Diastereoselective routes to side-chain truncated analogues of *N*-acetylneuraminic acid†

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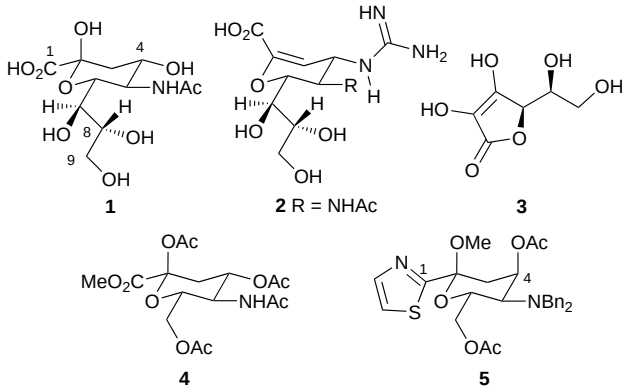
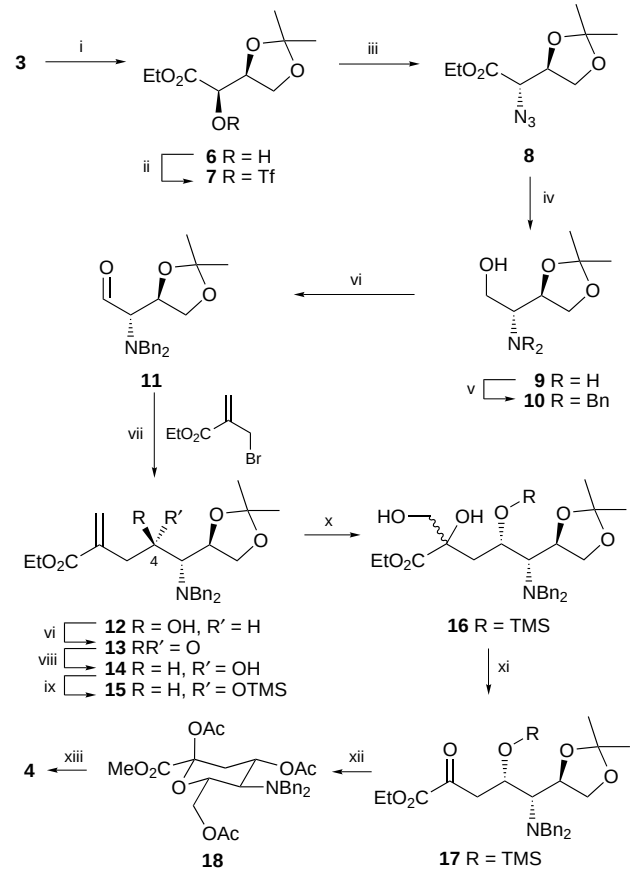
Vitamin C 3 has been converted, in a completely stereocontrolled manner, into the side-chain truncated analogues 4 and 5 of *N*-acetylneuraminic acid 1.

N-Acetylneuraminic acid **1** (Neu5Ac) and other members of the sialic acid class of carbohydrates play fundamental roles in many important biological processes, including cell adhesion and differentiation, immune responses, tumour metastasis and the development of neural cells.[1] In addition, they constitute a ligand commonly recognised by many infectious pathogens such as viruses, bacteria and parasites.[1] Consequently, sialic acids and various derivatives including the potent anti-influenza drug GG167 **2**[2] are assuming increasing importance as pharmacological tools and/or therapeutic agents.[3] In this regard there is now considerable interest[4] in side-chain truncated analogues of Neu5Ac which are currently only accessible *via* degradation of the natural product **1**.[3,4] Therefore, we report herein on the stereocontrolled conversion of abundant vitamin C **3** into compounds **4** and **5**, each of which embodies the sialic



acid core but lacks the C-8/C-9 (side-chain) assemblage associated with the parent system **1**. The reaction sequences used for these conversions offer possibilities for the synthesis[5] of a range of novel sialic acid analogues which can vary in both the nature and stereochemistry of the substituents attached to the pyranose ring.

