Hydrozirconation/bromination, followed by a Michaelis-Arbuzov reaction, as a convenient approach towards polyfunctional glycosylphosphonates

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Hydrozirconation / Bromination, followed by a Michaelis-Arbuzov Reaction, as a Convenient Approach Towards Polyfunctional Glycosylphosphonates

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Abstract

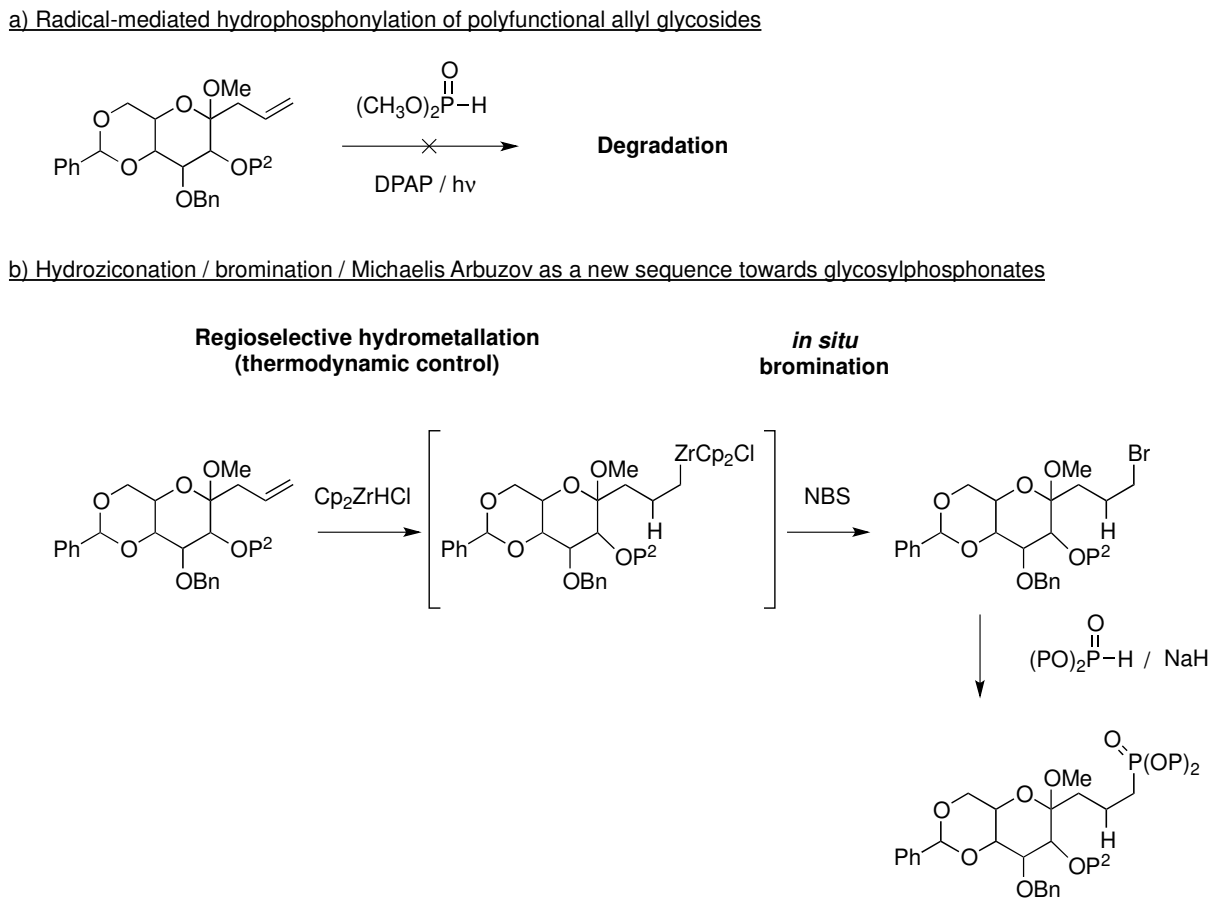
In this note, an hydrozirconation / bromination / Michaelis-Arbuzov sequence was developped to introduce a trimethylene phosphonate unit on ketopyranosides. Performed on polyfunctional substrates bearing orthogonal protecting groups, this new approach provided a straightforward entry towards a large diversity of glycophosphomimetics having a quaternary anomeric position.

Keywords:

1. Introduction

The design of carbohydrate mimics has been a matter of strong interest to decipher the complex roles played by sugars in physiological and pathological processes.[1] More particularly, glycosylphosphonates have been used for decades as stable analogues of natural substrates to explore the structure and mechanism of numerous carbohydrate-active enzymes.[2] Recently, a trimethylene phosphonate connected to the anomeric position has been shown to mimic the α-phosphate of glycosyl donors activated in the form of nucleotide

diphosphates, which are the common substrates of glycosyltransferases and mutases.[3] In the context of an on-going research program dedicated to the preparation of non-natural carbohydrate derivatives with a quaternary center,[4] we thus wanted to introduce a trimethylene phosphonate unit at the anomeric position of ketopyranosides in order to develop highly modular molecular platforms for studying carbohydrate-active enzymes. After protection of position 2 of the quaternary allylic derivatives previously reported by our group, [5] we initially tried to prepare the targeted compounds using a straightforward free-radical hydrophosphonylation of these terminal olefins.[6] However, this approach delivered a complex mixture of unidentified products, presumably because of the highly reactive benzylic positions that should have led to side reactions under those radicalar conditions (Scheme 1a).[7]

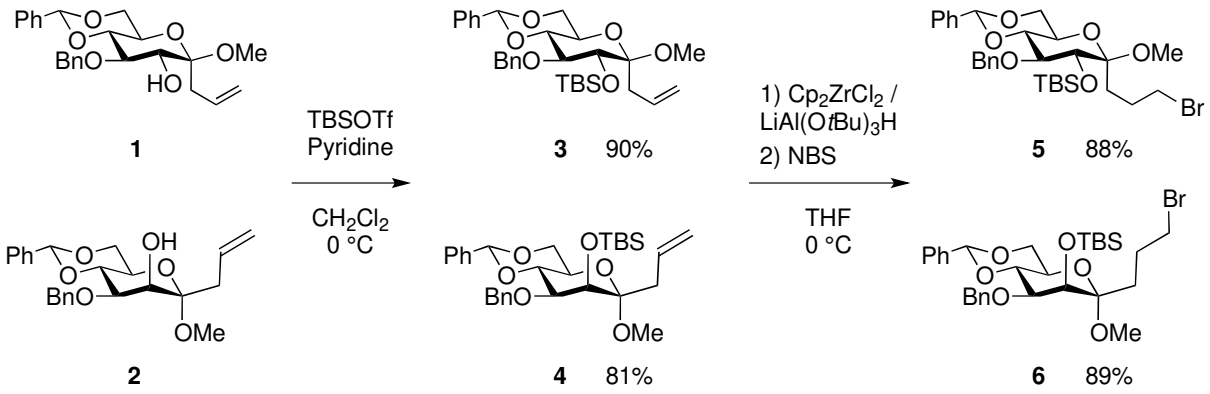


Scheme 1. Approaches for the preparation of trimethylene glycosylphosphonates.

