JOC The Journal of Organic Chemistry

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Accessing C-1 Phosphonylated 2-Acylamino Uronic Acids via 2-Nitro-glycals

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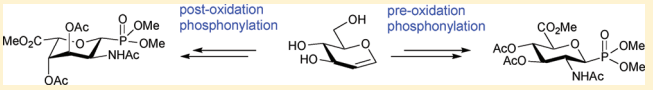
Supporting Information

ABSTRACT: Two approaches are described for the synthesis of 2-acylamino uronic acid glycosyl phosphonates from readily accessible D-glucal. The first approach that entailed oxidation of the C-6 hydroxyl group followed by phosphonylation of the uronate 2-nitro-glycal, resulted in the formation of the β-L-*gulo*-configured phosphonate. Reversing the reaction order resulted in the exclusive formation of the β-D-*gluco*-configured phosphonate. In both cases the thermodynamic 1,2-*trans*-di-equatorial phosphonylation product is obtained.

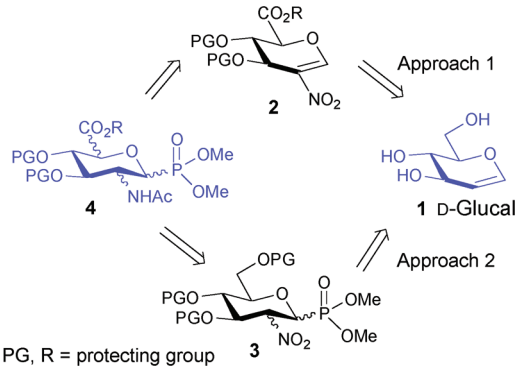


Phosphonylated carbohydrates are of interest as biological probes because of the stability of the C−P bond to hydrolysis by enzymes involved in phosphate cleavage. Glycosyl phosphonates are therefore considered to act as stable biomimetics of the corresponding glycosyl phosphates.[1] Interestingly, and to the best of our knowledge, uronosyl phosphonates are not described in the literature, despite the fact that uronic acids are important carbohydrates in mammalian[2,3] and microbial[4] biology. Of particular interest to us are functionalized β-phosphonates of glucuronic acid because of their potential value as intermediates in influenza virus sialidase uronic acid-based inhibitor synthesis[5−8] and their potential utility in probing glycosyltransferases such as UDP-glucose:dolichyl-phosphate β-D-glucosyltransferase [EC 2.4.1.117]. This glycosyltransferase is important in *N*-glycan biosynthesis[9] and provides the activated β-glucosyl phosphate, dolichyl β-D-glucosyl phosphate, that is enzymatically transferred to a dolichol oligosaccharide precursor (DOP). The oligosaccharide precursor is then enzymatically transferred to asparagine residues of nascent proteins.[9]

Our interest in the chemistry of 2-acylamino-2-deoxy-uronic acids[5−8] led us to select this framework for the synthesis of the corresponding glucuronosyl phosphonate. In considering approaches to glycosyl phosphonates of 2-acylamino-2-deoxy-uronic acids we found no reports of direct C-1 phosphonylation of 2-acylamino-2-deoxy sugars. Indeed in our own attempts at Lewis acid-mediated phosphonylation of 2-acylamino-2-deoxy-hexose 1-*O*-acetyl,[10] trichloroacetimidyl,[11] or oxazoline derivatives, we found these substrates to be unreactive.[12] Instead, access to 2-*N*-substituted glucosyl phosphonates has been achieved through phosphonylation of 2-azido-1-*O*-trichloroacetimidyl sugars,[11,13] or by Michael-type addition of $HPO(OMe)_2$ to 2-nitro-glycals.[14] As 2-nitro-glycals are versatile intermediates that are amenable to a range of Michael-type addition reactions,[15] we explored the applicability of this approach to access glycosyl phosphonates of 2-acylamino-2-deoxy-uronic acids.

Two approaches were envisaged for the synthesis of 2-acetamido uronic acid glycosyl phosphonates **4** *via* 2-nitro-glycals, from the common precursor D-glucal **1** (Scheme 1). In both approaches, the key steps are the introduction of the anomeric phosphonate moiety and oxidation of the C-6 hydroxyl group to form the uronate; chemical manipulation of the 2-nitro group is used to install the 2-acetamido group. In the first approach, the C-6 hydroxyl group of a selectively protected derivative of D-glucal **1** is oxidized prior to nitration at C-2 and phosphonylation at C-1, with final reduction of the nitro group. In the second approach, the reaction sequence begins with nitration at C-2 of a protected D-glucal derivative, followed by phosphonylation at C-1, reduction of the nitro group, and finally oxidation of the C-6 hydroxyl group to provide the protected 2-acetamido glucuronosyl phosphonate **4**.

Scheme 1. Retrosynthetic Approaches to Uronyl Phosphonates 4

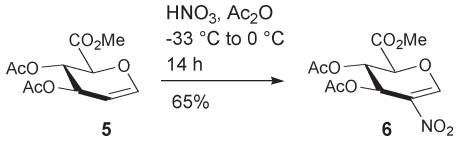


Approach 1 (Scheme 1) to uronosyl phosphonates **4** required preparation of the previously unknown 2-nitro-uronate glycals of type **2**. In the first instance advantage was taken of the ready accessibility of 3,4-di-*O*-acetylated uronate glycal **5**.[16] Reaction of **5** with acetyl nitrate (preformed *in situ* from HNO_3 and

