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Facile synthesis of core intermediates toward sialyl nucleoside mimetics

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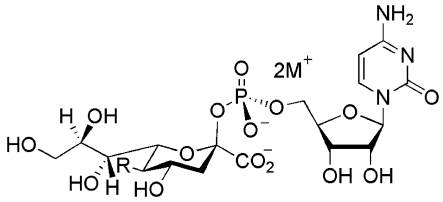
ABSTRACT

6-Deoxyphosphonated intermediates, **8** and **12**, were efficiently synthesized from D-fructose and sucrose, respectively. These novel intermediates will be useful to synthesize various D-tagato- and fructofuranoside derivatives as inhibitors of sialyl transferase or sialidase.

Sialic acids, which are abundant on human cell surfaces, are crucial receptors at the non-reducing end of oligosaccharide chains in cell wall glycoconjugates.[1–3] They are, therefore, ideally located for a wide variety of functions such as cell–cell communication, blood coagulation, fertilization, and other biological events.[4,5] In addition, sialic acids involvement in the pathogenesis of a variety of diseases including inflammatory disease, cancer metastasis, and virus infection has led to a wide interest in the synthesis of modified sialic acids including sialyl nucleoside mimetics as probes for the study of sialic acid-recognizing proteins.[6,7] Our interest lies in investigating mimetics of CMP-Neu5Ac or CMP-KDN (Fig. 1) through the synthesis of compounds of the general structure **1**. These sialylmimetics are designed to retain the structural features essential for the interaction with a particular protein, but are structurally simpler compounds with potentially improved pharmacological profiles.

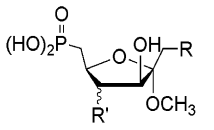
An earlier investigation into the importance of the sialyl moiety of transition-state analogues of CMP-Neu5Ac revealed that the complete Neu5Ac residue may not be required for high enzyme affinity.[8] Thus, our design for sialylmimetics contained a phosphonate group that has replaced the entire sialic acid portion (Fig. 2, structure 1).[9] This approach would allow attachment of an acceptor as a monoester while at the same time retaining a negative charge under physiological conditions. In addition, we are interested in investigating the role of the C-4 position of the nucleoside and the pyrimidine base in the binding affinity. Herein, we report the synthesis of two key intermediates of phosphonate monoester sialylmimetics based on very inexpensive carbohydrates, D-fructose and sucrose. These intermediates, D-fructofuranoside and D-tagatofuranoside derivatives, would allow us to explore the hydrophobicity, hydrophilicity, and steric bulk and also the effect of epimerization at C-4 position on sialic acid recognizing proteins.



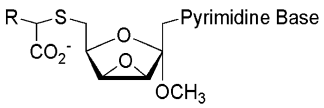
CMP-Neu5Ac (R = NHAc)
CMP-KDN (R = OH)

Figure 1.

In a previous report, a route was developed for the preparation of sialyl nucleoside mimetic of the general structure **2** (Fig. 2) starting from the carbohydrate D-fructose.[10] However, in the first step, the methyl glycoside was prepared via a Fischer type methodology



1 R = base, or any alkyls
R' = N_3, NHR', SR



2 R = methyl, ethyl, phenyl

Figure 2.

