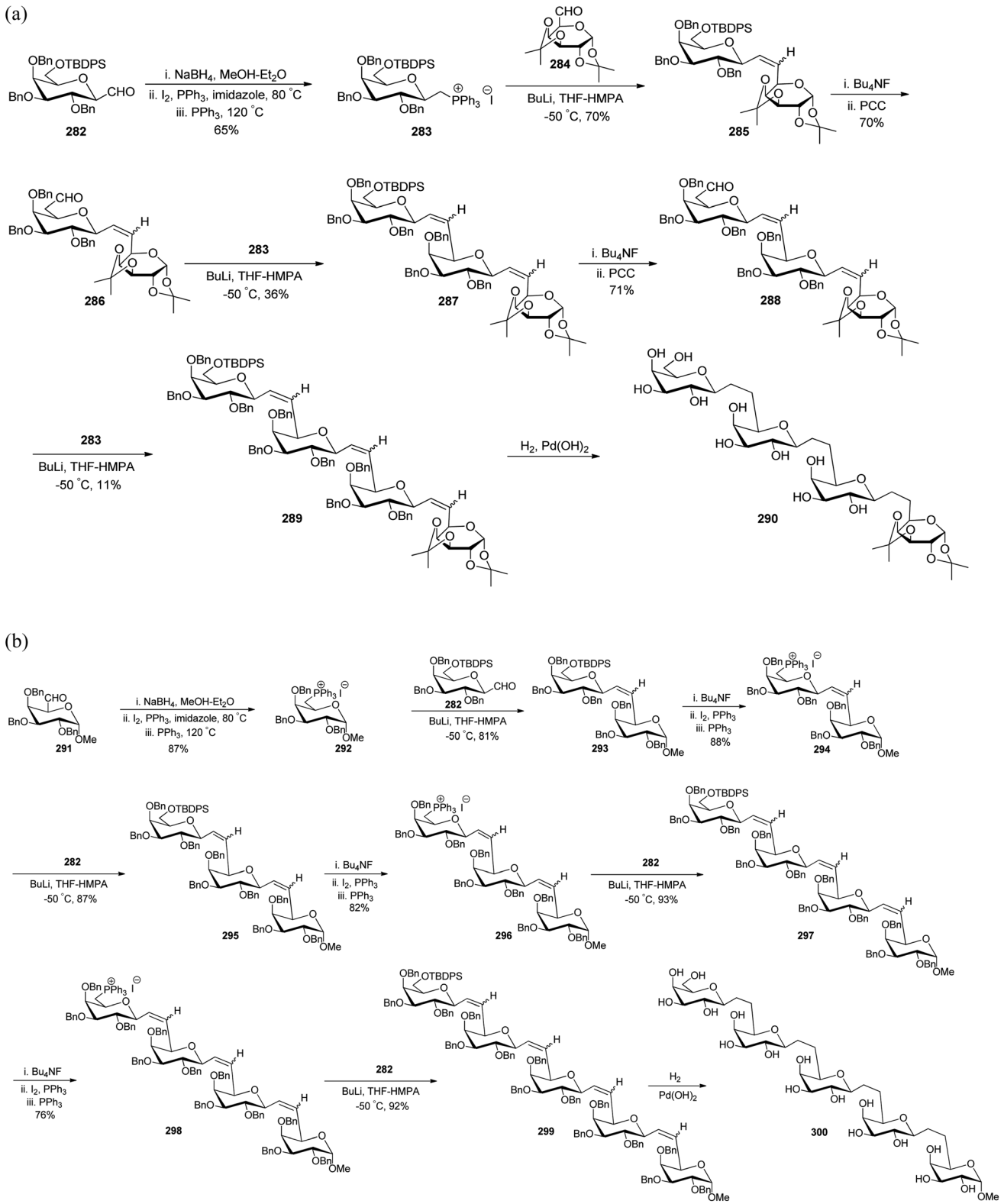
Similarly, *C*-glycopyranosyl aldehydes **4a–d** were reacted with glucose 6-phosphorane **278** under Wittig conditions to furnish alkenes **279a–d** with 53–77% yield, which on treatment with H_2, $Pd(OH)_2$ followed by Amberlite IR-120 resin produced disaccharides **280a–d**. Further, disaccharides **280a–d** were acetylated using acetic anhydride in pyridine to afford **281a–d** (Scheme 44b).

Dondoni *et al.*[75–77] worked on designing synthetic routes for oligosaccharides and glycoconjugates both being mediators in inflammation, fertilization, cancer metastasis, and viral and bacterial infections in human beings. For the synthesis of these oligosaccharides, two complementary routes were designed taking *C*-galactopyranosyl aldehyde **282** in the first route while in the second, α-linked galactosylmethylenephosphorane **10** was taken as the starting material. The formyl group of *C*-galactospyranosyl aldehyde **282** on reaction with $NaBH_4$ reduces to alcohol followed by iodination with I_2 and PPh_3 finally phosphination in the presence of PPh_3 yielding galactosylmethylenephosphonium iodide **283** in 65% yield, which reacted with galactose derived aldehyde **284** in the presence of BuLi. The reaction afforded olefin **285** in a good yield, which further undergoes removal of the silyl protecting group followed by oxidation to primary alcohol to yield aldehyde **286** in 70% yield. The same sequence of addition of galactosylmethylenephosphonium iodide **283** followed by oxidation of alcohol to aldehyde with Bu_4NF and PCC resulted in the formation of the desired oligosaccharide chain **290** in very low overall yield (Scheme 45a). In the other route, galactosylmethylenephosphorane **292** was reacted with *C*-glycopyranoside **282** in the presence of BuLi in THF-HMPA, affording biglycosylated olefin **293** in excellent yield. Further, olefin **293** upon subsequent installation of the phosphonium group *via* desilylation (Bu_4NF), followed by iodination (I_2, PPh_3), and phosphanation (PPh_3) yielded sugar phosphonium iodide **294** in 88% yield, which on further reaction with *C*-glactopyranosyl aldehyde **282** followed by the same sequence of steps yielded bis-olefin **295** in 87% yield and same steps were followed to obtain oligosaccharide **299**, which on debenzylation and hydrogenation produced oligosaccharide **300** with good overall yield (Scheme 45b).

3.3 *C*-Glycopyranosyl amino acid precursors

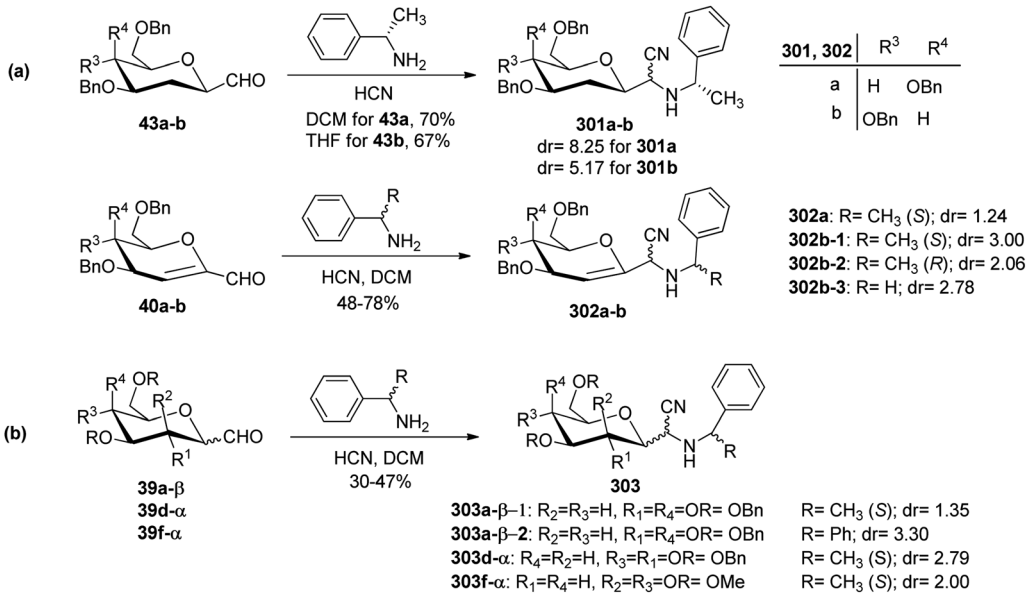
Sipos *et al.*[78] designed the synthesis of *C*-glycosyl-aminoacetonitriles **301a–b**, **302a–b**, and **303** under Strecker reaction conditions from various *C*-glycopyranosyl aldehydes. *C*-glycosyl aminoacetonitriles **301a–b** were formed in 67–70% yield by Strecker reaction upon **43a–b** with DCM for **43a** and THF for **43b**. The diastereomeric ratios for **301a–b** were 8.25 and 5.17, respectively. Similarly, **302a–b** were formed in 48–78% yield by Strecker reaction upon **40a–b** by reacting them with chiral amines such as *S*- or *R*-PEA or achiral amines such as benzylamine (BA), benzhydrylamine (BHA) in the presence of cyanide donor HCN. The diastereomeric ratio and yield obtained for *C*-glycosyl-aminoacetonitriles are shown in Scheme 46.

In addition, glycosyl-formaldehydes **39a**, **39d**, and **39f** also underwent Strecker reaction leading to the formation of *C*-glycosyl aminoacetonitriles **303a**, **303d**, and **303f** (Scheme 46b). The hydrolysis of these *C*-glycosyl-α-aminoacetonitrile led to the formation of *C*-glycosyl glycine, which can be used for the development of biologically-active glycol-peptidomimetics.

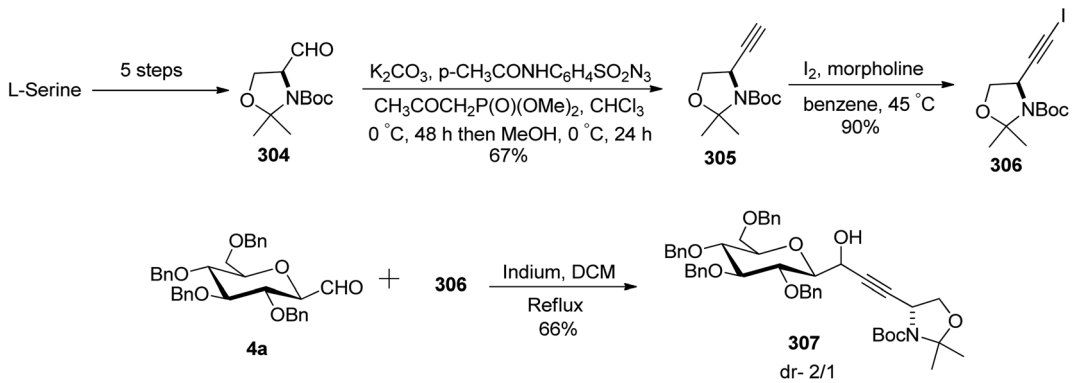


Scheme 45 (a) Synthesis of oligosaccharide **290**. (b) Synthesis of oligosaccharide **300**.

Charfedinne *et al.*[79] described the synthesis of some alkynes and iodoalkynes bearing protected amino alcohol moieties as amino acid precursors, which were used for the alkynylation reaction of sugar derivatives. The alkynyl iodide **306** was obtained in a multi-step reaction process (Scheme 47). Garner's aldehyde **304** was synthesised from L-serine in



Scheme 46 Synthesis of 2-amino-2-*C*-D-glycosyl-acetonitriles **301a–b**, **302a–b**, **303**.



Scheme 47 Synthesis of *C*-glycopyranosyl propargylic alcohol **307**.

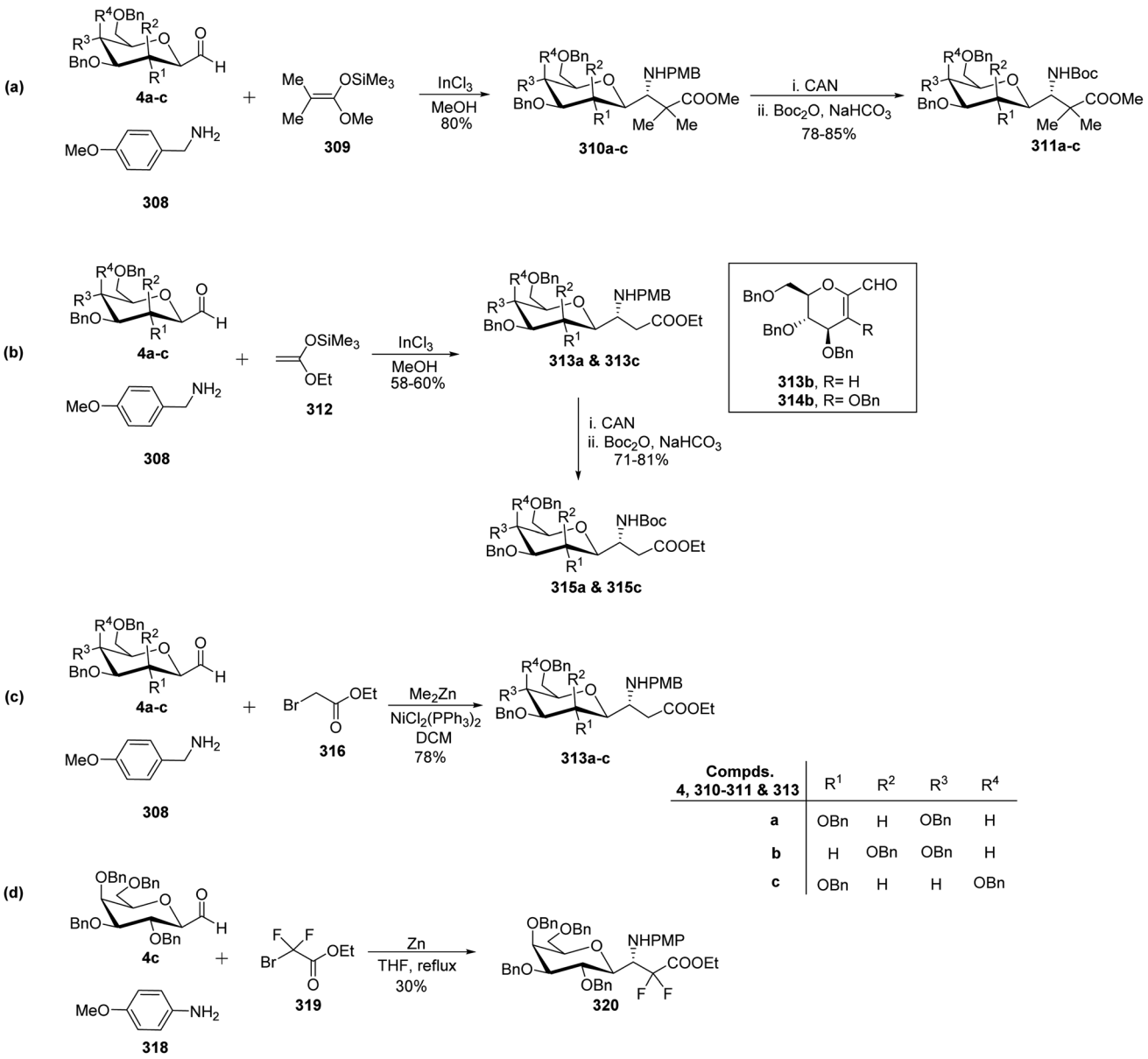
a five-step procedure.[80] This aldehyde was then homologated into terminal alkyne **305** with 67% yield using Ohira–Bestman reagents (Seyferth–Colvin–Gilbert reaction). The alkyne derivative **305** when treated with iodine and morpholine in benzene at 45 °C resulted in iodinated *tert*-butyl-(*R*)-4-iodoethynyl-2,2-dimethylexazelidine-3-carboxylate (**306**) in 90% yield.

The reaction of alkynyl-iodide **306** with 2,3,4,5-tetra-*O*-benzyl-1-formylglucopyranose (**4a**) in the presence of metallic indium in dichloromethane resulted in a coupling reaction producing the corresponding propargylic alcohol **307** in 66% yield with a diastereomeric ratio of 2/1 (Scheme 47).

3.4 *C*-Glycopyranosylamino acids and dipeptides

Dondoni *et al.*[81,82] developed complementary one-pot Mannich- and Reformatsky-type multicomponent approaches to synthesise a library of *C*-glycosyl β-amino acids (Scheme 48). Both methods involved *C*-glycopyranosyl aldehydes **4a–c** as starting compounds. Mannich route coupled *C*-glycopyranosyl aldehyde **4a–c**, *p*-methoxy benzylamine **308**, and commercially available ketene silyl acetal **309** in the presence of indium chloride in methanol to afford *C*-glycosyl β-amino ester **310a–c** as single diastereomer observed by ^{1}H NMR analysis with 80% yields. In the case of **4b** (*manno* sugar), DCM was chosen as the solvent because of the insolubility of the intermediate in methanol and also reaction was performed at 0 °C to avoid the formation of glycal amino ester (resulting from the elimination of BnOH from C-1 and C-2 of *manno* sugar). Further, for the reagent diversity ketene silyl acetal **312** was also chosen (Scheme 48b). Unfortunately, this process suffered from low yields of *C*-glycosyl β-amino esters **313a** and **313c** in 58–60% yield as well as undesired product formation **313b** and **314b** in case of **4b** (*manno* sugar).

In view of Boc-based peptide synthesis, all amino esters, **310a–c**, **313a**, and **313c**, were transformed into their corresponding *N*-Boc derivatives **311a–c**, **315a**, and **315c** by treatment of ceric ammonium nitrate (CAN) followed by Boc_2O and $NaHCO_3$ in 78–85% and 71–81% yields, respectively (Scheme 48a–b).



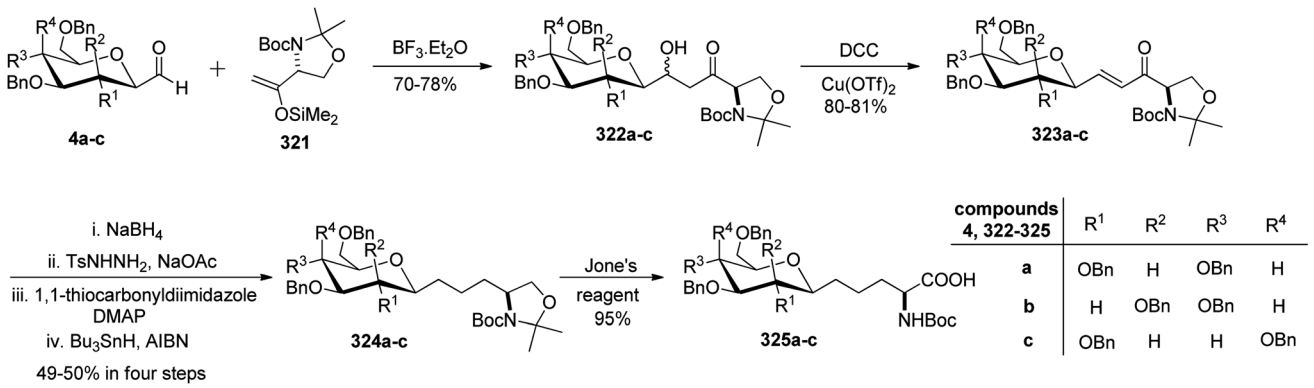
Compds. 4, 310-311 & 313	R^1	R^2	R^3	R^4
a	OBn	H	OBn	H
b	H	OBn	OBn	H
c	OBn	H	H	OBn

Scheme 48 Synthesis of *C*-glycopyranosyl β-amino acids **311**, **313**, **315**, **320**.

Due to some limitations in the above Mannich-type approach another route for the synthesis of *C*-glycosyl β-amino esters was performed. Here, ethyl bromoacetate **316** was taken in place of ketene silyl acetate (Scheme 48c). *C*-glycopyranosyl aldehyde **4a–c**, *p*-methoxy benzylamine **308**, and ethyl bromoacetate **316** were reacted in the presence of zinc donor Me_2Zn, $NiCl_2(PPh_3)_2$ as a catalyst in DCM to produce *C*-glycosyl β-amino esters **313a–c** in 78% yield. Thus, the Reformatsky route demonstrated over the Mannich route in terms of overall yield and desired products.

