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Mild Oxidation of Cytidine-Sialic Acid Phosphite Derivatives Using Dimethyldioxirane

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Abstract: The dimethyldioxirane oxidation of several Cytidine-Neu5Ac phosphite analogs is described.
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Sialic acids are present at the non-reducing termini of the class of glycolipids known as gangliosides, and play an important role in many cellular processes, including cell adhesion and tumor metastasis.[1] The sialic acid moiety is therefore an attractive target for derivatization in order to further explore its biological functions. An effective method for the incorporation of sialic acid analogs into oligosaccharides utilizes sialyl transferase enzymes, which catalyze the glycosylation of lactose- and lactosamine-derived acceptors with sialic acid. Derivatives of cytidine monophospho-*N*-acetylneuraminic acid (CMP-Neu5Ac, **1**, Figure 1) are used as the sialyl donors.[2,3] While the synthesis of some CMP-Neu5Ac congeners can be accomplished enzymatically through the use of CMP-Neu5Ac synthetase, few modifications of the sialic acid moiety are tolerated by this enzyme on a preparative scale.[4] Consequently, a chemical method for the synthesis of these compounds has been developed in our laboratories.[5]

During the course of our studies on the synthesis of CMP-Neu5Ac analogs, a mild method for phosphite oxidations was required. Although initial results with *tert*-butyl hydroperoxide afforded acceptable yields and purity for several cytidine-Neu5Ac phosphite congeners, product hydrolysis became problematic with more labile

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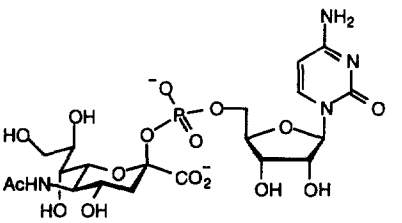
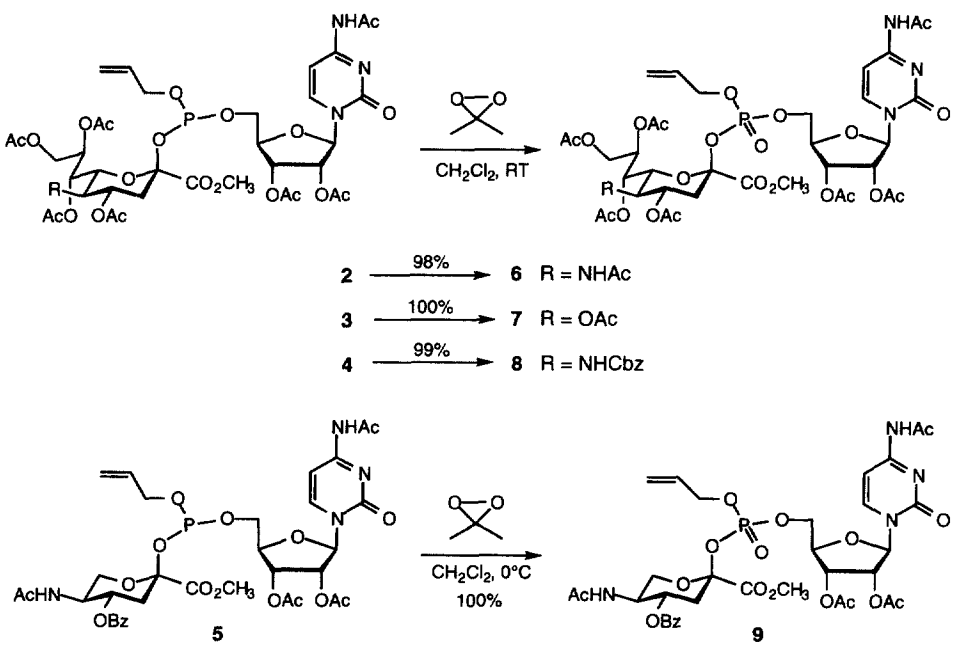


CMP-Neu5Ac (1)

Figure 1

derivatives, which led to low yields and impure products. In addition to being acid and base labile, the protected phosphates are also prone to hydrolysis during silica gel chromatography, thus making it difficult to remove decomposition products. Therefore, dimethyldioxirane was looked to as a mild, anhydrous oxidant that would overcome the aforementioned obstacles.



Scheme 1

Dimethyldioxirane (DMD) has been extensively studied and used to carry out a variety of synthetically important transformations.[6] To the best of our knowledge, this report is the first instance where DMD has been utilized in phosphite oxidations. Treatment of the phosphites (**2-5**) with a slight excess of DMD, as an anhydrous solution in acetone, led to near quantitative phosphite oxidation in 10 minutes with no trace of phosphate

hydrolysis or unwanted byproducts, such as olefin epoxidation (Scheme 1).[7] Noteworthy is the oxidation of compound **5** to provide phosphate **9**, which suffered significant decomposition under the *tert*-butyl hydroperoxide oxidation conditions.

Dimethyldioxirane was prepared by the caroate (Oxone®) oxidation of acetone and isolated as 0.07-0.10 M acetone solutions.[8] These solutions can be conveniently dried over calcium sulfate to provide an anhydrous oxidant that avoids the dangers of anhydrous *tert*-butyl hydroperoxide. The DMD solutions are also approximately neutral pH, thus making them particularly useful in cases where the oxidation products are acid or base labile. Another attractive feature of this method is the volatility of dimethyldioxirane. Concentration of the reaction removes all traces of the oxidant and avoids the need for a work-up or chromatographic purification.

