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PII: S0008-6215(17)30503-7

DOI: 10.1016/j.carres.2017.08.014

Reference: CAR 7439

To appear in: *Carbohydrate Research*

Received Date: 24 July 2017

Revised Date: 28 August 2017

Accepted Date: 29 August 2017

Please cite this article as: S. Ahmadipour, G.J. Miller, Recent advances in the chemical synthesis of sugar-nucleotides, *Carbohydrate Research* (2017), doi: 10.1016/j.carres.2017.08.014.

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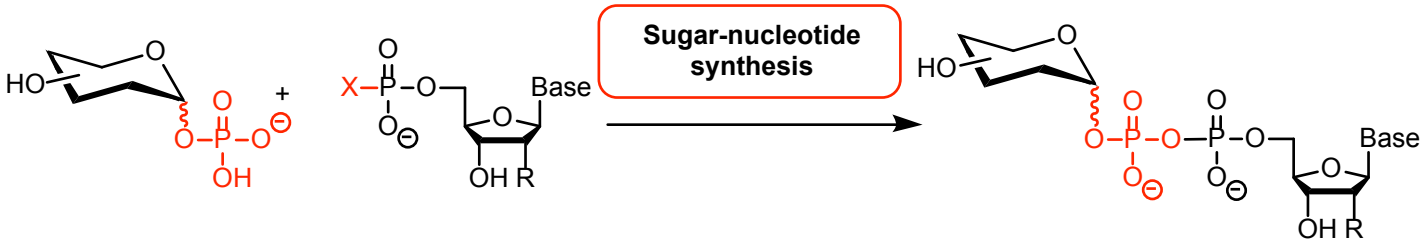
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Recent advances in the chemical synthesis of sugar-nucleotides

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Keywords: sugar-nucleotide, sugar-1-phosphate, pyrophosphorylation, nucleoside, diphosphate

1. Introduction

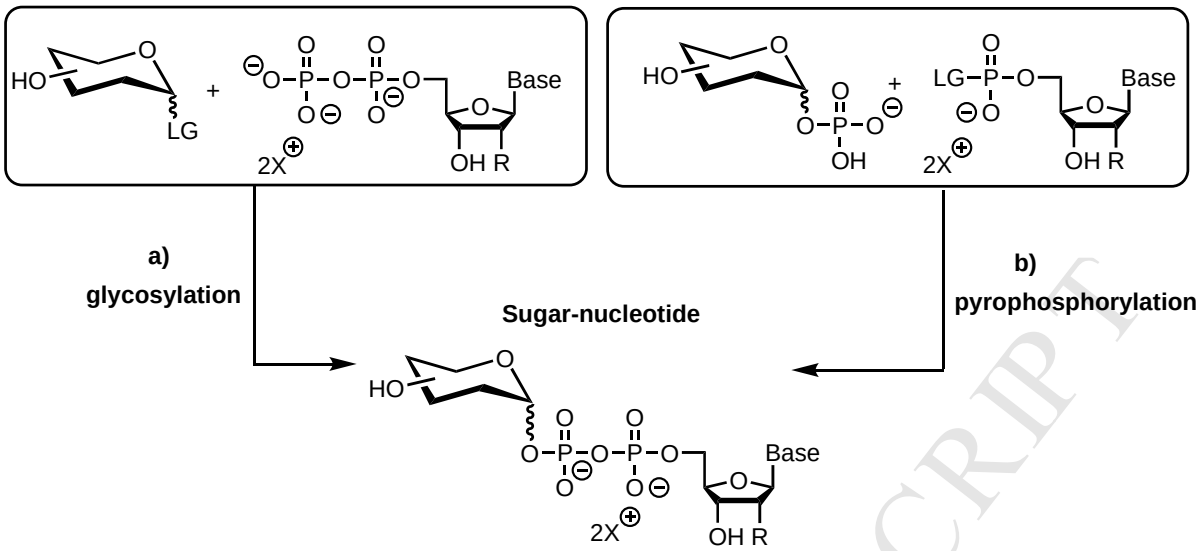
Sugar-nucleoside diphosphates (sugar-nucleotides) are imperative to carbohydrate metabolism and glycoconjugate biosynthesis. They are composed of an activated sugar donor that is glycosylated onto a diverse range of acceptors,[1] typified by glycosyltransferase catalysed processes for the assembly of glycosides and oligo- or poly-saccharides.[2] They are of considerable interest as carbohydrate-based tools for the study of glycoconjugate biosynthesis and for their potential as enzyme inhibitors in therapeutic intervention strategies.[3] In addition, they are requisite for unambiguous biochemical assay development and for the provision of structurally defined homogenous analytical standards. Thorough reviews concerning chemical[4] and enzymatic[5] methods for sugar-nucleotide synthesis were completed almost a decade ago along with recent reviews of nucleotide,[6] pyrophosphate analogue[7] and phosphate ester/anhydride synthesis.[7,8] We seek here to update this exciting branch of glycoscience and present a current state of the art (2009-onwards) for the chemical synthesis of natural and mimetic sugar-nucleotides.

2. Synthetic approaches towards sugar-nucleotides

Sugar-nucleotide's are structurally diverse, consisting of a sugar linked to a nucleoside diphosphate (sugar nucleoside monophosphates, such as CMP-sialic acid, are not covered here). Figure 1 illustrates a generic sugar-nucleotide, alongside two common methodologies for their chemical synthesis. Disconnection approaches have focused on the phosphate linkage between the sugar and nucleoside components, most commonly favouring pyrophosphorylation using a sugar-1-phosphate (sugar-1-P) and an activated nucleoside monophosphate (NMP) (Figure 1, pathway b). Sugar-nucleotides have also been prepared *via* direct glycosylation using a nucleoside diphosphate (NDP) with a glycosyl donor[4,9] (Figure 1, pathway a).

In animal cells the most commonly occurring sugar-nucleotides utilise a uridine or guanidine-containing nucleoside diphosphate (UDP or GDP) along with a sugar; this includes aldopentose (UDP-Xyl), aldohexose (UDP-Glc, UDP-Gal), aldohexosamine (UDP-GlcNAc, UDP-GalNAc) and uronic acid (UDP-GlcA) components. These common mammalian examples are illustrated in Figure 1 c) , alongside some examples found in bacteria, such as GDP-ManA, UDP-Gal*f* and dTDP-L-Rha.

In recent years, chemical approaches to synthesise sugar-nucleotides have favoured a P^V-P^V pyrophosporylation coupling, alongside effective P^V-P^{III} coupling chemistries.[10] In this mini-review we first discuss recent advances towards the synthesis of anomeric sugar-1-Ps, followed by diphosphate-forming approaches to the parent sugar-nucleotide.



c) representative mammalian and bacterial sugar-nucleotides

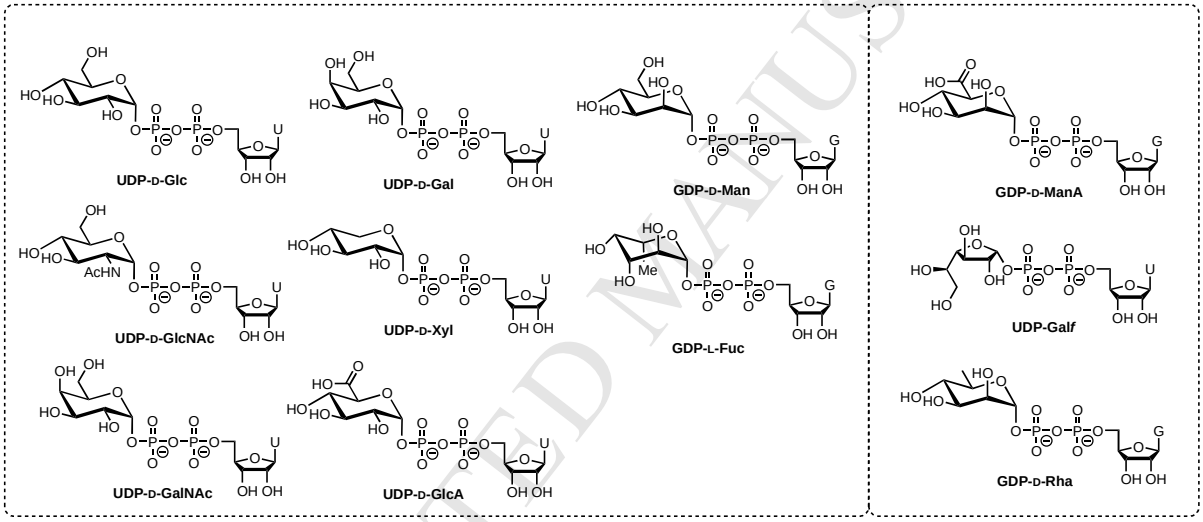


Figure 1. Approaches to sugar-nucleotides: a) direct glycosylation strategy with a nucleoside diphosphate and glycosyl donor b) pyrophosphorylation using a sugar-1-P and nucleoside monophosphate. LG = leaving group, R = H/OH, Base = heterocycle (C, U, T, G, A), X = phosphate or diphosphate counter ion c) representative examples of common mammalian and bacterial sugar-nucleotides.

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3. Synthesis of anomeric sugar-1-phosphates

