

Diastereoselective synthesis of (–)-*N*-acetylneuraminic acid (Neu5Ac) from a non-carbohydrate source †

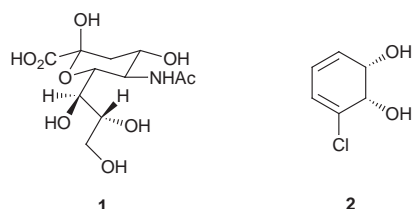
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cis-1,2-Dihydrocatechol **2**, a product of microbial oxidation of chlorobenzene, has been converted into a protected form, **17**, of (–)-Neu5Ac (**1**) via a fifteen step reaction sequence.

Sialic acids such as *N*-acetylneuraminic acid [(–)-Neu5Ac, **1**] have been implicated in a wide range of biologically important processes including cell-to-cell recognition, cell-adhesion, neural cell development and tumour metastasis.¹ These compounds also constitute a ligand class commonly recognised by many infectious pathogens such as viruses, bacteria and parasites. Consequently, there has been considerable interest in developing effective methods for the synthesis² of both sialic acids and analogues that would help elucidate their roles *in vivo*. Various enzymatic procedures including an aldolase-catalysed condensation of *N*-acetyl-D-mannosamine with pyruvic acid have been shown to provide useful quantities of compound **1**.³ Elegant



chemical variations on this approach which use, in the penultimate step, 2-(metallomethyl)acrylates as pyruvate anion equivalents have been developed by the groups of Vasella,⁴ Chan⁵ and Whitesides.⁶ We now report an enantiospecific and diastereoselective synthesis of a protected form of (–)-Neu5Ac that involves a related end game but which starts with the enantiopure *cis*-1,2-dihydrocatechol **2**,⁷ a compound available in quantity *via* microbial oxidation of chlorobenzene. The only previous synthesis of the title compound from a non-carbohydrate source has been reported by Danishefsky *et al.*⁸ who used a hetero-Diels–Alder reaction between a diene and an aldehyde to establish the pyranoid core. The present work was modelled on our recently disclosed⁹ synthesis of KDN and should allow for the preparation of a wide range of ¹⁷O-, ¹³C- and/or ²H-labelled (–)-Neu5Ac derivatives.

The reaction sequence leading from compound **2** to the protected form, **17**, of (–)-Neu5Ac is shown in Scheme 1. Thus, the acetonide derivative, **3**,¹⁰ of **2** was converted into the azido alcohol **4** by established procedures.¹¹ The benzyl ether derivative, **5** ‡ {70%, [α]_D –113 (*c* 5.3)}, of compound **4** was subjected to ozonolytic cleavage and a reductive work-up with NaBH₄ and in this way the diol **6** {70%, [α]_D +10 (*c* 1.0)} was obtained. Hydrogenolysis of the azido and benzyl ether moieties within

compound **6** was achieved using dihydrogen in the presence of 10% palladium on carbon and the resulting aminotriol **7** was immediately subjected to reaction with benzyl bromide in the presence of K₂CO₃. The *N,N*-dibenzylated material **8** {90% from **6**, [α]_D –13 (*c* 4.7)} so-formed was treated with acetone and a trace of trifluoromethanesulfonic acid (TfOH) and the ensuing reaction produced bis-acetonide **9** {62%, [α]_D +59 (*c* 1.3)} which was identical with an authentic sample prepared from δ -gluconolactone.¶ Subjection of compound **9** to Swern oxidation conditions afforded the D-mannosamine derivative **10** {100%, [α]_D +52 (*c* 3.9)} which was condensed with the organozinc reagent derived from bromoacrylate **11** to give the *anti*-addition product **12** {85% at 90% conversion, [α]_D +5 (*c* 5.9)}.¹² Swern oxidation of this last compound then provided the highly unstable ketone **13** which was immediately reduced, in a diastereoselective fashion, with NaBH₄. The resulting alcohol was protected as the corresponding TMS ether **14** {60% from **12** at 67% conversion [α]_D +0.4 (*c* 2.3)}. Ozonolysis of the C–C double bond within alkene **14** could not be effected selectively because of competing oxidation of the *N,N*-dibenzyl moiety so the compound was reacted with AD-mix- α ¹³ and the resulting mixture of diastereoisomeric diols cleaved with lead tetraacetate to give the unstable ketone **15** (89%). Treatment of product **15** with methanolic HCl at room temperature for 18 h followed by acetylation of the crude reaction mixture afforded the nonulosonic acid derivative **16** {60%, [α]_D –51 (*c* 0.7)}. Debenzylation of the latter compound was readily achieved using formic acid–palladium black¹⁴ and the intermediate amine acetylated to give the sialic acid derivative **17**¹⁵ {75%, [α]_D –27 (*c* 1.0)}. This material was identical, in all respects, with an authentic sample {[α]_D –26 (*c* 1.4)} prepared from sialic acid according to the method¹⁵ of Sinaÿ. Compound **17** is a versatile building block that has found considerable use¹⁶ in the preparation of a wide range of sialic acid analogues.

