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Synthesis of galactosides locked in a $^{1,4}B$ boat conformation and functionalized at the anomeric position

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Abstract—A new methodology for the preparation of carbohydrates locked in a $^{1,4}B$ boat conformation is presented. The constrained molecules thus obtained are functionalized at the anomeric position by iodo-, fluoro-, hydroxyl- or/and phosphono-methylene moieties. A remarkable diastereoselective opening of these quaternary acetals was also observed under non-acidic conditions.

1. Introduction

Constrained molecules are valuable tools for exploring and probing enzyme's binding and/or catalytic sites. By locking a molecule in a chosen conformation and measuring its affinity to a receptor or a biocatalyst, one may obtain interesting insights into either the real ground state conformation adopted by a molecule inside a protein cavity or even a transient conformation through which a molecule is transformed within an enzyme binding site.[1] Due to the importance of conformational and stereoelectronic effects in glycosciences,[2,3] the obtention of locked glycosides is highly desirable since they might be interesting mechanistic probes or selective inhibitors. Nucleoside analogues with conformationally restricted ribosyl moieties have been extensively studied and provided oligonucleotides with finely tuned binding properties.[4,5] In addition, synthetic methods for constraining glycosides to probe usual glycosyl processing enzymes (or lectins) have also been explored. For the glycosidases[6] and the nucleotide-sugar binding proteins,[7] glycosides adopting *half-chair* or flattened *chair* conformations have been designed to mimic high energy intermediates such as oxycarbenium species.[8] As a recent example, the biological evaluation of a locked analogue of a biologically active heparin fragment demonstrated that the conformation adopted by a key L-iduronic acid residue when bound to antithrombin AT-III was indeed a *skew-boat* conformation.[9] *Boat*-locked molecules may also be enzymatically relevant.[10] In the course of the mechanistic study of UDP-galactose mutase (UGM),[11–14] we synthesized the constrained sugar nucleotide **A** in order to probe the conformational itinerary of the galactose moiety during the enzymatic interconversion of UDP-galactopyranose (UDP-Gal*p*) and UDP-galactofuranose (UDP-Gal*f*, Fig. 1).[11]

Thus, we needed to develop a general synthetic strategy to reach $^{1,4}B$ boat-locked galactosides such as **A** (Fig. 1). The few described methods that allow the construction of $^{1,4}B$-locked bicyclic glycosides are based either on a transketalization of galactosides[15,16] or on cycloadditions followed

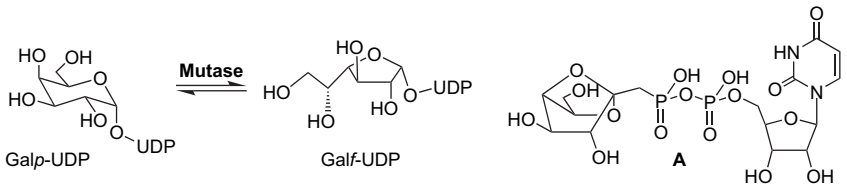

Figure 1. Conformational probe (**A**) of the mutase catalyzed interconversion of UDP-Galactopyranose and UDP-galactofuranose.

Keywords: Boat conformation; C-glycosides; α-Fluoro-phosphonate; Glycals.
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by asymmetric dihydroxylations,[10,17,18] or epoxidation.[19] Recently, Thomas et al. described the synthesis of a methylene analogue of 1,4-anhydrogalactose, which also presents a $^{1,4}B$ boat conformation.[19] However, none of these reactions described molecules functionalized at the anomeric position, that is, with a quaternary anomeric carbon. The purpose of the methodological study presented here was to explore the chemistry allowing for the construction of galactosides locked in a defined conformation with the simultaneous installation of diverse functional groups at the vicinity of the anomeric center. Given the number of potential enzymatic targets (galactosyl transferases, galactofuranosyl transferases, UGM…), we particularly explored the synthesis of methylene-phosphonate derivatives. Here we report a straightforward approach allowing the preparation of boat-locked galactosides functionalized at the anomeric position with phosphonyl-, iodo-, hydroxyl-, and fluoro-methylene groups.

2. Results and discussion

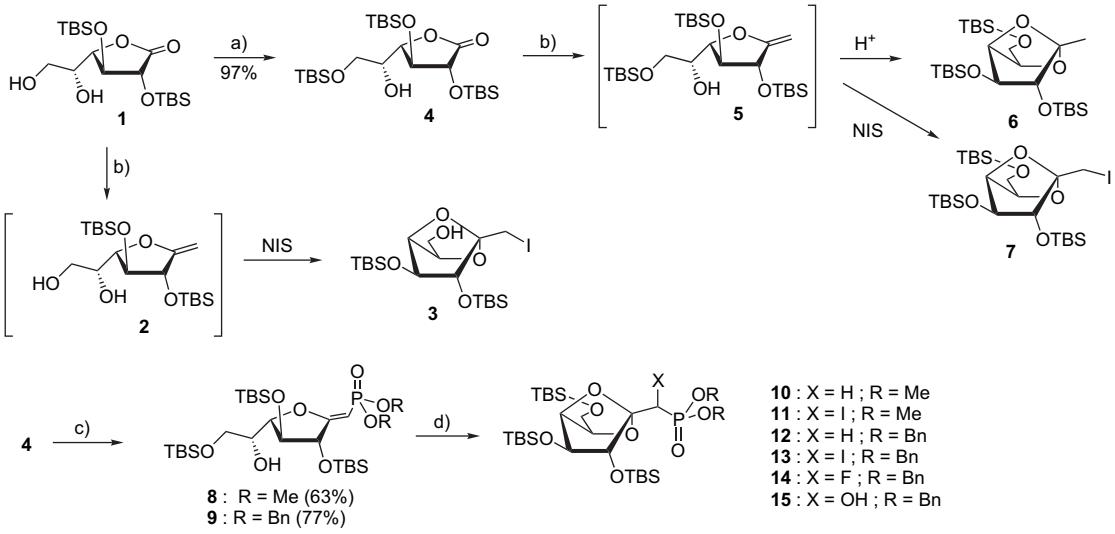
Our synthetic strategy relied on a key cyclization of methylene-*exo*-glycals **2** and **5** and phosphonylated *exo*-glycals **8** and **9** (Scheme 1), unprotected at the 5-position. These glycals were prepared from a common precursor **1** easily obtained in three steps from 1,4-galactonolactone.[20] Methylene-*exo*-glycals **2** and **5** could be synthesized from the corresponding lactones through a methylenation using Tebbe's reagent. Due to their instability on silica gel, molecules **2** and **5** were directly subjected to cyclization experiments without purification. The phosphonylated *exo*-glycals **8** and **9** were prepared in a stepwise procedure recently developed by Lin et al., which consists in the addition of the lithium anion of dialkyl methyl phosphonate, yielding an intermediate lactol, which is directly subjected to an efficient and diastereoselective elimination (Scheme 1).[21,22]