3.1. α-linked sugar-1-phosphates

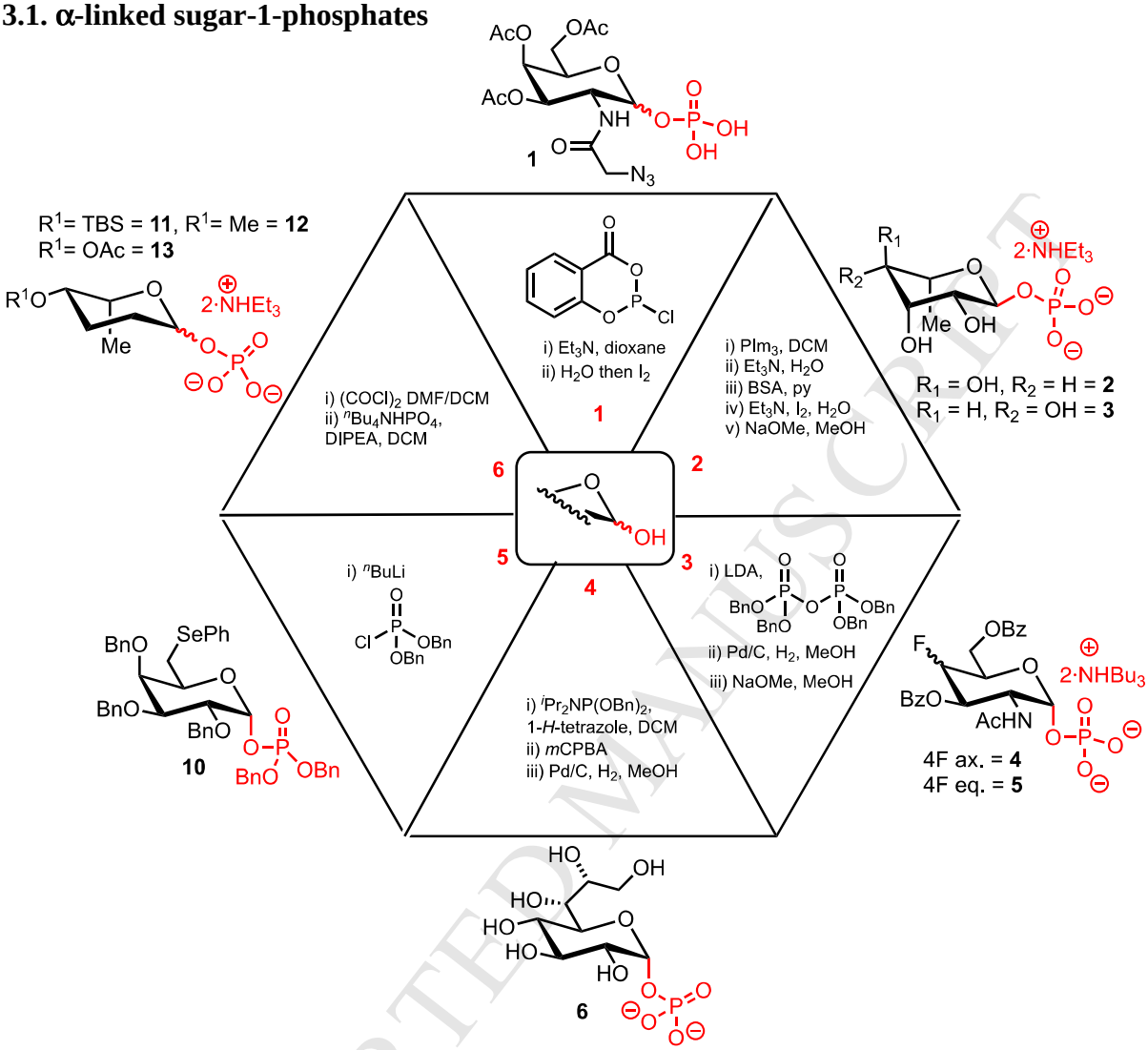


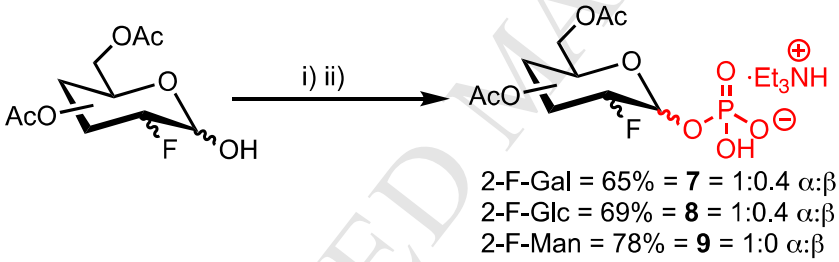
Figure 2. Overview of recent strategies used for the synthesis of α-linked sugar-1-P's. Each red numbered option is subsequently referred to in the discussion.

Figure 2 illustrates some of the different approaches that have been introduced since 2009 for the synthesis of sugar-1-Ps with an α-anomeric configuration. This constitutes an important development within the field, whereby a range of conditions, high yields and good anomeric selectivity now compliment the diverse substrate scope that glycosyl-1-Ps represent for native and mimetic sugar-nucleotide access and evolves from more traditional methods, such as Macdonald phosphorylation.[11] Generally beginning from a hemi-acetal, sugar-1-P's can be obtained from several different phosphorous sources, either directly at the P^{V} oxidation level or using a P^{III} approach, followed by oxidation. These are discussed first, followed by access from alternative anomeric substituents.

Janda *et al.*[12] synthesised α,β-GalNAz-1-phosphate **1** as part of their approach towards UDP-GalNAz (see Scheme 11). The group treated α,β-GalNAz-1-OH with salicyl chlorophosphite, followed by aqueous hydrolysis of the resultant cyclic phosphite to deliver a P^{III} species, which was oxidized with I_2 to deliver **1** in 62% yield over three steps (Figure 2, option 1). Sun and co-workers[13] synthesised α-1-phosphates of L-Rha **2** and L-

6dTal **3** using a two-stage approach again starting at P^{III} (Figure 2, option 2). Hemi-acetal phosphitylation with triimidazole phosphite (PIm_3) and subsequent basic hydrolysis (Et_3N/H_2O) delivered sugar-1-*H*-phosphonate monoesters in 93-95% yield. The 1-*H*-phosphonates were then converted to silylated phosphite triesters using *N*,*O*-bis(trimethylsilyl)acetamaide (BSA), followed by oxidation under basic conditions (I_2/Et_3N) to deliver the P^V products in 87-89% yield. The group noted that the basic oxidation conditions for the second stage were essential to counter the TMSI generated upon silyl phosphite ether cleavage and prevent unwanted degradation of the product.

Linhardt's group[14] recently reported their chemical synthesis of fluorinated mimetic sugar-nucleotides (see Scheme 7), whereby the group accessed the required sugar-1-Ps through deprotonation of the hemi-acetal (using LDA) and reaction with the electrophilic P^V reagent, tetrabenzylpyrophosphate. This furnished the desired α-linked phosphates **4** and **5** in very good yields (72% for **4** and 77% for **5**) and excellent α-selectivity (Figure 2, option 3). Liu *et al*[15] took an alternative approach when synthesizing the glycosyl-1-phosphate precursor of GDP-α-D-octose, necessary for elucidation of the biosynthesis of a clinically useful antibiotic, Lincomycin A. Using a hemi-acetal as the nucleophile, the group employed the phosphoramidite reagent $^{i}Pr_2N(OBn)_2$ and 1-*H*-tetrazole activation, followed by oxidation of the phosphite to P^V, using *m*-CPBA, delivering α-D-octose-1-phosphate **6** in 23% yield, over three steps (Figure 2, option 4). Meier and co-workers[16] also used the same phosphoramidite reagent in combination with 4,5-dicyanoimidazole (DCI), followed by oxidation, to synthesise a series of protected 2-fluorinated sugar-1-P's **7**-**9** in good yields (57-83%, Scheme 1) and, in the case of mannose derivative **9**, with complete α-selectivity.

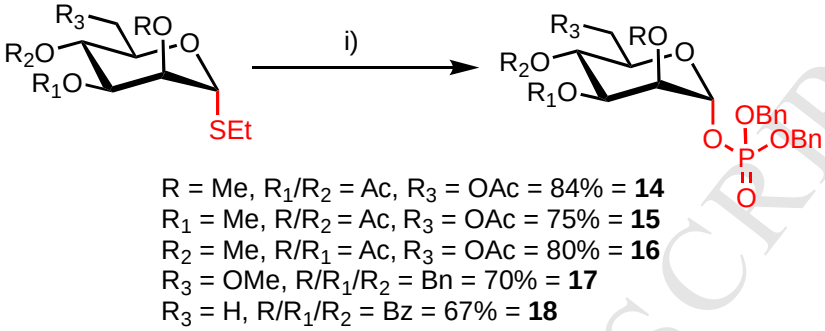


Scheme 1. Synthesis of 2-F substituted Gal- Glc- and Man-1-P derivatives **7**-**9**. i) $^{i}Pr_2N(OBn)_2$, DCI, DCM, 16 h ii) *m*-CPBA, 4 h.

The Liu group[17] utilised the P^V reagent dibenzyl phosphorochloridate to achieve anomeric phosphorylation in their synthesis of fluorinated sugar-nulceotide mimetics (see Schemes 8 and 9), which they achieved using an oxidative chlorination step, combining P^{III} dibenzyl-1-*H*-phosphonate and *N*-chlorosuccinamide (Figure 2, option 5). Starting from the anomeric hemi-acetal, deprotonation with ^{n}BuLi and subsequent reaction with the P^V phosphorochloridate afforded the desired Bn-protected-1-phosphate **10** in 48% yield (2 steps, including formation of the phosphorochloridate) and exclusive α-selectivity.

Zhou's group[18] synthesised a series of *O*-4-substituted 2,3,6 trideoxy-*L*-rhodinose-1-phosphates by first converting the hemi-acetal to the corresponding glycosyl chloride (Figure 2, option 6). They achieved this using oxalyl chloride, interestingly noting a faster decomposition of the chloride for 4-position electron donating substituents, such as OTBS, and rationalising this as contributing a destabilising effect upon the oxocarbenium ion intermediate. Phosphorylation was effected using tetra-*N*-butylammonium hydrogen phosphate for nucleophilic substitution in acceptable yields (35-48%, for **11**-**13**) and furnishing α/β mixtures. The group proposed that the anomeric ratio of the product sugar-1-Ps correlated to the size of the substituent on *O*-4, with OTBS displaying the lowest preference for the β-anomer compared with OMe or OAc.

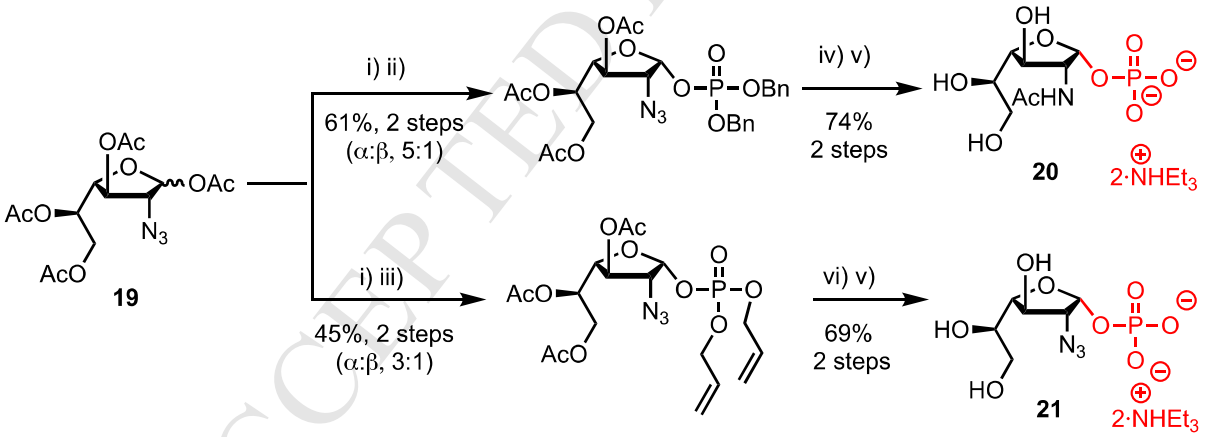
Lowary *et al*[19] recently sought a series of methoxy and deoxy GDP-Man derivatives and in doing so explored the substrate tolerance of a GDP-mannose pyrophosphorylase from *Salmonella enterica* towards a selection of non-native mannose sugar 1-Ps. From the ethyl thioglycoside the group installed dibenzylphosphate using NIS/AgOTf activation conditions and obtained the series of protected Man-1-P derivatives **14**-**18** in good yields (67-84%, Scheme 2). The anomeric stereochemistry for the group's series of sugar-1-Ps was confirmed by the size of the $^{1}J_{C1\text{-}H1}$ coupling constant, which was 177.9 Hz for **14**, consistent with α-stereochemistry.



R = Me, R_1/R_2 = Ac, R_3 = OAc = 84% = **14**
R_1 = Me, R/R_2 = Ac, R_3 = OAc = 75% = **15**
R_2 = Me, R/R_1 = Ac, R_3 = OAc = 80% = **16**
R_3 = OMe, $R/R_1/R_2$ = Bn = 70% = **17**
R_3 = H, $R/R_1/R_2$ = Bz = 67% = **18**

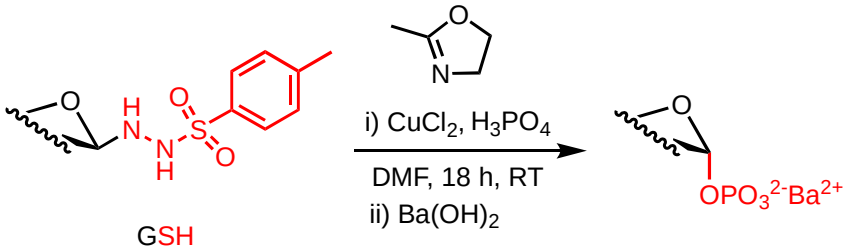
Scheme 2. Synthesis of 2-, 3-, 4-, 6-*O*-methyl and 6-deoxy protected Man-1-P derivatives **14**-**18**. i) HO-P(O)$(OBn)_2$, NIS, AgOTf, DCM.

