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Total Synthesis of Fully Acetylated *N*-Acetylneuraminic Acid (Neu5Ac), 2-Deoxy-β-Neu5Ac, and 4-*epi*-2-Deoxy-β-Neu5Ac from D-glucose

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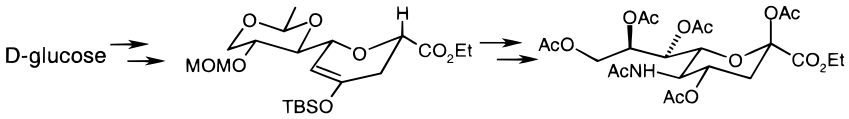
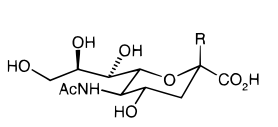
ABSTRACT

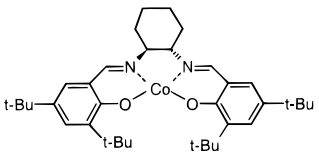


Sialic acid and its analogues have been synthesized using a salenCo(II) complex catalyzed hetero Diels–Alder reaction and oxidative azidation (CAN/NaN_3) of silyl enol ether as the key steps.

Sialic acids (especially *N*-acetylneuraminic acid, Neu5Ac **1**) frequently occur at the terminal end of glycoconjugates, such as glycoproteins, glycolipids, and oligosaccharides, in cell membranes and nerve tissues of various living organisms.[1] They play a vital role[2] in numerous biological processes including cell-to-cell recognition, cell-adhesion, and tumor metastasis. Among the analogues of **1**, *N*-acetyl-2-deoxy-neuraminic acid (**2**) and its 4-epimer are of particular interest, because they are inhibitors of Neu5Ac-associated enzymes such as *Vibio cholerae* sialidase[3] and influenza viral neuraminidase.[4] Considerable attention has therefore been paid to developing effective methods for synthesis of both Neu5Ac (**1**)[5,6] and its 2-deoxy-2-H derivative (**2**).[3,6d,7] Herein we wish to report an efficient approach to *N*-acetylneuraminic acid (Neu5Ac), 2-deoxy-β-Neu5Ac, and 4-*epi*-2-deoxy-β-Neu5Ac from D-glucose based on salenCo(II) (**3**) complex[8] catalyzed hetero Diels−Alder reactions.



R=OH, Neu5Ac, **1**
R=H, 2-deoxy-Neu5Ac, **2**



(*S*, *S*)-salenCo(II), **3**

The desired silyloxy diene **8** was prepared from the readily available D-glucose as shown in Scheme 1. Thus, 2,4-*O*-ethylidene-D-erythrose (**5**) was obtained using the established procedures.[9] Wittig reaction of **5** with $Ph_3P{=}CHCOCH_3$ afforded unsaturated ketone **6**, which was then protected as

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(3) Wallimann, K.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 1520−1532.
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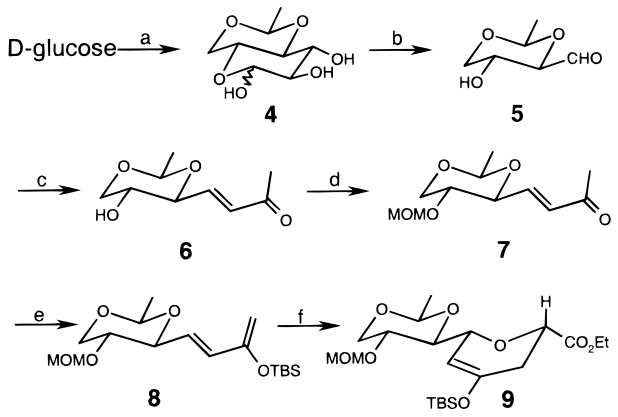
Scheme 1[a]

