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A New Synthesis of Neu5Ac from D-Glucono-δ-lactone

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A new route to Neu5Ac methyl ester (**23**) with a readily available sugar D-glucono-δ-lactone as starting material has been developed. A diastereoselective propargylation of α-acetamino aldehyde and a subsequent $KMnO_4$ oxidation of the terminal alkyne served as the key steps.

Naturally occurring biomolecules often play significant roles in numerous physiological processes. Examples of important functions in which cell−surface glycoconjugates are involved include cell−bimolecule interactions and the masking of receptors by cell−surface glycans. Such glycoconjugates also serve as markers in certain cancers and as ligands for proteins.[1,2] Among the various functional sugars, the sialic acids are one family of carbohydrates intimately involved in many biological processes. These naturally occurring 2-keto-3-deoxynonulsonic acids are a diverse group that are commonly found as the α-ketosidically linked terminal sugars on cell−surface glycoconjugates and are the most abundant terminal sugars on mammalian glycoconjugates.[1,2] The most commonly found derivatives are those derived from 5-acetamido-D-glycero-D-galacto-2-nonulosonic acid (Neu5Ac, **1**). Due to the importance of sialic acids in biological investigations, many chemists are involved in developing efficient synthetic approaches to these compounds and their derivatives.[3] Both enzymatic or chemoenzymatic and purely chemical approaches were reported during the past decades. It is noteworthy that structural modification has been made at every position of the sialic acid molecule, mostly targeting at Neu5Ac. Since the first[4] chemical synthesis of Neu5Ac by Cornforth et al. in 1958, numerous efforts as extensions of the pioneering work were reported.[5] However, because of either the inconvenient procedures or the expensive reagents employed, most of these routes reported up to now are not easily adaptable to gram-sacle preparation of sialic acids and derivatives. On the basis of our previous study on the diasteroselective propargylation[6] and subsequent oxidation of terminal alkyne,[7] herein we would like to report a successful synthesis of Neu5Ac on a larger scale starting from the inexpensive chemical D-glucono-δ-lactone.

From the view of retrosynthesis (Figure 1), the keto-sugar structure of Neu5Ac (**1**) can be constructed by an intramolecular ketal-formation transformation from the α-ketocarboxylate **2**. This intermediate in turn can be prepared from the homopropargyl alcohol **3** by an oxidation of terminal alkyne, which can be further transformed backward to a commonly available chemical D-glucono-δ-lactone.

First of all, treatment of D-glucono-δ-lactone with 2,2-dimethoxypropane in acetone and methanol under catalysis of pTsOH hydrate afforded the methyl ester **6** in high yield (83%) after simple distillation[8] (Scheme 1). The following $LiAlH_4$ reduction of **6** gave the corresponding diol **7** in 85% yield[8] as a white low-melting solid, which was pure enough for direct use in the next step without further purification. Chemoselective protection of the primary alcohol **7** was achieved by the dibutyltin oxide strategy.[9] The original separation procedure, however, was modified here to avoid chromatographic purification. After completion of the reaction, the whole mixture was cooled in an ice−salt bath and most of the tin oxide was removed by filtration. The filtrate was then concentrated under reduced pressure to afford the monobenzyl ether **5** in 89% yield. Alcohol **5** was converted to azide **9** (57%) by a two-step procedure through mesylate **8**. When prepared on a large scale, this compound (**9**) could be easily purified by recrystallization.

Azide **9** was then converted to the corresponding amine **10** by $LiAlH_4$ reduction, which on treatment with Na in liquid ammonia to remove the benzyl protection group

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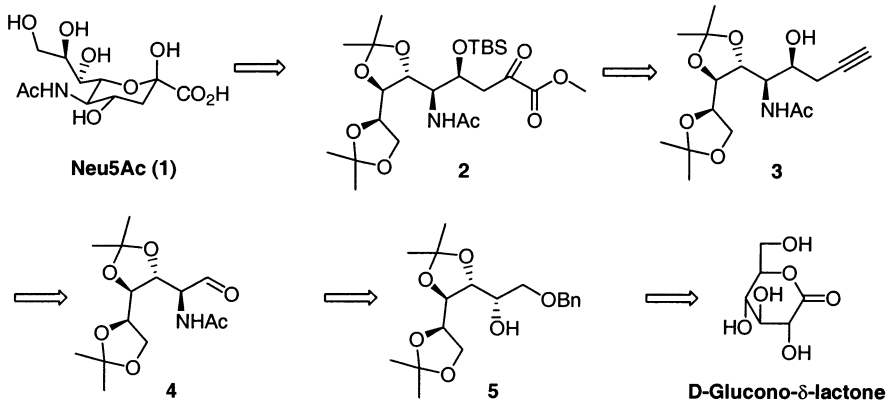
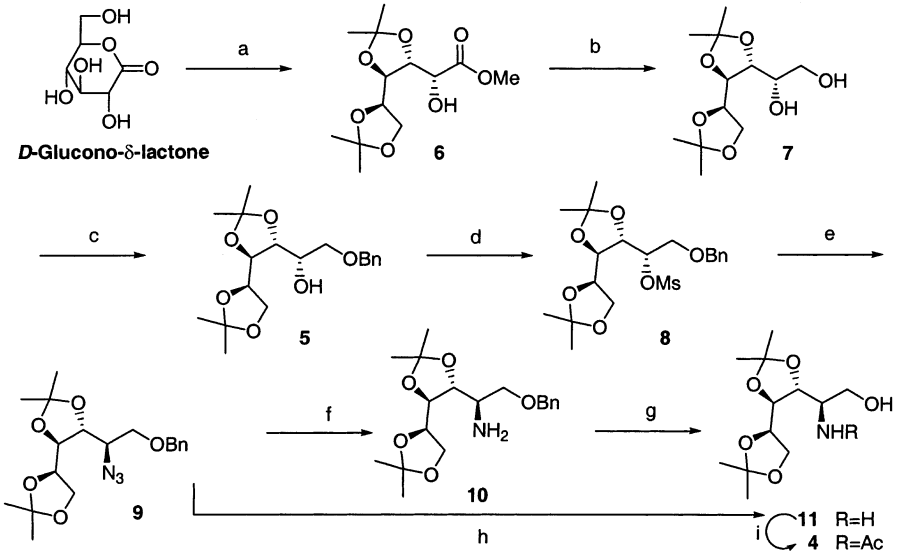