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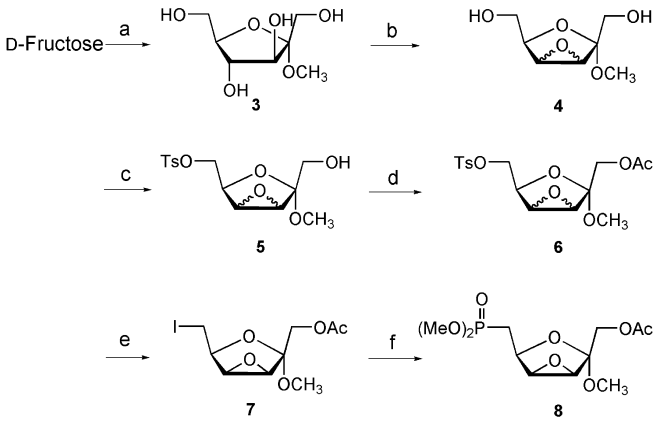
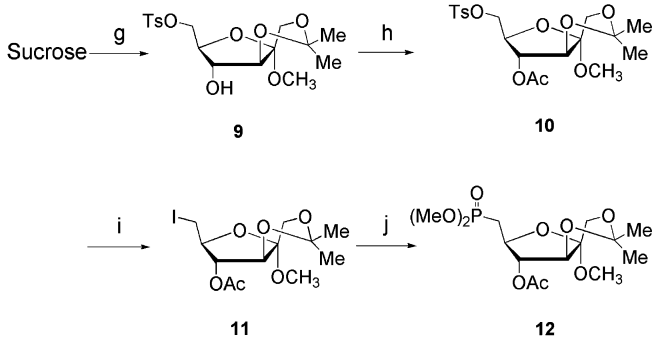


Scheme 1. Reagents and conditions: (a) AcCl, CH_3OH, 38%; (b) PPH_3, DIAD, *N*,*N*-DMF, 0 °C, 65%; (c) TsCl, pyridine, 0 °C, 66%; (d) Ac_2O, pyridine, 0 °C, 86%; (e) NaI, acetone, 95 °C, 72%; (f) $P(OMe)_3$, reflux, 72%.



Scheme 2. Reagents and conditions: (g) (i) 2,2-DMP, *p*-TsOH, 1,4-dioxane, 80 °C; (ii) TsCl, pyridine, 0 °C, overall 53%; (h) Ac_2O, pyridine, 0 °C, 83%; (i) NaI, acetone, 95 °C, 79%; (j) $P(OMe)_3$, reflux, 80%.

which resulted in a mixture of α/β fructofuranoside and fructopyranoside, respectively (Scheme 1). The tetrahydroxyl compound **3** obtained was then purified by passing through an ion-exchange resin column with water as eluent which proved to be an exceedingly time-consuming step. In our current synthesis of compound **3**, we modified the purification method by performing an efficient column chromatography using 40% methanol in ethyl acetate to obtain the pure compound. Following modified Mitsunobu condition,[11,12] epoxide **4** was obtained as a mixture of stereoisomers in 9:1 ratio as determined from ^{1}H NMR data.

Regioselective tosylation of the 6-hydroxy group in compound **4** gave the tosylate **5**. Subsequent acetylation afforded fully protected compound **6**. It should be noted that we only report analytical data for the major isomer of compounds **4**, **5,** and **6** in this note.

Interestingly, iodination of the mixture of isomers **6** resulted in a single compound **7** in 72% yield after purification. This iodo compound **7** was treated with freshly distilled $P(OMe)_3$ to obtain the corresponding 6-deoxy-6-dimethoxy phosphonate **8**.[13] A series of nucleophiles can then be introduced at the C-4 position of phosphonate **8** to build a library of fructofuranoside derivatives.

In our effort to access tagatofuranoside derivatives we attempted a different route using an inexpensive starting material, sucrose, as shown in Scheme 2.

6-Tosylated 1,3-isopropylidene **9** was synthesized directly from sucrose using a previously reported method.[14] Compound **9** was treated with acetic anhydride-pyridine to give 4-*O*-acetyl derivative **10**, which was converted into the 6-iodo fructofuranose **11** in good yield. Michaelis-Arbuzov reaction[15] of iodo compound **11** with $P(OMe)_3$ afforded 6-deoxy-6-dimethoxyphosphinyl derivative **12**.[16] The acetyl group at C-4 position of compound **12** can be easily converted to a leaving group which can then undergo S_N2-type reaction resulting in tagatofuranoside derivatives.