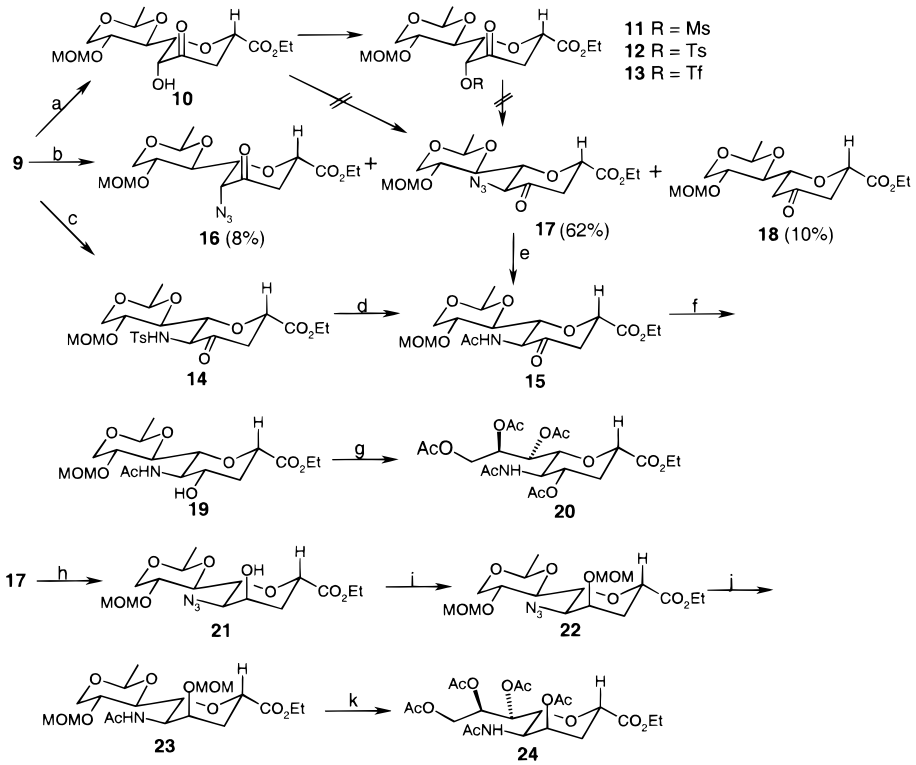


[a] Reagents and conditions: (a) Paraldehyde, cat. H_2SO_4, 43%; (b) $NaIO_4$, $NaHCO_3$, H_2O; (c) $Ph_3P{=}CHCOCH_3$, toluene, 90 °C, 66% over two steps; (d) methylal, cat. P_2O_5, $CHCl_3$, 0 °C → room temperature, 88%; (e) $TBSOT_f$, Et_3N, 0 °C, 99%; (f) ethyl glyoxylate, **3** (10% mol), CH_2Cl_2, room temperature, 62%.

MOM ether **7** (88% yield). Treatment of compound **7** with triflate and triethylamine at 0 °C for 30 min provided the corresponding diene **8** in 99% yield**.** The hetero Diels−Alder reaction between compound **8** and ethyl glyoxylate (freshly distilled) catalyzed by (*S*,*S*)-salenCo(II) complex (**3**) (10% mol) at room temperature afforded cycloaddition product **9** in 62% isolated yield, along with a small amount of an isomer (<5% yield) and the byproducts[10] from the Mukaiyama reaction.

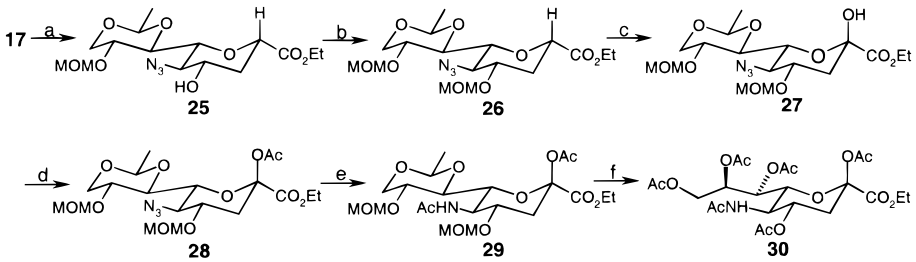
The next key step of our synthesis was to introduce an amine group at the C-5. We first tried to prepare α-hydroxy ketone **10** by an AD reaction[11] of **9** under conditions similar to those used previously[8d] (Scheme 2). **10** was then transformed in parallel into mesylate **11**, tosylate **12**, or triflate **13** and treated separately with NaN_3. To our surprise, the anticipated S_N2 reaction leading to **17** did not occur. Instead, all runs gave predominantly the elimination product, presumably due to the steric crowding caused[12] by the larger substituent at C-6. We then tested the Mitsunobu reaction[13] (using DEAD, DPPA, Ph_3P); the reaction was very complicated. The Sharpless asymmetric aminohydroxylation reaction[14] [LiOH/AcNHBr/$K_2Os(OH)_4O_2$ in *t*-BuOH/H_2O] of **9** did not afford any **15** either. The Evans' copper-mediated aziridination reaction[15] gave the expected α-amino ketone adduct **14** in 39% isolated yield, when **9** was treated with 10 mol % of $CuClO_4$[16] or $Cu(OTf)_2$ and 1.5 equiv (with respect to **9**) of PhI=NTs[17] in anhydrous MeCN at −30 °C.