FIGURE 1. Retrosynthetic view of Neu5Ac (**1**).

SCHEME 1[a]



[a] Reagents and conditions: (a) PTsOH/acetone/DMOP/MeOH, 83%; (b) $LiAlH_4$/THF, 85%; (c) Bu_2SnO/Bu_4NI/BnBr/toluene, 89%; (d) $MsCl/Et_3N/CH_2Cl_2$, 86%; (e) NaN_3/DMF, 57%; (f) $LiAlH_4$/THF, 98%; (g) Na/NH_3 (liquid), 85%; (h) H_2 (30 atm), 10% Pd−C, 5% HOAc in MeOH, 75%; (i) $Ac_2O/NaHCO_3$/water−MeOH, 82%.

afforded aminol **11** (84% over two steps). Alternatively, **9** could be directly transformed into **11** (75% to 85% yield) by palladium-catalyzed medium-pressure (30 atm) hydrogenation in MeOH containing 5% HOAc.

The resulting amine **11** was directly treated with Ac_2O in aqueous $NaHCO_3$ and methanol to give **4**[10] in 82% yield. It is noteworthy that compound **4** is fairly soluble in water. To ensure a high yield of **4**, the aqueous phase must be checked by TLC after solvent extraction. Other attempts to prepare the azides all failed (Scheme 2).

Further transformations from **4** are shown in Scheme 3. First of all, alcohol **4** was treated with Dess−Martin periodinane[11] to afford aldehyde **19** in 75% yield after chromatography. In preparative runs, however, it was not necessary to purify **19**. The crude product could be satifactorily used in the next step. The subsequent propargylation reaction[6] was performed by treatment of **19** with zinc dust and propargyl bromide in DMF and ether (1:1 (v/v)) to afford **3** and **20** in 70% yield. The diastereoselectivity between *threo*-**3** and *erythro*-**20** was 74:11 based on the isolated yields. The configuration of **3** was confirmed by X-ray crystallographic analysis of a single crystal (see Supporting Information).

Most of the major product **3** could be obtained from the crude product by a single recrystallization from EtOAc/hexanes, although the precise yields of **3** and **20** could be obtained only by chromatographic separation of the diastereomeric mixture. The propargylation also could be performed in THF−water in the presence of NH_4Cl and afforded a similar result to that in DMF. The newly produced hydroxyl was protected as TBS ether **21** (88%) before the terminal alkyne was converted to bromide **22** (95%) with NBS in acetone. The following $KMnO_4$-based oxidation[7] of **22** in slightly basic aqueous methanol afforded α-keto methyl ester **2** in 60% yield. Finally, the methyl ester of Neu5Ac (**23**) was obtained in 45% isolated yield after treatment of **22** with 5% HF in MeCN. All physical data for **23** ($[\alpha]_D$ −23.4 (*c* 1.0, CH_3-