The group also installed α-anomeric phosphates onto protected 2-azido-2-deoxy-α-D-galactofuranose **19** (Scheme 3).[20] Starting from the corresponding glycosyl bromide (obtained using $TiBr_4$ from the anomeric acetate) and using protected phosphates (dibenzyl to access 2-NHAc species and diallyl to access 2-N_3) they obtained good α-selectivity and intriguingly noted a higher diastereoselection for the dibenzyl phosphate system (5:1, α:β) *vs* diallyl (3:1, α:β).



Scheme 3. Synthesis of 2-deoxy-α-D-Gal*f*-1-phosphates **20** and **21**. i) $TiBr_4$, CH_2Cl_2, EtOAc, rt, 4 days; ii) HO-P(O)$(OBn)_2$, Et_3N, toluene, rt, 3 h; ii) HO-P(O)$(OAll)_2$, Et_3N, toluene, rt, 3 h; iv) Pd/C, H_2, Et_3N, Ac_2O, rt, 3 days; v) MeOH, H_2O, Et_3N; vi) $Pd(OAc)_2$, NaOMe, H_2O, AcOH, rt, 16 h.

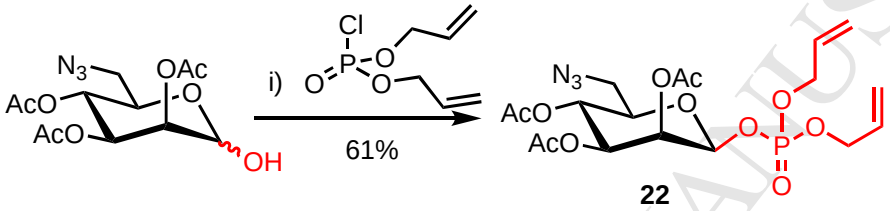
Finally, the Nitz group[21] recently introduced a protecting-group-free synthesis of glycosyl-1-Ps (Scheme 4). Following β-selective formation of N'-glycopyranosylsulfonohydrazide (GSH[22]) donors in excellent yields, subsequent oxidation of the GSH using $CuCl_2$ in the presence of a coordinating ligand (2-methyl-2-oxazoline) and nucleophilic phosphoric acid delivered α-enriched-sugar 1-P's in respectable yields (45-64%) across a range of hexoses and, importantly, a disaccharide example in 73% yield.



Scheme 4. Phosphorylation using oxidative cleavage of GSH donors.

3.1. β-linked sugar-1-phosphates

Less accessible by conventional methods, due to their lack of thermodynamic anomeric stabilisation, β-linked sugar-1-phosphates are nonetheless required for the construction of β-linked sugar-nucleotides; which play critical roles, for example, as donor substrates for the biosynthesis of bacterial cell wall and LPS components. Vincent and co-workers[23] reported a novel approach to the synthesis of β-phosphoryl-6-azido mannose **22**, which can be used in a azide-alkyne cycloaddition reactions (Scheme 5).



Scheme 5. Diallyl chlorophosphate for the synthesis of β-1-phosphate **22**. i) DMAP, DCM, 4h.

The group employed the electrophilic P^V reagent diallyl chlorophosphate which was added slowly (1.6 mL/h) to the lactol nucleophile source, encouraging reaction with the more nucleophilic equatorial OH, and delivering **22** in good yield (61%) and excellent β-selectivity (1:20, α:β). The regent diallyl chlorophosphate is not commercially available and the authors also reported a convenient method for its synthesis and subsequently demonstrated the scope of their approach towards substituted mannose derivatives, D-Glc, D-Gal, L-Fuc and lactose. Soulère *et al*[24] have also recently shown that using a P^{III} tri-*O*-allyl phosphite/I_2 system, in place of P^V diallyl chlorophosphate, successfully synthesised β-1-phosphate derivatives of per-*O*-acyl D-Glc and D-Gal with comparable yields and selectivity.

Fujimoto *et al*[25] used a Mitsunobu approach to install an anomeric β-1-phosphate in their synthesis of protected D-glycero-D-manno-heptose-1,7-bisphosphate **24** (Scheme 6). The group used dibenzylphosphate as the nucleophile with a DEAD/Et_3N/$^nBu_3P$ reagent combination, obtaining **24** in good yield (56%), although with only a marginal anomeric selectivity (2:3, α:β). At the same time the group of Zamyatina[26] were also effecting a synthesis of alternatively protected D-manno-heptose **23**, where the workers here chose to use a slow addition (0.5 equiv./h) of diphenyl phosphorochloridate to achieve better anomeric selectivity, delivering **23** (1:4, α:β) in 51% yield (Scheme 6).

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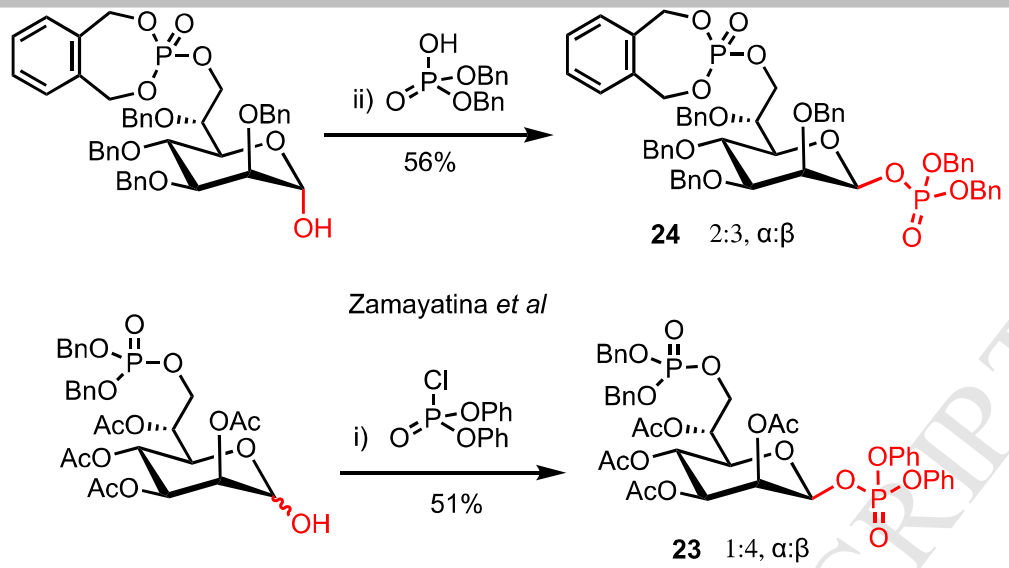


Scheme 6. Synthetic approaches of Zamyatina and Fujimoto towards D-glycero- D-manno-heptose-1,7-bisphosphates **23** and **24**. i) DMAP, DCM, rt; ii) DIAD, $^{n}Bu_3P$, Et_3N, DCM, rt.

4. Chemical synthesis of sugar-nucleotides

4.1. Pyrophosphorylation approaches

The second half of this mini-review focuses on developments in the coupling of sugar-1-P's with activated NMP derivatives. The seminal work of Khorana[27] is still widely applied, alongside Wong's 1-*H*-tetrazole modification.[28] However, exciting advances beyond this classical phosphomorpholidate strategy have been made: a notable example being developments in phosphorimidazolide strategies.[20,23,29,30] A summary of the general approach for coupling NMP's with sugar-1-Ps is shown in Figure 3, alongside some of the challenges inherent to their chemical synthesis.

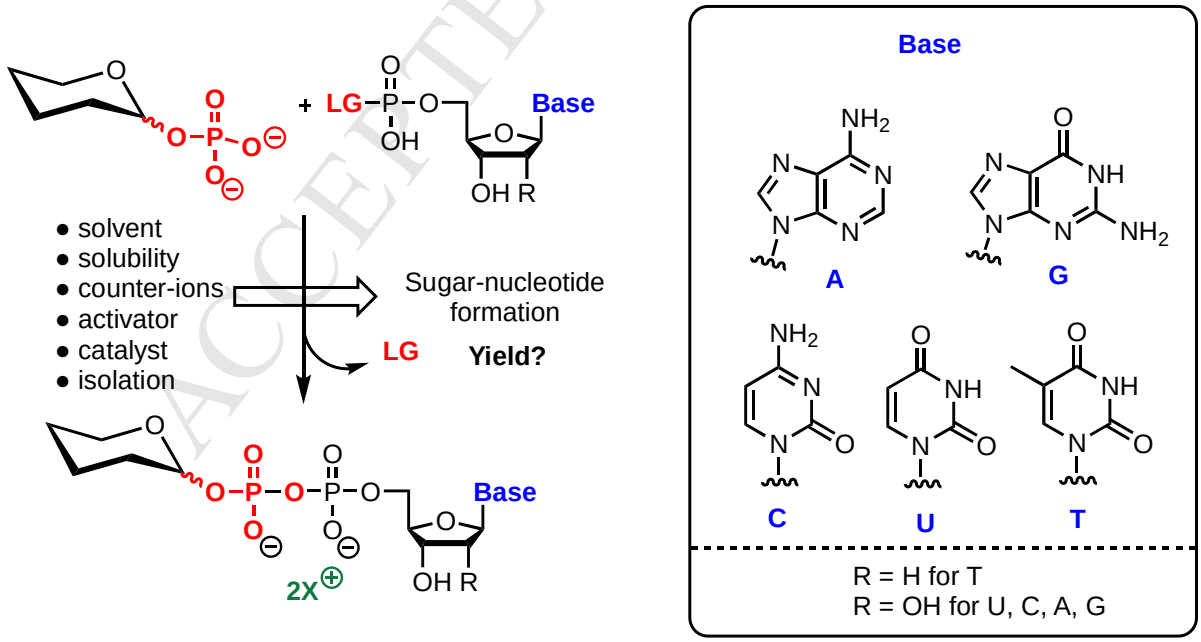
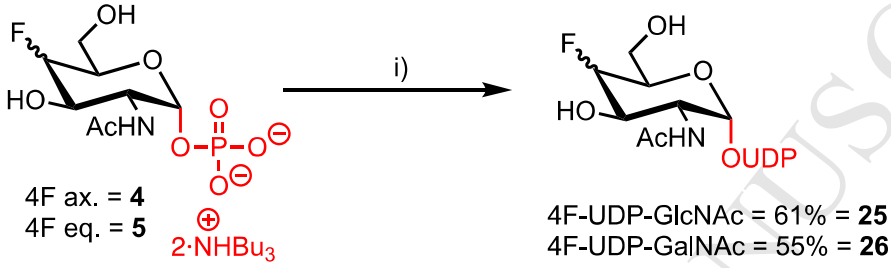


Figure 3. Summary of NMP activation and considerations for diphosphate formation. LG = phospho-leaving group such as morpholine. X = sugar-nucleotide counter-ion; most commonly the di-Na^+ form is isolated (and stored) using an appropriate anion exchange resin.