Having recently shown that zirconium hydrides could promote highly selective transformation on polyfunctional carbohydrate derivatives,[8] we planned to develop a new method for the introduction of a phosphonate moiety relying on the hydrozirconation / bromination of an olefin, followed by a Michael Arbuzov reaction (Scheme 1b).[9] Compared to the classical hydroboration / oxidation / bromination sequence,[10] this new approach would deliver the key bromo sugars in a single pot, and with complete regioselectivity thanks to the reversible nature of the hydrozirconation process that exclusively leads to the most stable primary organometallic intermediate.[11]

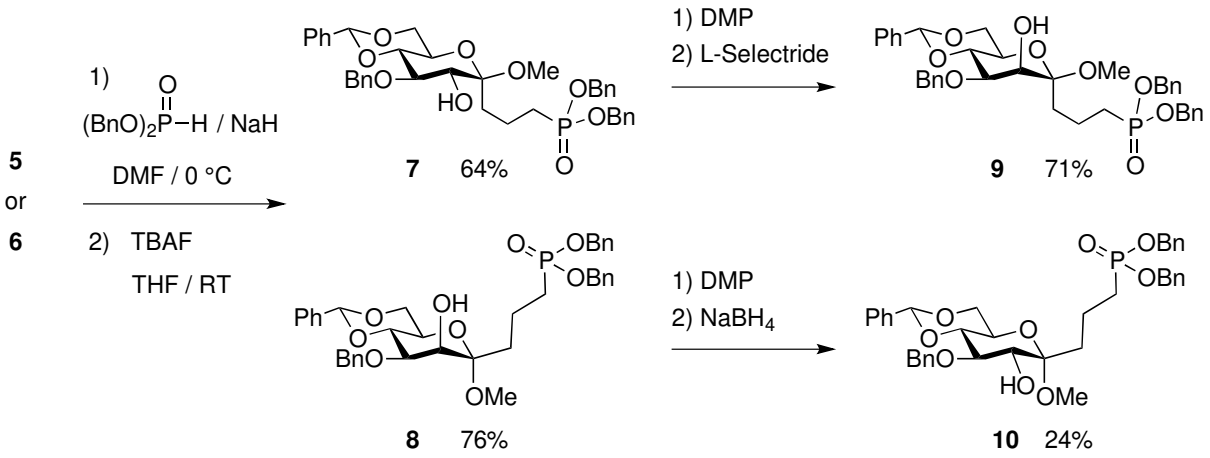
2. Results and discussion

Our sequence started from **1** and **2**, in the *β-gluco* and *α-manno* series respectively, that can be obtained on a gram scale following our previous work.[5] Protection of position 2 as a TBS ether first gave the quaternary sugars **3** and **4**, with a complete set of orthogonal protecting groups, in 90 and 81% yield respectively. Those compounds were then subjected to hydrozirconation by the Schwartz' reagent Cp_2ZrHCl, which was generated *in situ* following a recent protocol reported by Snieckus *et al.*.[12] In a typical procedure, a solution of the substrate (1 equiv.) and Cp_2ZrCl_2 (5 equiv.) in THF at room temperature was added with a 1M solution of $LiAlH(OtBu)_3$ in THF (4.9 equiv.), and stirred for 2 hours. The primary alkyl zirconocenes were then trapped by addition of *N*-bromosuccinimide (5.5 equiv.) to give *in a single pot* the desired bromo sugars **5** and **6** in 88 and 89 % yield respectively (Scheme 2).



Scheme 2. Hydrozirconation / bromination of polyfunctional allyl ketopyranosides.

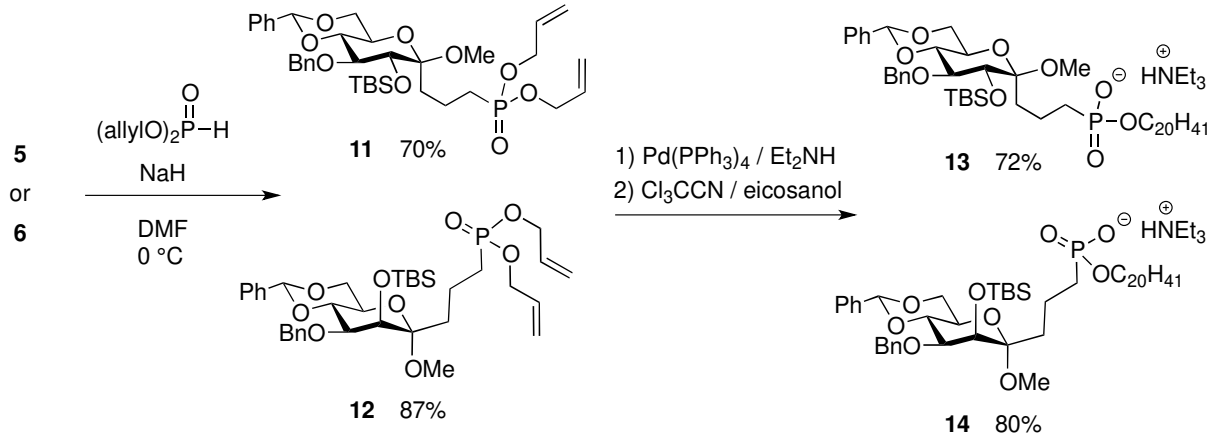
These versatile intermediates were then converted into trimethylene phosphonates under Michaelis-Arbuzov conditions.[13] First, treatment of bromo sugars **5** and **6** with dibenzyl *H*-phosphate and NaH in DMF, followed by chemoselective deprotection of position 2, gave the *β-gluco* and *α-manno* dibenzylphosphonates **7** and **8** in 64 and 76 % yield respectively over two steps (Scheme 3). An oxidation / reduction sequence was then used to prepare quaternary glycosylphosphonates in the two missing *β-manno* and *α-gluco* series.[5] First, oxidation of **7** with Dess-Martin Periodinane (DMP) was followed by a reduction with L-Selectride to give the quaternary *β-manno* phosphonate **9** in a very good 71% yield over the two steps. From **8**, oxidation was followed by reduction of the 2-uloside with $NaBH_4$ as previously reported.[5] Unfortunately, in this α-series, the reduction took place with a very low stereoselectivity, and the desired quaternary *gluco* derivative **10** could only be obtained in a very modest 24% yield over two steps.



Scheme 3. Michaelis-Arbuzov reaction and diversification at position 2.

In order to achieve selective transformations on the phosphonate unit,[14] diallyl *H*-phosphate was next used in the Michaelis Arbuzov reaction to prepare **11** and **12** in 70 and 87 % yield respectively (Scheme 4). Chemoselective deprotection of the phosphonate was then performed under mild Tsuji-Trost reaction conditions[15] with $Pd(PPh_3)_4$ and diethylamine as the scavenger.[16],[17] Finally, treatment of the ammonium phosphate intermediates with trichloroacetonitrile, followed by *in situ* addition of eicosanol, resulted in a monophosphoesterification that gave **13** and **14** in 72 and 80% yield over two steps

respectively. These quaternary phosphonates, which are mimics of dolichol phosphosugars glycosyl donors, should represent valuable chemical probes to study group C glycosyltransferases in the next future.



Scheme 4. Michaelis Arbuzov reaction and functionalization of the phosphonate unit.

3. Conclusion

In conclusion, a new approach for the synthesis of glycosyl trimethylenephosphonates, relying on a key hydrozirconation / bromation reaction, has been developed. Involving a very soft metal hydride, this transformation has been achieved on polyfunctional carbohydrates, and with a complete regioselectivity, to deliver primary bromo sugars in high yields. After a Michaelis-Arbuzov reaction, site-selective transformations were finally performed at position 2, or on the phosphonate unit, thanks to the presence of a complete set of orthogonal protecting groups, to give a large diversity of glycomimetics having a high potential biological interest.

