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Synthesis of Sialyl Lewis x Mimetics as Selectin Inhibitors by Enzymatic Aldol Condensation Reactions

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Abstract—Several D-mannosyl phosphate/phosphonate derivatives have been enzymatically prepared as sialyl Lewis x tetrasaccharide mimics, which showed strong-to-moderate inhibition against E-, P-, and L-selectins. The synthesis of these mimics is very straightforward; mannosyl aldehyde derivatives are condensed with dihydroxyacetone phosphate (DHAP) in the presence of a DHAP-dependent aldolase to provide mannosyl phosphates.

Introduction

The discovery that the inflammatory response is triggered by a highly selective carbohydrate–protein interaction has led to an intensive search for compounds to block the interaction.[1] The initial step of this carbohydrate-mediated biological process is the rolling adhesion of the leukocytes to the vascular endothelium in the early stage of leukocyte migration to the site of inflammation or tissue injury.[2] The adhesion process involves the interaction of sialyl Lewis x (SLe^x, Fig. 1), a terminal tetrasaccharide of glycoproteins and glycolipids, with E-, P-, and L-selectins.[3] Several sialylated and sulfated Lewis a or Lewis x are also ligands for E-, P-, and L-selectins.[4] Inhibition of the SLe^x/selectin interaction has been reported to be an effective strategy for the treatment of certain inflammatory diseases such as reperfusion injury and heart attack.[5] Although the synthesis of SLe^x on large scale has been developed for clinical evaluation,[6] the binding affinity of this natural saccharide to the selectins is relatively weak ($IC_{50}\sim0.5$ mM against E-selectin) and can only be used in its injectable form for acute symptoms as it has low oral availability due to its low lipophilicity and labile glycosidic linkages.[7] Therefore, the development of SLe^x mimetics with higher affinity for the receptors, better oral activity and higher stability against glycosidases[7] has become a subject of current interest.[8]

The bound conformation of SLe^x with selectins[9] and the functional groups essential for recognition by selectins have been determined, including the carboxylate group of the NeuAc moiety, the 2-, 3- and 4-hydroxyl groups of the L-fucose moiety and the 4- and 6-hydroxyl groups of the D-galactose moiety,[10] as shown in Figure 1. This recognition model provides useful information for the design of SLe^x mimics.[8] In addition, the presence of a phosphate group in sugar derivatives was reported to be beneficial for inhibition of selectin binding.[11]

Results and Discussion

In our preliminary work,[12] we have reported that mannosyl phosphates **1** and **2** are good inhibitors of P- and L-selectins. Molecular modeling showed that both **1** and **2** overlap well with the active conformations of SLe^x. Here, we present the detailed synthesis of **1** and **2** and related structures using enzymatic aldol condensation, and analysis of those structures as inhibitors of the three selectins. As shown in Figure 1, *O*- and *C*-mannosyl aldehydes were chosen as aldolase substrates because D-mannose has been successfully used as the L-fucose equivalent in the design of SLe^x mimetics.[13] The aldol condensation of the aldehyde with dihydroxyacetone phosphate (DHAP) and the corresponding phosphonate (*C*-DHAP) using different DHAP-dependent aldolases generates two hydroxyl groups which we postulate to mimic the 4- and 6-hydroxy groups of the galactose moiety, and the phosphate/phosphonate group which mimics the carboxylate negative charge. This strategy creates two new stereogenic centers for use

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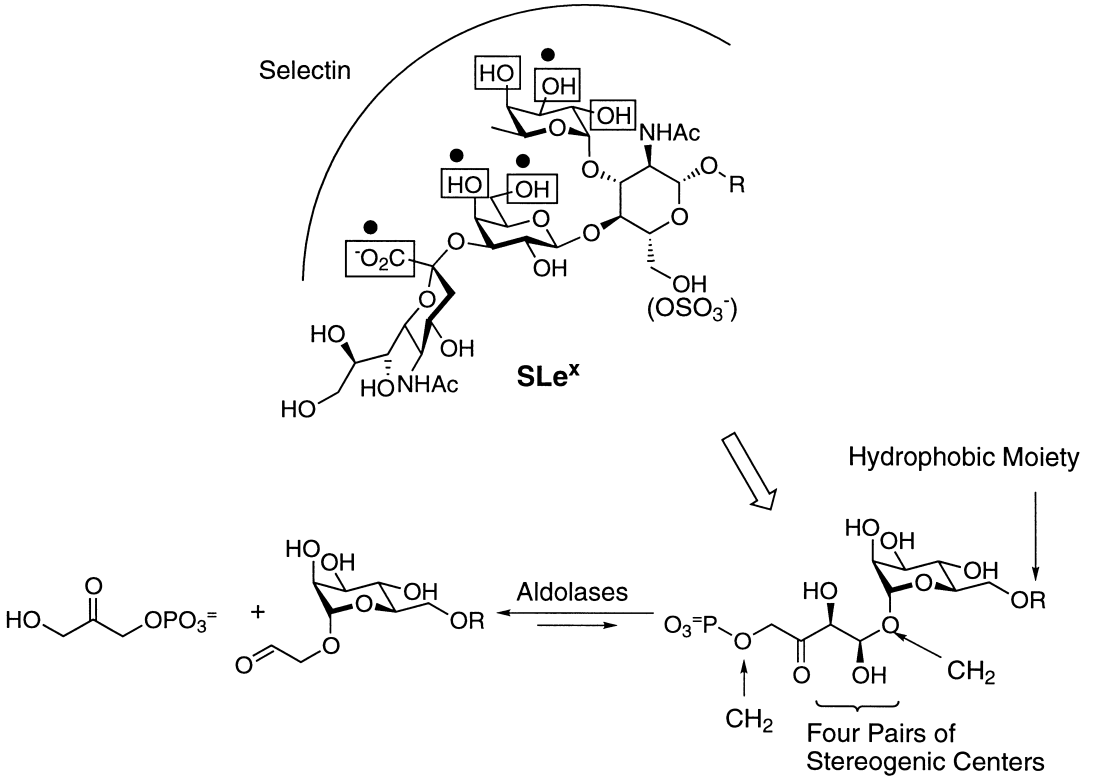


Figure 1. A model showing the structure and functional groups of SLe^x interacting with E- ( ), P- (●) and L-selectin ( ). Both E- and P-selectins bind SLe^x in a similar manner with the carboxylate of NeuAc pointing behind the plane. L-selectin recognized the free form of SLe^x, with the NeuAc-CO_2H pointing above the plane as indicated in this figure.

to screen for the best mimic of the galactose residue and is flexible enough to furnish a number of derivatives while keeping the other essential groups in appropriate spatial distance and orientation (see **3–7**, Fig. 2). In addition, the 6-position of the sugar moiety can be changed to hydrophobic functional groups which are expected to increase the binding activity with E- and P-selectin.[12,14]