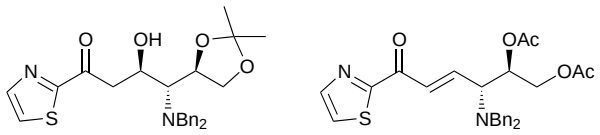
The reaction sequence (Scheme 1) leading to compound **4** starts with a literature procedure[6] for the oxidative degradation of vitamin C **3** to the α-hydroxy ester **6**. The triflate derivative **7** of the latter compound was then prepared in quantitative yield by standard methods[7] and underwent a smooth S_N2 reaction with lithium azide[8] in DMF at room temperature to give the azide **8** {80%, $[\alpha]_D$ −14.7 (*c* 2.6)§}. Reduction of this α-azido ester with LAH afforded the amino alcohol **9** {100%, $[\alpha]_D$ −10.5 (*c* 1.5)} which was immediately protected as its *N*,*N*-dibenzyl derivative **10** {90%, $[\alpha]_D$ +1.2 (*c* 2.1)}. Oxidation of compound **10** using the Swern reagent gave aldehyde **11**[9] {95%, $[\alpha]_D$ +3.9 (*c* 3.8)} which upon reaction with ethyl (2-bromomethyl)acrylate, zinc dust and saturated aq. NH_4Cl[10] in THF afforded the homoallylic alcohol **12** {87%, $[\alpha]_D$ −14.8 (*c* 2.1)} in a completely diastereoselective fashion.[11] Oxidation of the latter compound with the Swern reagent afforded ketone **13** {90%, $[\alpha]_D$ −72.9 (*c* 2.5)} and this was immediately reduced with $NaBH_4$ in EtOH to alcohol **14** {82%, $[\alpha]_D$ −5.9 (*c* 2.3)} which proved to be the only isolable product of the reaction. Attempts to cleave the C=C double bond[12] within this last compound using ozone failed because of competing reaction at the aromatic rings associated with the *N*,*N*-dibenzylamino moiety. Consequently, a somewhat more circuitous method was devised for achieving this end. Thus, compound **14** was



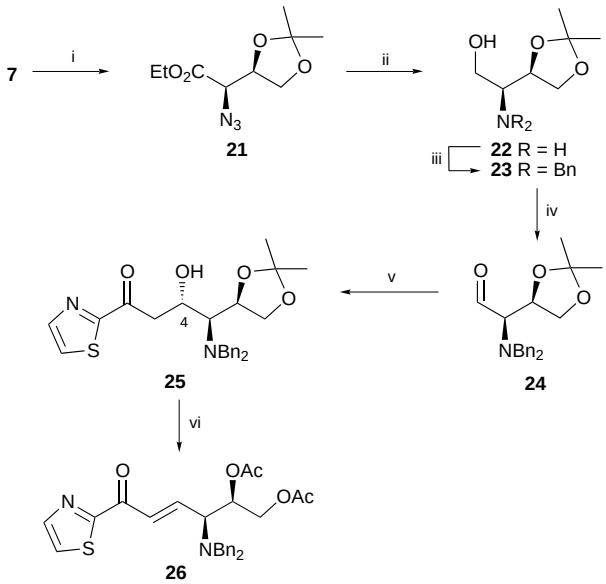
Scheme 1 *Reagents and conditions*: i, see ref. 6; ii, Tf_2O (1.3 equiv.), 2,6-lutidine (1.3 equiv.), CH_2Cl_2, −50 to −10 °C, 0.75 h; iii, LiN_3 (2.5 equiv.), DMF, 18 °C, 3 h; iv, LAH (3.5 equiv.), THF, 18 to 65 °C, 3 h; v, BnBr (2.2 equiv.), K_2CO_3 (2 equiv.), MeCN, 60 °C, 14 h; vi, $(COCl)_2$ (1.2 equiv.), DMSO, CH_2Cl_2, −78 to 0 °C, 1 h, then Et_3N (2.6 equiv.); vii, Zn dust (1.2 equiv.), sat. aq. NH_4Cl, THF, 60 °C, 0.75 h; viii, $NaBH_4$ (6 equiv.), EtOH, −10 °C, 1.5 h; ix, TMSCl (4.0 equiv.), hexamethyldisilazane (4.0 equiv.), pyridine, 0 to 18 °C, 19 h; x, AD-mix-α (2.2 equiv.), Bu^tOH, H_2O, 18 °C, 22 h; xi, $Pb(OAc)_4$ (0.9 equiv.), $CaCO_3$ (11 equiv.), CH_2Cl_2, 18 °C, 0.33 h; xii, 6% w/v HCl in MeOH, 18 °C, 18 h then Ac_2O (10 equiv.), DMAP (trace), pyridine, 18 °C, 20 h; xiii, Pd black, 5% w/v HCO_2H in MeOH, 18 °C, 0.5 h, then Ac_2O (10 equiv.), DMAP (trace), pyridine, 18 °C, 20 h

converted into the corresponding Me_3Si-ether **15** {83%, $[\alpha]_D$ −12.9 (*c* 3.0)} and the C=C double bond within this latter compound was dihydroxylated using AD-mix-α.[13] The resulting 1 : 1 mixture of diastereoisomeric diols **16** (83%) was then cleaved with lead tetraacetate to give the α-keto ester **17** {90%, $[\alpha]_D$ −21.7 (*c* 2.3)}. Treatment of compound **17** with 6% w/v methanolic HCl at room temperature for 18 h and subsequent peracetylation of the crude reaction mixture resulted in formation of the sialic acid analogue **18** {72%, $[\alpha]_D$ −81.3 (*c* 5.7)}. The benzyl protecting groups within this last compound could be removed using palladium black and formic acid[14] in MeOH and the resulting primary amine was acetylated to give the target compound **4** {80% at 80% conversion, $[\alpha]_D$ −97.1 (*c* 1.0)}, the structure of which follows from spectroscopic data.