In summary, we have synthesized two 6-deoxy-6-dimethoxy phosphonates, **8** and **12**, which can be manipulated to prepare novel sialyl nucleoside mimetics for the inhibition of sialic acid recognizing proteins. Both compounds **8** and **12** provide flexibility in terms of introduction of functionality in the unit but while intermediate **8** gives access to fructofuranoside derivatives, intermediate **12** results in tagatofuranoside derivatives allowing us to explore the importance of C-4 position of the nucleoside.

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Financial support from the Australian Research Council (International Fellowship Grant) is gratefully acknowledged. We also thank the Regional Technology Innovation Program of the Ministry of Knowledge Economy (MKE), Korea, for financial support (Grant No. RTI05-01-02).

Supplementary data

Representative experimental details for the synthesis and the characterization data for key intermediates are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.050.

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13. *Selected data for* ***8***: R_f = 0.53 (9:1 EtOAc–acetone); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.11 (s, 3H, MeCO), 2.15 (dd, 1H, $J_{6,P}$ = 1.8, $J_{6,6'}$ = 18.6 Hz, H-6), 2.17 (dd, 1H, $J_{6',P}$ = 1.8, $J_{6',6}$ = 18.6 Hz, H-6′), 3.29 (s, 3H, OMe), 3.68 (d, 1H, $J_{3,4}$ = 2.7 Hz, H-3), 3.70 (d, 3H, $J_{Me,P}$ = 10.9 Hz, POMe), 3.71 (d, 3H, $J_{Me,P}$ = 10.9 Hz, POMe), 3.85 (d, 1H, $J_{4,3}$ = 2.7 Hz, H-4), 3.95 (d, 1H, $J_{1,1'}$ = 12.1 Hz, H-1), 4.38 (q, 1H, J = 6.2 Hz, H-5), 4.44 (d, 1H, $J_{1',1}$ = 12.1 Hz, H-1′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 26.3 (d, $J_{C\text{-}P}$ = 139.5 Hz), 49.5, 52.3 (d, $J_{C\text{-}P}$ = 6.5 Hz), 52.7 (d, $J_{C\text{-}P}$ = 6.2 Hz), 56.8 (d, $J_{C\text{-}P}$ = 6.4 Hz), 58.2, 59.7, 72.6, 103.6, 170.3; ^{31}P NMR (85% H_3PO_4) δ 29.59; HRESI-MS *m/z*: $[M + Na]^+$ calcd for 333.0709. Found 333.0710.
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16. *Selected data for* ***12***: R_f = 0.43 (*E*); ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H, Me_2C), 1.38 (s, 3H, Me_2C), 2.05 (s, 3H, MeCO), 2.32 (m, 2H, H-6, H-6′), 3.25 (s, 3H, OMe), 3.69 (d, 3H, $J_{Me,P}$ = 9.0 Hz, POMe), 3.75 (d, 3H, $J_{Me,P}$ = 9.0 Hz, POMe), 3.81 (d, 1H, $J_{1,1'}$ = 12.3 Hz, H-1), 3.87 (d, 1H, $J_{1',1}$ = 12.3 Hz, H′-1), 4.01 (br s, 1H, H-3), 4.23 (m, 1H, H-5), 4.78 (bd, 1H, $J_{4,5}$ = 4.2 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ 20.2, 20.9, 27.1, 29.8 (d, $J_{c,p}$ = 140.6 Hz), 48.5, 52.1 (d, $J_{c,p}$ = 6.4 Hz), 52.8 (d, $J_{c,p}$ = 6.3 Hz), 62.2, 78.0 (d, $J_{c,p}$ = 6.2 Hz), 79.3, 82.4 (d, $J_{c,p}$ = 14.6 Hz), 99.2, 102.1, 170.3; ^{31}P NMR (85% H_3PO_4) δ 29.14; HRESI-MS *m/z*: $[M+Na]^+$ calcd for $C_{14}H_{25}O_9P$391.1128. Found 391.1119.