Indium-Mediated Coupling of α-(Bromomethyl)acrylic Acid with Carbonyl Compounds in Aqueous Media. Concise Syntheses of (+)-3-Deoxy-D-*glycero*-D-*galacto*-nonulosonic Acid and *N*-Acetylneuraminic Acid

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Indium mediates the coupling of α-(bromomethyl)acrylic acid with carbonyl compounds in aqueous media to give the corresponding γ-hydroxy-α-methylene carboxylic acids. The reaction has been applied to the syntheses of (+)-3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid and *N*-acetylneuraminic acid.

Introduction

During the past decade, a number of metal-mediated coupling reactions in aqueous media have been developed.[1-3] Metals that have been utilized for these reactions include tin, zinc, and, more recently, indium.[4] Indium is considered to be particularly effective because the reaction requires no activation and produces few side products. Such organometallic-type reactions in aqueous media offer the practical advantage of not requiring flammable and/or anhydrous organic solvents.

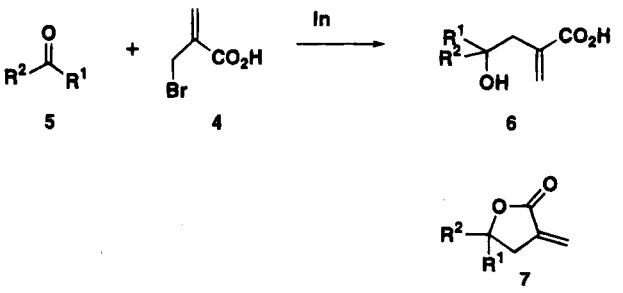
Another obvious consequence of the aqueous media is that hydroxy functional groups do not require protection at the carbon–carbon bond formation step. This is particularly useful in the area of carbohydrate chemistry since the water-soluble carbohydrate molecules can react directly without the protection–deprotection often required in conventional carbohydrate chemistry. Previous work in our laboratory[5] demonstrated the advantage of such reactions in a concise synthesis of (+)-3-deoxy-D-*glycero*-D-*galacto*-nonulosonic acid (KDN, **1**) that was based on an indium-mediated coupling reaction (Scheme 1). Recently, a similar approach has been applied to the synthesis of *N*-acetylneuraminic acid (**2**).[6] However, in this case, the free acid **2** was not isolated but was converted to the peracetyl derivative. It should be noted that, in the syntheses of both **1** and **2**, the α-(bromomethyl)acrylate ester **3** was used as the coupling reagent.

We recently found that the carboxylic acid function is compatible with the indium-mediated reaction conditions.[7] We here report on the examination of the coupling reactions between α-(bromomethyl)acrylic acid (**4**) and carbonyl compounds mediated by indium in aqueous media.

Results and Discussion

Synthesis of α-Methylene-γ-hydroxy Carboxylic Acids. α-(Bromomethyl)acrylic acid (**4**) reacts directly with carbonyl compounds (**5**) and indium in water to give the corresponding γ-hydroxy-α-methylene carboxylic acids (**6**) in good yields (Table 1). Either aldehydes (entries 1–5) or ketones (entry 6) can be used as the carbonyl component. In the case of cinnamaldehyde (entry 5), the reaction occurred selectively to give the 1,2-addition product. In some cases, the indium powder and the organic substrate "clumped" together into a ball, which rendered the stirring of the reaction mixture difficult, and the reaction proceeded poorly. The problem can be relieved by reducing the volume of water or, more effectively, by the addition of some ethanol (entry 5b). Addition of aprotic solvents such as THF (entry 1b) was ineffective, and in fact, no desired product was obtained at all.

The acids **6** readily cyclized to the corresponding α-methylene-γ-butyrolactones (**7**) in good yields. This



route therefore provides an effective method for the synthesis of **7** which is a common structural feature of many biologically active natural products.[8] More interestingly, the acids **6** are often crystalline compounds (Table 1) and can be purified more readily than the corresponding esters. This is useful in the purification of stereoisomers. For example, in the coupling of **4** with phenylpropanal, the product **6d** was a mixture of syn and anti isomers in a ratio of 62:38. The major syn isomer

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(1) (a) Uneyama, K.; Kamaki, N.; Moriya, A.; Torii, S. *J. Org. Chem.* **1985**, *50*, 5396. (b) Petrier, C.; Einhorn, J.; Luche, J. L. *Tetrahedron Lett.* **1985**, *26*, 1449. (c) Petrier, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910. (d) Einhorn, C.; Luche, J. L. *J. Organomet. Chem.* **1987**, *322*, 177. (e) Wilson, S. R.; Guazzaroni, M. E. *J. Org. Chem.* **1989**, *54*, 3087.

