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Diastereoselective Synthesis of Novel Iminosugar-Containing UDP-Gal*f* Mimics: Potential Inhibitors of UDP-Gal Mutase and UDP-Gal*f* Transferases

Virginie Liautard, Alphert E. Christina, Valérie Desvergnes, and Olivier R. Martin*

Institut de Chimie Organique et Analytique, CNRS & Université d'Orléans, BP 6759, 45067 Orléans, France

olivier.martin@univ-orleans.fr

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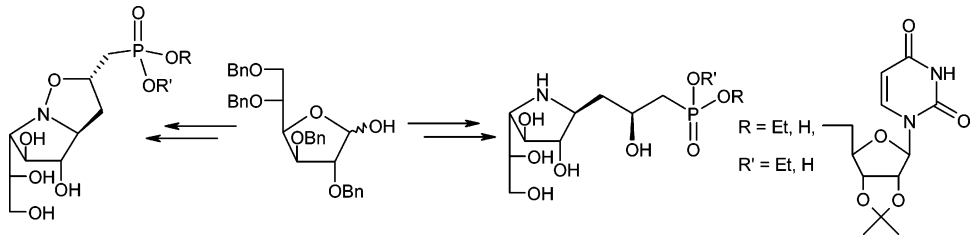

Tetra-*O*-benzyl-D-glucofuranose was converted into uridine diphosphono-β-Gal*f* mimics based on an iminosugar skeleton linked to UMP by a 2-hydroxypropyl tether. The synthesis is based on the highly regio- and stereoselective cycloaddition of an original uridin-5′-yl allylphosphonate with a 1,4-dideoxy-1,4-iminogalactitol-derived cyclic nitrone, followed by the reductive elaboration of the cycloaddition product. The resulting iminogalactose−UMP conjugates are novel sugar nucleotide mimics which could be useful as inhibitors of UDP-Gal mutase and UDP-Gal*f* transferases.

Introduction

While D-galactose is widely distributed in higher eukaryotes as a glycoside in the pyranose form (Gal*p*), the furanoid form (Gal*f*) of this hexose occurs much less frequently and is a characteristic sugar component of bacterial and fungal cell wall glycoconjugates.[1] Because of its specificity to a number of pathogenic microorganisms, the biosynthetic pathway of galactofuranose-containing glycans is becoming an important target for the development of new antibiotic agents, especially antimycobacterial agents.[2] The incorporation of D-galactofuranose into these complex glycans involves two steps: isomerization of UDP-Gal*p* into UDP-Gal*f* by UDP-Gal mutase[3] and transfer of Gal*f* into galactans by one or more UDP-Gal*f* transferases.[4] The mechanism of the remarkable ring contraction promoted by the mutase is not yet fully elucidated, despite the availability of the X-ray crystal structure of the enzyme[3] and elegant bioorganic studies by the groups of Liu,[5] Kiessling,[6] and Sinaÿ,[7] in particular. Investigations on Gal*f* transferases are still in their infancy, and only one enzyme of this family has yet been characterized.[8] Interestingly, mycobacterial galactans appear to be assembled by the action of a single enzyme.[4b,8]

* To whom correspondence should be addressed. Tel: ++ 33 2 38 49 45 81. Fax: ++ 33 2 38 41 72 81. E-mail: Olivier.Martin@univ-orleans.fr.

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10.1021/jo061130e CCC: $33.50
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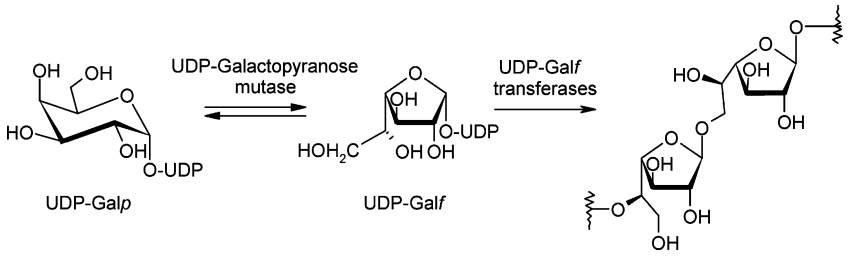
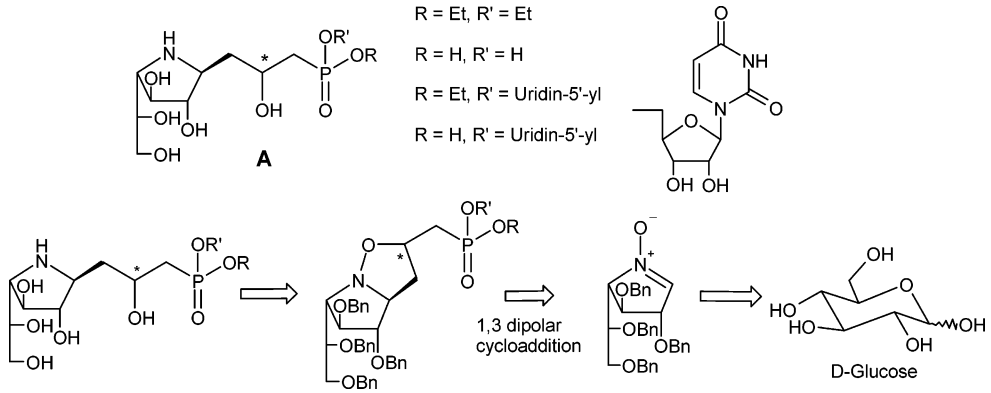
SCHEME 1. UDP-Galactofuranose Biosynthesis



SCHEME 2. Synthetic Targets and Retrosynthesis



Nevertheless, it is accepted that both of those two enzymes' families involve in their reaction an oxocarbenium-type transition state, and it is well-known that five-membered ring iminosugars are efficient mimics of putative oxocarbenium intermediates. In this context and in relation with our studies on iminosugar-containing glycoside analogues,[9] we initiated a research program on the synthesis of new UDP-Gal*f* mimics based on a 1,4-dideoxy-1,4-imino-D-galactitol entity. As potential inhibitors of these enzymatic processes,[10] such compounds may prove useful as tools for biochemical investigations and may constitute leads for the development of new families of antibiotic agents. The first and only examples of iminosugar-based analogues of UDP-Gal*f* have been reported by Fleet and co-workers;[11] in these structures, uridine is linked to the iminogalactitol core by a dipeptide-like tether.

Synthetic Design. We have recently reported the stereoselective synthesis of α-linked UDP-Gal*f* mimics containing a carbon tether between 1,4-dideoxy-1,4-iminogalactitol and UMP.[12] In this paper, we wish to report a different, efficient, and stereoselective methodology leading to mimics of *β*-linked UDP-Gal*f* illustrated by structure **A**. Our retrosynthetic analysis takes advantage of D-glucose as the chiral starting material and is based on a galactofuranose-derived cyclic nitrone as the key intermediate. The key step of our strategy is the cycloaddition of a uridine derivative carrying an allylphosphono group with the cyclic nitrone, followed by the elaboration of the resulting bicyclic system (Scheme 2).

Related iminosugar-derived cyclic nitrones are convenient precursors that have been recently exploited for the preparation of natural products, such as alexines,[13] lentiginosine,[14] and laccarin,[15] or to reach glycoside analogues, such as imino-C-disaccharides[16] and other compounds of biological interest.[17] To the best of our knowledge, two examples of cycloaddition of sugar-derived cyclic nitrones with a simple alkenylphosphonate have been reported.[18]

Results and Discussion

Preparation of Nitrone 4. Our synthesis started from tetra-*O*-benzyl-D-glucofuranose **1**. This versatile substrate was prepared in three steps from D-glucose by glycosylation with 1-octanol in the presence of $FeCl_3$, under conditions adapted from Ferrières et al.,[19,20] benzylation of the resulting glucofuranoside, and hydrolysis of the glycoside. Compound **1** was converted into the corresponding open chain O-silylated oxime (with *O*-*tert*-butyldiphenylsilylhydroxylamine[21]) under conditions described by Tamura.[15] The oxime **2** was mesylated at O-4, and the resulting *aldehydo*-glucose oxime **3** was cyclized

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(20) For improvement of the procedure, see ref 12.

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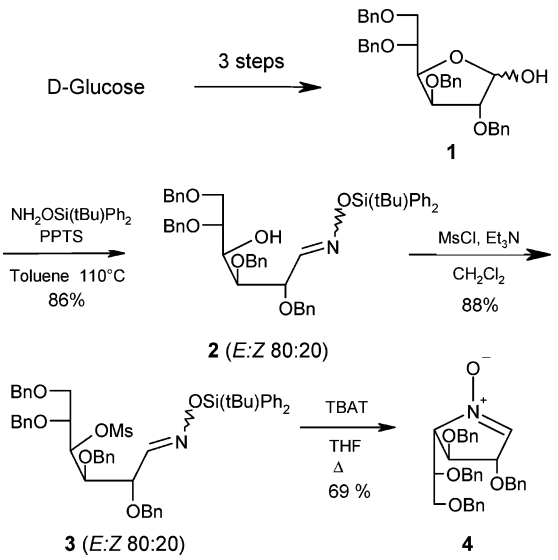
SCHEME 3



by treatment with tetrabutylammonium triphenyldifluorosiliconate[15] to give the *galacto*-configured cyclic nitrone **4** in 69% isolated yield. The reaction with TBAF gave **4** in lower yield due to the partial desilylation of the substrate. Compound **4** is the first example of a hexofuranose-derived cyclic nitrone and is a convenient starting material for the synthesis of a diversity of galactofuranoside mimics based on a 1,4-iminogalactitol skeleton. To develop a methodology for the coupling of uridine monophosphate derivatives with the iminogalactitol moiety, we investigated the [3 + 2] dipolar cycloaddition of nitrone **4** with various unsaturated phosphonates. In a first model experiment, the reaction of **4** with commercial diethyl vinylphosphonate was found to give a mixture of stereoisomers in good yield; however, the isomers could not be separated. The cycloaddition process using diethyl allylphosphonate[22] **5** as the dipolarophile model proved more interesting. After 16 h at 90 °C in tetrachloroethylene, the reaction gave a cycloadduct with a very high degree of regio- and stereoselectivity. Only one product as a single stereoisomer was observed and isolated. Indeed, compound **6** was isolated in 88% yield after chromatography (Scheme 4). The NMR data confirmed that the C−C bond formation had taken place at the terminal position of the allyl group, as predicted from previous studies on the cycloaddition of cyclic nitrones related to **4** and monosubstituted alkenes, such as, for example, allyl alcohol.[13a,b,17a,23,24]