4. Experimental

4.1 General Methods

Anhydrous dichloromethane (DCM) and tetrahydrofuran (THF) were purified and dried on a solvent dispensing system MBRAUN MB-SPS-800. Pyridine, DMF and methanol were

purchased anhydrous. Diethylamine was distilled over CaH_2. Flash chromatography was performed on silica gel (60-240 mesh). Analytical thin layer chromatography (TLC) was performed on silica gel plates (Merck 60F254) and visualized with a UV lamp (254 nm) and PMA stain (Phosphomolybdic acid). Organic extracts were dried over anhydrous $MgSO_4$. ^1H NMR, ^{13}C NMR, and ^{31}P spectra were recorded on Bruker Avance-III, at 300 MHz (^1H value), 75 MHz (^{13}C value), and 121 Mhz (^{31}P value) in $CDCl_3$. Spectra were referenced to residual chloroform (7.26 ppm, ^1H; 77.16 ppm, ^{13}C). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet or unresolved), br (broad signal), app (apparent signal). Coupling constants, *J*, are reported in hertz (Hz). All NMR spectra were obtained at 300K. Compounds **1** and **2** were prepared according to our own procedures.[5]

4.2 Experimental Procedures

4.2.1 Methyl 1-*C*-allyl-β-glucopyranoside **3**:

To a solution of **1** (180 mg, 0.44 mmol) and pyridine (71 µL, 0.88 mmol, 2 eq) in DCM (1.6 mL) under argon at 0 °C was added trifluoromethanesulfonic acid *tert*-butyldimethylsilylester (152 µL, 0.66 mmol, 1,5 eq). The reaction mixture was stirred at 0 °C until TLC (cyclohexane / ethyl acetate 3/1) showed complete consumption of the starting material, and quenched with methanol (0.2 mL). Dichloromethane (8 mL), and a saturated aqueous solution of $NaHCO_3$ (4 mL) were then added. After separation, the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (cyclohexane / ethyl acetate 95/5) gave **3** as a colorless oil (210 mg, 90%). R_f = 0.32 (silica, cyclohexane / ethyl acetate 95/5); ^1H NMR (300 MHz, $CDCl_3$): δ 7.48–7.24 (m, 10H, H_{Ar}), 5.87 (m, 1H, CH_2-$\underline{CH}$=CH_2), 5.55 (s, 1H, H_7), 5.17 (app t, *J* = 6 Hz, 1H, CH_2-CH=$\underline{CH_2}$), 5.12 (app s, 1H, CH_2-CH=$\underline{CH_2}$), 4.97 (d, *J* = 11.4 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.73 (d, *J* = 11.4 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.31 (dd, *J* = 3.0 Hz, 8.7 Hz, 1H, H_{6eq}), 3.88 (d, *J* = 6.6 Hz, 1H, H_2), 3.84 (t, *J* = 8.7 Hz, 1H, H_4), 3.73–3,64 (m, 3H, H_{6ax}, H_3, H_5), 3.31 (s, 3H, OMe), 2.72 (dd, *J* = 5.7 Hz, 15.6 Hz, 1H, $\underline{CH_2}$-CH=CH_2), 2.59 (dd, *J* = 8.0 Hz, 15.6 Hz, 1H, $\underline{CH_2}$-CH=CH_2), 0.90 (s, 9H, SiC($\underline{CH_3}$)$_3$), 0.10 (s, 3H, Si$\underline{CH_3}$), 0.01 (s, 3H, Si$\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6 (C_{QAr}), 137.5 (C_{QAr}), 132.3 (CH_2-$\underline{CH}$=CH_2), 129.0 (C_{Ar}), 128.3 (C_{Ar}), 128.0 (C_{Ar}), 127.6 (C_{Ar}), 126.0 (C_{Ar}), 117.9 (CH_2-CH=$\underline{CH_2}$), 103.1 (C_1), 101.2 (C_7), 82.6 (C_2), 81.1 (C_4), 74.2 (O-$\underline{CH_2}$-Ph), 72.8 (C_3), 69.5 (C_6), 64.0 (C_5), 48.5 (OMe), 36.1 ($\underline{CH_2}$-CH=CH_2), 27.0 (SiC($\underline{CH_3}$)$_3$), 18,2 (Si$\underline{C}$(CH_3)$_3$), -4.2 (Si$\underline{CH_3}$), -4.9 (Si$\underline{CH_3}$); IR (neat): ν 3074, 3034, 2950, 2931, 2855, 1453,

1382, 1363, 1244, 1235, 1167, 1135, 1121, 1104, 1071, 1045, 1030, 1009, 988, 977, 916, 859, 832, 776, 748, 696, 670, 655, 556, 522, 495, 466, 408; HRMS (ESI): m/z calculated for $C_{30}H_{43}O_6Si$ $[M + H]^+$: 527.2829, found 527.2840; $[\alpha]_D^{20}$ = -24 ($CHCl_3$, c = 0.5).

4.2.2 Methyl 1-*C*-allyl-α-mannopyranoside **4**:

To a solution of **2** (260 mg, 0.63 mmol) and pyridine (305 µL, 3.8 mmol) in DCM (3.2 mL) under argon at 0 °C was added trifluoromethanesulfonic acid *tert*-butyldimethylsilylester (434 µL, 1.9 mmol). The reaction mixture was stirred at 0 °C until TLC (cyclohexane / ethyl acetate 3/1) showed complete consumption of the starting material, and quenched with methanol (0.2 mL). Dichloromethane (8 mL) and a saturated aqueous solution of $NaHCO_3$ (4 mL) were then added. After separation, the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane / ethyl acetate 95/5) to give **4** (270 mg, 81%) as a colorless oil. R_f = 0.46 (silica, cyclohexane / ethyl acetate 95/5); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.23 (m, 10H, H_{Ar}), 5.69 (m, 1H, CH_2-$\underline{CH}$=CH_2), 5.60 (s, 1H, H_7), 5.17 (app s, 1H, CH_2-CH=$\underline{CH_2}$), 5.14 (app d, J = 2.7 Hz, 1H, CH_2-CH=$\underline{CH_2}$), 4.81 (d, J = 11.7 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.68 (d, J = 11.7 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.24 (dd, J = 4.5 Hz, 10.2 Hz, 1H, H_{6eq}), 4.04 (m, 3H, H_2, H_3, H_4), 3.82 (t, J = 10.2 Hz, 1H, H_{6ax}), 3.62 (ddd, J = 4.5 Hz, 8.7 Hz, 10.2 Hz, 1H, H_5), 3.20 (s, 3H, OMe), 2.73 (dd, J = 5.2 Hz, 15.5 Hz, 1H, H_9), 2.41 (dd, J = 8.4 Hz, 15.5 Hz, 1H, $H_{9'}$), 0.87 (s, 9H, SiC($\underline{CH_3}$)$_3$), 0.07 (s, 3H, Si$\underline{CH_3}$), 0.03 (s, 3H, Si$\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6 (C_{QAr}), 137.7 (C_{QAr}), 131.6 (CH_2-$\underline{CH}$=CH_2), 128.8 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 127.4 (C_{Ar}), 126.1 (C_{Ar}), 118.5 (CH_2-CH=$\underline{CH_2}$), 103.4 (C_1), 101.5 (C_7), 79.5 (C_4), 76.4 (C_3), 73.5 (O-$\underline{CH_2}$-Ph), 72.2 (C_2), 69.3 (C_6), 65.2 (C_5), 47.5 (OMe), 34.8 ($\underline{CH_2}$-CH=CH_2), 26.3 (SiC($\underline{CH_3}$)$_3$), 18.7 (Si$\underline{C}$(CH_3)$_3$), -3.4 ($SiCH_3$), -4.9 ($SiCH_3$); IR (neat): ν 2956, 2928, 2856, 1472, 1455, 1374, 1252, 1214, 1138, 1096, 1060, 1038, 1028, 939, 916, 862, 830, 776, 748, 696, 677; HRMS (ESI): *m/z* calculated for $C_{30}H_{43}O_6Si$ $[M + H]^+$: 527.2829, found: 527.2817; $[\alpha]_D^{20}$ = -8 ($CHCl_3$, c = 0.1).

