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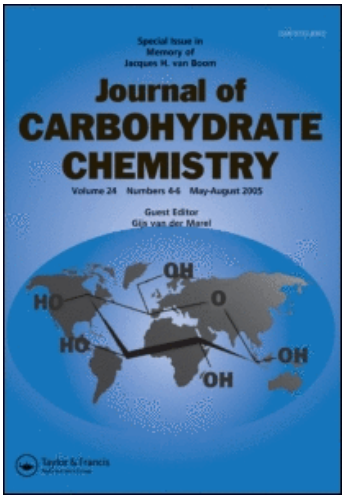

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ALLYLPHOSPHONATES BY HETEROANALOGOUS ZINC-SILVER/GRAPHITE MEDIATED DREIDING-SCHMIDT REACTIONS

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ABSTRACT

Allylphosphonates can be prepared in high yields, under mild conditions and in a stereospecific way by the reaction of uloses or dialdohexoses with 1-bromo-2-propenyl phosphonate and the highly active zinc-silver/graphite surface compound.

INTRODUCTION

The α-methylene-γ-butyrolactone moiety has been found in a broad variety of natural products;[1,2] most of these compounds have been in the focus of interest due to their pronounced cytotoxic activity. Interestingly enough, preliminary testing has shown that the biological activity of their phosphorous analogues, the α-methylene-γ-phostones, is quite different from that of the corresponding carba analogues.[3] Very simple phostones have previously been prepared from the corresponding aldehydes or ketones by their Zn-mediated reaction[3] with diethyl 1-bromo-2-propenyl phosphonate (1),[4-6] albeit the yields were rather low especially for cycloalkanones. Recently, an organo-indium mediated allylation of unprotected carbohydrate derived aldehydes led – after several functional

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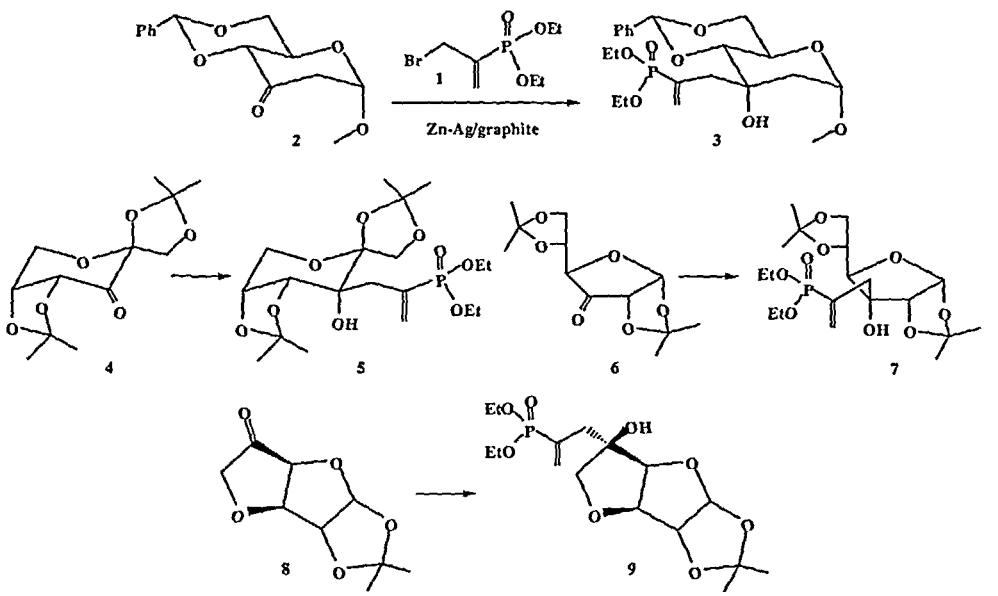
group modifications – to the phosphonic acid analogues of the sialic acids *N*-acetyl-neuraminic acid and its 4-hydroxy analogue KDN.[7-9] Although this organo-indium based approach is rather attractive due to the use of unprotected carbohydrates it suffers from rather long reaction times (up to 6 days) and low yields (40-50%).

RESULTS AND DISCUSSION

Alternatively we propose the use of the highly active [10] zinc-silver graphite surface compound and Dreiding-Schmidt conditions[11] for the synthesis of carbohydrate derived phosphonate analogues. Thus, reaction of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hex-3-ulopyranoside (**2**) with **1** in the presence of zinc-silver/graphite gave 75% of **3** as a colorless oil that is characterized in its NMR spectra by the presence of two ethoxy groups, therefore indicating that no ring closure to the corresponding phostone has taken place. The stereospecific formation of a D-*ribo*-configured product can be rationalized by a kinetically controlled attack onto the *re*-face of the carbonyl group since an axial attack is strongly hindered by the axially-oriented anomeric methoxy group. Attempts of either acid or base catalyzed cyclization of **3** failed and resulted in huge deterioration of the starting material.