Furthermore, the detected NOE effects in **6** (Figure 1) provided evidence for a pseudo-β configuration of the newly created C−C bond (C-3a(*S*) configuration) and an *endo* orientation of the H−C(2) proton (C-2(*S*)). From the structure of the final product thus determined, it is inferred that the cycloaddition took place highly selectively in an *exo-anti* mode, namely, by addition to the least hindered *Si* face of the nitrone (*anti* with respect to the substituent at C-2) and with the alkene substituent in the *exo* direction. The reaction of nitrone **4** with reagent **5** thus occurred with the same orientation as that of the cycloadditions of related cyclic nitrones to simple monosubstituted

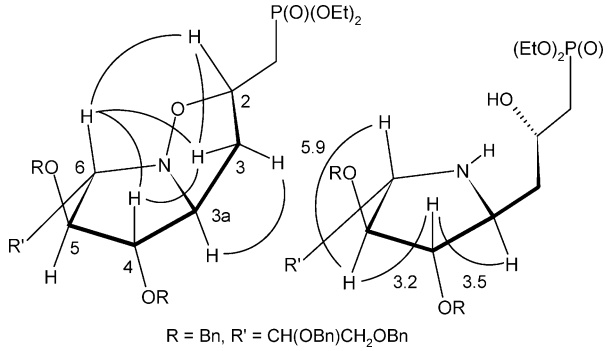


FIGURE 1. Observed NOE's in **6** and $^3J_{H,H}$ (Hz) data for **7**.

alkenes,[13a,b,23] but with a higher degree of stereoselectivity. By this process, in one step, one C−C and one C−O bond were efficiently created with a very high control of the two stereogenic centers that were generated.

The N−O bond in compound **6** could be cleaved selectively using Zn in the presence of a catalytic amount of copper(II) acetate,[25] thus affording imino-C-glycofuranosyl compound **7**. The NMR data (Figure 1) of **7** confirmed its 1,2-*trans* configuration (β-C-glycosidic linkage). Under hydrogenolytic conditions, compound **6** was converted into the novel Gal*f* pyrophosphate mimic **8** in 40% yield. A two-step sequence based on the cleavage of the N−O bond using Zn dust in acetic acid, followed by deprotection of the benzyl ethers using BCl_3[26] in dichloromethane, provided more efficiently compound **8** as hydrochloride salt[27] in 94% overall yield. Interestingly, it was possible to cleave selectively the benzyl groups without affecting the N−O bond by performing the deprotection with a large excess of BCl_3; this process provided the original and interesting pyrrolidino-isoxazolidine **9** in 85% yield. This reaction widened the scope of our investigation by increasing the structural diversity of the tether between the iminosugar skeleton and the UMP moiety.

The corresponding free phosphonic acids **10** and **11** were efficiently obtained as hydrobromides of the iminosugar by treatment of **8** and **9**, respectively, with an excess of trimethylsilyl bromide (Scheme 5).[28] These two new iminosugar phosphonates are of interest as potential inhibitors of various carbohydrate-processing enzymes.

To obtain β-linked UMP-Gal*f* mimics, the required allylphosphonate carrying a uridin-5′-yl group as ester substituent was prepared from reagent **5** by way of a very convenient, direct conversion of the phosphonate into the corresponding phosphonochloridate using oxalyl chloride (Scheme 6).[29]

The reaction of **5** with this reagent gave chiral chloride **12** in situ, which was reacted with 2′,3′-*O*-isopropylideneuridine in

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(27) The salts were obtained when no filtration on basic resin was performed in order to avoid degradation.

(28) For phosphonate deprotection using $BrSiMe_3$, see for example: (a) Vidil, C.; Morère, A.; Garcia, M.; Barragan, V.; Hamdaoui, B.; Rochefort, H.; Montero, J.-L. *Eur. J. Org. Chem.* **1999**, 447−450. (b) Ladame, S.; Fauré, R.; Denier, C.; Lakhdar-Ghazal, F.; Wilson, M. *Org. Biomol. Chem.* **2005**, *3*, 2070−2072.

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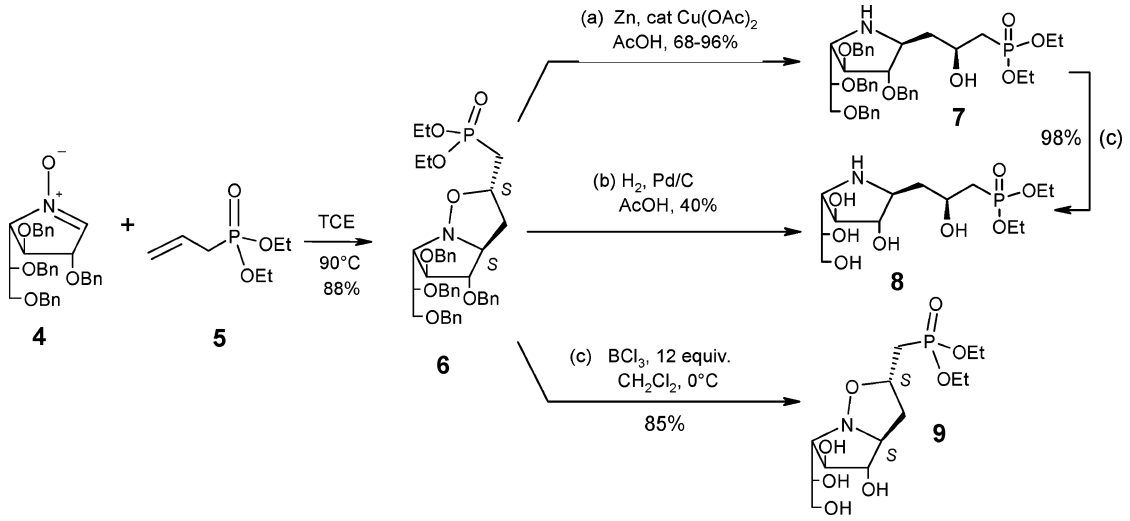
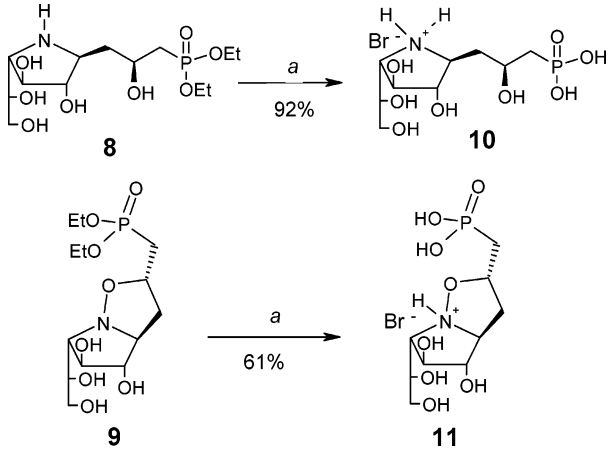
SCHEME 4

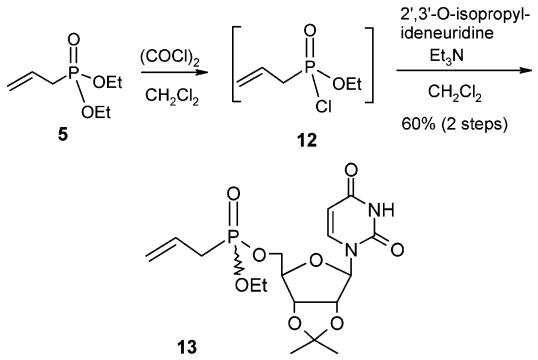


SCHEME 5[a]



[a] Conditions: $BrSiMe_3$ (10 equiv), CH_3CN, 4 h.

SCHEME 6



CH_2Cl_2 in the presence of triethylamine. This provided quickly and efficiently the ethyl, uridin-5′-yl allylphosphonate **13** as a mixture of P-diastereomers in 60% yield after purification by chromatography (two steps).

The cycloaddition of nitrone **4** with **13** was performed under the same conditions as with **5** and afforded the expected coupling product **14** in an isolated yield of 80% (Scheme 7).