Table 1 summarizes the experiments we performed to define the scope of the cyclization reaction leading to 1,4-anhydrogalactopyranosyl derivatives. We varied different parameters such as the activator, the substrate and the solvent. In all cases, the $^{1,4}B$ conformation was confirmed by comparison with ^{1}H NMR data of analogous compounds, with typically small coupling constants between H-2, H-3, H-4, and H-5 ($0.9<J<1.2$ Hz).[16–18]

Table 1. Cyclizations of *exo*-glycals

Entry	Glycal	Activator	Product	Solvent	*T*	Yield (%)
1	**5**	Silica gel	**6**	CH_2Cl_2	rt	57 (two steps)
2	**5**	NIS	**7**	CH_2Cl_2	rt	62 (two steps)
3	**2**	NIS	**3**	CH_2Cl_2	rt	58 (two steps)
4	**8**	CSA	**10**	CH_2Cl_2	reflux	70
5	**8**	NIS	**11**	CH_2Cl_2	rt	86
6	**9**	CSA	**12**	CH_2Cl_2	reflux	88
7	**9**	NIS	**13**	CH_2Cl_2	rt	79
8	**9**	Selectfluor	**14**	CH_3NO_2	50 °C	62
9	**9**	*m*-CPBA, CSA	**15**	CH_2Cl_2	rt	75
10	**9**	DMDO	**15**	Acetone/ CH_2Cl_2	rt	64

Different types of enol ether activation were also screened: a catalytic acidic activation or stoichiometric electrophilic ones. Not surprisingly, the glycals bearing the phosphonyl group (molecules **8** and **9**) were found less reactive under acidic or electrophilic activation and more stable in acidic conditions, such as silica gel chromatography, than their non-phosphonylated analogues (molecules **2** and **5**). This is likely due to the electron-withdrawing character of the (dialkoxy)phosphoryl moiety. Thus, under acidic activation, methylene-*exo*-glycals reacted at room temperature (entry 1) whereas phosphono-*exo*-glycals **8** and **9** needed to be refluxed in CH_2Cl_2 to react (entries 4 and 6). These preliminary experiments constituted the base for the synthesis of molecule **A** (Fig. 1).[11] Several acids were tested and camphorsulfonic acid (CSA, entries 4 and 6) appeared to give the best results regarding the kinetics of the reaction and the absence of side-reaction (nucleophilic acids may give addition products). $PPh_3\cdot HBr$, which is a valuable tool in glycal



Scheme 1. Synthesis of functionalized 1,4-boat locked galactosides. Reagents: (a) TBDMSCl, Im, DMF; (b) Tebbe's reagent, then activator; (c) $(RO)_2POCH_2Li$, THF, then Py/THF, $(CF_3CO)_2O$; (d) activator.

chemistry[23] was also found amenable for this reaction, although giving lower yields than CSA (data not shown).

We found interesting to obtain constrained α-iodo-phosphonates such as **11** and **13** since the iodo group may allow a subsequent derivatization via nucleophilic substitution or via radical chemistry. When activated by NIS, the cyclization reactions were all complete within a few hours at room temperature, regardless of the presence/absence of the phosphonyl moiety (entries 2, 3, 5, and 7). Interestingly, the reaction with the 5,6-diol **1** exclusively gave the expected 1,4-anhydrogalactopyranose structure (entry 3). The other possible product (cyclization with the 6-OH group yielding a 1,6-anhydrogalactofuranose structure) could not be isolated. In this case the formation of the [2.2.1]-bicyclic glycoside was specific over the formation of the [3.2.1]-bicyclic structure. The cyclization reaction performed with NIS on phosphonylated glycals **8** and **9** was found diastereospecific (entries 5 and 7), the NIS attack specifically occurring from one face of the enol ether.

We also considered the fluoro-cyclization of particular importance (entry 8). Indeed, the electron-withdrawing character of the fluorine atom induces a decrease of the pK_a values of the deprotected phosphonic diacid, which might be a critical element for the binding processes with enzymes. For this particular reaction we extrapolated the chemistry of Selectfluor mediated 2-fluoro-glycosylations.[24,25] After optimization, we obtained the fluoro-phosphonate **14** in 62% yield as a 9/1 mixture of two separable diastereomers (entry 8). The temperature of this cyclization was a very important parameter to optimize: performing the reaction at temperatures higher than 50 °C led to side-reactions and much lower yields.

For the very same reasons (influence on the pK_a of the phosphonate), the synthesis of the α-hydroxy-phosphonate **15** was developed either with *m*-CPBA (entry 9) or with DMDO (entry 10), in 75% and 64% yields, respectively. Given the literature data on the epoxidation of *endo*-glycals,[26] we first attempted the reaction with DMDO (entry 10). Exposing *exo*-glycal **9** to DMDO (or *m*-CPBA) yielded an unstable epoxide that directly cyclized to give the expected constrained acetal **15**. However, this product was found difficult to purify under optimized conditions (entry 10). We then explored a more recent methodology developed for epoxidizing *exo*-glycals based on the in situ generation of trifluoro-DMDO.[27] However, applied to molecule **9**, this methodology gave very poor yields of alcohol **15** (data not shown). We finally obtained a reproducible procedure by using dry *m*-CPBA and a catalytic amount of CSA (entry 9). This result was particularly interesting and surprising since peracids are, usually, not suitable for epoxidizing *exo*- or *endo*-glycals since their corresponding carboxylic acids, once formed, react with the generated epoxide. In the case of this specific reaction (entry 9), it is reasonable to assume that the cyclization is quicker than the reaction of the transient epoxide with *m*-chloroperbenzoic acid and/or chlorobenzoic acid. Monitoring this reaction by ^{31}P NMR showed that a single diastereomer was formed under these conditions. Unfortunately, we never obtained monocrystals of molecules **13**, **14**, and **15** that would have allowed the determination of the absolute configuration of the new asymmetric center by X-ray diffraction analysis.