The biological activities of compounds **3–7** were evaluated as inhibitors of E-, P-, and L-selectins using the procedure described previously.[15] The IC_{50} values are shown in Table 1. For *O*-glycoside mimetics, the rabbit muscle FDP aldolase (RAMA) product **1** is a better inhibitor than the rhamnulose 1-phosphate aldolase (RhaA) product **3** and fuculose rhamnulose 1-phosphate aldolase (FucA) product **4**. When comparing compounds **1** and **2**, the *O*-glycoside mimetic is more active than the *C*-glycoside mimetic. This remarkable enhancement of inhibition may be due to some additional interactions of the aglycon group with some unidentified groups of P- and L-selectins (e.g. the electrophilic carbonyl group with the lysine-NH_2 group). However, when the phosphate group was changed to the phosphonate group, compound **7**, the activity decreased, perhaps due to the decrease in polarity, resulting in a weaker interaction with the protein. The inhibition activity also decreased when a 6-amide group, compound **6**, is present. This lower activity may result from the drastic change of the structure through the amide bond formation or from the loss of a hydrogen bonding interaction between the 6-OH group and E-selectin (Table 1).

The synthesis of the *O*-mannosyl aldehyde is shown in Scheme 1. The anomeric center of mannose was protected as an allyl group (compound **8**) and subsequent ozonolysis gave aldehyde **9**, which was detected as its hydrate form by NMR. Compound **9** was condensed with DHAP using RhaA and FucA, respectively, to give compounds **3** and **4**. The phosphate products were isolated as barium salts. There was no requirement for any chromatographic separation in the purification procedure. The barium chloride solution (4 equiv) was added to the enzymatic reaction mixture which contained inorganic phosphate (from DHAP preparation), sulfate (from aldolase), organic phosphate (desired product), and other neutral species (starting material). After precipitation to remove most of inorganic phosphate, the supernatant was treated with 2 volumes of acetone to precipitate out the organic phosphate, leaving the neutral compounds in solution. Then, the organic phosphate barium salt was acidified by Dowex 50 to pH 2 and the resulting solution was neutralized to pH 7 by 1 N NaOH to give the desired phosphate mimetic. In order to obtain the 6-azido phosphate **5**, the primary hydroxyl group of compound **8** was converted to the azide group. Tosylation of the primary hydroxyl group of **8** followed by azide displacement gave compound **10**. Similarly, ozonolysis of compound **10** followed by coupling with DHAP afforded compound **5**.

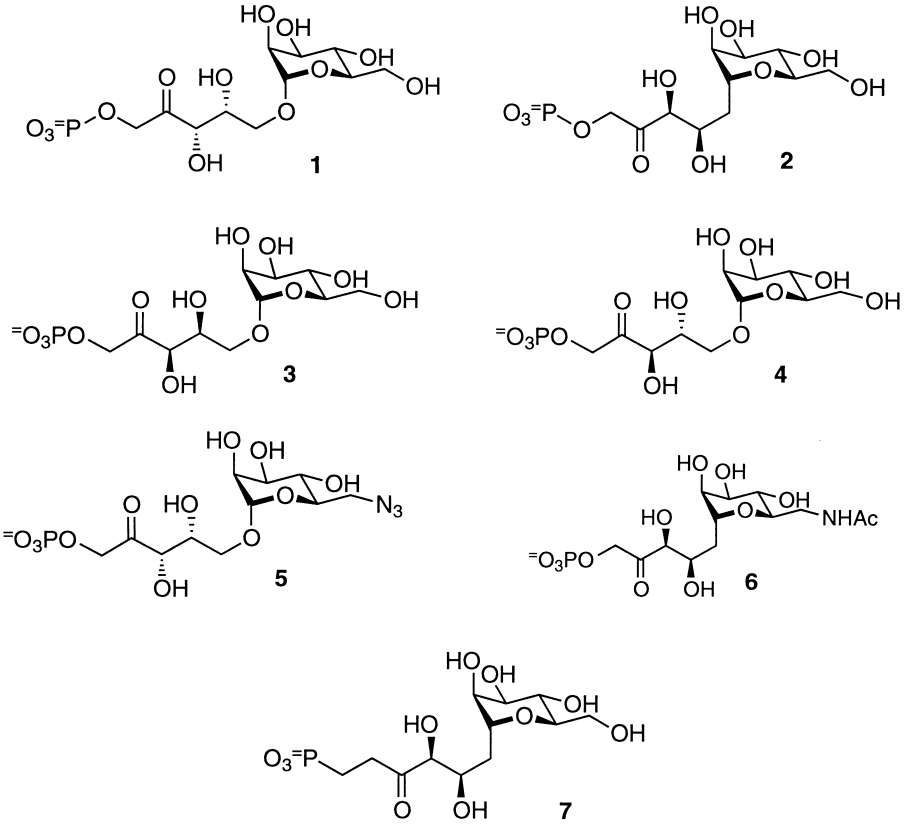


Figure 2. Mannosyl phosphate/phosphonate SLe^x mimetics.

