A facile and direct entry to functionalised Neu5Ac2en derivatives from the methyl ketoside of Neu5Ac methyl esters

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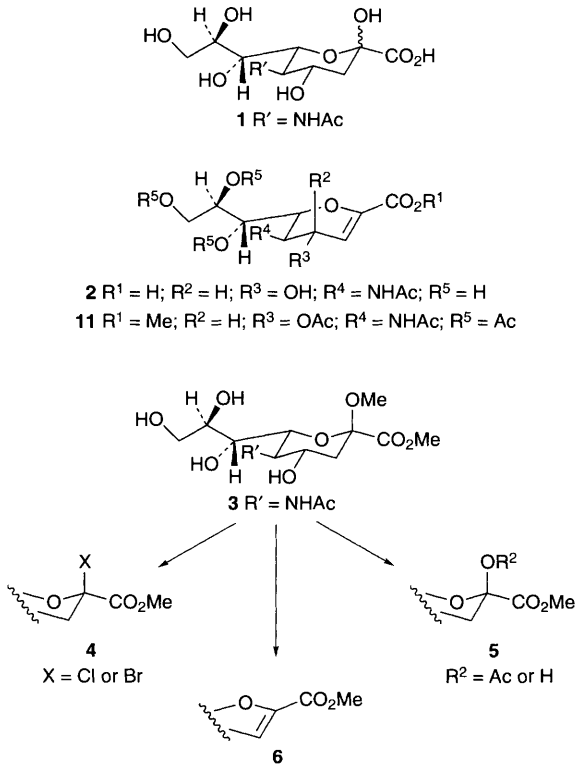
Acetolysis of some methyl ketosides of *N*-acetylneuraminic acid (Neu5Ac) methyl esters, in a one-pot reaction, provides a rapid and efficient access to the corresponding 2,3-unsaturated Neu5Ac (Neu5Ac2en) derivatives.

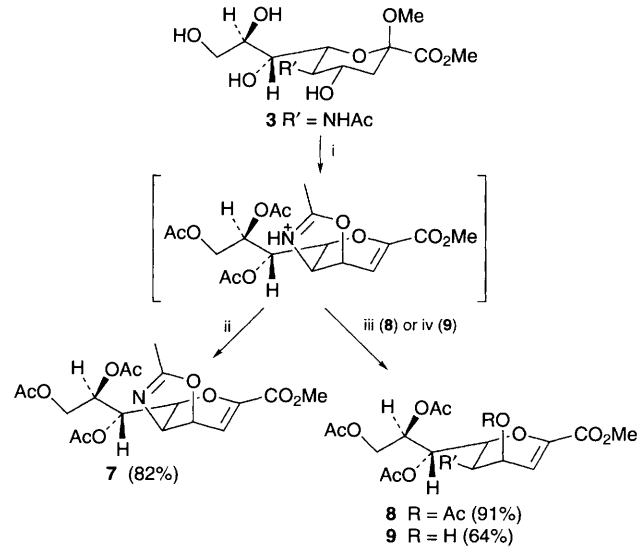
The chemistry and biology of sialic acids, particularly *N*-acetylneuraminic acid (Neu5Ac,**1**), have received much attention in recent years.[1] These sugars are important constituents of cellular and bacterial membranes and have been implicated in a myriad of biological functions.[2] The 2,3-unsaturated derivatives of Neu5Ac are potent inhibitors of some bacterial and viral sialidases. For example, 5-acetamido-2,6-anhydro-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-enonic acid (Neu5Ac2en, **2**) is one of the most potent competitive inhibitors of sialidase (EC 3.2.1.18) from *Vibrio cholerae*.[3] Thus, to gain insight into the structure–activity relationship of these biomolecules, many structural transformations of Neu5Ac have been carried out over the past years.[4,5] More recently, two rationally designed analogues of Neu5Ac2en, modified at the C-4 position, have been synthesised and found to be potent inhibitors of influenza virus sialidase.[5]

To the best of our knowledge most, if not all, existing 2,3-unsaturated derivatives of Neu5Ac have been prepared *via* structural variation of Neu5Ac2en **2** itself. However, this approach has its limitations. For instance, certain functional group manipulations, *e.g.* hydrogenation, halogenation or oxidation, are not generally well-tolerated by the existing 2,3-alkenic double bond in the system.

Owing to these synthetic limitations, we envisaged that Neu5Ac itself could serve as the starting material in an alternative approach to functionalised Neu5Ac2en derivatives. The key intermediate in this pathway would be the readily accessible β-methyl ketoside methyl ester of Neu5Ac **3** (Scheme 1). Structural modification to **3** followed by liberation of the methyl glycosidic bond and elimination should install the desired 2,3-alkenic double bond into the system. However, existing methodologies available for the cleavage of the methyl glycosidic bond are few and limited. As outlined in Scheme 1, the two common alternatives for achieving this involve strategies employing either the unstable acetohalogenoses (**4**, X = Cl or Br) or the anomeric acetate (**5**, R^2 = Ac). In the former case, this involves treatment[6] of the ketoside **3** with either HCl or HBr, followed by base-catalysed elimination of HX to afford the glycal **6**. Entry into the acetate (**5** R^2 = Ac) can only be achieved by first converting the glycoside into the free sugar (**5**, R^2 = H) followed by acetylation. In the case of some α-methyl ketosides of *N*-acetylneuraminic acid, deglycosidation can be achieved using enzymatic cleavage employing fowl plague sialidase[7]; in most cases however, cleavage of the glycosidic bond can only be accomplished[8] under forcing conditions with aqueous acid hydrolysis at elevated temperatures. Recently, it has been shown that elimination of acetic acid with trimethylsilyl trifluoromethanesulfonate facilitates the