Due to the application of fluorinated amino acids in biological and medicinal studies, synthesis of α,α-difluoro *C*-glycosyl β-amino acid **320** was also achieved by the Refromatsky-type reaction in 30% yield (Scheme 48d).

Dondoni *et al.*[83,84] employed threonine-derived silyl enol ethers **321** to serve as a synthetic equivalent of the homoalanine carbanion to introduce α-amino side chains at the anomeric carbon position of sugar moieties. This functionalized silyl enol ether **321** was prepared from methyl *N*-Boc-L-threoninate in six steps with a 48% yield. Tetra-*O*-benzylated formyl *C*-glycopyranoside **4a–c** upon condensation with **321** in the presence of Lewis acid boron trifluoride etherate underwent Mukaiyama coupling in CH_2Cl_2 at −30 °C, which afforded aldols **322a–c** in 70–78% yield. The α,β-enones **323a–c** were obtained with 80–81% yield from dehydration of **322a–c** using DCC-$Cu(OTf)_2$ for α,β-elimination reaction. The carbonyl and carbon–carbon double bonds were then reduced by following a sequence of reactions on **323a–c** to yield **324a–c** with 49–50% yield in four steps. Next, when compounds **324a–c** were subjected to Jones' reagent, they



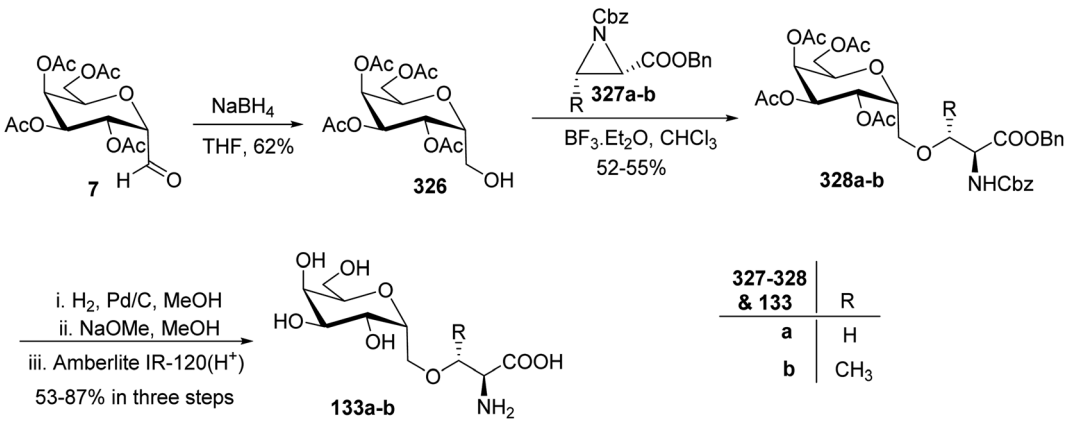
Scheme 49 Synthesis of *C*-glycosyl amino acids **325a–c**.

underwent oxidative cleavage of oxazolidine ring, which afforded *C*-glycosyl amino acids β-D-galactose $(CH_2)_2$-asparagine (β-Gal-$(CH_2)_2$-Asn, **325c**), and the corresponding *gluco*- and *manno*-isomers **325a** and **325b**, respectively in 95% yield (Scheme 49).

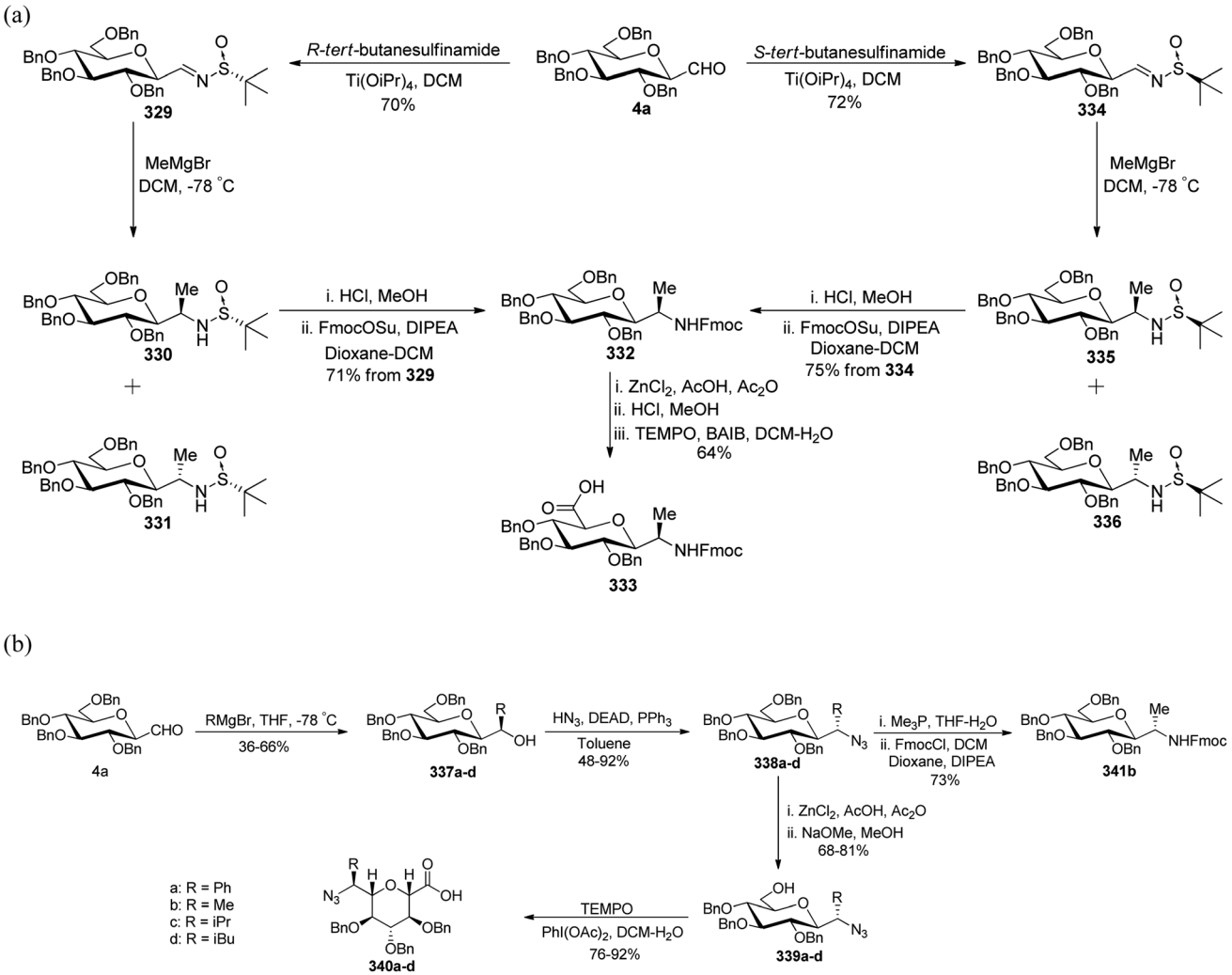
Kroger *et al.*[25] synthesised *O*-glycosyl amino acid mimetics 3′-*O*-(2,6-anhydro-D-*glycero*-L-*gluco*-heptitol-1-yl)-L-serine (**328a**) and -L-threonine (**328b**), which acted as building blocks for *O*-glycopeptides. The synthesis proceeded *via* α-*C*-galactopyranosyl aldehyde **7**, which in turn was prepared from 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose **5** *via* an allene approach. Aldehyde **7** on reduction with sodium borohydride gave *C*-glycosidic methylene galactitol **326** in 62% yield. Compound **326** in the presence of Lewis acid $BF_3 \cdot Et_2O$ in toluene, reacted with the activated aziridine ring containing compounds **327a–b** to form compounds **328a–b** in 52–55% yield. The *C*-glycosyl amino acids **133a–b** in 53–87% yields were obtained by hydrogenolytic deprotection followed by Zemplen deacetylation of compounds **328a–b** (Scheme 50). *C*-Glycosyl amino acids **133a–b** were found to be a competitive inhibitor of α-glycosidase from *Aspergillus niger*.

Risseeuw *et al.*[85] worked to design two synthetic pathways to obtain δ-substituted pyranoid sugar amino acids (SAAs). This synthesis was initiated from easily and readily available *C*-glucopyranosyl aldehyde **4a**. Condensation of formyl tetra-*O*-benzyl-β-D-*C*-glucopyranoside **4a** with *R*-*tert*-butanesulfinyl amide yielded *R*-*tert*-butanesulfamide **329** in 70% yield, which on alkylation in the presence of MeMgBr in DCM afforded *R*-methyl adduct **330** in excess over the corresponding *Z*-diastereoisomer **331**. Adduct **330** on further acid-mediated hydrolysis and installation of Fmoc protecting group resulted in **332** in 70% yield, which on selective acidolysis of primary benzyl ether, ester hydrolysis, and oxidation afforded the carboxylate **333** in 64% yield. The same stereoisomer **332** was formed in 75% yield when the whole reaction sequence was repeated with *S*-*tert*-butanesulfinamide, and the final product obtained was carboxylate **333** (Scheme 51a).

Treatment of *C*-glucopyranosyl aldehyde **4a** with different Grignard reagents afforded single isolated diastereomers **337a–d** in 36–68% yield. Further, Mitsunobu displacement using HN_3, DEAD, and PPh_3 in toluene afforded azide **338a–d** in 48–92% yield, with inverted stereochemistry. The reduction of azide **338b** using Me_3P, THF–H_2O followed by Fmoc protection produced **341b** in 73% yield. Selective acidolysis of primary benzyl protection of compounds **338a–d** with $ZnCl_2$–AcOH yielded compounds **339a–d** in 68–81% yield, which were further oxidized with TEMPO to afford L,L dipeptide isosters **340a–d** in 76–92% yield (Scheme 51b).



Scheme 50 Synthesis of *C*-glycosyl amino acids **133a–b**.



Scheme 51 (a) Synthesis of δ-substituted pyranoid sugar amino acid **333**. (b) Synthesis of L,L-dipeptides isosters **340a–d**.

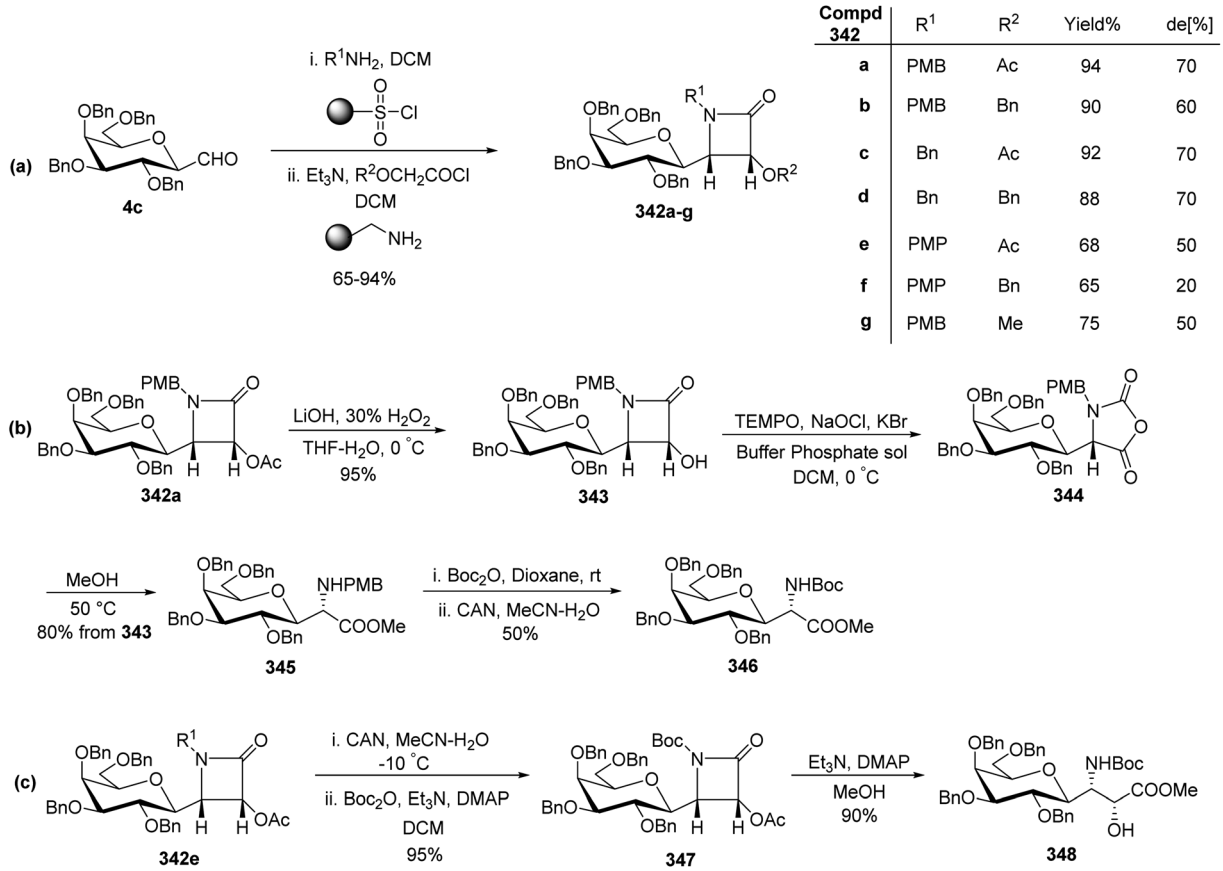
Three-component reaction on *C*-glycopyranosyl aldehyde was achieved by Dondoni *et al.*[86] to synthesize *C*-glycopyranosyl-β-lactams and further elaborated synthesis of *C*-glycosyl isoserines and dipeptide precursors. *C*-Galactopyranosyl aldehyde **4c** was reacted with easily available primary amines and substituted with acetyl chlorides to give a small library of *C*-galactopyranosyl-β-lactams **342a–g** with 65–94% yield (Scheme 52a).

First, *C*-glycosylimine was generated by the reaction between *C*-galactopyranosyl aldehyde and an excess amount of primary amine derivatives in DCM, and thereafter resin supported sulfonyl chloride removed the excess of unreacted alkylamine from the solution. The resulting mixture was treated with substituted acetyl chloride in the presence of triethylamine to afford *C*-galactopyranosyl-β-lactam. The amino-methylated resin was used to remove excess ketene and unreacted acetyl chloride from the reaction mixture. These β-lactams could be utilised to synthesise other classes of biologically active compounds, *i.e.* β-amino acids.

Deacetylation of *C*-glycosyl-β-lactam **342a** was achieved using LiOH-30% H_2O_2 to afford **343** in 95% yield, which on oxidation with TEMPO-NaOCl furnished *N*-carboxy anhydride **344** (Scheme 52). Ring-opening of **344** using methanol followed by protection of –NH with Boc group and deprotection of PMB functional group with CAN produced compound **346** in 50% yield (Scheme 52b).

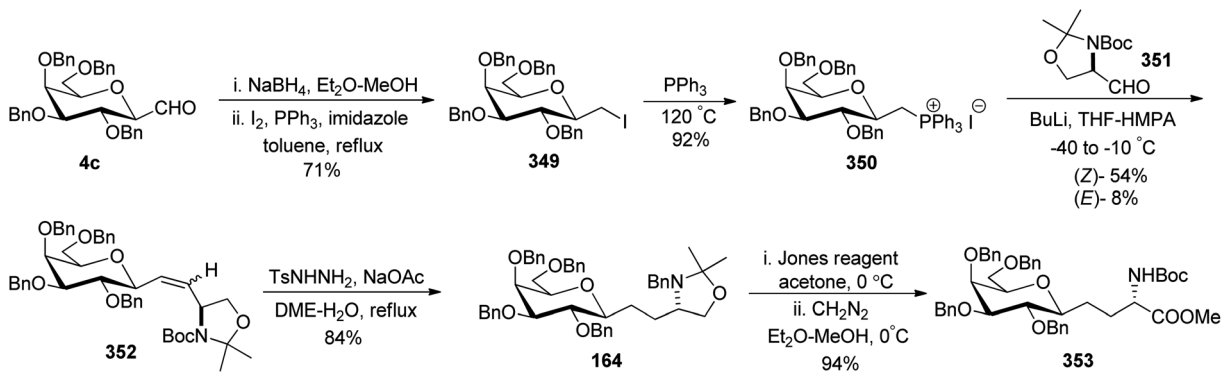
Synthesis of *C*-galactopyranosyliso-serine ester **348** was achieved with 90% yield by conversion of *C*-glycosyl-β-lactam **342e** into **347** with 95% yield *via* switching of N-protective group using Et_3N–DMAP in MeOH (Scheme 52c).

In 1998, Dondoni *et al.*[64] reported the synthesis of *C*-galactopyranosyl-α-amino acids *i.e.* *C*-analogue of β-D-galactopyranosyl-L-serine. First of all, β-*C*-galactopyranosyl aldehyde **4c** was reduced using $NaBH_4$ in MeOH followed by iodination with iodine–PPh_3–imidazole furnished compound **349** in 71% yield, which was efficiently converted into sugar-based Wittig reagent **350** in 92% yield by reaction with PPh_3. Subsequently, Wittig coupling between **350** and **351** in the presence of butyl lithium–THF–HMPA afforded **352** with as a mixture of stereoisomers (*Z*-54%, *E*-8%). Reduction with diimide (generated *in situ*) gave **164** in 84% yield, which was



Compd 342	R^1	R^2	Yield%	de[%]
a	PMB	Ac	94	70
b	PMB	Bn	90	60
c	Bn	Ac	92	70
d	Bn	Bn	88	70
e	PMP	Ac	68	50
f	PMP	Bn	65	20
g	PMB	Me	75	50

Scheme 52 Synthesis of *C*-galactopyranosyl-β-lactams **342a–g**, α-amino ester **346**, *C*-galactosyl isoserine methyl ester **348**.

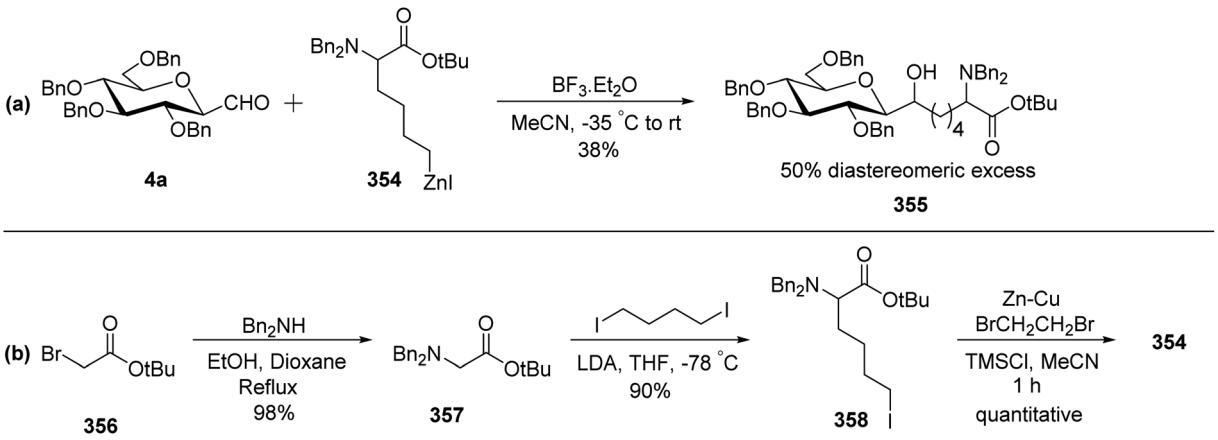


Scheme 53 Synthesis of β-D-galactopyranosyl-L-serine **353**.