Similarly, 1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulo-2,6-pyranose (**4**) gave 74% of the (β-D-fructopyranos-3-ylethyl)phosphonate **5**. For the furanoid ketone 1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-ulofuranose (**6**) an attack from the

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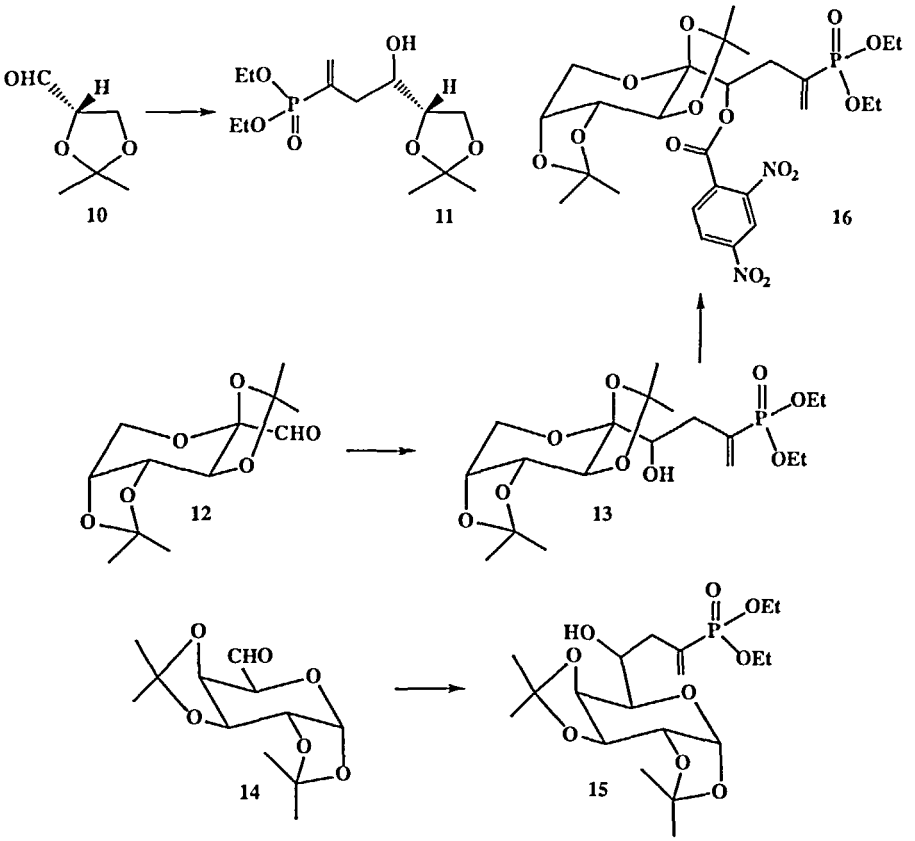
less hindered side resulted in the formation of a D-*allo*-furanosyl derivative **7** in 80% yield. The furanoid ketone 3,6-anhydro-1,2-*O*-isopropylidene-hex-5-ulo-α-D-*xylo*-furanose (**8**) gave 76% of chain-elongated **9**. Due to the steric hindrance of the anellated ring system the carbonyl group in **9** is attacked stereoselectively resulting in the formation of only one product possessing a D-*gluco* configuration.



The carbohydrate derived ketones gave clean reactions at 0 °C within several h whereas aldehydes reacted even at -78 °C within 30-60 min. Thus, 2,3-*O*-isopropylidene-D-glyceraldehyde (**10**) gave 85% of the phosphonate **11**, 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexos-2-ulo-2,6-pyranose (**12**) was converted to **13** (83%) and 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-hexodialdopyranose (**14**) gave 74% of **15**. Oily **13** was treated with 2,4-dinitrobenzoyl chloride to produce crystalline **16**, however, no crystals of **16** were obtained suitable for x-ray analysis, even applying many different conditions of crystalization.

The ^{1}H NMR spectra of all chain elongated products show the characteristic signals for the olefinic protons at δ = 6.0-6.3 and 5.9-6.4 ppm, respectively; the *trans*-

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oriented protons show a $^3J_{H,P}$ of 46.6-51.7 Hz whereas the *cis*-oriented protons possess a $^3J_{H,P}$ = 21.6-23.9 Hz. The quaternary carbon of the olefinic bond at δ = 131.0-135.4 ppm is easily identified by its large $J_{C,P}$ = 174.1-180.2 Hz. In contrast to the zinc, magnesium or samarium(II)iodide mediated reaction of 2-bromomethylacrylate[12,13] the corresponding phosphonate analogues failed to react with the carbonyl group of carbohydrate derived lactones.

EXPERIMENTAL

General. Melting points are uncorrected (*Reichert* hot stage microscope), optical rotations were obtained using a Perkin–Elmer 243B polarimeter (1 cm micro–cell), NMR spectra (internal Me_4Si) were recorded using either a Bruker AM250 or a Varian XL300 instrument (δ given in ppm, *J* in Hz, internal Me_4Si), IR spectra (film or KBr pellet) on a Perkin–Elmer 298 instrument or on a Perkin–Elmer 1605 FT–IR, MS spectra were taken either on a MAT311A or a Varian–112S instrument; for elemental analysis a Foss–Heraeus Vario EL instrument was used. TLC was performed on silica gel (Merck 5554, detection by dipping in a solution containing 10% sulfuric acid (400 mL), ammonium molybdate (20 g) and cerium(IV) sulfate (20 mg) followed by heating to 150 °C. The tetrahydrofuran used throughout for all reactions was freshly distilled from sodium/benzophenone; all reactions were performed under dry argon.