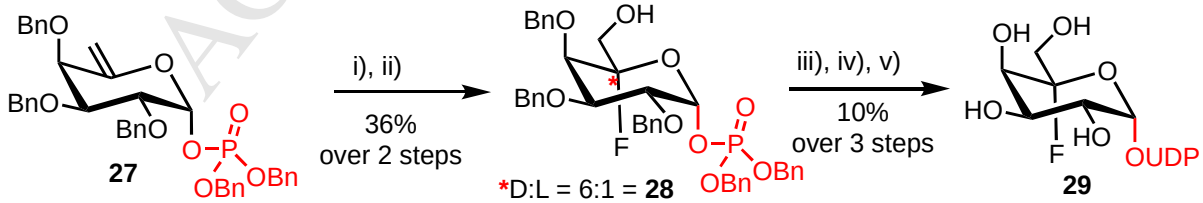
4.1.1. Pyrophosphorylation using phosphomorpholidates and phosphopiperidates

Linhardt *et al*[14] recently investigated the synthesis of non-natural UDP-donors and their use for the construction of chain terminated glycosaminoglycans (GAG's). Their synthesis of UDP-4F-GlcNAc **25** and UDP-4F-GalNAc **26** mimetics required modification at C4, the native position for GAG chain extension. As such, C4-F pyranose monophosphates **4** and **5** were utilised in 1-*H*-tetrazole catalysed pyrophosphorylation with UMP-morpholidate to deliver **25** and **26** in acceptable yields (Scheme 7). The group noted that purification of the target compounds was initially hampered by the presence of organic phosphate salts, but that these could be successfully removed by conversion of all phosphates to their sodium form and purification using BioGel PS SEC. Application of the mimetic tools demonstrated that **25** was successfully transferred to the non-reducing terminus of heparosan tetra- and hexasaccharides using PmHS1 catalysis and established proof of concept for modulating GAG chain length with mimetic sugar-nucleotides.



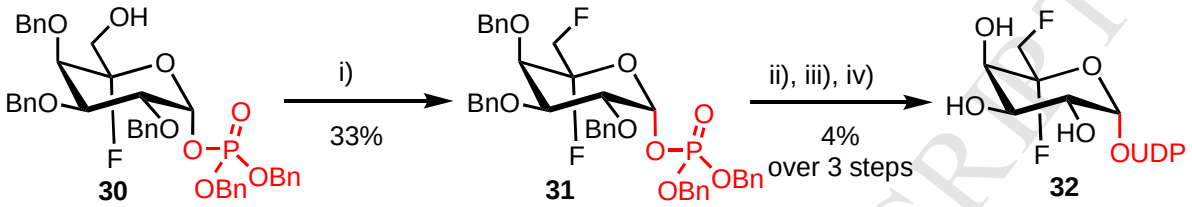
Scheme 7. Chemical synthesis of UDP-4F-GlcNAc and UDP-4F-GalNAc mimetics **25** and **26**. i) UMP-morpholidate, 1-*H*-tetrazole, py, rt, 3 days.

Liu and co-workers[17] also investigated the synthesis of mimetic sugar-nucleotides to study the mechanism of action of UDP-galactopyranose mutase (UGM), an important enzyme for pathogenic bacteria that converts UDP-Gal*p* to UDP-Gal*f* and, due to its absence in mammalian systems, is a potential target for anti-microbial therapeutic intervention. Their route prepared uridine 5'-diphosphate-5-fluorogalactopyranose (UDP-5F-Gal*p*) **29** by applying Coward's epoxide fluoridolysis strategy.[31] A synthesis starting from methyl-α-D-galactopyranoside afforded *exo* olefin **27** and the pivotal fluorohydrin **28** was accessed *via in situ* epoxidation with DMDO, followed by ring opening with HF to deliver the target D-sugar in excess over its L-isomer (Scheme 8). Coupling of **28** with UMP-morpholidate using 1-*H*-tetrazole provided **29** in 10% yield over three steps from **28**. C5-F mimetic **29** was shown to form a substrate-co-factor adduct with reduced FAD, facilitated by UGM and hydrolysing **29**. The key premise of a C5-F was then invoked to form a gem-fluorohydrin at C5, which irreversibly expelled HF, forming a C5-oxo species which prevented the reverse enzymatic pathway to Gal*p* and confirmed further evidence towards the mechanism of action for UGM.



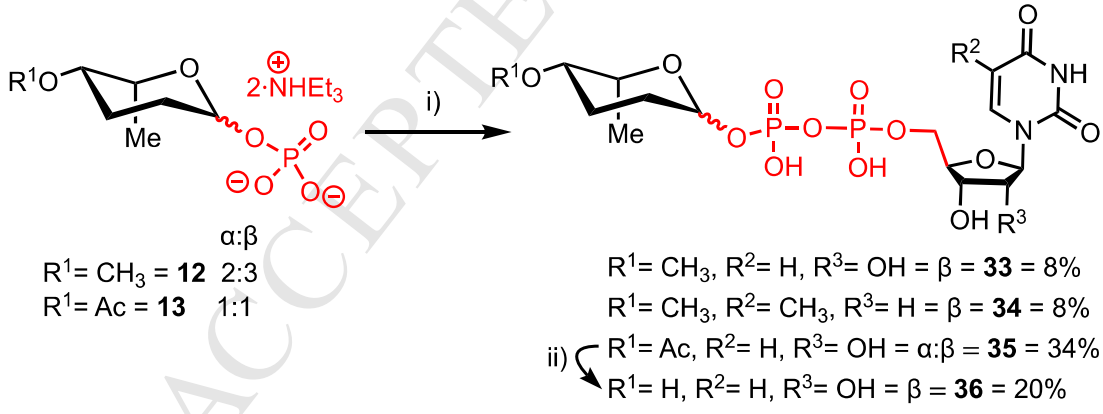
Scheme 8. Chemical synthesis of UDP-5F-Gal **29** from *exo* olefin **27**. i) Oxone™, $NaHCO_3$, MeCN:EDTA (0.4 mM):acetone = 1:1:2, rt, 3.5 h; ii) HF, py, CH_2Cl_2, -78 °C, 1 h, 36% over 2 steps; iii) H_2 (1 atm), 10% Pd/C, MeOH, rt, 3 h; iv) Dowex (HN^+Bu_3), H_2O, 4 °C, 18 h; v) UMP-morpholidate, 1-*H*-tetrazole, py, rt, 3 days.

To further explore UGM, the group sought to present an electrophilic group at C6 for potential interaction with nucleophilic active site residues. Accordingly, they demonstrated a first chemical synthesis of UDP-[5,6-F_2]-Gal **32** starting from C5-F glycosyl phosphate **30**. Fluorination of C6 using DAST generated the bis-fluorinated derivative **31**. After removal of the benzyl protecting groups and conversion of the phosphorylated reagent to its $^{n}Bu_3NH^{+}$ form (increasing organic solubility) a coupling reaction with UMP-morpholidate delivered mimetic probe UDP-[5,6-F_2]-Gal **32** in 4% yield over three steps (Scheme 9). No decrease in UGM activity was noted when **32** was incubated with the enzyme for up to 24 h.



Scheme 9. Chemical synthesis of C-6 probe UDP-[5,6-F_2]-Gal **32** i) DAST, py:CH_2Cl_2 (1:10), -40 °C to rt, 12 h, reflux, 2 h, 33%; ii) H_2, 10% Pd/C, MeOH, rt, 3 h; iii) Dowex ($HN^{+}Bu_3$), H_2O, 4 °C, 18 h; iv) UMP-morpholidate, 1-*H*-tetrazole, py, rt, 3 days.

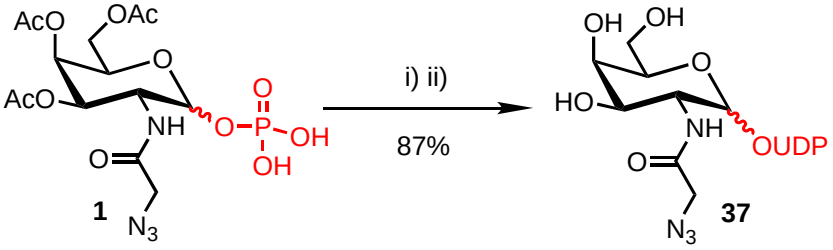
Zhou's group[18] reported a synthesis of 4-substituted L-rhodinose sugar-nucleotides using glycosyl monophosphates and NMP-morpholidates in the presence of 1-*H*-tetrazole (Scheme 10). Deoxysugar-nucleotides are generally considered a more challenging synthetic target as the removal of electron-withdrawing ring hydroxyls renders the positively charged oxocarbenium intermediate more stable: conferring a higher propensity towards hydrolytic cleavage. To this end the group used their sugar-nucleotides **33**-**36** to conclude that the stability of these compounds was maximised in elevated buffer pH (≥7) at 5 °C and *O*-4 substitution (TBS, Me, Ac) improved hydrolytic stability, as did the kinetically more stable α-form. Their work gave insight for the use of such sugar-nucleotides to probe relevant biological pathways and their potential for chemoenzymatic applications in natural product synthesis.



Scheme 10. Synthesis of 4-substituted NDP-α,β-L-rhodinose derivatives **33**-**36**. i) UMP morpholidate or TMP morpholidate, 1-*H*-tetrazole, py, 2 days. ii) NaOMe, MeOH.

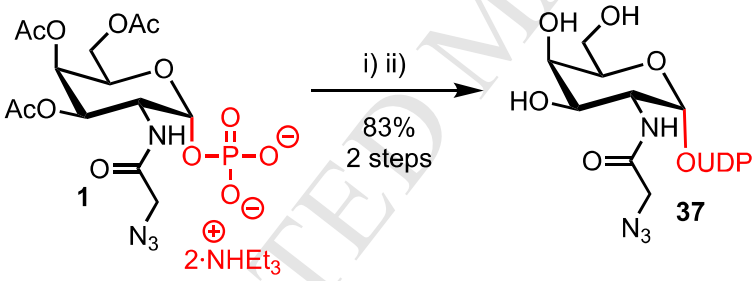
The Janda group[12] recently described their efficient synthetic method to an azide-modified sugar-nucleotide: UDP-*N*-azidoacetylgalactosylamine **37** (UDP-α,β-GalNAz). The coupling reaction of sugar-1-P **1** with UMP-morpholidate in the presence of 1-*H*-tetrazole as catalyst, followed by deacylation delivered mimetic **37** in 87% yield over 2 steps (Scheme 11). UDP-GalNAc **37** was utilised as a tool for the development of site specific antibody drug conjugates, loading azide **37** onto an antibody using a recombinant galactosyltransferase and

then demonstrating click functionalisation with an Alexa Fluor 488 tagged alkyne (bibenzylcyclooctynol, DIBO). This strategy delivered a fluorescently labelled antibody drug conjugate and a platform to methodology towards the next generation of these materials.



Scheme 11. Synthesis of UDP-α,β-GalNAz **37**. i) UMP-morpholidate, 1-*H*-tetrazole, py; ii) Et_3N, MeOH.