Experimental

Compound 6

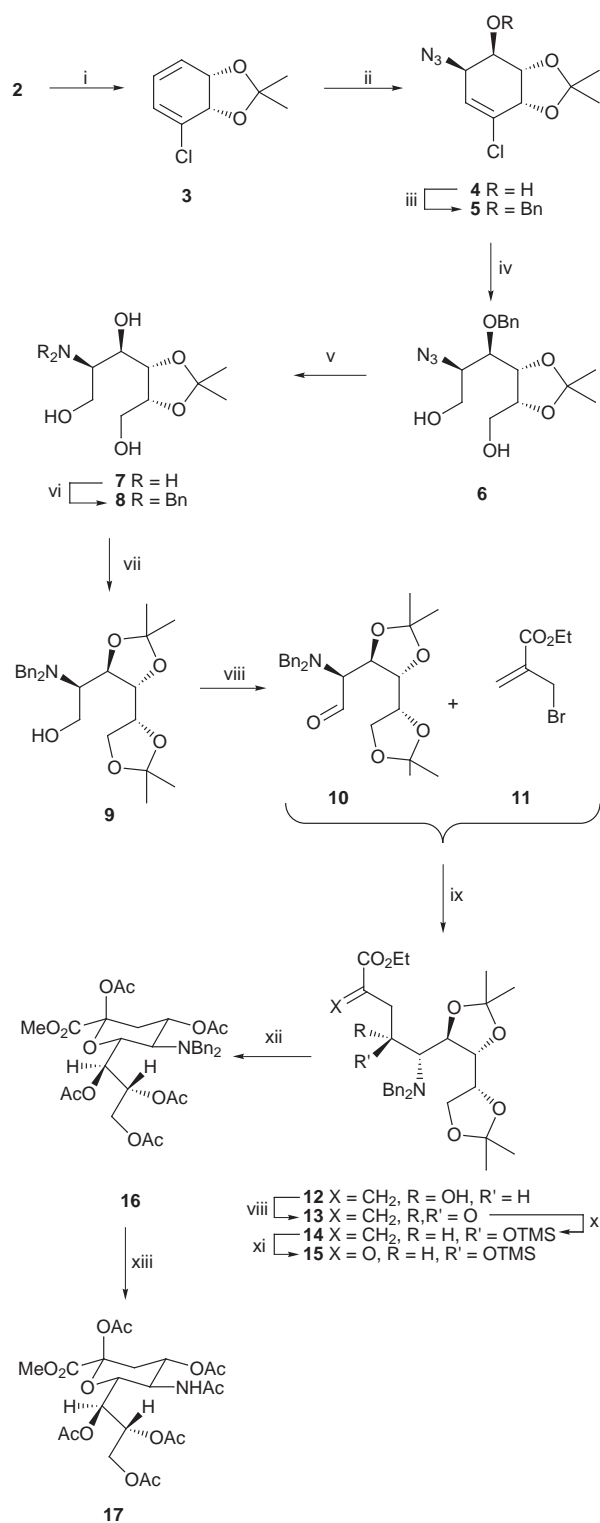
A solution of compound **5** (1.30 g, 3.86 mmol) in methanol (20 ml) was cooled to –78 °C (dry-ice–acetone bath) and treated with a stream of ozone (*ca.* 40% ozone in oxygen) being produced by a Fischer Model 502 ozone generator. When the blue colour of ozone persisted and TLC analysis indicated that no starting material remained (*ca.* 0.66 h), the reaction mixture was purged with nitrogen for 0.5 h then warmed to 0 °C over 0.5 h. Sodium borohydride (1.00 g, 26 mmol) was added, in portions over 3 h, to the reaction mixture which was then warmed to 18 °C and treated with additional quantities of sodium borohydride (285 mg, 7.4 mmol). After a further 5.0 h, the reaction mixture was diluted with water (50 ml) then acidified (using 1 M aqueous HCl) to pH 3.0 and extracted with ethyl acetate (4 × 200 ml). The combined organic extracts were washed with brine (2 × 300 ml) then dried (MgSO₄), filtered and concen-

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

‡ All new and stable compounds had spectroscopic data (IR, UV, NMR, mass spectrum) consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral data were obtained for new compounds and/or suitable derivatives.