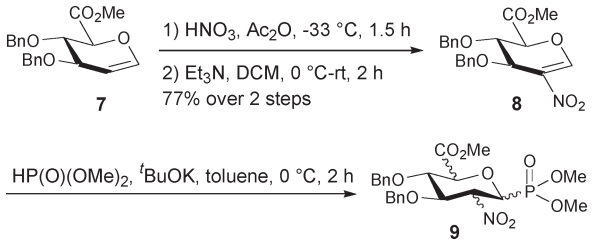
Received: February 4, 2011
Published: April 15, 2011

dx.doi.org/10.1021/jo2002193 | *J. Org. Chem.* 2011, 76, 4099–4104

Scheme 2. Synthesis of Acetate-Protected 2-Nitro-uronate Glycal 6



Scheme 3. Synthesis of 2-Nitro-uronosyl Phosphonate 9

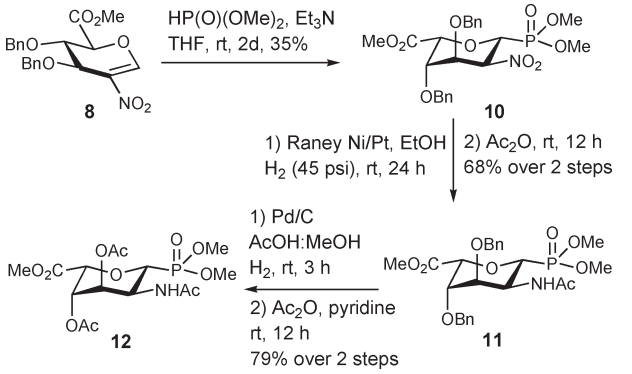


Ac_2O)[17,18] directly produced 2-nitro-glycal **6** (Scheme 2), without the need for addition of base to eliminate HOAc from the intermediate 2-nitro-glycosyl acetate, as required for benzylated 2-nitro-glycals[18] (see Scheme 3). Attempted phosphonylation of **6** using conditions [$HP(O)(OMe)_2$ ^{t}BuOK, anhydrous toluene, 0 °C, 2 h] reported for phosphonylation of 3,4,6-tri-*O*-benzyl-2-nitro-D-glucal,[14] however, returned unreacted starting material. Increased reaction time (to 12 h) and temperature (to rt), also returned unreacted **6**, while reaction at 40 °C led to decomposition. Variation of the base (DBU, Et_3N) and solvent also failed to produce any of the desired product.

Given that 3,4,6-tri-*O*-benzylated 2-nitro D-glucal and D-galactal show reactivity toward a range of Michael-type additions,[15] including phosphonylation,[14] we wondered if the acetate protecting groups may have been contributing to the lack of reactivity of **6**. Synthesis of the benzyl-protected 2-nitro-uronate **8** was therefore pursued. Direct synthesis of the required precursor 3,4-di-*O*-benzylated uronate glycal **7** from acetylated **5**, by de-*O*-acetylation and subsequent 3,4-di-*O*-benzylation under acidic (TfOH[19] or TMSOTf,[20] benzyl trichloroacetimidate) or basic (NaH, benzyl bromide) conditions, was complicated by the formation of mixtures of components in each case. The 3,4-di-*O*-benzylated uronate glycal **7** was therefore prepared using an established approach[21] over seven steps starting from D-glucal **1**. The target 3,4-di-*O*-benzylated 2-nitro-glycal derivative **8** was then readily formed in a two-step, addition−elimination sequence. Thus, treatment of **7** with preformed acetyl nitrate, followed by reaction of the product with Et_3N afforded the novel 2-nitro-uronate glycal **8** in 77% yield over two steps (Scheme 3).

Phosphonylation of benzylated uronate 2-nitro-glycal **8** (Scheme 3) was initially attempted repeating the conditions reported for phosphonylation of tri-*O*-benzyl-2-nitro-D-glucal.[14] Where acetate-protected analogue **6** had been unreactive, the benzylated derivative **8** was indeed phosphonylated; however, the product was a mixture of isomers (represented by **9**), as judged by the complex ^{1}H NMR spectrum. Replacing the ^{t}BuOK with bases such as DBU and KHMDS also gave a less than satisfactory outcome. The use of Et_3N in THF, however, provided a single phosphonate isomer **10** in 35% yield (43% yield based on recovered starting material) (Scheme 4).

Scheme 4. Synthesis of Uronosyl Phosphonates (10, 11, 12)



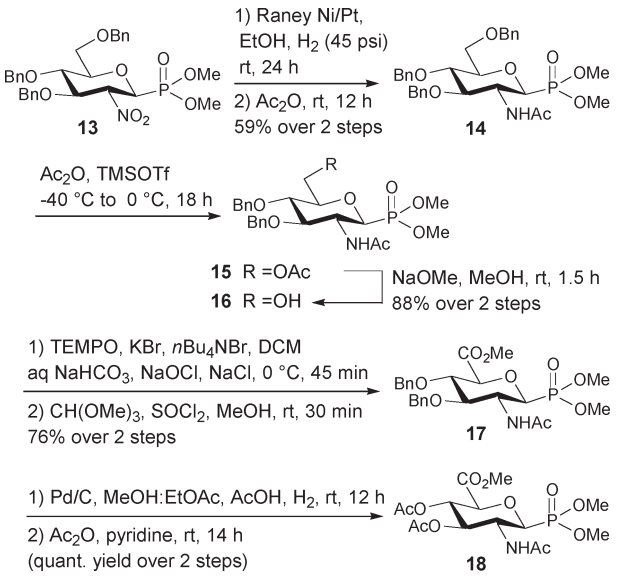
Phosphonate **10** was further manipulated to produce the acetate-protected 2-acetamido derivative **12** (Scheme 4). Reduction of the nitro group of benzyl-protected **10** was successfully accomplished using platinized Raney nickel[14,22] (Scheme 4). The intermediate amino compound was then acetylated to give the 2-acetamido derivative **11** (68% yield over two steps). Subsequent debenzylation under standard conditions, followed by acetylation of the isolated crude diol afforded compound **12** (79% yield over two steps).