Scheme 2[a]



[a] Reagents and conditions: (a) $K_2OsO_2(OH)_4$ (5% mol), $(DHQD)_2$−PHAL (5% mol), $NaHCO_3$ (3 equiv), K_2CO_3 (3 equiv), $K_3Fe(CN)_6$ (3 equiv), t-BuOH/H_2O (1:1), 0 °C, 78%; (b) NaN_3 (3 equiv), CAN (2.5 equiv), CH_3CN, −25 °C, 61%; (c) PhI=NTs (1 equiv), $Cu(CH_3CN)_4ClO_4$ (10% mol), CH_3CN, −20 → −10 °C, 39%; (d) Na/NH_3, or Na/naphthalene, THF, −78 °C, ≤ 10%; (e) CH_3COSH, room temperature, 90%; (f) $NaBH_4$, EtOH, −30 °C, 85%; (g) *p*-TsOH (2 equiv), EtOH, reflux, then Ac_2O, Et_3N, DMAP, CH_2Cl_2, 96%; (h) $LiAl[O(CH_3)_3]_3H$, THF, −10 °C, 80%; (i) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 91%; (j) H_2, Pd/C (10%), room temperature, then Ac_2O, Et_3N, DMAP, CH_2Cl_2, 95%; (k) same as (g), 92%.

Scheme 3[a]



[a] Reagents and conditions: (a) $NaBH_4$, EtOH, −30 °C, 83%; (b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C → room temperature, 90% (c) LDA, MoOPH, THF, −78 °C, 50%; (d) Ac_2O, Py, DMAP, CH_2Cl_2, room temperature, 84%; (e) H_2, Pd/C (10%), EtOH, 30 °C, then Ac_2O, Et_3N, DMAP, CH_2Cl_2, room temperature, 68%; (f) *p*-TsOH, EtOH, reflux, then Ac_2O, Py, DMAP, CH_2Cl_2, room temperature, 73%.

However, the following removal of the tosyl group in **14** using either Na/NH_3 or Na/naphthalene suffered from very low yield (<10%), although the expected product **15** did form. This difficulty made us reconsider introducing an azide group at C-5 first.

Oxidative azidation (CAN/NaN_3) of silyl enol ether is also an established means to prepare α-azido ketone. Although there are reports[18,19] on the ineffectiveness of this reaction, we found that the yield could be significantly improved by modifying the procedure. Thus, treatment of **9** with NaN_3 (3.0 equiv) in anhydrous CH_3CN at −25 °C followed by slow addition of CAN (2.5 equiv in CH_3CN) led to the desired product **17** in a 61% isolated yield, together with a small amount of **18** (10%). It is noteworthy that unlike all the previously reported procedures, the present one can be run easily on larger scales (1.5−2.5 g) without lowering the yield.

Conversion of **17** to the corresponding acetamide **15** using a modification of Rosen's method[20] (Scheme 2) was realized in 90% yield. Reduction of the ketone of **15** with $NaBH_4$ at −30 °C afforded the desired *anti* product **19** in 85% yield. All the protecting groups in compound **19** were then removed by treatment with *p*-TsOH in refluxing EtOH. Acetylation of the unmasked hydroxyl groups to afford the corresponding acetate **20**[21] was fulfilled (96%) using acetic anhydride in the presence of Et_3N and a catalytic amount of DMAP.

The 4-*epi* analogue **24** was also prepared according to Scheme 2. Reduction of the ketone carbonyl in **17** with the bulky reducing reagent $LiAl[O(CH_3)_3]_3H$[22] at −10 °C gave *syn* product **21** in 80% isolated yield. After protection of the C-4 hydroxyl as the MOM ether (**22**, 91% yield), the azido functionality was hydrogenated to give an amine, which was converted to **23** in high yield (95%). Then, under the same conditions, compound **23** was transformed into **24**, the fully acetylated 4-*epi*-2-deoxy-β-Neu5Ac, in 92% yield.[23]

The total synthesis of sialic acid from intermediate **17** require oxidation at C-2. Thus, reduction of the ketone,