(2) (a) Chan, T. H.; Li, C. J.; Wei, Z. Y. *J. Chem. Soc., Chem. Commun.* **1990**, 505. (b) Chan, T. H.; Li, C. J. *Organometallics* **1990**, *9*, 2649. (c) Li, C. J.; Chan, T. H. *Organometallics* **1991**, *10*, 2548. (d) Chan, T. H.; Li, C. J. *Can. J. Chem.* **1992**, *70*, 2726.

(3) (a) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (b) Li, C. J. Ph.D. Thesis, McGill University, 1992.

(4) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017.

(5) Chan, T. H.; Li, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 747.

(6) Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 7937.

(7) (a) Mattes, H.; Benezra, C. *Tetrahedron Lett.* **1985**, *26*, 5697. (b) Uneyama, K.; Ueda, K.; Torii, S. *Chem. Lett.* **1986**, 1201. (c) Talaga, P.; Schaeffer, M.; Benezra, C.; Stampf, J.-L. *Synthesis* **1990**, 530. (d) Chan, T. H.; Li, C. J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181.

(8) For reviews, see: (a) Grieco, P. A. *Synthesis* **1975**, 67. (b) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625.

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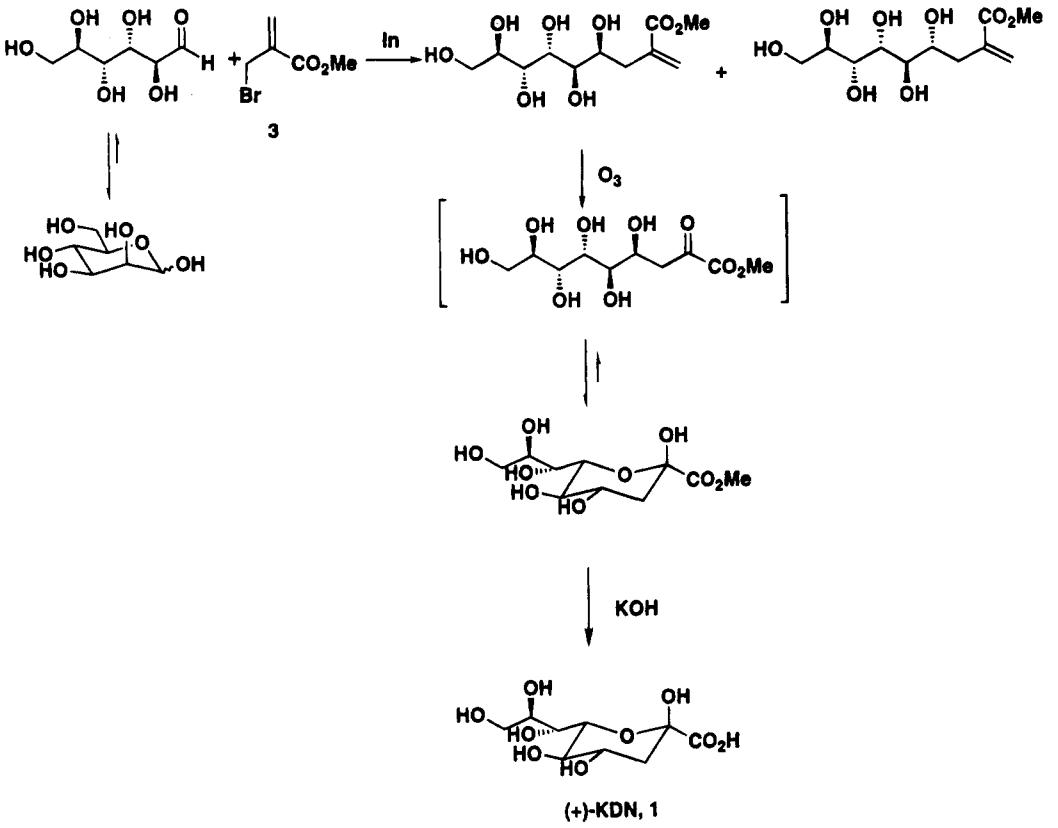
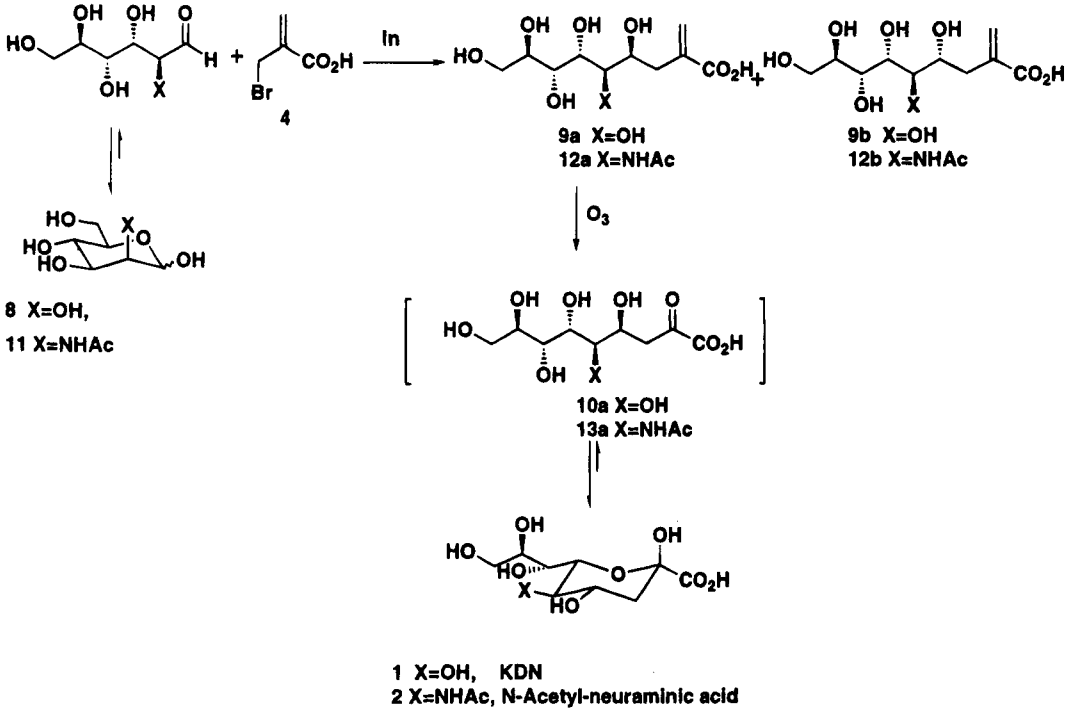
Scheme 1



Scheme 2. Synthesis of KDN and Neu5NAc



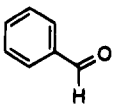
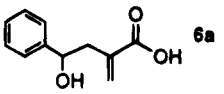
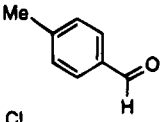
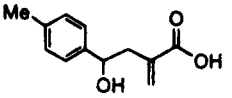
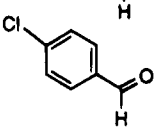
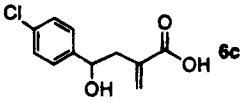
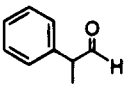
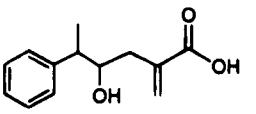
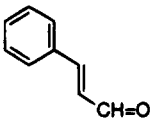
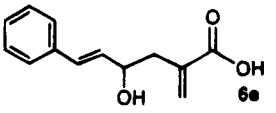
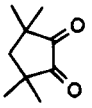
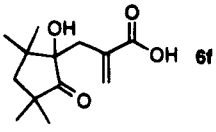
could be crystallized out. This ease of crystallization proved to be useful in the syntheses of KDN and *N*-acetylneuraminic acid.