In the ^{1}H NMR spectra of **10**, **11**, and **12**, the observed H-4/H-5 coupling constant ($J_{4,5}$ 1.5 Hz) was consistent with an L-sugar, indicating epimerization at C-5 had occurred during the phosphonylation reaction. The observation of epimerization at C-5 under these phosphonylation conditions is presumably related to the acidity of H-5 in either 2-nitro-uronate glycal **8** or the corresponding phosphonate and the reaction's basic conditions. Examples of L-*ido* uronates, that preferentially exist in a $^1C_4$ conformation, have been reported to have $J_{4,5}$ values of 1.5 Hz.[23,24] The large H-1/H-2 coupling in both **10** ($J_{1,2}$ 7.8 Hz) and **12** ($J_{1,2}$ 10.5 Hz) indicated a diaxial relationship between the two protons. In conjunction with $J_{3,2}$ and $J_{3,4}$ values in **12** of ~3.0 and 3.9 Hz, respectively, the NMR data for phosphonates **10**−**12** is consistent with a β-L-*gulo* configured sugar in a $^1C_4$ conformation, that has essentially axial substituents at C-3 and C-4 and equatorial substituents at C-1, C-2, and C-5. In addition, the observed $^3J_{H\text{-}2,P}$ coupling of ~8 Hz is in the region anticipated for this configuration.[10] This structure indicates the formation of the thermodynamically more stable 1,2-diequatorial 2-nitro-phosphonate under the reaction conditions used, as seen previously for the phosphonylation products of benzylated D-glucal and L-rhamnal.[14]

The second approach (Approach 2, Scheme 1) to the target uronosyl phosphonates **4** was based on manipulation of 3,4,6-tri-*O*-benzyl-2-nitro-β-D-glucosyl phosphonate **13**,[14] prepared by phosphonylation of 3,4,6-tri-*O*-benzyl-2-nitro-D-glucal. In the first step (Scheme 5), **13** was converted to the 2-acetamido-β-D-glucosyl phosphonate **14**, using reaction conditions identical to those described above for the 2-nitro-uronate derivative **10**. Global debenzylation of **14** and subsequent conversion of the resultant 3,4,6-trihydroxy intermediate to the fully protected methyl glucuronate **18** in a three-step, one-pot, reaction involving selective TEMPO-catalyzed oxidation[25] of the primary hydroxyl group, followed by esterification, and finally acetylation of the secondary hydroxyl groups, appeared an attractive approach. In practice, however, isolation of the final product **18** following this reaction sequence proved to be problematic, with poor reproducibility and often only low overall yield of **18** from **14**.

dx.doi.org/10.1021/jo2002193 |J. Org. Chem. 2011, 76, 4099–4104

Scheme 5. Synthesis of Uronosyl Phosphonates (17, 18)



To improve the synthesis of **18**, a stepwise approach was followed beginning with the TMSOTf/Ac_2O-mediated selective acetolysis[26] of the primary 6-*O*-benzyl group. Accordingly, 3,4,6-tri-*O*-benzylated phosphonate **14** in DCM was treated with Ac_2O in the presence of TMSOTf at −40 °C to give the corresponding 6-*O*-acetylated derivative **15**. The resulting 6-*O*-acetate group of **15** was then removed under Zemplén conditions to give 6-hydroxy derivative **16** in 88% yield over two steps. TEMPO-based oxidation[27] of the primary hydroxyl group of **16**, was followed by acidic esterification[28] of the crude product to furnish the benzyl-protected methyl ester **17** in 76% yield over two steps.

Subsequent hydrogenolysis of the benzyl groups of **17**, followed by acetylation under standard conditions (Ac_2O, pyridine), furnished the acetate protected methyl uronate **18** in good overall yield from **14**. ^{1}H NMR spectral analysis of **18**, showed the $J_{1,2}$, $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ vicinal coupling constants to be greater than 9.0 Hz, and $^3J_{H\text{-}2,P}$ to be in the range of ∼9−10 Hz,[10] consistent with the expected β-D-*gluco*- configuration.

In summary, the present study provides two approaches to 2-acylamino uronic acid glycosyl phosphonates. Interestingly, two conformationally distinct uronosyl phosphonates resulted from the two described phosphonylation approaches (Scheme 1). The 3,4-di-*O*-benzylated uronate 2-nitro-glycal **8**, reported here, should prove a valuable addition to the range of 2-nitro-glycals that provide reactive substrates for various Michael-type addition reactions.[15,29]

EXPERIMENTAL SECTION

For ^{1}H and ^{13}C spectra, chemical shifts are expressed as parts per million (ppm, δ) and are relative to the solvent used [$CDCl_3$: 7.26 (s) for ^{1}H; 77.0 (t) for ^{13}C]. ^{31}P NMR chemical shifts are quoted in ppm downfield relative to 85% phosphoric acid (H_3PO_4) as external reference (0.00 ppm). The use of (′) and (″) in the labeling of chemical structures is purely to aid the assignment of signals in the ^{1}H and ^{13}C NMR spectra and does not correspond with the chemical names.

Methyl 3,4-Di-*O*-acetyl-1,5-anhydro-2-nitro-2-deoxy-D-*arabino*-hex-1-enuronate (6). Prepared using a procedure adapted from Das and Schmidt,[18] Ac_2O (2.9 mL) was placed in RBF, cooled to 10 °C, and to it was added 70% w/w HNO_3 (0.42 mL, 6.54 mmol) dropwise with stirring under Ar. The external temperature was further lowered to −10 °C to keep the internal temperature in the range of 20−25 °C during the addition. Once the addition was complete, the solution was further cooled to −33 °C using acetone−dry ice cooling bath. Then, a solution of methyl 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enuronate **5**[16] (0.5 g, 1.93 mmol) in Ac_2O (2 mL) was added slowly, and the reaction mixture was stirred at −33 °C for 2 h and then at 0 °C for 12 h. The reaction mixture was poured into 15 mL ice-cold H_2O, brine (10 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The pasty residue obtained was crystallized from MeOH to yield **6** (0.383 g, 65%) as white crystals. R_f 0.30 (EtOAc/hexane, 1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (s, 1H, H-1), 5.92 (dd, 1H, $J_{3,5}$ 1.5 Hz, $J_{3,4}$ 2.7 Hz, H-3), 5.52 (dd, 1H, $J_{4,5}$ 1.8 Hz, $J_{4,3}$ 2.7 Hz, H-4), 5.06 (app t, 1H, $J_{5,3} = J_{5,4}$ 1.8 Hz, H-5), 3.79 (s, 3H, CO_2CH_3), 2.10 (s, 3H, $OCOCH_3$), 2.00 (s, 3H, $OCOCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.8, 168.5 ($OCOCH_3$), 164.9 (CO_2CH_3), 155.7 (C-1), 128.3 (C-2), 73.9 (C-5), 65.8 (C-4), 60.6 (C-3), 53.1 (CO_2CH_3), 20.7, 20.5 ($OCOCH_3$); LRMS (ESI): *m*/*z* 326 [(M + Na)$^+$ 100%].