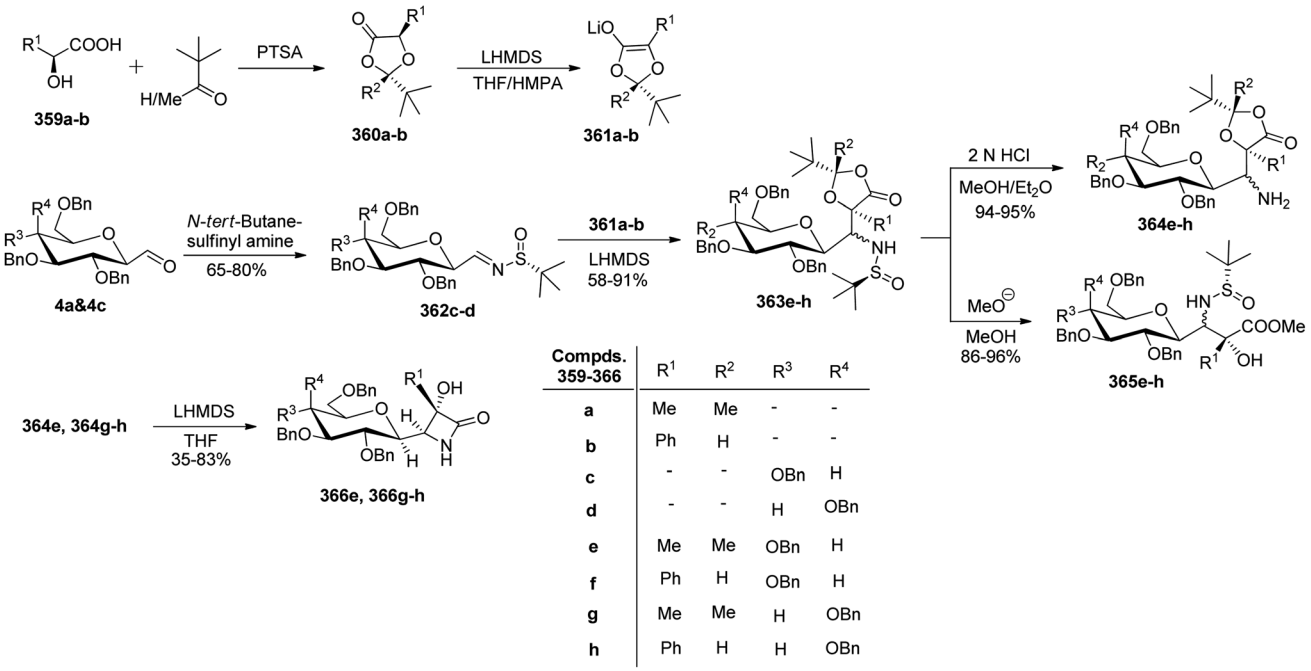
treated with Jones' reagent and then methylation with diazomethane afforded *C*-linked analogue of β-D-galactopyranosyl-L-serine **353** in 94% yield (Scheme 53).

Boutard *et al.*[87] synthesized *C*-glucopyranosyl-α-amino acids **355** in 38% yield with 50% diastereomeric excess where the reaction between *C*-glucopyranosyl aldehyde **4a** and organozinc reagent of amino acid **354** was carried out in presence of Lewis acid $BF_3 \cdot Et_2O$ in acetonitrile (Scheme 54a). Compound **354** was synthesized from α-bromo ester in three steps as shown in (Scheme 54b).

Guerrini *et al.*[88] designed one-pot synthesis of constrained *N*,*O*-orthogonally protected *C*-glycosyl norstatines (α-hydroxy-β-amino acids) **365e–h,** which was formed by the reaction of enolates of dioxolanones **361a–b** with (*S*)-*N*-sulfinyl azomethines **362c–d** following Seebach's SRS (Self-Regenerating Stereocenters) principle (Scheme 55). In the compounds **363e–h,** the *N* and *O* were orthogonally protected with the sulfinyl group at the nitrogen atom and the acetal moiety of the dioxolanone ring. The sulfinyl group present in the compounds **363e–h** was removed by using 2 N HCl acidic condition in a solvent mixture



Scheme 54 Synthesis of *C*-glucopyranosyl-α-amino acid **355**.



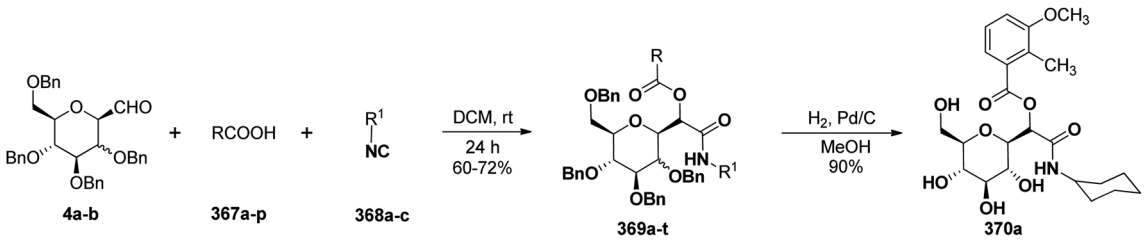
Compds. 359-366	R^1	R^2	R^3	R^4
a	Me	Me	-	-
b	Ph	H	-	-
c	-	-	OBn	H
d	-	-	H	OBn
e	Me	Me	OBn	H
f	Ph	H	OBn	H
g	Me	Me	H	OBn
h	Ph	H	H	OBn

Scheme 55 Synthesis of *C*-glycosyl norstatines (α-hydroxy-β-amino acids) **365e–h**.

of methanol and diethyl ether (1 : 1) leading to the formation of *N*-deprotected 1-*C*-glycosyl amino-dioxolan-4-ones **364e–h** in 94–95% yield. The acetal groups of **363e–h** were removed by methoxide-induced methanolysis forming, corresponding methyl *C*-glycosyl-sulfinylamino-isoserinates **365e–h** with 86–96% yield. Compounds **364e** and **364g–h** were converted into corresponding β-lactams **366e** and **366g–h**, respectively, with 35–83% yield using LHMDS in THF (Scheme 55).

Kumar *et al.*[89] recently designed a protocol based on the Passerini[90] multi-component reaction to synthesize a library of β-*C*-glycopyranosyl-α-acyloxy amides (Scheme 56). The component *C*-glycopyranosyl aldehyde **4a–b**, aryl/alkyl acid derivatives **367a–p**, and isocyanides **368a–c** were reacted by using DCM as the solvent at room temperature to afford glucopyranosyl α-acyloxy amides **369a–t** in good to excellent yield (60–72%). These glucopyranosyl α-acyloxy amides are commonly known as depsipeptides and are biologically significant. Further, **369a** was debenzylated using H_2, Pd/C in methanol to obtain **370a** in 90% yield.

Raunkjaer *et al.*[91] synthesised highly functional, novel dipeptide isosters *via* diastereoselective alkylation/arylation of sugar amino acids. This novel sugar amino acid (SAA) when applied in peptide synthesis protocol afforded a cyclic tetramer with excellent overall yield. The synthesis started with perbenzylated β-*C*-glucopyranosyl aldehyde **4a**, which on condensation with (*R*)-*tert*-butylsulfinamide in the presence of anhydrous $CuSO_4$ in DCM-derived sulfinimine **329** in 70% yield, which was treated with PhMgBr in toluene leading to the formation of sulfinamide **371** in >95% diastereomeric excess. Compound **371** was desulfinylated by HCl in methanol giving HCl salt of **372**,



a: Cyclohexyl isocyanide
b: tert-butyl isocyanide
c: p-toluenesulfonyl methyl isocyanide

compds 367 & 369	R		R		R= -Ph(o-Me, m-OMe)
a	-Ph(*o*-Me, *m*-OMe)	i	-Ph(*o*-Cl)	q	R^1= tert-butyl, from **4a**
b	-Ph(*p*-*tert*-butyl)	j	-Ph(*p*-Me)	r	R^1= cyclohexyl, from **4b**
c	-Ph	k	$-CH_3$	s	R^1= tert-butyl, from **4b**
d	$-C_5H_{11}$	l	$-C_3H_7$	t	R^1= *p*-Ts methyl, from **4b**
e	$-CH_2Cl$	m	-Ph(*p*-F)		
f	$-C_7H_{15}$	n	$-CH_2$(*p*-Cl-Ph)		
g	-Ph(*p*-CF_3)	o	-Ph(*o*-Me)		
h	-CH=CHPh)	p	-Ph(*p*-NO_2)		

Derived from **4a**, R^1= Cyclohexyl

Scheme 56 Synthesis of depsipeptides **369a–t** and **370a**.

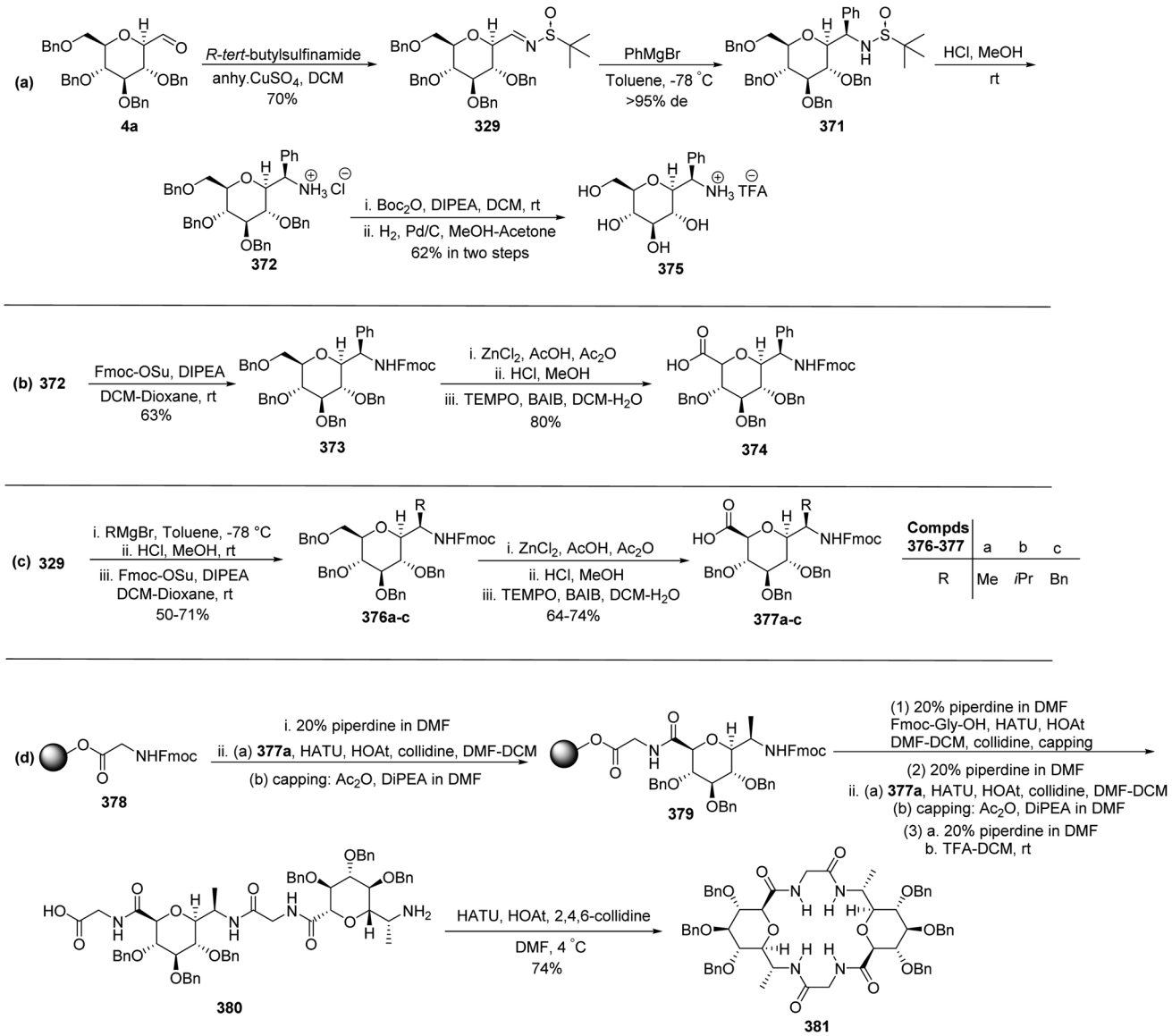
which was Boc protected using Boc_2O, DIPEA in DCM to produce corresponding *tert*-butoxycarbonylate, which underwent hydrogenolysis of benzyl ether group in the presence of Pd/C followed by removal of protecting group leading to the synthesis of compound **375** in 62% yield (Scheme 57a). The HCl salt of compound **372** was Fmoc protected to derive **373** with 63% yield in the presence of Fmoc-OSu, DIPEA, and DCM in dioxane. Compound **373** underwent selective debenzylation at the primary hydroxyl group on treatment with anhydrous $ZnCl_2$ in AcOH and Ac_2O, followed by acid-catalyzed deacetylation (HCl in MeOH) and oxidation using TEMPO and BAIB, leading to sugar amino acid **374** in 80% yield (Scheme 57b).

The sulfinimine derivative **329** was employed to synthesize a series of substituted SAAs **377a–c**. Compound **329** was treated with RMgBr in toluene and HCl in methanol followed by the removal of the sulfoxyl auxiliary and Fmoc protection, which led to the production of compounds **376a–c** in 50–71% yield. The primary benzyl-protected hydroxyl functionalities were converted into corresponding carboxylic acid groups following the reaction sequence leading to the formation of compounds **377a–c** in 64–74% yield (Scheme 57c). The alkylated SAAs were synthesized for their incorporation into oligomeric sequences. SAA **377a** was condensed with glycine-functionalized Wang resin **378** (Scheme 57d), thus producing immobilized product **379**, which upon removal of the Fmoc protecting group, and repetition of coupling steps followed by TFA-mediated cleavage from the solid support transformed into the linear tetramer **380**. This linear tetramer **380** was cyclized under high dilution to afford benzylated cyclic tetramer **381** in 74% yield.

Singh *et al.*[92] reported the synthesis of sugar–amino acid hybrid macrocycle starting from 2,6-anhydro heptitol **383a**, which was synthesized from *C*-glycopyranosyl aldehyde **4a**. Synthesis of 2,6-anhydro heptitol **383a–c** was achieved by Khatri *et al.*[52] from the reduction of aldehyde **4a–c** using $NaBH_4$ in methanol afforded **382a–c** in 90–95% yield, followed by treatment with trifluoro acetic acid, acetic anhydride, and sodium methoxide in methanol (Scheme 58a). 2,6-Anhydroheptitol **383a** was condensed with *N*-boc-glycinate using EDC·HCl, DMAP in dichloromethane produced 2,6-anhydro heptitolyl bis-glycinate **384** in 99% yield. Treatment with trifluoro acetic acid afforded deprotection of the Boc-group to produce **385** in 99% yield, which was reacted with succinic/pyridine dicarboxylic acid to obtain sugar–amino acid hybrid macrocycle **386** and **388** in 40% yield (Scheme 58b). The deprotection of the benzyl group using Pd/C in methanol was achieved on macrocycle **386** to produce macrocycle **387** in 95% yield. Further host–guest anion interaction studies were carried out on macrocycles **386** and **388** with TBA salt of Boc-glycinate. Based on ^{1}H NMR titration experiments, it was found that the carboxylate anion of Boc-glycinate salt exhibits interaction with the host macrocycle through hydrogen bonding. The macrocyclic compounds **386** and **388** have binding constants (K_a) of 9.201×10^3 M^{-1} and 1.437×10^4 M^{-1}, respectively.

Leclere *et al.*[46] reported a highly selective synthesis of *C*-AFGP analogue **125** (Scheme 59). Julia–Kocienski–Lythgoe (JKL) olefination reaction was carried out between *C*-glycopyranosyl aldehyde **90** and sulfone **389** to obtain glycopyranosyl alkene **390** in 65% yield. The sulfone **389** used here could be synthesized from orthogonally protected L-serine methyl ester **394** (Scheme 59b). Thus, the Mitsunbou reaction of **389** with 5-phenyl tetrazolyl thiol furnished **395** in 82% yield. Subsequently, reduction with lithium borohydride followed by *N*,*O*-isopropylidene formation and oxidation using sharpless conditions furnished **396** in 65% yield.

The glycopyranosyl alkene **390** was reduced with concomitant deprotection of the Cbz group afforded amino alcohol **391**



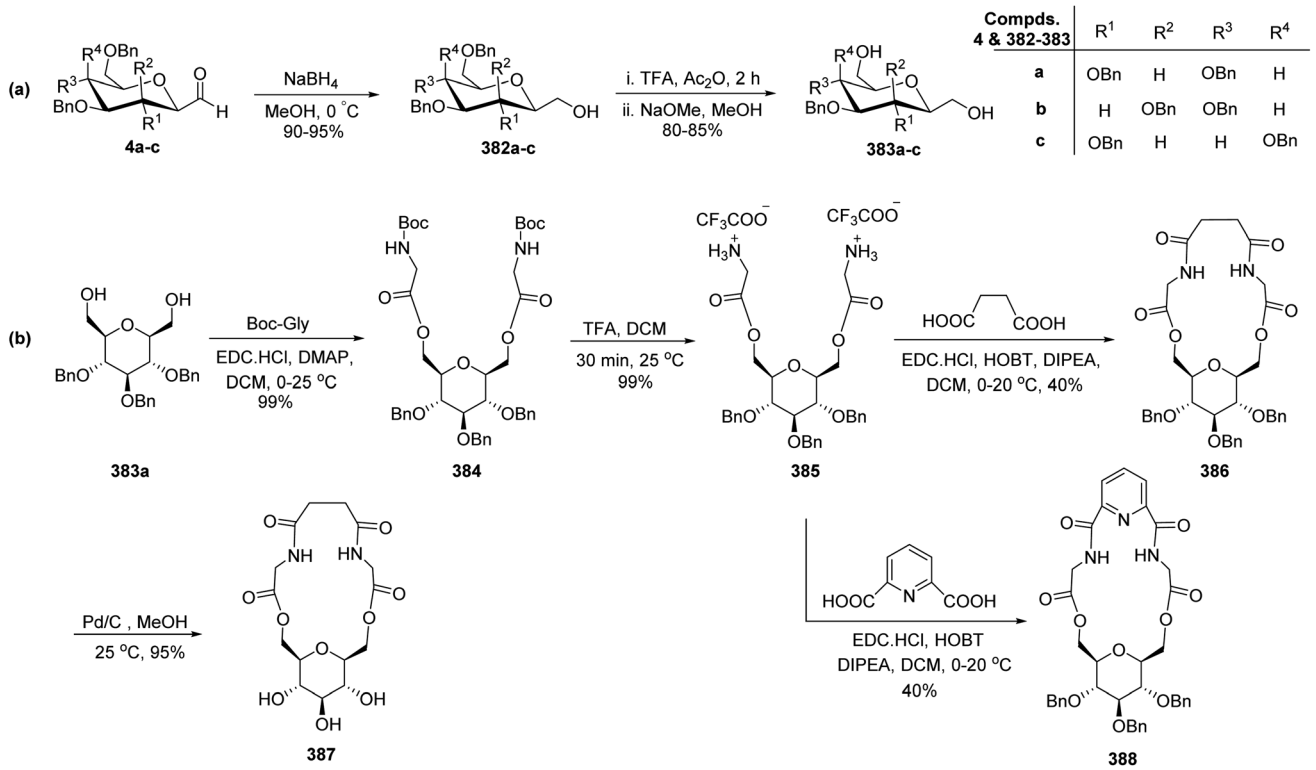
Scheme 57 Synthesis of benzylated cyclic tetramer **381**.

in 95% yield using H_2, $Pd(OH)_2$ in ethanol. Protection with Fmoc carbamate furnished **392** in 75% yield, which was oxidised to carboxylic acid **393** with 80% yield using TEMPO, $PhI(OAc)_2$, and $NaClO_2$. Finally, synthesis of glycoconjugate **125** was achieved using standard Fmoc-based solid phase synthesis with Wang resin in 20% yield. Glycoconjugate **125** is a potent inhibitor of ice recrystallization and could protect embryonic liver cells from cryo-injury at millimolar concentration. Thus *C*-AFGP analogue **125** is an effective cryoprotectant for human embryonic liver cells and inhibition of ice recrystallization in the course of cryopreservation is an important function for a cryoprotectant.