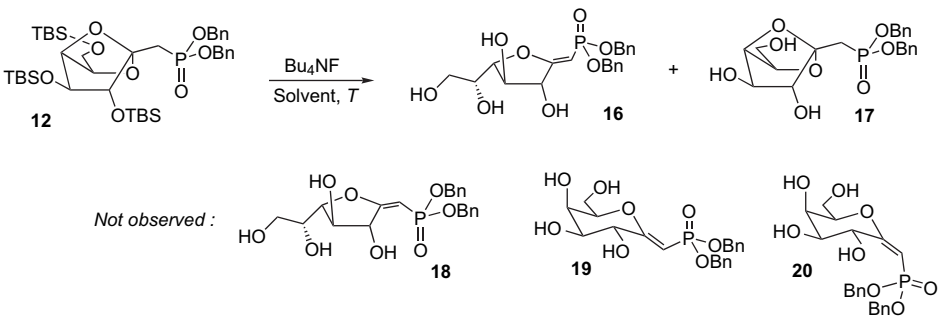
When constrained acetal **12** was subjected to deprotection using Bu_4NF, a remarkable side-reaction was observed: the expected triol **17** was contaminated by *exo*-glycal **16** (Scheme 2). This enol ether formation resulted from a β-elimination or a *retro*-Michael addition. Surprisingly, none of the three other possible isomers **18**, **19**, and **20** could be observed at the end of the reaction. Indeed, this deprotection could be monitored by ^{31}P and ^{1}H NMR, thus confirming the presence in the crude reaction mixture of only two products, molecules **17** and **16**, once the desilylation was complete.

The structure of *exo*-glycal **16** has been unambiguously determined by its independent synthesis from **12**. The (*Z*)-configuration was assigned by ^{1}H NMR and NOE experiments.[11,21,22] In order to optimize the preparation of **17**, we analyzed the ratio **17/16** as a function of the reaction conditions (Table 2).

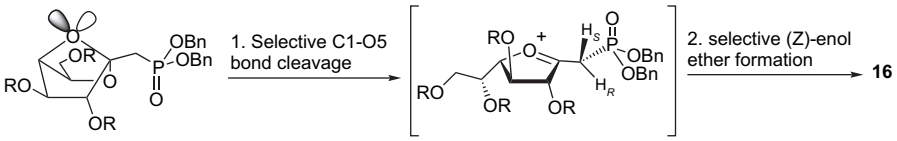
Table 2. Transformation of phosphonate **12** into **16** and/or **17**

Entry	Solvent	Bu_4NF (equiv)	*T* (°C)	Time (h)	Ratio **17/16**[a]	Yield[b] (%)
1	THF	3	rt	6	59/41	nd[d]
2	THF	5	rt	6	56/44	nd[d]
3	THF	10	rt	6	50/50	nd[d]
4	THF/^{i}PrOH 3/1	3	rt	6	60/40	40[c]
5	THF	3	−50→rt	12	85/15	70[c]
6	THF	3	−50→10	12	88/12	70[c]
7	THF	3	−50→−5	36	96/4	83[c]
8	THF/^{t}BuOH 3/1	3	40	2	0/100	60[e]

[a] Determined by ^{31}P and ^{1}H NMR.
[b] After silica gel chromatography (AcOEt/EtOH 9/1, then acetone/DCM 8/2).
[c] Isolated yield of acetal **17**.
[d] Not determined: the reaction was stopped when the deprotections were complete but the products were not isolated.
[e] Isolated yield of *exo*-glycal **16**.



Scheme 2. Fluoride induced deprotections and selective formation of *exo*-glycal **16**.



Scheme 3. Hypothetical mechanism of the diastereoselective elimination.

When the reaction was performed at room temperature (entries 1–3), the *exo*-glycal formation was slightly favored by increasing the concentration of Bu_4NF. The chromatographic separation of **17** and **16** proved very demanding, thus explaining that the isolated yields were always poorer than the conversions observed by NMR. For instance, entry 4 describes an experiment for which a poor selectivity was observed: the reaction was stopped when molecules **17** and **16** were the only final products. Under these conditions, the obtention of pure acetal **17** required two silica gel purifications. We finally discovered that the elimination leading to *exo*-glycal **16** was highly temperature dependent (entries 5–8). The optimal conditions, at low temperature, to minimize the formation of side-product **16**, while maintaining a reasonable desilylation rate, are described in entry 7 (Table 2). On the other hand, by heating the reaction mixture at 40 °C, the elimination leading to **16** became predominant (entry 8). This last reaction is significant since, to our knowledge, methods describing the formation of an *exo*-glycal from an acetal are rare.[28] ^{i}PrOH or ^{t}BuOH (entries 4 and 8) was used as cosolvent to prevent the precipitation of deprotected polyols.

The remarkable diastereoselectivity of this reaction might be rationalized by decomposing this elimination into two distinct mechanistic steps. The first elemental step could be the acetal opening giving rise to a single *furanic* oxycarbenium intermediate (Scheme 3). It is now well-established that 1,4-anhydro-galactosides give only galacto*furano*sides when exposed to nucleophiles under acidic conditions,[16,29] thus showing that an intermediate *pyranic* oxycarbenium is not formed. A stereoelectronic control has been invoked to justify this specificity: given the positions of the lone pair electrons of the oxygen O-4 and O-5 relative to the C1–O4 and C1–O5 σ bonds, the C1–O5 bond may be considered weakened due to its antiperiplanarity with one of the O-4 doublets. In this case, the acetal opening, under slightly basic conditions, would not be justified by an acidic activation but by a decrease of ring strain while the [2.2.1]-bicyclic glycoside collapses into a furanoside.

Then, the observed (*Z*)-specificity may be explained by a specific kinetic deprotonation of one of the two diastereotopic hydrogen atoms of the phosphono-methylene moiety. This possibility has already been invoked by Lin et al. for the stereospecific formation of (*Z*)-*exo*-glycals.[30] Thus, it would signify that, in the transition state, the oxycarbenium adopts a well-defined conformation placing the phosphonyl moiety at the opposite of the C-2 position of the carbohydrate.

However, we have to outline that this reaction depends on the presence of the basic fluoride anion (Table 1, entries 1–3). The starting quaternary acetal **12** has been found stable under slightly acidic conditions (Table 1, entry 6, CSA in refluxing CH_2Cl_2), or in neutral conditions (molecule **17** is stable for days in methanolic water at room temperature). These observations are contrasting with the usual reactivity of constrained quaternary acetals. Therefore, a concerted E_2 type elimination, or even an E_1cb, cannot be ruled out at this stage. A cautious mechanistic investigation will be necessary to unravel the fundamental origin of this surprising diastereoselective transformation.

3. Conclusion

In conclusion, we developed an efficient methodology for the synthesis of galactose derivatives locked in a $^{1,4}B$ boat conformation. Since these molecules are functionalized at the anomeric position, they may be useful conformational probes for glycosyl processing enzymes, such as galactosidases, galactosyl transferases, and UDP-galactopyranose mutase. The possibility of functionalizing the core structure **A** at the vicinity of the anomeric center with electron-withdrawing or charged groups should, in principle, enhance its inhibition properties.