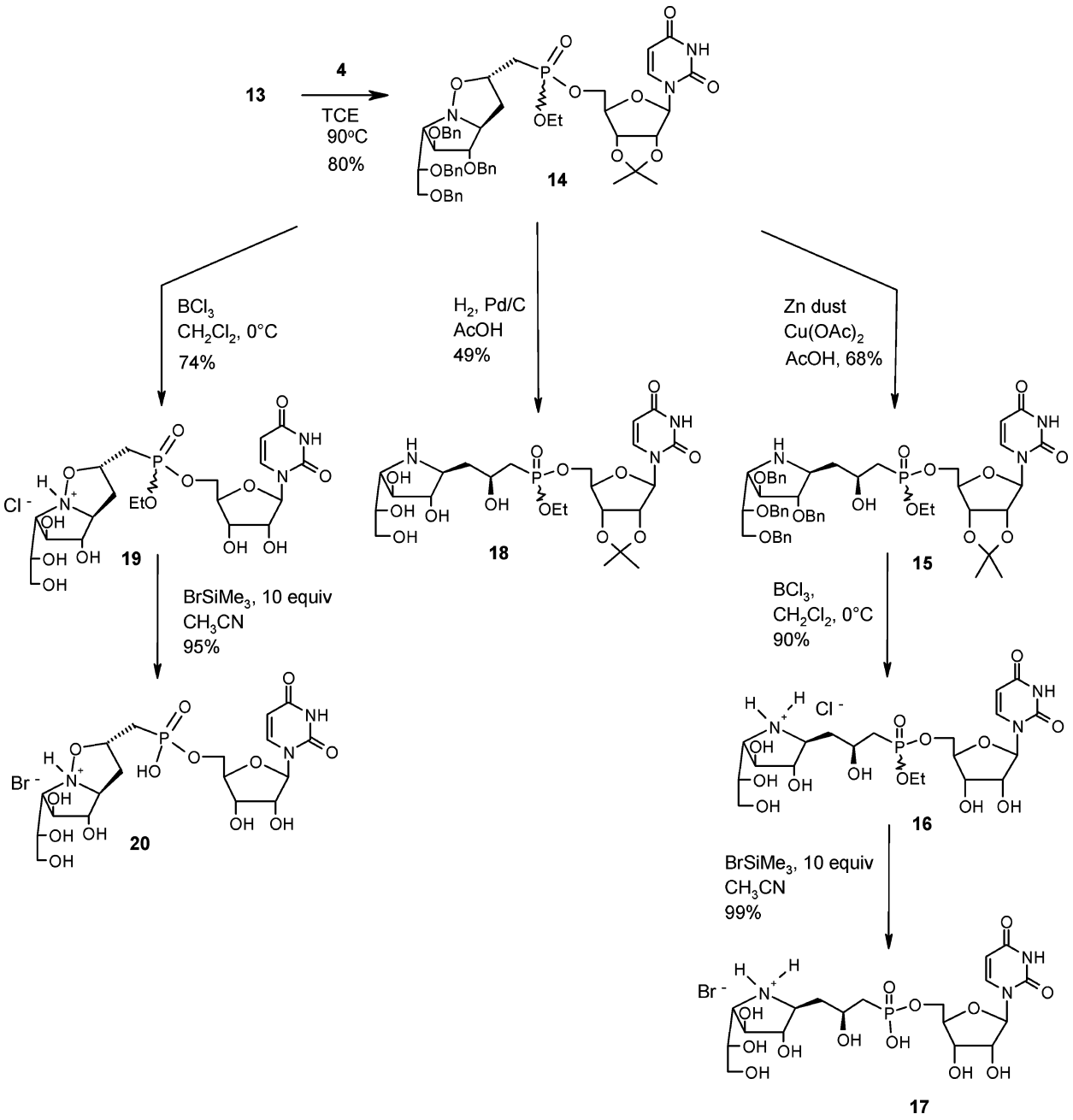
Although they are complicated by the presence of diastereomers at phosphorus (1:1 ratio), the NMR spectra of **14** demonstrated clearly that the cycloaddition took place with the same regio- and stereoselectivity as the reaction of model allylphosphonate **5**. Separation of the diastereomers proved impossible, and compound **14** was characterized as the mixture of P-epimers. We first investigated the deprotection of **14** by hydrogenolysis, a reaction that afforded the novel UMP-imino-1,4-galactitol conjugate **18**. This compound was, however, difficult to isolate because of degradation during the purification step; further deprotection by cleavage of the isopropylidene group was not attempted. The conditions developed for the elaboration of diethylphosphonate **6** proved also successful for **14**: the two-step sequence[30] (Zn/AcOH then BCl_3) provided efficiently the ethyl uridinyl phosphonate **16** by way of **15**. Treatment of **16** with an excess $BrSiMe_3$ gave, after purification by reverse-phase flash chromatography, the original β-linked UDP-Gal*f* mimic **17** in excellent yield. Compounds **16** and **17** are significant in that they contain a uridine moiety at the same distance with respect to the sugar unit as uridine in UDP-Gal*f*, one phosphate being replaced by an isosteric 2-hydroxypropyl group; the presence of the OH function in this group is important as it provides, with the phosphate present, a bidentate ligand for possible complexation of the sugar nucleotide analogue with the divalent metal cation that may be present in the active site of the UDP-Gal*f* transferases.

As described in the diethylphosphonate series, deprotection of **14** using only BCl_3 provided the original bicyclic analogue **19**; selective cleavage of the ethyl phosphonate group could also be performed in this case by reacting **19** with excess $BrSiMe_3$. This provided the unusual, bicyclic UDP-Gal*f* mimic **20**, in which the pyrophosphate-like tether and the uridine moiety are in a constrained conformation. Biological investigations of compounds **16**, **17**, **19**, and **20** are in progress, and the results will be reported in due course.

In conclusion, the 1,3-dipolar cycloaddition of an iminogalactitol-derived nitrone with an original uridin-5′-yl allylphosphonate provided an efficient approach to new UDP-Gal*f* analogues incorporating an iminogalactitol moiety and UMP. The tactical combination of successive deprotection steps provided an efficient and practical access to a diversity of novel functionalized sugar nucleotide mimics. The resulting compounds are potential inhibitors of UDP-Gal mutase and of UDP-

(30) This two-step sequence could be performed without further purification of **15** to provide **16** in 78% yield.

SCHEME 7



Gal*f* transferases, and their biological investigation should help us better understand these two enzyme families.

Experimental Section

(*E*,*Z*)-2,3,5,6-Tetra-*O*-benzyl-*aldehydo*-D-glucose *O*-(*t*-butyldiphenylsilyl)oxime (2). To a solution of 2,3,5,6-tetra-*O*-benzyl-D-glucofuranose[19,20] (10 g, 20 mmol) in dry toluene (10 mL/g) (freshly distilled over CaH_2) were added $MgSO_4$ (250 mg), *O*-(*tert*-butyldiphenylsilyl)hydroxylamine[21] (10 g, 37 mmol, 1.85 equiv), and a catalytic amount of PPTS (pyridinium *p*-toluenesulfonate). The reaction mixture was stirred for 30 min at 110 °C and cooled to rt. The solids were removed by filtration, and water (50 mL) was added. The filtrate was extracted with CH_2Cl_2 (3 × 50 mL), and the organic layers were dried with Na_2SO_4 then filtered and concentrated under reduced pressure. The resulting colorless residue was submitted to flash chromatography on silica gel (petroleum ether/AcOEt 95/5 to 85/15) to afford compound **2** (13.65 g, 86%) as a colorless oil. The ^{1}H NMR spectrum indicates the presence of a *E*/*Z* mixture (*E*/*Z* ∼ 4:1 ratio). ^{1}H NMR (500 MHz, $CDC1_3$) (M is major isomer, m is minor isomer): δ 7.83 M (d, 0.8 H, J = 8.3 Hz, H1), 7.67−7.72 (m, 4 H, H_{Ar}), 7.12−7.36 (m, 26.2 H, H_{Ar} + H1m), 5.38 m (t, 0.2 H, J = 6.6 Hz, H2), 4.80 and 4.42 m (2 d, 2 × 0.2 H, J = 11.2 Hz), 4.66 (m, 2 H, OCH_2Ph), 4.52 (m, 3 H, OCH_2Ph), 4.29 (m, 3.4 H, OCH_2Ph + H2M), 4.09 m (br d, 0.2 H, J = 6.5 Hz, H3), 3.96 M (dd, 0.8 H, J = 6.5, 0.8 Hz, H3), 3.91 M + m (m, 1 H, H4), 3.83 (dd, 1 H, J = 10.3, 2.6 Hz, H6aM + H6am), 3.71 m (m, 0.2 H, H6b), 3.66 (m, 1 H, H6bM + H5m), 3.61 M (m, 0.8 H, H5), 2.95 m (d, 0.2 H, J = 6.9 Hz, OH), 2.54 M (d, 0.8 H, J = 8.5 Hz, OH), 1.12 M (s, 6.8 H, ^{t}Bu), 1.11 m (s, 2.2 H, ^{t}Bu). ^{13}C NMR (125 MHz, $CDC1_3$): δ 154.9 m (C1), 153.9 M (C1), 138.1 m + M (2Cq_{Ar}), 138.0 m (Cq_{Ar}), 137.9 M (Cq_{Ar}), 137.8 m (Cq_{Ar}), 137.6 M (Cq_{Ar}), 137.2 M (Cq_{Ar}), 137.1 m (Cq_{Ar}), 135.2 M (2CH_{Ar}), 135.2 m (CH_{Ar}), 135.1 m (CH_{Ar}), 133.1 M (Cq_{Ar}), 133.0 M (Cq_{Ar}), 132.7 m (2Cq_{Ar}), 129.5 m (CH_{Ar}), 129.4 M (CH_{Ar}), 127.2−128.2 M + m (CH_{Ar}), 77.7 M (C5), 77.5 m (C5), 77.0 m

(C3), 76.6 M (C3), 76.3 M (C2), 74.2 m (O*C*H$_2$Ph), 73.2 M (O*C*H$_2$-Ph), 73.1 M (O*C*H$_2$Ph), 73.1 m (O*C*H$_2$Ph), 72.5 m (C2), 72.0 m (O*C*H$_2$Ph), 71.6 M (O*C*H$_2$Ph), 71.4 m (O*C*H$_2$Ph), 70.6 M (O*C*H$_2$-Ph), 70.1 m (C4), 69.9 M (C6), 69.6 m (C6), 69.6 M (C4), 26.9 m (^{t}Bu), 26.8 M (^{t}Bu). HRMS (ESI) calcd for $[M + Na]^+$: 816.3696. Found: 816.3691. Anal. Calcd for $C_{50}H_{55}NO_6Si$: C, 75.63; H, 6.98; N, 1.76. Found: C, 75.49; H, 7.19; N, 1.77.