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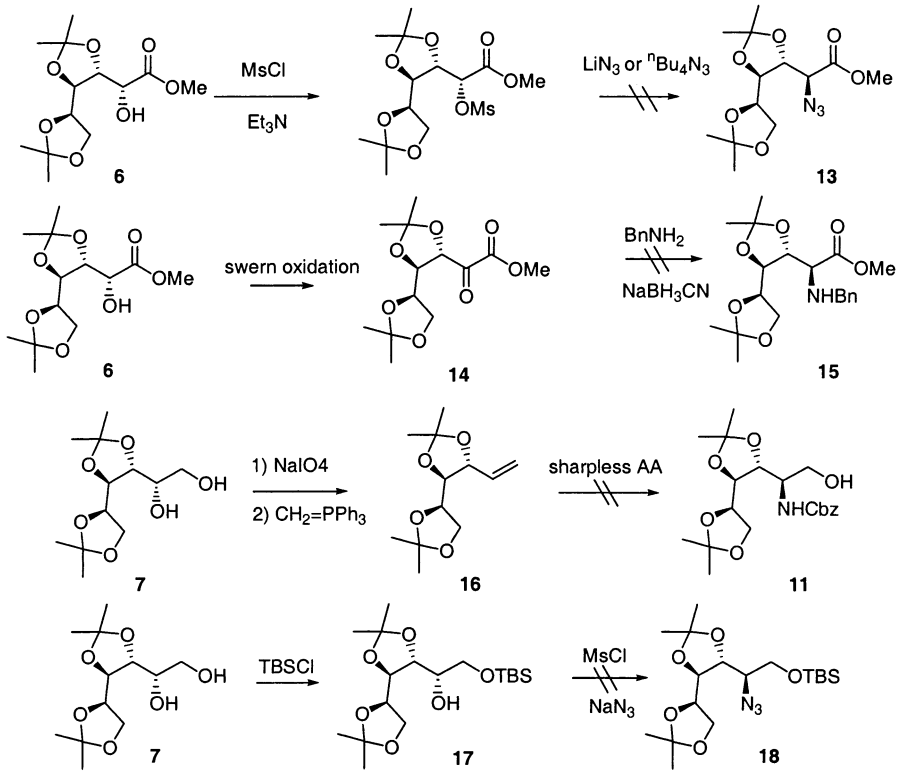
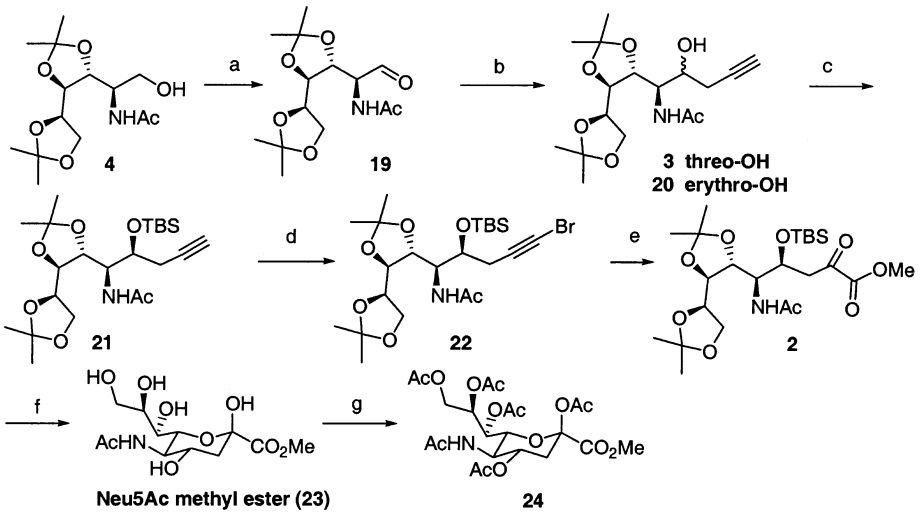
SCHEME 2



SCHEME 3[a]



[a] Reagents and conditions: (a) Dess−Martin, CH_2Cl_2, 75%; (b) C_3H_3Br, Zn, DMF/Et_2O, 70%, **3**:**20** = 74:11; (c) TBSCl/DMF, 88%; (d) NBS/acetone, 95%; (e) $KMnO_4$/MeOH, 60%; (f) 40% HF/MeCN, 45%; (g) Ac_2O/Py, 50%.

OH); ref 12 $[\alpha]_D$ −27 (*c* 1, CH_3OH)) and its acetate **24** ($[\alpha]_D$ −17.6 (*c* 2.5, $CHCl_3$); ref 5h $[\alpha]_D$ −13.8 (*c* 0.56, $CHCl_3$)) were identical with the reported data.[5h,12]

To synthesize **23** on larger scales, the the later steps of the procedures were improved (Scheme 4). First of all, the homo-propargyl alcohol **3** was protected as a dimethylacetal **25** (73%) with DMOP in the presence of a catalytic amount of *p*TsOH. Then bromination of the terminal alkyne C−H was achieved by using NBS to afford **26** (87%). The following oxidation of **26** gave the corresponding α-ketoester **27**[5j] in 54% yield, which was subjected to 5% HF in MeCN to give the final product **23** in 65% yield. Compared with the previous procedures, the modification described here has several advantages: First, the intermediates are more stable and easier to separate. Second, all the reaction conditions employed are milder and the progress of the reactions is easier to follow by TLC. Finally, the yield for the last step is improved and the end product is easier to purify by normal phase chromatography on silica gel.

In conclusion, a new laboratory procedure for the synthesis of Neu5Ac methyl ester (**23**) has been devel-

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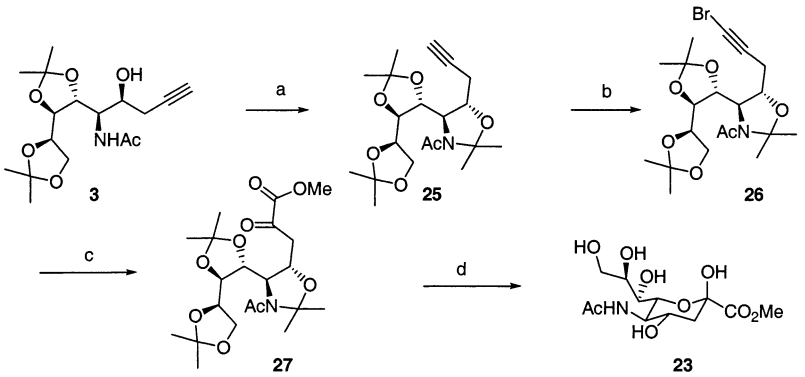
SCHEME 4[a]



[a] Reagents and conditions: (a) DMOP, DMF, pTsOH, 73%; (b) NBS, acetone, 87%; (c) $KMnO_4$, $NaHCO_3$, $MgSO_4$, 54%; (d) 5% HF, MeCN, 65%.

oped. It enjoys several advantages, including (i) very cheap and readily available staring materials and reagents, (ii) better diastereoselectivity, (iii) chromatography-free purifications for the intermediates **6**, **7**, **5**, **9**, and **3**, and (iv) gram-scale synthesis of the final product. In addition, it provides more opportunities to develop new sialic acid analogues through the newly reported intermediates.

