

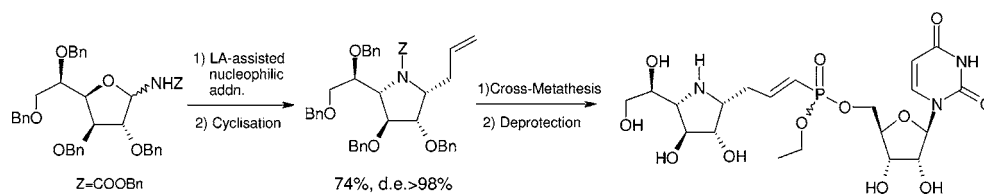
Stereoselective Synthesis of α -C-Substituted 1,4-Dideoxy-1,4-imino-D-galactitols. Toward Original UDP-Galf Mimics via Cross-Metathesis

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ABSTRACT



Various α -C-substituted 1,4-dideoxy-1,4-imino-D-galactitols were prepared efficiently from 1-O-acetyl-2,3,5,6-tetra-O-benzyl-D-glucopyranosylamine by a four-step sequence involving as the key step the highly *syn*-selective TMSOTf-catalyzed addition of silylated nucleophiles to a glycofuranosylamine. Cross-metathesis of the α -C-allylated iminogalactofuranose derivative with an original uridine-5'-yl vinylphosphonate led to novel UDP-galactofuranose mimics. Such compounds are of interest as potential inhibitors of the mycobacterial galactan biosynthesis pathway.

Mycobacterial viability is dependent upon the ability of the organism to produce an intact cell wall. Therefore, compounds that interfere with the biosynthesis of the cell wall complex glycans have the potential to become new drugs for the treatment of mycobacterial infections.¹ The oligosaccharide galactan is one of the major structural components of the outer wall of the microorganism. It is constituted of roughly 30 galactofuranose (Galf) residues linked alternatively by β -1,5 and β -1,6 linkages; this form of galactose is present in several pathogenic prokaryotes, but it is not found in mammals.² The use of gene knockout techniques has demonstrated that Galf is essential for cell growth and survival,³ and therefore, its biosynthesis constitutes a new drug target.⁴ The biosynthetic process involves several enzymes having uridine-diphosphogalactofuranose (UDP-

Galf) as the substrate: uridine 5'-diphospho-(UDP)-galactopyranose mutase which catalyzes the interconversion of UDP-galactopyranose into UDP-galactofuranose, as well as Galf transferases. As the mechanism⁵ of the mutase interconversion is still unclear, we are seeking and designing molecules that could be mechanistic probes and/or inhibitors. Our initial objective was the synthesis of original UDP-Galf mimics based on an iminosugar skeleton linked to UMP by structurally diverse tethers. During the past decade, interest

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in so-called iminosugars has widely increased. Indeed, these nitrogen-containing sugar analogues constitute leads for the development of new therapeutic agents in a range of diseases (viral infections, diabetes, lysosomal diseases).⁶ 1,4-Dideoxy-1,4-imino-D-galactitol **1** is the first known inhibitor of *E. coli* K12 UDP-Galp mutase and of mycobacterial galactan biosynthesis, although the inhibitory effect was rather weak.⁷ It was also shown that analogue **2** with a short aglycone, such as a α -hydroxymethyl group, was somewhat more active (Figure 1). Analogues of galactofuranose in the 1-*N*-

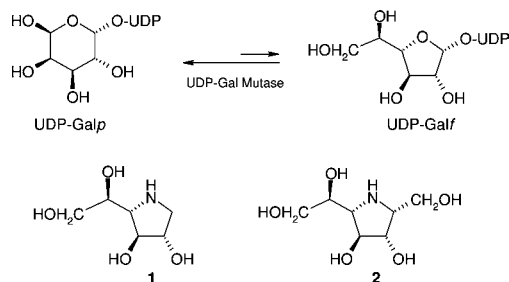


Figure 1.

iminosugar series have also been reported as moderate inhibitors of galactan biosynthesis.⁸

We wish to report in this paper, the efficient and stereoselective synthesis of α -*C*-substituted 1,4-imino-galactitol derivatives and their conversion by cross-metathesis into a novel type of UDP-Galf mimics in which UMP is linked to the iminogalactitol by a C_3 -tether.

