Indium-Mediated Stereoselective Synthesis of Truncated, 6- and 7-Carbon Sialic Acids

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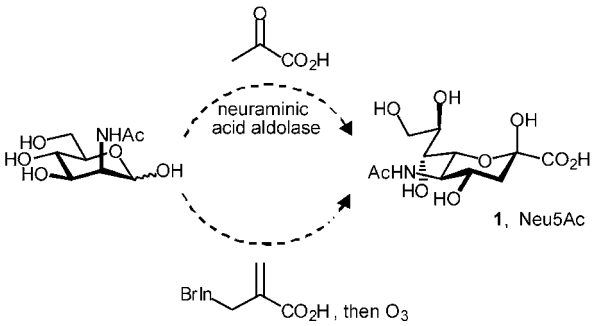
Abstract: Several 6- and 7-carbon sialic acid derivatives were synthesized, without tedious protecting group manipulations, in high overall yields. A key step of the synthesis was the chain extension of suitable α-amino aldehyde derivatives by an indium-mediated addition of ethyl 2-(bromomethyl)acrylate. Under acidic reaction conditions, the corresponding extended enoates were obtained with high *trans*-stereoselectivity. Ozonolysis furnished the desired 4-acylamino-substituted hexulosonic and heptulosonic acids in free form for biochemical studies.

Key words: allylations, Barbier-type reactions, indium, α-amino aldehydes, sialic acids

Sialic acids, having an 8- or 9-carbon backbone, are mainly found as terminal components of cell surface glycoproteins, glycolipids and oligosaccharides[1] that are of decisive importance in many physiological and pathological processes.[2] For an improved understanding of the structure-activity relationship in sialooligosaccharide binding motifs and their metabolism (specifically concerning sialyltransferases and sialosidases) there is a need for a synthetic access to modified and lower homologous, non-natural sialic acid derivatives.

A number of enzymatic[3] and nonenzymatic[4] syntheses of sialic acids have been developed, especially for the most important *N*-acetylneuraminic acid (Neu5Ac, **1**, Scheme 1). In the case of truncated sialic acids having a 6- or 7-carbon backbone, the conventional enzymatic approach fails because C_3 or C_4 aldehyde precursors are generally not, or only very poor, substrates for Neu5Ac aldolase.[5] Therefore, the truncated C_7-sialic acid had usually not been prepared by synthesis, but by an oxidative chain degradation of natural sialooligosaccharides (e.g., by periodate oxidation/borohydride reduction/hydrolysis).[6]

On the other hand, the length of an aldehyde precursor poses, in principle, no limitation to the most notable chemical route, which is the indium-mediated chain extension of unprotected aldoses leading to common C_8 and C_9 sialic acids.[4] To our knowledge however, only three synthetic routes have been explored yet for the preparation of lower sialic acids that do not start from **1** or its conjugates, but using strategies that involve tedious protection-deprotection schemes.[7] In the context of a program to develop new routes towards neo-oligosaccharides containing modified sialic acids[8] we became interested in an efficient synthetic access to truncated sialic acids that would allow for the introduction of structural diversity by the *N*-acyl group. Herein, we report a new synthetic strategy that is based on the preparation of α-amino aldehydes from allylamine precursors, followed by an indium-mediated chain-extension with ethyl 2-(bromomethyl)acrylate. This methodology is known to be compatible with a broad variety of functional groups and thus obviates the need for tedious protective group manipulations.



Scheme 1 Chemical and enzymatic routes for synthesis of *N*-acetylneuraminic acid.

α-Amino aldehydes are notorious for their high chemical reactivity and configurational lability.[9] Some α-amino propionaldehyde derivatives, which would be suitable for our approach, had previously been synthesized starting from the corresponding amino acids.[7,9a] According to our experience, however, ozonolysis of olefinic precursors is a preferable, clean and practical alternative to prepare pure α-amino aldehydes.[10] This procedure renders further purification unnecessary, so that the unstable compounds can be used immediately for further conversions. This is particularly useful for compounds that carry further polar functions as required in this study, such as in 2-amino-2-deoxyglyceraldehyde (**4**) or 2-amino-2-deoxyerythrose (**7**) derivatives.