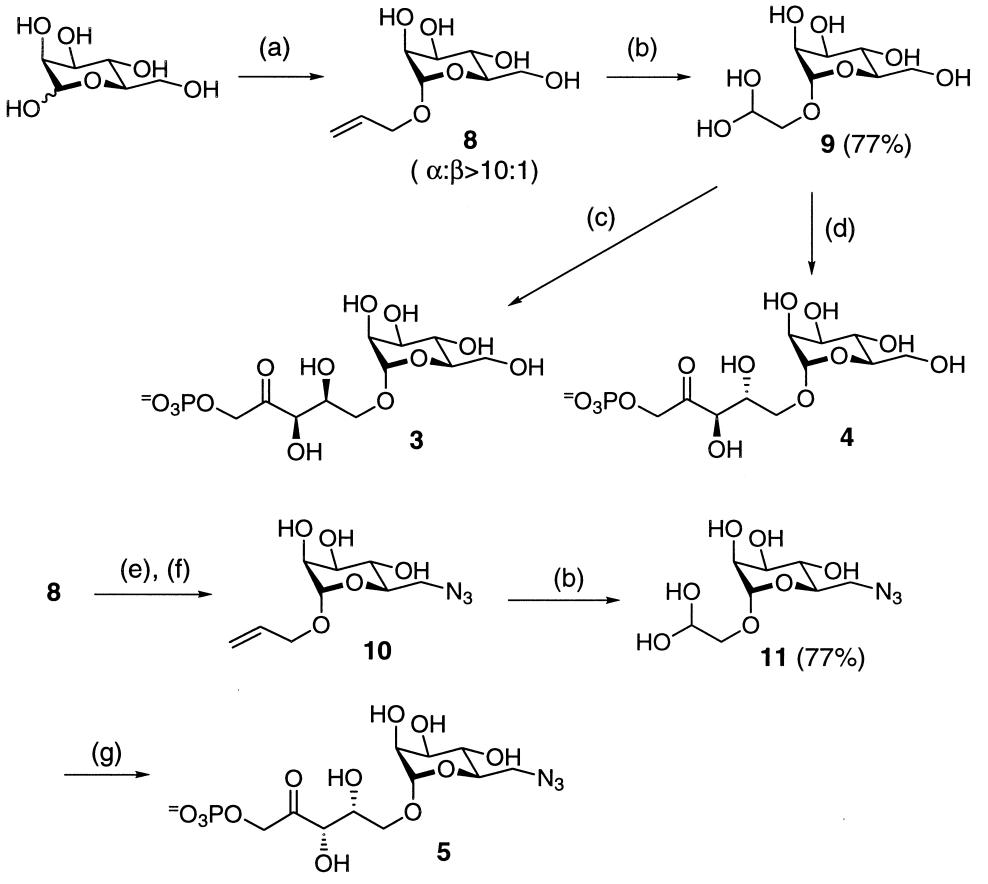
Scheme 2 illustrates the preparation of the enzymatically generated 6-amide *C*-glycoside phosphate mimetic. The benzyl protecting group of the primary hydroxy group of compound **12** was changed to the acetyl group in an acetic anhydride solution containing 0.3% H_2SO_4.[16] Interestingly, this transformation can be done in a one-pot reaction to form the *C*-glycoside **13** if acetic anhydride was added to the reaction mixture of allyl TMS and compound **12** before workup. As shown in Scheme 2, hydrolysis of the acetyl group of compound **13** followed by Mitsunobu reaction yielded the azido compound **14**[17] which was then reduced to amine **22** by triphenyl phospine.[18] The free amine of **15** was coupled with acetic anhydride, 3-phenylpropionic acid and stearic acid, respectively, to give compounds **16–18**. Osmium mediated dihydroxylation of the olefin and periodate cleavage of the diol followed by debenzylation to give the aldehydes in the hydrate form, compounds **19–21**. RAMA was used to catalyze the condensation of DHAP and 6-NAc aldehyde **19** to produce phosphate mimetic **6**. Because of the low water solubility of compounds **20** and **21**, no aldol codensation products were found.

The *C*-glycosidic bond is stable against glycosidases in vitro. However, the primary phosphate may be labile in vivo to a number of phosphatases. For this reason, it is highly desirable to prepare phosphate analogues stable under biological conditions. Interestingly, the phosphonate analogue of DHAP, namely 4-hydroxy-3-oxobutylphosphonic acid **25**, is a donor substrate for DHAP dependent aldolases. The synthesis of compound **25** is shown in Scheme 3. The hydroxy group of glycidol **22** was protected as TBDMS and the resulting epoxide was then opened by dimethyl methyl phosphonate and BuLi to give compound **23**, which was then oxidized to compound **24**. The methoxyl and TBDMS protecting groups of compound **24** were deprotected by TMSBr followed by neutralization with NaOH to pH 7.0 to yield the sodium salt form of compound **25**. Condensation of **25** with **26** gave compound **7**. Though *C*-DHAP is a poor substrate for RAMA (it took approximately

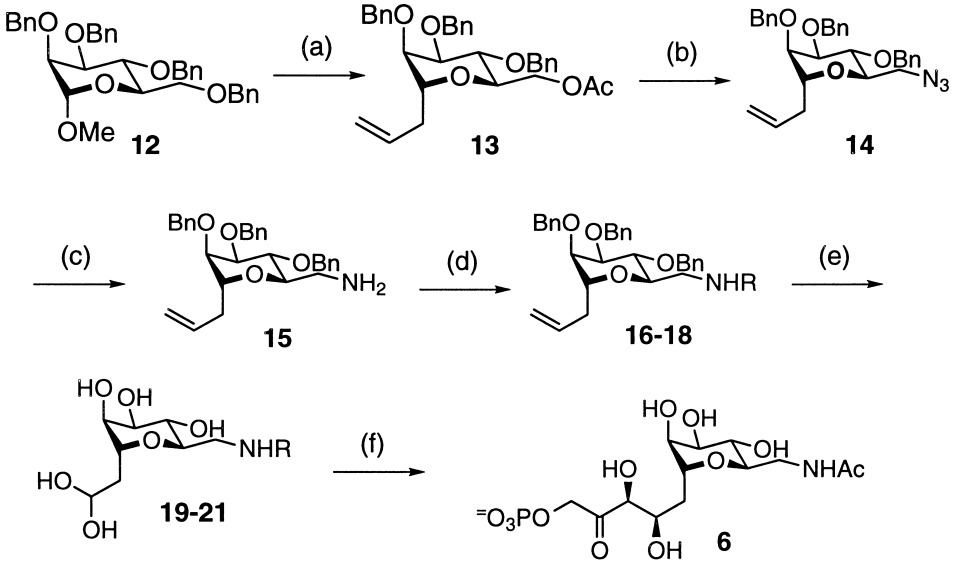
Table 1. IC_{50} (μM) values in selectin inhibition[a]

	1	2	3	4	5	6	7	SLe^x
E-	100	800	1500	160 inactive	3000	3300	500 (720)[b]	
P-	0.6	5	140	320	inactive	900	> 3000 (8000)[b]	
L-	95	40	270	200	ND[c]	2230	ND[c]	1300 (3900)[b]

[a]Determined in a cell-free assay (ref 15) based on the polymeric SLe^a interaction with a microtiter plate coated selectin. The values represent the average of three measurements, with ± 10% error.
[b]The number is taken from the NMR study (ref 9a).
[c]Not determined.