Experimental Section

General. ^{1}H NMR was recorded in $CDCl_3$ or CD_3OD with TMS as the internal standard. Elemental analyses were carried out at the Microanalytic Laboratory of the Shanghai Institute of Organic Chemistry. Flash column chromatography was performed on silica gel H (10−40 μm).

1-*O*-Benzyl-3,4:5,6-di-*O*-isopropylidene-D-glucitol (5). In a flask equipped with a Dean−Stark trap was heated a suspension of diol **7** (50 g, 0.19 mol) and dibutyltin oxide (50 g, 0.20 mol) in toluene (400 mL) under reflux for 15 h. After concentration in vacuo to ca. 80 mL, benzyl bromide (50 mL, 0.40 mol) and tetrabutylammonium bromide (12.5 g, 0.04 mol) were added. The mixture was stirred at 70 °C for 15 h. After the solvent was removed in vacuo, the residue was diluted with ether and cooled in an ice−salt bath to precipitate most of the tin oxides. The solids were filtered off. The organic filtrate was concentrated and distilled in high vacuum to afford compound **5** (60.3 g, 89%). $[\alpha]_D$ +9.8 (*c* 2.28, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.36 (m, 5H), 4.61 (AB, d, 1H, J = 12.0 Hz), 4.55 (AB, d, 1H, J = 12.0 Hz), 4.14 (dd, 1H, J = 8.1, 5.4 Hz), 3.94−4.08 (m, 5H), 3.58−3.62 (m, 2H), 2.43 (d, 1H, J = 7.2 Hz), 1.43 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H) ppm. EIMS (*m*/*z*, %) 353 (M^+ + 1, 5.16), 337 (M^+ − Me, 13.26), 295 (28.27), 143 (13.66), 91 (100). IR (film) 3487, 2988, 2935, 1455, 1381, 1372, 1250, 1072 cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.76; H, 7.85.

1-*O*-Benzyl-2-*O*-methansulfonyl-3,4:5,6-di-*O*-isopropylidene-D-glucitol (8) To a solution of **5** (60.3 g, 0.17 mol) in dichloromethane (600 mL) containg triethylamine (84.4 mL, 0.6 mol) was added dropwise methanesulfonyl chloride (24.1 mL, 0.31 mol). After the mixture was stirred at 20 °C for 3 h, water was added. The mixture was then extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield compound **8** (63.5 g, 86%) without further purification. $[\alpha]_D$ +1.6 (*c* 1.35, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) 7.28−7.37 (m, 5H), 5.02 (ddd, 1H, J = 8.4, 3.3, 2.2 Hz), 4.58 (s, 2H), 4.17 (dd, 1H, J = 8.2, 5.5 Hz), 3.93−4.08 (m, 4H), 3.87 (dd, 1H, J = 11.0, 3.3 Hz), 3.74 (dd, 1H, J = 11.0, 8.4 Hz), 3.08 (s, 3H), 1.38 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H) 1.28 (s, 3H) ppm. EIMS (*m*/*z*, %) 431(M^+ + 1, 0.11), 416 (M^+ − Me, 2.84), 205 (1.79), 143 (6.76), 91 (100). IR (film) 2989, 2938, 2878, 1456, 1382, 1371, 1251, 1070 cm^{-1}.

(2*R*)-1-*O*-Benzyl-2-azido-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-mannitol (9). To a solution of **8** (56.4 g, 0.13 mol) in DMF (960 mL) was added sodium azide (63 g, 0.99 mol) at room temperature. The mixture was heated to 120 °C for 24 h. After concentration in vacuo, water was added. The mixture was extracted with ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and then concentrated in vacuo. The reside was recrystallized from hexanes to give compound **9** (28.4 g, 57%) as a colorless solid. Mp 27−28 °C. $[\alpha]_D$ +10.7 (*c* 3.90, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.38 (m, 5H), 4.59 (s, 2H), 4.04−4.15 (m, 3H), 3.92−3.99 (m, 2H), 3.82 (m, 1H), 3.77 (dd, 1H, J = 9.9, 3.7 Hz), 3.63 (dd, 1H, J = 9.9, 8.0 Hz), 1.41 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H) ppm. EIMS (*m*/*z*, %) 362 (M^+ − Me, 5.58), 292 (0.99), 262 (0.62), 143 (30.78), 91 (100). IR (KBr) 3348, 3030, 2997, 2933, 2102, 1497, 1370, 1214, 1066 cm^{-1}. Anal. Calcd for $C_{19}H_{27}N3O_6$: C, 60.46; H, 7.21; N, 11.13. Found: C, 60.54; H, 7.16; N, 11.15.