Scheme 1



Scheme 2 *Reagents and conditions*: i, Ac_2O, HOAc, conc. H_2SO_4 (10 : 10 : 1; *v/v*); ii, saturated $NaHCO_3$ (pH 9); iii, NaOAc (pH 5); iv, H_2O (pH 2)

conversion of the anomeric acetate (**5** R^2 = Ac) into the corresponding 2,3-unsaturated derivative.[9]

Here we describe a mild and efficient direct conversion of the β-methyl ketoside of Neu5Ac methyl ester **3** into the Neu5Ac2en derivatives **7**, **8** or **9** (Scheme 2). Acetolysis of the methyl ketoside **3** in the presence of concentrated sulfuric acid was performed at room temperature for 48 h. Variation in the work-up procedure resulted in the formation of either the oxazoline **7**, 4-*epi*-Neu4,5,7,8,9$Ac_5$2en1Me **8**, or 4-*epi*-Neu5,7,8,9$Ac_4$2en1Me **9**, in good yield.† Prolonged acetolysis (up to 2 weeks) did not alter the yield or outcome of this reaction.

To further illustrate the synthetic potential of this reaction, we have examined a range of other substrates (Table 1). From Table 1 it can be seen that both α- and β-methyl ketosides of Neu5Ac are readily transformed into the corresponding Neu5Ac2en derivative. Thus, the α-methyl ketoside **10** and the closely related β-methyl ketoside **14** were readily transformed into the 4-*epi*-Neu5Ac2en derivative **8**, when a sodium acetate-based work-up was employed. Interestingly, acetolysis of both **8** and **11** resulted in the formation of the oxazoline **7** when an aqueous sodium hydrogen carbonate work-up was employed. This suggests to us that oxazoline ring formation occurs through an allylic cation and is therefore insensitive to the stereochemistry about the C-4 centre on the ketoside. As would be expected, the isopropylidene protecting group in compounds **10**, **15**, **17** and **19** and the 9-*O*-*tert*-butyldiphenylsilyl ether in compound **14** are cleaved and replaced by acetates under the reaction conditions.

The facile conversion of the 4-oxo-Neu5Ac derivative **15** into the 4-oxo-Neu5Ac2en derivative **16** is particularly noteworthy. Our previous attempts at synthesising the enone **16** by oxidation of the allylic alcohol **9** with manganese dioxide[13] met with limited success.

Importantly, good yields of the compounds **7**, **8** or **9** can be achieved in only two steps, *via* sequential methanolysis and acetolysis, from Neu5Ac itself. Interestingly, Kumar and co-workers have reported[14] obtaining the peracetylated methyl esters of Neu5Ac2en and its 4-epimer **8** by treatment of the methyl ester of Neu5Ac with acetic anhydride and sulfuric acid. However, in this case, the reaction was non-selective and a 1 : 1 mixture of the two aforementioned isomers were obtained; together with 2–4% of the oxazoline **7**.

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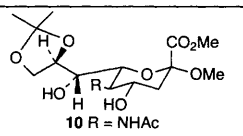
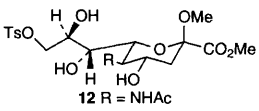
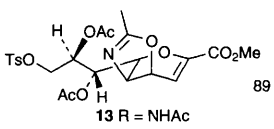
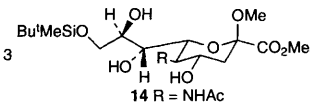
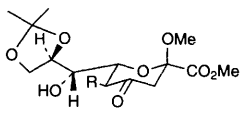
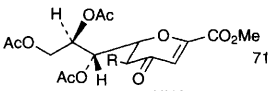
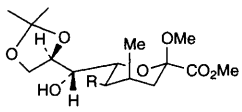
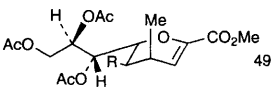
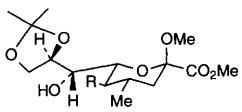
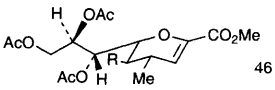
Table 1 Acetolysis[a] of some functionalised methyl ketosides of Neu5Ac

Entry[b]	Ketoside[c]	Work up procedure[d]	Product[e]	Isolated yield (%)
1	 **10** R = NHAc	B	**8**	91
2	 **12** R = NHAc	A	 **13** R = NHAc	89
3	 **14** R = NHAc	B	**8**	90
4	 **15** R = NHAc	A	 **16** R = NHAc	71
5	 **17** R = NHAc	A	 **18** R = NHAc	49
6	 **19** R = NHAc	A	 **20** R = NHAc	46

[a] Typical experimental procedure: Concentrated sulfuric acid (0.1 ml) was added to a stirred solution of the ketoside (100 mg) in glacial acetic acid (1.0 ml) and acetic anhydride (1.0 ml) at room temp. under nitrogen. The resulting mixture was then stirred for a further 48 h (unless otherwise specified). [b] The reaction time for entry 5 was 96 h. [c] Compounds **10**, **15** and both **17** and **19** were prepared according to references 10, 11 and 12 respectively. [d] Work-up procedures. Method A: Saturated sodium hydrogen carbonate was added (pH 9) and the mixture stirred for 2 h before extraction with ethyl acetate. Method B: Solid sodium acetate was added (pH 5) and the mixture stirred for 4 h before extraction with ethyl acetate. Method C: Water was added and after 4 h the mixture was extracted with ethyl acetate. [e] Satisfactory HRMS and spectroscopic data were obtained for all new compounds.

Footnote

† Near quantitative yield of crude product was obtained; isolated yields are given in Scheme 2; crude **7** and **9** contained *ca.* 5–8% of **8** (by ^{1}H NMR spectroscopy).

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