Since glucofuranose derivatives are readily available, the formation of a glucofuranosylamine followed by the addition of an organometallic species to the corresponding open-chain imine and ring closure with inversion of configuration appeared to be a most useful approach to the desired α -*C*-substituted 1,4-iminogalactitol derivatives.⁹ Kobayashi et al.¹⁰ have recently reported a method for the direct synthesis of *Z*-protected glycosylamines from simple glycosyl donors and carbamates in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf). In addition, these glycosylamines are

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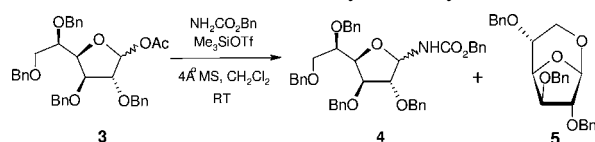
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Scheme 1. Glucofuranosylamine Synthesis



excellent substrates for Lewis acid (LA)-catalyzed ring opening with silylated nucleophiles leading to syn addition product, as required for the eventual formation of a pseudo- α -configuration of the galactofuranose mimic. We report the first application of this methodology to a hexofuranose sugar derivative and the conversion of the addition product to a UDP-Galf mimic.

The starting material, namely 1-*O*-acetyl-2,3,5,6-tetra-*O*-benzyl-D-glucopyranose **3**, was prepared in four steps from D-glucose: the procedure described by Ferrières et al.¹¹ required optimization¹² and provided **3** in an average of 41% yield for the four steps (30 g scale).

The formation of the corresponding *N*-*Z*-glycosylamine was then investigated: under the conditions reported by Kobayashi (*Z*-NH₂, TMSOTf),¹⁰ we obtained the desired product **4** as well as the byproduct **5** (1,6-anhydro-2,3,5-tri-*O*-benzyl- β -D-glucopyranose)¹³ (Scheme 1 and Table 1, entry

Table 1^a

entry	Lewis acid	yield of 4 (%)	4/5	solvent	reaction time
1	TMSOTf	58	84/16	CH ₂ Cl ₂	30 min
2	TMSOTf	59	96/4	CH ₂ Cl ₂	3h20
3	TMSOTf	15	100/0	CH ₂ Cl ₂	7 days
4	TMSOTf ^b	85	100/0	CH ₂ Cl ₂	1h
5	TMSOTf	68	100/0	CH ₃ CN	30 min
6	BF ₃ ·Et ₂ O	45	83/17	CH ₂ Cl ₂	84 h
7	SnCl ₄	7	30/70	CH ₂ Cl ₂	15 min
8	Sc(OTf) ₃ ^c			CH ₂ Cl ₂	30 min
9	ZnCl ₂ ^c			CH ₂ Cl ₂	20 min
10	TiCl ₄ ^d	6		CH ₂ Cl ₂	20 min
11	Bi(OTf) ₃	43	90/10	CH ₂ Cl ₂	20 min

^a All reactions were performed using 1.1 equiv of NH₂CO₂Bn except for entries 2 (1.5 equiv), 4, and 5 (2 equiv) and using 1 equiv of Lewis acid except for entries 3 (0.1 equiv) and 6 (2 equiv). ^b Reaction performed on a 3 g scale. ^c No reaction occurred; the starting material was recovered. ^d Only traces of compounds **4** and **5** and starting material **3** were detected (NMR). Degradation products were observed on TLC and NMR spectra.