(2*R*)-1-*O*-Benzyl-2-amino-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-mannitol (10). A solution of **9** (24.8 g, 66 mmol) in THF (20 mL) was added to a suspension of $LiAlH_4$ (3.94 g, 99 mmol) in THF (300 mL) with stirring at 0 °C. The reaction mixture was stirred for another 30 min before being heated to reflux for 2 h. After the mixture was cooled to room temperature, solid $Na_2SO_4 \cdot 10H_2O$ was added to decompose the excess hydride. The solids were removed by filtration through a pad of Celite (washing with ether). The combined organic filtrate/washings were washed with brine, dried (Na_2SO_4), and then concentrated in vacuo to afford compound **10** (22.6 g, 98%) as a yellow oil, which was used directly in the next step.

(2*R*)-2-Amino-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-mannitol (11): Method 1. A solution of compound **10** (8.0 g, 22.8 mmol) in anhydrous THF (10 mL) was added into liquid ammonia (300 mL). Sodium metal was added until a dark blue color persisted. The mixture was stirred at the refluxing temperature of ammonia for 30 min. Solid ammonium chloride was added carefully to quench the reaction. Ammonia was allow to evaporate. The solid reside was dissolved into MeOH and dichloromethane. The organic layer was concentrated in vacuo to give compound **11** (5.06 g, 85%) as a yellow oil without further purification.

Method 2. A mixture of compound **9** (4 g, 10.6 mmol), 10% Pd−C (1.2 g), MeOH (50 mL), and acetic acid (2.65 mL) was stirred under a hydrogen atmosphere (30 atm) for 3 days at room temperature. The solid was filtered off through a pad of Celite (washing with MeOH). The combined filtrate/washings were concentrated to give compound **11** (2.16 g, 75%).

(2*R*)-2-Acetamido-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-mannitol (4). To a solution of compound **11** (13.6 g, 50 mmol) in MeOH (150 mL) stirred at room temperature were

added aqueous saturated $NaHCO_3$ (132 mL) and acetic anhydride (13.2 mL). After 10 min, the reaction mixture was extracted with ethyl acetate four times. The combined organic layers were washed with brine, dried (Na_2SO_4), and then purified by flash chromatography with hexanes−ethyl acetate (1:2 to 1:3) as elute to give compound **4**[10] (12.9 g, 82%). $[\alpha]_D$ +16.8 (*c* 0.835, $CHCl_3$); ref 10 $[\alpha]_D^{20}$ +14.6 (*c* 6.19, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 6.35 (br, 1H), 4.18 (dd, 1H, J = 8.4, 6.2 Hz), 4.00−4.10 (m, 3H), 3.93−3.86 (m, 4H), 3.07 (br, 1H), 2.02 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.37 (s, 6H) ppm. EIMS (*m*/*z*, %) 304 (M^+ + 1, 30.65), 288 (M^+ − Me, 8.78), 270 (1.66), 246 (100). IR (KBr) 3306, 2987, 2935, 1654, 1520, 1453, 1371 cm^{-1}.

(2*S*)-2-Acetamido-2-deoxy-3,4:5,6-di-*O*-isopropylidene-D-mannitol (19). A solution of compound **4** (10.5 g, 35 mmol) in dry CH_2Cl_2 (40 mL) was added over 15 min to a stirred solution of Dess−Martin periodinane (16.46 g, 39 mmol) in dry CH_2Cl_2 (200 mL). After 30 min the homogeneous mixture was diluted with ether and poured into cold saturated $NaHCO_3$ (200 mL) containing $Na_2S_2O_3$ (43 g). The combined organic layers were washed with aqueous saturated $NaHCO_3$ and brine and dried ($MgSO_4$). The solvents were evaporated below 20 °C to give compound **19**[10] (7.8 g, 75%). The yellow residue was immediately used for the next step.

(4*S*,5*R*,6*R*,7*R*,8*R*)-4-Hydroxy-5-acetamido-6,7:8,9-di-*O*-isopropylidene-1-nonyne (3) and (4*R*,5*R*,6*R*,7*R*,8*R*)-4-Hydroxy-5-acetamido-6,7:8,9-di-*O*-isopropylidene-1-nonyne (20). Zinc dust (0.203 g, 3.12 mmol) was added in portions to a solution of aldehyde **19** (300 mg, 1 mmol) and propagyl bromide (0.286 g, 2.4 mmol) in DMF/ether (1:1, 8 mL). After a few minutes, an exothermic reaction occurred. After the reaction was stirred at room temperature for 5 h, the mixture was filtered through a Celite pad. The filtrates were evaporated and the residue was dissolved in dichloromethane and washed with brine, dried over Na_2SO_4, and then purified by flash chromatography (ether−hexane, 9:1) to give **3** and **20** as colorless solids (239 mg, 70%, ratio 74:11). The structure of **3** was confirmed by the X-ray method.