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General procedure for the synthesis of the phosphonates. Graphite (Fluka AG, Buchs, 0.90 g, 75.0 mmol) was degassed at 150 °C under argon for 1 h and then clean potassium (0.35 g, 8.82 mmol) was added in several portions under vigorous stirring. After cooling to 25 °C the bronze–colored C_8K was suspended in dry THF (30 mL) and a mixture of anhydrous zinc chloride (0.60 g, 4.41 mmol) and silver(I) acetate (0.06 g, 0.36 mmol) was added causing the solvent to reflux. After heating under reflux for an additional 30 min the suspension was cooled to –5 °C and a solution of the corresponding carbonyl compound in abs. THF (5 mL) and of the corresponding bromoester in THF (5 mL) was added and stirring was continued at –5 °C → 0 °C until the reaction had come to completion (as checked by TLC). The reaction mixture was filtered through a pad of Celite, the filter cake was washed with ethyl acetate (150 mL), the filtrates were combined and washed with aqueous hydrochloric acid (1 M, 10 mL) and brine (10 mL), the organic layer was dried ($MgSO_4$), filtered, the solvents were evaporated under diminished pressure and the residue was subjected to column chromatography.

Diethyl (1-Bromo-2-propenyl)phosphonate (1). A solution of tetraethylmethylene diphosphonate (28.8 g, 10.0 mmol) in aqueous formaldehyde (30%, 70 mL)

was heated under reflux. During 3 h a solution of potassium carbonate (28.0 g, 202.6 mmol in 35 mL of water) was slowly added *via* a syringe pump. After cooling to room temperature the reaction mixture was extracted with chloroform (continuously, overnight), the organic layer was washed with brine (2 x 10 mL), dried (Na_2SO_4), the solvent was evaporated and the residue subjected to vacuum distillation to afford diethyl (3-hydroxy-2-propenyl)phosphonate [(16.1 g, 83%): bp 95-100 °C/0.1 torr (lit.[4] 115-120 °C/0.4 torr), n_D^{20} 1.4502 (lit [4,5] 1.4504); IR (film) ν = 3380*br.s*, 2995*m*, 2540*w*, 2920*w*, 1395*w*, 1235*s*, 1190*m*, 1170*m*, 1100*m*, 1050*s*, 1015*s*, 970*s*, 795*s*; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.34 (*t*, *J* = 6.1 Hz, 6 H, 2 x CH_3), 4.15-4.25 (*m*, 6 H, 3 x CH_2O), 5.10 (*br. s*, 1 H, OH, exchangeable with D_2O), 6.03 (*d*, $^3J_{H,P}$ = 23.9 Hz, 1 H, CH_{cis}), 6.17 (*d*, $^3J_{H,P}$ = 47.5 Hz, 1 H, CH_{trans}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.30 (*dq*, $J_{C,P}$ = 6.7 Hz, 2 x CH_3), 62.15 (*dt*, $J_{C,P}$ = 6.0 Hz, 2 x OCH_2), 62.32 (*dt*, $J_{C,P}$ = 12.0 Hz, CH_2O), 128.55 (*dt*, $J_{C,P}$ = 6.7 Hz, $=CH_2$), 139.24 (*d*, $J_{C,P}$ = 172.0 Hz, C_q); MS (ei, 80 eV, 93°C): 194 (2.3%), 193 (21.3%), 177 (20.6%), 1498 (24.2%), 148 (21.5%), 138 (56.4%), 137 (89.5%), 121 (55.0%), 109 (100%). HRMS Calcd for $C_7H_{15}PO_4$: 194.07078, found: 194.07077; Anal. Calcd for $C_7H_{15}O_4P$ (194.168): C, 43.30; H, 7.79; P, 15.95. Found: C, 43.17; H, 7.95; P, 15.74]. To a solution of this phosphonate (14.0 g, 72.1 mmol) in abs diethyl ether (100 mL) at -20 °C was slowly added during 1 h a solution of phosphorus tribromide (9.8 g, 36.2 mmol) in abs. diethyl ether (15 mL). Then the reaction mixture was allowed to warm to room temperature and stirred for another 5 h. After cooling to 0 °C an ice cold solution of NaCl/Na_2CO_3 (saturated, 20 mL, 1:1) was added. The mixture was extracted with dichloromethane (10 x 50 mL), dried ($MgSO_4$), the solvents were evaporated *in vacuo* and the oily residue subjected to a vacuum distillation to afford **1** (12.0 g, 65 g) as a colorless liquid; bp 68-70°C/0.01 torr; n_D^{20} = 1.4655; IR (film): ν = 2990*s*, 2940*m*, 2910*m*, 1475*w*, 1445*m*, 1395*m*, 1370*w*, 1250*s*, 1165*s*, 1100*m*, 1050*s*, 1025*s*, 975*s*, 800*s*; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.34 (*t*, *J* = 6.2 Hz, 6 H, 2 x CH_3), 3.98-4.15 (*m*, 6 H, 3 x CH_2), 6.31 (*d*, $^3J_{H,P}$ = 44.8 Hz, 1 H, CH_{trans}), 6.28 (*d*, $^3J_{H,P}$ = 22.1 Hz, 1 H, CH_{cis}); ^{13}C NMR (75 MHz, $CDCl_3$): 16.31 (*dq*, $J_{C,P}$ = 6.2 Hz, 2 x CH_3), 29.73 (*dt*, $J_{C,P}$ = 16.7 Hz, CH_2Br), 62.34 (*dt*, $J_{C,P}$ = 5.3 Hz, 2 x OCH_2), 134.41 (*dt*, $J_{C,P}$ = 8.1 Hz, $=CH_2$), 135.80 (*d*, $J_{C,P}$ = 184.8 Hz, C_q); MS (ei, 80 eV, 78°C): 259 (0.5%), 258 (0.7%), 257 (1.1%), 256 (0.7%), 255 (0.5%), 231 (1.6%), 230 (1.9%), 229 (2.0%), 228 (1.4%), 185 (11.4%), 183 (11.5%), 177 (77.1%), 149 (100%). HRMS Calcd for $C_7H_{14}BrO_3P$: 255.9864, found: 255.9865.