Synthesis of (+)-3-Deoxy-D-*glycero*-D-*galacto*-nonulosonic Acid (KDN). KDN (**1**) was first isolated by Inoue[9] and co-workers from the membrane polysialoglycoproteins (PSGP) of *Salmo gaidneri* (rainbow trout) eggs. A number of chemical syntheses of KDN, including our own,[5] have been previously reported. Of special interest is the enzymic synthesis of KDN using aldolase.[10] We found that reaction of α-(bromomethyl)acrylic acid (**4**) with D-(+)-mannose (**8**) and indium powder (**4**:**8**:In =

(9) Nadano, D.; Iwasaki, M.; Endo, S.; Kitajima, K.; Inoue, S.; Inoue, Y. *J. Biol. Chem.* **1986**, *261*, 11550.

(10) Lin, C. H.; Sugar, T.; Halcomb, R. L.; Ichikawa, Y.; Wong, C. H. *J. Am. Chem. Soc.* **1992**, *114*, 10138.

Table 1. Allylation of Carbonyl Compounds with α-(Bromomethyl)acrylic Acid[a]

Entry	Carbonyl compound	solvent	product(6)	product m.p.(°C)	% isolated yield (yield based on ^{1}H nmr)
1a		H_2O	 6a	109	82(92)
1b		THF/H_2O(20%)			0
1c		EtOH/H_2O(20%)			74(85)
2		H_2O	 6b	121-122	80(88)
3		H_2O	 6c	123	93(96)
4		H_2O	 6d	124[b]	29[b](89)[c]
5		H_2O	 6e	111	(39[d])
5b		EtOH/H_2O(20%)			55(89)
6		H_2O	 6f	118	76(90)

[a] Reactions were carried out on α-(bromomethyl)acrylic acid/In/carbonyl (1:1:1) at room temperature for 8 h. [b] Only the syn isomer was crystallized out. [c] Syn:anti = 62:38. [d] Incomplete reaction due to the clumping of reaction components.

2:1:2) at room temperature in water after 8 h resulted in about 78% consumption of the the mannose, as estimated from the ^{1}H NMR spectrum of the product mixture. When the ratio of **4** and indium was increased to four relative to the mannose (**4**:**8**:In = 4:1:4), the mannose was completely consumed after 11 h of reaction time. After lyophilization of the reaction mixture, the resulting crude white powder was washed with ethyl acetate/hexane (3:1 v:v) to give a diastereomeric mixture of **9a** and **9b** in a ratio of 5:1. The pure diastereomer **9a** could be crystallized from ethyl acetate/methanol in 64% yield (based on mannose). Ozonolysis of **9a** in methanol at −78 °C afforded the keto acid **10** which cyclized to (+)-KDN in 95% yield. This is perhaps the most efficient synthesis of KDN in view of the high overall yield and the high purity of the product obtained.

Synthesis of 5-Acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-ulosonic Acid (*N*-Acetylneuraminic Acid, Neu5NAc). Neu5NAc (**2**), the sialic acid occurring in the human species,[11] is found at the nonreducing terminus of oligosaccharides on the cell surface. These cell-surface oligosaccharides are associated with a variety of cell functions such as adhesion,[12] recognition, and growth regulation.[13] Neu5NAc is thought to play an important role in these biological processes.[14] Many syntheses of Neu5NAc have been reported,[6,15] including a recent enzymic synthesis.[16]

(11) (a) Corfielf, A. P.; Schauer, R. In *Sialic acids, Chemistry, Metabolism and Function*; Schauer, R., Ed.; Springer-Verlag Wien: Vienna, 1982; Vol. 11, pp 5–50. (b) Reutter, W.; Kottgen, E.; Bauer, C.; Gerok, W. In *Sialic acids, Chemistry, Metabolism and Function*; Schauer, R., Ed.; Springer-Verlag, Wien: Vienna, 1982; Vol. 10, pp 263–305.

(12) Hirabayashi, Y.; Hyogo, A.; Nakao, T.; Tsuchiya, K.; Suzuki, Y.; Matsumoto, M.; Kon, K.; Ando, S. *J. Biol. Chem.* **1990**, *265*, 8144.

(13) (a) Polivkova, J.; Vosmikova, K.; Horak, L. *Neoplasma* **1992**, *39*, 233. (b) Ebel, F.; Schmidt, E.; Peter-Katalinic, J.; Kniep, B.; Muhlradt, P. F. *Biochemistry* **1992**, *31*, 12190.