Data for compound 3: Mp 185−187 °C. $[\alpha]_D$ +21.7 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 6.02 (d, 1H, J = 8.5 Hz), 4.12−4.31 (m, 4H), 4.02−4.09 (m, 1H), 3.87−3.92 (m, 2H), 2.97 (br, 1H), 2.38−2.42 (m, 2H), 2.05 (s, 1H), 2.04 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H) ppm. EIMS (*m*/*z*, %) 326 (M^+ − Me, 24.08), 143 (82.89), 114 (33.72), 59 (37.14), 43 (100). IR (KBr) 3466, 23284, 2996, 2933, 2902, 2879, 2117, 1648, 1327, 1258 cm^{-1}. Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 59.77; H, 8.06; N, 3.93.

Data for the diasteromer 20: Mp 71−73 °C. $[\alpha]_D$ +2.4 (*c* 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 6.34 (d, 1H, J = 5.8 Hz), 4.11−4.23 (m, 4H), 3.98−4.06 (m, 1H), 3.83−3.91 (m, 2H), 2.48−2.52 (m, 2H), 2.05 (s, 1H), 2.03 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H) 1.38 (s, 3H) ppm. (The acidic proton of the hydoxyl group could not be observed.) EIMS (*m*/*z*, %) 326 (M^+ − CH_3, 27.09), 43 (100). IR (KBr) 3462, 3280, 2995, 2930, 2900, 2118,1645, 1540 cm^{-1}.

(4*S*,5*R*,6*R*,7*R*,8*R*)-4-*tert*-Butyldimethylsilyoxy-5-acetamido-6,7:8,9-di-*O*-isopropylidene-1-nonyne (21). To a solution of **3** (468 mg, 1.37 mmol) in DMF (0.7 mL) stirred at 0 °C were added TBSCl (288 mg, 1.78 mmol) and imidazole (280 mg, 4.11 mmol). The reaction mixture was stirred at room temperature for 24 h. Water and ethyl acetate were then added. The phases were separated. The aqueous phase was back extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NH_4Cl and brine and dried over Na_2SO_4, then purified by column chromatography (hexane−ethyl acetate 4:1) to give **21** (533 mg, 88%) as a colorless solid. Mp 101−102 °C. $[\alpha]_D$ +27.8 (*c* 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (d, 1H, J = 9.6 Hz), 4.24−4.37 (m, 2H), 3.90−4.13 (m, 4H), 3.80 (dd, 1H, J = 8.0, 7.1 Hz), 2.33 (m, 2H), 2.03 (s, 1H), 2.02 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 0.93 (s, 9H), 0.15 (s, 6H) ppm. EIMS (*m*/*z*, %) 440 (M^+ − CH_3, 29.34), 340 (100). IR (KBr) 2988, 2935, 2861, 2120, 1668, 1650, 1525 cm^{-1}. Anal. Calcd for $C_{23}H_{41}NO_6Si$: C, 60.60; H, 9.07; N, 3.07. Found: C, 60.69; H, 9.05; N, 2.90.

(4*S*,5*R*,6*R*,7*R*,8*R*)-4-*tert*-Butyldimethylsilyoxy-5-acetamido-6,7:8,9-di-*O*-isopropylidene-1-nonynyl Bromide (22). To a solution of **21** (0.17 g, 0.37 mmol) in acetone (2.5 mL) were added NBS (0.094 g, 0.46 mmol) and silver acetate (0.019 g, 0.11 mmol). The reaction mixture was stirred at room temperature in the dark for 4 h. The solids were removed by filtration through a Celite pad (washing with ether). The combined organic filtrates were washed with water and brine, dried (Na_2SO_4), and then purified by column chromatography (hexane−ethyl acetate 4:1) to give **22** (0.190 g, 95%) as a colorless solid. Mp 102−103 °C. $[\alpha]_D$ +13.9 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (d, 1H, J = 9.8 Hz), 4.19−4.26 (m, 2H), 4.10 (dd, 1H, J = 8.2, 6.1 Hz), 3.88−4.03 (m, 3H), 3.79 (dd, 1H, J = 7.9, 6.7 Hz), 2.40 (dd, 1H, J = 17.1, 7.8 Hz), 2.30 (dd, 1H, J = 17.1, 5.0 Hz), 1.94 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 0.92 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H) ppm. EIMS (*m*/*z*, %) 520 (M^+ − CH_3, 13.86), 518 (M^+ − CH_3, 13.45), 478 (37.85), 476 (36.04), 75 (100.00). IR (KBr) 2983, 2933, 2860, 2200, 1667, 1648, 1523 cm^{-1}. Anal. Calcd for $C_{23}H_{40}NO_6Si$: C, 51.68; H, 7.54; N, 2.62. Found: C, 51.66; H, 7.54; N, 2.36.