Anal. Calcd for $C_7H_{14}BrO_3P$ (257.066): C, 32.71; H, 5.49; Br, 31.08; P, 12.05. Found: C, 32.61; H, 5.62; Br, 31.13; P, 12.17.

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Diethyl [1-Methylidene-2-(1-methyl-4,6-*O*-benzylidene-2-deoxy-α-D-ribo-hexo-pyranosid-3-*C*-yl)ethyl]phosphonate (3). Following the general procedure from **2** (0.53 g, 2.01 mmol) and **1** (1.13 g, 4.4 mmol mmol) after a reaction time of 2 h at 0 °C followed by column chromatography (silica gel, hexane/ethyl acetate 1:3 → 0:1), **3** (0.67 g, 75%) was obtained as a colorless oil; $[\alpha]_D^{20}$ +43.5° (*c* 0.6, $CHCl_3$), R_F 0.45 (hexane/ethyl acetate 1:1); IR (film): ν = 3506*m*, 2981*m*, 2935*m*, 2910*w*, 2868*w*, 1616*w*, 1443*m*, 1393*m*, 1372*m*, 1222*s*, 1124*m*, 1104*m*, 1028*s*, 969*s*, 920*m*, 901*m*, 801*m*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98 (*dd*, *J* = 14.8, 4.0 Hz, 1 H, H_A-C(2)), 2.08 (*d*, *J* = 14.8 Hz, 1 H, H_B-C(2)), 2.40 (*dd*, *J* = 16.8, 14.4 Hz, 1 H, H_A-C(3′)), 2.79 (*dd*, *J* = 14.8, 14.4 Hz, 1 H, H_B-C(3′)), 3.39 (*s*, 3 H, OCH_3), 3.53 (*d*, *J* = 9.5 Hz, 1 H, H-C(4)), 3.77 (*dd*, *J* = 10.3, 10.1 Hz, 1 H, H_A-C(6)), 4.01-4.19 (*m*, 5 H, H-C(5) and CH_2(OEt)), 4.32 (*dd*, *J* = 10.1, 5.1 Hz, H_B-C(6)), 4.81 (*d*, *J* = 3.2 Hz, 1 H, H-C(1)), 5.59 (*s*, 1 H, H-C(benzylidene)), 6.13 (*d*, *J* = 47.1 Hz, 1 H, H_A-C(3′′′)), 6.14(*d*, *J* = 22.5 Hz, 1 H, H_B-C(3′′′)), 7.33-7.38 (*m*, 3 H) and 7.50-7.53 (*m*, 2 H, H-C(phenyl)); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.28, 16.38 (each *q*, CH_3(OEt)), 38.04 (*dt*, $J_{C,P}$ = 12.3 Hz, C(3′)), 38.33 (*t*, C(2)), 55.32 (*q*, OCH_3), 59.54 (*d*, C(5)), 62.02, 62.12 (each *t*, CH_2(OEt)), 69.30 (*t*, C(6)), 70.74 (*s*, C(3)), 82.15 (*d*, C(4)), 98.75, 101.75 (each *d*, C(1) and CH(benzylidene)), 126.31, 128.17, 128.95 (each *d*, CH(phenyl)), 131.00 (*d*, $J_{C,P}$ = 180.3 Hz, C(3′′)), 136.25 (*dt*, $J_{C,P}$ = 7.7 Hz, C(3′′′)), 137.24 (*s*, C_q(phenyl)); MS (ei, 80 eV, 185°C): 442 (1.4%), 393 (5.5%), 366 (0.6%), 303 (0.8%), 286 (17.2%), 265 (33.5%), 249 (14.1%), 233 (13.8%), 205 (7.7%), 178 (100.0%), 159 (13.9%), 150 (27.4%), 149 (28.5%), 127 (16.0%), 122 (22.5%), 105 (38.9%, 91. HRMS Calcd for $C_{21}H_{31}O_8P$: 442.1756. Found: 442.1755.

Diethyl [1-Methylidene-2-(1,2;4,5-di-*O*-isopropylidene-β-D-fructopyranos-3-yl) ethyl]phosphonate (5). Following the general procedure from **4** (0.52 g, 2.01 mmol) and **1** (1.13 g, 4.4 mmol) after a reaction time of 5 h at 0 °C followed by column chromatography (silica gel, hexane/ethyl acetate 1:1 → 0:1), **5** (0.65 g, 74%) was obtained as a colorless oil; $[\alpha]_D^{20}$ -74.5° (*c* 1.2, $CHCl_3$), R_F 0.20 (hexane/ethyl acetate 1:1) IR (film): ν = 3304*m*, 2985*s*, 2935*m*, 1682*w*, 1443*m*, 1383*s*, 1274*m*, 1214*s*, 1165*m*, 1117*m*, 1084*s*, 1053*s*, 1024*s*, 997*s*, 969*s*, 878*m*, 854*m*, 791*m*; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33, 1.37 (each *m*, CH_3(OEt)), 1.31, 1.46, 1.51, 1.58 (each *s*, CH_3 of isopropylidene)), 2.53-2.96 (*m*, H_2-C(3′)), 4.06-4.25 (*m*, 9 H, H_A-C(1), H-C(4), H-C(5), H_2-C(6), CH_2(OEt)), 4.42 (*d*, *J* = 9.7 Hz, 1 H, H_B-C(1)), 5.43 (*s*, 1 H, OH), 5.91 (*d*, *J* = 46.6 Hz, 1 H, H_A-C(3′′′)), 6.00 (*d*, *J* = 21.6 Hz, 1 H, H_B-C(3′′′)); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.08, 16.16 (each *q*, CH_3(OEt)), 25.24, 25.73, 26.15, 26.25 (each *q*, CH_3 of isopropylidene)), 40.59 (*dt*, $J_{C,P}$ = 13.4 Hz, C(3′)), 59.99 (*t*, C(6)), 62.10 (*dt*, $J_{C,P}$ = 6.2

