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Solution Phase Synthesis of (1→5)-Amide Linked Sugar Amino Acid Dimers Derived from Sialic Acids

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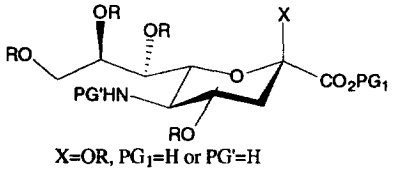
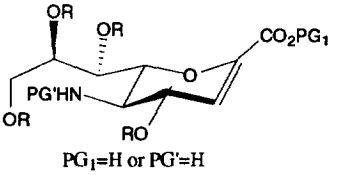
Abstract: Carboxy-protected amino derivatives and amino-protected carboxy derivatives of three different C-2 analogs as well as a 2,3-dehydro NeuAc were prepared. These monomers were coupled in solution using BOP activation of the carboxy terminus to form (1→5)-amide linked dimers of sialyl amino acid derivatives. © 1997 Elsevier Science Ltd. All rights reserved.

Sugar amino acids are carbohydrate based compounds that possess an amino functionality as well as a carboxylic acid.[1] They are components of some naturally occurring antibiotics,[2] and recently they have received considerable attention as substrates for combinatorial synthetic strategies,[3] and as potential peptidomimetics.[4] The sialic acids are naturally occurring sugar amino acids. However the most abundant form, *N*-acetyl neuraminic acid (NeuAc, **1**), possesses an acetamido functionality rather than the required amine. Although amino derivatives of **1** have been prepared,[5] until now they have not been incorporated into polyamide bond forming protocols. We are particularly interested in sialic acid based oligomeric materials since naturally occurring homooligomers of sialic acid, linked through a glycosidic bond, are helical in solution.[6] Amide linked oligomeric materials may also be helical due to restricted rotation about the amide bond. Furthermore, the group at C-2 (X) of the sialyl amino acid monomer unit may play an important role in providing conformationally distinct oligomeric materials. Reported herein are studies describing the synthesis of sialic acid based sugar amino acid monomers suitable for elaboration into oligomers. Solution phase coupling of the monomers to form amide linked dimers is also demonstrated.



X=OR, PG_1=H or PG'=H
X=H, PG_1=H or PG'=H
X=OMe, PG_1=H or PG'=H



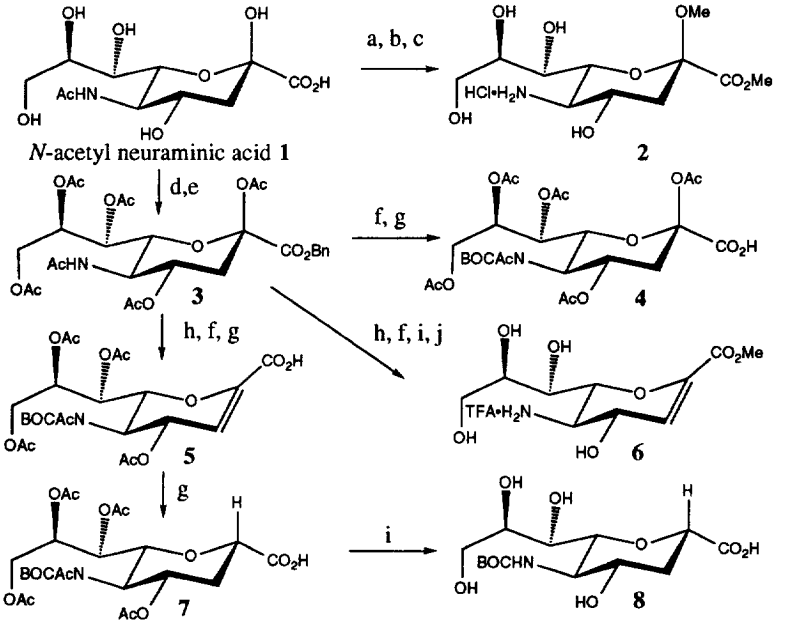
PG_1=H or PG'=H

Figure 1

We envisioned preparing four different classes of monomer units - three differing at the C-2 position and a 2,3-dehydro analog as shown in Figure 1. Synthetic routes to the 2-deoxy-2-hydrido,[7] the 2-methoxy,[8] and the 2,3-dehydro[9] derivatives of NeuAc had previously been established, so *N*-deacylation became our first challenge.