(14) (a) Philips, M. L.; Nudelman, E.; Gaeta, F. C. A.; Perez, M.; Singhal, A. K.; Hakomori, S.; Paulson, J. C. *Science* **1990**, *250*, 1130. (b) Springer, T. A.; Lasky, L. A. *Nature* **1991**, *349*, 196.

When we applied our procedure to the coupling of **4** with *N*-acetyl-D-(+)-mannosamine (**11**), there were some difficulties. Even when the ratio of **4** and indium was increased to 12 times the amount of **11**, a large amount of **11** remained unreacted. The maximum yield of the expected product **12** was estimated to be about 12%. However, when ethanol was used as the solvent with the addition of 0.1 N HCl, the coupling of **4** with **11** mediated by indium occurred smoothly to give 77% of the expected product **12**, as a powder after ion-exchange column chromatography. The threo:erythro ratio was found to be 3:1 according to the ^{1}H NMR spectrum. Extensive efforts to crystallize the major isomer out at this stage proved to be unsuccessful. Ozonolysis of **12** in THF/water (9:1) at −60 °C gave a mixture of Neu5NAc (**2**) and its 4-epimer (**2b**) (**2**:**2b** = 3:1) as a white powder in 74% yield. Recrystallization of the mixture from ether/wet methanol afforded pure (+)-Neu5NAc, identical in all respects with an authentic sample.

Summary. Coupling of lower monosaccharides with α-(bromomethyl)acrylic acid mediated by indium gives the corresponding adducts in good yields. Conversion of the methylene moiety into the keto function by ozonolysis provides a facile synthesis of higher ulosonic acids. In that sense, the indium/α-(bromomethyl)acrylic acid combination can be considered to be the equivalent of phosphoenolpyruvate used in enzymic synthesis. It is interesting to note that both chemical and enzymic couplings give similar stereochemical results.[16]

Experimental Section

Melting points (mp) are uncorrected. The ^{1}H NMR spectra were recorded on a 200 or 500 MHz spectrometer, and chemical shifts are reported in the δ scales in parts per million (ppm) with solvent residue as references. Singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (b) were recorded at the center of the peaks and are used throughout. ^{13}C NMR spectra were recorded on a 50 or 125 MHz spectrometer.

Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plastic-backed plates and was visualized by dipping into a solution of ammonium molybdate (2.5 g) and ceric sulfate (1 g) in concentrated H_2SO_4/H_2O (10 mL/90 mL) and heated with a heat gun.

Solvents were reagent grade unless otherwise specified. THF was dried and distilled from Na. Indium powder (150 mesh, 99.99%, 5 g packing) was freshly opened for use and stored under argon after use. α-(Bromomethyl)acrylic acid was recrystallized from EtOAc/hexane and used in 2 weeks when stored below 0 °C under argon. Carbonyl compounds were checked for purity by ^{1}H NMR and were distilled or recrystallized if impure. Dowex-1X8-100 resin was purified by eluting with 0.1 N HCl, washed with deionized water thoroughly until the water washing became colorless, and then dried on vacuum suction (water aspirator) for over 2 days. Dowex 50X2-100 resin (chloride form) was washed with deionized water and converted into the formate form by eluting with 1 N formic acid.

Ozonolysis was carried out by bubbling ozone at a flow rate of 0.7 mL/min within the desired time. Lyophilization was done on a Labcono (12 L) freeze-drying machine with the sample prefreezed.

General Method for Allylation of Carbonyl Compounds. To a mixture of α-(bromomethyl)acrylic acid (**4**, 165 mg, 1.0 mmol), carbonyl compound (1.0 mmol), and water or 20% ethanol/water (5 mL) in a 5 mL round-bottomed flask was added indium powder (115 mg, 1.0 mmol) at room temperature while the mixture was stirred vigorously. The reaction mixture kept being stirred and gradually became milky white. After 8 h, the pH value was between 2.5 and 3.0 (pH paper). The mixture was then filtered through a plug of Celite, water (10 mL) was added, and the mixture was extracted with ethyl acetate/hexane (3:1 v:v, 2 × 15 mL). The organic portion was dried (Na_2SO_4) and the solvent evaporated. Recrystallization of the residue from the appropriate solvent (EtOAc/hexane or CH_2Cl_2/hexane) gave the products as crystals.