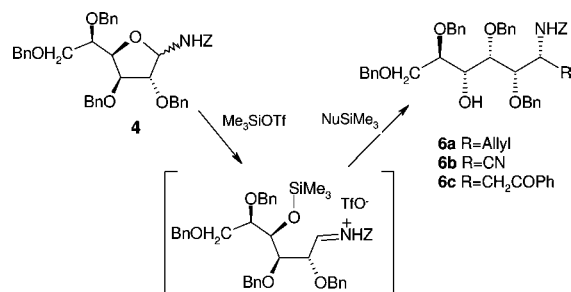
1). This side product **5** arose from the participation of the benzyloxy group at C-6 as a nucleophile trapping the intermediate oxocarbenium ion and undergoing subsequent *O*-debenzylation of the resulting benzyloxonium ion. Such Lewis acid mediated regioselective de-*O*-benzylations in the presence of Lewis acids were previously reported on other

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Scheme 2. Lewis Acid-Assisted Nucleophilic Addition to **4**



sugar substrates.¹⁴ A wide range of conditions and Lewis acids were explored in order to minimize the formation of **5** (Table 1). It was found eventually that, using an excess of benzyl carbamate in CH₂Cl₂ or MeCN (2.0 equiv, entries 4 and 5), the formation of byproduct **5** could be eliminated. It is important to note that, when TMSOTf was used, the conversion of the starting material was complete and provided good quality ¹H NMR spectra of the crude product. On a small scale, the reactions gave lower yields because of some degradation of the glycosylamine **4** during purification on silica gel.

The glucofuranosylamine **4** (α,β mixture) was then subjected to the TMSOTf-catalyzed reaction with various silylated nucleophiles (Scheme 2, Table 2). Using allyltri-

Table 2^a

entry	NuSiMe ₃	LA equiv (equiv)	yield of 6 (%)	de	reaction time (h)	
1	CH ₂ =CHCH ₂ SiMe ₃	2	0.2	35	>98	44
2	CH ₂ =CHCH ₂ SiMe ₃ ^b	6	1	56	>98	62
3	CH ₂ =CHCH ₂ SiMe ₃ ^b	7	0.5	74	>98	65
4	CH ₂ =CHCH ₂ SiMe ₃ ^b	7	1.25	86	>98	72
5	CH ₂ =CHOSiMe ₃ ^c	6	0.25			39
6	TMSCN ^d	7	0.5	63	>98	15
7	TMS-thiazole ^e	7	0.5			92
8	CH ₂ =C(Ph)OSiMe ₃ ^b	7	0.5	62	>98	22

^a All reactions were performed in dried CH₃CN at -40 °C and under Ar. ^b 4 equiv of NuSiMe₃ and 0.5 equiv of LA were first introduced in the flask, and then an additional 1 equiv of NuSiMe₃ and 0.25 equiv of LA were added every 2 h (3×). ^c No reaction occurred; the starting material **4** was recovered. ^d 100% conversion, but **6c** degraded during purification on silica gel.

methylsilane, it was found after extensive investigation that 1.25 equiv of LA and 7 equiv of reagent (added in portions) were necessary for the reaction to go to completion (entry 4). Compound **6a** was isolated in a good yield of 86%. With TMSCN, the reaction led to product **6b** in a unoptimized yield of 63% (entry 6). Compound **6b** was used without any purification in subsequent synthetic sequences.

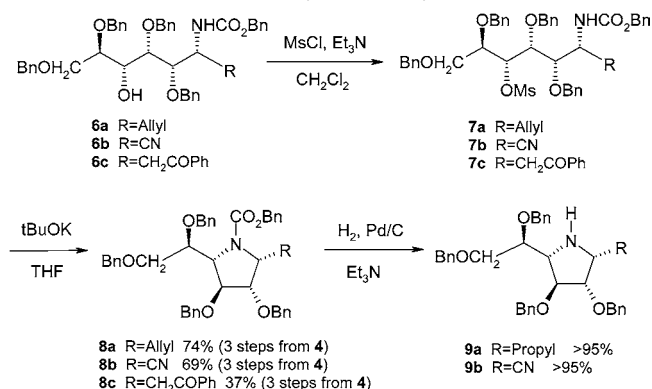
With 1-phenyl-1-trimethylsilyloxyethylene, the reaction gave compound **6c** in good yield (entry 8). The reactions with vinyloxytrimethylsilane and TMS-thiazole, the latter being well-known to perform nucleophilic attack onto aldehydes,¹⁵ were unsuccessful (entries 5 and 7).