Roy and Pon reported that sialylglycoconjugates can be *N*-deacetylated using NaOH.[10] While this method is suitable for the anomeric methoxy derivative, the hydrido derivative epimerizes under these conditions,[11] and the anomeric hydroxyl undergoes β-elimination. Therefore, alternative routes were sought for these analogs. Selective *N*-deacylation of peracetylated glycosamines can be accomplished with triethyloxonium tetrafluoroborate,[12] and while our substrates underwent alkylation, subsequent hydrolysis failed to provide the desired material. We next explored the possibility of preparing *N-tert*-butyloxycarbonyl derivatives followed by selective hydrazinolysis of the *N*-acetyl functionality.[13] Although the acyl carbamates could be prepared in good yield, the benzyl ester did not survive hydrazinolysis conditions. After attempting several other modifications, we were able to realize our goals using the mild hydrolysis conditions published by Grieco and coworkers.[14] The synthetic strategies are outlined in Scheme 1.

Scheme 1



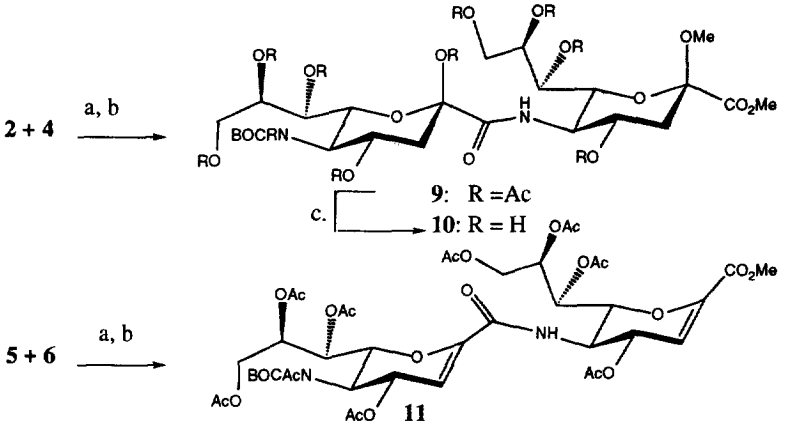
a) MeOH, Dowex H^+, 70°C, 48h, 70% yield. b) 2N NaOH, 100°C, 48h, 72% yield. c) MeOH,/HCl, 70°C, 6h, 93% yield. d) Ac_2O, pyridine, r.t. 18h. e) KF, BnBr, DMF, r.t. 18h, 80% combined yield for d and e. f) BOC_2O, DMAP, CH_2Cl_2, TEA, r.t. 18h, 60% yield. g) H_2, 10% Pd/C, ethanol, 6h, 85% yield for **4**; 12h, 95% for **5**; 18h, 66% for **7**. h) TMSOTf, CH_3CN, 0°C, 9h, 66% yield. i) NaOMe, MeOH r.t. 18h, Dowex H^+/MeOH, 44% yield for **6**; Dowex/H_2O for **8**. j) TFA:MeOH:H_2O 2:1:1, 62% yield.

The β-methyl glycoside of NeuAc methyl ester was prepared by reacting **1** with methanol under acidic conditions.[7] Removal of the *N*-acetyl was accomplished by reacting the methyl glycoside methyl ester with 2N NaOH for 48 hours at 100°C, and the methyl ester was reintroduced by reacting the amino acid with methanolic

HCl to give **2** in 93% yield. Alternatively, NeuAc was reacted with acetic anhydride in pyridine followed by esterification with benzyl bromide in the presence of potassium fluoride to afford **3**.[15] The peracetylated benzyl ester (**3**) was reacted with di-*tert*-butyldicarbonate (BOC_2O) and dimethylaminopyridine (DMAP) to provide an *N*-acetylated carbamate which was subsequently subjected to hydrogenation to afford **4**. Reaction of **3** with 2.2 equivalents of trimethylsilyltriflate at 0°C resulted in elimination of the anomeric acetate to give 2,3 dehydro NeuAc.[16] This material was treated with BOC_2O and partial hydrogenation resulted in selective removal of the benzyl ester, providing **5**. The *N*-acetyl functionality was removed along with the *O*-acetates upon treatment with sodium methoxide. Subsequent reaction with trifluoroacetic acid in methanol/water resulted in removal of the BOC protecting group to give **6**. Further hydrogenation of **5** gave exclusively the axial hydride **7**, and the acetates were removed to give the selectively protected amine (**8**).

With the selectively protected sialyl sugar amino acids in hand, we next studied their solution phase coupling reactions. In the course of our investigations, we discovered that the hydroxyls of the carboxy coupling partner had to be protected in order for coupling to occur. Activation of amino-protected carboxy monomers having free hydroxyls resulted in intramolecular lactone formation rather than dimer formation. Similarly the hydroxyls of the carboxy-protected amino component could not be acetylated, since this created the possibility of acyl transfer from oxygen to nitrogen.

Scheme 2



a) BOP, Hunig's base, DMF, 48h. b) Ac_2O, pyridine, 18h, 27% combined yield for **9** and 21% for **11**. c) NaOMe, MeOH, 18h, 96% yield.