Extension of this chemistry to the preparation of compound **5** is readily achieved. Thus, aldol condensation of the enolate anion derived from 2-acetylthiazole[15] with aldehyde **11** afforded the β-hydroxy ketone **19** {72%, $[\alpha]_D$ −58 (*c* 0.7)} in a completely stereoselective manner. Reaction of this last compound with 20% w/v methanolic HCl at room temperature for 18 h and subsequent peracetylation of the crude reaction mixture afforded compound **5** {70%. $[\alpha]_D$ −182.1 (*c* 1.0)} together with quantities (30%) of the open-chain dehydration product **20** {$[\alpha]_D$ −154.2 (*c* 0.6)}.



While the reaction sequence just described delivers a sialic acid analogue **5** which possesses the unnatural configuration at C-4, there are some constraints associated with the stereochemical variations that are available. This situation is highlighted by the outcome of the reaction sequence outlined in Scheme 2. Thus, treatment of triflate **7** with sodium azide in DMF at 75 °C for 6 h afforded azide **21** {85%, $[\alpha]_D$ +42.5 (*c* 2.7)} together with minor amounts (*ca*. 8%) of its C-2 epimer **8** which could be removed chromatographically. Reduction of compound **21** with LAH then provided the corresponding amino alcohol **22** {83%, $[\alpha]_D$ + 1.0 (*c* 5.7)} which was converted into the *N*,*N*-dibenzyl derivative **23** {92%, $[\alpha]_D$ −80.0 (*c* 6.8)}. Oxidation of this latter compound afforded the C-2 epimer of α-amino aldehyde **11**, namely compound **24** {88%, $[\alpha]_D$ +58.7 (*c* 7.9)}, which underwent stereoselective aldol condensation with the enolate anion derived from 2-acetylthiazole to give amino alcohol **25** {79%, $[\alpha]_D$ −5.5 (*c* 3.7)}. The stereochemistry at C-4 within compound **25** has not been rigorously proven but is assigned as illustrated on the basis of the well-known[9,11] directing effect of an α-(*N*,*N*-dibenzylamino) substituent on nucleophilic additions to aldehydes. In an effort to achieve a cyclisation reaction, compound **25** was treated with 8% w/v methanolic HCl, then the crude reaction mixture was subjected to exhaustive acetylation. However, no cyclisation products were observed. The only compound obtained was the open-chain dehydration product **26** {70%, mp 123–125 °C, $[\alpha]_D$ +106.3 (*c* 0.7)}, the structure of which was established by spectroscopic and X-ray crystallographic methods.¶



Scheme 2 *Reagents and conditions*: i, NaN_3 (2 equiv.), DMF, 75 °C, 6 h; ii, LAH (3.5 equiv.), THF, 18 to 65 °C, 3 h; iii, BnBr (2.2 equiv.), K_2CO_3 (2 equiv.), MeCN, 60 °C, 14 h; iv, $(COCl)_2$ (1.2 equiv.), DMSO, CH_2Cl_2, −78 to 0 °C, 1 h then Et_3N (2.6 equiv.); v, Bu^tOH (1 equiv.), Bu^nLi (1.2 equiv.), THF, 18 °C, 0.66 h, then 2-acetylthiazole (1.2 equiv.), −50 °C, 2.5 h; vi, 8% w/v HCl in MeOH, 18 °C, 18 h, then Ac_2O (10 equiv.), DMAP (trace), pyridine, 18 °C, 20 h

Notes and References

† The work described herein is the subject of a patent application (AIPO Patent Office Provisional Application No. PO8998, lodged September 5th, 1997).

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§ All optical rotations were determined in $CHCl_3$ at 20 °C.

¶ *Crystal data* for **26**: $C_{27}H_{28}N_2O_5S$, M = 492.59, T = 193(1) K, monoclinic, space group $P2_1$, a = 11.346(4), b = 7.778(2), c = 15.473(6) Å, β = 109.34(3)°, U = 1288.4(3) Å^3, D_c (Z = 2) = 1.270 g cm^{-3}, F(000) = 520, μ(Cu-Kα) = 14.42 cm^{-1}, semi-empirical absorption correction; 2085 unique data ($2\theta_{max}$ = 120.1°), 1583 with $I > 3\sigma(I)$; R = 0.033, wR = 0.029, GOF = 1.44. CCDC 182/739.

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Received in Cambridge, UK, 28th November 1997; 7/08594J