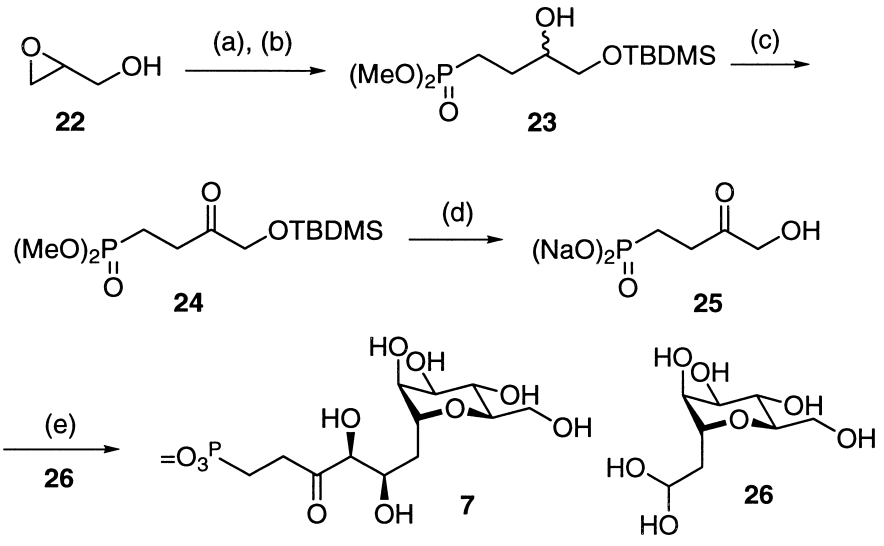


Scheme 1. Conditions: (a) allyl alcohol, cat. CSA, 90 °C, overnight, 80%; (b) (i) O_3, $CH_3Cl/MeOH = 4/1$, −78 °C; (ii) PPh_3, rt, 72%; (c) pH 6.7, DHAP, RhaA, 31%; (d) pH 6.7, DHAP, FucA, 30%; (e) TsCl, Py, 0 °C, 4 h, 62%; (f) NaN3, DMF, 60 °C, 5 h, 54%; (g) pH 6.7, DHAP, FDPA, 30%.



16, 19 R = Ac
17, 20 R = $CO(CH_2)_2Ph$
18, 21 R = $CO(CH_2)_{16}CH_3$

Scheme 2. Conditions: (a) (i) Allyl TMS, TMSOTf, CH_3CN, 0 °C; (ii) Ac_2O, 83%; (b) (i) NaOMe MeOH, 97%; (ii) DEAD, PPh_3, $N_3P(O)(OPh)_2$, 88%; (c) PPh_3, H_2O, benzene, 82%; (d) EDC, HOBT, Acids, CH_2Cl_2, 82–97%; (e) (i) OsO_4, MNO; (ii) $NaIO_4$; (iii) H_2, Pd/C, $THF/H_2O = 1/1$, 61–67%; (f) DHAP, RAMA, pH 6.7, 32%.



Scheme 3. Conditions: (a) TBDMSCI, imidazol, CH_2Cl_2, 91%; (b) MeP(O)$(OMe)_2$, BuLi, Bf_3 OEt_2, THF, −78 °C, 61%; (c) Dess–Martin reagent, CH_2Cl_2, 68%; (d) (i) TMSBr, CH_2Cl_2; (ii) NaOH to pH 7.0, 75%; (e) DHAP, RAMA, pH 6.7, 7 days, 25%.

one week for the starting phosphonate to be consumed), the phosphonate product can be prepared for inhibition analysis. Although the two new stereogenic centers generated in the aldolase reactions have not been determined with regard to their absolute configurations, the stereospecificities of these aldolase reactions are assumed to be the same as described previously.[12]

Conclusion

In brief, this study describes a concise synthesis method to prepare SLe^x mimetics. The results show that of the three DHAP-dependant aldolases investigated, RAMA generated the desired aglycon configuration. Work is in progress to investigate the mechanisms of binding to selectins and to prepare a stable version of **1**.

Experimental

General procedures

^1H and ^{13}C NMR spectra were recorded either on a AMX-400 or AMX-500 spectrometer. Coupling constants were measured in Hertz (Hz). High-resolution mass spectra (HRMS) were obtained on a VG ZAB-ZSE Mass Spectrometer using fast atom bombardment (FAB) method in a *m*-nitrobenzylalcohol (NBA) matrix doped with NaI or CsI. Column chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Analytical thin-layer chromatography was performed using precoated glass-backed plates (Merck Kieselgel F_{254}) and visualized by cerium phosphomolybdate or ninhydrin. Diethyl ether and THF were distilled from sodium-benzophenone ketyl, dichloromethane from calcium hydride, toluene from sodium, and methanol from magnesium. Other solvents and reagents were purified by standard procedures if necessary. Compounds **1** and **2** were prepared according to the procedure described previously.[12]

***α*-*O*-Allyl-D mannopyranoside 8.** D-Mannose (1.5 g, 8.3 mmol) was added to 10 mL of allyl alcohol together with a catalytic amount (10 mg) of camphorsulfonic acid. The mixture was heated to 90 °C overnight, then the allyl alcohol was evaporated in vacuum. The residue was purified by flash chromatography (EtOAc/MeOH, 6/1 then 4/1) to give the desired product (80% yield): ^{13}C NMR (125 MHz, CD_3OD) δ 136.3, 118.3, 101.5, 75.5, 73.5, 73.0, 69.7, 69.4, 64.7.

Formylmethyl-*α*-*O*-mannopyranoside 9. A solution of compound **8** (482 mg, 2.2 mmol) and catalytic amount of $NaHCO_3$ (10 mg) in CH_2Cl_2/MeOH (4/1, 40 mL) was cooled to −78 °C. O_3 was bubbled through the solution until a blue color was observed (10 min) then N_2 was bubbled through the solution until it became colorless. Triphenylphosphine (577 mg, 6.6 mmol) was added and the mixture was warmed to rt and stirred overnight. After filtration, the solution was extracted with water and the aqueous layer was evaporated under reduced pressure. The residue showed only one compound (**9**, 72%) as dihydrate form: ^{13}C NMR (125 MHz, D_2O) d 100.1, 88.2, 72.7, 70.4, 70.0, 69.8, 66.7, 60.9.7.

Compound 3. Compound **9** (330 mg, 1.5 mmol) and DHAP (0.5 mmol) were dissolved in Tris buffer (50 mM, pH 7.4, 10 mL). The solution was adjusted to pH 6.7 by adding 1 N NaOH and then 50 U of RhaA (from Boehringer Mannheim) was added. The reaction mixture was shook under N_2 at rt. The progress of the reaction was followed by DHAP consumption (assay by glycerol phosphate dehydrogenase in the presence of NADH) until >90% of the DHAP had been consumed (about 14 h). The reaction mixture was adjusted to pH 7.5 and $BaCl_2 \cdot H_2O$ (1.0 M, 2 mmol) was added slowly. The cloudy mixture was kept at 4 °C for 1 h and the precipitates were removed by centrifugation. To the supernatant, 2 volumes of acetone were added and the mixture was stored at 4 °C for 2 h. The precipitates were collected by centrifugation and the supernatant was

discarded. The pellet was treated with Dowex-50 H^+ to pH 2 (the solid was dissolved) and the resin was filtered off. The filtrate was adjusted to pH 7.0–7.5 by adding 0.2 N NaOH. Lyophilization yielded compound **3** (133 mg, 31%) as a white powder: ^{1}H NMR (500 MHz, D_2O) δ 4.72 (br, 1H), 4.67 (dd, J = 20.5, 5.5 Hz, 1H), 4.61 (dd, J = 20.5, 5.5 Hz, 1H), 4.53 (d, J = 2.5 Hz, 1H), 4.31–4.29 (m, 1H), 3.94–3.54 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 100.5, 76.2, 73.2, 71.6, 70.3, 70.1, 68.3, 66.9, 66.1 ($^2J_{c,p}$ = 5.0 Hz), 61.1.