(*E*,*Z*)-2,3,5,6-Tetra-*O*-benzyl-4-*O*-methanesulfonyl-*aldehydo*-D-glucose *O*-(*t*-butyldiphenylsilyl)oxime (3). To a solution of oxime **2** (4 g, 5 mmol) in dry CH_2Cl_2 (60 mL) was added dropwise Et_3N (906 μL, 0.065 mol, 1.3 equiv) at rt. The mixture was stirred for 30 min at rt, and then methanesulfonyl chloride (503 μL, 0.065 mol, 1.3 equiv) was added. After having been stirred for 16 h at rt, the reaction mixture was concentrated under reduced pressure. The residue was submitted to flash chromatography on silica gel (petroleum ether/AcOEt 85/15) which afforded mesylate **3** (3.83 g, 88%) as a colorless syrup (*E*/*Z* mixture). ^{1}H NMR (500 MHz, CDC1$_3$) (M is major isomer, m is minor isomer): δ 7.70 and 7.2−7.36 (m, 31 H, H1, H$_{Ar}$), 5.37 m (dd, 0.2 H, J = 8.3, 2 Hz, H4), 5.26 M (dd, 0.8 H, J = 7.6, 2.3 Hz, H4), 5.00 m (dd, 0.2 H, J = 5.6, 2.7 Hz, H2), 4.80 M + m (2d, 1 H, OC*H*$_2$Ph), 4.58 (2d, 0.4 H, OC*H*$_2$Ph), 4.38−4.49 (m, 2.8 H, OC*H*$_2$Ph), 4.23−4.33 (m, 3 H, OC*H*$_2$Ph), 4.11 (m, 1.8 H, OC*H*$_2$Ph, H2M, H3m), 3.85 M (dd, 0.8 H, J = 7.6, 3.6 Hz, H3), 3.73 m (dt, 0.2 H, J = 6, 6, 1.9 Hz, H5), 3.59 (m, 1.8 H, H5M + H6b), 3.45 (m, 1 H, H6a), 2.88 m (s, 0.6 H, SO$_2$C*H*$_3$), 2.86 M (s, 2.4 H, SO$_2$C*H*$_3$), 1.15 m (s, 1.7 H, ^{t}Bu), 1.13 M (s, 7.3 H, ^{t}Bu). ^{13}C NMR (125 MHz, CDC1$_3$): δ 155.5 m (C1), 154.0 M (C1), 137.7 m, 137.6 m, 137.5 M, 137.2 M, 137.1, 136.6, and 136.2 m (Cq$_{Ar}$'s), 135.5 M (CH$_{Ar}$), 135.5 M (CH$_{Ar}$), 135.4 m (CH$_{Ar}$), 135.3 m (CH$_{Ar}$), 133.1 M, 133.0 M, 132.8 m, and 132.7 m (Cq$_{Ar}$'s), 129.9−127.4 (CH$_{Ar}$), 82.6 m (C4), 82.5 M (C4), 78.3 M (C3), 77.3 m (C3), 76.9 m (C5), 76.4 M (C5), 75.4 m (O*C*H$_2$Ph), 75.1 M (C2), 75.0 M (O*C*H$_2$Ph), 73.0 M (O*C*H$_2$Ph), 72.9 m (CH$_2$), 72.2 m (CH$_2$), 72.1 M (O*C*H$_2$Ph), 71.8 m (CH$_2$), 71.0 m (C2), 70.5 M (O*C*H$_2$Ph), 68.8 m (CH$_2$), 68.1 M (C6), 38.8 M (SO$_2$*C*H$_3$), 38.7 m (SO$_2$*C*H$_3$), 25.2 m (^{t}Bu), 26.9 M (^{t}Bu). HRMS (ESI) calcd for $[M + Na]^+$: 894.3472. Found: 894.3480. Anal. Calcd for $C_{51}H_{57}NO_8SSi\cdot H_2O$: C, 68.81; H, 6.68; N, 1.57. Found: C, 69.27; H, 6.77; N, 1.57.

Internal Nitrone of 2,3,5,6-Tetra-*O*-benzyl-4-deoxy-4-hydroxylamino-*aldehydo*-D-galactose [(3*S*,4*S*,5*S*)-3,4-dibenzyloxy-5-[(1*S*)-1,2-dibenzyloxyethyl]-1-pyrroline *N*-oxide] (4). Oxime **3** (4.62 g, 5.30 mmol) as a mixture of *E*,*Z*-isomers was dissolved in dry tetrahydrofuran (30 mL); 4 Å molecular sieves and tetrabutylammonium triphenyldifluorosilicate (3.43 g, 6.36 mmol, 1.2 equiv) were added, and the mixture was stirred for 45 min at reflux temperature. The solids were then removed by filtration, and the filtrate was concentrated. Pure nitrone **4** (1.44 g, 2.68 mmol, 51%) was obtained as a white solid after purification by flash chromatography on silica gel (EtOAc/petroleum ether, 35/65 to 50/50). $[\alpha]^{25}_D$ + 42.9 (c = 1.0, MeOH). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.22−7.31 (m, 20 H, H$_{Ar}$), 6.85 (narrow m, 1 H, H1), 4.82 (d, 1 H, J = 12 Hz), 4.67 (d, 1 H, J = 11.5 Hz, OC*H*$_2$Bn), 4.56 (narrow t, 1 H, J = 1.6 Hz, H2), 4.41−4.52 (m, 6 H, 3 OC*H*$_2$Ph), 4.30 (br q, 1 H, H5), 4.25 (narrow m, 1 H, H3), 4.21 (m, 1 H, H4), 3.79 (m, 2 H, 2H6). ^{13}C NMR (125 MHz, CDCl$_3$): δ 138.2, 137.8, 137.1 (Cq$_{Ar}$), 133.0 (C1), 127.5−128.5 (*C*H$_{Ar}$), 82.9, 79.9, 78.8, 75.0, 73.3, 73.0, 71.6, 71.5, 70.2. IR (NaCl): 3425, 3031, 2867, 1577, 1273, 1096, 1028, 911, 817, 738, 698, 674 cm^{-1}. HRMS (ESI) calcd for $[M + Na]^+$: 560.2413. Found: 560.2411. Anal. Calcd for $C_{34}H_{35}NO_5$: C, 75.95; H, 6.56; N, 2.61. Found: C, 75.62; H, 6.60; N, 2.51.

Diethyl (2*S*,3a*S*,4*S*,5*S*,6*S*)-4,5-Dibenzyloxy-6-[(1*S*)-1,2-dibenzyloxyethyl]hexahydropyrrolo[1,2-b]isoxazole-2-methylphosphonate (6). To a solution of nitrone **4** (200 mg, 372 μmol) in tetrachloroethylene (1.5 mL) was added diethyl allylphosphonate **5** (133 mg, 745 μmol, 2 equiv). The mixture was stirred overnight at 50 °C. After evaporation of the solvent, the crude mixture was submitted to flash chromatography on silica gel (EtOAc/petroleum ether 40/60 to 65/35) which afforded cycloaddition product **6** (234 mg, 327 μmol, 88%) as a slightly yellow oil. $[\alpha]^{25}_D$ +11.4 (c = 1.0, MeOH). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.21−7.33 (m, 20 H, H$_{Ar}$), 4.79 (d, 1 H, J = 12.0 Hz), 4.51−4.58 (m, 6 H), 4.36 (d, 1 H, J = 12.0 Hz) (4 OC*H*$_2$Ph), 4.31 (m, 1 H, H2), 4.06 (m, 5 H, 2 OC*H*$_2$CH$_3$, H5), 3.89 (t, 1 H, J = 6.0 Hz, H4), 3.82 (m, 3 H, C*H*OBn−C*H*$_2$OBn), 3.74 (m, 1 H, H3a), 3.31 (dd, 1 H, J = 1.0, 7.0 Hz, H6), 2.33 (ddd, 1 H, J = 3.5, 6, 12.5, H3$_B$), 2.18 (m, 2 H, H3$_A$, CH$_B$P), 1.93 (ddd, 1 H, J = 9, 15.0, 18.5 Hz, CH$_A$P), 1.30, 1.29 (2 t, 6 H, OCH$_2$C*H*$_3$). ^{13}C NMR (125 MHz, CDCl$_3$): δ 138.6, 138.4, 138.0, 137.7 (Cq$_{Ar}$), 127.3−128.4 (CH$_{Ar}$), 87.5 (C4), 81.9 (C5), 76.3, 73.3, 72.9, 72.5, 71.9 (2C) (4 OCH_2Ph, *C*HOBn, *C*H$_2$-OBn), 70.5 (C2), 69.9 (C6), 67.7 (C3a), 61.7 (d, $J_{C,P}$ = 6.3 Hz), 61.6 (d, $J_{C,P}$ = 6.3 Hz) (OCH$_2$CH$_3$), 41.1 (d, $J_{C,P}$ = 4.6 Hz, C3), 30.0 (d, $J_{C,P}$ = 138.8 Hz, CH$_2$P), 16.3 (d, $J_{C,P}$ = 5.9 Hz, OCH$_2$*C*H$_3$). ^{31}P NMR (202 MHz, CDCl$_3$): δ 26.69. IR (neat): 3086, 3061, 3029, 2979, 2907, 2866, 1496, 1453, 1391, 1365, 1251, 1209, 1158, 1098, 1055, 1027, 963, 915, 825, 738, 698 cm^{-1}. HRMS (ESI) calcd for $[M + H]^+$: 716.3352. Found: 716.3349. Calcd for $[M + Na]^+$: 738.3172. Found: 738.3176. Anal. Calcd for $C_{41}H_{50}NO_8P\cdot H_2O$: C, 67.11; H, 7.14; N, 1.91. Found: C, 67.21; H, 7.12; N, 1.84.