4.2.3 Methyl 1-*C*-bromopropyl-β-glucopyranoside **5**:

A solution of **3** (80 mg, 0.15 mmol) in THF (1.45 mL) under argon was added with zirconocene dichloride (219 mg, 0.75 mmol), and a 1M solution of lithium tri-*tert*-butoxyaluminum hydride in THF (712 µL, 0.72 mmol). After being stirred for 2 h at room temperature, *N*-bromosuccinimide (147 mg, 0.83 mmol) was added. After 2h30 at room temperature, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (0,1 mL). Dichloromethane (5 mL) and a 1M aqueous solution of citric acid (5 mL)

were then added, and the mixture was stirred overnight. After separation of the organic layer, the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After purification by silica gel chromatography (cyclohexane / ethyl acetate 95/5), **5** was obtained as a colorless oil (80 mg, 88%). R_f = 0.31 (silica, cyclohexane / ethyl acetate 95/5); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.28 (m, 10H, H_{Ar}), 5.58 (s, 1H, H_7), 5.00 (d, J = 11.1 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.74 (d, J = 11.1 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.36 (dd, J = 4.5 Hz, 10.2 Hz, 1H, H_{6eq}), 3.89 (d, J = 6.9 Hz, 1H, H_2), 3.81–3.66 (m, 4H, H_4, H_{6ax}, H_3, H_5), 3.49 (m, 2H, H_{10}), 3.29 (s, 3H, OMe), 1.97 (m, 4H, H_8, H_9), 0.93 (s, 9H, SiC($\underline{CH_3}$)$_3$), 0.13 (s, 3H, Si$\underline{CH_3}$), 0.05 (s, 3H, Si$\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6 (C_{QAr}),137.4 (C_{QAr}), 129.0 (C_{Ar}), 128.3 (C_{Ar}), 128.3 (C_{Ar}), 128.1(C_{Ar}), 127.6 (C_{Ar}), 126.0 (C_{Ar}), 103.5 (C_1), 101.3 (C_7), 82.6 (C_4), 81.0 (C_3), 74.4 (O-$\underline{CH_2}$-Ph), 72.3 (C_2), 69.5 (C_6), 64.3 (C_5), 48.3 (OMe), 34.4 (C_{10}), 29.6 (C_8), 25.9 (SiC($\underline{C}H_3$)$_3$), 25.6 (C_9), 18.3 (Si$\underline{C}$(CH$_3$)$_3$), -4.1 (SiCH$_3$), -4.9 (SiCH$_3$); IR (neat): ν 2956, 2926, 2855, 1455, 1375, 1250, 1213, 1145, 1086, 1029, 1005, 858, 836, 778, 749, 673, 696; HRMS (ESI): *m/z* calculated for $C_{30}H_{44}BrO_6Si$ $[M + H]^+$: 608.2019, found: 608.2022; $[\alpha]_D^{20}$ = -4 ($CHCl_3$, c = 0.5).

4.2.4 Methyl 1-*C*-bromopropyl-α-mannopyranoside **6**:

A solution of **4** (80 mg, 0.15 mmol) in THF (1.45 mL) under argon was added with zirconocene dichloride (219 mg, 0.75 mmol) and a 1M solution of lithium tri-*tert*-butoxyaluminum hydride in THF (712 µL, 0.72 mmol). After 2 h at room temperature, *N*-bromosuccinimide (147 mg, 0.83 mmol) was added. After 2h30 at room temperature, the reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (0,1 mL). Dichloromethane (5 mL) and a 1M aqueous solution of citric acid (5 mL) were then added, and the mixture was stirred overnight. After separation of the organic layer, the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After purification by silica gel chromatography (cyclohexane / ethyl acetate 95/5), **6** was obtained as colorless oil (81 mg, 89%). R_f = 0.46 (silica, cyclohexane / ethyl acetate 95/5); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53–7.24 (m, 10H, H_{Ar}), 5.61 (s, 1H, H_7), 4.84 (d, J = 11.7 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.69 (d, J = 11.7 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.24 (dd, J = 4.5 Hz, 10.2 Hz, 1H, $H_{6éq}$), 4.04 (m, 2H, H_4, H_3), 3.93 (d, J = 2.1 Hz, 1H, H_2), 3.80 (t, J = 10.2 Hz, 1H, H_{6ax}), 3.61 (m, 1H, H_5), 3.45 (m, 1H, H_{10}), 3.28 (m, 1H, $H_{10'}$), 3.18 (s, 3H, OMe), 1.82 (m, 4H, H_8, H_9), 0.88 (s, 9H, SiC($\underline{CH_3}$)$_3$), 0.09 (s, 3H, Si$\underline{CH_3}$), 0.03 (s, 3H, Si$\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6 (C_{QAr}), 137.9 (C_{QAr}), 128.9 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 127.6 (C_{Ar}), 126.2 (C_{Ar}), 103.6 (C_1), 101.6 (C_7), 79.6 (C_4), 76.5 (C_3), 73.8 (O-$\underline{CH_2}$-Ph), 72.4 (C_2), 69.3 (C_6), 65.3 (C_5), 47.6 (OMe), 33.1 (C_{10}), 29.2 (C_9), 26.6 (C_8) 26.3 (SiC($\underline{CH_3}$)$_3$), 18.8 (Si$\underline{C}$(CH$_3$)$_3$), -3.2 (SiCH$_3$), -5.1 (SiCH$_3$); IR (neat):

ν 2956, 2925, 2854, 1740, 1684, 1642, 1456, 1377, 1253, 1213, 1139, 1099, 1061, 1006, 917, 832, 778, 749, 697, 582, 509, 419; HRMS (ESI): *m/z* calculated for $C_{30}H_{44}BrO_6Si$ [M + H]$^+$: 608.2019, found: 608.2024; $[\alpha]_D^{20}$ = -6 ($CHCl_3$, c = 0.1).

4.2.5 Methyl 1-*C*-dibenzylpropylphosphonate β-glucopyranoside **7**:

A suspension of NaH (60% dispersion in mineral oil, 80 mg, 2 mmol) in DMF (2.5 mL) under argon was cooled to 0°C, and added with dibenzyl *H*-phosphonate (445 µL, 2 mmol) dropwise. A solution of **5** (408 mg, 0.67 mmol) in DMF (1 mL) was then added dropwise, and the mixture was stirred at room temperature for 3h before addition of *iso*-propanol (0.2 mL). Dichloromethane (10 mL) and saturated aqueous solution of $NaHCO_3$ (10 mL) were then added. After separation, the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After evaporation of solvent under reduced pressure, the residue was used in the next step without further purification. A solution of the crude product in THF (3 mL) was added with TBAF (496 mg, 1.9 mmol) and stirred at room temperature until TLC showed complete consumption of the starting material. Dichloromethane (10mL) and water (5 mL) were added. After separation, the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After purification over silica gel chromatography (cyclohexane/ethyl acetate 45: 55), **7** was obtained as a colorless film (290 mg, 64%). R_f = 0.26 (silica, cyclohexane / ethyl acetate 4/6); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 20H, H_{Ar}), 5.50 (s, 1H, H_7), 4.85 (m, 6H, O-$\underline{CH_2}$-Ph, P-O-$\underline{CH_2}$-Ph), 4.18 (dd, J = 4.6 Hz, 10.5 Hz, 1H, H_{6eq}), 3.80 (d, J = 7.2 Hz, 1H, H_2), 3.62 (m, 3H, H_3, H_4, H_{6ax}),3.42 (td, J = 4.6 Hz, 9.3 Hz, 1H, H_5), 3.21 (s, 3H, OMe), 2.52 (s, 1H, OH), 1.66 (m, 6H, H_8, H_9, H_{10}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2 (C_{QAr}), 137.3 (C_{QAr}), 136.4 (C_{QAr}), 136.5 (C_{QAr}), 129.1 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 128.1 (C_{Ar}), 128.0 (C_{Ar}), 126.0 (C_{Ar}), 102.6 (d, J = 2.4 Hz, C_1), 101.3 (C_7), 82.2 (C_4), 80.0 (C_3), 74.6 (O-$\underline{CH_2}$-Ph), 71.0 (C_2), 69.2 (C_6), 67.2 (d, J = 4.5 Hz, P-O-$\underline{CH_2}$-Ph), 67.1 (d, J = 4.5 Hz, P-O-$\underline{CH_2}$-Ph), 64.8 (C_5), 48.6 (OMe), 30.7 (d, J = 15.8 Hz, C_9), 25.0 (d, J = 139.5 Hz, C_{10}), 14.6 (d, J = 4.5 Hz, C_8); ^{31}P NMR (121 MHz, $CDCl_3$): δ 33.29; IR (neat): ν 3342, 3065, 3035, 2925, 1727, 1497, 1455, 1376, 1235, 1211, 1180, 1081, 992, 918, 864, 734, 695, 459; HRMS (ESI): *m/z* calculated for $C_{38}H_{43}O_9PNa$ [M + Na]$^+$: 697.2542, found: 697.2542; $[\alpha]_D^{20}$ = +14 ($CHCl_3$, c = 0.1).