In summary, a new procedure for cytidine-Neu5Ac phosphite oxidations utilizing dimethyldioxirane is presented. This method provides a way to synthesize labile CMP-Neu5Ac derivatives without the need for purification. The DMD system has afforded significant increases in yield and purity over previous procedures and has improved the overall efficiency of our CMP-Neu5Ac analog syntheses.

General Procedure for the Phosphite-Dimethyldioxirane Oxidations.

A solution containing 12.7 mg (0.0122 mmol) of **4** in 1.0 mL of freshly distilled CH_2Cl_2 was treated with 0.162 mL (0.0131 mmol) of a 0.083 M solution of dimethyldioxirane[8] in acetone at room temperature. After 10 min. the reaction mixture was concentrated *in vacuo* to provide 12.8 mg (0.0121 mmol) of **8** in quantitative yield as a white foam.

The oxidation of **5** to provide the extremely labile phosphate **9** was accomplished following the general procedure except that both the reaction and solvent removal were performed at 0°C.[9]

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7. For spectral data on compounds **6** and **7**, see ref. 5. Compounds **8** and **9** are contaminated with a small amount of the α linked diastereomers. **Compound 8**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.77 (s, 0.9 H), 8.68-8.57 (s, 1.2 H), 8.51 (d, 1.0 H, J = 10.1 Hz), 7.77 (s, 0.3 H, J = 7.5 Hz), 7.66 (d, 0.6 H, J = 7.6 Hz), 7.42-7.25 (m, 15.8 H), 6.94 (d, 0.6 H, J = 9.7 Hz), 6.43 (d, 0.3 H, J = 11.1 Hz), 5.98-5.87 (m, 2.5 H), 5.83 (dd, 0.8 H, J = 3.0, 6.6 Hz), 5.77 (t, 0.9 H, J = 7.0 Hz), 5.73-5.67 (m, 1.3 H), 5.65-5.59 (m, 1.8 H), 5.57-5.55 (m, 0.7 H), 5.52-5.49 (m, 0.6 H), 5.42-5.08 (m, 15.4 H), 4.96 (d, 1.4 H, J = 12.7 Hz), 4.81 (d, 0.7 H, J = 12.5 Hz), 4.76 (dd, 0.8 H, J = 1.6, 10.5 Hz), 4.67-4.55 (m, 7.8 H), 4.48-4.34 (m, 6.8 H), 4.32-4.18 (m, 3.7 H), 4.10-4.02 (m, 0.7 H), 3.98-3.88 (m, 0.7 H), 3.83 (s, 1.8 H), 3.82 (s, 2.9 H), 3.80 (s, 2.8 H), 2.92 (m, 0.4 H), 2.76 (dd, 1.0 H, J = 5.2, 13.5 Hz), 2.69 (dd, 0.9 H, J = 4.6, 13.5 Hz), 2.23 (s, 2.9 H), 2.15 (s, 11.3H), 2.09-2.05 (m, 17.6 H), 2.03 (s, 3.1 H), 2.00 (s, 3.2 H), 1.98 (s, 2.2 H), 1.96-1.95 (m, 4.8 H), 1.92 (s, 3.9 H), 1.90 (s, 3.6 H), 1.86 (s, 3.7 H), 1.83-1.81 (m, 11.4 H), 1.74-1.67 (m, 3.5 H); ^{31}P NMR (203 MHz, $CDCl_3$) δ -4.29, -6.06, -6.74. **Compound 9**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (s, 0.9 H), 8.90 (s, 1.2 H), 8.56 (d, 1.1 H, J = 7.7 Hz), 8.02-7.92 (m, 5.4 H), 7.83 (d, 0.5 H, J = 7.3 Hz), 7.58-7.53 (m, 2.5 H), 7.48-7.36 (m, 7.9 H), 6.95 (d, 0.8 H, J = 8.7 Hz), 6.67 (d, 0.8 H, J = 7.7 Hz), 6.37 (d, 0.9 H, J = 6.2 Hz), 6.24 (d, 1.0 H, J = 2.8 Hz), 6.02-5.89 (m, 2.6 H), 5.64 (dd, 1.0 H, J = 4.0, 4.8 Hz), 5.54-5.47 (m, 1.5 H), 5.44 (d, 2.5 H, J = 3.6 Hz), 5.40-5.26 (m, 6.6 H), 4.69 (t, 2.0 H, J = 7.4 Hz), 4.63-4.54 (m, 4.0 H), 4.49-4.29 (m, 10.2 H), 4.22-4.18 (m, 2.6 H), 3.90-3.85 (m, 1.8 H), 3.82 (s, 3.4 H), 3.80 (s, 3.2 H), 3.80-3.76 (m, 1.8 H), 3.32 (dd, 0.2 H, J = 4.4, 14.9 Hz), 2.92 (dd, 1.4 H, J = 4.4, 13.7 Hz), 2.74 (dd, 1.0 H, J = 4.8, 13.5 Hz), 2.25 (s, 3.7 H), 2.22 (s, 4.4 H), 2.15 (s, 15.2 H), 2.08 (s, 12.0 H), 2.02 (s, 3.3 H), 2.02 (s, 3.3 H), 1.91 (s, 3.2 H), 1.89 (s, 4.3 H); ^{31}P NMR (203 MHz, $CDCl_3$) δ -4.54, -4.60.
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9. Treatment of **5** with DMD at room temperature and concentration on the rotorary evaporator led to some decomposition of the phosphate **9**.