(1*S*)-2,3,5,6-Tetra-*O*-benzyl-1,4-dideoxy-1-C-[(2*S*)-3-diethoxyphosphoryl-2-hydroxypropyl]-1,4-imino-D-galactitol (7). Zinc dust (31 mg, 0.48 mmol) was added to a solution of copper(II) acetate (0.1 mg) in glacial acetic acid (0.5 mL) under argon atmosphere, and the mixture was stirred at rt for 10 min until the color disappeared. Compound **6** (30 mg, 0.042 mmol) in glacial acetic acid (0.7 mL) and water (0.3 mL) were added successively, and the reaction mixture was heated at 70 °C for 1 h. After cooling to rt, EDTA (sodium salt, 0.1 g) was added, and the mixture was stirred for 10 min, then made alkaline to pH 10 by addition of 3 N aqueous NaOH. The resulting solution was extracted with chloroform (3 × 10 mL), and the combined organic phases were concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (AcOEt/petroleum ether 70/30 to 100% AcOEt) to afford the desired galactitol **7** (18 mg, 0.025 mmol, 62%) as a colorless liquid. $[\alpha]^{25}_D$ −26 (c = 0.64, MeOH). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.27−7.32 (m, 20 H, H$_{Ar}$), 4.72 (d, 1 H, J = 11.5 Hz, CH$_2$Ph), 4.47−4.55 (m, 5 H, CH$_2$-Ph), 4.40, 4.38 (2d, 2 H, CH$_2$Ph), 4.25 (m, 1 H, H8), 4.09 (m, 4 H, OC*H*$_2$CH$_3$), 3.88 (dd, 1 H, J = 3.0, 6 Hz, H3), 3.81 (t, 1 H, J = 3.5 Hz, H2), 3.74 (m, 1 H, H5), 3.64 (dd, 1 H, H6$_B$), 3.59 (dd, 1 H, H6$_A$), 3.50 (m, 1 H, H1), 3.27 (dd, 1 H, J = 6, 4 Hz, H4), 1.88−2.11 (m, 3 H, H7$_B$, 2H9), 1.68 (m, 1 H, H7$_A$), 1.30 (t, 3 H, OCH$_2$C*H*$_3$), 1.29 (t, 3 H, J = 7.5 Hz, OCH$_2$C*H*$_3$). ^{13}C NMR (125 MHz, CDCl$_3$): δ 138.0 (Cq$_{Ar}$), 127.6−127.4 (CH$_{Ar}$), 88.8 (C2), 85.5 (C3), 75.8 (C5), 73.5, 73.0, 72.0, 71.8, 71.7 (4 OCH_2Ph, C6), 65.6 (C8), 63.0 (C4), 61.5−62.0 (OCH_2CH$_3$), 59.4 (C1), 37.3 (d, $J_{C,P}$ = 10.4 Hz, C7), 33.5 (d, $J_{C,P}$ = 135.8 Hz, C9), 16.5 (OCH$_2$*C*H$_3$), 16.4 (OCH$_2$*C*H$_3$). ^{31}P NMR (202 MHz, CDCl$_3$): δ 29.16. IR (NaCl): 3395, 2923, 1719, 1599, 1496, 1453, 1209, 1156, 1095, 1027, 965, 737, 698, 669. HRMS (ESI) calcd for $[M + H]^+$: 718.3509. Found: 718.3522. Calcd for $[M + Na]^+$: 740. 3328. Found: 740.3328. Anal. Calcd for $C_{41}H_{52}NO_8P\cdot H_2O$: C, 66.92; H, 7.40; N, 1.90. Found: C, 66.64; H, 7.30; N, 1.95.

(1*S*)-1,4-Dideoxy-1-C-[(2*S*)-3-diethoxyphosphoryl-2-hydroxypropyl]-1,4-imino-D-galactitol (8). To a solution of phosphonate **7** (117 mg, 163 μmol) in acetic acid (1.0 mL) was added a catalytic amount of palladium on active charcoal (10%), and the mixture was stirred overnight at rt under hydrogen atmosphere. The solids were then removed by filtration and rinsed with CH_2Cl_2. After evaporation of the solvents, the crude product was purified by flash chromatography on silica gel (MeOH/CH_2Cl_2/pyridine 25/74/1). This afforded the desired iminogalactitol **8** (23 mg, 64 μmol, 39%) as a yellow oil. $[\alpha]^{25}_D$ −21.3 (c = 1.0, MeOH). ^{1}H NMR (500 MHz, CD$_3$OD): δ 4.08−4.14 (m, 5 H, H8, 2 OC*H*$_2$CH$_3$), 3.89 (t, 1 H, J = 7 Hz, H3), 3.70 (br q, 1 H, H5), 3.64 (t, 1 H, H2), 3.61 (dd, 1 H, J = 4.5, 11 Hz, H6$_B$), 3.55 (dd, 1 H, J = 6, 11.5 Hz,

$H6_A$), 3.14 (dt, 1 H, J = 4.5, 8.0, 8.0 Hz, H1), 2.97 (dd, 1 H, J = 7.5, 4.5 Hz, H4), 2.05 (higher order signal, 2 H, CH_2P), 1.79, (m, 2 H, 2H7), 1.32 (m, 6 H, 2 OCH_2CH_3). ^{13}C NMR (125 MHz, CD_3OD): δ 82.5 (C2), 79.4 (C3), 72.4 (C5), 65.6 (d, $J_{C,P}$ = 3.1 Hz, C8), 65.5 (C6), 64.0 (C4), 63.4 (d, $J_{C,P}$ = 6.3 Hz, $POCH_2CH_3$), 63.2 (d, $J_{C,P}$ = 6.5 Hz, $POCH_2CH_3$), 59.8 (C1), 42.2 (d, $J_{C,P}$ = 12.0 Hz, C7), 34.8 (d, $J_{C,P}$ = 138 Hz, C9), 16.7 (d, $J_{C,P}$ = 6.1 Hz, $POCH_2CH_3$). ^{31}P NMR (202 MHz, CD_3OD): δ 29.91. HRMS (ESI) calcd for $[M + H]^+$: 358.1631. Found: 358.1625.

BCl_3 Debenzylation of 7 (General Procedure A). To a solution of phosphonate **7** (110 mg, 0.154 mmol) in dry CH_2Cl_2 (3 mL) was added at 0 °C a 1 M BCl_3 solution in hexane (1.8 mL, 1.8 mmol, 12 equiv). The medium was stirred overnight at 0 °C, and then the solid formed was dissolved by addition of MeOH (20 mL) and a few drops of water. The reaction mixture was then concentrated under reduced pressure. Purification of the crude product by flash chromatography on C18-reverse phase silica gel (H_2O/MeOH 1/0 to 7/3) provided the colorless oily compound **8** as its hydrochloride salt (52.7 mg, 87%). $[\alpha]^{25}_D = -30$ (c = 0.82, MeOH). ^1H NMR (250 MHz, CD_3OD): δ 4.31−4.20 (m, 1 H, H8), 4.19−4.03 (m, 5 H, H3, CH_2CH_3), 3.95 (q, 1 H, J = 4 Hz, H5), 3.86 (dd, 1 H, J = 6.7, 8.2 Hz, H2), 3.62−3.76 (m, 2 H, H6), 3.46−3.58 (m, 2 H, H4 and H1), 2.05−2.12, (m, 4 H, H9 and H7), 1.34 (t, 6 H, J = 7.1 Hz, CH_3). ^{13}C NMR (62.5 MHz, CD_3OD): δ 79.1 (C2), 76.8 (C3), 69.0 (C5), 65.2 (C6), 65.0 (C4), 64.8 (d, $J_{C,P}$ = 2.3 Hz, C8), 63.5 (d, $J_{C,P}$ = 6.4 Hz, $POCH_2CH_3$), 63.4 (d, $J_{C,P}$ = 6.6 Hz, $POCH_2CH_3$), 60.7 (C1), 37.9 (d, $J_{C,P}$ = 10.6 Hz, C7), 34.1 (d, $J_{C,P}$ = 137 Hz, C9), 16.7 (d, $J_{C,P}$ = 6 Hz, $POCH_2CH_3$). ^{31}P NMR (202 MHz, CD_3OD): δ 28.19. HRMS (ESI) calcd for $[M + H]^+$: 358.1631. Found: 358.1629.

Diethyl (2*S*,3a*S*,4*S*,5*S*,6*S*)-4,5-Dihydroxy-6-[(1*S*)-1,2-dihydroxyethyl]hexahydropyrrolo[1,2-b]isoxazole-2-methylphosphonate (9). Compound **9** was obtained using the general procedure A starting from compound **6** (89 mg, 0.124 mmol). After stirring overnight at 0 °C, the solid crude product was dissolved with MeOH (5 mL), and three successive evaporations of the solvents (3 × 5 mL) were performed. Then, the residue was dissolved with MeOH and water (5 mL, 20/1), and the solution was quickly filtered through ion-exchange resin (Dowex 1X8, OH^- form) which was then washed with MeOH (20 mL × 2) and water (10 mL). Purification of the crude product by flash chromatography on C18-reverse phase silica gel (H_2O/MeOH 1/0 to 7/3) provided the colorless oily compound **9** (37.6 mg, 85%). $[\alpha]^{25}_D = +24$ (c = 9.3, MeOH). ^1H NMR (500 MHz, CD_3OD): δ 4.30 (m, 1 H, H2), 4.08 (m, 4 H, CH_2CH_3), 3.87 (t, 1 H, J = 8 Hz, H7), 3.76−3.73 (m, 2 H, H4 and H5), 3.66 (m, 2 H, H8), 3.46 (t, 1 H, J = 8 Hz, H3a), 3.02 (d, 1 H, J = 8.5 Hz, H6), 2.40−2.37 (dd, 1 H, J = 3.5, 12.5 Hz, $H3_B$), 2.27−2.12 (m, 2 H, CH_2P), 2.08−2.04 (m, 1 H, $H3_A$), 1.34 (t, 6 H, J = 7.5 Hz, CH_3CH_2). ^{13}C NMR (62.5 MHz, CD_3OD): δ 81.8 (C4 or C5), 75.5 (C7), 71.6 (C6), 72.2 (C2), 71.3 (C4 or C5), 69.5 (C3a), 65.5 (C8), 63.6 (d, J_{C-P} = 6.4 Hz, CH_2CH_3), 63.4 (d, J_{C-P} = 6.5 Hz, CH_2CH_3), 42.0 (d, J_{C-P} = 8.9 Hz, C3), 29.3 (d, J_{C-P} = 140 Hz, CH_2P), 16.7 (d, J_{C-P} = 6.18 Hz, CH_3CH_2). ^{31}P NMR (202 MHz, CD_3OD): δ 28.17. HRMS (ESI) calcd for $[M + Na]^+$: 378.1294. Found: 378.1290. Calcd for $[M + K]^+$: 394.1033. Found: 394.1004.