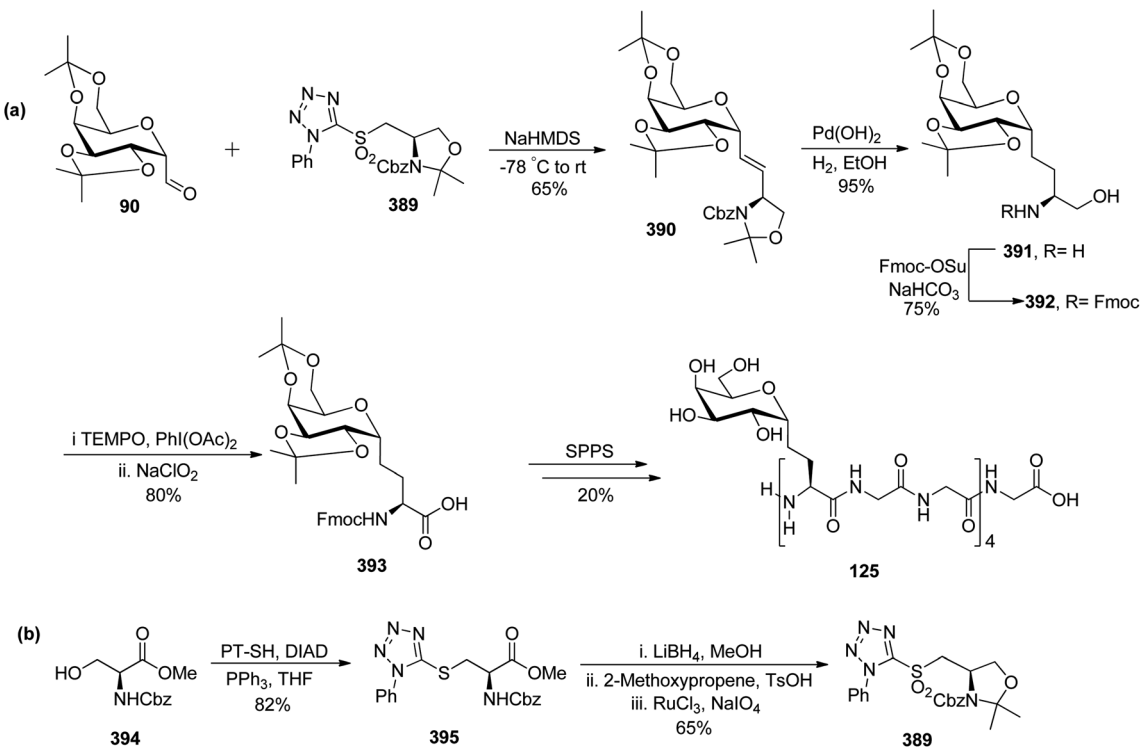
3.5 *C*-Glycopyranosyl phenyl methane and its derivatives

Kolympadi *et al.*[26] synthesized (α-D-galactosyl)phenylmethane (**402**) and α- and β-D-galactosyl)-(difluoro)phenylmethane, *i.e.* anomers **401** and **398**, respectively. α- and β-Glycopyranosyl aldehydes **4c** and **3c** on the addition of phenylmagnesium bromide followed by oxidation with PCC in DCM afforded corresponding ketones **396** and **399** in 50% and 45% yields, respectively. Ketones **396** and **399** upon difluorination with Deoxo-Fluor reagent in the presence of catalytic HF in pyridine afforded β- and α-CF_2 protected sugar analogues **397** and **400** in 23% and 77% yields, respectively. Finally, benzyl protection of compounds **397** and **400** was deprotected by hydrogenolysis to give (β- and α-D-alactosyl)-(difluoro)phenylmethane **398** and **401** in 67% and 70% yield, respectively. (α-D-Galactosyl)phenylmethane **402** was obtained from glycopyranosyl ketone **399** by reduction with catalytic hydrogenolysis followed by deprotection of benzyl ether (Scheme 60).

McGrane *et al.*[93] worked on designing a synthetic route for *C*-mannosides analogues, which specifically block uropathogenic

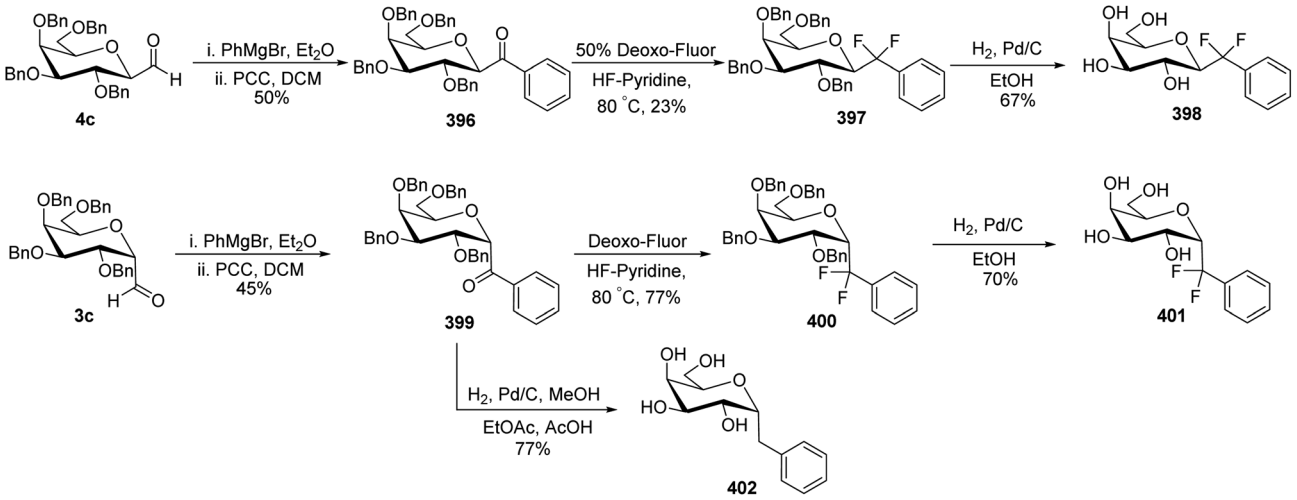


Scheme 58 Synthesis of 2,6-anhydro heptitol **383a–c** and sugar-amino acid hybrid macrocycles **386–388**.

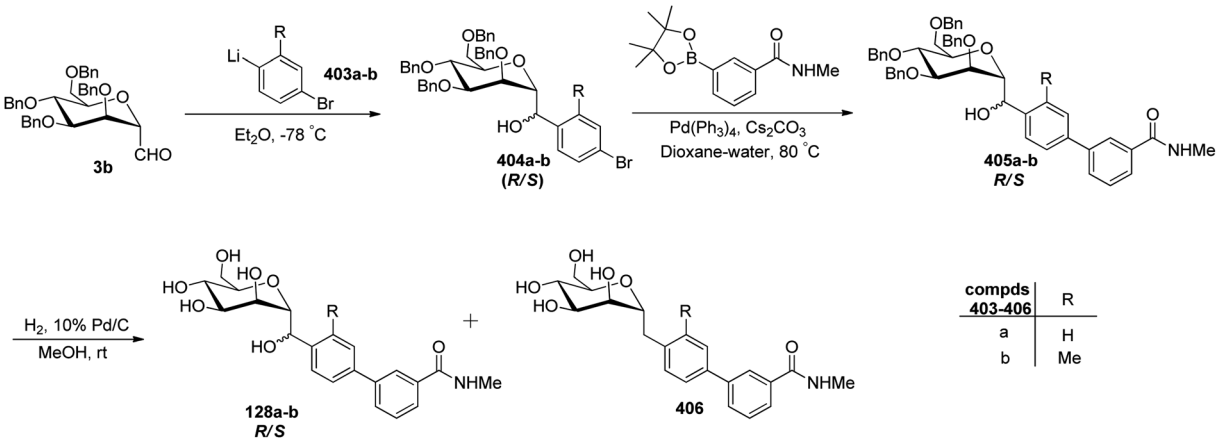


Scheme 59 Synthesis of *C*-AFGP analogue **125**.

Escherichia coli from colonizing the lower urinary tract. *C*-Mannosides were synthesised *via* a new pathway starting from *C*-linked glycopyranosyl aldehyde **3b**, which on reaction with organolithium reagent **403a–b** formed *in situ* by lithiation of 1,4-dibromobenzene with butyl lithium afforded *R*/*S* mixture of alcohol **404a–b**. The palladium-mediated reaction of alcohol



Scheme 60 Synthesis of compounds **398**, **401**, and **402**.



Scheme 61 Synthesis of *C*-mannosides analogues **128a–b** and **406**.

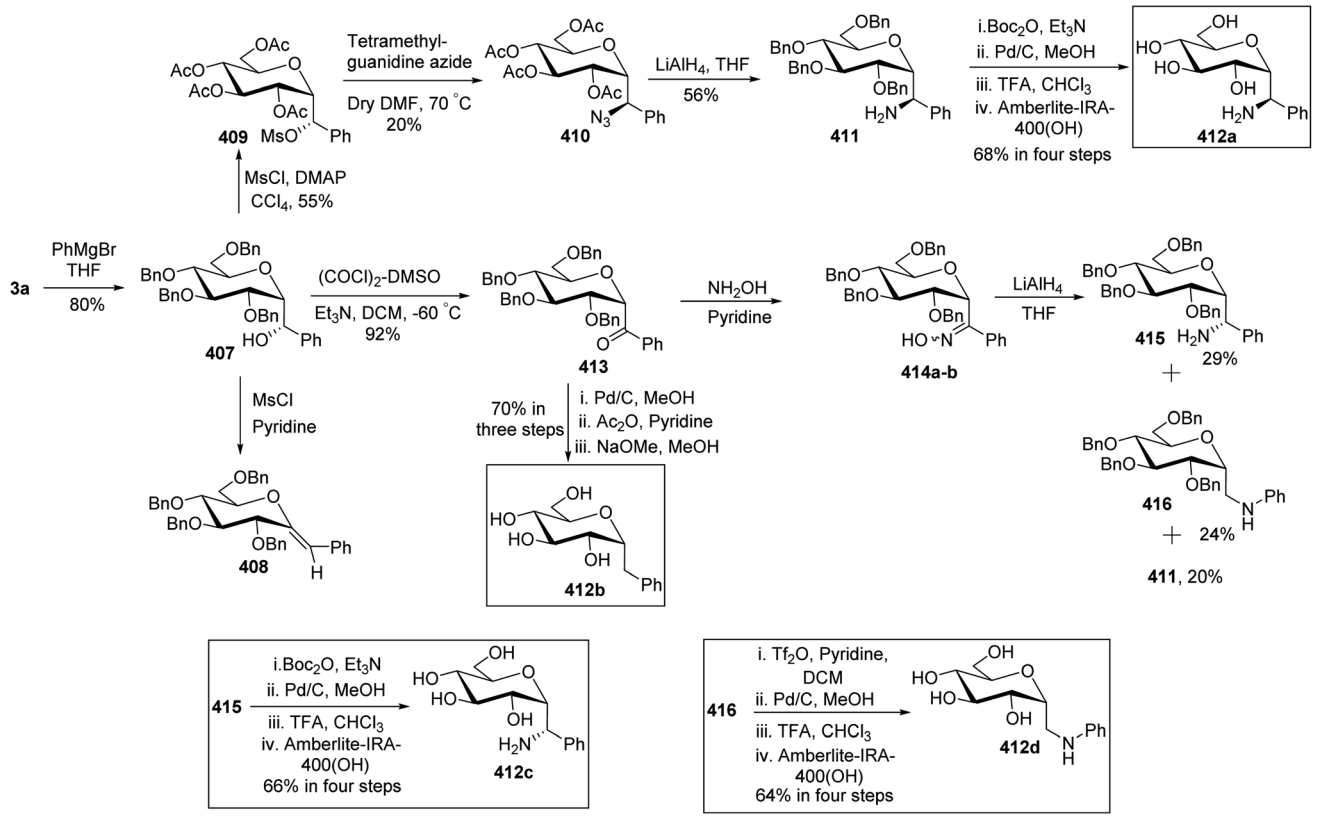
404a–b with 3-(*N*-methylaminocarbonyl)phenylboronate furnished the cross-coupled carboxamide **405a–b**, which on further hydrogenation with H_2, Pd/C afforded mannosides **128a–b** and **406** (Scheme 61). Methylene *C*-mannoside can be synthesised only by differing the organolithium reagent (4-bromo-2-methyliodobenzene).

Dietrich *et al.*[42] utilised the α-*C*-glycopyranosyl aldehyde for the synthesis of benzyl-α-*C*-glucosides and anilinomethyl-α-*C*-glucosides **412a–d**, which act as α-glucosidase inhibitors. α-*C*-glucopyranosyl aldehyde **3a** was treated with Grignard reagent phenylmagnesium bromide to afford diastereoselectively one isomer of compound **407** in 80% yield. Phenylcarbinol derivative **407** was converted into mesylated product **409**, which on treatment with tetramethylguanidine azide in DMF afforded **410** together with elimination product **408**. Azido compound **410** was reduced with $LiAlH_4$ to furnish **411** in 56% yield, which was converted into one of the desired compounds **412a** *via* a sequence of reactions (Scheme 62).

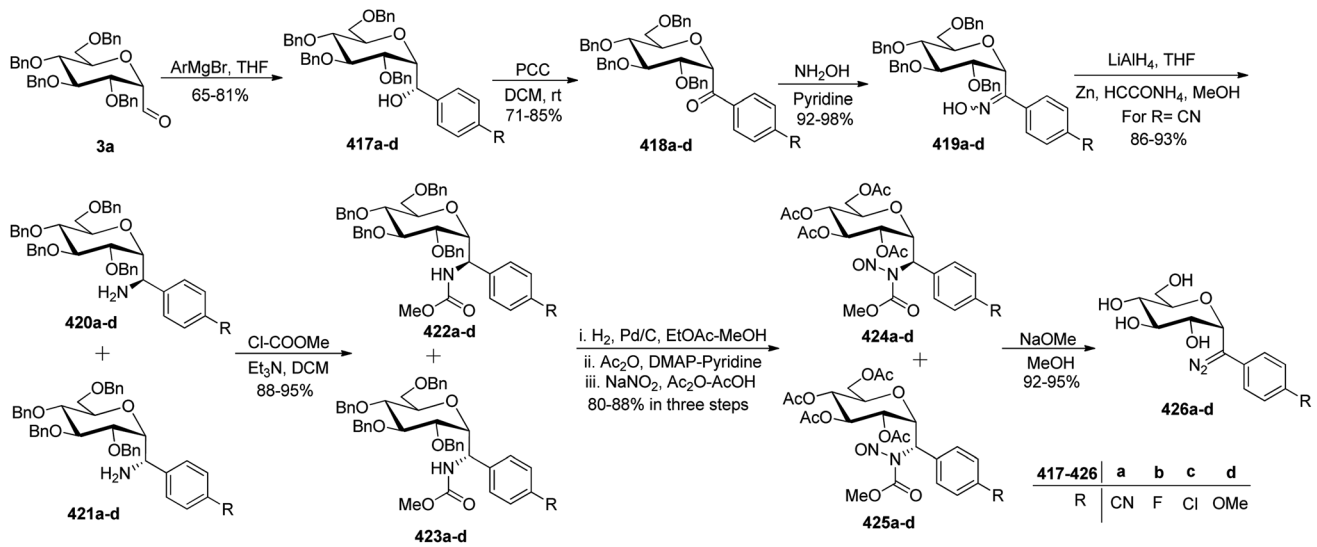
Due to the low yield of the product, another route for the synthesis of **412a** was investigated. Swern oxidation of **407** afforded compound **413** in 92% yield, which on treatment with hydroxylammonium chloride produced diastereomeric oximes **414a–b** in a 1 : 1 ratio. Reduction of an isomeric mixture of **414a–b** with $LiAlH_4$ furnished diastereomeric amines **411**, **415** and **416** in a ratio of 1 : 1 : 1 with 20%, 29%, and 24% yield, respectively. Finally, desired **412a**, **412c**, and **412d** were obtained in 64–68% yield in four steps from **411**, **415**, and **416** following the reaction sequence as shown in Scheme 62.

Direct hydrogenolysis of compound **413** with palladium on charcoal following *O*-acetylation of crude product and treatment with sodium methoxide was carried out to obtain desired **412b** in 70% yield.

Geng *et al.*[94] synthesized *C*-(α-D-glucopyranosyl)-phenyldiazomethane using α-*C*-glucopyranosyl aldehyde **3a** as the starting precursor (Scheme 63). A library of compounds with different substituent groups at the para position of the phenyl ring was prepared and further investigated for their stability. *C*-Glucopyranosyl aldehyde **3a** was reacted with different substituted arylmagnesium bromide in THF to afford α-*C*-glucopyranosyl benzylic alcohols **417a–d** in 65–81% yield with



Scheme 62 Synthesis of benzyl-α-*C*-glucosides and anilinomethyl-α-*C*-glucosides **412a–d**.



Scheme 63 Synthesis of *C*-(α-D-glucopyranosyl)-phenyldiazomethanes **426a–d**.

different substituents at the para position of the phenyl ring. Further oxidation with PCC in DCM led to the formation of **418a–d** with 71–85% yield, which on reaction with hydroxylammonium chloride furnished compounds **419a–d** with 92–98% yield. Reduction of oximes **419a–d** was carried out to furnish a diastereomeric mixture of amines **420a–d** and **421a–d** in 86–93% yield. Reaction with methylchloroformate and triethylamine with each of these diastereomers **420a–d** and **421a–d** afforded **422a–d** and **423a–d**, respectively in 88–95% yield. Hydrogenolytic debenzylation with H_2–Pd/C followed by acetylation with acetic anhydride, further treatment with $NaNO_2$ in Ac_2O–AcOH mixture afforded **424a–d** and **425a–d**, respectively in 80–88% yield in three steps. Both diastereomers on treatment with sodium methoxide in methanol furnished *C*-

(α-D-glucopyranosyl)-phenyldiazomethanes **426a–d** in 92–95% yield.

Investigation of the stability of these diazo compounds showed that substituent groups on the phenyl ring had a strong influence. The presence of an electron-withdrawing cyano group at the phenyl ring as in the case of compound **426a** was found to be stable enough to resist the solvolysis. Compound **426a** was further tested for inhibiting activity and type of inhibition towards α-glucosidase from *Saccharomyces cerevisiae* and found that compound was an irreversible inhibitor of α-glucosidase.