4.2.6 Methyl 1-*C*-dibenzylpropylphosphonate α-mannopyranoside **8**:

A suspension of NaH (60% dispersion in mineral oil, 100 mg, 2.5 mmol) in DMF (3 mL) un der argon was cooled to 0°C, and added with dibenzyl *H*-phosphonate (550 µL, 2.5 mmol)dropwise. A solution of **6** (515 mg, 0.85 mmol) in DMF (1 mL) was then added dropwise, and the mixture was stirred at room temperature for 3h before addition of *iso*-propanol (0.2 mL). Dichloromethane (10 mL) and saturated aqueous solution of $NaHCO_3$ (10 mL) were then added. After separation, the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After evaporation of solvent under reduced pressure, the residue was used in the next step without further purification. A solution of the crude product in THF (3 mL) was added with TBAF (627 mg, 2.4 mmol) and stirred at room temperature until TLC showed complete consumption of the starting material. Dichloromethane (10mL) and water (5 mL) were added. After separation, the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. After purification over silica gel chromatography (cyclohexane/ethyl acetate 45: 55), **8** was obtained as a colorless oil (437 mg, 76%). R_f = 0.13 (silica, cyclohexane / ethyl acetate 6/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–7.17 (m, 20H, Ar), 5.50 (s, H_7), 4.94 (m, 4H, P-O-$\underline{CH_2}$-Ph), 4.74 (d, J = 12.0 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.63 (d, J = 12.0 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.16 (dd, J = 4.8 Hz, 10.2 Hz, 1H, H_{6eq}), 3.92 (m, 1H, H_4), 3.87 (dd, J = 3.3 Hz, 9.6 Hz, 1H, H_3), 3.78 (d, J = 3 Hz, 1H, H_2), 3.73 (t, J = 10.5 Hz,1H, H_{6ax}), 3.53 (td, J = 4.5 Hz, 9.6 Hz, 1H, H_5), 3.01 (s, 3H, OMe), 2.55 (s, 1H, OH), 1.66 (m, 6H, H_8, H_9, H_{10}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2 (C_{QAr}), 137.7 (C_{QAr}), 136.6 (C_{QAr}), 136.5 (C_{QAr}), 129.0 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 128.11 (C_{Ar}), 128.09 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 126.1 (C_{Ar}), 102.7 (d, J = 3 Hz, C_1), 101.6 (C_7), 78.7 (C_4), 76.1 (C_3), 73.0 (O-$\underline{CH_2}$-Ph), 69.4 (C_2), 69.1 (C_6), 67.3 (d, J = 2.7 Hz, P-O-$\underline{CH_2}$-Ph), 67.2 (d, J = 2.7 Hz, P-O-$\underline{CH_2}$-Ph), 64.1 (C_5), 47.36 (OMe), 31.4 (d, J = 16.5 Hz, C_9), 26.0 (d, J = 140 Hz, C_{10}), 16.1 (d, J = 4.5 Hz, C_8); ^{31}P NMR (121 MHz, $CDCl_3$): δ 33.06; IR (neat): ν 3371, 3064, 3033, 2924, 1497, 1455, 1378, 1313, 1096, 1024, 991, 965, 912, 861, 821, 734, 695; HRMS (ESI): *m/z* calculated for $C_{38}H_{43}O_9PNa$ $[M + Na]^+$: 697.2542, found: 697.2542; $[\alpha]_D^{20}$ = -4 ($CHCl_3$, c = 0.1).

4.2.7 Methyl 1-*C*-dibenzylpropylphosphonate β-mannopyranoside **9**:

A solution of Dess-Martin periodinane (64.2 mg, 0.15 mmol) in pyridine (0.3 mL) under argon was stirred at room temperature for 30 min, and added with a solution of **7** (100 mg, 0.15 mmol) in dichloromethane (0.3 mL). After 1 h of stirring at room temperature, dichloromethane (4 mL), a saturated aqueous solution of $NaHCO_3$ (2 mL), and a saturated aqueous solution of $Na_2S_2O_3$ (2 mL) were then added. After separation, the aqueous layer

was extracted with dichloromethane (3 x 5 mL), and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane and filtered on a short pad of silica. After evaporation of solvent under reduced pressure, the residue (88 mg, 87%) was used in the next step without further purification. To a solution of this ketone in THF (1.5 mL) under argon at -78°C was added dropwise L-selectride (1M in THF, 450 µL, 0.45 mmol). After 30 min at -78°C, dichloromethane (5 mL) and a 1M aqueous solution of Rochelle's salt (5 mL) were added. After 18h of vigorous stirring at room temperature, the organic layer was separated and the aqueous layer extracted with dichloromethane (2 x 5 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. A silica gel chromatography was performed (cyclohexane/ethyl acetate 1:5) to give 82 mg (82 %) of the **9** as a colorless oil. R_f = 0.12 (silica, cyclohexane / ethyl acetate 4/6); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.19 (m, 20H, Ar), 5.47 (s, 1H, H_7), 4.92 (m, 4H, P-O-$\underline{CH_2}$-Ph), 4.76 (d, J = 12.0 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.64 (d, J = 12.0 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.15 (m, 2H, H_{6eq}, H_4), 3.82 (d, J = 6.0 Hz, 1H, H_2), 3.67 (m, 2H, H_3, H_{6ax}), 3.36 (td, J = 6.0 Hz, 9.0 Hz, 1H, H_5), 3.18 (s, 3H, OMe), 2.83 (s_{br}, 1H, OH), 1.53 (m, 6H, H_8, H_9, H_{10}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.2 (C_{QAr}), 137.7 (C_{QAr}), 136.6 (C_{QAr}), 136.5 (C_{QAr}), 129.0 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 128.11 (C_{Ar}), 128.09 (C_{Ar}), 128.0 (C_{Ar}), 127.9 (C_{Ar}), 126.1 (C_{Ar}), 101.43 (C_7), 101.36 (d, J = 2.3 Hz, C_1), 79.6 (C_4), 75.6 (C_3), 73.3 (O-$\underline{CH_2}$-Ph), 69.7 (C_6), 69.3 (C_2), 67.34 (d, J = 1.5 Hz, P-O-$\underline{CH_2}$-Ph), 67.25 (d, J = 1.5 Hz, P-O-$\underline{CH_2}$-Ph), 65.0 (C_5), 49.1 (OMe), 31.6 (d, J = 14.2 Hz, C_9), 26.1 (d, J = 140 Hz, C_{10}), 16.9 (d, J = 5.3 Hz, C_8); ^{31}P NMR (121 MHz, $CDCl_3$): δ 32.48; IR (neat): ν 3434, 3064, 3033, 2928, 1724, 1606, 1497, 1455, 1376, 1314, 1212, 1089, 1047, 991, 966, 734, 695, 461; HRMS (ESI): *m/z* calculated for $C_{38}H_{43}O_9PNa$ $[M + Na]^+$: 697.2542, found: 697.2542; $[\alpha]_D^{20}$ = +6 ($CHCl_3$, c = 0.1).