Deprotection of 8: General Procedure B for the Preparation of Free Phosphonic Acids. (1*S*)-1,4-Dideoxy-1-[(2*S*)-3-phosphono-2-hydroxypropyl]-1,4-imino-D-galactitol (10). To a solution of phosphonate **8** (78 mg, 0.2 mmol) in dry MeCN (3 mL) was added $BrSiMe_3$ (0.264 mL, 2 mmol, 10 equiv) at rt. The mixture was stirred for 2 days; the mixture was then diluted with MeOH (15 mL) and concentrated under reduced pressure. The dilution and evaporation process was repeated twice. The residue was then taken up with water and the mixture extracted with CH_2Cl_2 to remove traces of less polar organic compounds. The aqueous phase was concentrated under reduced pressure. Chromatography of the crude product on C18-reverse phase silica gel (H_2O/MeOH 1/0 to 8/2) provided compound **10** (hydrobromide) (70 mg, 92%) as a white foam. $[\alpha]^{25}_D$ −9 (c =1.27, MeOH). ^1H NMR (500 MHz, CD_3OD): δ 4.28−4.22 (m, 1 H, H8), 4.09−4.06 (m, 1 H, H3), 3.96 (dd, 1 H, J = 4.5, 8.5 Hz, H5), 3.92−3.88 (m, 1 H, H2), 3.73 (dd, 1 H, J = 4, 11.5 Hz, $H6_B$), 3.67 (dd, 1 H, J = 4, 11.5 Hz, $H6_A$), 3.58−3.56 (m, 1 H, H4), 3.52−3.49 (dd, 1 H, J = 4, 8 Hz, H1), 2.23−2.17, (m, 1 H, $H7_B$), 2.10−2.04 (m, 3 H, H9 and $H7_A$). ^{13}C NMR (125 MHz, CD_3OD): δ 79.0 (C2), 76.8 (C3), 69.0 (C5), 65.3, 65.2, 64.9 (C6 or C4 or C8), 60.9 (C1), 37.7 (d, $J_{C,P}$ = 8.8 Hz, C7), 36.2 (d, $J_{C,P}$ = 135 Hz, C9). ^{31}P NMR (202 MHz, CD_3OD): δ 25.29. HRMS (ESI) calcd for $[M + H]^+$: 302.1005. Found: 302.0995. Calcd for $[M + Na]^+$: 324.0824. Found: 324.0814.

Diethyl (2*S*,3a*S*,4*S*,5*S*,6*S*)-4,5-Dihydroxy-6-[(1*S*)-1,2-dihydroxyethyl]hexahydropyrrolo[1,2-b]isoxazole-2-methylphosphonate (11). Compound **11** was prepared by general procedure B starting from compound **9** (70 mg, 0.197 mmol). After 4 h stirring, the reaction medium was treated and the product purified under the same conditions as described above (preparation of **10**) to provide **11** (hydrobromide) as a brown oily compound (46 mg, 61%). ^1H NMR (500 MHz, CD_3OD): δ 4.96 (m, 1 H, H2), 4.18 (m, 1 H, H3a), 4.09−4.07 (m, 2 H, H4 and H5), 3.97−3.94 (m, 1 H, H7), 3.80−3.78 (m, 1 H, H6), 3.71 (dd, 1 H, J = 5.5, 11.5 Hz, $H8_B$), 3.65 (dd, 1 H, J = 6, 11.5 Hz, $H8_A$), 2.84 (dd, 1 H, J = 3.5, 13 Hz, $H3_B$), 2.42 (td, 1 H, J = 9, 13.5 Hz, $H3_A$), 2.32 (ddd, 1 H, J = 5.5, 15, 20 Hz, $CH_{2B}P$), 2.18−2.10 (m, 1 H, $CH_{2A}P$). ^{13}C NMR (62.5 MHz, CD_3OD): δ 80.1 (C2), 78.5 (C4 or C5), 76.4 (C6), 76.0 (C4 or C5), 73.5 (C3a), 68.2 (C7), 63.9 (C8), 38.6 (d, J_{C-P} = 5.7 Hz, C3), 31.2 (d, J_{C-P} = 135 Hz, CH_2P). ^{31}P NMR (202 MHz, CD_3OD): δ 20.99. HRMS (ESI) calcd for $[M + Na]^+$: 322.0668. Found: 322.0668.

Ethyl (2′,3′-*O*-Isopropylideneuridin-5′-yl)allylphosphonate (13). Diethyl allylphosphonate **5** (200 mg, 1.12 mmol) was allowed to react with oxalyl chloride (490 μL, 5.62 mmol, 5 equiv) in anhydrous CH_2Cl_2 (5 mL) under argon for 2 days. The conversion can be monitored by TLC (eluant: EtOAc containing a few drops of AcOH). For this purpose, the bottom of the TLC plate spotted with the reaction mixture was dipped into water containing a few drops of triethylamine and dried before development. When TLC showed no more starting material, the solvent was removed under vacuum along with the excess oxalyl chloride. The residue was dissolved in anhydrous CH_2Cl_2, and 2′,3′-*O*-isopropylideneuridine (684 mg, 2.41 mmol, 2.15 equiv) and triethylamine (344 μL, 2.46 mmol, 2.2 equiv) were added. The reaction mixture was stirred at 40 °C for 8 h and at rt for 2 days. Subsequently, the resulting emulsion was treated with water, and the aqueous phase was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated to afford the crude phosphonate **13**, which was purified by flash chromatography on silica gel (EtOAc). This provided the expected product (253 mg, 607 μmol) as a mixture of P*-diastereomers in 54% yield for the two steps. ^1H NMR (250 MHz, $CDCl_3$): δ 10.00 (br s, 1 H, H3), 7.43 and 7.38 (2 d, 1 H, H6), 5.76 (m, 3 H, H1′, H5, $CH{=}CH_2$), 5.23 (m, 2 H, $CH{=}CH_2$), 4.91 (m, 1 H, H2′), 4.86 (m, 1 H, H3′), 4.35 (m, 1 H, H4′), 4.28 (m, 2 H, 2H5′), 4.14 (m, 2 H, OCH_2CH_3), 2.67 (dd, 2 H, $J_{H,H}$ = 7.3 Hz, $J_{H,P}$ = 22.0 Hz, CH_2P), 1.57 and 1.35 (2s, 2 × 3 H, CMe_2), 1.32 and 1.31 (2t, 3 H, OCH_2CH_3). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 163.5 (C4), 150.1 (C2), 141.7 and 141.8 (C6), 126.7, 126.8, 126.9, 127.00 (δ of each line is given; 2d, $CH{=}CH_2$), 120.1, 120.2, 120.4, 120.5 (δ of each line is given; 2d, $CH{=}CH_2$), 114.4 and 114.5 (CMe_2), 102.4 and 102.5 (C5), 93.8 and 93.9 (C1′), 85.4−85.6 (2d, C4′), 84.3 and 84.4 (C2′), 80.6 (C3′), 65.1 and 65.2 (C5′), 62.4, 62.4, 62.5, 62.6 (δ of each line is given; 2d, $POCH_2CH_3$), 31.5 (d, $J_{C,P}$ = 138.4 Hz) and 31.4 (d, $J_{C,P}$ = 138.2 Hz) (CH_2P), 27.0, 25.2 (CMe_2), 16.4 and 16.3 ($POCH_2CH_3$). ^{31}P NMR (202 MHz, $CDCl_3$): δ 27.88 (0.5P), 27.62 (0.5P). IR (neat): 3610, 3170, 2998, 2818, 1690, 1458, 1420, 1376, 1216, 1257, 1166, 1062, 1032, 852, 822, 762 cm^{-1}. HRMS (ESI) calcd for $[M + Na]^+$: 439.1246. Found: 439.1248.