Methyl 1,5-Anhydro-3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enuronate (7). A solution of 1,5-anhydro-3,4-di-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enuronate[30] (1 g, 3.06 mmol) in anhydrous DCM (2 mL) was added dropwise to a solution of Dess−Martin periodinane (DMP) reagent (1.56 g, 3.68 mmol) in anhydrous DCM (8 mL). The solution was stirred vigorously at room temperature and monitored by TLC analysis (EtOAc/hexane, 3:7). After 2 h, the reaction was complete, and the solution was diluted with diethyl ether (10 mL) and poured into saturated ice-cold $NaHCO_3$ solution. The organic phase was separated and washed successively with H_2O (2 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was taken up in ^{t}BuOH (13.2 mL) and treated with 2-methyl-2-butene (0.54 mL, 5.09 mmol) at room temperature. To this mixture was added a solution of $NaOCl_2$ (0.6 g, 6.79 mmol) and NaH_2PO_4 (0.6 g, 5.09 mmol) in H_2O (3.3 mL), and the reaction was stirred for 2 h after which time TLC analysis indicated completion of reaction. The reaction mixture was concentrated under reduced pressure, the residue was taken up in H_2O (10 mL) and extracted with hexane (10 mL) to remove organic impurities. The aq solution was acidified to pH 3 with dil HCl and then extracted with diethyl ether (3 × 30 mL). The combined Et_2O phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude acid was dissolved in anhydrous DMF (5 mL), and to it was added $KHCO_3$ (0.42 g 4.25 mmol) followed by MeI (0.26 mL, 4.18 mmol). The reaction mixture was stirred at room temperature for 3 h at which time TLC analysis (EtOAc/hexane, 1:4) indicated complete conversion of an acid to the product. The reaction mixture was then diluted with H_2O and extracted with diethyl ether (3 × 30 mL). The combined organic phase was successively washed with H_2O (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction material was purified by column chromatography (EtOAc/hexane, 0.3:9.7→0.8:9.2) to give title compound **7** (0.836 g, 77% over three steps) as a white solid. R_f 0.28 (EtOAc/hexane, 1.5:8.5); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27−7.15 (m, 10H, aromatic H), 6.54 (d, 1H, $J_{1,2}$ 6.3 Hz, H-1), 4.92 (app t, 1H, $J_{2,1} = J_{2,3}$ 6.0 Hz, H-2), 4.70−4.69 (m, 1H, H-5), 4.60 (dd, 2H, J_{gem} 12.0 Hz, J_{gem} 12.3 Hz, CH_2Ph), 4.33 (dd, 2H, J_{gem} 11.4 Hz, J_{gem} 11.4 Hz, CH_2Ph), 4.13−4.10 (m, 1H, H-4), 3.77−3.75 (m, 1H, H-3), 3.47 (s, 3H, CO_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.5 (CO_2CH_3), 144.9 (C-1), 137.7, 137.3, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 127.5 (aromatic), 98.4 (C-2), 73.0 (C-4), 72.6 (C-5), 71.8, 69.4 (2 × CH_2Ph), 67.7 (C-3), 52.0 (CO_2CH_3); LRMS (ESI): *m*/*z* 377 [(M + Na)$^+$ 100%].

dx.doi.org/10.1021/jo2002193 |J. Org. Chem. 2011, 76, 4099–4104

Methyl 1,5-Anhydro-3,4-di-*O*-benzyl-2-nitro-2-deoxy-D-*arabino*-hex-1-enuronate (8). Prepared using a procedure adapted from Das and Schmidt,[18] Ac_2O (5.6 mL) was placed in RBF and cooled to 10 °C; to it was added 70% w/w HNO_3 (0.56 mL, 6.32 mmol) dropwise with stirring under Ar. The external temperature was further lowered to −10 °C to keep the internal temperature in the range of 20−25 °C during the addition. Once the addition was complete, the solution was further cooled to −33 °C using acetone−dry ice cooling bath. Then, a solution of compound **7** (0.59 g, 1.66 mmol) in Ac_2O (2 mL) was added slowly, and the reaction mixture was stirred at −33 °C for 1.5 h at which time TLC analysis (EtOAc/hexane, 1.5:8.5) indicated complete consumption of the starting material. The reaction mixture was poured into 20 mL ice-cold H_2O, brine (10 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered, and the solvent was coevaporated with toluene until dryness. The residue was dissolved in DCM (5 mL), the solution was cooled to 0 °C, and Et_3N (0.27 mL, 1.99 mmol) was added under Ar. After complete addition of Et_3N, the cooling bath was removed and stirring continued for 2 h at room temperature after which time DCM (10 mL) was added to the reaction. The reaction solution was washed successively with 1 M HCl (10 mL) solution, H_2O (2 × 20 mL), and brine (10 mL), dried over anhydrous Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure. The crude product was loaded onto the column of silica-gel saturated with 1% Et_3N and then purified by column chromatography (EtOAc/hexane/Et_3N, 0.2:8.8:1→1:8:1) to furnish 2-nitro compound **8** (0.51 g, 77% yield over two steps)] as white solid. R_f 0.31 (EtOAc/hexane, 1.5:8.5); The ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (s, 1H, H-1), 7.41−7.26 (m, 10H, aromatic H), 5.00 (br s, 1H, H-5), 4.73 (br s, 1H, H-3), 4.62 (br s, 2H, CH_2Ph), 4.55 (br s, 2H, CH_2Ph), 4.33 (app d, 1H, $J_{4,3}$ 1.8 Hz, H-4), 3.48 (s, 3H, CO_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 166.0 (CO_2CH_3), 154.5 (C-1), 136.8, 136.3 (aromatic), 130.9 (C-2), 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.7 (aromatic), 74.3 (C-5), 72.3, 72.0 (2 × CH_2Ph), 71.6 (C-4), 66.7 (C-3), 52.6 (CO_2CH_3); LRMS (ESI): m/z 441 [$(M + H_2O + Na)^+$ 100%].