γ-Hydroxy-α-methylene-4-phenylbutanoic acid (6a): mp 109 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) 2.67 (ddd, J = 18.6, 13.3, and 4.4 Hz, 2H), 4.92 (dd, J = 8.2 and 4.6 Hz, 1H), 5.69 (bs, 1H), 6.37 (d, J = 1.2 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) 42.4, 73.7, 126.2, 128.1, 128.9, 131.3, 136.8, 144.1, 172.7; IR (KBr) 3397, 2925, 1698, 1631, 1449, 1412, 1043, 1015, 745, 715 cm^{-1}; MS (FAB) m/z 193 (M + 1); HRMS (EI) calcd for $C_{11}H_{10}O_2$ (M − H_2O) 174.0681, found 174.0685.

γ-Hydroxy-α-methylene-4-(4′-methylphenyl)butanoic acid (6b): mp 121−122 °C; ^{1}H NMR (acetone-d_6, 200 MHz) 2.27 (s, 3H), 2.62 (dd, J = 3.5 and 1.1 Hz, 1H), 2.65 (collapsed dd, J = 1.3 Hz, 1H), 4.30 (br, 1H), 4.83 (dd, J = 7.5 and 5.8 Hz, 1H), 5.59 (d, J = 1.8 Hz, 1H), 6.14 (d, J = 1.8 Hz, 1H), 7.17 (AB, J = 8.0 Hz, 4H); ^{13}C NMR (acetone-d_6, 50 MHz) 25.9, 48.1, 77.6, 131.4, 132.7, 134.2, 141.8, 143.5, 148.2, 173.5; MS (FAB) m/z 207 (M + 1); HRMS (EI) calcd for $C_{12}H_{12}O_2$ (M − H_2O) 188.0837, found 188.0839.

γ-Hydroxy-α-methylene-4-(4′-chlorophenyl)butanoic acid (6c): mp 123 °C; ^{1}H NMR (acetone-d_6, 200 MHz) 2.65 (dd, J = 18.6 and 8.2 Hz, 2H), 2.68 (dd, J = 18.6 and 4.5 Hz, 1H), 4.55 (bs, 1H), 4.91 (dd, J = 8.2 and 4.5 Hz, 1H), 5.63 (s, 1H), 6.19 (s, 1H), 7.37 (AB, J = 5.9 Hz, 4H), 10.90 (br, 1H); ^{13}C NMR (acetone-d_6, 50 MHz) 42.4, 73.7, 126.2, 128.1, 128.9, 131.3, 136.8, 144.1, 172.7; IR (KBr) 3399, 1696, 1653, 1411, 1452 cm^{-1}; MS (FAB) m/z 227 (M + 1); HRMS (EI) calcd for $C_{11}H_9ClO_2$ (M − H_2O) 208.0291, found 208.0294.

γ-Hydroxy-α-methylene-5-phenylhexanoic acid (6d): major (syn) isomer; mp 124 °C; ^{1}H NMR (acetone-d_6, 500 MHz) 1.32 (d, J = 6.8 Hz, 3H), 2.18 (dd, J = 14.2 and 9.3 Hz, 1H), 2.42 (dd, J = 14.2 and 2.4 Hz, 1H), 2.73 (quintet, J = 6.8 Hz, 1H), 3.78 (br, 1H), 3.89 (ddd, J = 9.3, 6.8, and 2.4 Hz, 1H), 5.62 (s, 1H), 6.16 (s, 1H), 7.18 (m, 1H), 7.27 (m, 4H), 10.81 (br, 1H); ^{13}C NMR (acetone-d_6, 50 MHz) 19.9, 41.0, 49.1, 76.4, 127.7, 128.1, 129.5, 129.8, 140.2, 146.9, 169.2; MS (FAB) m/z 221 (M + 1); HRMS (EI) calcd for $C_{13}H_{14}O_2$ (M − H_2O) 202.0994, found 202.0998.