4.2.8 Methyl 1-*C*-dibenzylpropylphosphonate α-glucopyranoside **10**:

A solution of Dess-Martin periodinane (90 mg, 0.19 mmol) in pyridine (0.4 mL) under argon was stirred at room temperature for 30 min, and added with a solution of **8** (130 mg, 0.19 mmol) in dichloromethane (0.4 mL). After 2 h of stirring at room temperature, additional Dess-Martin periodinane (90 mg, 0.19 mmol) in solution in pyridine was added. After complete consumption of the starting material, dichloromethane (4 mL), a saturated aqueous solution of $NaHCO_3$ (2 mL), and a saturated aqueous solution of $Na_2S_2O_3$ (2 mL) were then added. After separation, the aqueous layer was extracted with dichloromethane (3 x 5 mL), and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane and filtered on a short pad of silica. After evaporation of solvent under reduced pressure, the residue (80 mg, 62%) was

used in the next step without further purification. To a solution of this ketone in 1:1 dichloromethane/methanol (1.5 mL) at 0°C was added $NaBH_4$ (23 mg, 0.6 mmol). After 15 min, dichloromethane (2.5 mL) and a 2% aqueous solution of AcOH (2.5 mL) were added, and the mixture was stirred at room temperature for 30 min. After separation, the aqueous layer was extracted with dichloromethane (2 x 5 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (cyclohexane/ethyl acetate 4:6) gave **8** (30 mg, 30%) and **10** (38 mg, 37%) as colorless films. **10:** R_f = 0.15 (silica, cyclohexane / ethyl acetate 1/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–7.17 (m, 20H, Ar), 5.46 (s, 1H, H_7), 4.90 (m, 6H, P-O-$\underline{CH_2}$-Ph, O-$\underline{CH_2}$-Ph), 4.68 (d, J = 12.0 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.15 (m, 1H, H_{6eq}), 3.75 (t, J = 9.0 Hz, 1H, H_3,) 3.55 (m, 4H, H_2, H_4, H_5, H_{6ax}), 3.11 (s, 3H, OMe), 2.22 (s_{br}, 1H, OH), 1.66 (m, 6H, H_8, H_9, H_{10}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7 (C_{QAr}), 137.5 (C_{QAr}), 136.6 (C_{QAr}), 136.5 (C_{QAr}), 129.1 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.1 (C_{Ar}), 127.9 (C_{Ar}), 126.1 (C_{Ar}), 101.9 (d, J = 3.0 Hz, C_1), 101.3 (C_7), 82.2 (C_4), 79.4 (C_3), 75.0 (O-$\underline{CH_2}$-Ph), 73.5 (C_2), 69.1 (C_6), 67.3 (P-O-$\underline{CH_2}$-Ph), 67.2 (P-O-$\underline{CH_2}$-Ph), 63.6 (C_5), 47.7 (OMe), 33.1 (d, J = 16.5 Hz, C_9), 26.3 (d, J = 140 Hz, C_{10}), 17.0 (d, J = 4.5 Hz, C_8); ^{31}P NMR (121 MHz, $CDCl_3$): δ 32.98; IR (neat): ν 3371, 3065, 3033, 2919, 1498, 1455, 1376, 1312, 1213, 1179, 1085, 1041, 992, 863, 734, 696, 593, 461; HRMS (ESI): *m/z* calculated for $C_{38}H_{43}O_9PNa$ $[M + Na]^+$: 697.2542, found: 697.2536; $[\alpha]_D^{20}$ = +17 ($CHCl_3$, c = 0.1).

4.2.9 Methyl 1-*C*-diallylpropylphosphonate β-glucopyranoside **11**:

A suspension of NaH (60% dispersion in mineral oil, 14 mg, 0.35 mmol) in DMF (0.5 mL) under argon was cooled to 0°C, and added with diallyl *H*-phosphonate (51 µL, 0.35 mmol) dropwise. A solution of **5** (70 mg, 0,115 mmol) in DMF (0.5 mL) was then added dropwise, and the mixture was stirred at room temperature for 3h before addition of *iso*-propanol (0.1 mL). Dichloromethane (5 mL) and saturated aqueous solution of $NaHCO_3$ (5 mL) were then added. After separation, the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (cyclohexane / ethyl acetate 60/40) to give compound **11** (56 mg, 70%, 87% based on recovered starting material) as colorless oil. R_f = 0.32 (silica, cyclohexane / ethyl acetate 95/5); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.29 (m, 10H, Ar), 5.99 (tdd, J = 5.4 Hz, 10.2 Hz, 17.4 Hz, 2H, O-CH_2-$\underline{CH}$=CH_2), 5.59 (s, 1H, H_7), 5.40 (d, J = 17.4 Hz, 2H, O-CH_2-CH=$\underline{CH_2}$), 5.28 (d, J = 10.2 Hz, 2H, O-CH_2-CH=$\underline{CH_2}$), 4.98 (d, J = 11.4 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.74 (d, J = 11.4 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.58 (m, 4H, O-$\underline{CH_2}$-CH=CH_2), 4.37 (dd, J = 4.6 Hz, 10.1 Hz, 1H, $H_{6éq}$), 3.89 (d, J = 6.6 Hz, 1H,

H_2), 3.85 (t, J = 9.0 Hz, 1H, H_4), 3.75 (t, J = 10.1 Hz, 1H, H_{6ax}), 3.64 (m, 2H, H_3, H_5), 3.29 (s, 3H, OMe), 1.80 (m, 6H, H_8, H_9, H_{10}), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.11 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6 (C_{QAr}), 137.5 (C_{QAr}), 133.2 (d, J = 6.2 Hz, O-CH_2-$\underline{CH}$=CH_2), 129.0 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 128.1 (C_{Ar}), 127.6 (C_{Ar}), 126.1 (C_{Ar}), 118.0 (O-CH_2-CH=$\underline{CH_2}$), 103.4 (d, J = 1.5 Hz, C_1), 101.3 (C_7), 82.6 (C_4), 81.0 (C_3), 74.2 (O-$\underline{CH_2}$-Ph), 72.4 (C_2), 69.6 (C_6), 66.1 (d, J = 1.9 Hz, O-$\underline{CH_2}$-CH=CH_2), 66.0 (d, J = 1.9 Hz, C_{11}), 64.2 (C_5), 48.2 (OMe), 31.7 (d, J = 16.7 Hz, C_9), 26.1 (d, J = 140 Hz, C_{10}), 25.9 ($SiC(\underline{CH_3})_3$), 18.3 ($Si\underline{C}(CH_3)_3$), 15.3 (d, J = 4.7 Hz, C_8), - 4.2 ($SiCH_3$), - 4.9 ($SiCH_3$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 33.59; IR (neat): ν 2929, 2856, 1455, 1370; 1246, 1144, 1085, 1027, 988, 921, 856, 836, 778, 750, 697; HRMS (ESI): *m/z* calculated for $C_{36}H_{53}O_9PSiNa$ $[M + Na]^+$: 711.3094, found: 711.3102; $[\alpha]_D^{20}$ = -7 ($CHCl_3$, c = 0.1);