The most remarkable feature of these addition reactions is their diastereoselectivity. Indeed, in each case, only one diastereoisomer was observed, which was anticipated to be the *Re* face addition product leading to a syn stereochemistry.¹⁰ The configurational assignment of the products **6a,b** could, however, be made only after conversion to pyrrolidine derivatives **9a,b**.

A two-step sequence with inversion at C-4 provided original imino- α -C-galactofuranosyl compounds **8a-c**: mesylation of the free hydroxyl group of compounds **6a-c** followed by treatment of the resulting sulfonate **7a-c** with potassium *tert*-butoxide gave the corresponding pyrrolidine having a D-galacto configuration by internal nucleophilic displacement.

Because of the presence of rotamers, it was impossible to determine directly the configuration of compounds **8a-c** by NOE-NMR analysis, even at 80 °C. Compounds **8a,b** were therefore *N*-deprotected by mild hydrogenolysis to provide quantitatively pyrrolidines **9a,b** (Scheme 3). The connec-

Scheme 3. Pyrrolidine Synthesis



tivities determined by NOESY experiments as well as the magnitude of the vicinal coupling constants supported a 1,2-*cis* configuration in the 1,4-iminoalditol,¹⁶ thus establishing the formation of syn products **6a-c** as unique diastereoisomers in the addition reaction. In addition, comparison with similar pyrrolidine structures¹⁷ having an unambiguous pseudo- β -configuration obtained in our laboratory confirmed the stereochemistry of **8a-c**.

With the original imino- α -C-galactofuranoside derivatives **8a-c** in hand, we envisaged their transformation into neoglycoconjugates mimicking UDP-galactofuranose by various coupling processes. In particular, we decided to investigate the coupling of the α -1-C-allyl derivatives with

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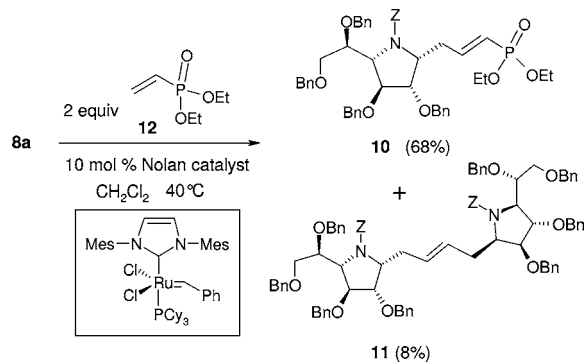
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unsaturated UMP derivatives by cross-metathesis. While ring-closing metathesis has been widely used in glycochemistry,¹⁸ there are few applications of selective cross-metathesis processes. In particular, our group has recently exploited this reaction for a general access to iminosugar C-glycosides,¹⁹ and more recently, Dondoni et al.²⁰ reported the synthesis of imino-C-glycosyl α -amino acids using this powerful procedure.

Surprisingly, initial investigations on the cross-metathesis reaction between **8a** and vinylphosphonates using second-generation Grubbs catalyst failed under various experimental conditions. On the other hand, the expected cross-coupling products could be obtained using 5–10 mol % of Nolan's catalyst.²¹ The reaction was performed first with diethyl vinylphosphonate **12** to set up the conditions. The iminophosphonate **10** was obtained in a moderate 68% yield and with excellent stereoselectivity as the (*E*)-stereoisomer.²² Some homodimerization product **11** and unreacted **8a** were also isolated (total yield 17%) (Scheme 4).