To obtain suitable olefinic precursors to the desired *N*-protected 2-amino-2-deoxyglyceraldehyde derivatives **4a**/**b** (Scheme 2), cinnamaldehyde (**2**) was converted to (*E*)-2-azido-4-phenyl-3-buten-1-ol according to a literature procedure,[10] and the azide was reduced with triphenylphosphine. *N*-Acylation provided the stable precursors **3a**/**b**. The acetyl and phenylacetyl groups were chosen for *N*-acyl modification, because the former would

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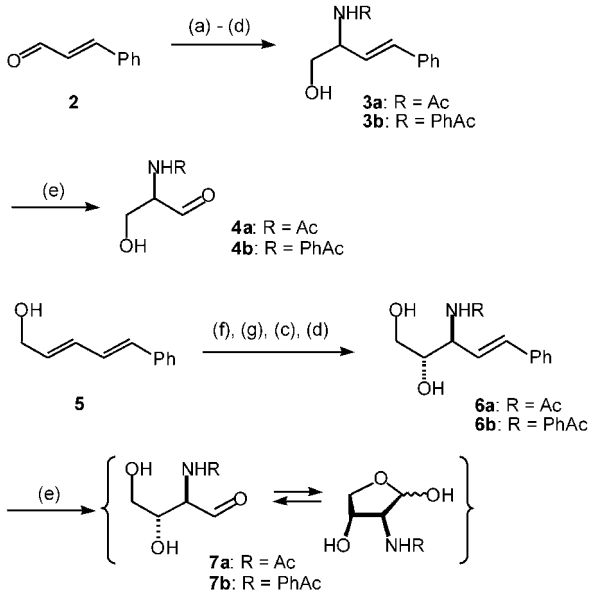
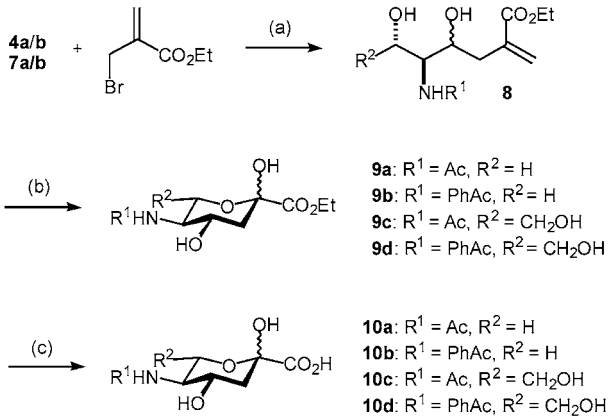
match the natural substitution pattern of neuraminic acid, and the latter would provide a convenient opportunity for further modification at a final product stage because phenylacetyl amides can be hydrolyzed selectively under mild conditions using a penicillin G acylase.[11] Ozonolysis of the styrene moiety in **3a/b** followed by reductive work-up smoothly provided the free aldehydes **4a**/**b** in aqueous solution, which were used immediately for the next step.



Scheme 2 *Reagents and conditions:* (a) $Me_3S^+I^-$, NaH, DMSO–THF; (b) NaN_3, aq acetone; (c) PPh_3, aq THF; (d) Ac_2O, pyridine or PhAcCl, Et_3N, MeOH; (e) O_3, then Me_2S; (f) $VO(acac)_2$, *t*-BuOOH; (g) $[(NMe_2)_2CNH_2]^+N_3^-$.

For the higher homologous precursor to give a C_7 sialic acid analog, a *syn*-arrangement of functional groups was required. The synthesis was similarly designed to start from 5-phenyl-2,4-pentadien-1-ol (**5**, Scheme 2) and involved allyl-selective mono-epoxidation using *tert*-butyl hydroperoxide in the presence of vanadate, followed by epoxide-opening in situ using tetramethylguanidinium azide to afford the corresponding *anti*-configured azido compound in 40% overall yield. Reduction of the azide group and selective *N*-acylation of the resulting amino alcohol produced stable aminodiols **6a**/**b**. Subsequent ozonolysis smoothly generated the desired 2-amino-2-deoxyerythrose derivatives **7a**/**b** which were used directly in the ensuing conversion. In comparison with other methods for the synthesis of *N*-protected α-amino aldehydes,[12,9a] the use of an olefinic precursor indeed proved advantageous in that it offered short reaction sequences and higher overall yields.