The work reported by Janda's group can be compared with that reported by Kahne *et* al,[32] who examined the use of *N*-methylimidazolium chloride (NMI·HCl) as a catalyst for the synthesis of **37,** instead of 1-*H*-tetrazole used by Janda. They concluded that NMI was superior in terms of activity, cost and safety and reduced the pyrophosphate coupling reaction time of GalNAz-1-phosphate **1** with UMP-phosphomorpholidate from three days (using 1-*H*-tetrazole) to 12 h using NMI·HCl. They also reported that the yield of **37** was improved from 71%[28] to 83% using their system (Scheme 12). The authors suggested that the role of NMI could be that of a nucleophile as well as an acid, indicating that the electronically neutral phosphomorpholidate could be substituted by NMI to form a cationic phosphor-*N*-methylimidazolide intermediate. Upon addition of NMI they supportively observed a downfield shift in the ^{31}P NMR resonance of UMP-morpholidate.



Scheme 12. Chemical synthesis of UDP-GalNAz **37** using NMI in place of 1-*H*-tetrazole. i) NMI·HCl, UMP-morpholidate, DMF, 12 h; ii) NaOMe, MeOH.

Following their description of a new class of allosteric galactosyltransferase inhibitors[33,34] and a requirement to further develop the robustness of the synthetic protocols that afford essential precursors thereto, Wagner *et al*[35] investigated the synthesis of 5''-substituted UDP-sugars using a UMP-phosphoromorpholidate and NMI as promoter, as developed by Kahne.[32] Pleasingly, the group could apply the results of this work for their synthesis of both 5''-I-UDP-Gal **38** and 5''-I-UDP-GlcNAc **39** in good yields using DMF as solvent and with a reaction time of only 8 h (Scheme 13). Subsequent Suzuki-Miyaura coupling with 5-formylthien-2-yl boronic acid was successful for both **38** and **39** and allowed the biological evaluation of sugar-nucleotide mimetics **40** and **41** against the GlcNAc transferase GnT-V. The group have also used a phosphomorpholidate/1-*H*-tetrazole approach to access 5''-substituted-UDP-Gal mimetics and an anomeric *C*-glycosidic analogue.[36]

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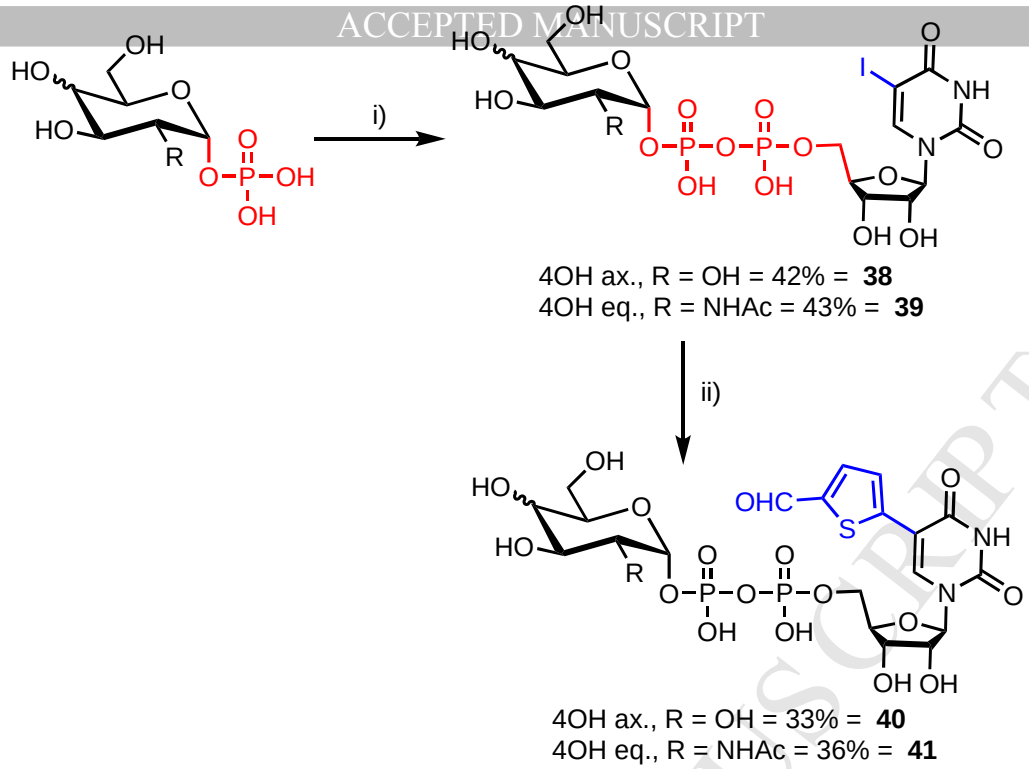
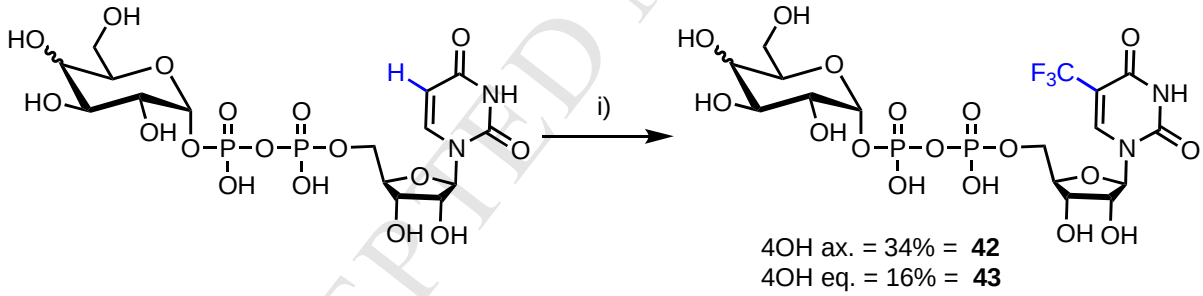


Scheme 13. Synthesis of 5-substituted UDP-Gal **40** and UDP-GlcNAc **41**. i) NMI·HCl, 5''-I-UMP-morpholidate, DMF, 8 h, rt; ii) 5-formyl-2-thiopheneboronic acid, $CsCO_3$, Na_2PdCl_4, TPPTS, H_2O, 2 h, 50 °C.

Additionally, the group described the first synthetic route to prepare 5''-CF_3-UDP-Glc **42** and 5''-CF_3-UDP-Gal **43** directly from the corresponding 5''-unsubstituted UDP-sugars in a one-step reaction (Scheme 14).[37]



Scheme 14. Synthesis of 5''-CF_3-UDP-Glc **42** and 5''-CF_3-UDP-Gal **43**. i) $NaSO_2CF_3$, ^tBuOOH, H_2O.

Sun *et al*[13,38] developed a novel P^V-N activation strategy based on the excellent reactivity of a phosphoropiperidate/4,5-dicyanoimidazole (DCI) system which shortened the reaction times of pyrophosphorylation significantly, from days to 6-8 hours, to afford a series of 6-deoxy-L-sugar nucleotides in 70-85% isolated yields. The group first synthesised protected nucleoside 5'-phosphoropiperidates *via* phosphitylation of protected nucleotides **44** and **45** with benzyl *N*,*N*-diisopropylchlorophosphoramidite, followed by 1-*H*-tetrazole catalysed hydrolysis and oxidative coupling with piperidine using CCl_4/Et_3N, to afford nucleoside 5'-phosphoropiperidates **46** and **47** in excellent isolated yields over four consecutive steps (Scheme 15).

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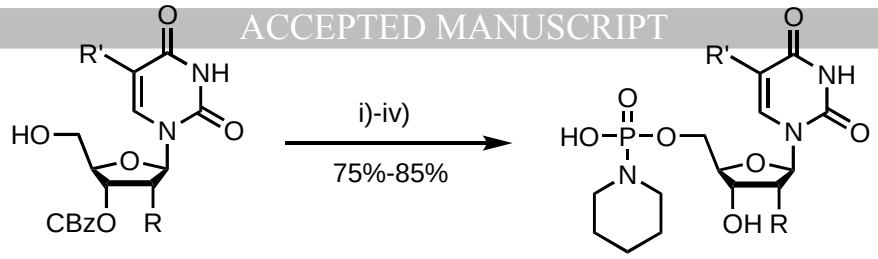
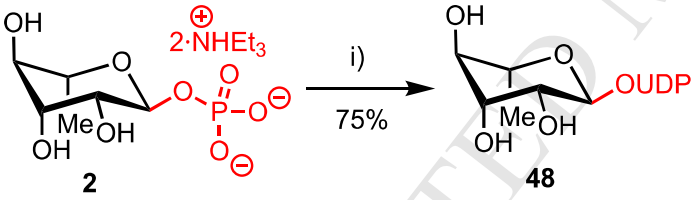


R' = Me, R = H = **44**
R' = H, R = OCBz = **45**

R' = Me, R = H = **46**
R' = H, R = OH = **47**

Scheme 15. Chemical synthesis of uridine-5'-phosphoropiperidates. i) (^{i}Pr)$_2$NP(OBn)Cl, Et_3N, CH_2Cl_2, 20 °C, 30 min; ii) 1-*H*-tetrazole, H_2O, MeCN, 20 °C, 30 min; iii) CCl_4, Et_3N, piperidine, MeCN, 0-20 °C, 30 min; iv) H_2, Pd/C, DMF, 3 h.

Using a control experiment with UMP 5'-phosphoromorpholidate, the group showed that the reactivity of their piperidate analogues **46** and **47** reduced the time required for pyrophosphorylation from 28 days to 5 days using 1-*H*-tetrazole promotion, suggesting that the higher pK_{aH} of piperdine (relative to morpholine) increased the rate of acid promoted activation required for reaction. They then sought to screen a series of weakly acidic activation systems, to further reduce the reaction times associated with using 1-*H*-tetrazole. Of the compounds investigated, DCI and *N*-methylimidazolium chloride showed the best reduction in comparable reaction time (12 h) with similar yields, but the lower hydroscopicity and better solubility in organic solvents prompted them to favour DCI. The uridine-5'-phosphoropiperidates were then coupled with 6-deoxy-L-sugar-1-phosphates **2** and **3** using DCI as activator. A representative example to deliver UDP-α-L-rhamnose **48** is shown in Scheme 16. This work suggests that DCI-promoted-nucleoside phosphoropiperidate pyrophosphorylation is a system that improves upon more traditional approaches, however, its general applicability across a broader substrate scope is still to be established.



2 **48**

Scheme 16. P^V-N activation method for the synthesis of UDP-6-deoxy-L-rhamnose **48**. i) uridine-5'-phosphoropiperidate, DCI, DMF, 30 °C, 6 h.

Jacobson and co-workers[39] recently synthesized a range of UDP-α-D-Glc derivatives to build an SAR profile and probe the physiological function for endogenous ligand binding to the $P2Y_{14}$ receptor: a ligand-gated nucleotide signaling protein that plays a role in the neuroimmune system. The group synthesized several derivatives to probe the effect of modification on the heterocyclic U base, ribose ring and Glc residue. When focusing upon Glc, they constructed several deoxy-fluoro mimetics, GlcA and C-2 or C-6 linked sugar-nucleotides. In most examples, the group adopted the Khorana-UMP-morpholidate strategy along with the tetra-*N*-butyl ammonium salt form of the relevant sugar-1-P. However, in the case of U modified species the group switched to using CDI[40] activation of the modified nucleoside monophosphate, followed by diphosphate coupling.

Finally, the Liu group[15] completed their impressive chemical synthesis of GDP-α-D-octose **49** using Khorana's phosphomorpholidate approach, delivering the material in 19% yield (Scheme 17).