4. Experimental part

4.1. Materials and procedures

All chemicals were purchased from Sigma, Aldrich or Fluka and were used without further purification. Tetrahydrofuran and toluene were freshly distilled over sodium benzophenone, dichloromethane over P_2O_5, and nitromethane over CaH_2.^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR spectra were recorded with Bruker AC-250 and AMX-400 spectrometers. All new compounds were characterized by ^{1}H, ^{13}C, ^{31}P, ^{19}F NMR as well as by ^{1}H–^{1}H and ^{1}H–^{13}C correlation experiments. Specific optical rotations were measured on a Perkin Elmer 241 Polarimeter in a 1 dm cell. Melting points were determined with a Büchi 535 apparatus. Column chromatographies were performed on silica gel Kieselgel Si 60 (40–63 μm). Molecules **1** and **4** were prepared following literature data.[20] Compounds **6**, **7**, **8**, **9**, and **12** were previously described.[11]

4.2. Atom and position numberings

We systematically numbered the phosphonate-methylene group 1′ and adopted the usual numbering for carbohydrates from 1 to 6 with 1 for the anomeric position.

4.2.1. 1,4-Anhydro-2,3-di-*O*-*tert*-butyldimethylsilyl-1-deoxy-1-iodomethyl-D-galactopyranose (3). Tebbe's reagent (1.0 mL, 0.4 M in toluene, 0.4 mmol, 3.1 equiv) was added dropwise at 0 °C on a solution of 2,3-di-*O*-*tert*-butyldimethylsilyl-D-galactono-1,4-lactone **1**[20] (55 mg, 0.13 mmol) dissolved in a mixture of toluene/THF/Py 1/1/0.3

(2.3 mL). The dark red solution obtained was stirred for 1 h at 0 °C and 30 min at room temperature after which the reaction was stopped by adding an aqueous solution of NaOH (2.0 mL, 1 M) at 0 °C. The resulting solution was filtered through Celite® and concentrated under vacuum. The residue was dried by azeotropic evaporation with anhydrous toluene (2×10 mL) and then dissolved in anhydrous CH_2Cl_2 (5 mL) under argon atmosphere. To this solution were successively added molecular sieves 4 Å (200 mg) and NIS (66 mg, 0.29 mmol, 2.2 equiv). The solution was stirred for 45 min at 0 °C, filtered through Celite®, diluted with CH_2Cl_2 (15 mL), and then washed twice with a saturated solution of $Na_2S_2O_3$ (10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography on silica gel (eluent cyclohexane/EtOAc: 20/1) to give compound **3** (31.7 mg, 58% yield) as a colorless oil.

$[\alpha]_D^{21}$ +47.8 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (d, J_{3-4}=1.4 Hz, 1H, H-4), 4.01 (t, J_{2-3}=J_{3-4}=1.4 Hz, 1H, H-3), 3.93 (dd, J_{5-6a}=4.3 Hz, J_{5-6b}=5.1 Hz, 1H, H-5), 3.87 (d, J_{2-3}=1.4 Hz, 1H, H-2), 3.77 (ABX, J_{5-6a}=4.3 Hz, J_{6a-6b}=11.6 Hz, 1H, H-6a), 3.70 (ABX, J_{5-6b}=5.2 Hz, J_{6a-6b}=11.6 Hz, 1H, H-6b), 3.54 (AB, J_{AB}=11.6 Hz, 2H, CH_2–I), 0.94 (s, 9H, Si–^{t}Bu), 0.93 (s, 9H, Si–^{t}Bu), 0.14 (s, 9H, 3Si–Me), 0.10 (s, 3H, Si–Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.44 (C-1), 84.60 (C-3), 83.78 (C-4), 81.97 (C-2), 77.09 (C-5), 63.50 (C-6), 25.70 (2Si–C(CH_3)$_3$), 18.05 (Si–C(CH_3)$_3$), 17.93 (Si–C(CH_3)$_3$), 1.31 (CH_2–I), −4.71 (2Si–Me), −4.75 (2Si–Me); MS (DCI-NH_3): *m*/*z* 531 (100%) $[M+H]^+$, 548 (5%) $[M+NH_4]^+$; HRMS for $C_{19}H_{40}O_5Si_2I$: calcd 531.1459; meas. 531.1464.

4.2.2. 1,4-Anhydro-2,3,6-tri-*O*-*tert*-butyldimethylsilyl-1-deoxy-1-(dimethoxyphosphoryl)methyl-D-galactopyranose (10). To a solution of **8** (386 mg, 0.62 mmol) and molecular sieves 4 Å (600 mg) in dry dichloromethane (7 mL) under argon atmosphere was added 10-*d,l*-camphorsulfonic acid CSA (214 mg, 0.92 mmol, 1.5 equiv). The mixture was refluxed under argon for 15 h. The suspension was then filtered through a pad of Celite® and the filtrate was washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The final mixture was chromatographed on a silica gel column with cyclohexane/EtOAc (1.5/1) as eluent and product **10** (270 mg, 70% yield) was obtained as a colorless oil.

$[\alpha]_D^{24}$ +36.4 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (d, J_{3-4}=1.3 Hz, 1H, H-4), 4.04 (t, J_{2-3}=J_{3-4}=1.3 Hz, 1H, H-3), 3.81 (d, J_{H-P}=11.0 Hz, 3H, OCH_3), 3.79 (d, J_{H-P}=11.1 Hz, 3H, OCH_3), 3.67 (br s, 1H, H-2), 3.66 (dd, J_{5-6a}=4.5 Hz, 1H, H-5), 3.57 (ABX, J_{5-6a}=4.5 Hz, J_{6a-6b}=9.7 Hz, 1H, H-6a), 3.46 (t, J_{5-6b}=J_{6a-6b}=9.8 Hz, 1H, H-6b), 2.43 (ABX, $J_{1'a-1'b}$=15.7 Hz, $J_{1'a-P}$=19.3 Hz, 1H, H-1′a), 2.38 (ABX, $J_{1'a-1'b}$=15.7 Hz, $J_{1'b-P}$=19.3 Hz, 1H, H-1′b), 0.93 (2s, 18H, Si–^{t}Bu), 0.91 (s, 9H, Si–^{t}Bu), 0.14 (2s, 6H, 2Si–Me), 0.12 (2s, 6H, 2Si–Me), 0.08 (s, 6H, 2Si–Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.22 (d, J_{1-P}=4.9 Hz, C-1), 86.69 (d, J_{3-P}=6.7 Hz, C-3), 84.08 (C-4), 79.91 (d, J_{2-P}=1.4 Hz, C-2), 76.52 (C-5), 61.89 (C-6), 52.73 (d, J_{C-P}=6.1 Hz, OCH_3), 52.45 (d, J_{C-P}=6.0 Hz, OCH_3), 26.53 (d, $J_{1'-P}$=142.1 Hz, C-1′), 25.75 (2Si–C(CH_3)$_3$), 25.70 (Si–C(CH_3)$_3$), 18.06 (Si–C(CH_3)$_3$), 17.90 (Si–C(CH_3)$_3$), 17.83 (Si–C(CH_3)$_3$), −4.21 (Si–Me), −4.51 (Si–Me), −4.70 (Si–Me), −4.82 (Si–Me), −5.44 (Si–Me), −5.45 (Si–Me); ^{31}P NMR (101 MHz, $CDCl_3$) δ 26.62; MS (DCI-NH_3): *m*/*z* 627 $[M+H]^+$; elemental analysis for $C_{27}H_{59}O_8PSi_3$: calcd (%) C 51.72, H 9.48; meas. C 51.73, H 9.62.