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(21) NMR data for compound **20**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.59 (1H, d, *J* = 8.5 Hz, NH), 5.42 (1H, ddd, *J* = 7.1, 5.1, 1.2 Hz), 5.25 (1H, dd, *J* = 4.7, 1.6 Hz), 5.11 (1H, ddd, *J* = 5.1, dt, *J* = 11.5, 4.9 Hz), 4.60 (1H, dd, *J* = 12.1, 2.2 Hz), 4.29 (1H, dd, *J* = 12.3, 6.9 Hz), 4.22 (2H, dq, *J* = 7.1, 1.3 Hz), 4.05 (1H, dd, *J* = 12.1, 2.2 Hz), 3.95 (1H, q, *J* = 10.2 Hz), 3.67 (1H, *J* = 10.6, 1.4 Hz), 2.39 (1H, ddd, *J* = 12.6, 4.9, 2.2 Hz), 2.11, 2.10, 2.06, 2.05, 1.98 (15H, 5s), 1.76 (1H, q, *J* = 12.1 Hz), 1.28 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.81, 170.64, 170.31, 170.25, 170.08, 168.71, 78.70, 74.12, 71.40, 70.82, 69.85, 62.73, 61.50, 51.84, 33.78, 23.24, 21.01, 20.94, 20.91, 20.72, 14.00; EIMS (*m*/*z*) 490 (M^+ + 1); $[\alpha]_D$ = 34.2 (*c* 0.25, $CHCl_3$).

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(23) NMR data for compound **24**: ^1H NMR (600 MHz, $CDCl_3$) δ 5.82 (1H, d, *J* = 9.0 Hz, NH), 5.43 (1H, dt, *J* = 9.0, 2.4 Hz), 5.26 (1H, dd, *J* = 6.6, 3.0 Hz), 5.10 (1H, m), 4.47 (1H, dd, *J* = 12.6, 2.4 Hz), 4.43 (1H, dd, *J* = 6.6, 2.4 Hz), 4.28−4.22 (3H, m), 4.12 (1H, t, *J* = 7.2 Hz), 4.14−4.11 (1H, m), 2.52 (1H, ddd, *J* = 15.0, 4.2, 2.4 Hz), 2.17, 2.12, 2.05, 2.04, 2.01 (15H, 5s), 2.09 (1H, ddd, *J* = 15.0, 7.2, 3.0 Hz), 1.26 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.08, 171.05, 170.62, 170.38, 170.23, 169.42, 70.83, 70.65, 69.37, 68.78, 62.38, 61.19, 60.35, 47.24, 30.08, 23.19, 20.96, 20.91, 20.75, 20.69, 13.69; EIMS (*m*/*z*) 490 (M^+ + 1); $[\alpha]_D$ = 98.6 (*c* 1.09, $CHCl_3$).

following protection of the resulting hydroxy, furnished the desired *anti*-azido MOM ether **26** (Scheme 3). Oxidation of the lithium enolate of **26** with MoO_5·Py·HMPA (MoOPH)[24] gave the 2-α-OH product (along with traces of the 2-*β*-OH isomer) in 50% isolated yield (70%, based on recovered **26**). Acetylation of the hydroxyl at C-2 afforded compound **28** (84%). Then following a procedure similar to that described above, **28** was transformed into pentaacetylated ethyl ester **30**.[25] The physical data of our synthetic sample are identical to those reported[5f] by Whitesides.

In summary, we have established an effective synthesis of both sialic acid and its analogues. Further studies on the total synthesis of Neu2en5Ac and Zanamivir[26] (GG167) are currently ongoing in this laboratory, and the results will be reported in due time.

Acknowledgment. We thank the Chinese Academy of Sciences (KJ-952-S1-503, KJ-95-A1-504), the Chinese Natural Science Foundation (29790126, 29872049), and the State Ministry of Science and Technology of China (970211006-6) for financial support.

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(25) NMR data of compound **30**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (1H, d, J = 9.3 Hz, NH), 5.49 (1H, ddd, J = 10.4, 5.8, 3.6 Hz), 5.26 (1H, dd, J = 5.0, 1.6 Hz), 5.22−5.18 (1H, m), 4.63 (1H, dd, J = 12.4, 2.5 Hz), 4.29 (1H, dd, J = 9.0, 7.9 Hz), 4.23 (2H, q, J = 7.1 Hz), 4.12 (1H, q, J = 10.2 Hz), 3.75 (1H, dd, J = 10.9, 1.9 Hz), 2.36 (1H, dd, J = 13.5, 4.9 Hz), 1.85 (1H, dd, J = 13.5, 11.2 Hz), 2.09, 2.08, 2.05, 2.04, 2.03, 1.98 (18H, 6s), 1.29 (3H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ171.08, 170.75, 170.29 × 2, 170.03, 169.76, 167.29, 98.31, 73.19, 71.25, 69.65, 68.79, 62.83, 61.96, 51.34, 37.53, 23.20, 20.98, 20.91, 20.79, 20.74, 14.00; $[\alpha]_D$ = 40.4 (c 0.52, $CHCl_3$).

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