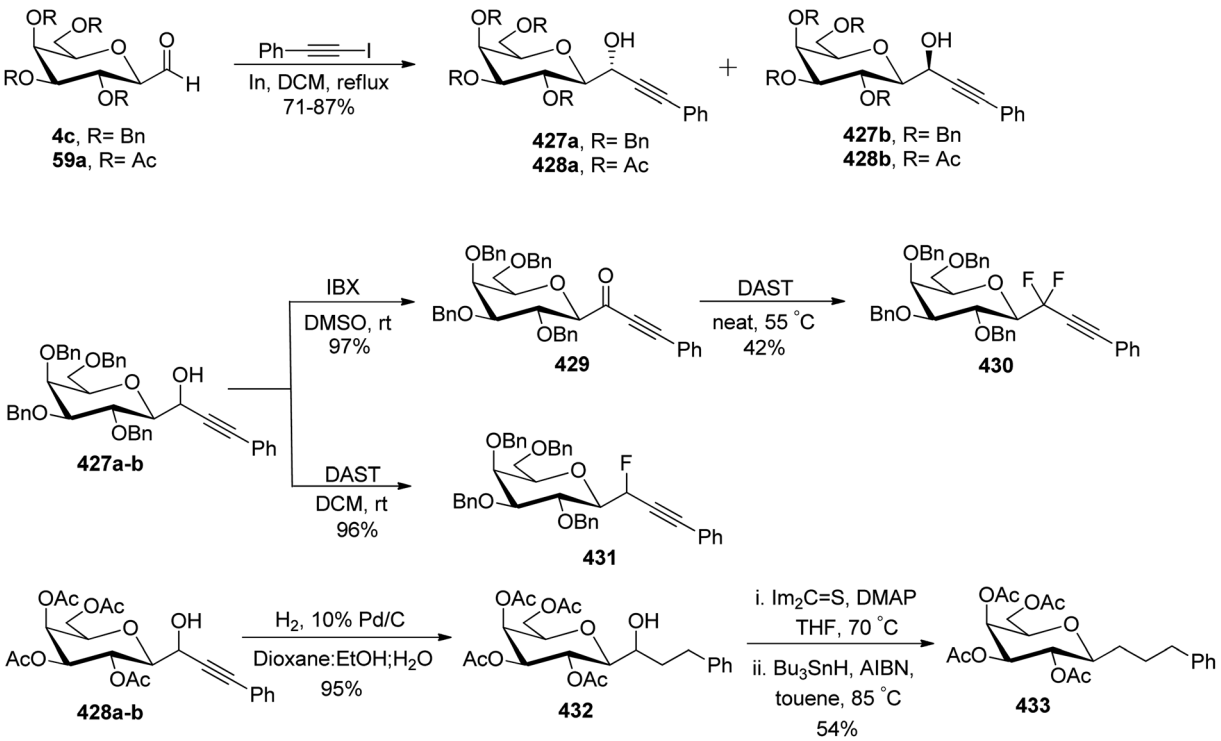
Picard *et al.*[95] introduced the indium-mediated alkynylation of β-*C*-galactopyranosyl aldehydes in order to synthesize various β-*C*-glycosides. Galactopyranosyl aldehydes **4c** and **59a** were reacted with phenylacetylene iodide in the presence of indium in DCM, which resulted in the formation of corresponding propargylic alcohols **427a–b** and **428a–b,** respectively in 71–87% yield, as a diastereomeric mixture (65 : 35). Propargylic alcohols **427a–b** upon oxidation with 2-iodoxybenzoicacid (IBX) in DMSO led to the formation of propargylic ketone **429** with 97% yield. Ketone **429** gave difluorinated product **430** on treatment with neat diethylaminosulfur trifluoride DAST (Scheme 64).

Also, propargylic alcohols **427a–b** were mono-fluorinated by treatment with DAST, forming corresponding fluorinated compound **431** in 96% yield (Scheme 64). The propargylic alcohol **428a–b** underwent palladium-catalysed hydrogenation leading to the formation of alcohol **432** in 95% yield, which upon treatment with thiocarbonyldiimidazole and tributyltin hydride afforded dehydroxylated compound **433** in 54% yield (Scheme 64).

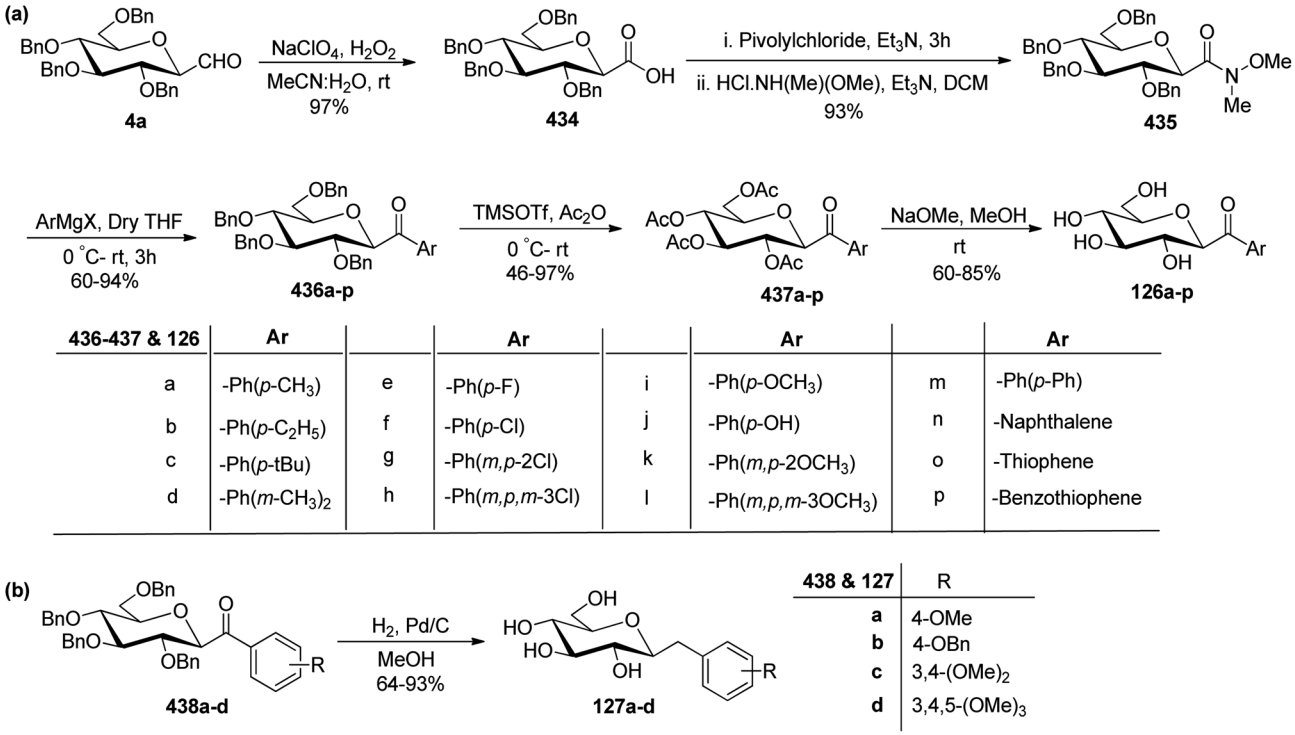
Reddy *et al.*[58] developed a scalable synthetic approach to synthesise acyl-*C*-β-D-glucosides and benzyl-*C*-β-D-glucosides, which proved to promote glucose-uptake activity in C2C12 mytotubes. The synthesis of these acyls and benzyl-*C*-β-D-glucosides was executed from β-*C*-glucopyranosyl aldehyde **4a**, which was oxidised under Pinnick oxidation reaction conditions using $NaClO_4$ and H_2O_2 affording carboxylic acid **434** in 97% yield. Carboxylic acid **434** on reaction with pivolyl chloride in Et_3N followed by HCl·NH(Me)(Ome) in DCM afforded amide **435** in 93% yield. The amide **435** was easily converted to a range of ketone derivatives **436a–p** in 60–94% yields with differently substituted aryl groups by Grignard reagent ArMgX in dry THF. The ketone derivatives **436a–p** were converted to corresponding acyl-*C*-β-D-glucoside derivatives by first reacting with TMSOTf in acetic anhydride yielding peracetylated compounds **437a–p** in 46–97% yield, followed by its deprotection using NaOMe in methanol afforded acyl-*C*-β-D-glucosides **126a–p** in 60–85% yield (Scheme 65a).

The *C*-β-D-glucosides **438a–d** were also synthesised by one-pot reduction of the carbonyl group and benzyl ether deprotection from the corresponding perbenzylated-*C*-β-D-glucosides **127a–d** using H_2, Pd/C in methanol in 64–93% yield (Scheme 65b).

Zeitouni *et al.*[70] reported a new strategy for the formation of *C*-glycosides by using the Mukaiyama aldol reaction. *C*-Glucopyranosyl aldehyde **4a** was reacted with trimethylsilyl enol ether **439** using Mukaiyama aldol reaction in the presence of $Yb(Otf)_3$ to furnish **440** and **441** as a diastereomeric mixture in ratio 59 : 41 with 95% yield (Scheme 66).



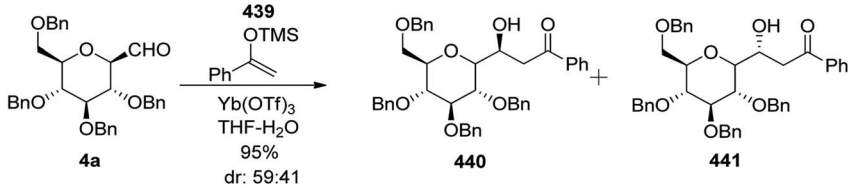
Scheme 64 Synthesis of β-*C*-glycosides **430–433**.



436-437 & 126	Ar		Ar		Ar		Ar
a	-Ph(*p*-CH_3)	e	-Ph(*p*-F)	i	-Ph(*p*-OCH_3)	m	-Ph(*p*-Ph)
b	-Ph(*p*-C_2H_5)	f	-Ph(*p*-Cl)	j	-Ph(*p*-OH)	n	-Naphthalene
c	-Ph(*p*-tBu)	g	-Ph(*m,p*-2Cl)	k	-Ph(*m,p*-2OCH_3)	o	-Thiophene
d	-Ph(*m*-CH_3)$_2$	h	-Ph(*m,p,m*-3Cl)	l	-Ph(*m,p,m*-3OCH_3)	p	-Benzothiophene

438 & 127	R
a	4-OMe
b	4-OBn
c	3,4-(OMe)$_2$
d	3,4,5-(OMe)$_3$

Scheme 65 Synthesis of *C*-β-D-glucosides **126a–p** and **127a–d**.



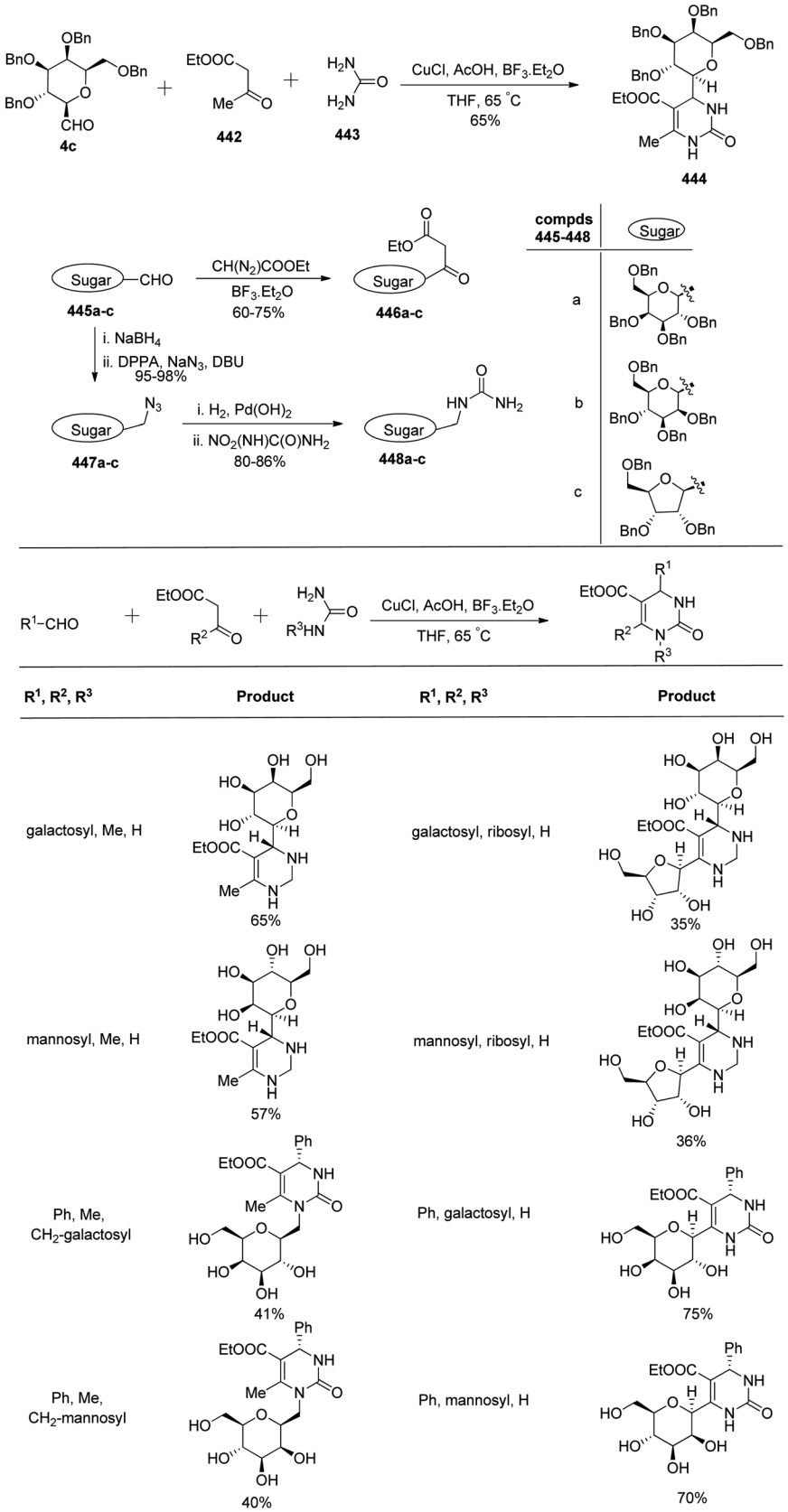
Scheme 66 Synthesis of *C*-glycosides **440** and **441**.

3.6 *C*-Glycopyranosyl heterocycles

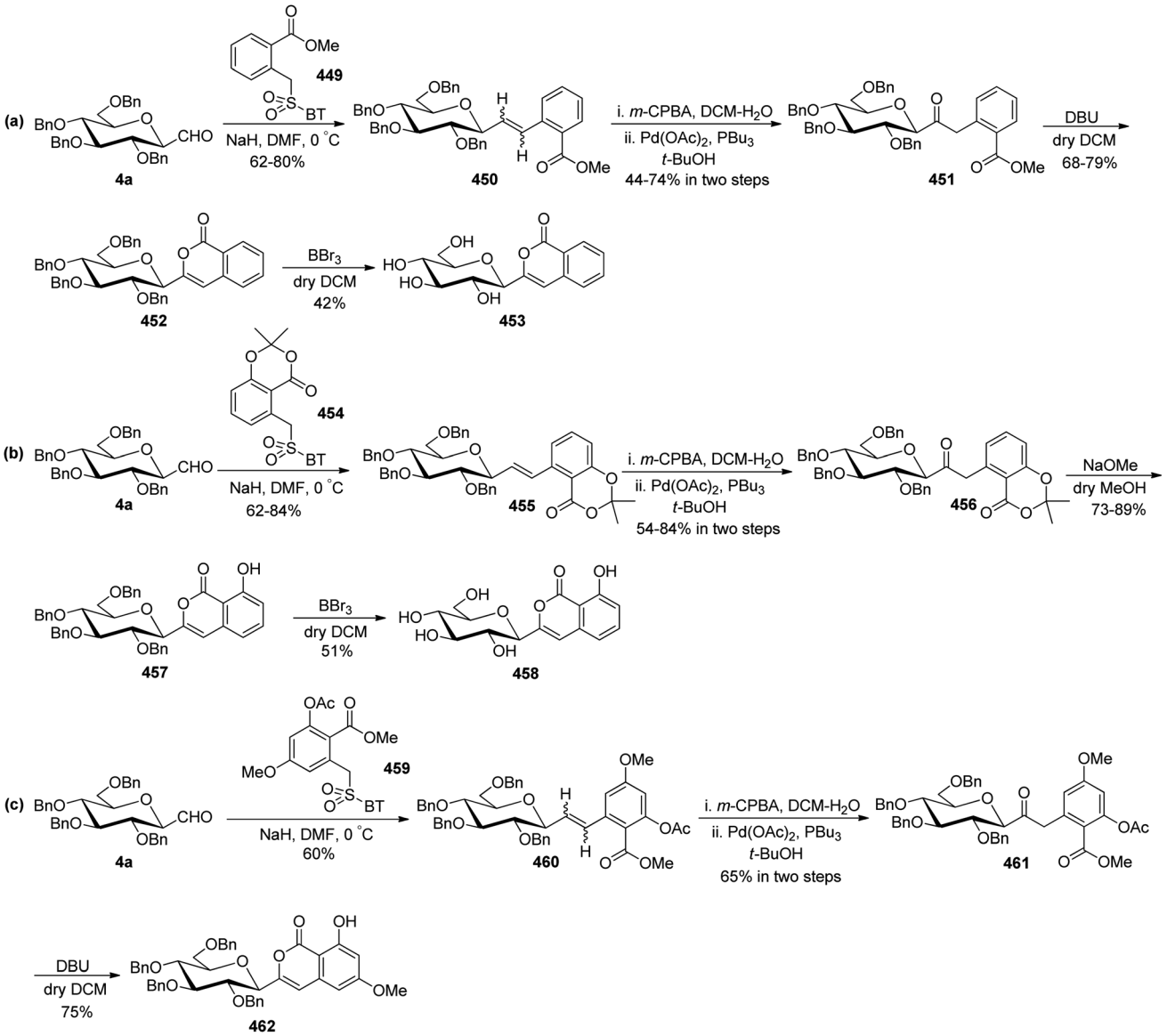
The three-component Biginelli cyclo condensation reaction involving aldehyde–ketoester–urea was explored by Dondoni *et al.*[96] using *C*-glycopyranosyl aldehyde to design a potential library of dihydropyrimidinone glycoconjugates. Under suitable acid additive and optimal reaction conditions, perbenzylated formyl *C*-galactopyranosyl aldehyde **4c**, ethyl acetoacetate **442**, and urea **443** were combined to form the cyclocondensed product **444** in 65% yield (Scheme 67).

Aiming to prepare a collection of mono-glycosylated and multiple-glycosylated DHPM derivatives, various substituted sugar residues were employed as substrates, which were in turn prepared from sugar aldehydes (Scheme 67). The *C*-glycosyl-β-ketoesters **446a–c** were synthesised in 60–75% yield starting from sugar aldehydes **445a–c** *via* coupling with ethyl diazoacetate in the presence of $BF_3 \cdot Et_2O$. Similarly, the sugar aldehydes **445a–c** were reduced in the presence of $NaBH_4$ followed by DPPA (diphenylphosphorylazide), DBU, and sodium azide to synthesize glycosylmethylazides **447a–c** in 95–98% yield *via* the formation of corresponding alcohol molecules as intermediate. Azides **447a–c** upon catalytic hydrogenation formed the corresponding amine, which on condensation with nitrourea afforded ureido sugars **448a–c** with good overall yields (80–86%). Thus, various cyclocondensations were studied taking differently substituted substrates *via* the Biginelli reaction and the results were found to adhere to the standard method, giving a collection of glycosylated DHPM derivatives (Scheme 67).