Methyl [(Dimethyl phosphonyl) 3,4-di-*O*-benzyl-2-nitro-1,2-dideoxy-β-L-gulopyranosid]uronate (10). A solution of compound **8** (0.8 g, 2 mmol) in THF (5 mL) was added to a solution of dimethyl phosphonate (2.2 mL, 24 mmol) and Et_3N (4.2 mL, 30 mmol) in THF (5 mL) at room temperature under Ar. The reaction mixture was stirred for 48 h, after which it was concentrated under reduced pressure, and the residue was loaded onto a column of silica gel and purified by chromatography (EtOAc/hexane, 2.5:7.5→3:2) to furnish the title compound **10** [0.36 g, 35%; 43% based on recovered starting material (0.14 g)] as a clear oil. R_f 0.31 (EtOAc/hexane, 3:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.27 (m, 8H, aromatic H), 7.13−7.08 (m, 2H, aromatic H), 5.24 (dd, 1H, $J_{1,2}$ 7.8 Hz, $J_{H\text{-}1,P}$ 10.8 Hz, H-1), 5.13−5.05 (m, 1H, H-2), 4.62 (dd, 2H, J_{gem} 12.0 Hz, J_{gem} 12.0 Hz, CH_2Ph), 4.51 (br d, 1H, $J_{5,4}$ 1.5 Hz, H-5), 4.32 (dd, 2H, J_{gem} 11.1 Hz, J_{gem} 11.4 Hz, CH_2Ph), 4.27−4.21 (m, 2H, H-3, H-4), 3.83 (d, 3H, $J_{H,P}$ 4.8 Hz, POCH_3), 3.80 (d, 3H, $J_{H,P}$ 4.5 Hz, POCH_3), 3.46 (s, 3H, CO_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.7 (CO_2CH_3), 136.6, 135.8, 128.7, 128.6, 128.4, 128.3, 128.1, 127.9, 127.8, 127.6 (aromatic), 78.9 (d, $J_{C,P}$ 2.2 Hz, C-2), 74.0 (d, $J_{C,P}$ 8.3 Hz, C-3), 73.2 (CH_2Ph), 73.1 (C-4), 72.2 (CH_2Ph), 72.0 (d, $J_{C,P}$ 12.8 Hz, C-5), 64.9 (d, $J_{C,P}$ 173.6 Hz, C-1), 54.0 (d, $J_{C,P}$ 6.7 Hz, POCH_3), 53.7 (d, $J_{C,P}$ 6.7 Hz, POCH_3), 52.3 (CO_2CH_3); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ +20.30; LRMS (ESI): m/z 532 [$(M + Na)^+$ 100%]; HRMS calcd for $C_{23}H_{28}NO_{10}P_1$ $[M + H]^+$ 510.152359, found 510.154906.

Methyl [(Dimethyl phosphonyl) 2-acetamido-3,4-di-*O*-benzyl-1,2-dideoxy-β-L-gulopyranosid]uronate (11). 2-Nitro compound **10** (0.2 g, 0.39 mmol) was dissolved in EtOH (5 mL) and transferred to a hydrogenation vessel. Platinized Raney nickel catalyst was freshly prepared according to the method of Nishimura.[22] The material obtained from 1.5 g of Raney nickel/aluminum alloy was suspended in EtOH (10 mL) and added to the reaction vessel, and the mixture was shaken in a Parr hydrogenation apparatus at a hydrogen pressure of 45 psi. After 24 h, the catalyst was carefully filtered through Celite, and the filtrate was evaporated under reduced pressure to yield the crude amine which was dissolved in Ac_2O (2 mL) and stirred overnight at room temperature under N_2. Coevaporation of the Ac_2O with toluene, followed by column chromatography (EtOAc→MeOH/EtOAc 0.4:9.6) afforded the 2-acetamido compound **11** (0.14 g, 68% over two steps)] as an oil. R_f 0.42 (MeOH/EtOAc, 0.4:9.6); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.26 (m, 8H, aromatic H), 7.15−7.11 (m, 2H, aromatic H), 5.87 (d, 1H, $J_{NH,H\text{-}2}$ 7.8 Hz, NH), 4.74−4.56 (m, 4H, H-2, H-1, CH_2Ph), 4.48 (br d, 1H, $J_{5,4}$ 1.5 Hz, H-5), 4.43 (d, 1H, J_{gem} 11.7 Hz, CHPh), 4.21 (d, 1H, J_{gem} 11.7 Hz, CHPh), 4.16 (dt, 1H, $J_{4,5}$ 1.8 Hz, $J_{4,3}$ 3.9 Hz, $J_{H\text{-}4,P}$ 1.8 Hz, H-4), 3.85 (d, 3H, $J_{H,P}$ 10.8 Hz, POCH_3), 3.87−3.83 (m, 1H, H-3), 3.80 (d, 3H, $J_{H,P}$ 10.5 Hz, POCH_3), 3.52 (s, 3H, CO_2CH_3), 1.84 (s, 3H, NHCOCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 169.6 (NHCOCH$_3$), 169.4 (CO_2CH_3), 137.2, 136.9, 128.6, 128.5, 128.2, 128.0, 127.9 (aromatic), 73.7 (d, $J_{C,P}$ 11.3 Hz, C-3), 73.1 (C-4), 73.0 (C-5), 72.6, 71.8 (2 × CH_2Ph), 65.5 (d, $J_{C,P}$ 168.3 Hz, C-1), 53.8 (d, $J_{C,P}$ 7.5 Hz, POCH_3), 53.4 (d, $J_{C,P}$ 6.0 Hz, POCH_3), 52.1 (CO_2CH_3), 44.5 (C-2), 23.3 (NHCOCH_3); LRMS (ESI): m/z 544 [$(M + Na)^+$ 100%].