After considerable experimentation, we found that sialyl amino acid dimers could be formed using benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) as a coupling agent. As shown in Scheme 2, reaction of **2** with **4** in the presence of BOP and Hunig's base in dimethylformamide provided the coupled product **9** in 27% yield (after acetylation to simplify characterization). This material was subsequently deacetylated to form the differentially protected dimer **10** in 96% yield. We considered the possibility that the poor coupling yield could be caused by steric congestion of the neopentyl-like carboxy

terminus present in **4**, so a similar coupling involving **5** and **6** was attempted. Here again the coupled product (**11**) was formed in only 21% yield, suggesting that low yields are more likely a consequence of solubility differences between the differentially protected amino and carboxy monomers. One way of overcoming solubility problems is to employ solid support technologies,[4c] and resin bound coupling of the sialyl sugar amino acids prepared in Scheme 1 will be the topic of a forthcoming report from our laboratories.

In summary, we have demonstrated that several sialic acid-based sugar amino acids can be prepared and incorporated into amide linked dimers using solution phase coupling protocols. It is important that the hydroxyl groups of the acid coupling component be protected prior to activation in order to circumvent intramolecular lactone formation. This chemistry is currently being applied in the synthesis of oligomeric compounds with the aim of producing novel helical materials.

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References:

1. Several different terms have been used to describe these compounds including sugar amino acids, carbopeptoids, sugar-like amino carboxylic acids, saccharide-peptide hybrids, and saccharopeptides. In some cases the sugar amino acids are linked to naturally occurring amino acids, whereas in other examples they are completely carbohydrate derived. In order to readily distinguish between these two possibilities we would like to propose that terms including "peptide" be reserved for classes of molecules containing amino acids common in proteins and that the linkage between carbohydrate derived amino acids be referred to as an amide bond.
2. For leading references see: Knapp, S. *Chem. Rev.* **1995**, *95*, 1859.
3. McDevitt, J.P.; Lansbury, P.T. *J. Am Chem. Soc.* **1996**, *118*, 3818.
4. (a) Graf von Roedern, E.; Lohof, E.; Hessler, G.; Hoffmann, M.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 10156. (b) Suhara, Y.; Hildreth, J.E.K.; Ichikawa, Y. *Tetrahedron Lett.* **1996**, *37*, 1575. (c) Suhara, Y.; Ichikawa, M.; Hildreth, J.E.K.; Ichikawa, Y. *Tetrahedron Lett.* **1996**, *37*, 2549. (d) Muller, C.; Kitas, E.; Wessel, H.P. *J. Chem. Soc. Chem. Comm.* **1995**, 2425. (e) Wessel, H.P.; Mitchell, C.; Lobota, C.M.; Schmid, G. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2712. (f) Nicolaou, K.C.; Florke, H.; Egan, M.G.; Barth, T.; Estevez, V.A. *Tetrahedron Lett.* **1995**, *36*, 1775. (g) Graf von Roedern, E.; Kessler, H. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 687. (h) Poitout, L.; Merrer, Y.L.; Depezay, J.-C. *Tetrahedron Lett.* **1995**, *36*, 6887. (i) Apostolopoulos, C.D.; Couladouras, E.A.; Georgiadis, M.P. *Liebigs Ann. Chem.* **1994**, 781. (j) Yoshimura, J.; Ando, H.; Sato, T.; Tsuchida, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2511.
5. Schreiner, E.; Zbiral, E.; Kleineidam, R.G.; Schauer, R. *Liebigs Ann. Chem.* **1991**, 129.
6.(a) Michon, F.; Brisson, J.; Jennings, H. J. *Biochemistry* **1987**, *26*, 8399-8405. (b) Yamasaki, R.; Bacon, B. *Biochemistry* **1991**, *30*, 851-857.
7. Schmid, W.; Christian, R.; Zbiral, E. *Tetrahedron Lett.* **1988**, *29*, 3643.
8. Yu, R.K.; Ledeen, R.J. *J. Biol. Chem.* **1969**, *244*, 1306.
9. Driguez, P.-A.; Barrere, B.; Quash, G.; Doutheau, A. *Carbohydr. Res.* **1994**, *262*, 297.
10. Roy, R.; Pon, R.A. *Glycoconjugate J.* **1990**, *7*, 3.
11. Wallimann, K.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 1520.
12. Hanessian, S. *Tetrahedron Lett.* **1967**, *16*, 1549.
13. Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *J. Chem. Soc., Chem. Commun.* **1985**, 1317.
14. Flynn, D.L.; Zelle, R.E.; Grieco, P.A. *J. Org. Chem.* **1983**, *48*, 2424.
15. Ratcliff, M.R.; Venot, A.P.; Abbas, Z.S.; Eur. Pat. Appl. EP 319,253 (*Chem. Abstr.* **1990**, 112, 175281a).
16. Claesson, A.; Luthman, K.; *Acta. Chem. Scand. B* **1982**, *36*, 731.

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