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Hz, CH_2(OEt)), 62.65 (*dt*, $J_{C,P}$ = 4.9 Hz, CH_2(OEt)), 71.95 (*d*, C(4)), 71.57 (*s*, C(3)), 72.15 (*t*, C(1)), 74.19 (*d*, C(5)), 106.65 (*s*, C(2)), 108.71, 111.84 (each *s*, C_q of isopropylidene)), 132.79 (*dt*, $J_{C,P}$ = 7.8 Hz, C(3′′′)), 135.26 (*d*, $J_{C,P}$ = 174.1 Hz, C(3′′)); MS (ei, 80 eV, 165°C): 421 (0.5%), 375 (0.7%), 335 (2.2%), 292 (2.0%), 273 (2.4%), 260 (3.8%), 249 (6.8%), 233 (5.2%), 221 (5.7%), 203 (8.2%), 191 (3.9%), 178 (16.3%), 163 (5.0%), 149 (11.8%), 135 (4.7%), 122 (6.2%), 111 (5.8%), 82 (7.7%), 58 (17.8%), 42 (100.0%). HRMS Calcd for $C_{19}H_{33}O_9P$: 436.1864. Found: 436.1866.

Diethyl [1-Methylidene-2-(1,2;5,6-di-*O*-isopropylidene-α-D-allo-furanos-3-*C*-yl)ethyl]phosphonate (7). Following the general procedure from **6** (0.52 g, 2.01 mmol) and **1** (1.13 g, 4.4 mmol) after a reaction time of 2 h at 0 °C followed by column chromatography (silica gel, hexane/ethyl acetate 1:1 → 0:1), **7** (0.70 g, 80%) was obtained as a colorless oil; $[\alpha]_D^{20}$ +9.8° (*c* 0.8, $CHCl_3$), R_F 0.26 (hexane/ethyl acetate 1:3); IR (film): ν = 3466*m*, 2986*s*, 2937*m*, 1479*m*, 1444*m*, 1373*s*, 1217*s*, 1166*s*, 1022*s*, 970*s*, 874*m*, 847*m*, 794*m*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (*m*, 6 H, CH_3(OEt)), 1.36, 1.37, 1.47, 1.59 (each *s*, CH_3 of isopropylidene), 2.36 (*dd*, *J* = 15.6 Hz, H_A-C(3′)), 2.80 (*dd*, *J* = 15.6 Hz, 11.8, H_B-C(3′)), 3.81 (*d*, *J* = 8.2 Hz, 1 H, H-C(4)), 9.94 (*m*, 1 H, H-C(5)), 4.09-4.24 (*m*, 4 H, CH_2(OEt)), 4.49 (*d*, *J* = 7.7 Hz, 1 H, H-C(2)), 7.74 (*d*, *J* = 3.7 Hz, 1 H, H-C(1)), 6.35 (*d*, *J* = 23.4 Hz, 1 H, H_A-C(3′′′)), 6.41 (*d*, *J* = 50.5 Hz, 1 H, H_B-C(3′′′)); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.29, 16.32 (each *q*, CH_3(OEt)), 25.32, 26.48, 26.53, 26.63 (each *q*, CH_3 of isopropylidene), 31.71 (*dt*, $J_{C,P}$ = 12.2 Hz, C(3′)), 62.92, 63.02 (each *t*, CH_2(OEt)), 67.92 (*t*, C(6)), 79.70 (*d*, $J_{C,P}$ = 5.8 Hz, C(3)), 73.04, 80.39, 82.23 (each *d*, C(2,4,5)), 103.59 (*d*, C(1)), 109.67, 112.46 (each *s*, C_q of isopropylidene)), 132.77 (*d*, $J_{C,P}$ = 178.6 Hz, C(3′′)), 135.56 (*dt*, $J_{C,P}$ = 6.6 Hz, C(3′′′)); MS (ei, 80 eV, 161°C): 436 (0.5%), 421 (8.7%), 378 (8.7%), 305 (10.5%), 303 (9.0%), 285 (5.3%), 277 (7.7%), 261 (6.5%), 248 (8.7%), 205 (5.5%), 178 (31.6%), 149 (12.5%), 111 (12.9%), 101 (14.0%), 100 (100.0%). HRMS Calcd for $C_{19}H_{33}O_9P$: 436.1864. Found: 436.1865.