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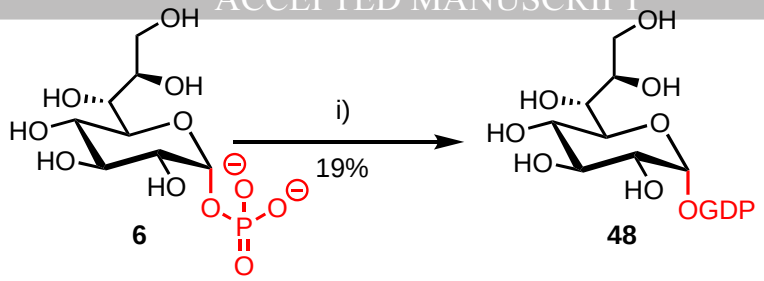
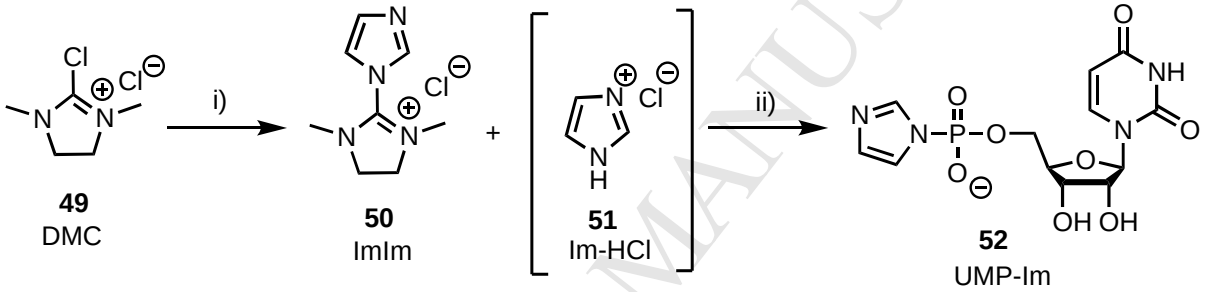


Scheme 17. Formation of GDP-α-D-octose **48**. i) GMP-morpholidate, 1-*H*-tetrazole, pyridine.

4.1.2. Pyrophosphorylation using phosphorimidazolides

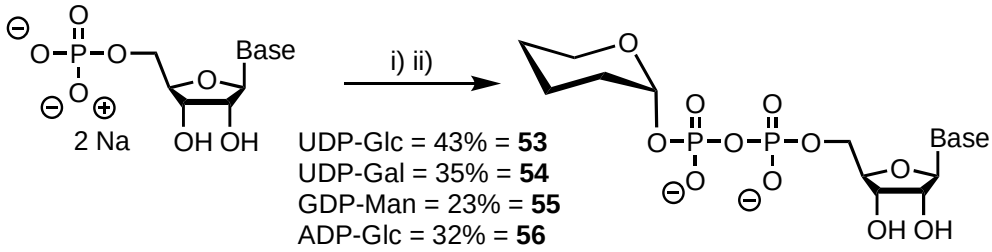
Hindsgaul *et al*[29] established a one-pot synthetic approach to form sugar-nucleotides in water that required only a sequential addition of commercially available materials and could harness the crude reaction product as a donor for immediate use in glycosyltransferase-mediated synthesis. The workers showed that reaction of DMC **49** with imidazole readily gave ImIm **50** and reasoned then whether **50** could subsequently activate a nucleotide monophosphate to its phosphorimidazolide to effect pyrophosphorylation (Scheme 18).



Scheme 18. Formation of UMP-Im **52**. i) Imidazole, D_2O, <5min., rt (1L/mol DMC) ii) UMP disodium salt.

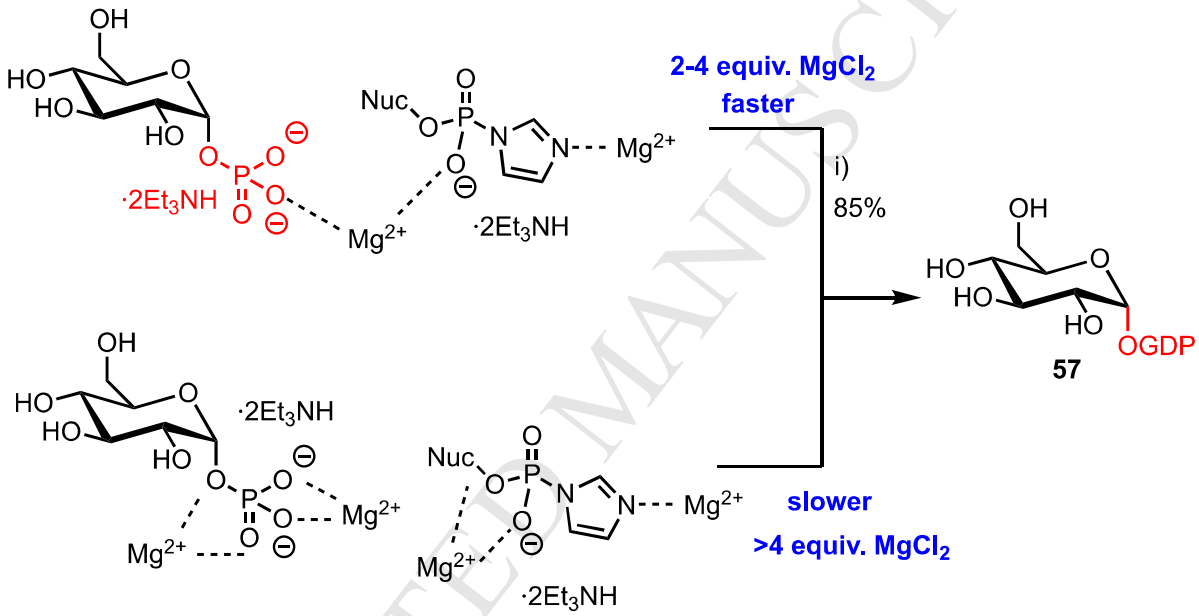
Activation of UMP with **50** to produce UMP-Im **52** and urea was demonstrated, with the authors observing using ^{1}H NMR monitoring in D_2O that reaction times of longer than 1 h led to hydrolysis of **52**. They also noted that the reaction was more efficient in D_2O than H_2O, with yields of **52** in H_2O only 60-70% of those observed using D_2O.

Subsequently the group examined the capability of **52** to form a series of sugar-nucleotides **53**-**56** (Scheme 19). Finally, they utilised the crude and chemically benign reaction solutions containing the sugar-NDP as requisite donors in a series of chemoenzymatic oligosaccharide syntheses. Overall, this work aimed to offer a solution for the production and utilisation of sugar-nucleotides for those without a prior expertise in the manipulation of sugar protecting groups and in performing moisture sensitive reactions. All the reagents are commercially available and provided the timing of their addition to the reaction is carefully monitored, the desired sugar-nucleotides can be accessed and used immediately as requisite donors. The Lowary group[20] has successfully adopted this procedure to synthesise UDP-Gal*f*NAc and UDP-Gal*f*N_3, reporting both sugar-nucleotides in modest yields (16% and 23% respectively) although these were comparable to previously reported yields for similar substrates.



Scheme 19. Formation of sugar-nucleotides **53-56** using the ImIm method. Yields shown are isolated following ion-exchange chromatography purification. i) **52**, D_2O, 1 h, 37 °C ii) Sugar-1-P.

Jemielity's group[30] described a protecting group free, magnesium chloride-promoted synthesis of sugar-nucleotides from the corresponding nucleoside 5'-phosphorimidazolides and sugar 1-Ps in DMF (Scheme 20).



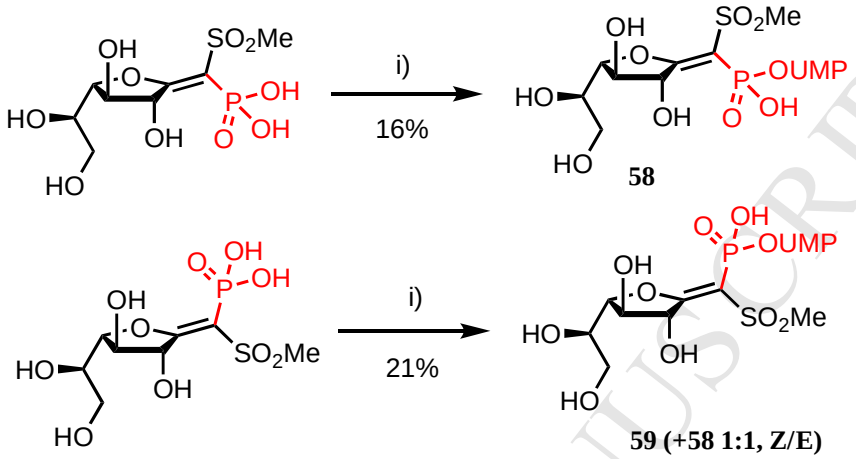
Scheme 20. Proposed model for $MgCl_2$ promoted pyrophosphate formation and an example for the synthesis of GDP-α-D-Glc **57** i) DMF, rt. Nuc = nucleotide.

Working on a consensus that phosphorimidazole-directed sugar-nucleotide synthesis is not accelerated by acid catalysis (i.e. 1-*H*-tetrazole), the group investigated the use of Lewis acid-promoted pyrophosphorylation. Their work demonstrated improvements to sugar-nucleotide formation as follows: the addition of a metal chloride ($ZnCl_2$ or $MgCl_2$) significantly improved the solubility of the reagents, which otherwise are generally poorly soluble in DMF; the Lewis acid acting as a catalyst, activating imidazole as a leaving group and coordinating both reaction partners to form the diphosphate. The optimal reaction rate enhancement was achieved using 2 to 4 equivalents of $MgCl_2$ and any further addition retarded the rate, possibly through excessive coordination of the sugar-1-P, by Mg^{2+}, decreasing its nucleophilicity.

They applied their technology to a range of different nucleoside 5'-phosphorimidazolides (A, G and U-containing) and sugar-1-P pairings (1-Glc, 1-Gal, 1-Fuc) obtaining good isolated yields (63-92%) and observing a significant reduction in reaction times (as low as 10 min. for GDP-α-D-Glc **57**, Scheme 20) on small scale. Notably, when the scale was increased, to 100 mg for **57**, the reaction time increased to 3 h, suggesting that the

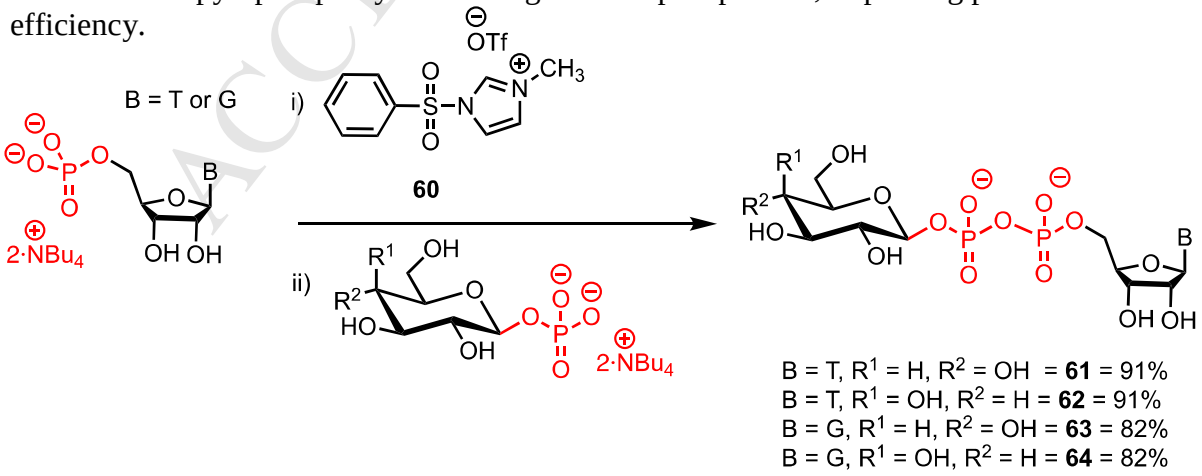
reaction concentration and homogeneity for sugar-nucleotide formation is crucial for access to larger amounts of these materials.