Compound 4. Compound **4** was synthesized similarly as described in the synthesis of compound **3**: ^{1}H NMR (500 MHz, D_2O) δ 4.76 (d, J = 1.6 Hz, 1H), 4.64 (dd, J = 19.3, 5.0 Hz, 1H), 4.61 (dd, J = 19.3, 5.0 Hz, 1H), 4.51 (d, J = 4.0 Hz, 1H), 4.30–4.27 (m, 1H), 3.91–3.46 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.9 ($^3J_{c,p}$ = 15 Hz), 100.7, 76.8, 73.9, 71.0, 70.8, 70.7, 67.5, 66.5, 63.6 ($^2J_{c,p}$ = 2.2 Hz), 61.8.

Compound 10. To a solution of compound **8** (4.57 g, 20.8 mmol) in dry pryridine (51 mL) at 0 °C was added tosyl chloride (5.15 g, 27.0 mmol) dissolved in CH_2Cl_2 (75 mL), and the reaction was monitored by TLC. After 4 h, the starting material was consumed completely. The reaction mixture was extracted with CH_2Cl_2 and washed with 1 N HCl, saturated $NaHCO_3$, and brine, and purified by flash chromatography using EtOAc as eluent to yield the desired compound (4.82 g, 62%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 8.2 Hz, 2H), 5.93–5.83 (m, 1H), 5.27–5.22 (m, 1H), 5.17–5.14 (m, 1H), 4.68 (d, J = 1.6 Hz, 1H), 4.33 (dd, J = 10.6, 1.8 Hz, 1H), 4.14 (dd, J = 10.6, 7.0 Hz, 1H), 4.08 (ddt, J = 12.1, 5.1, 1.5 Hz, 1H), 3.90 (ddt, J = 12.1, 6.0, 1.3 Hz, 1H), 3.76 (dd, J = 3.3, 1.6 Hz, 1H), 3.67–3.61 (m, 2H), 3.49 (t, J = 9.6 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 131.3, 129.5, 117.8, 101.3, 72.8, 72.6, 72.2, 71.7, 69.3, 68.5, 21.9; HRMS calcd for $C_{16}H_{22}O_8NaS$ (M + Na): 397.0933, found 397.0945.

To a solution of the above compound (1.59 g, 4.3 mmol) in DMF was added 15 equiv of NaN_3 (4.14 g, 63.8 mmol) and this mixture was heated to 60 °C for overnight. The solvent was removed in vacuo, and the residue chromatographed on SiO_2 using EtOAc as eluent to yield compound **10** (557 mg, 54%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94–5.87 (m, 1H), 5.33–5.30 (m, 1H), 5.23–5.20 (m, 1H) 4.90 (br, 1H), 4.24–4.20 (m, 1H), 4.06–4.01 (m, 1H), 3.84–3.80 (m, 1H), 3.78–3.74 (m, 1H), 3.71 (d, J = 5.3, 3.7 Hz, 1H), 3.69–3.68 (m, 1H), 3.56–3.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4, 117.7, 98.8, 71.7, 71.5, 70.6, 68.6, 68.1, 51.5.

Compound 11. Compound **11** was synthesized similarly as described in the synthesis of compound **9**: ^{1}H NMR (400 MHz, D_2O) δ 5.20–5.17 (m, 1H), 4.87 (br, 1H), 3.98–3.96 (m, 1H), 3.82–3.75 (m, 2H), 3.70–3.61 (m, 3H), 3.58–3.52 (m, 1H), 3.52–3.47 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 102.8, 90.6, 74.0, 72.7, 72.2, 69.8, 53.5, 41.1.

Compound 5. Compound **5** was synthesized similarly as described in the synthesis of compound **3**: ^{1}H NMR (400 MHz, D_2O) δ 4.80 (d, J = 1.7 Hz, 1H), 4.70 (dd, J = 18.0, 6.3 Hz, 1H), 4.58 (dd, J = 19.6, 6.3 Hz, 1H), 4.53 (d, J = 3.0 Hz, 1H), 4.30–4.26 (m, 1H), 4.0–3.5 (m, 8H); ^{13}C NMR (100 MHz, D_2O) δ 217.8, 102.6, 78.3, 77.9, 74.1, 72.5, 72.3, 70.5, 69.9 (d, $^2J_{C\text{-}P}$ = 3.8 Hz), 65.1, 53.7.

Compound 13. A solution of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside (11.2 g, 20.3 mmol) in 32 mL of dry MeCN was cooled to 0 °C under N_2. Allyltrimethylsiane (6.5 mL, 40.5 mmol) and trimethylsilyl triflate (1.9/mL, 10.2 mmol) were added. The solution was stirred for 20 h at 0 °C. Acetic anhydride (8 mL, 80 mmol) was added and the resulting mixture was stirred for 30 min at rt. The deep orange solution was diluted with 130 mL of CH_2Cl_2 and quenched with 70 mL of saturated $NaHCO_3$ solution. The aqueous layer was washed twice with 30 mL of CH_2Cl_2. The organic layers were combined and then dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (hexane/EtOAc, 9/1) to obtain compound **13** (8.7 g, 83 %, α/β > 15/1) as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.28 (m, 15H), 5.72 (dddd, J = 17.0, 10.3, 6.9, 6.9 Hz, 1H), 5.04–5.00 (m, 2H), 4.75 (d, J = 11.2 Hz, 1H), 4.63–4.53 (m, 5H), 4.39 (dd, J = 11.6, 6.4 Hz, 1H), 4.25 (dd, J = 11.6, 2.8 Hz, 1H), 4.09–4.06 (m, 1H), 3.83–3.75 (m, 3H), 3.62 (dd, J = 4.4, 2.7 Hz, 1H), 2.38–2.27 (m, 2H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 138.1, 138.0, 134.0, 128.6, 128.5, 128.4, 128.4, 128.3, 128.3, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 117.3, 77.0, 75.0, 74.8, 74.0, 72.3, 72.2, 72.1, 71.5, 63.2, 34.4, 20.9; HRMS calcd for $C_{32}H_{36}O_6Cs$ (M + Cs): 649.1566, found 649.1589.