Methyl [(Dimethyl phosphonyl) 2-acetamido-3,4-di-*O*-acetyl-1,2-dideoxy-β-L-gulopyranosid]uronate (12). Compound **11** (0.14 g, 0.268 mmol) was dissolved in methanol (2 mL) under N_2, then Pd/C (60 mg, 10% Pd/C) was added, cautiously followed by AcOH (2 mL), and the reaction was stirred under an H_2 atmosphere for 3 h. The reaction mixture was then carefully filtered through Celite, the solvent was evaporated, and the crude diol was subsequently treated with Ac_2O (0.5 mL) in pyridine (1 mL) under N_2. The reaction mixture was stirred overnight at room temperature and then coevaporated with toluene. The crude residue was purified by column chromatography (EtOAc→MeOH/EtOAc, 0.6:9.4) to yield title compound **12** (90 mg, 79% over two steps) as a colorless viscous syrup. R_f 0.25 (MeOH/EtOAc, 0.4:9.6); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.79 (d, 1H, $J_{NH,H\text{-}2}$ 7.5 Hz, NH), 5.37 (dt, 1H, $J_{4,5}$ 1.8 Hz, $J_{4,3}$ 3.9 Hz, $J_{H\text{-}4,P}$ 1.8 Hz, H-4), 5.24 (app q, 1H, $J_{3,4}$ 3.6 Hz, $J_{3,2}$ 3.6 Hz, $J_{H\text{-}3,P}$ 3.3 Hz, H-3), 4.79−4.69 (app dtd, 1H, $J_{2,3}$ ~2.7 Hz, $J_{2,NH}$ 7.8 Hz, $J_{2,1}$ 10.5 Hz, $J_{H\text{-}2,P}$ ~8.0 Hz, H-2), 4.61 (app t, 1H, $J_{1,2}$ 10.5 Hz, $J_{H\text{-}1,P}$ 10.8 Hz, H-1), 4.56 (br d, 1H, $J_{5,4}$ 1.5 Hz, H-5), 3.92 (d, 3H, $J_{H,P}$ 11.1 Hz, POCH_3), 3.83 (d, 3H, $J_{H,P}$ 10.8 Hz, POCH_3), 3.77 (s, 3H, CO_2CH_3), 2.16 (s, 3H, OCOCH_3), 2.03 (s, 3H, OCOCH_3), 1.96 (s, 3H, NHCOCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.0, 169.6 (OCOCH$_3$), 168.6 (NHCOCH$_3$), 168.2 (CO_2CH_3), 73.0 (d, $J_{C,P}$ 12.0 Hz, C-5), 67.8, 67.7 (C-3, C-4), 65.6 (d, $J_{C,P}$ 167.6 Hz, C-1), 53.7, 53.6 (2 × POCH$_3$), 52.4 (CO_2CH_3), 44.2 (C-2), 23.1 (NHCOCH$_3$), 21.0, 20.5 (OCOCH$_3$); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ +20.96; LRMS (ESI): m/z 448 [$(M + Na)^+$ 100%]; HRMS calcd for $C_{15}H_{24}NO_{11}P_1$ $[M + H]^+$ 426.115974, found 426.118069.

Dimethyl (2-Acetamido-3,4,6-tri-*O*-benzyl-1,2-dideoxy-β-D-glucopyranosyl)phosphonate (14). 3,4,6-Tri-*O*-benzyl-2-nitro-β-D-glucosyl phosphonate **13**,[14] (2 g, 3.50 mmol) was dissolved in EtOH (50 mL) and transferred to a hydrogenation vessel. Platinized Raney nickel catalyst was freshly prepared according to the method of Nishimura.[22] The material obtained from 10 g of Raney nickel/aluminum alloy was suspended in EtOH (50 mL) and added to the reaction vessel, and the mixture was shaken in a Parr hydrogenation apparatus at a hydrogen pressure of 45 psi. After 24 h, the catalyst was carefully filtered through Celite, and the filtrate was evaporated under reduced pressure to yield the crude amine which was dissolved in Ac_2O (20 mL) and stirred overnight at room temperature under N_2. Coevaporation of the Ac_2O with toluene, followed by column chromatography (EtOAc/hexane, 1:1→MeOH/EtOAc, 0.4:9.6) afforded the 2-acetamido compound **14** [0.99 g, 48% over two steps; 59% based on recovered starting material (0.35 g)] as an oil. R_f 0.43 (MeOH/EtOAc, 0.4:9.6);

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28−7.17 (m, 15H, aromatic H), 5.70 (br s, 1H, NH), 4.81 (app t, 2H, J_{gem} 12.3 Hz, CH_2Ph), 4.65 (d, 1H, J_{gem} 10.8 Hz, C*H*Ph), 4.56 (d, 1H, J_{gem} 10.8 Hz, C*H*Ph), 4.51 (br s, 2H, CH_2Ph), 4.33−4.12 (m, 2H, H-1, H-3), 3.81−3.53 (m, 11H, 2 × POCH_3, H-6, H-6′, H-4, H-2, H-5), 1.82 (s, 3H, NHCOCH_3); LRMS (ESI): m/z 606 [(M + Na)$^+$ 100%]; HRMS calcd for $C_{31}H_{38}NO_8P_1$ [M + H]$^+$ 584.24078, found 584.241636.