Ethyl (2′,3′-*O*-Isopropylideneuridin-5′-yl)(2*S*,3a*S*,4*S*,5*S*,6*S*)-4,5-dibenzyloxy-6-[(1*S*)-1,2-dibenzyloxyethyl]hexahydropyrrolo-[1,2-b]isoxazole-2-methylphosphonate (14). Ethyl (2′,3′-*O*-isopropylideneuridin-5′-yl)allylphosphonate (**13**) (153 mg, 367 μmol, 1.7 equiv) was added to a solution of nitrone **4** (116 mg, 216 μmol) in tetrachloroethylene (3 mL). The mixture was stirred for 12 h at 60 °C and for 24 h at 70 °C. After concentration, the crude product was purified by flash chromatography on silica gel (EtOAc/MeOH 100/0 to 95/10) to give cycloadduct **14** (120 mg, 125 μmol, 58%) as a colorless oil and as a mixture of P*-diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 and 8.60 (2 br s, 1 H, NH), 7.2−7.35 (m, 20.5 H, 20H_{Ar}, 0.5 H6), 7.14 (d, 0.5 H, J = 8.0 Hz, 0.5 H6), 5.67 (dd, J = 1.8, 8.0 Hz) and 5.61 (dd, J = 1.8, 8.0 Hz) (1 H, H5), 5.605 and 5.52 (2 br s, 1 H, H1′), 4.97 (dd, J = 6.4, 1.7 Hz) and 4.95 (dd, J = 6.5, 2.0 Hz) (1 H, H2′), 4.85 (dd, J = 3.8, 6.3 Hz) and 4.82 (dd, J = 3.7, 6.4 Hz) (1 H, H3′), 4.76 (d, 0.5 H), 4.73 (d, 0.5 H), 4.48−4.57 (m, 6 H), 4.44 (d, 0.5 H), 4.39 (d, 0.5 H) (4 OCH_2Ph), 4.35 (m, 1 H, H2″), 4.04−4.27 (several m, 6 H, H4′, 2H5′, H5″, OCH_2CH_3), 3.96 (t, J = 5.7 Hz) and 3.94 (t, J = 5.7 Hz) (1 H, H4″), 3.78−3.82 (m, 3 H, CH_2OBn + CHOBn), 3.73 (m, 1 H, H3a″), 3.34 (br d, 1 H, J = 7.7 Hz, H6″), 2.33 (m, 1 H, H3″$_B$), 2.16 (m, 2 H, CH_BP, H3″$_A$), 1.98 (m, 1 H, CH_AP), 1.55 and 1.54 (2s, 3 H, CMe_2), 1.33 and 1.32 (2s, 3 H, CMe_2), 1.30 and 1.27 (2t, 3 H, CH_3CH_2O). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.93 and 163.90 (C4), 149.88 (C2), 142.40 and 142.23 (C6), 138.62, 138.56, 138.45, 138.41, 137.88, 137.81, 137.75 (Cq_{Ar}), 127.4−128.4 (CH_{Ar}), 114.54 and 114.43 (*C*Me_2), 102.6 (C5), 95.22 and 94.44 (C1′), 87.4 (C4″), 86.08 and 85.54 (2d, $J_{C,P}$ = 6.6 Hz, C4′), 84.19 and 84.13 (C2′), 82.08 and 81.80 (C5″), 80.77 and 80.59 (C3′), 76.41 and 76.33 (CHOBn), 73.3, 73.27, 73.01, 72.95, 72.45, 71.94, 71.73, 71.68 (4 *C*H_2Ph + *C*H_2OBn), 70.48 and 70.27, 69.97 and 69.76 (C6″, C2″), 67.78 and 67.71 (C3a″), 65.06 (d, $J_{C,P}$ = 5.9 Hz) and 64.80 (d, $J_{C,P}$ = 6.2 Hz) (C5′), 62.25 (d, $J_{C,P}$ = 6.4 Hz) and 62.06 (d, $J_{C,P}$ = 6.2 Hz) (O*C*H_2CH$_3$), 41.40 (d, $J_{C,P}$ = 6.6 Hz) and 41.24 (d, $J_{C,P}$ = 6 Hz) (C3″), 30.13 (d, $J_{C,P}$ = 139 Hz, CH_2P), 27.12 and 27.08, 25.31 and 25.25 (CMe_2), 16.40 and 16.35 (*C*H_3CH$_2$O). ^{31}P NMR (202 MHz, $CDCl_3$): δ 27.81, 27.51. IR (NaCl): 3463, 3055, 3033, 2986, 2935, 2869, 1695, 1633, 1497, 1455, 1422, 1382, 1266, 1214, 1158, 1093, 1069, 1027, 972, 886, 860, 810, 737, 701 cm^{-1}. HRMS (ESI) calcd for [M + Na]$^+$: 976.3762. Found: 976.3753. Calcd for [M + K]$^+$: 992.3501. Found: 992.3521. Anal. Calcd for $C_{51}H_{60}N_3O_{13}P$: C, 64.21; H, 6.34; N, 4.40. Found: C, 64.32; H, 6.14; N, 4.60.

(1*S*)-2,3,5,6-Tetra-*O*-benzyl-1,4-dideoxy-1-C-{(2*S*)-3-[(ethyl)-(2′,3′-*O*-isopropylideneuridin-5′-yl)phosphoryl]-2-hydroxypropyl}-1,4-imino-D-galactitol (15). Zinc dust (64.3 mg, 1.05 mmol) was added to a solution of copper(II) acetate (0.3 mg) in glacial acetic acid (3 mL) under argon, and the mixture was stirred at rt for 10 min until the color disappeared. Compound **14** (200 mg, 0.209 mmol) in glacial acetic acid (4.2 mL) and water (1.8 mL) were added successively, and the reaction mixture was heated at 70 °C for 1 h. After cooling to rt, EDTA (sodium salt, 500 mg) was added, and the mixture was stirred for 10 min, then made alkaline to pH 10 by addition of 2 N aqueous NaOH. The resulting solution was extracted with chloroform (3 × 100 mL), and the combined organic phases were concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (100% AcOEt to AcOEt/MeOH 99/1) to afford the desired galactitol **15** (137.1 mg, 68%) as a colorless foam and as a nonseparable mixture of P*-diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$; all signals belong to both diastereomers): δ 7.33−7.24 (m, 21 H, CH_{Ar} and H6), 5.71−5.63 (m, 2 H, H1′ and H5), 4.92−4.88 (m, 1 H, H2′), 4.97−4.85 (m, 1 H, H3′), 4.72 (d, 1 H, J = 11.5 Hz, OCH_2Ph), 4.50−4.37 (m, 7 H, OCH_2Ph), 4.32−4.17 (m, 4 H, H8, H4′ and H5′), 4.05−4.14 (m, 2 H, OCH_2CH_3), 3.88 (m, 1 H, H3″), 3.82−3.80 (m, 1 H, H2″), 3.75−3.71 (m, 1 H, H5″), 3.65−3.57 (m, 2 H, H-6″), 3.48−3.43 (m, 1 H, H1″), 3.30−3.26 (m, 1 H, H4″), 1.92−2.10 (m, 2 H, CH_2P), 1.90−1.83 (m, 1 H, H7$_B$), 1.66−1.59 (m, 1 H, H7$_A$), 1.54 (s, 3 H, CMe_2), 1.26−1.3 (m, 6 H, OCH_2CH_3 and CMe_2). ^{13}C NMR (125 MHz, $CDCl_3$; d1, d2 = diastereomer 1 and 2): δ 163.1 and 163.0 (C4, d1 and d2), 150.1−150.0 (C2), 142.2 and 141.9 (C6, d1 and d2), 138.3, 138.2, 138.1 (Cq_{Ar}), 128.5−127.7 (*C*H_{Ar}), 114.6 and 114.5 (*C*Me_2, d1 and d2), 102.7 and 102.6 (C5, d1 and d2), 94.4 and 94.0 (C1′, d1 and d2), 88.7 and 88.6 (C2″, d1 and d2), 85.5−85.7 (m, C4′, C3″), 84.5 and 84.4 (C2′, d1 and d2), 80.8 and 80.7 (C3′, d1 and d2), 75.9 and 75.8 (C5″), 73.6, 73.0, 72.1 (3 O*C*H_2Ph), 71.9, 71.8, 71.7 (C6″ and 2 O*C*H_2Ph), 65.5 (C8), 64.7 (d, J_{C-P} = 6 Hz) and 64.8 (d, J_{C-P} = 6 Hz) (C5′, d1 and d2), 63.0 (C4″), 62.3 (d, J_{C-P} = 6.2 Hz) and 62.1 (d, J_{C-P} = 6.25 Hz) (*C*H_2CH$_3$, d1 and d2), 59.5 and 59.4 (C1″, d1 and d2), 37.5−37.8 (m, C7), 33.9 (d, J_{C-P} = 136 Hz, C9), 27.3 and 25.5 (CMe_2, d1 and d2), 16.6 and 16.5 (OCH$_2$-*C*H$_3$, d1 and d2). ^{31}P NMR (202 MHz, $CDCl_3$): δ 30.11, 31.71. IR (NaCl): 3474, 3054, 3033, 2986, 2908, 2868, 1695, 1651, 1586, 1497, 1455, 1422, 1383, 1265, 1215, 1158, 1070, 1028, 971, 895, 862, 815, 744, 702 cm^{-1}. HRMS (ESI) calcd for [M + Na]$^+$: 978.3918. Found: 978.3959. Calcd for [M + H]$^+$: 956.4099. Found: 956.4108. Anal. Calcd for $C_{51}H_{62}N_3O_{13}P$: C, 64.07; H, 6.54. Found: C, 64.13; H, 6.85.