Compound 14. A solution of compound **13** (5.3 g, 10.3 mmol) and NaOMe (0.23 g, 4.3 mmol) in 50 mL MeOH was stirred at rt for 1 h. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc, 1/1) to afford the title compound (4.7 g, 97%) as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.29 (m, 15H), 5.68 (dddd, J = 17.0, 10.2, 7.0, 7.0 Hz, 1H), 5.05–5.00 (m, 2H), 4.82 (d, J = 11.1 Hz, 1H), 4.66 (d, J = 11.1 Hz, 1H), 4.63 (d, J = 11.1 Hz, 2H), 4.61 (d, J = 11.9 Hz, 1H), 4.57 (d, J = 11.9 Hz, 1H), 4.03 (ddd, J = 9.2, 6.3, 3.5 Hz, 1H), 3.86–3.77 (m, 3H), 3.72 (ddd, J = 11.5, 6.8, 3.2 Hz, 1H), 3.64–3.59 (m, 2H), 2.39–2.33 (m, 1H), 2.25–2.20 (m, 1H), 2.03 (t, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 133.8, 128.5, 128.4, 128.4, 128.3, 128.0, 128.0, 127.8, 127.8, 127.7, 117.6, 78.0, 75.3, 75.3, 74.5, 73.9, 73.5, 72.2, 72.0, 62.2, 34.2; HRMS calcd for $C_{30}H_{34}O_5Cs$ (M + Cs): 607.1461, found 607.1473.

To a solution of the above compound (3.2 g, 6.4 mmol) in THF (14 mL) at 0 °C was added DEAD (1.0 mL, 6.4 mmol) and PPh_3 (1.74 g, 6.4 mmol) successively, and the mixture was stirred for 20 min at 0 °C. Diphenylphosphoryl azide (1.4 mL, 6.4 mmol) was then added dropwise and the resulting mixture was stirred at rt overnight. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc, 4/1) to yield

compound **14** (3.0 g, 87.6%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 15H), 5.73 (dddd, J = 17.0, 10.2, 6.9, 6.9 Hz, 1H), 5.06–5.00 (m, 2H), 4.80 (d, J = 11.3 Hz, 1H), 4.64 (d, J = 12.2 Hz, 1H), 4.60 (d, J = 12.2 Hz, 1H), 4.59 (d, J = 12.1 Hz, 1H), 4.56 (d, J = 11.3 Hz, 1H), 4.54 (d, J = 12.1 Hz, 1H), 4.05 (ddd, J = 8.3, 6.2, 4.1 Hz, 1H), 3.79–3.71 (m, 3H), 3.64–3.63 (m, 1H), 3.52 (dd, J = 12.9, 6.8 Hz, 1H), 3.36 (dd, J = 12.9, 3.1 Hz, 1H), 2.40–2.34 (m, 1H), 2.30–2.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 138.0, 133.8, 130.0, 128.5, 128.4, 128.4, 128.4, 128.0, 127.9, 127.8, 127.7, 126.1, 120.2, 120.2, 117.5, 77.4, 75.6, 74.9, 74.3, 73.4, 72.8, 72.1, 71.7, 51.2, 34.3; HRMS calcd for $C_{30}H_{33}N_3O_4Cs$ (M + Cs): 632.1525, found 632.1540.

Compound 15. A mixture of compound **14** (1.7 g, 3.5 mmol) and PPh_3 (1.83 mg, 7.0 mmol) was refluxed in a mixture of benzene (20 mL) and water (0.13 mL) for 5 h. The reaction mixture was evaporated in vacuo and the residue was applied to silica gel column chromatography ($CHCl_3$/MeOH = 20/1 then 10/1) to obtain compound **15** (1.35 mg, 82 %): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.29 (m, 15H), 5.71 (dddd, J = 17.0, 10.3, 6.9, 6.9 Hz, 1H), 5.04–5.00 (m, 2H), 4.80 (d, J = 11.2 Hz, 1H), 4.64 (s, 2H), 4.60 (d, J = 11.9 Hz, 1H), 4.58 (d, J = 11.2 Hz, 1H), 4.55 (d, J = 11.9 Hz, 1H), 4.01 (ddd, J = 9.2, 6.0, 3.4 Hz, 1H), 3.77 (dd, J = 7.7, 3.4 Hz, 1H), 3.68 (t, J = 7.7 Hz, 1H), 3.63 (t, J = 3.4 Hz, 1H), 3.48 (ddd, J = 7.7, 7.7, 3.5 Hz, 1H), 2.94 (dd, J = 13.3, 7.7 Hz, 1H), 2.89 (dd, J = 13.3, 3.5 Hz, 1H), 2.39–2.33 (m, 1H), 2.27–2.21 (m, 1H), 1.41 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 134.2, 128.4, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.7, 117.4, 78.0, 76.3, 75.4, 75.3, 74.3, 72.9, 72.1, 71.8, 43.0, 34.3; HRMS calcd for $C_{30}H_{36}NO_4$ (M + H): 474.2644, found 474.2655.

Compound 17. To a solution of amine **15** (1.11 g, 2.34 mmol) and 3-phenylpropionic acid (0.46 g, 3.0 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.3 mL), HOBT (0.4 g, 3.0 mmol), and EDC (0.58 g, 3.0 mmol) successively at 0 °C. The solution was stirred at 0 °C for 30 min and allowed to rise to room temperature within 6 h. The reaction mixture was evaporated under reduced pressure and residue was dissolved in EtOAc (20 mL). The EtOAc solution was washed with 1 N HCl, saturated $NaHCO_3$, and brine, successively. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 2/1) to yield compound **17** (1.38 g, 96.7%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.25 (m, 18H), 7.19–7.16 (m, 2H), 5.77 (br, 1H), 5.67 (dddd, J = 17.2, 10.2, 7.1, 7.1 Hz, 1H), 5.04–4.99 (m, 2H), 4.70 (d, J = 10.9 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.2 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.2 Hz, 1H), 4.54 (d, J = 10.9 Hz, 1H), 3.99–3.95 (m, 1H), 3.75 (dd, J = 7.4, 3.0 Hz, 1H), 3.68 (t, J = 7.4 Hz, 1H), 3.63–3.51 (m, 4H), 2.93 (t, J = 7.8 Hz, 2H), 2.44–2.39 (m, 2H), 2.33–2.27 (m, 1H), 2.25–2.17 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 140.8, 137.9, 134.0, 128.4, 128.3, 128.2, 128.1, 127.8, 127.8, 127.7, 126.0, 117.4, 78.8, 75.7, 74.3, 72.2, 72.1, 71.8, 58.2, 39.5, 38.2, 34.0, 31.5; HRMS calcd for $C_{39}H_{44}NO_5$ (M + H): 606.3219, found 606.3217.