γ-Hydroxy-α-methylene-6-phenylhex-5-enoic acid (6e): mp 111 °C; ^{1}H NMR (acetone-d_6, 200 MHz) 2.60 (AB of ABX, J = 13.7, 7.3, and 5.9 Hz, 2H), 4.45 (dtd, J = 7.3, 5.9, and 1.2 Hz, 1H), 5.73 (d, J = 1.8 Hz, 1H), 6.22 (d, J = 1.8 Hz, 1H), 6.31 (dd, J = 16.0 and 5.9 Hz, 1H), 6.65 (dd, J = 16.0 and 1.2 Hz, 1H), 7.33 (m, 5H); ^{13}C NMR (acetone-d_6, 50 MHz) 80.7, 91.2, 115.5, 148.9, 147.6, 147.8, 149.0, 149.6, 153.8, 158.2, 188.2; IR (KBr) 3362, 2917, 1698, 1632, 1039, 1012, 749 cm^{-1}; MS (FAB) m/z 241 (M + 23); HRMS (EI) calcd for $C_{13}H_{12}O_2$ (M − H_2O) 200.0837, found 200.0832.

γ-Hydroxy-α-methylene-3-(2′-oxo-3′,3′,5′,5′- tetramethylcyclopentanyl)propanoic acid (6f): mp 118 °C; ^{1}H NMR (CD_2Cl_2, 200 MHz) 0.97 (s, 3H), 1.09 (s, 3H), 1.60 (s, 3H), 1.77 (s, 3H), 1.80 (AB, J = 13.5 Hz, 2H), 2.67 (AB, J = 14.8 Hz, 2H), 5.77 (s, 1H), 6.41 (s, 1H); ^{13}C NMR (CD_2Cl_2, 50 MHz) 24.3, 25.3, 28.8, 34.8, 40.8, 41.4, 49.3, 83.3, 131.0, 134.4, 171.2, 221.9; IR (KBr) 3446, 2932, 1729, 1681, 1650, 1618, 1459 cm^{-1}; MS (FAB) m/z 263 (M + 23); HRMS (EI) calcd for $C_{13}H_{18}O_3$ (M − H_2O) 222.1256, found 222.1259.

Synthesis of (+)-3-Deoxy-D-*glycero*-D-*galacto*-nonulosonic Acid (KDN). 4,5,6,7,8,9-Hexahydroxy-2-methylene-D-nonanoic Acid (9a). To a solution of D-(+)-mannose (**8**, 360 mg, 2.0 mmol) and α-(bromomethyl)acrylic acid (**4**, 1.32 g, 8.0 mmol) in water (20 mL) stirred at room temperature was added powdered indium (920 mg, 8.0 mmol), and the mixture was stirred for 11 h. The reaction mixture was filtered through a plug of Celite and the Celite rinsed with water (20 mL). The combined filtrate was deionized with Dowex 50X2-

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100(H^+) resin (3 g dried weight). The resin was again filtered and the aqueous solution lyophilized. The resulting white powder was washed with ethyl acetate/hexane (3:1 v:v) solution (15 mL) to remove exess **4**. The residue was shown to be a mixture of **9a** and **9b** (5:1) by ^1H NMR. The isomeric mixture was then crystallized from methanol/ethyl acetate to give pure **9a** (335 mg, 64%): mp 194 °C (under argon in sealed tube); ^1H NMR (D_2O, 500 MHz) 2.53 (dd, J = 14.0 and 5.5 Hz, 1H), 2.55 (dd, J = 14.0 and 8.0 Hz, 1H), 3.52 (dd, J = 9.5 and 1.5 Hz, 1H), 3.60 (dd, J = 11.7 and 6.0 Hz, 1H), 3.70 (ddd, J = 9.0, 6.0, and 3.0 Hz, 1H), 3.76 (d, J = 9.0 Hz, 1H), 3.81 (dd, J = 11.7 and 3.0 Hz, 1H), 3.84 (d, J = 9.5 Hz, 1H), 4.06 (ddd, J = 8.0, 5.5, and 1.5 Hz, 1H), 5.64 (s, 1H), 6.11 (s, 1H); ^{13}C NMR (D_2O, 125 MHz) 39.7, 66.7, 71.8, 71.9, 72.7, 74.3, 74.5, 131.8, 139.4, 173.4; IR (KBr) 3357, 2923, 1692, 1682, 1653, 1622, 1087, 1025 cm^{-1}; MS (FAB) m/z 267 (M + 1); HRMS (CI − NH_3) calcd for $C_{10}H_{20}O_7N$ (M + NH_4 − H_2O) 266.1240, found 266.1226.