4.2.3. 1,4-Anhydro-2,3,6-tri-*O*-*tert*-butyldimethylsilyl-1-deoxy-1-(dimethoxyphosphoryl)iodomethyl-D-galactopyranose (11). To a solution of **8** (58.4 mg, 0.09 mmol) and molecular sieves 4 Å (150 mg) in dry dichloromethane (5 mL) cooled to 0 °C was added NIS (50.3 mg, 0.22 mmol, 2.5 equiv). The reaction mixture was stirred for 1 h at 0 °C after which it was allowed to warm to room temperature and stirred overnight. The solution was then filtered through a pad of Celite® and the filtrate was washed with an aqueous solution of $Na_2S_2O_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The final mixture was chromatographed on silica gel with cyclohexane/EtOAc (2/1) as eluent. Product **11** (60 mg, 86% yield) was obtained as a pale yellow solid.

$[\alpha]_D^{20}$ +25.2 (*c* 0.9, $CHCl_3$); mp 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (d, J_{3-4}=1.5 Hz, 1H, H-4), 4.44 (s, 1H, H-3), 4.13 (d, $J_{1'-P}$=13.8 Hz, 1H, H-1′), 3.87 (d, J_{H-P}=11.2 Hz, 3H, OCH_3), 3.86 (d, J_{H-P}=11.1 Hz, 3H, OCH_3), 3.85 (dd, J_{5-6a}=4.6 Hz, J_{5-6b}=9.8 Hz, 1H, H-5), 3.72 (s, 1H, H-2), 3.61 (ABX, J_{5-6a}=4.6 Hz, J_{6a-6b}=9.8 Hz, 1H, H-6a), 3.53 (t, J_{5-6b}=J_{6a-6b}=9.8 Hz, 1H, H-6b), 0.94 (s, 9H, Si–^{t}Bu), 0.93 (s, 9H, Si–^{t}Bu), 0.90 (s, 9H, Si–^{t}Bu), 0.21 (s, 3H, Si–Me), 0.17 (s, 3H, Si–Me), 0.12 (s, 6H, 2Si–Me), 0.07 (s, 6H, 2Si–Me); ^{13}C NMR(100 MHz, $CDCl_3$) δ 106.44 (d, J_{1-P}=5.1 Hz, C-1), 86.08 (d, J_{3-P}=7.3 Hz, C-3), 83.84 (C-4), 80.08 (d, J_{2-P}=2.0 Hz, C-2), 78.24 (C-5), 61.57 (C-6), 54.12 (d, J_{C-P}=6.5 Hz, OCH_3), 54.09 (d, J_{C-P}=6.6 Hz, OCH_3), 25.81 (Si–C(CH_3)$_3$), 25.74 (Si–C(CH_3)$_3$), 25.70 (Si–C(CH_3)$_3$), 18.04 (Si–C(CH_3)$_3$), 17.85 (Si–C(CH_3)$_3$), 17.82 (Si–C(CH_3)$_3$), 8.77 (d, $J_{1'-P}$ = 150.3 Hz, C-1′), −4.01 (Si–Me), −4.29 (Si–Me), −4.42 (Si–Me), −4.78 (Si–Me), −5.42 (Si–Me), −5.45 (Si–Me); ^{31}P NMR (101 MHz, $CDCl_3$) δ 20.65; MS (DCI-NH_3): *m*/*z* 770 $[M+NH_4]^+$; elemental analysis for $C_{27}H_{58}IO_8PSi_3$: calcd (%) C 43.07, H 7.76; meas. C 43.35, H 8.21.

4.2.4. 1,4-Anhydro-1-deoxy-1-(dibenzyloxyphosphoryl)-iodomethyl-2,3,6-tri-*O*-*tert*-butyldimethylsilyl-D-galactopyranose (13). Compound **9** (77.6 mg, 0.10 mmol) was treated with NIS (112 mg, 0.50 mmol) according to the same procedure described for **11**. The reaction time was 12 h at room temperature and the crude was purified by silica gel chromatography with cyclohexane/EtOAc (3/1) as eluent to give **13** (71.2 mg, 79% yield) as a pale yellow solid.

$[\alpha]_D^{24}$ +24.4 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 10H, H arom.), 5.16 and 5.14 (2AX, J_{H-P}=1.9 and 2.0 Hz, 4H, CH_2Ph), 4.49 (br s, 1H, H-3), 4.47 (d, J_{3-4}=1.6 Hz, 1H, H-4), 4.22 (d, $J_{1'-P}$=13.9 Hz, 1H, H-1′), 3.85 (dd, J_{5-6a}=6.3 Hz, J_{5-6b}=8.2 Hz, 1H, H-5), 3.74 (s, 1H, H-2), 3.55–3.50 (m, 2H, H-6a, H-6b), 0.95 (s, 9H, Si–^{t}Bu), 0.94 (s, 9H, Si–^{t}Bu), 0.88 (s, 9H, Si–^{t}Bu), 0.21 (s, 3H, Si–Me), 0.18 (s, 3H, Si–Me), 0.13 (2s, 6H, 2Si–Me), 0.02 (s, 6H, 2Si–Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.31 (d, J_{C-P}=6.6 Hz, C^q arom.), 136.15 (d,