Sudarshan *et al.*[97] developed a route for the synthesis of 3-glycosylated isocoumarins by using modified Julia-olefination for initial C–C bond formation between *C*-glycopyranosyl aldehyde and benzylic-sulfones (Scheme 68). *C*-Glucopyranosyl aldehyde **4a** and benzyl-sulfones **449**, **454**, and **459** were subjected to Julia-olefination reaction to afford alkenes **450**, **455**, and **460** in 62–80%, 62–84%, and 60% yields, respectively, with *E*-isomer as the major product (Scheme 67a–c). These olefins further oxidised to ketone intermediates **451**, **456**, and **461** in 44–74%, 54–84%, and 65% yields, respectively, using palladium-catalysed Meinwald rearrangement *i.e.* *m*-CPBA in DCM-H_2O followed by $Pd(OAc)_2$, PBu_3 in *tert*-butanol with good yields. The ketone intermediates **451**, **456**, and **461** were



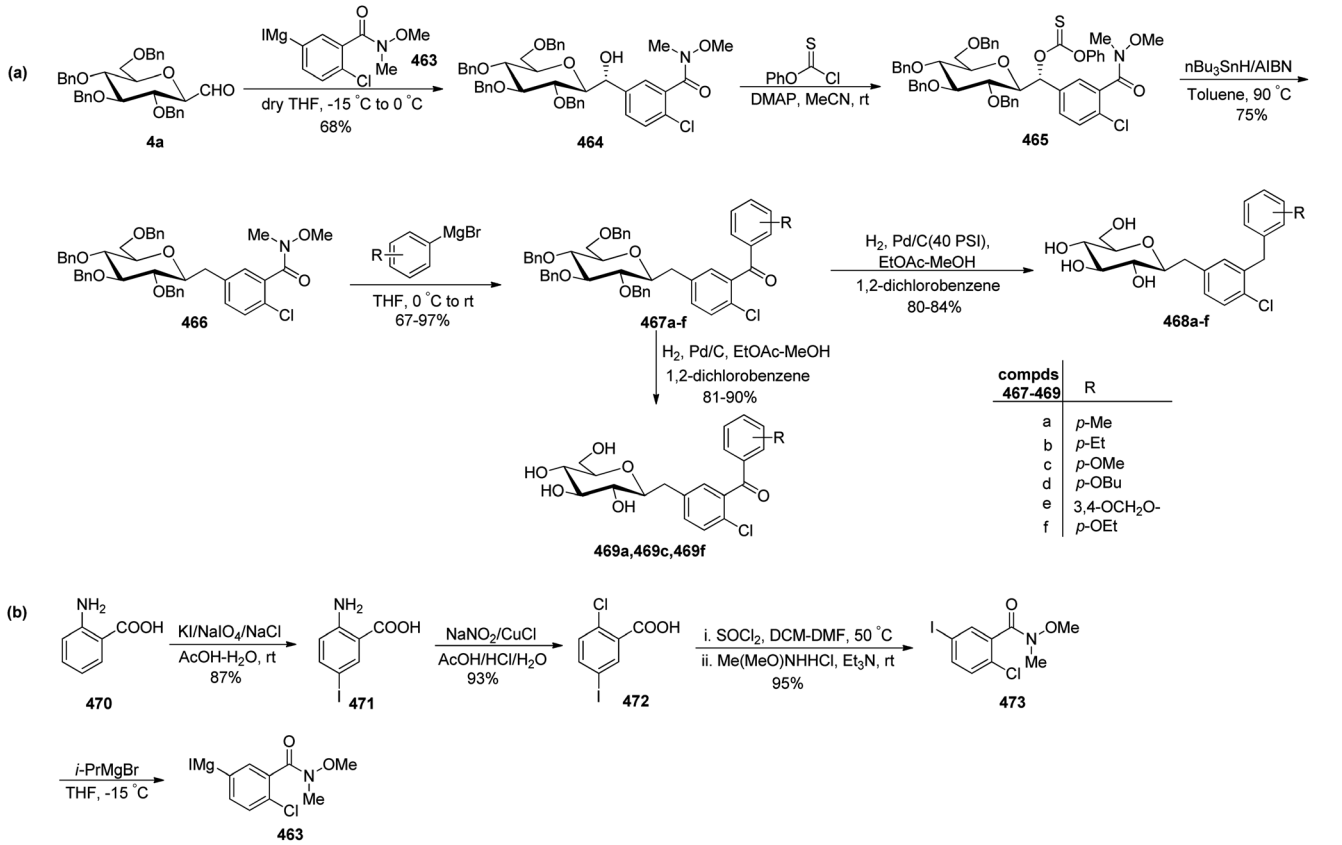
Scheme 67 Synthesis of various sugar-based dihydropyrimidinones.



Scheme 68 Synthesis of 3-glycosylated isocoumarins **453**, **458**, and **462**.

transformed into isocoumarins **452**, **457**, and **462** by base-promoted intramolecular cyclisation using DBU in dry DCM. Finally, 3-glycosylated isocoumarin **453** and **458** were obtained in 42% and 51% yield by debenzylation of **452** and **457** using boron tribromide in dry DCM.

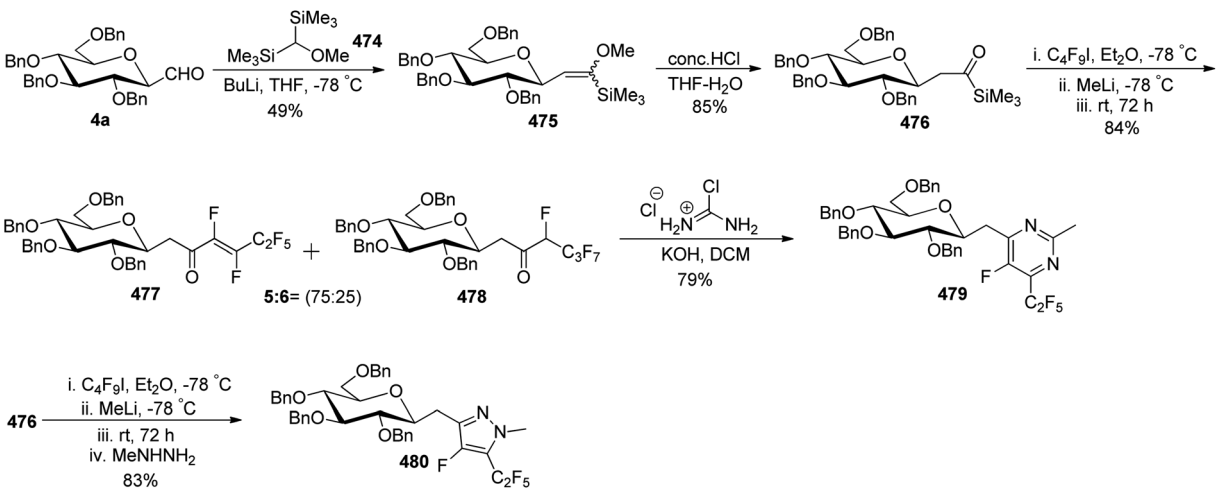
Mukkamala *et al.*[98] discovered a pathway to synthesise *C*-aryl glucoside analogues of Dapagliflozin, which act as SGLT inhibitors for the treatment of type-2 diabetes. Key products benzyl *C*-glucosyl aryl ketone **464** was synthesised from glucopyranosyl aldehyde **4a** and functionalized Grignard reagent **463** generated *in situ* from anthranilic acid **470**. Iodinated anthranilic acid **471** was obtained with 87% yield by the reaction of **470** with KI/$NaIO_4$/NaCl in acetic acid. Acid **471** on diazotisation reaction followed by the replacement of the diazonium group by chloro-group afforded carboxylic acid **472** in 93% yield, which afforded Weinerb-amide **473** in 95% yield on the reaction with $SOCl_2$ in DCM–DMF followed by Me(MeO)NHHCl. Functionalized arylmagnesium bromide **463** was obtained by reacting acid **473** with *i*PrMgBr under Paul Knochel's condition (Scheme 69b). Synthesised Grignard reagent **463** was reacted directly with aldehyde **4a** to afford addition product **464** in 68% yield, which undergoes subsequent deoxygenation on reaction with phenyl chlorothionocarbonate in 4-dimethylaminopyridine (DMAP) and acetonitrile yielding thionocarbonate derivative **465**. Compound **465** on radical de-oxygenation in tri-*n*-butyl tin hydride and AIBN in toluene afforded functionalized benzyl *C*-glucoside **466** in 75% yield, which upon addition of arylmagnesium bromides afforded benzyl *C*-glucosyl diaryl ketones **467a–f** in 67–97% yield. Ketone **467a–f** when subjected to simple hydrogenation with H_2, Pd/C in dichlorobenzene afforded de-protected *C*-benzylglucosyl ketones **469a**, **469c**, and **469f** in 81–90% yield while for other derivatives the hydrogenation was performed with 40 psi



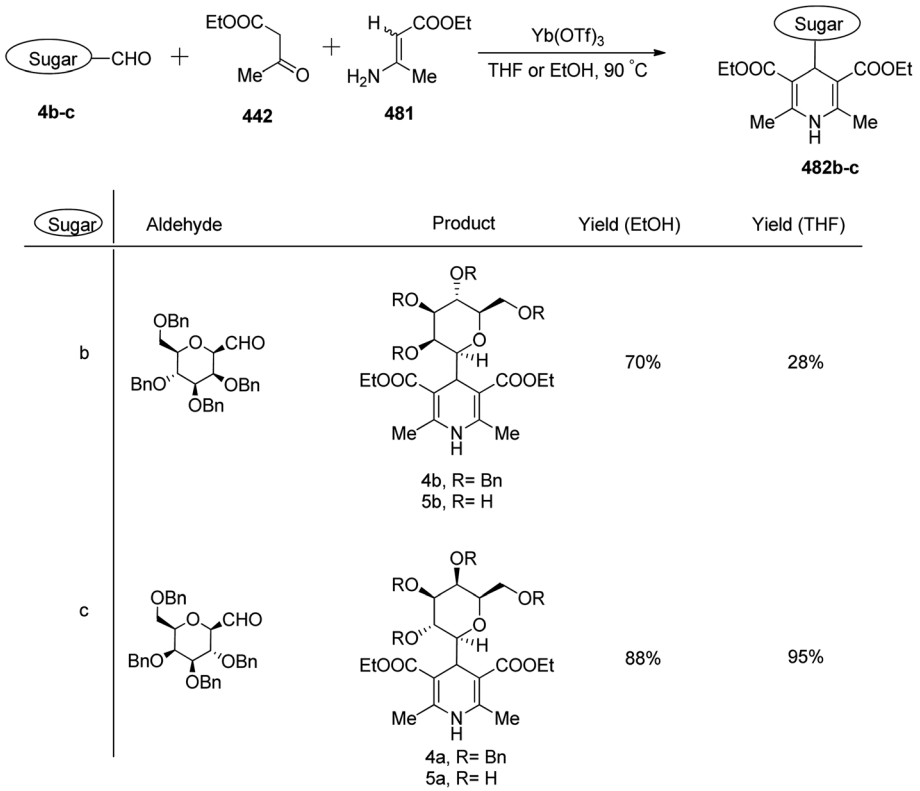
Scheme 69 Synthesis of *C*-aryl glucoside **467–469**.

pressure affording *C*-benzyl analogues of dapagliflozin **468a–f** in 80–84% yield (Scheme 69a).

Chanteau *et al.*[99] designed a stereo-controlled synthetic pathway for the synthesis of carbohydrate-derived acylsilanes starting from *C*-glucopyranosyl aldehyde **4a**. The aldehyde **4a** undergoes nucleophilic addition on reaction with bis(-trimethylsilyl)methoxymethane (**474**) in *n*-butyl lithium–THF *via* Peterson reaction to furnish enol ether **475** in 49% yield. Acidic hydrolysis of ether **475** with HCl in THF–H_2O afforded acylsilane **476** in 85% yield, which on treatment with perfluorobutyl iodide with methyllithium furnished the corresponding hemifluorinatedenone **477** and α-hydroperfluorobutyl ketone **478** in a ratio of 75 : 25 in 84% yield. The mixture of **477** and **478** when reacted with acetamide leads to cyclisation affording the pyridine derivative **479** with a 79% yield. Also, acylsilane **476** when reacted with perfluorobutyl



Scheme 70 Synthesis of glycopyranosyl pyridine and pyrazole derivatives **479** and **480**.

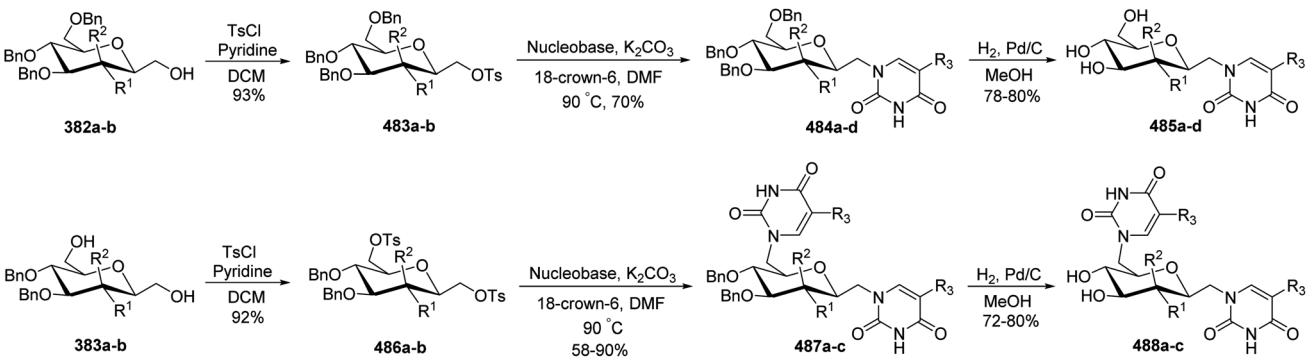


Scheme 71 Synthesis of *C*-glycosylated dihydropyridine **482b–c**.

iodide with methyllithium followed by methylhydrazine at room temperature afforded pyrazole derivative **480** with 83% yield (Scheme 70).

Dondoni *et al.*[100,101] synthesized *C*-glycosylated dihydropyridine by Hantzsch condensation reaction using *C*-glycopyranosyl aldehyde (Scheme 71). One pot three-component reaction was performed by taking *C*-glycopyranosyl aldehyde **4b–c**, ethyl acetoacetate **442**, and ethyl 3-aminobut-2-enoate **481** in the presence of $Yb(OTf)_3$ in THF or EtOH to furnish C(4)-glycosylated dihydropyridine **482b–c**. The overall yield with respect to the solvent taken is given in Scheme 71.

Verma *et al.*[102] reported a very simple methodology for the synthesis of hexopyranosyl pyrimidine homonucleosides and hexopyranosyl double-headed pyrimidine homonucleosides using *C*-glycopyranosyl aldehyde as a precursor. 2,6-anhydro heptitols **382a–b** and **383a–b** were converted into their tosylated



	382a-383a	382b-383b	483a & 486a	483b & 486b	484a & 487a	484b & 487b	484c & 487c	484d	485a & 488a	485b & 488b	485c & 488c	485d
R^1	OBn	H	OBn	H	OBn	H	OBn	H	OH	H	OH	H
R^2	H	OBn	H	OBn	H	OBn	H	OBn	H	OH	H	OH
R^3	-	-	-	-	H	H	CH_3	CH_3	H	H	CH_3	CH_3

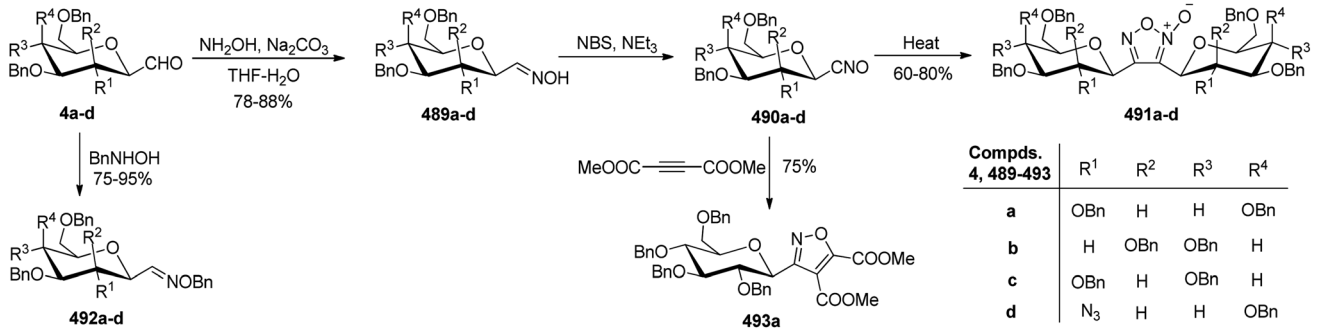
Scheme 72 Synthesis of homonucleosides **485a–d** and **488a–c**.

form using tosyl chloride in pyridine-DCM to afford **483a–b** and **486a–b** in 92–93% yield, respectively. Further nucleophilic substitution reactions on **483a–b** and **486a–b** were carried out using thymine/uracil as nucleobase, K_2CO_3, 18-*crown*-6 in DMF to obtain hexopyranosyl homonucleosides **484a–d**, and **487a–c**, respectively. Treatment with H_2, Pd/C in methanol afforded debenzylated form of homonucleosides **485a–d** and **488a–c** in 78–80% and 72–80% yield, respectively (Scheme 72).

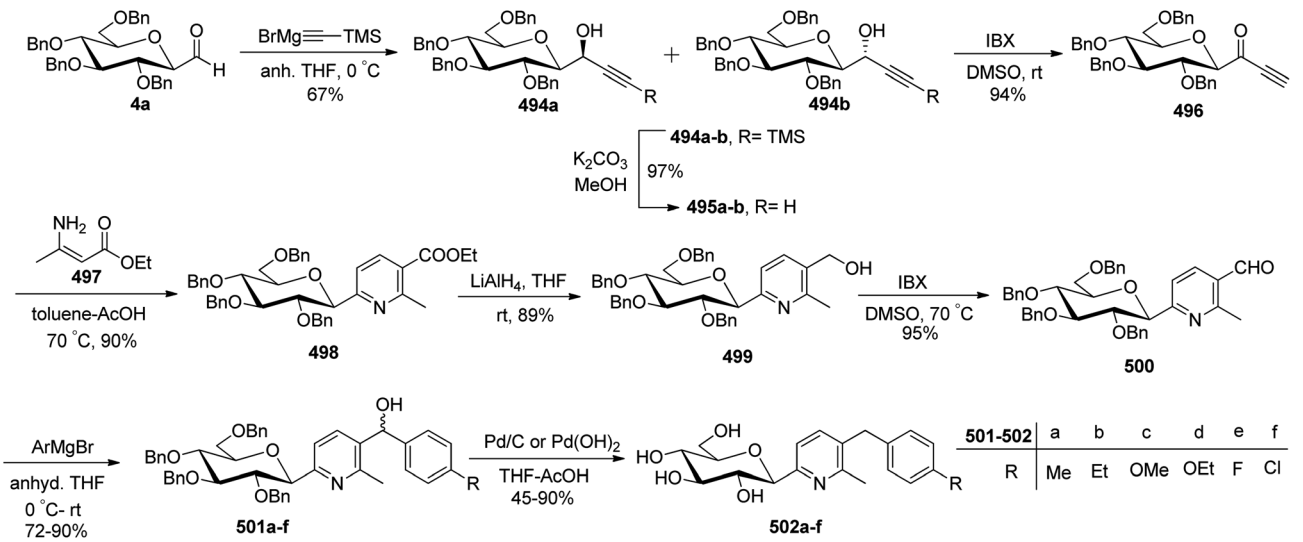
Dondoni *et al.*[103] used β-*C*-glycopyranosyl aldehydes for the synthesis of glycosyl nitrile oxides and nitrones, which in turn could be used for the synthesis of more complex *C*-glycoconjugates. *C*-Glycopyranosyl aldehydes **4a–d** on treatment with hydroxylamine and sodium carbonate in THF–H_2O at room temperature afforded corresponding oximes **489a–d** in 78–88% yield. Oximes **489a–d** on treatment with *N*-bromosuccimimide (NBS) followed by triethylamine, led to the formation of nitrile oxide **490a–d.** Upon heating, these nitrile oxides dimerised to give furoxans **491a–d** in 60–80% yield. Compound **490a** reacted with dimethyl acetylenedicarboxylate, which underwent the cycloaddition reaction and afforded corresponding *C*-glycosylated isoxazole **493a** with 75% yield. Also, compounds **4a–d** afforded the corresponding *N*-benzyl nitrones **492a–d** in 75–95% yield on treatment with *N*-benzylhydroxyl-amine (Scheme 73).

Reddy *et al.*[104] reported the synthesis of 2-β-D-glucopyranosyl pyridines by using Bohlmann–Rahtz hetero-annulation starting from β-*C*-glucopyranosyl aldehyde (Scheme 74). Nucleophilic addition of TMS–ethynyl magnesium bromide was carried out on *C*-glucopyranosyl aldehyde **4a** to afford a diastereomeric mixture of **494a** and **494b** in 67% yield, which on further treatment with K_2CO_3 in methanol removed the TMS group and furnished **495a** and **495b**, respectively, in 97% yield. Oxidation of the diastereomeric mixture of **495a–b** with IBX in DMSO produced **496** in 94% yield, which was followed by Bohlmann–Rahtz hetero-annulation reaction conditions with β-aminocrotonate **497** in toluene–AcOH at 70 °C to afford trisubstituted pyridine **498** in 90% yield.