Dimethyl (2-Acetamido-6-*O*-acetyl-3,4-di-*O*-benzyl-1,2-dideoxy-β-D-glucopyranosyl)phosphonate (15). Compound **14** (0.8 g, 1.37 mmol) was taken up in anhydrous DCM (16 mL), and to this solution was added Ac_2O (7.8 mL) followed by addition of a solution of TMSOTf (1 mL, 5.5 mmol) in DCM (10 mL) at −40 °C under Ar. The reaction mixture was stirred at −40 °C and monitored by TLC analysis (MeOH/EtOAc 0.4:9.6). After 6 h, TLC analysis indicated slow conversion of the starting material, so the reaction mixture was brought to 0−4 °C and then stirred at this temperature for 12 h, at which time TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by addition of satd aq $NaHCO_3$ (20 mL). The aq. layer was extracted with DCM (3 × 30 mL) and the combined organic phase was washed successively with H_2O (50 mL), brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford compound **15** (0.74 g) as a white solid. The product was pure by ^{1}H NMR analysis and therefore was used as such for the next step. R_f 0.36 (MeOH/DCM, 0.4:9.6); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28−7.18 (m, 10H, aromatic H), 5.70 (d, 1H, $J_{NH,H\text{-}2}$ 7.8 Hz, NH), 4.79 (d, 1H, J_{gem} 11.7 Hz, C*H*Ph), 4.77 (d, 1H, J_{gem} 11.1 Hz, C*H*Ph), 4.61 (d, 1H, J_{gem} 11.4 Hz, C*H*Ph), 4.50 (d, 1H, J_{gem} 10.8 Hz, C*H*Ph), 4.34−4.22 (m, 2H, H-6′, H-1), 4.17 (app t, 1H, $J_{3,4} = J_{3,2}$ 9.3 Hz, H-3), 4.05 (dd, 1H, $J_{6,5}$ 5.1 Hz, $J_{6,6'}$ 12.0 Hz, H-6), 3.73 (d, 3H, $J_{H,P}$ 10.5 Hz, POCH_3), 3.67 (d, 3H, $J_{H,P}$ 10.8 Hz, POCH_3), 3.60−3.49 (m, 2H, H-2, H-5), 3.40 (t, 1H, $J_{4,3}$ 9.3 Hz, H-4), 1.95 (s, 3H, OCOCH_3), 1.77 (s, 3H, NHCOCH_3).

Dimethyl (2-Acetamido-3,4-di-*O*-benzyl-1,2-dideoxy-β-D-glucopyranosyl)phosphonate (16). To a stirred solution of crude **15** (0.74 g, 1.38 mmol) in anhydrous methanol (20 mL) was added a methanolic solution of NaOMe (1.5 mL of a 1 M solution) at 0 °C under N_2. The reaction mixture was allowed to reach room temperature and was stirred for 1.5 h at which time TLC analysis (MeOH/DCM 0.4:9.6) indicated complete conversion to the product. The resulting solution was neutralized with Amberlite IR-120 (H^+) resin, and then the resin was removed by filtration, washed several times with MeOH, and the combined filtrate was evaporated under reduced pressure to give yellow oil which was purified by column chromatography (DCM→MeOH/DCM, 0.8:9.2) to provide the product **16** (0.60 g, 88% over two steps from pure compound **14**). R_f 0.23 (MeOH/DCM, 0.4:9.6); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28−7.19 (m, 10H, aromatic H), 6.08 (d, 1H, $J_{NH,H\text{-}2}$ 7.8 Hz, NH), 4.79 (d, 1H, J_{gem} 11.4 Hz, C*H*Ph), 4.77 (d, 1H, J_{gem} 11.1 Hz, C*H*Ph), 4.61 (d, 1H, J_{gem} 11.4 Hz, C*H*Ph), 4.58 (d, 1H, J_{gem} 10.8 Hz, C*H*Ph), 4.28 (app dd, 1H, $J_{1,2}$ 9.6 Hz, $J_{H\text{-}1,P}$ 10.8 Hz, H-1), 4.12 (app t, 1H, $J_{3,4} = J_{3,2}$ 9.3 Hz, H-3), 3.81−3.77 (m, 1H, H-6′), 3.73 (d, 3H, $J_{H,P}$ 10.8 Hz, POCH_3), 3.68 (d, 3H, $J_{H,P}$ 10.5 Hz, POCH_3), 3.67−3.57 (m, 2H, H-2, H-6), 3.50 (app t, 1H, $J_{4,5} = J_{4,3}$ 9.9 Hz, H-4), 3.41−3.35 (m, 1H, H-5), 1.78 (s, 3H, NHCOCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.0 (NHCOCH$_3$), 138.4, 137.9, 128.7, 128.5, 128.4, 128.2, 128.0, 127.9, 127.7 (aromatic), 81.7 (d, $J_{C,P}$ 8.4 Hz, C-3), 81.5 (d, $J_{C,P}$ 7.0 Hz, C-5), 78.3 (C-4), 75.2, 74.9 (2 × CH_2Ph), 72.0 (d, $J_{C,P}$ 170.4 Hz, C-1), 61.9 (C-6), 54.2 (d, $J_{C,P}$ 6.5 Hz, POCH$_3$), 53.5 (C-2), 53.2 (d, $J_{C,P}$ 7.0 Hz, POCH$_3$), 23.4 (NHCOCH$_3$).