J_{C-P}=7.1 Hz, C^q arom.), 128.40–127.85 (10 CH arom.), 106.63 (d, J_{1-P}=4.5 Hz, C-1), 86.06 (d, J_{3-P}=7.4 Hz, C-3), 83.75 (C-4), 80.14 (d, J_{2-P}=1.9 Hz, C-2), 78.27 (C-5), 68.76 (d, J_{C-P}=6.4 Hz, *C*H$_2$Ph), 68.72 (d, J_{C-P}=6.5 Hz, *C*H$_2$Ph), 61.65 (C-6), 25.82 (Si–C(*C*H$_3$)$_3$), 25.72 (2Si–C(*C*H$_3$)$_3$), 18.00 (Si–*C*(CH$_3$)$_3$), 17.85 (2Si–*C*(CH$_3$)$_3$), 9.67 (d, $J_{1'-P}$ =150.1 Hz, C-1′), −4.00 (Si–Me), −4.27 (Si–Me), −4.40 (Si–Me), −4.74 (Si–Me), −5.46 (2Si–Me); ^{31}P NMR (101 MHz, CDCl$_3$) δ 18.83; MS (DCI-NH$_3$): *m*/*z* 905 [M+H]$^+$; elemental analysis for $C_{39}H_{66}IO_8PSi_3$: calcd (%) C 51.75, H 7.35; meas. C 51.58, H 7.53.

4.2.5. 1,4-Anhydro-1-deoxy-1-(dibenzyloxyphosphoryl)-fluoromethyl-2,3,6-tri-*O*-*tert*-butyldimethylsilyl-D-galactopyranose (14). Compound **9** (72 mg, 0.09 mmol) and molecular sieves 4 Å (300 mg) were dissolved in freshly distilled nitromethane (5 mL) under argon. The suspension was stirred for 1 h at room temperature and Selectfluor·BF_4^- (79 mg, 0.22 mmol, 2.4 equiv) was added and the solution was stirred at 50 °C for 8 h. The reaction mixture was then diluted with CH_2Cl_2 (30 mL), filtered through a pad of Celite® and concentrated. The residue was purified by chromatography on silica gel (eluent cyclohexane/EtOAc: 20/1→15/1) to give compound **14** (37 mg), then its epimer **14′** (8.2 mg) as colorless oils with a global yield of 62%.

4.2.5.1. Major compound 14. $[\alpha]_D^{22}$ +7.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38–7.30 (m, 10H, H arom.), 5.27 (ABX, J_{H-P}=7.3 Hz, J_{H-H}=11.8 Hz, 1H, C*H*Ph), 5.23 (ABX, J_{H-P}=8.6 Hz, J_{H-H}=11.8 Hz, 1H, C*H*Ph), 5.14 (ABX, J_{H-P}=7.4 Hz, J_{H-H}=11.9 Hz, 1H, C*H*Ph), 5.10 (ABX, J_{H-P}=8.6 Hz, J_{H-P}=11.9 Hz, 1H, C*H*Ph), 5.07 (dd, $J_{1'-P}$=8.6 Hz, $J_{1'-F}$=44.9 Hz, 1H, H-1′), 4.55 (s, 1H, H-3), 4.50 (s, 1H, H-4), 3.76 (dd, J_{5-6a}=4.5 Hz, J_{5-6b}=9.8 Hz, 1H, H-5), 3.74 (s, 1H, H-2), 3.64 (ABX, J_{5-6b}=4.5 Hz, J_{6a-6b}=9.8 Hz, 1H, H-6a), 3.47 (t, J_{5-6b}=J_{6a-6b}=9.8 Hz, 1H, H-6b), 0.93 (s, 9H, Si–^{t}Bu), 0.92 (s, 18H, 2Si–^{t}Bu), 0.21 (s, 3H, Si–Me), 0.16 (s, 3H, Si–Me), 0.14 (2s, 6H, 2Si–Me), 0.13 (s, 3H, Si–Me), 0.09 (s, 6H, 2Si–Me); ^{13}C NMR (100 MHz, CDCl$_3$) δ 136.19 (d, J_{C-P}=6.3 Hz, C^q arom.), 135.68 (d, J_{C-P}=5.9 Hz, C^q arom.), 128.51–127.85 (10 CH arom.), 105.87 (dd, J_{1-P}=5.6 Hz, J_{1-F}=17.8 Hz, C-1), 85.05 (C-3), 84.29 (C-4), 84.06 (dd, $J_{1'-P}$=165.0 Hz, $J_{1'-F}$=194.2 Hz, C-1′), 80.22 (d, J_{2-P}=1.6 Hz, C-2), 76.04 (C-5), 69.55 (d, J_{C-P}=5.8 Hz, *C*H$_2$Ph), 68.16 (d, J_{C-P}= 6.8 Hz, *C*H$_2$Ph), 61.80 (C-6), 25.76 (Si–C(*C*H$_3$)$_3$), 25.73 (Si–C(*C*H$_3$)$_3$), 25.64 (Si–C(*C*H$_3$)$_3$), 18.06 (Si–*C*(CH$_3$)$_3$), 17.85 (Si–*C*(CH$_3$)$_3$), 17.79 (Si–*C*(CH$_3$)$_3$), −4.29 (Si–Me), −4.69 (Si–Me), −4.79 (Si–Me), −4.83 (Si–Me), −5.44 (Si–Me), −5.46 (Si–Me); ^{31}P NMR (101 MHz, CDCl$_3$) δ 13.01 (d, J_{P-F}=66.8 Hz); ^{19}F NMR (235 MHz, CDCl$_3$) δ −220.16 (dd, J_{P-F}=66.8 Hz, $J_{F-H1'}$=44.8 Hz); MS (DCI-NH$_3$): *m*/*z* 797 [M+H]$^+$; HRMS for $C_{39}H_{67}O_8FSi_3P$: calcd 797.3865; meas. 797.3872.