4.2.10 Methyl 1-*C*-diallylpropylphosphonate α-mannopyranoside **12**:

A suspension of NaH (60% dispersion in mineral oil, 20 mg, 0.49 mmol) in DMF (0.5 mL) under argon was cooled to 0°C, and added with diallyl *H*-phosphonate (73 µL, 0.49 mmol) dropwise. A solution of **6** (100 mg, 0,16 mmol) in DMF (0.5 mL) was then added dropwise, and the mixture was stirred at room temperature for 3h before addition of *iso*-propanol (0.1 mL). Dichloromethane (5 mL) and saturated aqueous solution of $NaHCO_3$ (5 mL) were then added. After separation, the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (pure dichloromethane to dichloromethane / ethyl acetate 2/1) to give compound **12** (96 mg, 87%) as colorless oil. R_f = 0.23 (silica, cyclohexane / ethyl acetate 70/30); ^1H NMR (300 MHz, $CDCl_3$): δ 7.50–7.24 (m, 10H, Ar), 5.90 (dddd, J = 5.4 Hz, 6.6 Hz, 10.2 Hz, 17.1 Hz, 2H, O-CH_2-$\underline{CH}$=CH_2), 5.59 (s, 1H, H_7), 5.33 (d, J = 17.1 Hz, 2H, O-CH_2-CH=$\underline{CH_2}$), 5.22 (d, J = 10.4 Hz, 2H, O-CH_2-CH=$\underline{CH_2}$), 4.80 (d, J = 11.7 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.67 (d, J = 11.7 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.51 (app t, J = 6.6 Hz, 4H, O-$\underline{CH_2}$-CH=CH_2), 4.20 (dd, J = 4.6 Hz, 10.1 Hz, 1H, $H_{6éq}$), 4.04 (t, J = 9.3 Hz, 1H, H_4), 3.98 (d, J = 2.3 Hz, 1H, H_3), 3.94 (app s, 1H, H_2), 3.75 (t, J = 10.3 Hz, 1H, H_{6ax}), 3.59 (ddd, J = 4.5 Hz, 8.8 Hz, 10.3 Hz, 1H, H_5), 3.15 (s, 3H, OMe), 1.71 (m, 6H, H_8, H_9, H_{10}), 0.85 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6 (C_{QAr}), 137.9 (C_{QAr}), 133.2 (d, J = 5.9 Hz, O-CH_2-$\underline{CH}$=CH_2), 128.9 (C_{Ar}), 128.3 (C_{Ar}), 128.3 (C_{Ar}), 127.6 (C_{Ar}), 126.1 (C_{Ar}), 118.0 (d, J = 1.5 Hz, O-CH_2-CH=$\underline{CH_2}$), 103.7 (d, J = 3.6 Hz, C_1), 101.6 (C_7), 79.6 (C_4), 77.3 (C_3), 73.7 (O-$\underline{CH_2}$-Ph), 72.1 (C_2), 69.3 (C_6), 66.2 (d, J = 1.5 Hz, C_{11}), 66.1 (d, J = 1.5 Hz, O-$\underline{CH_2}$-CH=CH_2), 65.2 (C_5), 47.6 (OMe), 31.3 (d, J = 17.6 Hz, C_9), 26.3 ($SiC(\underline{CH_3})_3$), 25.8 (d, J = 140 Hz, C_{10}), 18.8 ($Si\underline{C}(CH_3)_3$), 16.4 (d, J = 4.7 Hz, C_8), - 3.3 ($SiCH_3$), - 5.1 ($SiCH_3$); ^{31}P NMR (121 MHz, $CDCl_3$) δ 33.19; IR (neat): ν 2949,

2929, 2856, 1456, 1438, 1378, 1247, 1213, 1141, 1098, 1003, 988, 923, 831, 777, 749, 697; HRMS (ESI): *m/z* calculated for $C_{36}H_{53}O_9SiPNa$ $[M + Na]^+$: 711.3094, found: 711.3084; $[\alpha]_D^{20}$ = -108 ($CHCl_3$, c = 0.1).

4.2.11 Methyl 1-*C*-icosylpropylphosphonate-β-glucopyranoside triethylammonium salt **13**:

To a solution of **11** (83 mg, 0.12 mmol) in THF (1.3 mL) under argon were added diethylamine (260 µL, 2.4 mmol), and $Pd(PPh_3)_4$ (30 mg, 0.026 mmol). After being stirred for 1h30, TLC (cyclohexane / ethyl acetate 50/50) showed complete conversion of the starting material, and Deloxan® (10 mg) was added. The reaction mixture was then filtered and concentrated under reduced pressure to give a residue that was used in the next step without further purification. To a solution of the crude product in pyridine (0.8 mL) under argon was added trichloroacetonitrile (120 µL, 1.2 mmol) and eicosanol (146 mg, 0.49 mmol). After stirring of the reaction mixture for 24 h at 60°C, TLC (dichloromethane/methanol/triethylamine 90/10/1) showed complete conversion of the starting material. After concentration under reduced pressure, the residue was purified by silica gel chromatography (dichloromethane/methanol/triethylamine 90/10/1) to give compound **13** (86 mg, 72%) as a white foam. R_f = 0.39 (silica, dichloromethane/methanol/triethylamine 90/10/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46–7.23 (m, 10H, Ar), 6.43 (br s, 1H, NH), 5.54 (s, 1H, H_7), 4.92 (d, J = 11.3 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.69 (d, J = 11.3 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.33 (dd, J = 4.0 Hz, 9.5 Hz, 1H, $H_{6éq}$), 3.92 (q, J = 6.7 Hz, 2H, H_{11}), 3.83 (m, 2H, H_2, H_4), 3.65 (m, 3H, H_3, H_5, H_{6ax}), 3.24 (s, 3H, OMe), 3.07 (q, J = 7.3 Hz, 4H, $NHEt_3$), 1,87 (m, 2H, H_9), 1.65 (m, 6H, H_8, H_{10}, H_{12}), 1.34 (t, J = 7.3 Hz, 9H, $NHEt_3$), 1.25 (m, 34H, $H_{eicosyl}$), 0.88 (app s, 12H, H_{13}, $SiC(CH_3)_3$), 0.07 (s, 3H, $SiCH_3$), - 0.02 (s, 3H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6 (C_{QAr}), 137.5 (C_{QAr}), 128.9 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 127.5 (C_{Ar}), 126.0 (C_{Ar}), 103.5 (d, J = 2.3 Hz, C_1), 101.1 (C_7), 82.6 (C_4), 81.1 (C_3), 74.1 (O-$\underline{CH_2}$-Ph), 72.6 (C_2), 69.6 (C_6), 64.6 (d, J = 6.0 Hz, C_{11}), 64.1 (C_5), 48.1 (OMe), 45.7 ($NHEt_3$), 32.0 (C_{alkyle}), 31.6 (d, J = 16.8 Hz, C_8), 30.9 (d, J = 4.7 Hz, C_9), 29.8 (C_{alkyle}), 29.5 ($C_{alkyles}$), 29.4 ($C_{alkyles}$), 26.4 (d, J = 140 Hz, C_{10}), 25.8 ($SiC(\underline{CH_3})_3$), 22.7 ($C_{alkyles}$), 18.2 ($Si\underline{C}(CH_3)_3$), 14.2 (C_{alkyle}), 8.7 ($NHEt_3$), - 4.2 ($SiCH_3$), - 4.9 ($SiCH_3$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 24.61; IR (neat): ν 2923, 2853, 1464, 1368, 1249, 1211, 1144, 1086, 1029, 1005, 858, 836, 778; 748, 696; HRMS (ESI): *m/z* calculated for $C_{50}H_{84}O_9PSi$ $[M]^-$: 887.5622, found: 887.5622; $[\alpha]_D^{20}$ = -4 ($CHCl_3$, c = 0.1).