Scheme 4. CM Reaction of Phosphonate **12**



To apply this methodology to a uridine-monophosphate derivative, we developed a simple two-step synthesis of ethyl uridin-5'-yl vinylphosphonate **14** (Scheme 5). First, diethyl vinylphosphonate was directly chlorinated using oxalyl chloride.²³ The resulting crude phosphochloridate **13** was then converted into the mixed diester **14** using 2',3'-*O*-isopropylideneuridine in the presence of triethylamine in 61% overall yield. Cross-metathesis reaction between **8a** and **14** was performed using 10 mol % of Nolan's catalyst. After 44 h

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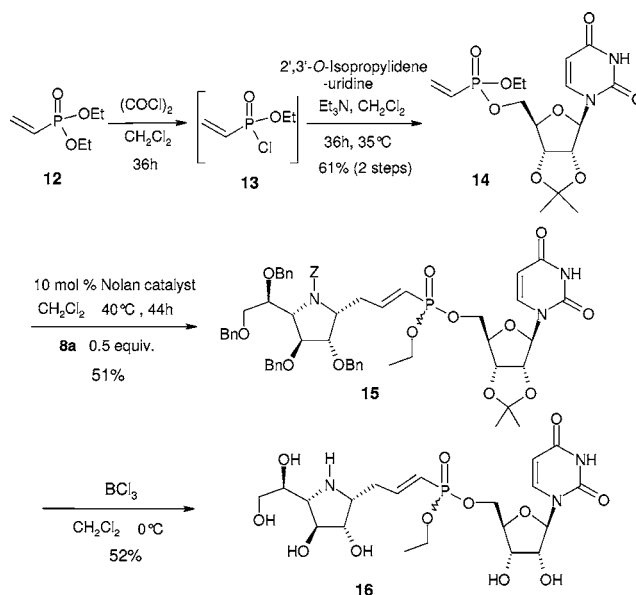
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Scheme 5. Synthesis of UDP-Galf Mimic **16**



at 40 °C, the iminosugar nucleotide conjugate **15** was isolated in a unoptimized yield of 51% as a mixture of nonseparable *P*-stereoisomers. A small amount of homodimerization product **11** (8%) was also obtained, and unreacted **8a** (9%) was recovered. Compound **15** was deprotected efficiently with an excess of BCl_3 in CH_2Cl_2 to give compound **16**, a significant UDP-galactofuranose analogue. In this compound, the iminosugar moiety mimicks a putative galactofuranosyl cation involved in the reactions catalyzed by UDP-Gal mutase and/or UDP-Galf transferases, and the three-carbon linker places the nucleotide fragment at an appropriate distance with respect to the pseudosugar moiety.

In conclusion, we report herein the first stereoselective synthesis of α -*C*-substituted 1,4-iminogalactitols by way of an expedient and versatile strategy. The α -1-*C*-allylated derivative was used as the starting material for the preparation of a new UDP-Galf analogue via a cross-metathesis coupling process. Compounds such as **16** are potential inhibitors of the enzymes involved in mycobacterial galactan biosynthesis. The elaboration of the double bond in **15** as well as the utilization of compounds **6b** and **6c** for the preparation of further new UDP-Galf mimics are now in progress, and results will be reported in due course.

Acknowledgment. Steve Nolan is warmly thanked for providing us with a sample of his catalyst. V.L. thanks the "Ministère de la Recherche et de la Technologie" for a Ph.D. fellowship. Partial funding of this research by CNRS is also gratefully acknowledged.

Supporting Information Available: Experimental procedures for the following compounds are provided (**3–5**, **6a–c**, **8a–c**, **9a,b**, **10**, and **13–16**). ^1H and ^{13}C NMR spectral data for selected compounds are reported. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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