4.2.5.2. Minor compound 14′. $[\alpha]_D^{21}$ +10.2 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38–7.30 (m, 10H, H arom.), 5.23 (ABX, J_{H-P}=7.3 Hz, J_{H-H}=11.8 Hz, 1H, C*H*Ph), 5.20 (ABX, J_{H-P}=8.1 Hz, J_{H-H}=11.8 Hz, 1H, C*H*Ph), 5.14 (AX, J_{H-P}=8.7 Hz, 2H, C*H*$_2$Ph), 4.99 (dd, $J_{1'-P}$= 7.6 Hz, $J_{1'-F}$=44.1 Hz, 1H, H-1′), 4.56 (d, J_{3-4}=1.4 Hz, 1H, H-4), 4.27 (dd, J_{2-3}=0.8 Hz, J_{3-4}=1.4 Hz, 1H, H-3), 3.75 (ddd, J_{4-5}=1.7 Hz, J_{5-6a}=4.8 Hz, J_{5-6b}=9.9 Hz, 1H, H-5), 3.73 (s, 1H, H-2), 3.55 (ABX, J_{5-6a}=4.8 Hz, J_{6a-6b}=9.9 Hz, 1H, H-6a), 3.51 (t, J_{5-6b}=J_{6a-6b}=9.9 Hz, 1H, H-6b), 0.95 (s, 9H, Si–^{t}Bu), 0.93 (s, 9H, Si–^{t}Bu), 0.85 (s, 9H, Si–^{t}Bu), 0.14 (s, 3H, Si–Me), 0.13 (s, 6H, 2Si–Me), 0.10 (s, 3H, Si–Me), 0.04 (s, 3H, Si–Me), 0.03 (s, 3H, Si–Me); ^{13}C NMR (100 MHz, CDCl$_3$) δ 136.08 (d, J_{C-P}=6.4 Hz, C^q arom.), 135.86 (d, J_{C-P}=6.5 Hz, C^q arom.), 128.50–127.86 (10 CH arom.), 103.79 (dd, J_{1-P}=8.3 Hz, J_{1-F}=17.7 Hz, C-1), 84.94, 83.51 (dd, $J_{3,4-P}$=3.7 Hz, $J_{3,4-F}$=3.7 Hz, C-3, C-4), 83.53 (dd, $J_{1'-P}$=167.2 Hz, $J_{1'-F}$=185.1 Hz, C-1′), 79.76 (C-2), 76.46 (C-5), 68.86 (d, J_{C-P}=6.0 Hz, *C*H$_2$Ph), 67.98 (d, J_{C-P}=6.4 Hz, *C*H$_2$Ph), 61.53 (C-6), 25.75 (Si–C(*C*H$_3$)$_3$), 25.72 (2Si–C(*C*H$_3$)$_3$), 18.06 (Si–*C*(CH$_3$)$_3$), 17.89 (2Si–*C*(CH$_3$)$_3$), −4.20 (Si–Me), −4.64 (Si–Me), −4.72 (Si–Me), −5.05 (Si–Me), −5.44 (Si–Me), −5.45 (Si–Me); ^{31}P NMR (101 MHz, CDCl$_3$) δ 13.87 (d, J_{P-F}=72.0 Hz); ^{19}F NMR (235 MHz, CDCl$_3$) δ −215.06 (dd, J_{P-F}=72.0 Hz, $J_{F-H1'}$= 44.2 Hz); MS (DCI-NH$_3$): *m*/*z* 797 (100%) [M+H]$^+$, 814 (10%) [M+NH$_4$]$^+$.

4.2.6. 1,4-Anhydro-1-deoxy-1-(dibenzyloxyphosphoryl)-hydroxymethyl-2,3,6-tri-*O*-*tert*-butyldimethylsilyl-D-galactopyranose (15).

4.2.6.1. Procedure using *m*-CPBA. Crushed, activated 3 Å molecular sieves and a solution of **9** (70 mg, 0.090 mmol) in anhydrous CH_2Cl_2 (1 mL) were introduced into a flame-dried flask filled with argon. 10-*d*,*l*-Camphorsulfonic acid (0.1 equiv, 2 mg, 0.064 mmol) and dry *m*-chloroperbenzoic acid (1.2 equiv, 20 mg, 0.077 mmol) were added at room temperature. The solution was then stirred for 15 h at 20 °C and filtered through a pad of Celite®. Saturated aqueous sodium bicarbonate solution (2 mL) was added and the mixture was extracted with CH_2Cl_2 (3×5 mL), washed with a saturated aqueous $Na_2S_2O_3$ solution (5 mL), a saturated aqueous $NaHCO_3$ solution (5 mL), and water (2 mL). The organic layers were dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The crude material was purified by preparative thin layer chromatography (cyclohexane/EtOAc: 70/30) affording **15** (54 mg, 75% yield) as a colorless oil.

4.2.6.2. Procedure using DMDO. Crushed, activated 3 Å molecular sieves and a solution of **9** (120 mg, 0.154 mmol) in anhydrous CH_2Cl_2 (2 mL) were introduced into a flame-dried flask filled with argon. The flask was cooled to 0 °C at each addition of a solution of dimethyldioxirane (0.08 M in acetone, 10 equiv, ~20 mL, 1.54 mmol) portionwise (5×2 equiv/2 h) and dropwise. After each addition of DMDO at 0 °C, the solution was allowed to warm to 15–20 °C. The resulting mixture was stirred for 15 h and filtered through a pad of Celite®. The solvent of the filtrate was removed under reduced pressure and the crude material was diluted in CH_2Cl_2, dried (Na_2SO_4), filtered, and concentrated. The crude epoxide was diluted in anhydrous CH_2Cl_2 (3 mL) and stirred with 3 Å molecular sieves (200 mg) at room temperature under an atmosphere of argon. After 1 h, 10-*d*,*l*-camphorsulfonic acid (0.2 equiv, 10 mg, 0.043 mmol, M.W. 232) was added. The resulting mixture was stirred for 5 h at room temperature, filtered through a pad of Celite®, and the solvents were removed under reduced pressure. Two subsequent purifications by preparative thin layer chromatography (cyclohexane/EtOAc: 90/10) afforded **15** (79 mg, 64% yield).