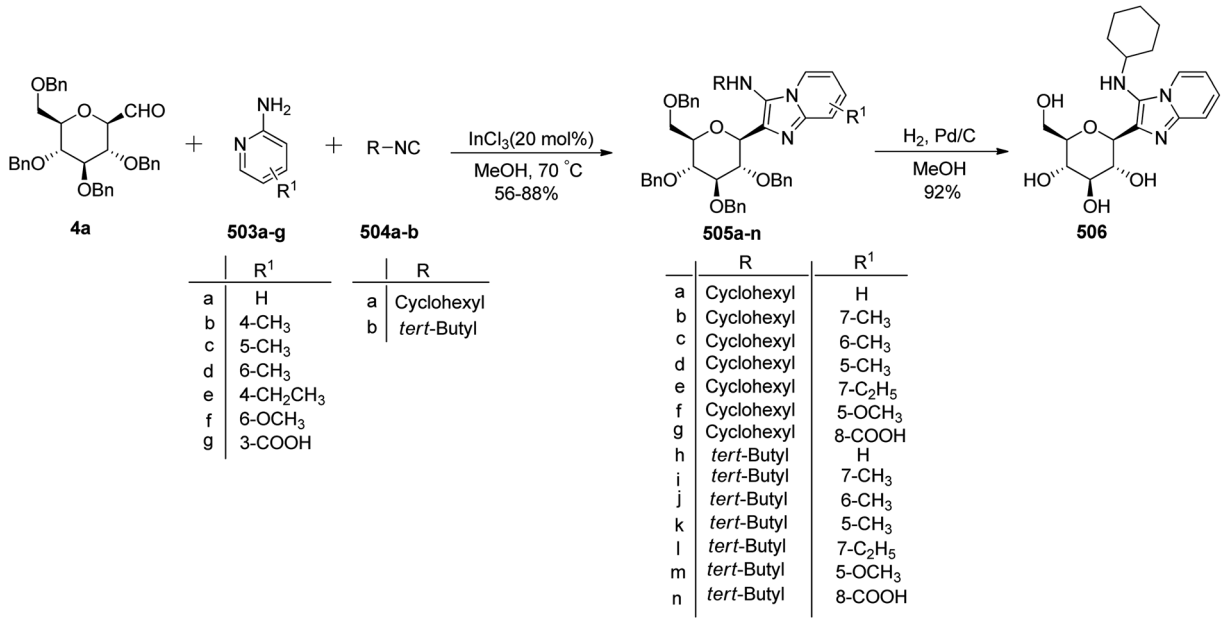
Further, reduction of glycoside **498** with $LiAlH_4$ produced **499** in 89% yield, which on oxidation with IBX in DMSO afforded **500** in 95% yield. Compound **500** was treated with substituted arylmagnesium bromide to afford a diastereomeric mixture of compounds **501a–f** in 72–90% yield, which on direct hydrogenation with palladium on charcoal afforded targeted compounds **502a–f** in 45–90% yield. These compounds were



Scheme 73 Synthesis of glycosyl nitrile oxide **490a** and glycosyl nitrones **492a–d**.



Scheme 74 Synthesis of 2-β-D-glucopyranosyl pyridines **502a–f**.



Scheme 75 Synthesis of *C*-glucosides of 1-azaindolizines **505a–n** and **506**.

found to be the potential analogue of Dapagaliflozin, an approved drug that lowers blood glucose levels by inhibiting the sodium-glucose transport in the kidney.

Very recently our research group has synthesized a library of *C*-glucosides of 1-azaindolizines from *C*-glucopyranosyl aldehyde using the Groebke–Blackburn–Bienayame[105–107] (GBB) reaction protocol (Scheme 75).[108] The multicomponent reaction of *C*-glucopyranosyl aldehyde (**4a**) with 2-aminopyridine derivatives **503a–g** and isocyanides **504a–b** was carried out in the presence of the catalytic amount of $InCl_3$ in MeOH at 70 °C to afford *C*-glucosides of 1-azaindolizines **505a–n** in 56–88% yield. Deprotection was carried out for **505h** using H_2, Pd/C in methanol to obtain **506** in 92% yield.

3.7 *C*-Glycopyranosyl based natural product fragments

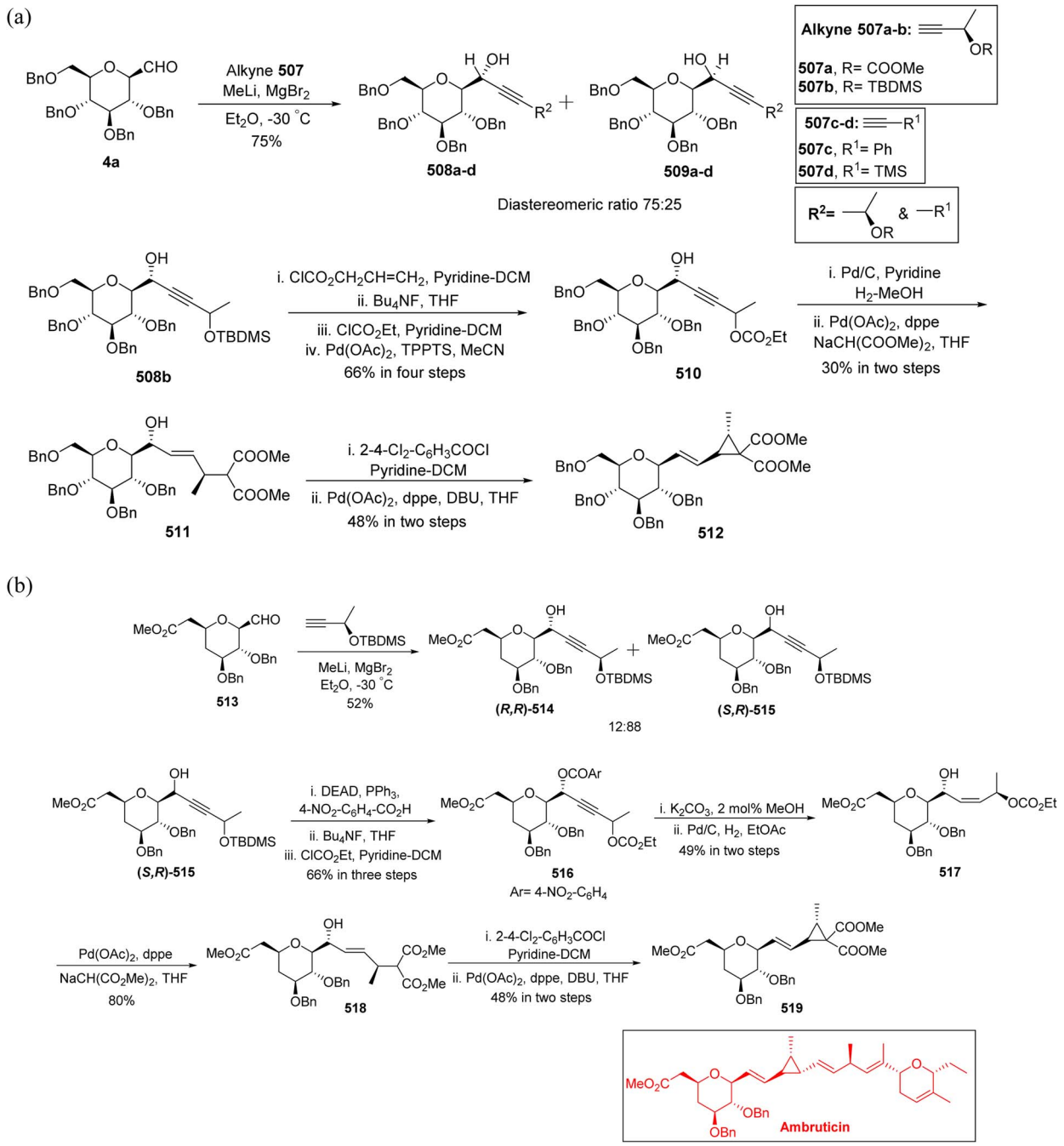
A new approach to the synthesis of ambruticin fragment by employing β-*C*-glycoside aldehyde as starting material was generated by Michelet *et al.*[109] The key phenomena introduced was stereoselective chain-elongating hydroxy alkylation of β-*C*-glucopyranosyl aldehyde **4a** by using various alkynyl derivatives **507a–d** in the presence of methyllithium and magnesium dibromide leading to formation of diastereomeric alcohols **508a–d** and **510a–d** with a diastereomeric ratio of 75 : 25 in 75% yield. The major alcohol derivative **508b** on treatment with a series of reagents led to the formation of alcohol **510** in 66% yield, which was hydrogenated in the presence of Pd/C followed by alkylation with $NaCH(COOMe)_2$, palladium acetate, and DPPE in THF forming compound **511** as a single isomer in just 30% yield. Alcohol **511** on activation with 2,4-dichlorobenzoyl chloride followed by cyclization afforded tetra-*O*-benzylated cyclopropane **512** in 48% yield (Scheme 76a), which in turn is the western part of ambruticin.

Synthesis of the western part of ambruticin was achieved from *C*-glycosyl aldehyde **513** (Scheme 76b). *C*-Glycosyl aldehyde **513** was reacted with alkyne **507b** in the presence of MeLi–$MgBr_2$ to afford alcohol mixtures in 12 : 88 diastereomeric ratio (***R*,*R*)-513** and (***S*,*R*)-514** in 52% yield. Mitsunobu reaction was applied on **(*S*,*R*)-514** to invert the stereochemistry of alcohol, which produced **516** in 66% yield. Further treatment of potassium carbonate in 2 mol% methanol followed by H_2, Pd/C in ethyl acetate produced **517** in 49% yield. Compound **518** was achieved using $Pd(OAc)_2$, dimethyl malonate sodium salt in THF. Finally, the western part of Ambruticin **519** was obtained in 48% yield using Pd-catalysed cyclization.

3.8 Miscellaneous

The Ugi reaction is a multicomponent reaction where aldehyde, amine, carboxylic acid, and isocyanide components are combined to form bis-amide (Scheme 77a). Lockhoff *et al.*[110] used this reaction to synthesise glycoconjugates libraries by using carbohydrate building blocks for the Ugi condensation. *C*-Glycosyl aldehyde **4a** which also serves as an aldehyde building block could be easily oxidised into carboxylic acid **520** in 81% yield by using $KMnO_4$–NaH_2PO_4. Similarly, amine and isocyanide building blocks were synthesised starting from *C*-glycosyl aldehyde (Scheme 77b). Compound **4a** was reduced with $LiBH_4$ to afford glycosylmethyl alcohol **521** in 95% yield, which was converted into amine **522** in 71% yield by following the reaction sequence, *i.e.* tosylation, azide substitution followed by reduction. Further, *N*-formylation of **522** and dehydration afforded isocyanide **523** in 52% yield. All these *C*-glycosides are the desired building blocks for Ugi condensation and were used to synthesise glycoconjugates (Table 4).

Dondoni *et al.*[111] synthesized [60]fulleropyrrolidine glycoconjugates by using *C*-glycosyl aldehyde **4c** and **524** (Scheme

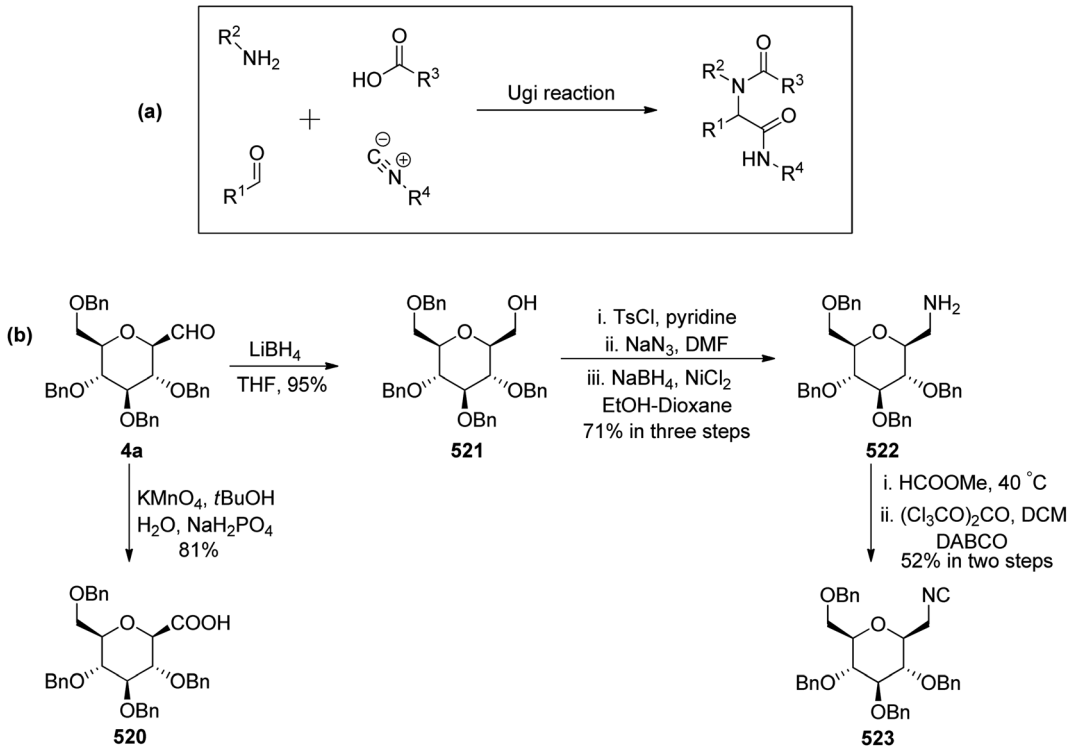


Scheme 76 (a) Synthesis of tetra-*O*-benzylated cyclopropane **512**. (b) Synthesis of the western part of Ambruticin **519**.

78). In this protocol, *C*-glycosyl aldehydes **4c** and **524**, [60] fullerene, and *N*-methylglycine (sarcosine) **525** were refluxed in toluene to afford a diastereomeric mixture of [60]fulleropyrrolidine glycoconjugates **527a–b** in 10–14% yield. The reaction proceeds through the formation of sugar azomethine ylide intermediate **526**. It was found that an attack of azomethine ylide **526** occurred on a 6,6-ring junction of C_{60} through 1,3-dipolar cycloaddition reaction. Deprotection of the benzoyl group was carried out to obtain **528b** using sodium methoxide in methanol-toluene.

Auge *et al.*[112] while studying vinyl halides realised that these are the building blocks of olefin synthesis and hence, they designed various vinyl halide synthesis. One of them involved the *C*-glycopyranosyl aldehydes as the starting product **4a**, which upon treatment with CHI_3 and $CrCl_3$ in the presence of zinc in sodium iodide yielded the corresponding vinyl iodide **529** in an isomeric mixture in 63% yield (Scheme 79).

Janes *et al.*[113] and team explored the scope of organometallic *C*-glycosides containing chromium carbene and used β-*C*-glucopyranosyl aldehyde **4a** for the synthesis. Glucopyranosyl aldehyde **4a** on reaction with pentacarbonyl[(methoxy)-



Scheme 77 Synthesis of sugar-based building blocks for the Ugi reaction, *i.e.* acid **520**, amine **522**, and isocyanide **523**.

Table 4 Various sugar-based bis-amides synthesized[a]

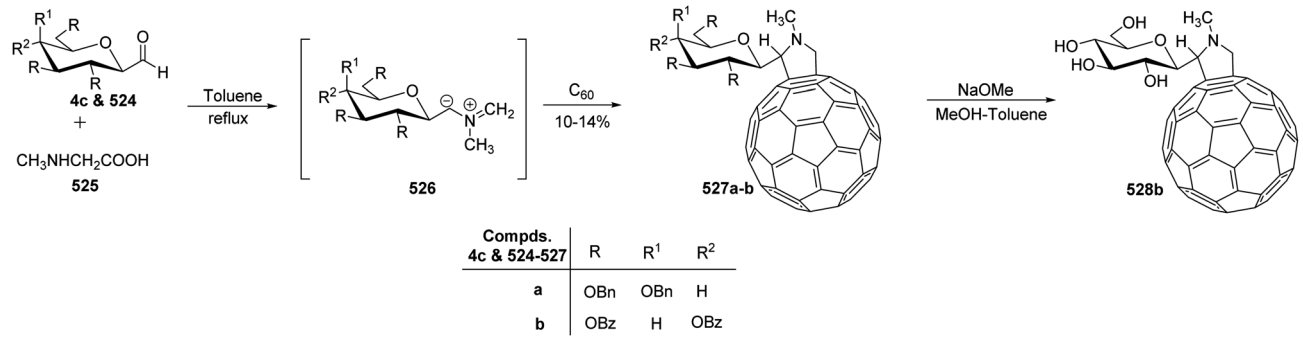
Ugi building blocks				Ugi product			
Aldehyde	Amine	Acid	Isocyanide	R^1	R^2	R^3	R^4
4a	PMB	Acetic acid	Cyclohexyl isocyanide	A	PMB	CH_3	C_6H_{11}
Benzaldehyde	522	Acetic acid	Cyclohexyl isocyanide	C_6H_5	A-CH_2	CH_3	C_6H_{11}
Benzaldehyde	PMB	520	Cyclohexyl isocyanide	C_6H_5	PMB	A	C_6H_{11}
Benzaldehyde	PMB	Acetic acid	523	C_6H_5	PMB	CH_3	A-CH_2
4a	522	Acetic acid	Cyclohexyl isocyanide	A	A-CH_2	CH_3	C_6H_{11}
4a	PMB	520	Cyclohexyl isocyanide	A	PMB	A	C_6H_{11}
4a	PMB	Acetic acid	523	A	PMB	CH_3	A-CH_2
Benzaldehyde	522	520	Cyclohexyl isocyanide	C_6H_5	A-CH_2	A	C_6H_{11}
Benzaldehyde	522	Acetic acid	523	C_6H_5	A-CH_2	CH_3	A-CH_2
Benzaldehyde	PMB	520	523	C_6H_5	PMB	A	A-CH_2
4a	522	520	Cyclohexyl isocyanide	A	A-CH_2	A	C_6H_{11}
4a	522	Acetic acid	523	A	A-CH_2	CH_3	A-CH_2
4a	PMB	520	523	A	PMB	A	A-CH_2
Benzaldehyde	522	520	523	C_6H_5	A-CH_2	A	A-CH_2
4a	522	520	523	A	A-CH_2	A	A-CH_2

[a] For R^1, R^2, R^3, R^4 see Scheme 77a, PMB = 4-methoxybenzyl, A = 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl.

methylcarbene] chromium **530** underwent aldol condensation in the presence of $TiCl_4$ in iPr_2NEt to afford the novel *C*-glycoside compound, 1-deoxy-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranose **531** in 54% yield (Scheme 80).

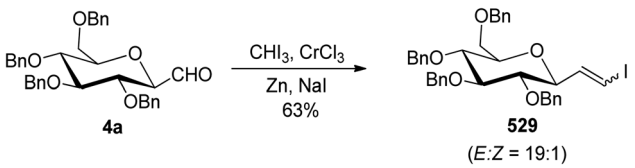
C-glycopyranosyl aldehydes **78a–b** synthesized from D-glucose and D-mannose by Xia *et al.*[41] were utilised for the synthesis of L-sugar derivatives also. Reduction of **78a–b** with sodium triacetoxyborohydride ($NaBH(OAc)_3$) afforded **532a–b**, which on further acetylation produced **533a–b**. The hydroxyl group at C5 was deprotected using TMSCl, NaI in acetonitrile to produce **534a–b** in 36–54% yield, which was oxidised to carboxylic acid **535a–b** in 70–85% yield using TEMPO, iodosobenzene diacetate (DIB) in MeCN–H_2O. Oxidative decarboxylation mediated by lead(iv)tetraacetate in THF-AcOH afforded L-sugar derivatives **536a–b** in 76–80% yield (Scheme 81).