(4*S*,5*R*,6*R*,7*R*,8*R*)-2-Oxo-4-*tert*-butyldimethylsilyoxy-5-acetamido-6,7:8,9-di-*O*-isopropylidene-1-nonanoic Acid Methyl Ester (2). To a solution of **22** (0.40 g, 0.748 mmol) in MeOH (11 mL) was added a solution of $NaHCO_3$ (0.037 g, 0.45 mmol) and $MgSO_4$ (0.179 g, 1.49 mmol) in water (11 mL) at 0 °C. The mixture was stirred for 10 min before $KMnO_4$ (0.414 g, 2.62 mmol) was added in portions. The mixture was stirred at 0 °C for 3 h before being poured into ice−water. The solids were removed by filtration through a Celite pad and washed with ethyl acetate. The aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), and then purified by flash chromatography (hexane−ethyl acetate 4:1 to 2:1) to give **2** (0.233 g, 60%) as a colorless solid. Mp 91−93 °C. $[\alpha]_D$ +4.0 (*c* 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (d, 1H, J = 9.2 Hz), 4.65 (dd, 1H, J = 7.6, 5.2 Hz), 4.13(dd, 1H, J = 8.3, 5.8 Hz), 3.84−4.01 (m, 5H), 3.88 (s, 3H), 3.13 (dd, 1H, J = 18.6, 8.3 Hz), 2.86 (dd, 1H, J = 18.6, 5.2 Hz), 2.00 (s, 3H), 1.51 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H) ppm. EIMS (*m*/*z*, %) 502 (M^+ − Me, 21.86), 402 (47.26), 245 (49.21), 143 (95.82), 73 (100). IR (KBr) 2992, 2953, 2857, 1732, 1666, 1535, 1372,1263 cm^{-1}. Anal. Calcd for $C_{24}H_{43}NO_9Si$: C, 55.68; H, 8.37; N, 2.71. Found: C, 55.90; H, 8.61; N, 2.49.

(4*S*,5*R*,6*R*,7*R*,8*R*)-N^5-Acetyl-4,5-*O*,*N*-isopropylidene-6,7:8,9-di-*O*-isopropylidene-1-nonyne (25). To a solution of **3** (2.01 g, 5.89 mmol) in DMF (30 mL) were added 2,2-dimethoxylpropane (7.6 mL, 60 mmol) and *p*-toluansulfonic acid (115 mg, 0.59 mmol). The reaction mixture was heated to 70 °C for 48 h. Triethylamine (0.1 mL) was added to neutralize the reaction mixture. The solvent was evaporated in vacuo. The residue was purified by column chromatography (hexane−ethyl acetate 4:1) to give **25** (1.63 mg, 73%) as a colorless solid. Mp 120−122 °C. $[\alpha]_D^{20}$ +20.6 (*c* 1.15, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 4.40 (dd, 1H, J = 8.6, 5.9 Hz), 4.23−4.27 (m, 2H), 4.18 (dd, 1H, J = 8.5, 6.0 Hz), 4.06 (ddd, 1H, J = 8.5, 6.0, 5.2), 3.90 (dd, 1H, J = 8.5, 5.2 Hz), 3.64 (dd, 1H, J = 8.5, 8.0 Hz), 2.44−2.62 (m, 2H), 2.19 (s, 3H), 2.01 (s, 1H), 1.61 (s, 6H), 1.45 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H) ppm. EIMS (*m*/*z*, %) 366 (M^+ − CH_3, 6.34), 323 (13.87), 265 (15.50), 180 (29.67), 138 (100.00). IR (KBr) 2991, 2939, 2909, 2125, 1653, 1403, 1373 cm^{-1}. Anal. Calcd for $C_{20}H_{31}NO_6$: C, 62.97; H, 8.19; N, 3.67. Found: C, 62.72; H, 8.05; N, 3.32.

(4*S*,5*R*,6*R*,7*R*,8*R*)-N^5-Acetyl-4,5-*O*,*N*-isopropylidene-6,7:8,9-di-*O*-isopropylidene-1-nonynyl Bromide (26). To a solution of **25** (1.57 g, 4.13 mmol) in acetone (35 mL) were added NBS (1.03 g, 5.31 mmol) and silver acetate (280 mg,

1.67 mmol). The reaction mixture was stirred at room temperature in the dark for 10 h. The solids were removed by filtration through a Celite pad and washed with ether. The combined organic layers were successively washed with water and brine and dried (Na_2SO_4). Concentration of the filtrates afforded crude **26** (1.90 g, 100%), which could be directly used in the next step. A further purification was carried out by column chromatography (hexanes−ethyl acetate 5:1) and afforded pure **26** (87.4%) as a colorless solid. $[\alpha]^{20}_D$ +40.9 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz,$CDCl_3$) δ 4.40 (ddd, 1H, J = 8.4, 5.1, 1.2 Hz), 4.28−4.19 (m, 3H), 4.07 (dt, 1H, J = 8.4, 5.4), 3.91 (dd, 1H, J = 8.7, 5.4 Hz), 3.57 (dd, 1H, J = 8.7, 7.6 Hz), 2.48−2.63 (m, 2H), 2.20 (s, 3H), 1.66 (s, 3H), 1.60 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H) ppm. EIMS (*m*/*z*, %) 445 ($M^+ - CH_3$, 36.28), 443 ($M^+ - CH_3$, 36.28) 402 (18.10), 400 (17.82), 344 (17.22), 342 (17.90) 43 (100.00). IR (KBr) 2993, 2944, 1655, 1406, 1372, 1095 cm^{-1}. Anal. Calcd for $C_{20}H_{30}NO_6B_r$: C, 52.18; H, 6.57; N, 3.04. Found: C, 52.02; H, 6.49; N, 2.97.