$[\alpha]_D^{20}$ +8.000 (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.39 (m, 10H, H arom.), 5.08–5.22 (m, 4H, CH_2Ph), 4.52 (s, 1H, H-3), 4.48 (d, J_{3-4}=1.2 Hz, 1H, H-4), 4.31 (dd, $J_{1'-OH}$=4.6 Hz, $J_{1'-P}$=12.0 Hz, 1H, H-1′), 3.74 (dd, J_{5-6a}=4.4 Hz, J_{5-6b}=9.2 Hz, 1H, H-5), 3.72 (s, 1H, H-2), 3.61 (ABX, J_{5-6a}=4.4 Hz, J_{6a-6b}=9.6 Hz, 1H, H-6a), 3.44 (t, J_{5-6b}=J_{6a-6b}=9.4 Hz, 1H, H-6b), 2.67 (dd, $J_{OH-1'}$=4.6 Hz, J_{OH-P}=16.6 Hz, 1H, OH), 0.89 (s, 18H, 2Si–^{t}Bu), 0.88 (s, 9H, Si–^{t}Bu), 0.11 (s, 3H, Si–Me), 0.10 (s, 3H, Si–Me), 0.09 (s, 6H, 2Si–Me), 0.05 (s, 6H, 2Si–Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.68 (C^q arom.), 136.22 (C^q arom.), 127.71–128.64 (10 *C*H arom.), 107.08 (d, J_{1-P}=5.9 Hz, C-1), 84.75 (C-3), 84.41 (C-4), 80.24 (C-2), 75.93 (C-5), 68.95 (d, J_{C-P}=6.68 Hz, CH_2Ph), 67.86 (d, J_{C-P}=6.67 Hz, CH_2Ph), 65.46 (d, $J_{1'-P}$=164 Hz, C-1′), 61.89 (C-6), 25.75 (2Si–$C(CH_3)_3$), 25.68 (Si–$C(CH_3)_3$), 18.08 (Si–C$(CH_3)_3$), 17.83 (Si–C$(CH_3)_3$), −4.24 (Si–Me), −4.61 (Si–Me), −4.75 (Si–Me), −5.44 (Si–Me); ^{31}P NMR (101 MHz, $CDCl_3$) δ 19.29; IR (KBr): 3345, 3067, 3035, 2956, 2931, 2889, 2858, 1949, 1758, 1499, 1470, 1388, 1363, 1305, 1256, 1217, 1101, 1020, 980, 940, 901, 838, 779, 758; MS (DCI-NH_3): *m/z* 550 (100%) $[M-2TBDMS-OH]^+$, 795 (15%) $[M+H]^+$, 812 (5%) $[M+NH_4]^+$; HRMS for $C_{39}H_{68}O_9Si_3P$: calcd 795.3909; meas. 795.3898.

4.2.7. (1(1′)*Z*)-1-Deoxy-1-(dibenzyloxyphosphoryl)-methylidene-D-galactofuranose (16) and 1,4-anhydro-1-deoxy-1-(dibenzyloxyphosphoryl)methyl-D-galactopyranose (17). To a solution of **12** (186 mg, 0.24 mmol) in distilled THF (10 mL) cooled to −50 °C was added tetrabutylammonium fluoride trihydrate (226 mg, 0.72 mmol, 3 equiv). The reaction mixture was stirred for 16 h at −5 °C. The solvent was then removed from the solution under reduced pressure and the crude was first purified by flash chromatography on silica gel column with EtOAc/EtOH (9/1) as eluent and secondly repurified by flash chromatography with acetone/CH_2Cl_2 (8/2) as eluent to separate **17** from *exo*-glycal **16**. Compound **16** (86 mg) was obtained in 83% yield as a colorless oil.

4.2.7.1. Compound 17. $[\alpha]_D^{24}$ +33.7 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ 7.56–7.52 (m, 10H, H arom.), 5.29–5.18 (2 ABX, 4H, 2CH_2Ph), 4.64 (d, J_{3-4}=1.5 Hz, 1H, H-4), 4.00 (t, J_{2-3}=J_{3-4}=1.3 Hz, 1H, H-3), 3.97 (dd, J_{5-6a}=6.0 Hz, J_{5-6b}=4.9 Hz, 1H, H-5), 3.88 (d, 1H, H-2), 3.72 (ABX, J_{5-6a}=6.0 Hz, J_{6a-6b}=11.6 Hz, 1H, H-6a), 3.67 (ABX, J_{5-6b}=4.9 Hz, J_{6a-6b}=11.6 Hz, 1H, H-6b), 2.84 (ABX, $J_{1'a-1'b}$=15.9 Hz, $J_{1'a-P}$=19.2 Hz, 1H, H-1′a), 2.80 (ABX, $J_{1'a-1'b}$=15.9 Hz, $J_{1'b-P}$=19.0 Hz, 1H, H-1′b); ^{13}C NMR (100 MHz, CD_3OD) δ 137.90 (d, J_{C-P}=6.0 Hz, C^q arom.), 137.87 (d, J_{C-P}=6.3 Hz, C^q arom.), 129.91–129.45 (10 CH arom.), 107.08 (d, J_{1-P}=5.9 Hz, C-1), 86.98 (d, J_{3-P}=8.1 Hz, C-3), 85.84 (C-4), 79.86 (d, J_{2-P}=1.6 Hz, C-2), 78.86 (C-5), 69.36 (d, J_{C-P}=6.5 Hz, CH_2Ph), 69.28 (d, J_{C-P}=6.5 Hz, CH_2Ph), 63.79 (C-6), 28.36 (d, $J_{1'-P}$=141.8 Hz, C-1′); ^{31}P NMR (101 MHz, $CDCl_3$) δ 26.94; MS (DCI-NH_3): *m/z* 437 (100%) $[M+H]^+$, 454 (20%) $[M+NH_4]^+$; elemental analysis for $C_{21}H_{25}O_8P$: calcd (%) C 57.80, H 5.77; meas. C 57.74, H 5.94.

4.2.7.2. Compound 16. $[\alpha]_D^{20}$ +19.9 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ 7.55–7.49 (m, 10H, H arom.), 5.22–5.18 (m, 4H, CH_2Ph), 4.90 (dd, $J_{1'-2}$=1.6 Hz, $J_{1'-P}$=11.4 Hz, 1H, H-1′), 4.65 (ddd, $J_{1'-2}$=1.6 Hz, J_{2-3}=7.9 Hz, J_{2-P}=4.2 Hz, 1H, H-2), 4.38–4.33 (m, J_{3-4}=5.6 Hz, J_{4-5}=1.9 Hz, 2H, H-3 and H-4), 3.94 (ddd, J_{4-5}=1.9 Hz, J_{5-6a}=7.3 Hz, J_{5-6b}=5.8 Hz, 1H, H-5), 3.86 (m, 2H, J_{6a-6b}=6.3 Hz, H-6a, H-6b); ^{13}C NMR (100 MHz, CD_3OD) δ 176.91 (d, J_{1-P}=1.9 Hz, C-1), 138.15 (d, J_{C-P}=7.2 Hz, C arom.), 138.08 (d, J_{C-P}=7.0 Hz, C arom.), 129.85–129.20 (10 CH arom.), 86.16 (C-4), 80.53 (d, $J_{1'-P}$=195.7 Hz, C-1′), 79.12 (d, J_{2-P}=12.9 Hz, C-2), 75.62 (C-3), 71.50 (C-5), 69.00 (d, J_{C-P}=5.2 Hz, CH_2Ph), 68.74 (d, J_{C-P}=5.2 Hz, CH_2Ph), 63.99 (C-6); ^{31}P NMR (101 MHz, $CDCl_3$) δ 21.35; MS (DCI-NH_3): *m/z* 437 (100%) $[M+H]^+$, 454 (55%) $[M+NH_4]^+$; HRMS for $C_{21}H_{26}O_8P$: calcd 437.1365; meas. 437.1372.

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