Diethyl [1-Methylidene-2-(3,6-anhydro-1,2-*O*-isopropylidene-α-D-gluco-furanos-5-*C*-yl)ethyl]phosphonate (9). Following the general procedure from **8** (0.40 g, 2.01 mmol) and **1** (1.13 g, 4.4 mmol) after a reaction time of 3 h at 0 °C followed by column chromatography (silica gel, hexane/ethyl acetate 1:2 → 0:1), **9** (0.57 g, 76%) was obtained as a colorless oil; $[\alpha]_D^{20}$ +15.5° (*c* 1.1, $CHCl_3$), R_F 0.12 (hexane/ethyl acetate 1:1); IR (film): ν = 3353*m*, 2984*s*, 2938*m*, 1443*m*, 1373*m*, 1236*s*, 1164*m*, 1024*m*, 969*s*, 797*m*; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34 (*s*, 3 H, CH_3 of isopropylidene), 1.34 (*t*, *J* = 7.0 Hz, 3 H, CH_3(OEt)), 1.35 (*t*, *J* = 7.1 Hz, 3 H, CH_3(OEt)), 1.48 (*s*, 3 H, CH_3 of isopropylidene), 2.57 (*d*, *J* = 14.6 Hz, 2 H, H_2-C(5′)), 3.59 (*d*, *J* = 8.9 Hz, 1 H, H_A-

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C(6)), 3.69 (*d*, J = 8.9 Hz, 1 H, H_B-C(6)), 3.82 (*s*, 1 H, OH), 4.07-4.22 (*m*, 4 H, CH_2(OEt)), 4.55 (*s*, 2 H, H-C(3) and H-C(4)), 4.63 (*d*, J = 3.6 Hz, 1 H, H-C(2)), 5.97 (*d*, J = 3.6 Hz, 1 H, H-C(1)), 6.14 (*d*, J = 48.6 Hz, 1 H, H_A-C(5′′′)), 6.22 (*d*, J = 23.2 Hz, 1 H, H_B-C(5′′′)); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.12, 16.22 (each *q*, CH_3(OEt)), 26.71, 27.31 (each *q*, CH_3 of isopropylidene), 37.23 (*dt*, $J_{C,P}$ = 12.3 Hz, C(5′)), 62.64, 62.73 (each *t*, CH_2(OEt)), 75.25 (*d*, C(6)), 79.49 (d, $J_{C,P}$ = 4.5 Hz, C(5)), 85.02, 85.27, 85.52 (each *d*, C(2,3,4)), 106.75 (*d*, C(1)), 112.67 (*s*, C_q of isopropylidene)), 133.25 (*d*, $J_{C,P}$ = 176.0 Hz, C(5′′)), 134.46 (*dt*, $J_{C,P}$ = 7.6 Hz, C(5′′′)); MS (ei, 80 eV, 155 °C): 378 (1.0%), 363 (5.6%), 261 (12.3%), 260 (12.5%), 237 (100.0%), 178 (40.5%), 177 (12.3%), 163 (9.7%), 150 (15.1%), 149 (12.9%), 122 (13.2%), 113 (27.0%), 110 (11.0%). HRMS Calcd for $C_{16}H_{27}O_8P$: 378.1445. Found: 378.1447.

Anal. Calcd for $C_{16}H_{27}O_8P$ (378.36): C, 50.79; H, 7.19; P, 8.19. Found: C, 50.50; H, 7.42; P, 8.42.

Diethyl {1-[(2*R*,*S*)-2-((4*R*)-2,2-Dimethyl-[1,3]-dioxolane-4-yl)-2-hydroxyethyl]vinyl}phosphonate (11). Following the general procedure from **10** (0.26 g, 2.01 mmol) and **1** (1.13 g, 4.4 mmol) after a reaction time of 0.5 h at -78 °C followed by column chromatography (silica gel, hexane/ethyl acetate 3:1 → 1:1), **11** (0.22 g, 85%) was obtained as a colorless oil; $[\alpha]_D^{20}$ 0.0° (*c* 1.1, $CHCl_3$), R_F 0.17 (hexane/ethyl acetate 1:1); IR (film): ν = 3374*m*, 2985*s*, 2935*m*, 2907*m*, 1443*m*, 1370*s*, 1219*s*, 1160*m*, 1026*s*, 986*s*, 851*m*, 794*m*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (*m*, 6 H, CH(OEt)), 1.35, 1.42 (each *s*, 3 H, CH_3 of isopropylidene), 2.30-2.48 (*m*, 1 H, H_A-C(2)), 2.66-2.77 (*m*, 1 H, H_B-C(2)), 3.77 (*m*, 1 H, H-C(3)), 3.87 (*d*, J = 3.7 Hz, 1 H, OH), 3.91-4.00 (*m*, 2 H, H_2-C(5)), 4.01-4.20 (*m*, 5 H, H-C(4) and CH_2(OEt)), 5.95 (*d*, J = 48.0 Hz, 1 H, H_A-C(1′)), 6.09 (*d*, J = 22.5 Hz, 1 H, H_B-(C1′)); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.25, 16.36 (each *q*, CH_3(OEt)), 25.34, 26.75 (each *q*, CH_3 of isopropylidene), 37.45 (*dt*, $J_{C,P}$ = 12.3 Hz, C(2)), 62.83, 62.93 (each *t*, CH_2(OEt)), 66.74 (*t*, C(5)), 71.63 (*d*, C(3)), 78.20 (*d*, C(4)), 109.28 (*s*, C_q of isopropylidene), 132.56 (*dt*, $J_{C,P}$ = 8.7 Hz, C(1′)), 135.35 (*d*, $J_{C,P}$ = 174.4 Hz, C(1)); MS (ei, 80 eV, 104°C): 293 (18.8%), 251 1.9%), 233 (5.9%), 207 (100.0%), 178 (38.0%), 151 (17.0%), 133 (15.8%), 122 (16.1%), 101 (9.0%), 82 (9.9%). HRMS Calcd for $C_{13}H_{25}O_6P$: 308.1390. Found: 308.1391.