Methyl [(Dimethyl phosphonyl) 2-acetamido-3,4-di-*O*-benzyl-1,2-dideoxy-β-D-glucopyranosid]uronate (17). To a solution of 6-hydroxy derivative **16** (0.1 g, 0.20 mmol) and TEMPO (0.40 mg, 0.0025 mmol) in DCM (1 mL) was added a solution of satd aq $NaHCO_3$ (0.4 mL) containing KBr (2.16 mg, 0.018 mmol) and nBu$_4$NBr (0.32 mg, 0.001 mmol). The biphasic solution was stirred vigorously at 0 °C, while a solution of aq NaOCl (12.5% w/v, 0.5 mL), containing satd aq $NaHCO_3$ (0.25 mL) and satd aq NaCl (0.4 mL), was added dropwise over 10 min. After 30 min, a further portion of aq NaOCl (12.5% w/v, 0.5 mL) was added and the reaction mixture was stirred for another 15 min. The resulting mixture was acidified to pH 2 using dilute HCl (4M) and diluted with $CHCl_3$ (10 mL). The layers were separated and the organic layer was washed with H_2O (2 × 10 mL) followed by brine (10 mL) and then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. To the residue in anhydrous MeOH (3 mL) under Ar was added trimethyl orthoformate (0.043 mL, 0.39 mmol), followed by cautious addition of $SOCl_2$ (0.015 mL, 0.20 mmol) and the reaction was stirred under Ar at rt for 30 min and then coevaporated with toluene until dryness. The crude reaction material was purified by column chromatography (DCM→MeOH/DCM, 0.6:9.4) to furnish the title compound **17** (0.08 g, 76% over two steps) as a colorless oil. R_f 0.46 (MeOH/EtOAc, 0.4:9.6); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29−7.11 (m, 10H, aromatic H), 6.11 (d, 1H, $J_{NH,H\text{-}2}$ 7.8 Hz, NH), 4.77 (d, 1H, J_{gem} 11.4 Hz, C*H*Ph), 4.69 (d, 1H, J_{gem} 10.8 Hz, C*H*Ph), 4.61 (d, 1H, J_{gem} 11.4 Hz, C*H*Ph), 4.52 (d, 1H, J_{gem} 10.8 Hz, C*H*Ph), 4.33 (dd, 1H, $J_{1,2}$ 9.9 Hz, $J_{H\text{-}1,P}$ 10.8 Hz, H-1), 4.18 (app t, 1H, $J_{3,2}$ 9.0 Hz, $J_{3,4}$ 9.6 Hz, H-3), 3.90 (d, 1H, $J_{5,4}$ 9.6 Hz, H-5), 3.75 (d, 3H, $J_{H,P}$ 10.5 Hz, POCH_3), 3.72−3.69 (m, 2H, H-4, H-2), 3.68 (d, 3H, $J_{H,P}$ 10.8 Hz, POCH_3), 3.63 (s, 3H, CO_2CH_3), 1.77 (s, 3H, NHCOCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 171.1 (NHCOCH$_3$), 168.6 (CO_2CH$_3$), 138.2, 137.6, 129.1, 128.9, 128.4, 127.9, 127.8 (aromatic), 80.8 (d, $J_{C,P}$ 16.8 Hz, C-3), 80.0 (C-4), 79.4 (d, $J_{C,P}$ 18.2 Hz, C-5), 75.2, 74.9 (2 × CH_2Ph), 72.4 (d, $J_{C,P}$ 169.8 Hz, C-1), 54.6 (d, $J_{C,P}$ 6.7 Hz, POCH$_3$), 53.5 (POCH$_3$), 53.4 (CO_2CH$_3$), 52.4 (C-2), 23.4 (NHCOCH$_3$); LRMS (ESI): m/z 544 [(M + Na)$^+$ 100%]; HRMS calcd for $C_{25}H_{32}NO_9P_1$ [M + H]$^+$ 522.188745, found 522.188419.

Methyl [(Dimethyl phosphonyl) 2-acetamido-3,4-di-*O*-acetyl-1,2-dideoxy-β-D-glucopyranosid]uronate (18). Compound **17** (0.89 g, 1.70 mmol) was dissolved in methanol (45 mL) and EtOAc (5 mL) under N_2, then Pd/C (300 mg, 10% Pd/C) was added cautiously followed by AcOH (1 mL), and the reaction was stirred under an H_2 atmosphere for 12 h. The reaction mixture was carefully filtered through Celite, and the solvent was evaporated under reduced pressure to yield the 3,4-diol that was subsequently treated with Ac_2O (5 mL) in pyridine (10 mL) under N_2. The reaction mixture was stirred overnight at room temperature and then coevaporated with toluene under reduced pressure to yield the title compound **18** (0.79 g, crude yield over two steps) as a light-yellow sticky foam. Due to difficulty in TLC visualization, the compound was not purified by column chromatography but was pure by NMR analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.61 (d, 1H, $J_{NH,H\text{-}2}$ 8.4 Hz, NH), 5.48 (dd, 1H, $J_{3,2}$ 9.3 Hz, $J_{3,4}$ 10.2 Hz, H-3), 5.08 (app t, 1H, $J_{4,3}$ 9.6 Hz, $J_{4,5}$ 9.9 Hz, H-4), 4.33 (app t, 1H, $J_{1,2}$ 10.2 Hz, $J_{H\text{-}1,P}$ 10.8 Hz, H-1), 4.08 (br app pent, 1H, $J_{2,1}$, $J_{2,3}$, $J_{2,NH}$, $J_{H\text{-}2,P} > \sim$9−10 Hz, H-2), 4.01 (d, 1H, $J_{5,4}$ 10.2 Hz, H-5), 3.82 (d, 3H, $J_{H,P}$ 10.8 Hz, POCH_3), 3.76 (d, 3H, $J_{H,P}$ 10.5 Hz, POCH_3), 3.67 (s, 3H, CO_2CH_3), 2.01 (s, 3H, OCOCH_3), 1.98 (s, 3H, OCOCH_3), 1.89 (s, 3H, NHCOCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 170.8, 170.4 (OCOCH$_3$), 169.4 (NHCOCH$_3$), 167.1 (CO_2CH$_3$), 77.2 (d, $J_{C,P}$ 17.7 Hz, C-5), 72.6 (d, $J_{C,P}$ 171.0 Hz, C-1), 72.0 (d, $J_{C,P}$ 18.4 Hz, C-3), 69.5 (C-4), 54.6 (d, $J_{C,P}$ 6.8 Hz, POCH$_3$), 54.0 (d, $J_{C,P}$ 7.1 Hz, POCH$_3$), 52.7 (CO_2CH$_3$), 51.0 (C-2), 23.1 (NHCOCH$_3$), 20.6, 20.4 (OCOCH$_3$); ^{31}P NMR (121.5 MHz, $CDCl_3$): δ +18.42; LRMS (ESI): m/z 448 [(M + Na)$^+$ 100%]; HRMS calcd for $C_{15}H_{24}NO_{11}P_1$ [M + H]$^+$ 426.115974, found 426.116790.

■ ASSOCIATED CONTENT

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ACKNOWLEDGMENT

M.v.I. gratefully acknowledges the support of the Australian Research Council through the award of a Federation Fellowship. B.B. thanks Griffith University for the award of a postgraduate scholarship and an international postgraduate research scholarship.

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