(+)-3-Deoxy-D-*glycero*-D-*galacto*-nonulosonic Acid (KDN, 1). A solution of **9a** (150 mg, 0.56 mmol) in methanol (25 mL) was bubbled with O_3 for 30 min at −78 °C. A quantity of Na_2SO_3 (150 mg, 1.2 mmol) was then added, and the solution was stirred overnight. After filtration and evaporation of the solvent, a white powder (144 mg, 95%) was obtained. ^1H NMR (with a trace amount of methanol left) of the product showed it to have characteristics identical to those of **1** reported in the literature.[10]

Synthesis of 5-Acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-ulosonic Acid (2, Neu5NAc). 5-Acetamido-2,3,5-trideoxy-2-methylidene-D-*glycero*-D-*galacto*-nononic Acid (12). To a mixture of *N*-acetyl-β-D-mannosamine (**11**, 957 mg, 4.0 mmol) and α-(bromomethyl)acrylic acid (**4**, 3.96 g, 24.0 mmol) in EtOH (24 mL) and 0.1 N HCl (4 mL) was added indium powder (1.84 g, 16.0 mmol) while the mixture was stirred. The reaction mixture was heated at 40 °C with a sealed cap. After 12 h, the small indium clump was removed from the solution, extra indium powder (920 mg, 8 mmol) was added, and the mixture was kept heated for another 12 h. After being cooled to room temperature, the mixture was filtered through a plug of Celite, and the Celite plug was rinsed with water (30 mL). The combined aqueous solution was deionized with Dowex 50X2-100(H^+) (5 g dried weight), filtered, and evaporated to dryness below 30 °C. Water (10 mL) was added, and the precipitate was filtered. The filtrate was lyophilized to give a colorless syrup which was chromatographed on Dowex 1X8-100(formate form) anion exchange resin by eluting with a O−2N formic acid gradient. The fractions (TLC (^{i}PrOH:H_2O = 7:3 v:v) R_f = 0.44 (tailing)) containing the desired product were pooled together and lyophilized to give a colorless crystalline **12** (943 mg, 77% with threo:erythro = 3.1, which was not separable). Threo-**12**: ^1H NMR (500 MHz, D_2O) 2.03 (s, 3H), 2.41 (dd, J = 14.0 and 7.6 Hz, 1H), 2.46 (dd, J = 14.0 and 6.0 Hz, 1H), 3.69 (ddd, J = 8.9, 6.2, and 2.7 Hz, 1H), 3.79 (dd, J = 11.5 and 2.7 Hz, 1H), 3.88 (d, J = 10.3 Hz, 1H), 3.92 (d, J = 10.3 Hz, 1H), 4.29 (dd, J = 7.6 and 6.0 Hz, 1H), 5.70 (s, 1H), 6.21 (s, 1H); ^{13}C NMR (D_2O, 125 MHz) 21.7, 36.3, 52.7, 62.9, 67.3, 67.4, 69.0, 70.3, 128.2, 174.2.

5-Acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-ulosonic Acid (2, Neu5NAc). A solution of **12** (128 mg, 0.39 mmol) in 9:1 THF/water (5 mL) was ozonized at −60 °C for 15 min. Oxygen was then bubbled through the solution for 10 min at 0 °C. After evaporation of the water, a white powder was obtained (89 mg, 74% with Neu5NAc:epi-Neu5NAc = 3.1). To the powder were added ~0.5 mL of D_2O, methanol (5 mL), and ether (8 mL). The cloudy solution was filtered through Celite, and ether (8 mL) was added to the filtrate. The solution was kept at 0 °C, and ether (5 mL) was added twice every 24 h. The crystals **2** (17 mg, 14% from **12**) were obtained from the solution, and their ^1H NMR (D_2O, 500 MHz) was identical with that of an authentic sample of Neu5NAc.

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Supplementary Material Available: ^1H and/or ^{13}C NMR spectra of **6a−f**, **9a**, and **12** (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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