Diethyl [1-Methylidene-2-((1*R*,*S*)-2,3;4,5-di-*O*-isopropylidene-β-D-fructopyranos-1-yl)ethyl]phosphonate (13). Following the general procedure from **12** (0.52 g, 2.01 mmol) and **1** (1.13 g, 2.01 mmol) after a reaction tome of 0.5 h at -78 °C followed by column chromatography (silica gel, hexane/ethyl acetate 1:1 → 1:5), **13** (0.73 g, 83%) was obtained as a colorless oil; $[\alpha]_D^{20}$ 0.0° (*c* 1.0, $CHCl_3$), R_F 0.11 (hexane/ethyl acetate 1:1); IR (film): ν = 3450*m*, 2987*s*, 2938*m*, 1667*w*, 1446*m*, 1374*s*, 1252*s*, 1212*s*, 1183s,

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1104*m*, 1064s, 1021*s*, 898*m*, 872*m*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (*s*, 3 H, CH_3 of isopropylidene)), 1.37 (*t*, *J* = 7.0 Hz, 3 H, CH_3 of isopropylidene)), 1.38 (*t*, *J* = 7.0 Hz, 3 H, CH_3 of isopropylidene)), 1.46, 1.48, 1.55 (each *s*, CH_3 of isopropylidene)), 2.44-2.56 (*m*, 1 H, H_A-C(1′)), 2.93-3.02 (*m*, 1 H, H_B-C(1′)), 3.77 (*d*, *J* = 13.0 Hz, 1 H, H_A-C(6)), 3.92 (*dd*, *J* = 13.0, 1.8 Hz, 1 H, H_B-C(6)), 3.93 (*bs*, 1 H, OH), 4.21-4.33 (*m*, 6 H, CH_2(OEt), H-C(5), H-C(1)), 4.51 (*d*, *J* = 2.6 Hz, 1 H, H-C(3)), 4.62 (*dd*, *J* = 7.9, 2.6 Hz, 1 H, H-C(4)), 6.12 (*d*, *J* = 51.7 Hz, 1 H, H_A-C(1′′′)), 6.29 (*d*, *J* = 23.9 Hz, H_B-C(1′′′)); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.09, 16.18 (each *q*, CH_3(OEt)), 23.95, 25.88, 25.89, 26.60 (each *q*, CH_3 of isopropylidene)), 61.40 (*t*, C(6)), 64.72 (*dt*, $J_{C,P}$ = 6.5 Hz, CH_2(OEt)), 64.82 (*dt*, $J_{C,P}$ = 9.1 Hz, CH_2(OEt)), 70.21, 70.25, 70.72, 72.40 (each *d*, C(3, 5, 6, 7)), 103.66 (*s*, C(2)), 108.99, 109.11 (each *s*, C_q of isopropylidene)), 133.02 (*d*, $J_{C,P}$ = 180.2 Hz, C(1′′)), 135.36 (*dt*, $J_{C,P}$ = 9.3 Hz, C(1′′′)); MS (ei, 80 eV, 150°C): 421 (0.2%), 376 (0.2%), 375 (1.5%), 333 (0.2%), 303 (0.3%), 275 (0.4%), 273 (0.2%), 229 (1.0%), 207 (4.8%), 178 (7.6%), 110 (46.3%), 108 (48.3%), 64 (24.6%), 58 (24.2%), 43 (100.0%). HRMS Calcd for $C_{19}H_{33}O_9P$: 436.1864. Found: 436.1866.

Diethyl [1-Methylidene-2-(1,2;3,4-di-*O*-isopropylidene-α-D-*galacto*-pyranos-6-*C*-yl)- ethyl]phosphonate (15). Following the general procedure from **14** (0.46 g, 2.01 mmol) and **1** (1.13 g, 4.4 mmol) after a reaction time of 1 h at –78 °C followed by column chromatography (silica gel, hexane/ethyl acetate 1:1 → 1:5), **15** (0.65 g, 74%) was obtained as a colorless oil; $[\alpha]_D^{20}$ –57.0° (*c* 1.1, $CHCl_3$), R_F 0.32 (hexane/ethyl acetate 1:1); IR (film): ν = 3383 *m*, 2985*s*, 2936*s*, 1443*m*, 1382*s*, 1215*s*, 1020*s*, 919*m*, 898*s*, 875*m*, 802*m*; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (*m*, 6 H, 2 x CH_3), 1.32, 1.36, 1.45, 1.51 (each *s*, 3 H, CH_3 of isopropylidene), 2.35-2.52 (*m*, 1 H, H_A-C(6′)), 2.79-2.90 (*m*, 1 H, H_B-C(6′)), 3.58 (*dd*, *J* = 7.7, 1.2 Hz, 1 H, H-C(5)), 3.76 (*bs*, 1 H, OH), 3.98 (*m*, 1 H, H-C(6)), 4.10-4.24 (*m*, 4 H, CH_2(OEt)), 4.31 (*dd*, *J* = 5.0, 2.1 Hz, 1 H, H-C(2)), 4.51 (*dd*, *J* = 8.0, 2.1 Hz, 1 H, H-C(4)), 4.62 (*dd*, *J* = 8.0, 2.1 Hz, 1 H, H-C(3)), 5.53 (*d*, *J* = 5.0 Hz, 1 H, H-C(1)), 6.05 (*d*, *J* = 49.2 Hz, 1 H, H_A-C(6′′′)), 6.16 (*d*, *J* = 22.8 Hz, H_B-C(6′′′)); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 16.07, 16.17 (each *q*, CH_3(OEt)), 24.33, 24.84, 25.89, 25.97 (each *q*, CH_3 of isopropylidene), 37.05 (*dt*, $J_{C,P}$ = 12.7 Hz, C(6′)), 63.22 (*dt*, $J_{C,P}$ = 6.3 Hz, CH_2(OEt)), 63.32 (*dt*, $J_{C,P}$ = 6.2 Hz, CH_2(OEt)), 69.13, 69.23, 69.44, 69.49, 70.58 (each *d*, C(2, 3, 4, 5, 6)), 96.40 (*s*, C(1)), 108.46, 109.05 (each *s*, C_q of isopropylidene), 133.86 (*dt*, $J_{C,P}$ = 8.4 Hz, C(6′′′)), 134.42 (*d*, $J_{C,P}$ = 176.6 Hz, C(6′′)); MS (ei, 80 eV, 168 °C): 436 (0.25%), 422 (2.1%), 421 (11.2%), 376 (4.6%), 375 (26.6%), 303 (3.5%), 285 (5.1%), 275 (5.0%), 274 (7.2%), 257 (9.2%), 229 (10.9%), 207 (71.3%), 203 (13.6%), 179 (12.2%), 178 (100.0%). HRMS Calcd for $C_{19}H_{33}O_9P$: 436.1864. Found: 436.1865.