Compound 18. Compound **18** was synthesized similarly as described in the synthesis of compound **17**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 15H), 5.84 (t, J = 4.6 Hz, 1H), 5.71 (dddd, J = 17.1, 14.0, 7.0, 7.0 Hz, 1H), 5.06–5.01 (m, 2H), 4.73 (d, J = 10.8 Hz, 1H), 4.65–4.58 (m, 5H), 4.02–3.98 (m, 1H), 3.77 (dd, J = 7.2, 2.9 Hz, 1H), 3.68–3.60 (m, 4H), 3.55 (dd, J = 10.3, 5.9 Hz, 1H), 2.33 (t, J = 6.9 Hz, 2H), 2.36–2.22 (m, 2H), 2.13–2.11 (m, 2H), 1.65–1.55 (m, 2H), 1.31–1.23 (m, 26H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 138.1, 138.0, 134.1, 128.4, 128.4, 128.3, 127.9, 127.8, 127.7, 117.6, 75.8, 75.4, 74.4, 72.8, 72.3, 71.9, 39.5, 36.8, 34.2, 33.9, 31.9, 29.7, 29.5, 29.4, 29.3, 29.1, 25.8, 24.7, 22.7, 14.1; HRMS calcd for $C_{48}H_{69}NO_5$ (M + Cs): 872.4230, found 872.4246.

Compound 19. To a solution of compound **15** (1.5 g, 3.2 mmol) in CH_2Cl_2 (10 mL) was added Ac_2O (1.5 mL, 16.0 mmol), and the mixture was stirred for 2 h at rt. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane/EtOAc, 2/1) to yield compound **16** (1.5 g, 91%).

To a solution of *N*-methylmorpholine *N*-oxide (0.35 g, 3.0 mmol) and 2.1 mL of 5/2 acetone/water was added a solution of OsO_4 in *tert*-butyl alcohol (0.33 mL, 2.5% w/w), and the heterogeneous mixture was stirred vigorously. Compound **16** (1.4 g, 2.7 mmol) was then added dropwise. The biphasic mixture was stirred at rt overnight and then quenched by addition of $Na_2S_2O_4$ (0.1 g), Florisil (1 g), and H_2O (5 mL). This mixture was neutralized to pH 7 with 1 N HCl and then concentrated. The resulting aqueous suspension was acidified to pH 1 with 1 N HCl and extracted with EtOAc (4×15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give diastereomeric diols as white solid, which was used in the next step without further purification.

To a solution of the diols in 10 mL THF and $NaIO_4$ (0.86 g, 4.0 mmol) was added in one portion. Water (10 mL) was then added over 5 min to the stirred slurry. After 1 h, THF was evaporated and the resulting slurry was extracted with ethyl acetate. The organic layer was then washed with brine, dried ($MgSO_4$), and concentrated to give the crude aldehyde product which was purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give the aldehyde compound (1.2 g, 86%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.36–7.29 (m, 15H), 6.72 (d, J = 11.9 Hz, 1H), 4.53 (d, J = 11.5 Hz, 1H), 4.51 (d, J = 12.5 Hz, 1H), 4.49 (d, J = 11.5 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.48–4.44 (m, 1H), 4.40 (d, J = 12.5 Hz, 1H), 4.37 (d, J = 11.6 Hz, 1H), 3.87–3.85 (m, 1H), 3.83–3.82 (m, 1H), 3.80–3.77 (m, 1H), 3.67 (ddd, J = 10.1 9.0, 3.9 Hz, 1H), 3.56 (dd, J = 9.0, 2.8 Hz, 1H), 3.51 (dd, J = 3.9, 1.8 Hz, 1H), 2.98 (dd, J = 18.5, 2.4 Hz, 1H), 2.66 (dd, J = 18.5, 10.1 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7, 170.1, 137.4, 128.4, 128.4, 128.0, 127.9, 127.9, 127.7, 75.1, 74.8, 74.2, 72.9, 72.8, 72.1, 71.2, 62.6, 45.4, 37.0, 23.1; HRMS calcd for $C_{31}H_{35}NO_6Cs$ (M + Cs): 650.1519, found 650.1533.

The above compound (0.83 g, 1.6 mmol) was dissolved in a mixture of tetrahydrofuran/water (1/1) solution and hydrogenated at 1 atm H_2 in the presence of catalytic amounts of Pd/C. After stirring at rt for 6 h, the reaction mixture was filtered off using a Celite pad. The solvent was removed under vacuum to give compound **19** (0.42 g, 98%) which was used in the next step without further purification. ^{13}C NMR (125 MHz, D_2O) δ 175.2, 89.2, 75.7, 75.6, 72.8, 72.0, 71.2, 69.3, 41.1, 22.5.

Compound 20. Compound **20** was synthesized similarly as described in the synthesis of compound **19**: for the intermediate aldehyde before hydrogenation ^1H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.36–7.15 (m, 20H), 6.67 (d, $J=6.1$ Hz, 1H), 4.53 (d, $J=12.1$ Hz, 1H), 4.52 (d, $J=11.9$ Hz, 1H), 4.49 (d, $J=12.1$ Hz, 1H), 4.48 (d, $J=11.6$ Hz, 1H), 4.43 (d, $J=1.8$ Hz, 1H), 4.39 (d, $J=11.9$ Hz, 1H), 4.37 (d, $J=11.6$ Hz, 1H), 3.83–3.79 (m, 2H), 3.74 (dd, $J=10.6$, 2.9 Hz, 1H), 3.70–3.64 (m, 1H), 3.55 (dd, $J=9.0$, 2.9 Hz, 1H), 3.49 (dd, $J=4.0$, 1.8 Hz, 1H), 2.70–2.92 (m, 3H), 2.67–2.60 (m, 1H), 2.57–2.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7, 172.2, 141.1, 140.2, 137.5, 128.5, 128.4, 128.1, 128.0, 127.8, 126.0, 75.2, 74.8, 74.2, 73.0, 72.8, 72.2, 71.3, 62.7, 45.4, 38.4, 37.0, 31.8; HRMS calcd for $C_{38}H_{41}NO_6Cs$ (M + Cs): 740.1988, found 740.1992. For compound **20**: ^{13}C NMR (125 MHz, D_2O) d 176.8, 141.1, 129.5, 129.3, 129.2, 127.2, 89.1, 75.7, 75.4, 73.0, 72.8, 72.1, 71.9, 71.2, 71.1, 69.4, 69.3, 58.8, 41.0, 38.1, 32.1, 32.1, 30.6 (rotamers present in NMR).

Compound 6. Compound **6** was synthesized similarly as described in the synthesis of compound **3**: ^1H NMR (500 MHz, D_2O) δ 4.78 (dd, $J=18.5$, 7.7 Hz, 1H), 4.67 (dd, $J=18.6$, 7.7 Hz, 1H), 4.38 (d, $J=2.1$ Hz, 1H), 4.14 (dt, $J=10.1$, 2.4 Hz, 1H), 4.08–4.06 (m, 1H), 3.87–3.85 (m, 1H), 3.80–3.75 (m, 2H), 3.55–3.52 (m, 3H), 3.38–3.34 (m, 1H), 2.04–1.98 (m, 1H), 2.00 (s, 3H), 1.69 (ddd, $J=14.2$, 10.5, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) d 175.4, 163.6, 78.8, 75.5, 72.7, 72.5, 71.3, 69.5, 68.5, 47.5, 41.2, 31.4, 22.7.