The α-amino aldehydes **4a**/**b** and **7a**/**b** generated in situ were used immediately for In-mediated *Barbier*-type reactions with ethyl 2-(bromomethyl)acrylate (Scheme 3).[12] Initially, under neutral reaction conditions only unsatisfactory selectivity was observed (e.g., *threo*:*erythro* ratio for **8a**/**c** = 60:40); very poor stereoselectivity, under neutral reaction conditions, has also been reported recently for the In-mediated methacrylate addition to the corresponding fully protected α-amino aldehyde.[7b] Recently, we had reported that the diastereoselectivity of indium-mediated addition reactions to carbohydrates can be significantly enhanced by employing aqueous acidic reaction conditions.[13] Indeed, we observed that the polar, short-chain aldehydes **4** and **7**, when exposed to the indium reagent system in an acidic ethanol–water mixture, also showed a significantly improved *threo*-diastereoselectivity (**8a**–**d**, consistent *threo*:*erythro* ratio = 83:17), which strongly supports a pronounced stereodiscriminating chelating effect upon protonation of intermediates en route to the transition state.[14] Because of their proclivity for polymerization, the acrylate adducts **8a**–**d** were usually not isolated but ozonized directly. The resultant α-ketoester intermediates spontaneously cyclized to give the truncated sialic acid esters as a mixture of stereoisomers, from which the desired major *threo*-diastereomers **9a**–**d** could be readily isolated by chromatography. The corresponding sialic acids **10a**–**d** were finally obtained by alkaline hydrolysis in 55–70% overall yield (based on the olefinic precursors **3** or **6**; 4 steps).[12]



Scheme 3 *Reagents and conditions*: (a) In, EtOH, aq HCl; (b) O_3, then Me_2S, and chromatographic separation (**9a** 69%, **9b** 67%, **9c** 65%, **9d** 79%); (c) aq LiOH (**10a** 93%, **10b** 90%, **10c** 84%, **10d** 88%).

The synthetic approach described here offers a convenient access to truncated sialic acids, with flexibility to introduce a broad structural variation in the *N*-acyl moiety. Such sialic acids will be of utility for further detailed studies into the substrate tolerance of enzymes involved in the metabolism of sialosides, and they offer new avenues into the preparation of neo-sialooligosaccharides that are of importance for biological studies.[15] It ought to be mentioned that the procedures described above yield racemic products, but that enantiomerically pure materials may be obtained by simple modifications of synthetic methods for their asymmeric variants (e.g., asymmetric epoxidation), or by kinetic resolution during the enzymatic activation to the nucleotide sugars.[8]