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Diethyl {1-Methylidene-2-[(1*R*,*S*)-2,3;4,5-di-*O*-isopropylidene-1-*O*-(3,5-dinitro-benzoyl)-β-D-fructopyranos-1-yl]ethyl}phosphonate (16). Compound **13** (0.083 g, 0.19 mmol) was dissolved in dry CH_2Cl_2 (1 mL), pyridine (0.2 mL) and dinitrobenzoyl chloride (0.055 g, 0.23 mmol) were added at 25 °C and the mixture was stirred for 16 h, filtered and the filtrate was concentrated to give a semicrystalline solid that was subjected to column chromatography (silica gel, hexane/ethyl acetate 1:1) to afford **16** (0.11 g, 87.5%) as slightly yellowish crystals; mp 47-50 °C, $[\alpha]_D^{20}$ +22.5° (*c* 0.9, $CHCl_3$), R_F 0.65 (hexane/ethyl acetate 1:1); IR (KBr): ν = 2989*m*, 2938*w*, 1740*m*, 1700*w*, 1653*m*, 1550*s*, 1457*w*, 1387*w*, 1345*s*, 1276*s*, 1255*s*, 1213*s*, 1166*s*, 1076*s*, 1054*s*, 1023*s*, 971*m*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (*t*, *J* = 7.0 Hz, CH_3(OEt)), 1.36 (*t*, *J* = 7.0 Hz, CH_3(OEt)), 1.38, 1.42, 1.50, 1.67 (each *s*, 3 H, CH_3 of isopropylidene)), 2.75-2.88 (*m*, 1 H, H_A-C(1′)), 3.18-3.27 (*m*, 1 H, H_B-C(1′)), 3.87 (*s*, 2 H, H_2-C(6)), 4.00-4.24 (*m*, 4 H, CH_2(OEt)), 4.26-4.28 (*m*, 2 H, H-C(3) and H-C(5)), 4.58 (*dd*, *J* = 8.1, 2.0 Hz, 1 H, H-C(4)), 5.71 (*d*, *J* = 10.3 Hz, 1 H, H-C(1)), 5.82 (*d*, *J* = 47.2 Hz, 1 H, H_A-C(1′′′)), 6.03 (*d*, *J* = 22.3 Hz, 1 H, H_B-C(1′′′)), 9.13-9.25 (*m*, 5 H, CH(phenyl)); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.36, 16.44 (each *q*, CH_3(OEt)), 23.65, 25.06, 25.60, 26.30 (each *q*, CH_3 of isopropylidene)), 32.29 (*dt*, $J_{C,P}$ = 11.3 Hz, C(1′)), 60.81 (*t*, C(6)), 61.86 (*dt*, $J_{C,P}$ = 5.4 Hz, CH_2(OEt)), 62.10 (*dt*, $J_{C,P}$ = 6.6 Hz, CH_2(OEt)), 70.11, 70.15, 71.05 (each *d*, C(3,4,5)), 76.75 (*d*, C(1)), 103.17 (*s*, C(3)), 108.44, 108.88 (each *s*, C_q of isopropylidene), 122.25, 129.50 (each *d*, CH(phenyl)), 132.65 (*dt*, $J_{C,P}$ = 9.2 Hz, C(1′′′)), 133.61 (*s*, C_q(phenyl)), 136.37 (*d*, $J_{C,P}$ = 175.4 Hz, C(1′′)), 148.48 (*s*, C_q(phenyl)), 161.48 (*s*, C=O(benzoyl)); MS (ei, 80 eV, 192°C): 615 (100.0%), 555 (34.4%), 497 (17.0%), 447 (13.9%), 402 (15.7%), 361 (39.3%), 360 (85.7%), 285 (9.7%), 257 (15.9%), 229 (44.6%), 195 (60.2%), 171 (56.4%), 161 (31.2%), 149 (28.7%), 133 (24.1%), 113 (18.9%), 95 (21.1%).

Anal. Calcd for $C_{26}H_{35}O_{14}N_2P$ (630.54): C, 49.53; H, 5.59; N, 4.44. Found: C, 49.39; H, 5.39; N, 3.90.

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