(4*S*,5*R*,6*R*,7*R*,8*R*)-2-Oxo-*N*^{5}-Acetyl-4,5-*O*,*N*-isopropylidene-6,7:8,9-di-*O*-isopropylidene-1-nonanoic Acid Methyl Ester (27). To a solution of **26** (1.95 g, 4.23 mmol) in MeOH stirred at 0 °C (65 mL) was added a solution of $NaHCO_3$ (0.22 g) and $MgSO_4$ (1.04 g) in water (65 mL). The mixture was stirred for 10 min. $KMnO_4$ (1.70 g, 10.6 mmol) was added in portions. The mixture was stirred at 0 °C for another 3 h before being poured into ice−water. The solids were removed by filtration through a Celite pad and washed with ethyl acetate. The aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), and then purified by flash chromatography (hexane−ethyl acetate 4:1 to 2:1) to give **27** (1.02 g, 54%) as a yellow oil. $[\alpha]^{20}_D$ −12.7 (*c* 0.5, $CHCl_3$) (ref 5j $[\alpha]^{20}_D$ −11.9 (*c* 1.46, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.8 (dd, 1H, J = 7.3, 6.1 Hz), 4.24−4.15 (m, 3H), 4.02 (dt, 1H, J = 8.6, 6.1 Hz), 3.93−3.96 (m, 1H), 3.89 (s, 3H), 3.75 (dd, 1H, J = 8.6, 7.9 Hz), 3.29 (dd, 1H, J = 17.7, 6.1 Hz), 3.14 (dd, 1H, J = 17.7, 7.3 Hz), 2.16 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.45 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H) ppm. EIMS (*m*/*z*, %) 444 (M^+ + 1, 35.43), 428 (27.89), 389 (83.27), 242 (66.78), 200 (97.18), 43 (100.00). IR (KBr) 2989, 2939, 1733, 1656, 1402, 1374,1259, 1064, 848 cm^{-1}.

Neu5Ac Methyl Ester (23): Method 1. To a solution of compound **2** (50 mg, 0.096 mmol) in acetonitrile (3 mL) in a plastic bottle was added an aqueous solution of HF (40%, 0.2 mL). The reaction mixture was stirred at room temperature for 48 h. The solution was brought to pH 6 by addition of saturated aqueous $NaHCO_3$. The solvent was removed. The precipitates were washed with ethanol twice. The combined organic phases were dried over $NaSO_4$, concentrated in vacuo, and purified by chromatography (chloroform−methanol 4:1) to give **23** (14 mg, 45%) as a colorless solid. $[\alpha]_D$ −23.4 (*c* 1.0, CH_3OH) (ref 12 $[\alpha]_D$ −27 (*c* 1, CH_3OH)). ^{1}H NMR (300 MHz, CD_3OD) δ 3.99−4.11 (m, 1H), 3.99 (1H, dd, J = 10.6, 1.5 Hz), 3.77−3.84 (m, 2H), 3.77 (s, 3H), 3.67−3.73 (m, 1H), 3.61 (dd, 1H, J = 11.1, 5.6 Hz), 3.47 (dd, 1H, J = 9.1, 1.5 Hz), 2.21 (dd, 1H, J = 12.9, 5.0 Hz), 2.01 (s, 3H), 1.88 (dd, 1H, J = 12.9 Hz, 11.4 Hz) ppm. ESI-MS (*m*/*z*, %) 346 (M^+ + 23, 100). IR (KBr): 3298, 1741, 1635, 1557, 1440, 1127, 1034 cm^{-1}.

Method 2. To a solution of **27** (2.21 g, 4.97 mmol) in acetonitrile (180 mL) in a plastic bottle was added an aqueous solution of HF (40%, 46 mL). The reaction mixture was stirred at room temperature for 1 h. The solution was brought to pH 6 by addition of saturated aqueous $NaHCO_3$. The solvent was removed. The precipitates were washed with ethanol twice. The combined organic phases were dried over $NaSO_4$ and concentrated in vacuo. The residue was purified by chromatography (chloroform−methanol 4:1) to give **23** (1.05 g, 65%) as a colorless solid.

Neu5Ac Methyl Ester *O*^{2,4,7,8,9}-Pentacetate (24). To a solution of **23** (10 mg, 0.031 mmol) in pyridine (0.7 mL, 8.65 mmol) was added acetic anhydride (0.3 mL, 3.17 mmol). The reaction mixture was stirred overnight at room temperature. The solvent was evaporated in vacuo and the residue was purified by flash chromatography (ethyl acetate−hexane 7:1) to give **24** (11 mg, 50%) as a yellow oil. $[\alpha]_D$ −17.6 (*c* 2.5, $CHCl_3$) (ref 5h $[\alpha]_D$ −13.8 (*c* 0.56, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$) 5.34−5.39 (m, 2H), 5.25 (m, 1H), 5.07 (m, 1H), 4.49 (dd, 1H, J = 12.2, 2.4 Hz), 4.09−4.15 (m, 3H, 3.79 (s, 3H), 2.55 (dd, 1H, J = 13.5, 4.9 Hz), 2.09 (dd, 1H, J = 13.5, 10.1 Hz), 2.15 (s, 6H), 2.09 (s, 3H), 2.04 (s, 6H), 1.90 (s, 3H). ESI-MS (*m*/*z*, %) 556 (M^+ + 23, 100). IR (neat) 3377, 2927, 2856, 1749, 1689, 1666, 1373, 1232, 1038 cm^{-1}.

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Supporting Information Available: X-ray crystallographic data (CIF file) and an X-ray crystallography image of compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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