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(12) Typical reaction conditions for the indium-mediated allylation: To a solution of the aminoaldehyde (1.0 mmol) and ethyl 2-(bromomethyl)-acrylate[16] (386 mg; 2.0 mmol) in a mixture made from 12.5 mL EtOH and 2.5 mL 0.1 M HCl was added indium powder (230 mg; 2.0 mmol) at r.t. The suspension was vigorously stirred until TLC indicated complete conversion of the starting material, and was then filtered through a pad of Celite. Water was added (20 mL), and the resulting mixture was concentrated to 20 mL under vacuum followed by extraction with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (1 × 20 mL) and water (1 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. Without further purification, the remaining crude colorless solid was taken up in MeOH and treated with ozone at –78 °C. Ozonide reduction (Me_2S, r.t.) followed by flash chromatography provided compounds **9a**–**d** as colorless syrups, which were hydrolyzed by treatment with 2 equivalents of aq LiOH to furnish stereoisomerically pure truncated sialic acid derivatives **10a**–**d**.
Spectroscopic data: **10a**: ^{1}H NMR (300 MHz, D_2O): δ = 3.82 (m, 1 H, 4-H), 3.67 (m, 2 H, 6-H), 3.53 (m, 1 H, 5-H), 2.15 (dd, 1 H, $J_{3eq,3ax}$ = 13.1 Hz, $J_{3eq,4}$ = 4.9 Hz, 3_{eq}-H), 1.90 (s, 3 H, CH_3), 1.69 (dd, 1 H, $J_{3ax,3eq}$ = 13.1 Hz, $J_{3ax,4}$ = 11.2 Hz, 3_{ax}-H); ^{13}C NMR (75 MHz, D_2O): δ = 177.23 (C-1), 175.07 (C=O), 97.75 (C-2), 68.27 (C-4), 63.67 (C-6), 54.36 (C-5), 41.33 (C-3), 24.40 (CH_3); ESI-MS: *m*/*z* = 218 ([M–H]$^-$, 100). **10b**: ^{1}H NMR (300 MHz, D_2O): δ = 7.26–7.38 (m, 5 H, H_{ar}), 3.58 (s, 2 H, CH_2), 3.48–3.96 (m, 4 H, 4-,5-,6-H), 2.14 (dd, 1 H, $J_{3eq,3ax}$ = 13.0 Hz, $J_{3eq,4}$ = 4.8 Hz, 3_{eq}-H), 1.88 (dd, 1 H, $J_{3ax,3eq}$ = 13.0 Hz, $J_{3ax,4}$ = 11.1 Hz, 3_{ax}-H); ^{13}C NMR (75 MHz, D_2O): δ = 178.27 (C=O), 177.98 (C-1), 138.07 (C_i), 131.64, 131.29, 129.63 ($CH_{o,m,p}$), 99.24 (C-2), 69.26 (C-4), 64.19 (C-6), 55.42 (C-5), 45.28 (CH_2), 42.50 (C-3); ESI-MS: *m*/*z* = 318 ([M + Na]$^+$, 100), 300(40). **10c**: ^{1}H NMR (300 MHz, D_2O): δ = 3.65–3.93 (5 H, m, 4-,5-,6-,7-H), 2.32 (1 H, dd, $J_{3eq,3ax}$ = 13.0 Hz, $J_{3eq,4}$ = 5.0 Hz, 3_{eq}-H), 2.04 (3 H, s, CH_3), 1.87 (1 H, dd, $J_{3ax,3eq}$ = 13.0 Hz, $J_{3ax,4}$ = 11.6 Hz, 3_{ax}-H); ^{13}C NMR (75 MHz, D_2O): δ = 177.77 (C-1), 175.1 (C=O), 98.17 (C-2), 75.80 (C-6), 69.39 (C-4), 63.80 (C-7), 55.22 (C-5), 41.91 (C-3), 25.03 (CH_3); ESI-MS: *m*/*z* = 248 ([M – H]$^-$, 100), 230(41). **10d**: ^{1}H NMR (300 MHz, D_2O): δ = 7.28–7.40 (5 H, m, H_{ar}), 3.63 (2 H, s, CH_2), 3.50–3.91 (5 H, m, 4-,5-,6-,7-H), 2.33 (1 H, dd, $J_{3eq,3ax}$ = 12.9 Hz, $J_{3eq,4}$ = 4.9 Hz, 3_{eq}-H), 1.84 (1 H, dd, $J_{3ax,3eq}$ = 12.9 Hz, $J_{3ax,4}$ = 11.8 Hz, 3_{ax}-H); ^{13}C NMR (75 MHz, D_2O): δ = 178.16 (C=O), 175.66 (C-1), 137.72 (C_i), 131.92, 131.78, 130.19 ($C_{o,m,p}$), 97.81 (C-2), 75.70 (C-6), 68.94 (C-4), 63.86 (C-7), 55.16 (C-5), 45.10 (CH_2), 41.79 (C-3); ESI-MS: *m*/*z* = 420 ([M + Na + 4 H_2O]$^+$, 100), 402 ([M + Na + 3 H_2O]$^+$, 95)

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