This method was successfully adopted by Vincent *et al*[23] for their synthesis of ADP-6-azido-6-deoxy-β-D-mannose (in 90% yield) and for construction of sulfonylated phosphono-*exo*-glycal sugar-nucleotide mimetics **58** and **59** (Scheme 21).[41] Here the authors noted that the Lewis acidic coupling conditions promoted an isomerisation of the *exo*-double bond in **59**, delivering the mimetic sugar-nucleotide as a separable *E*/*Z* mixture.



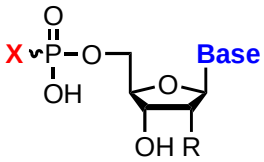
Scheme 21. Synthesis of sulfonylated phosphono-*exo*-glycals of UDP-Gal*f* **58** and **59**. i) uridine-5'-phosphorimidazolide, $MgCl_2$, DMF, rt, 16 h.

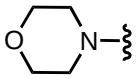
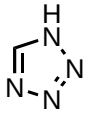
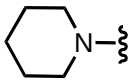
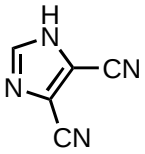
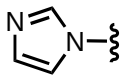
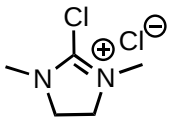
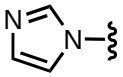
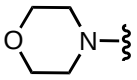
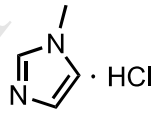
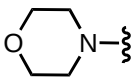
Taylor *et al*[42] reported a rapid and high yielding approach for preparing sugar-nucleotides **61**-**64** which obviated the commonly encountered protection/deprotection requirements of the donor and acceptor (Scheme 22). Sulfonylimidazolium salt **60** was used as the key reagent to activate the NMP component before reaction with a sugar-1-P. The authors reasoned that reaction between the negatively charged phosphate moiety and the positively charged sulfonylimidazolium salt afforded the donor before any competing reaction with other nucelophilic substrate functional groups. They also suggested that the coupling step could proceed either *via* a mixed P/S anhydride intermediate or an imidazolium species formed from initial reaction of **60** with a NMP, followed by substitution by NMI. Symmetrical dinucleoside diphosphate formation *via* dimerization was suppressed by using DIPEA instead of NMI and the authors also commented that any unreacted NMP could be removed after pyrophosphorylation using alkaline phosphatase, improving purification efficiency.



Scheme 22. Synthesis of GDP- and TDP-Gal/Glc **61**-**64** using sulfonylimidazolium salt **60**. i) DIPEA, DMF, rt, 1 min. ii) $MgCl_2$, rt, 0 °C, 30 min.

In Table 1, we summarise the variety of activation methods for nucleoside P^V monophosphate derivatives and their use in sugar-nucleotide synthesis.



X =	Additive /Activator	Target sugar-nucleotide	Yield (%)	Ref.
		UDP-4-F Glc*p*NAc	61	Linhardt[14]
		UDP-4-F Gal*p*NAc	55	Linhardt[14]
		UDP-5-F Gal*p*	10*	Liu[17]
		UDP-[5,6-F_2] Gal*p*	4$	Liu[17]
		U/TDP-4-substituted α,β-L-rhodinoses	8-34	Zhou[18]
		UDP-α,β-Gal*p*NAz	87	Janda[12]
		UDP-α-D-Octose	19	Liu[15]
		5'-I-UDP-Gal*p*	42	Wagner[36]
		UDP-L-Rha*p*/Tal*p*	70-75	Sun[13]
		dTDP-L-Rha*p*/Tal*p*	70-75	
		UDP-Glc*p*	43	Hindsgaul[29]
		UDP-Gal*p*	35	〃
		GDP-Man*p*	23	〃
		ADP-Glc*p*	32	〃
		UDP-Gal*f*NAc	16	Lowary[20]
		UDP-Gal*f*N_3	23	
	$MgCl_2$	ADP-Glc*p*	92	Jemielity[30]
		GDP-Glc*p*	85	〃
		UDP-Glc*p*	78	〃
		UDP-Gal*p*	83	〃
		GDP-β-Fuc*f*	63	〃
		ADP-6-N_3-β-Man*p*	90	Vincent[23]
	$ZnCl_2$	UDP-Gal*f* mimetics	16-21	Vincent[41]
		Dimeric ADP-ribose	79	Hergenrother[48]
		UDP-α-Gal*p*NAz	83$	Kahne[32]
		5'-I-UDP-Gal*p*	42	Wagner[35]
		5'-I-UDP-Glc*p*NAc	43	Wagner[35]
	None	UDP-β-Glc*p*	25	Jacobson[39]
		UDP-Fuc*f*	23	〃
		UDP-2-F-Glc*p*	11	〃
		UDP-3-F-Glc*p*	11	〃
		UDP-4-F-Glc*p*	7	〃

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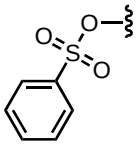
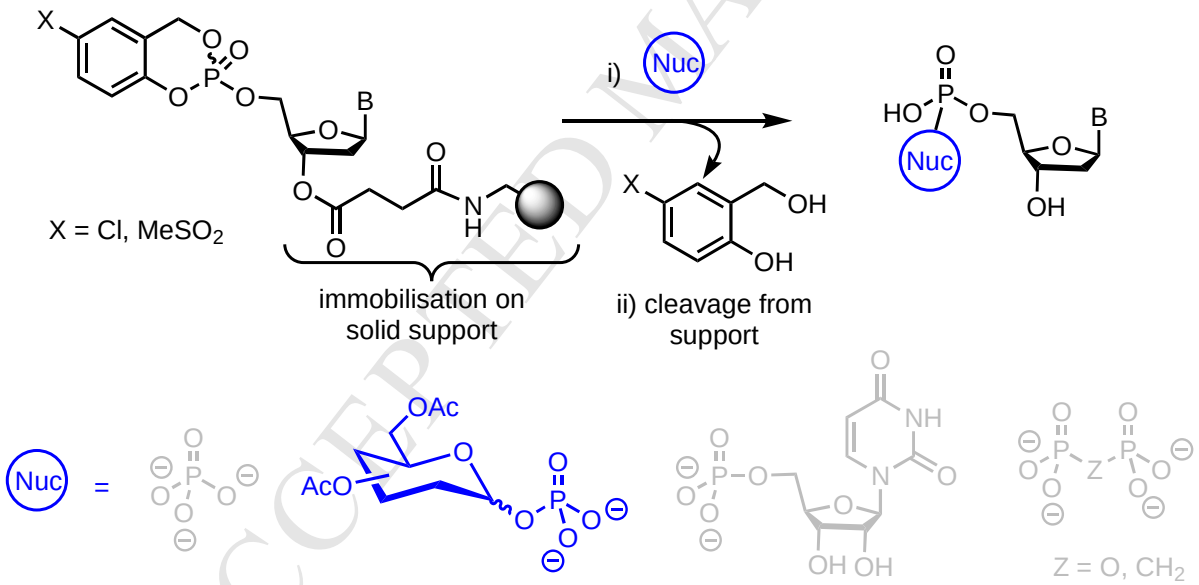
		UDP-4-F-Glc*p*	9	″
	$MgCl_2$	TDP-β-Glc*p* TDP-β-Gal*p* GDP-β-Glc*p* GDP-β-Gal*p*	91 91 82 82	Taylor[42]

Table 1. Summary of methods for pyrophosphate formation used activated P^V-N/O systems. * 3 steps, $ 2 steps.

4.1.3. Pyrophosphorylation using activated phosphate esters

Meier *et al*[43] recently utilised their *cyclo*Sal technology[44,45] on solid-support (Scheme 23), immobilising *cyclo*Sal-nucleotides *via* a succimidyl tether (through the furanose C3'-OH) onto an amino-methyl polystyrene resin. In a second step, the target molecules were delivered through reaction of the immobilized *cyclo*Sal-triester with a series of nucleophilic phosphate sources, followed by the cleavage from the resin. This technology provided a general access to nucleoside di- and triphosphates, sugar nucleotides and dinucleoside diphosphates. Their method delivered the materials in high overall purity, as the impurities from the phosphate nucleophile (which are generally problematic to remove *via* RP-chromatographic or ion-exchange systems) could be removed prior to cleavage from the resin.

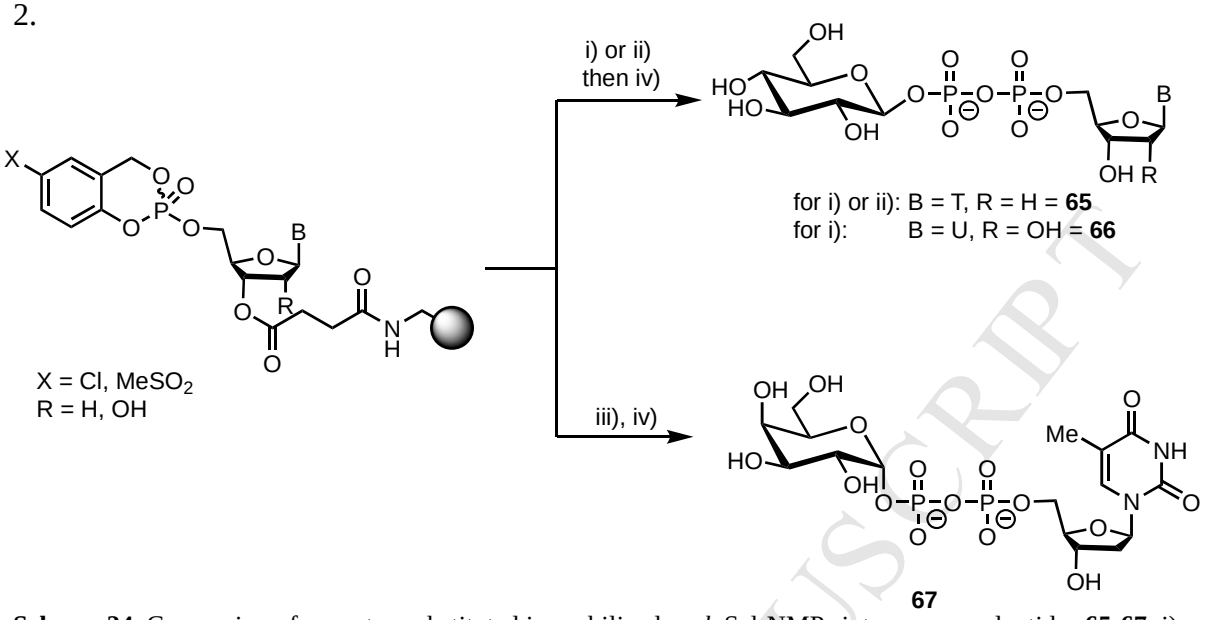


Scheme 23. Generic representation of immobilised *cyclo*Sal nucleotides (2-deoxy system shown).