C-Glycopyranosyl aldehydes synthesised by Petrusova *et al.*[57] *via* the nitromethane route were further utilised for the synthesis of 2-(β-D-glycopyranosyl)nitroethenes and



Compds. 4c & 524-527	R	R^1	R^2
a	OBn	OBn	H
b	OBz	H	OBz

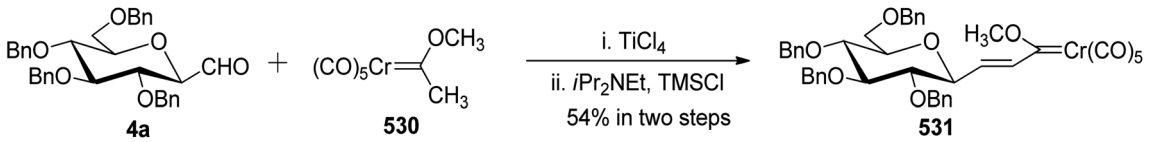
Scheme 78 Synthesis of [60]fulleropyrrolidine glycoconjugates **527a–b** and **528b**.



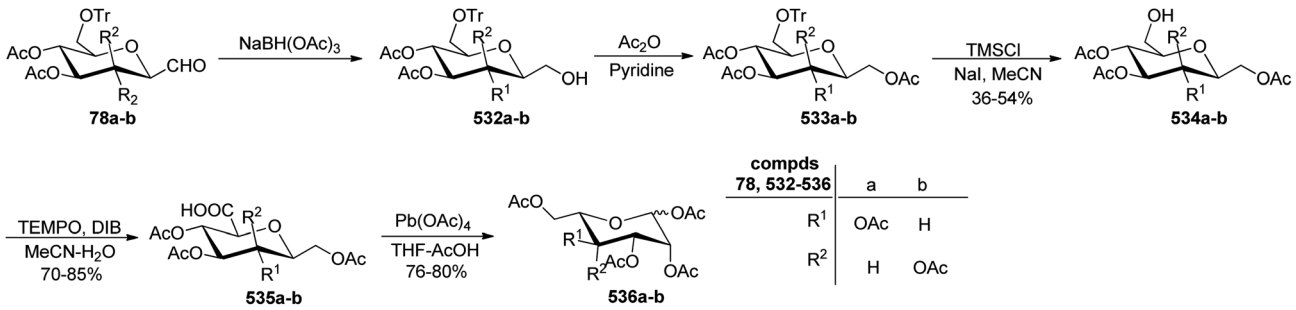
Scheme 79 Synthesis of *C*-glucopyranosyl vinyl iodide **529**.

-nitroethanes (Scheme 82). The addition of nitromethane in the presence of NaOMe afforded epimericnitroalcohols **537a–d** with 57% yield, which on further acetylation using acetic anhydride in the presence of sulfuric acid produced epimeric mixtures of **538a–c** in 85% yield. The treatment of compounds **538a–c** with sodium bicarbonate in benzene at 80 °C afforded 2-(β-D-glycopyranosyl)nitroethenes **539a–d** in 90–94% yield. Hydrogenolysis was carried out using H_2, Pd/C in ethyl acetate to give 2-(β-D-glycopyranosyl)nitroethanes **540a–d** in 80–86% yield. Finally, deacetylation was achieved using sodium methoxide in methanol to afford **541a–d** in 85–94% yield.

Lehmann *et al.*[114] explored the synthetic route for the synthesis of 4,8-anhydro-2,3-dideoxy-D-galacto- and -D-*gluco*-non-3-enose dimethyl acetals which can be used for the determination of the steric course of glycoside hydrolases-initiated protonation. *C*-Linked galacto- and glucopyranosyl aldehyde **59a–b** were treated with formylmethylenetriphenylphosphorane **542** in benzene to furnish β-D-galacto- and *gluco*-non-2-enose **543a–b** in 75% yield, respectively, which on addition of HBr followed by acetylation afforded diastereomeric 3-bromides **544a–b** in 42% yield. Elimination of HBr from **544a–b** in the presence of AgF in pyridine furnished dimethyl acetal **545a–b** with 80% yield, which upon treatment with sodium methoxide in methanol afforded acetylated product **546a–b** in 89% yield. Enzymatic deuteriohydration of **546b** was performed in the presence of α-D-galactosidase in the sodium/potassium phosphate–D_2O buffer to give 2,3-dideoxy-α-D-galacto-(3-^2H) nonos-4-ulose dimethyl acetal **547b** in 94% yield. The reduction was carried out using sodium borohydride in water to afford epimers **548** and **549** in 44% yield, which could be separated by HPLC technique and were treated separately with 0.5 M CF_3-COOH in methanol to afford 1,6-anhdro-2,3-dideoxy-3(*S*)-D-

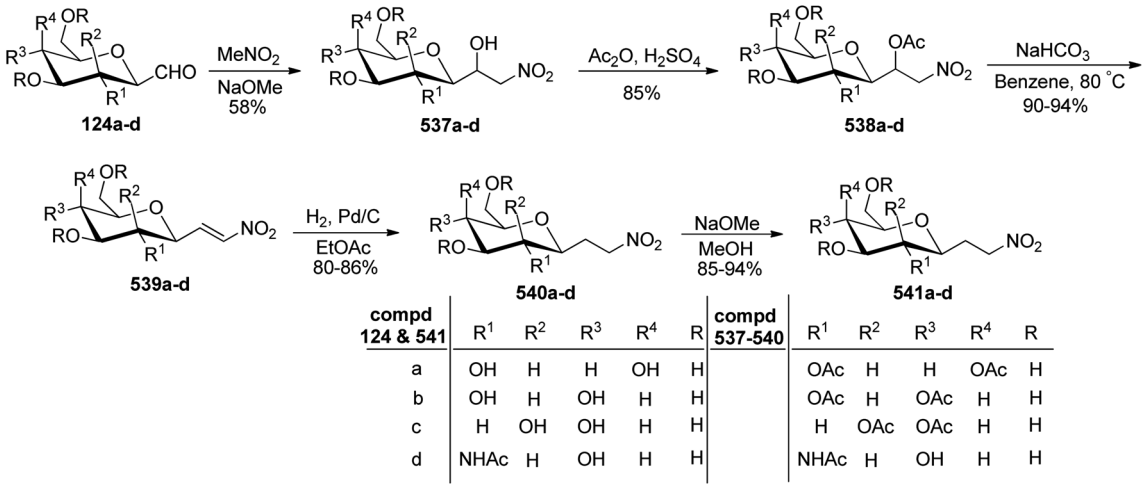


Scheme 80 Synthesis of organometallic *C*-glycosides **531**.



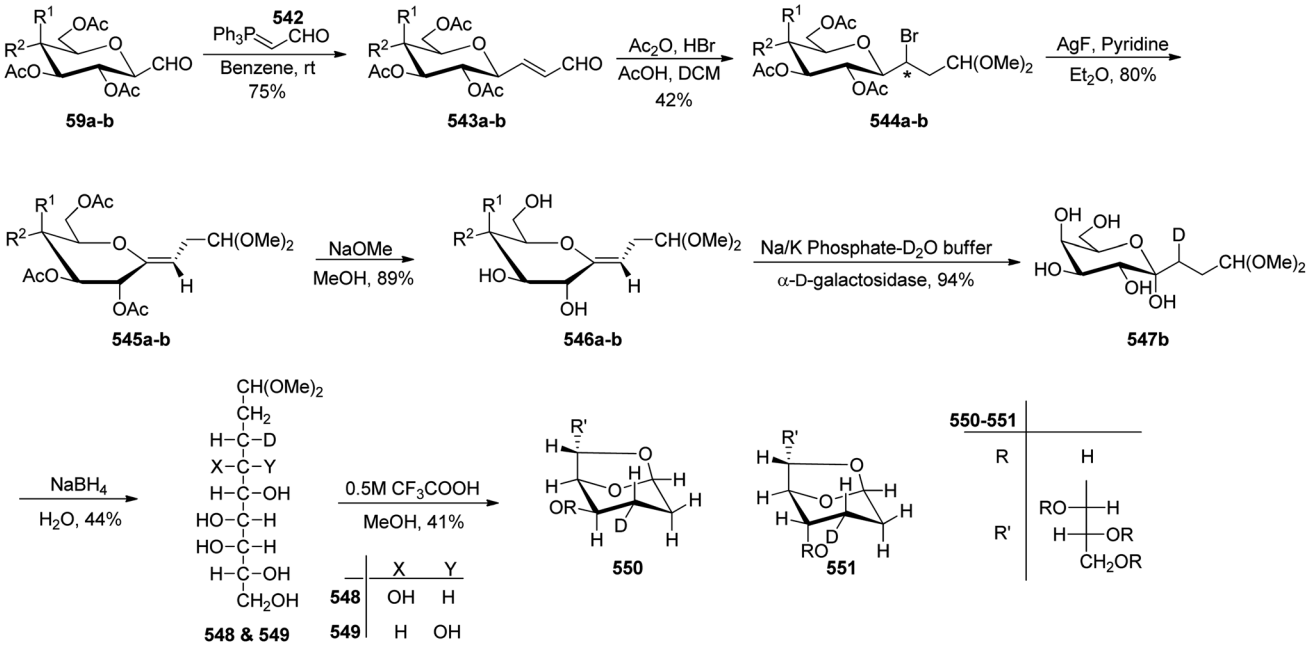
compds 78, 532-536	a	b
R^1	OAc	H
R^2	H	OAc

Scheme 81 Synthesis of L-sugar derivatives **536a–b**.



compd 124 & 541	R^1	R^2	R^3	R^4	R	compd 537-540	R^1	R^2	R^3	R^4	R
a	OH	H	H	OH	H		OAc	H	H	OAc	H
b	OH	H	OH	H	H		OAc	H	OAc	H	H
c	H	OH	OH	H	H		H	OAc	OAc	H	H
d	NHAc	H	OH	H	H		NHAc	H	OH	H	H

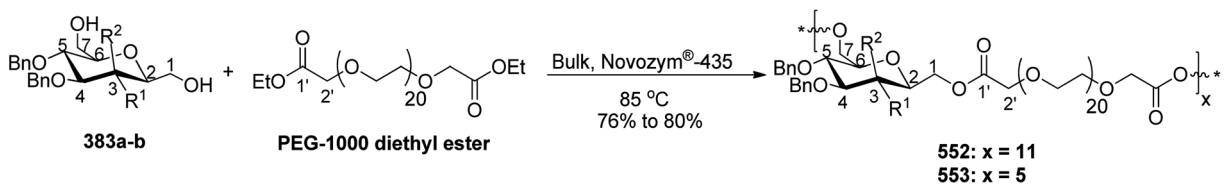
Scheme 82 Synthesis of 2-(β-D-glycopyranosyl)nitroethenes and -nitroethanes **539a–d** & **541a–d**.



	X	Y
548	OH	H
549	H	OH

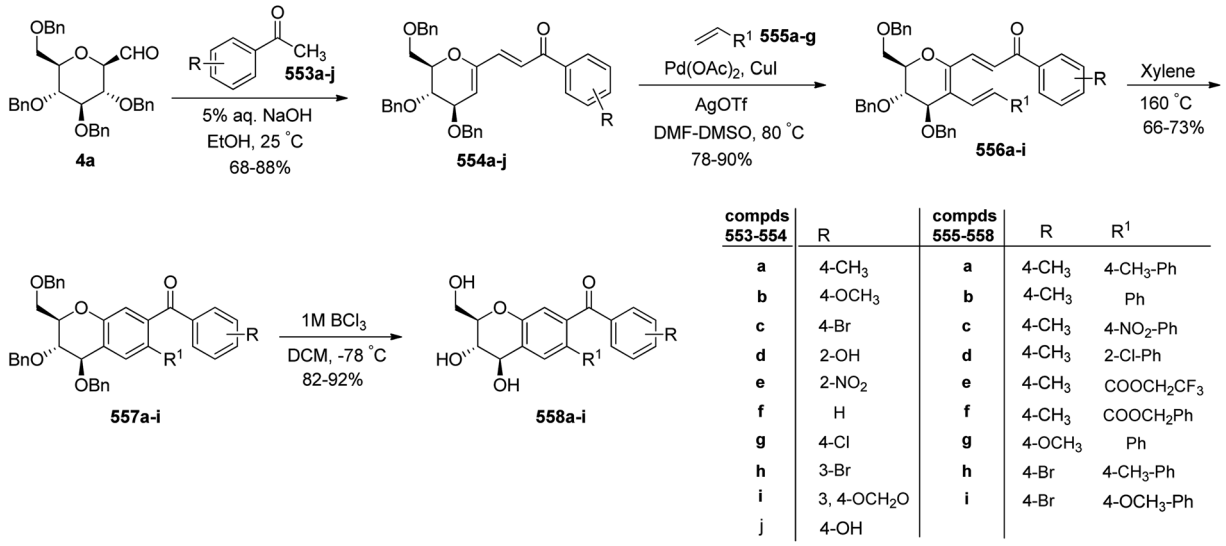
550-551	
R	H
R'	RO, H, H, OR, CH_2OR

Scheme 83 Synthesis of 1,6-anhydro-2,3-dideoxy-3(*S*)-D-*glycero*-L-*gluco*-(3-^2H)nonopyranose **550** and **551**.



compds 383, 552-553	a	b
R^1	OBn	H
R^2	H	OBn

Scheme 84 Synthesis of *gluco*- and *manno*-heptitol-PEG copolymers **552** and **553**.



compds 553-554	R	compds 555-558	R	R^1
a	4-CH_3	a	4-CH_3	4-CH_3-Ph
b	4-OCH_3	b	4-CH_3	Ph
c	4-Br	c	4-CH_3	4-NO_2-Ph
d	2-OH	d	4-CH_3	2-Cl-Ph
e	2-NO_2	e	4-CH_3	$COOCH_2CF_3$
f	H	f	4-CH_3	$COOCH_2Ph$
g	4-Cl	g	4-OCH_3	Ph
h	3-Br	h	4-Br	4-CH_3-Ph
i	3, 4-OCH_2O	i	4-Br	4-OCH_3-Ph
j	4-OH			

Scheme 85 Synthesis of (2*R*,3*S*,4*R*)-chromanes **558a–i**.

glycero-L-*gluco*-(3-^2H)nonopyranose **550** and **551** in 41% yield, respectively (Scheme 83).

Khatri *et al.*[115] recently synthesized a sugar–PEG copolymer starting from 2,6-anhydro heptitol **383a–b**, which was obtained from β-*C*-glycopyranosyl aldehydes **4a–b** by reduction with $NaBH_4$ followed by selective debenzylation of primary benzyl protection. The synthesized two diastereomeric sugar alcohol derived from D-glucose and D-mannose were employed for the synthesis of sugar PEG-based copolymers using PEG-1000 diethyl ester **552** and **553** in 80% and 76% yields, respectively (Scheme 84). This synthesis of copolymers was achieved by Novozym®-435 catalyzed transesterification reaction. The configurational change at one of the carbons of diastereomeric 2,6-anhydro-heptitols has a significant effect on the degree of polymerization of the synthesized polymers. The aqueous solution of these copolymers forms small spherical micelles, which have the capability to encapsulate Nile red dye.

Very recently our group developed an efficient methodology for the synthesis of (2*R*,3*S*,4*R*)-chromanes **558a–i** from *C*-glucopyranosyl aldehyde **4a** (Scheme 85).[116] Thus, *C*-glucopyranosyl aldehyde **4a** was submitted to Claisen–Schmidt condensation using various acetophenones **553a–j** in the presence of 5% aq. sodium hydroxide in ethanol to obtain 1-(*E*-1-arylpropenon-3-yl)-3,4,6-tri-*O*-benzyl-D-glucals **554a–j** in 68–88% yields. Further, a cross dehydrogenative reaction was carried out on these *C*-1 substituted glucalpropenones using alkenes **555a–g** in the presence of $Pd(OAc)_2$, CuI, AgOTf in DMF-DMSO solvent system at 80 °C to afford 1,2-disubstituted glucals **556a–i** in 78–90% yields. The CDC reaction afforded products with (*E*) stereoselectivity in good to excellent yield. Thus, *E*,*Z*,*E*-triene **556a–i** heated at 160 °C in xylene, which on 6π-electrocyclization followed by *in situ* dehydrogenative aromatization produced chromanes **557a–i** in 66–73% yields. The cyclization of trienes **557e** and **557f** was not achieved under optimised conditions. The benzyl protection was removed using 1 M BCl_3 in DCM at −78 °C to furnish desired (2*R*,3*S*,4*R*)-chromanes derivatives **558a–i** in 82–92% yields.

4. Conclusion

In this review, we have described various approaches for the synthesis of *C*-glycopyranosyl aldehydes and their applications in the synthesis of diverse biologically relevant *C*-glycoconjugates. A total of seven approaches have been designed based on the key intermediates involved in the synthesis of *C*-glycopyranosyl aldehydes, which refer to facile and efficient methods developed including multistep synthetic protocols. In addition, the purpose of this review is to scrutinize the importance of *C*-glycopyranosyl aldehydes to the vast field of organic synthesis. This review will serve as a collection of literature reports, where researchers will find both the synthetic methodologies to access *C*-glycopyranosyl aldehydes as well as their applications to synthesize various complex *C*-glycoconjugates as key precursor molecules.

5. Future prospects

This review describes a wide scope of syntheses of *C*-glycopyranosyl aldehydes *via* different key intermediates along with a vast library of *C*-glycoconjugates derived from them. Although many synthetic routes are found to be very interesting even though some methods are economically unfavourable due to very expensive reagents used in the synthetic routes, also in some procedures harsh conditions make the syntheses cumbersome. Therefore, there is a need to develop more synthetic protocols that must be simple, economical, and environment friendly. We believe that the upcoming decades will bring us many exciting reports on the syntheses of *C*-glycopyranosyl aldehydes and glycoconjugates. The synthesis of glycoconjugates must be explored in the desire of many biologically important sugar-based natural products and the total synthesis of target molecules. Since the last decade, we have had our own interest in these *C*-glycopyranosyl aldehydes and to further utilise these compounds for the syntheses of

glycoconjugates. At present, we are working on the cost-effective, greener, and easy synthetic routes for the synthesis of *C*-glycopyranosyl aldehydes and glycoconjugates and will discuss them in the coming years.

Abbreviations

AIBN	Azobisisobutyronitrile
BtOH	Butanol
BAIB	Bis(acetoxy)iodobenzene
BCl_3	Boron trichloride
$BF_3 \cdot Et_2O$	Boron trifluoride diethyl etherate
Bu_3SnH	Tributyltin hydride
CH_3COSH	Thioacetic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*-Dicyclohexylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DIBAL-H	Diisobutylaluminiumhydride
DAST	Diethylaminosulfur trifluoride
DPPE	1,2-Bis(diphenylphosphino)ethane
DMDO	Dimethyldioxirane
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
Et_3SiH	Triethylsilane
HOBt	Hydroxybenzotriazole
2-LTT	2-Lithiothiazole
PTSA	*para*-Toluenesulfonic acid
P_2O_5	Phosphorous pentoxide
Pd/C	Palladium on charcoal
PMB	*para*-Methoxybenzyl
PEG	Polyethylene glycol
TMSOTf	Trimethylsilyl triflate
TMSCl	Trimethylsilyl chloride

Author contributions

Sandeep Kumar and Vinod Khatri wrote the review. Priyanka Mangla and Rajni Johar checked the review thoroughly and made suitable changes. The review was written under the supervision of Virinder S. Parmar and Ashok K. Prasad.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

Sandeep Kumar thanks CSIR, New Delhi for the award of the SPM Research Fellowship [File No. 09/045(0269)/2018-EMR-1]. V. K. and P. M. thank CSIR-UGC, New Delhi for the award of Junior/Senior Research Fellowship.

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