§ All optical rotations were determined in chloroform solution at 20 °C.

¶ Details of this synthesis will be disclosed shortly.



Scheme 1 Reagents and conditions: (i) see reference 10; (ii) see reference 11; (iii) NaH (1.1 mol equiv.), THF, 0 °C, 0.75 h then BnBr (1.3 mol equiv.), 0–18 °C, 4 h; (iv) O₃, MeOH, –78 to 0 °C, 0.05 h then NaBH₄ (9.0 mol equiv.), 18 °C, 7 h; (v) dihydrogen (50 psi), 10% Pd on C (20 wt%), MeOH, 18 °C, 16 h; (vi) BnBr (2.3 mol equiv.), K₂CO₃ (2.2 mol equiv.), 2:1 MeCN–H₂O, 60 °C, 16 h; (vii) Me₂CO, TfOH (cat.), 0 °C, 3 h; (viii) (COCl)₂ (1.2 mol equiv.), DMSO, CH₂Cl₂, –78 to 0 °C, 1 h then Et₃N (2.6 mol equiv.); (ix) Zn dust (1.2 mol equiv.), sat. aq. NH₄Cl, THF, 0 to 18 °C, 0.75 h; (x) NaBH₄ (6 mol equiv.), EtOH, –10 °C, 4 h then TMSCl (4.0 mol equiv.), HMDS (4.0 mol equiv.), pyridine, 0 to 18 °C, 19 h; (xi) AD-mix- α (2.2 mol equiv.), Bu'OH, H₂O, 18 °C, 22 h then Pb(OAc)₄ (0.9 mol equiv.), CaCO₃ (11 mol equiv.), CH₂Cl₂, 18 °C, 0.33 h; (xii) 6% w/v HCl in MeOH, 18 °C, 18 h then Ac₂O (10 mol equiv.), DMAP (trace), pyridine, 18 °C, 20 h; (xiii) Pd black, 5% w/v HCO₂H in MeOH, 18 °C, 0.5 h then Ac₂O (10 mol equiv.), DMAP (trace), pyridine, 18 °C, 20 h. Bn = C₆H₅CH₂; DMAP = 4-(N,N-dimethylamino)pyridine; HMDS = hexamethyldisilazane.

trated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 3:2 hexane–ethyl acetate elution) afforded, after concentration of the appropriate fractions (*R*_f 0.2), the azido diol **6** (920 mg, 70%) as a clear, colourless oil [Found: (M – CH₃)⁺, 322.1408. C₁₆H₂₃N₃O₅ requires (M – CH₃)⁺, 322.1403]; ν_{\max} (NaCl)/cm⁻¹ 3854 and 2101; δ_{H} (300 MHz, CDCl₃) 7.40–7.27 (5 H, m), 4.80 (1 H, d, *J* 11.2 Hz), 4.74 (1 H, d, *J* 11.2 Hz), 4.35 (1 H, t, *J* 6.1 Hz), 4.26 (1 H, q, *J* 6.1 Hz), 3.96 (1 H, m), 3.90–3.79 (2 H, complex m), 3.77–3.60 (3 H, complex m), 2.29 (1 H, br s), 2.07 (1 H, br s), 1.52 (3 H, s), 1.40 (3 H, s); δ_{C} (75 MHz, CDCl₃) 137.5 (C), 128.4 (CH), 128.0 (CH), 127.9 (CH), 108.6 (C), 78.2 (CH), 77.5 (CH), 76.7 (CH), 74.1 (CH₂), 64.5 (CH), 61.6 (2 × CH₂), 27.5 (CH₃), 25.4 (CH₃); *m/z* (EI, 70 eV) 322 (<1%, (M – CH₃)⁺), 278 {21, [M – (H₃C)₂CO – H]⁺}, 91 (100).

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