(1*S*)-1,4-Dideoxy-1-C-{(2*S*)-3-[(ethyl)(uridin-5′-yl)phosphoryl]-2-hydroxypropyl}-1,4-imino-D-galactitol (16). Compound **16** (hydrochloride) was obtained as a white foam (146 mg, 78%) and as a mixture of nonseparable P*-diastereomers starting from **15** (283 mg, 0.296 mmol) and following the general procedure A. ^{1}H NMR (500 MHz, CD_3OD; all signals belong to both diastereomers, unless indicated otherwise): δ 7.75 (d, J = 8 Hz) and 7.73 (d, J = 8.5 Hz) (1 H, H6, d1 and d2), 5.85 (d, J = 4.5 Hz) and 5.84 (d, 1 H, J = 4.5 Hz) (1 H, H1′, d1 and d2), 5.75 (d, J = 8 Hz) and 5.74 (d, J = 8 Hz) (1 H, H5, d1 and d2), 4.37−4.12 (m, 8 H), 4.07 (t, 1 H, J = 7.5 Hz, H3″), 3.95 (q, 1H, J = 4 Hz, H5″), 3.89−3.85 (m, 1 H, H2″), 3.72 (dd, 1 H, J = 4, 11.5 Hz, H6″$_B$), 3.67 (dd, 1 H, J = 4, 11.5 Hz, H6″$_A$), 3.55 (ddd, 1 H, J = 8, 5 Hz, H8″), 3.51 (dd, 1 H, J = 4, 7.5 Hz, H4″), 2.05−2.25 (m, 4H, H9″ and H7″), 1.36 (t, 3H, CH_3, d1 and d2). ^{13}C NMR (62.5 MHz, CD_3OD): δ 166.0 (C4), 150.2 (C2), 142.7 (C6), 103.0 (C5), 91.6−91.7 (C1′), 83.6 and 83.7 (C4′, d1 and d2), 79.2 (C2″), 76.7 (C3″), 74.8 and 74.9 (C2′ or C3′), 70.9 (C2′ or C3′), 69.0 (C5″), 66.4−66.2 (m, C5′), 65.1 (C6″), 64.9 (C1″ or C4″), 64.7 and 64.6 (C1″ or C4″), 63.9 (d, J_{C-P} = 6.5 Hz) and 63.7 (d, J_{C-P} = 6.8 Hz) (O*C*H_2CH$_3$), 60.6 (C8), 38.4 (d, J_{C-P} = 12 Hz, C7), 34.9 and 33.0 (d, J_{C-P} = 137 Hz, C9), 16.7 and 16.8 (*C*H_3, d1 and d2). ^{31}P NMR (202 MHz, CD_3OD): δ 29.68, 30.07. HRMS (LSIMS) calcd for [M + H]$^+$: 556.1907. Found: 556.1906. Anal. Calcd for $C_{20}H_{43}ClN_3O_{17}P$: C, 36.18; H, 6.53; N, 6.33; Cl, 5.34; P, 4.66. Found: C, 35.72; H, 6.13; N, 6.00; Cl, 5.39; P, 4.29.

(1*S*)-1,4-Dideoxy-1-C-{(2*S*)-3-[(uridin-5′-yl)phosphono]-2-hydroxypropyl)}-1,4-imino-D-galactitol (17). Using general procedure B, compound **17** (hydrobromide) was obtained as a purple foam (66.3 mg, 99%) starting from **16** (65 mg, 0.109 mmol). $[\alpha]^{25}_D$ −15 (c = 1.62, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ 7.79 (d, 1 H, J = 8 Hz, H6), 5.87 (d, 1 H, J = 4.5 Hz, H1′), 5.7 (d, 1 H, J = 8 Hz, H5), 4.32−4.11 (m, 6 H), 4.08−4.05 (m, 1 H, H3″), 3.96−3.94 (m, 1 H, H5″), 3.88 (dd, 1 H, J = 6.5, 8.5 Hz, H2″), 3.72 (dd, 1 H, J = 4.5, 11.5 Hz, H6″$_B$), 3.66 (dd, 1 H, J = 4, 11.5 Hz, H6″$_A$), 3.58−3.54 (m, 1 H, H8), 3.51−3.48 (m, 1 H, H4″), 2.04−2.17 (m, 4 H, H7, H9). ^{13}C NMR (62.5 MHz, CD_3OD): δ 166.1 (C4), 152.3 (C2), 142.6 (C6), 102.9 (C5), 91.3 (C1′), 83.9 (d, J_{C-P} = 7 Hz, C4′), 79.1 (C2″), 76.8 (C3″), 75.1 (C2′ or C3′), 71.0 (C3′or C2′), 68.9 (C5″), 65.7 (d, J_{C-P} = 5.7 Hz, C5′), 65.2 (C6″), 65.1 (C4″ or C1″), 65.0 (C4″ or C1″), 60.8 (C8), 38.0 (d, J_{C-P} = 11 Hz, C7), 34.9 (d, J_{C-P} = 138 Hz, C9). ^{31}P NMR (202 MHz, CD_3OD): δ 27.64. HRMS (LSIMS) calcd for [M + H]$^+$: 528.1594. Found: 528.1600.

(1*S*)-1,4-Dideoxy-1-C-{(2*S*)-3-[(ethyl)(2′,3′-*O*-isopropylideneuridin-5′-yl)phosphoryl]-2-hydroxypropyl)}-1,4-imino-D-galactitol (18). To a solution of phosphonate **14** (75 mg, 76.8 μmol) in acetic acid (1.0 mL) was added a catalytic amount of palladium on active charcoal (10%), and the mixture was allowed to stir overnight

under hydrogen. The solids were then removed by filtration and rinsed with CH_2Cl_2. After evaporation of the solvent, the crude product was purified by flash chromatography on silica gel (MeOH/dichloromethane/pyridine 25/74/1 to remove impurities, and finally MeOH to elute the desired compound). This afforded the desired iminogalactitol **18** (22 mg, 37 μmol, 49%) as a pale yellow oil. MS (ESI): 596.5 $[M + H]^+$.

Ethyl (2′,3′-*O*-Isopropylideneuridin-5′-yl)-(2*S*,3a*S*,4*S*,5*S*,6*S*)-6-[(1*S*)-1,2-dihydroxyethyl]hexahydropyrrolo[1,2-b]isoxazole-2-methylphosphonate (19). Compound **19** (hydrochloride) was obtained as a white foam (150 mg, 74%) and as a mixture of P*-diastereomers, starting from **14** (349 mg, 0.366 mmol) and following the general procedure A. NMR data of free base: ^{1}H NMR (500 MHz, CD_3OD) δ 7.73 (d, $J = 8$ Hz) and 7.71 (d, $J = 8$ Hz) (1 H, H6, d1 and d2), 5.84−5.83 (m, 1 H, H1′), 5.74 (d, $J = 8$ Hz) and 5.73 (d, $J = 8$ Hz) (1 H, H5, d1 and d2), 4.37−4.12 (m, 8 H), 3.88−3.84 (m, 1 H, H5″), 3.77−3.71 (m, 2 H, H4″ and H7″), 3.66−3.65 (m, 2 H, H8″), 3.46 (t, 1 H, $J = 7.5$ Hz, H3″a), 3.04 (d, 1 H, $J = 8.5$ Hz, H6″), 2.40−2.37 (m, 1 H, $H3''_B$), 2.27 (dd, 2 H, $J = 6.5$, 18.5 Hz, CH_2P), 2.14−2.06 (m, 1 H, $H3''_A$), 1.34 (t, 3 H, $J = 7$ Hz, CH_3); ^{13}C NMR (125 MHz, CD_3OD): δ 166.0 (C4), 152.2 (C2), 142.8 and 142.7 (C6, d1 and d2), 102.9 (C5), 91.9 (C1′), 83.7−83.6 (m, C4′), 81.9 and 81.8 (C4″, d1 and d2), 75.9 and 75.9 (C5″, d1 and d2), 74.9 and 74.8 (C2′, d1 and d2), 71.9 and 71.8 (C6″, d1 and d2), 71.4, 71.3, 71.2 and 71.1 (C2″, C7″, d1 and d2), 70.9 (C3′), 69.7 and 69.6 (C3a, d1 and d2), 66.4 (d, 1 H, $J = 6.5$ Hz, C5′), 65.5 and 65.4 (C8″, d1 and d2), 63.8 (d, $J = 6.25$ Hz) and 64.0 (d, $J = 6.5$ Hz) (CH_2CH$_3$, d1 and d2), 42.1−42.0 (m, C3″, d1 and d2), 29.5 (d, $J_{C-P} = 140$ Hz) and 29.4 (d, $J_{C-P} = 140$ Hz) (CH_2P, d1 and d2), 16.7 and 16.6 (CH_3, d1 and d2); ^{31}P NMR (202 MHz, CD_3OD) δ 29.53, 29.04. HRMS (LSIMS) calcd for $[M + H]^+$: 554.1751. Found: 554.1768.

(2′3′-*O*-Isopropylideneuridin-5′-yl)-(2*S*,3a*S*,4*S*,5*S*,6*S*)-6-[(1*S*)-1,2-dihydroxyethyl]hexahydropyrrolo[1,2-b]isoxazole-2-methylphosphonate (20). Following the general procedure B, compound **20** (hydrobromide) was obtained as white foam (90 mg, 81%) starting from **19** (108 mg, 0.183 mmol). $[\alpha]^{25}_D$ +5 ($c = 1.29$, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ 7.79 (d, 1H, $J = 8$ Hz, H6), 5.86 (d, 2 H, $J = 4.5$ Hz, H1′), 5.76 (d, 1 H, $J = 8$ Hz, H5), 4.12−4.36 (m, 9 H), 4.00 (dd, 1 H, $J = 10$, 5.5 Hz, H7″), 3.88 (dd, 1 H, $J = 7.5$, 4.5 Hz, H6″), 3.73 (dd, 1 H, $J = 5$, 11.5 Hz, $H8''_B$), 3.68 (dd, 1 H, $J = 6$, 11.5 Hz, $H8''_A$), 2.91−2.87 (m, 1 H, $H3''_B$), 2.36−2.56 (m, 3 H, CH_2P, $H3''_A$). ^{13}C NMR (125 MHz, CD_3OD): δ 166.0 (C4), 152.2 (C2), 142.8 (C6), 103.0 (C1′), 91.4 (C5), 83.7 (d, $J_{C-P} = 6.6$ Hz, C4′), 79.9, 78.4, 77.1 (C6″), 76.3 (C5″), 74.8 (C2′), 73.8, 70.9, 68.3 (C7″), 66.1 (d, $J_{C-P} = 5.5$ Hz, C5′), 63.9 (C8″), 38.6 (d, $J_{C-P} = 7.5$ Hz, C3″), 30.0 (d, $J_{C-P} = 139$ Hz, CH_2P). ^{31}P NMR (202 MHz, CD_3OD): δ 23.74. HRMS (LSIMS) calcd for $[M + H]^+$: 526.1438. Found: 526.1431.

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Supporting Information Available: General experimental methods and ^{1}H and ^{13}C NMR spectral data for selected compounds (**2**, **3**, **4**, **6**, **7**, **8**, **9**, **11**, **15**, **16**, **17**, and **19**) are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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