4.2.12 Methyl 1-*C*-icosylpropylphosphonate-α-mannopyranoside triethylammonium salt **14**:

To a solution of **11** (100 mg, 0.15 mmol) in THF (1.5 mL) under argon were added diethylamine (750 µL, 7.5 mmol), and $Pd(PPh_3)_4$ (84 mg, 0.075 mmol). After being stirred for 1h30, TLC (cyclohexane / ethyl acetate 50/50) showed complete conversion of the starting material, and Deloxan® (10 mg) was added. The reaction mixture was then filtered and concentrated under reduced pressure to give a residue that was used in the next step without further purification. To a solution of the crude product in pyridine (1 mL) under argon was added trichloroacetonitrile (152 µL, 1.5 mmol)and eicosanol (180 mg, 0.6 mmol). After stirring of the reaction mixture for 24 h at 60°C, TLC (dichloromethane/methanol/triethylamine 90/10/1) showed complete conversion of the starting material. After concentration under reduced pressure, the residue was purified by silica gel chromatography (dichloromethane/methanol/triethylamine 90/10/1) to give compound **14** (126 mg, 85%) as a white foam. R_f = 0.38 (silica, dichloromethane/methanol/triethylamine 90/10/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.17 (br s, 1H, NH), 7.52–7.25 (m, 10H, Ar), 5.60 (s, 1H, H_7), 4.82 (d, J = 11.7 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.69 (d, J = 11.7 Hz, 1H, O-$\underline{CH_2}$-Ph), 4.20 (dd, J = 4.4 Hz, 10.0 Hz, 1H, $H_{6éq}$), 4.03 (m, 3H, H_2, H_3,H_4), 3.83 (m 3H, H_{11}, H_{6ax}), 3.58 (m, 1H, H_5), 3.16 (s, 3H, OMe), 3.05 (q, J = 7.3 Hz, 4H, $NHEt_3$), 1,87 (m, 2H, H_9), 1.59 (m, 6H, H_8, H_{10}, H_{12}), 1.37 (t, J = 7.3 Hz, 9H, $NHEt_3$), 1.25 (m, 34H, $H_{eicosyl}$), 0.88 (app s, 12H, H_{13}, $SiC(CH_3)_3$), 0.07 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6 (C_{QAr}), 137.8 (C_{QAr}), 128.8 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 127.4 (C_{Ar}), 126.0 (C_{Ar}), 103.6 (d, J = 3 Hz, C_1), 101.5 (C_7), 79.6 (C_4), 76.4 (C_3), 73.4 (O-$\underline{CH_2}$-Ph), 71.9 (C_2), 69.2 (C_6), 65.0 (C_5), 63.3 (d, J = 5.3 Hz, C_{11}), 47.4 (OMe), 45.7 ($NHEt_3$), 31.9 ($C_{alkyles}$), 31.4 (d, J = 17.1 Hz, C_8), 31.0 (d, J = 6.8 Hz, C_9), 29.8 (C_{alkyle}), 29.7 ($C_{alkyles}$), 29.6 ($C_{alkyles}$), 29.5 (d, J = 140 Hz, C_{10}), 26.2 ($SiC(\underline{CH_3})_3$), 25.9 ($C_{alkyles}$), 22.7 ($C_{alkyles}$), 18.6 ($Si\underline{C}(CH_3)_3$), 14.2 (C_{alkyle}), 11.3 (C_{alkyle}) 8.7 ($NHEt_3$), - 3.5 ($SiCH_3$), - 5.1 ($SiCH_3$); ^{31}P NMR (121 MHz, $CDCl_3$): δ 23.28; IR (neat): ν 3386, 2924, 2853, 1644, 1456, 1377, 1252, 1213, 1144, 1098, 1044, 968, 909, 934, 833, 777, 748, 969, 659; HRMS (ESI): *m/z* calculated for $C_{50}H_{84}O_9PSi$ $[M]^-$: 887.5622, found: 887.5612; $[\alpha]_D^{20}$ = -9 ($CHCl_3$, c = 0.1).

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References:

(1) For representative reviews, see: (a) Koester, D. C.; Holkenbrink, A.; Werz, D. B. *Synthesis* **2010**, 3217-3242; (b) Chen, N.; Xie, J. *Org. Biomol. Chem.* **2016**, *14*, 11028-11047; (c) Hazelard, D.; Compain, P. *Org. Biomol. Chem.* **2017**, *15*, 3806-3827; (d) Kiessling, L. L. *Bioorg. Med. Chem.* **2018**, *26*, 5229-5238.

(2) For representative examples, see: (a) Goyard, D.; Docsa, T.; Gergely; P.; Praly, J.-P.; Vidal, S. *Carbohydr. Res.* **2015**, *402*, 245-251; (b) Forget, S. M.; Jee, A.; Smithen, D. A.; Jagdhane, R.; Anjum, S.; Beaton, S. A.; Palmer, D. R. J.; Syvitski, R. T.; Jakeman, D. L. *Org. Biomol. Chem.* **2015**, *13*, 866-875; (c) Descroix, K.; Pesnot, T.; Yoshimura, Y.; Gehrke, S. S.; Wakarchuck, W.; Palcic, M. M.; Wagner, G. K. *J. Med. Chem.* **2012**, *55*, 2015-2024; (d) Barry, C. S.; Backus, K. M.; Barry, C. E.; Davis, B. G. *J. Am. Chem. Soc.* **2011**, *133*, 13232-13235; (e) Caravano, A.; Vincent, S. P. *Eur. J. Org. Chem.* **2009**, 1771-1780; (f) Schwörer, R.; Schmidt, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 1632-1637.

(3) Ghirardello, M.; de las Rivas, M.; Lacetera, A.; Delso, I.; Lira-Navarrete, E.; Tejero, T.; Martin-Santamaria, S.; Hurtado-Guerrero, R.; Merino, P. *Chem. Eur. J.* **2016**, *22*, 7215-7224.

(4) (a) Hammoud, J.; Joosten, A.; Lecourt, T. *Carbohydr. Res.* **2019**, *486*, 107834; (b) Boultadakis-Arapinis, M.; Prost, E.; Gandon, V.; Lemoine, P.; Turcaud, S.; Micouin, L.; Lecourt, T. *Chem. Eur. J.* **2013**, *19*, 2477-2491; (c) Boultadakis-Arapinis, M.; Lemoine, P.; Turcaud, S.; Micouin, L.; Lecourt, T. *J. Am. Chem. Soc.* **2010**, *132*, 15477-15479.

(5) Mébarki, K.; Gavel, M.; Heis, F.; Joosten, A. Y. P.; Lecourt, T. *J. Org. Chem.* **2017**, *82*, 9030-9037.

(6) Dondoni, A.; Staderini, S.; Marra, A. *Eur. J. Org. Chem.* **2013**, 5370-5375.

(7) Preparation of dibenzyl phosphonates following this free-radical hydrophosphonylation method only delivered the desired products in low yields: Geant, P.-Y.; Sisi Mohamed, B.; Périgaud, C.; Peyrottes, S.; Uttaro, J.-P.; Mathé, C. *New J. Chem.* **2016**, *40*, 5318-4324.

(8) Gavel, M.; Courant, T.; Joosten, A. Y. P.; Lecourt, T. *Org. Lett.* **2019**, *21*, 1948-1952.

(9) For a recent use of zirconium hydrides in glycochemistry, see: Foucart, Q.; Shimadate, Y.; Marrot, J.; Kato, A.; Désiré, J.; Blériot, Y. *Org. Biomol. Chem.* **2019**, *17*, 7204-7214.

(10) Xu, B; Stephens, A.; Kirschenheuter, G.; Greslin, A. F.; Cheng, X.; Sennelo, J.; Cattaneo, M.; Zighetti, M. L.; Chen, A.; Kim, S.-A.; Kim, H. S.; Bischofberger, N.; Cook, G.; Jacobson, K. A. *J. Med. Chem.* **2002**, *45*, 5694-5709.

(11) For reviews on hydrozirconation of alkenes and alkynes, see: (a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853-12910; (b) Negishi, E.-I.; Takahashi, T. *Synthesis* **1988**, 1-19.

(12) Zhao, Y.; Snieckus, V. *Org. Lett.* **2014**, *16*, 390-393.

(13) Yan, F.; Moon, S.; Liu, P.; Zhao, Z.; Lipscomb, J.; Liu, A.; Liu, H. *Biochemistry* **2007**, *46*, 12628-12638.

(14) For diallyl phosphate as convenient synthetic intermediate for the preparation of bioactive carbohydrates, see: Li, T.; Tikad, A.; Pan, W.; Vincent, S. P. *Org Lett.* **2014**, *16*, 5628-5631.

(15) Rigby, J. H.; Moore, T. L.; Rege, S. *J. Org. Chem.* **1986**, *51*, 2400-2402.

(16) Reaction with dimedone as nucleophilic scavenger resulted in degradation of the substrate.

(17) Takaya, K.; Nagahori, N.; Kurogochi, M.; Furuike, T.; Miura, N.; Monde, K.; Chuan Lee, Y.; Nishimura, S.-I. *J. Med. Chem.* **2005**, *48*, 6054-6065.

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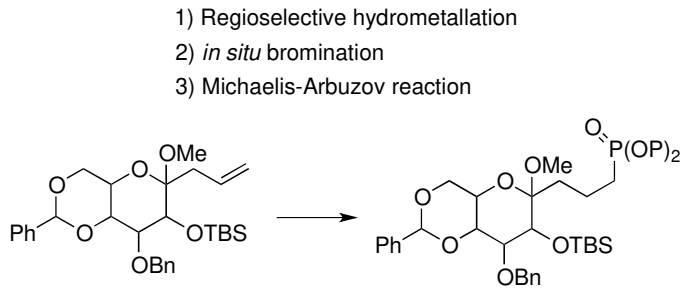

Polyfunctional quaternary trimethylene phosphonates