Compound 23. To a solution of glycidol **22** (10 g, 0.128 mol) in 108 mL of dry CH_2Cl_2 was added imidazole (7.85 g, 0.115 mol). The reaction mixture was stirred at 0 °C for 5 min and then TBDMSCl (17.4 g, 0.115 mol) was added in one portion. The solution was stirred at 0 °C for 1 h and allowed to rise to room temperature within 4 h. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in EtOAc (50 mL). The EtOAc solution was washed with 1 N HCl, saturated $NaHCO_3$, and brine, successively. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc, 95/5) to yield glycidyl-*tert*-butyldimethylsilyl ether (19.8 g, 91%): ^1H NMR (500 MHz, $CDCl_3$) δ 3.86 (dd, $J=11.9$, 3.1 Hz, 1H), 3.66 (dd, $J=11.9$, 4.8 Hz, 1H), 3.10–3.07 (m, 1H), 2.77 (dd, $J=5.1$, 4.1 Hz, 1H), 2.64 (dd, $J=5.1$, 2.7 Hz, 1H), 0.9 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.7, 52.4, 44.5, 25.8, −5.3, −5.4.

A solution of methyl dimethylphosphonate (3.1 mL, 28.4 mmol) in 32 ml of THF was cooled to −78 °C. Butyllithium (28.4 mmol, 11.4 mL of 2.5 M solution) was added and the mixture was stirred for 15 min. A solution of glycidyl-*tert*-butyldimethylsilyl ether (1.78 g, 9.5 mmol) in 10 mL of THF was then added to the reaction mixture dropwise, followed by addition of $BF_3{\cdot}Et_2O$ (4.8 ml, 37.9 mmol) and the mixture was allowed to react for 2 h at −78 °C. The reaction was quenched by adding a saturated aqueous NH_4Cl. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in Et_2O. The Et_2O solution was washed with 1 N HCl, saturated $NaHCO_3$, and brine, successively. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was then purified by silica gel column chromatography ($MeOH/CHCl_3$, 5/95) to yield compound **24** (1.8 g, 61%): ^1H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.71 (s, 3H), 3.65–3.62 (m, 1H), 3.60 (dd, $J=9.7$, 4.0 Hz, 1H), 3.42 (dd, $J=9.7$, 6.6 Hz, 1H), 2.67 (d, $J=4.0$ Hz, 1H), 2.04–1.60 (m, 4H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.4 (d, $^3J_{C\text{-}P}=14.7$ Hz), 66.7, 52.4 (d, $^2J_{C\text{-}P}=7.0$ Hz), 25.8, 20.8 (d, $^1J_{C\text{-}P}=142.1$ Hz), 18.3, −5.4 (×2); HRMS calcd for $C_{12}H_{30}O_5PSi$ (M + H): 313.1600, found 313.1610.

Compound 24. Compound **23** (4.8 g, 15.3 mmol) was dissolved in 150 mL of dry CH_2Cl_2 under argon atmosphere at room temperature. Dess–Martin reagent (9.8 g, 23 mmol) was added to the solution and the mixture was allowed to react for 1 h. 200 mL of Et_2O was added together with 7 equiv of sodium thiosulfate in saturated $NaHCO_3$ solution. After 30 min, the mixture was washed with $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was then purified by silica gel column chromatography (EtOAc/Hex, 1/1) to yield compound **24** (3.2 g, 68%): ^1H NMR (500 MHz, $CDCl_3$) δ 4.20 (s, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 2.86–2.80 (m, 2H), 2.08–2.01 (m, 2H), 0.93 (s, 9H), 0.1 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6 (d, $^3J_{C\text{-}P}=14.3$ Hz), 69.1, 52.4 (d, $^2J_{C\text{-}P}=6.6$ Hz), 31.4, 25.7, 17.8 (d, $^1J_{C\text{-}P}=145.0$ Hz), −5.6.

Compound 25. To a solution of **24** (3.0 g, 9.6 mmol) in 20 mL of dry CH_2Cl_2 was added 20 mmol of TMSBr (2.6 mL) dropwise under argon atmosphere at rt. The reaction mixture was stirred at rt for 30 min. The solvent was then evaporated and 10 mL of distilled water was added. After 30 min the mixture was extracted with AcOEt, the aqueous layer which contained the desired product was adjusted to pH 7.0 and evaporated to obtain 1.5 g of the product as sodium salt (75% yield). Further purification was carried out by passing the compound through a Dowex 1×8 (HCO_3^- form) column and washing with water and eluting with 300 mM of triethylammonium bicarbonate buffer. The fractions containing the product were pooled and passed through a column of Dowex 50W-X2 Na^+ form and lyophilized: ^1H NMR (500 MHz, D_2O) δ 4.20 (s, 2H), 2.45 (m, 2H), 1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8 (d, $^3J_{C\text{-}P}=14$ Hz), 68.3, 56.3 (d, $^2J_{C\text{-}P}=6$ Hz), 33.3, 21.9 (d, $^1J_{C\text{-}P}=135.0$ Hz).

Compound 7. Compound **7** was obtained similarly as described in the synthesis of compound **3**: ^1H NMR

(500 MHz, D_2O) δ 4.39 (d, $J=2.0$ Hz, 1H), 4.29 (ddd, $J=10.0$, 3.0, 2.0 Hz, 1H), 4.15 (ddd, $J=11.0$, 3.5, 3.3 Hz, 1H), 3.79 (dd, $J=12.3$, 4.4 Hz, 1H), 3.73 (dd, $J=3.3$, 2.3 Hz, 1H), 3.65 (dd, $J=9.4$, 2.3 Hz, 1H), 3.58 (dd, $J=12.3$, 5.8 Hz, 1H), 3.49 (t, $J=9.4$ Hz, 1H), 3.42 (ddd, $J=9.4$, 5.8, 4.4 Hz, 1H), 2.82 (m, 2H), 2.10 (ddd, $J=14.2$, 11.0, 3.0 Hz, 1H), 1.75 (ddd, $J=10.0$, 3.0, 2.0 Hz, 1H), 1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.8 (d, $^3J_{C\text{-}P}=15$ Hz), 78.4, 76.9, 75.0, 71.9, 71.4, 67.7, 63.5, 61.9, 34.2, 32.5, 25.7 (d, $^1J_{C\text{-}P}=138.0$ Hz).

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