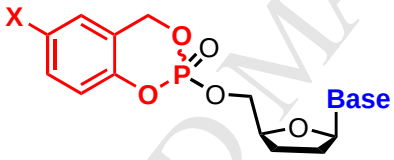
To access NDP-sugars the group demonstrated synthesis of TDP-β-D-glucose **65**, UDP-β-D-glucose **66** and TDP-α-D-galactose **67** (Scheme 24). Following cleavage from the resin compounds **65**-**67** were isolated in very good purity (78% for **65** and **66**). In the case of TDP-α-D-galactose **67** the isolated purity was lower (43%) as the group observed that the conditions used to effect resin cleavage caused the formation of the 1,2-cyclic phosphate derivative of α-Gal and TMP.

The group also recently extended their previously reported solution-phase *cyclo*Sal methodology[44,45] to access rare and non-natural NDP-sugars, including those containing

glucose-6-sulfate, L-galactose and 2-fluoro-2-deoxyglycopyranosides.[16] These results, along with synthesis using the solid phase approach to sugar-nucleotides, are summarised in Table 2.



Scheme 24. Conversion of acceptor-substituted immobilized *cyclo*Sal-NMPs into sugar-nucleotides **65**-**67**: i) (Et_3NH)-tetra-*O*-acetyl-β-D-glucosyl-1-phosphate, DMF, 4 days, rt; ii) [(^{n}Bu)$_4$N]-tetra-*O*-β-D-glucosyl-1-phosphate, DMF, 5 days, rt; iii) (Et_3NH)-tetra-*O*-acetyl-α-D-galactosyl-1-phosphate, DMF, 4 days, rt; iv) $CH_3OH/H_2O/Et_3N$ 7:3:1, 20 h, rt.



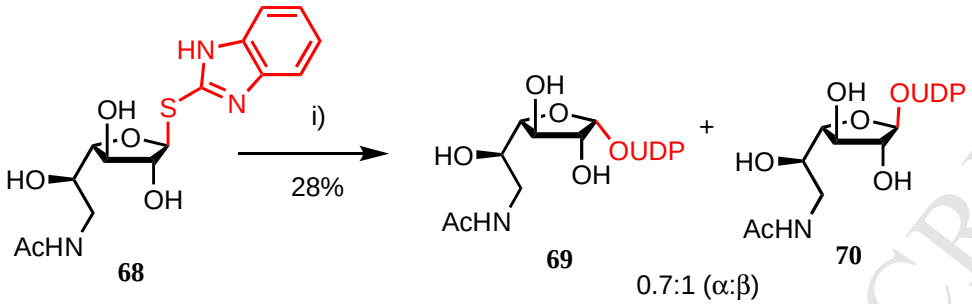
X =	Additive /Activator	Target Sugar-NDP	Yield (%)	Ref.
--	None	TDP-β-D-Glc*p*	78	Meier[43,16]
		UDP-β-D-Glc*p*	78	
		TDP-α-D-Gal*p*	43	
		UDP-α-D-sulfoquinovose	48	
		UDP-2-F-α-D-Man*p*	52	
		UDP-2-F-α/β-D-Glc*p*	72	
		UDP-2-F-α/β-D-Gal*p*	91	
		UDP-β-L-Gal*p*	63	

Table 2. Summary of sugar-nucleotides accessed using activated *cyclo*Sal phosphate ester systems.

4.1.4. Sugar-nucleotides from nucleoside diphosphates and sugar electrophiles

Daniellou and co-workers[46] recently introduced a short and versatile chemical synthesis for both anomers of UDP-6-NHAc-6-deoxy-Gal*f* (Scheme 25). The group were seeking to provide structure-function tools and potential inhibitor candidates for the lipophosphoglycan pathway in the parasite *Leishmania*, specifically concerning the activity

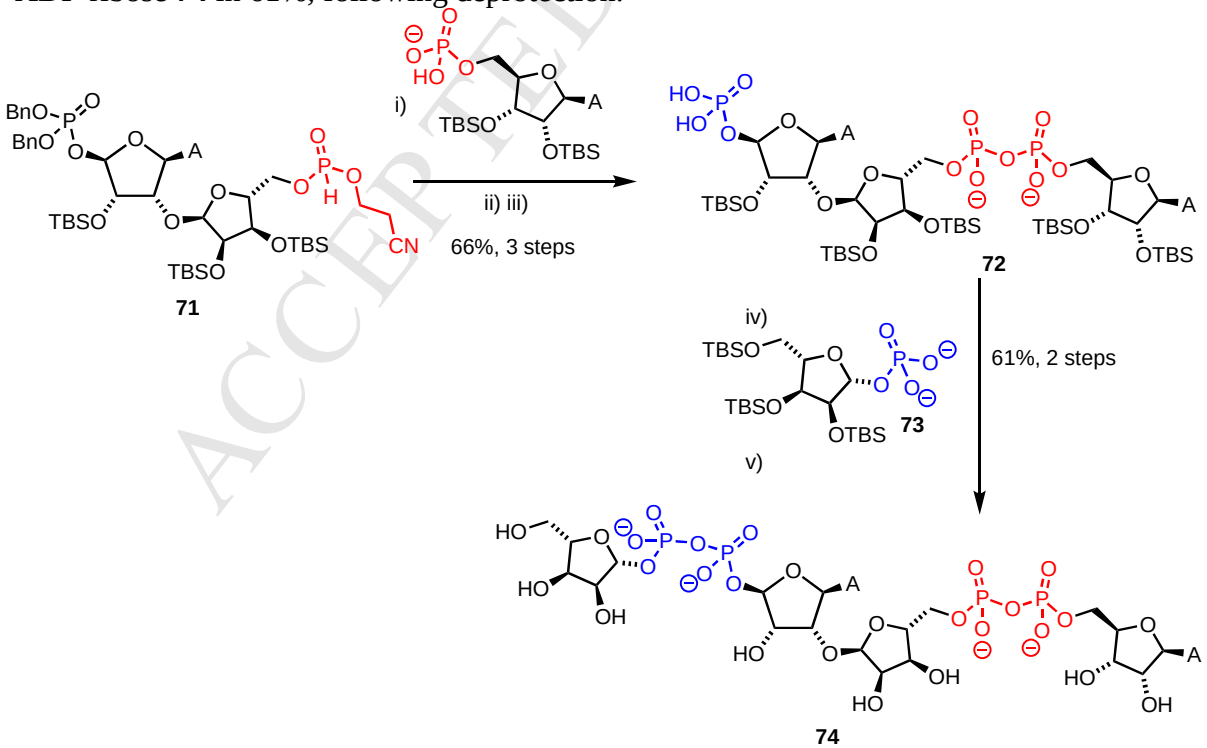
of the galactofuranosyl transferase and UGM, for which UDP-Gal*f* is the natural substrate. To do this, the group utilised 2-mercaptobenzimidazole furanose donor **68** in a direct diphosphate-forming glycosylation with the acidic form of UDP. Whilst this reaction was (expectedly) not diastereoselective, both anomers, **69** and **70**, of UDP-6-NHAc-6-deoxy-Gal*f* could be isolated in mg quantitates using semi-preparative RP-HPLC. Interestingly, the non-native 1,2-*trans* sugar-nucleotide mimetic **70** was the more proficient in retarding the growth of *L. donovani* promastigotes *in vitro*.



Scheme 25. Synthesis of UDP-6-NHAc-6-deoxy-Gal*f* **69** and **70**. i) UDP, DMF, 0 ^{o}C, 10 min.

4.1.5. Diphosphate formation using a P^{III}-P^{V} approach

Hergenrother *et al*[47] applied two different diphosphate-forming approaches in their synthesis of dimeric ADP-ribose **74** (Scheme 26). Firstly, the group used *H*-phosphonate **71** to couple with protected-AMP, an adaptation of the Atherton-Todd reaction,[48] suggesting that pyrophosphorylation occurs once the *H*-phosphonate has undergone oxidative chlorination with NCS to afford a chlorophosphate. Attempts to repeat this methodology to install a second pyrophosphate within **72** were unsuccessful and the group instead used phosphorimidazolide conditions (CDI, $ZnCl_2$) to effect coupling with **73**, delivering dimeric ADP-ribose **74** in 61%, following deprotection.



Scheme 26. Synthesis of ADP-ribose dimer **74**. i) NCS, DIPEA, MeCN, rt 20 min.; ii) DBU, MeCN, rt, 20 min.; iii) H_2, Pd/C Et_3N, ^{t}BuOH/H_2O, rt, 16 h; iv) CDI, Et_3N, py. rt, 2 h, then **73**, $ZnCl_2$, DMF, rt, 96 h; v) NH_3/MeOH, 20 h, then TBAF, THF, rt, 3h.

Van der Marel and Flippov utilised their earlier reported P^{III}-P^{V} pyrophosphorylation approach[10a] for a solid-phase synthesis of adenosine diphosphate ribose (ADPR) dimers, noting an important acceleration in oxidation of the phosphite-phosphate intermediate by using CSO [(1S)-(+)-(10-camphorsulfonyl)oxaziridine] in place of the more commonly encountered ^{t}BuOOH.[10b] The group also applied this modification for the synthesis of mono-ADP-ribosylated peptides[10c] and extended their P^{III}-P^{V} approach for the synthesis of methylene bisphosphonates, replacing the diphosphate linking oxygen with CH_2 and opening a route to mimetic methylene bisphosphonates of ADP, ATP, ADPR and FAD.[10]

5. Summary and outlook

Since the last review concerning the synthesis of sugar-nucleotides, there have been significant developments within this key branch of synthetic carbohydrate chemistry. Of particular note is advance in the number of chemical methods now available to access the crucial precursors, sugar-1-phosphates, across a range of monosaccharide systems, inclusive of mimetic and rare sugars. Reaction yields have generally improved and, perhaps more importantly, alternate conditions delivered (to the classically acidic environment used for phosphate introduction), opening new avenues for pre-modification of the sugar component.

Towards the central sugar-nucleotide forming reaction, the use of established phosphomorpholidate-activation chemistry is still commonplace. Activation is frequently accomplished using 1-*H*-tetrazole, however NMI has shown promise on a small number of mimetic examples. The emergence of a phosphorimidazolide-activation strategy (using Lewis acids or DMC as activator) provides a second nucleoside monophosphate derivative which has proven its capability on a number of examples in several laboratories. Perhaps most notable with this activation method is its use to access a broader pool of nucleoside components (ADP, GDP, UDP), compared with the classical morpholidate strategy (UDP only). This observation should be taken in context however, as the most common synthetic sugar-nucleotide targets are UDP-hexopyranose systems; particularly non-native species where the inclusion of one or multiple ring fluorine atoms and heterocycle base modifications confirms the necessity for robust chemical methodologies to address carbohydrate-based tools not accessible using chemoenzymatic strategies.

In conclusion, advances centered around P^{V}-P^{V} coupling chemistries mean that whilst a *general synthetic protocol* towards any sugar-nucleotide remains ever elusive, there is a robust and diverse body of synthetic possibilities capable of addressing access to a significant number of both native and mimetic structures. We hope that this key area of glycochemistry will continue to explore and deliver innovative new strategies for synthesising this essential class of biomolecule.

Acknowledgements

The EPSRC [EP/P000762/1] are thanked for project grant funding.

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