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SYNTHESIS OF A TETRASUBSTITUTED BICYCLO [2.2.2] OCTANE AS A POTENTIAL INHIBITOR OF INFLUENZA VIRUS SIALIDASE

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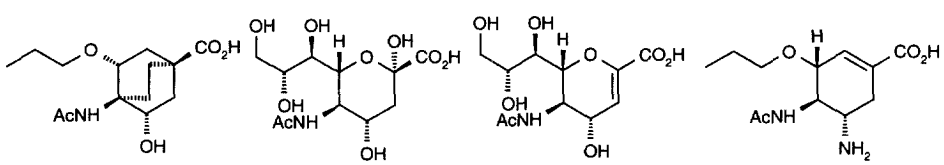
Abstract: A novel synthesis of the bicyclo [2.2.2] octane ring system has been achieved utilising a tandem Henry cyclisation as the key stage. This chemistry has been employed in the synthesis of a potential inhibitor of influenza virus sialidase

There has been considerable recent attention directed towards the synthesis of novel inhibitors of influenza virus sialidase.[1] All the high affinity inhibitors described in the literature to date are cyclic transition state analogues characterised by their ability to appropriately present four binding substituents to the viral enzymes. Inhibitors which contain fewer substituents, or present groups with inappropriate geometry all show significantly reduced binding affinity.[2] In the search for further potent sialidase inhibitors we and others have explored a number of alternative cyclic templates upon which to display appropriate substituents to the viral enzyme.[3-6] At the outset of this work, we postulated that a tetra-substituted bicyclo [2.2.2] octane might be a molecular scaffold which would effectively mimic the high-energy twist-boat conformation adopted by sialic acid **2** when bound into the viral sialidase (Figure 1).[7] Thus by the introduction of appropriate pendant functionality onto the bicyclo [2.2.2] octane skeleton we anticipated that potent inhibitors of influenza sialidase could be prepared. Target compound **1** was selected as a prototype for this strategy based upon the known sialidase inhibitors Neu5ac2en (DANA) **3**[8] and the Gilead propyl ether **4**.[9] Herein we describe the synthesis of **1,** utilising a double intramolecular Henry cyclisation, and report its sialidase inhibitory activity.



1 **2** **3** **4**

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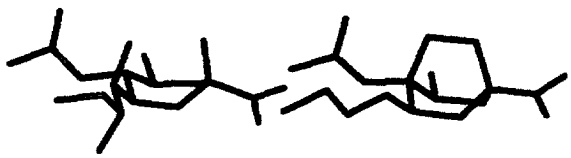
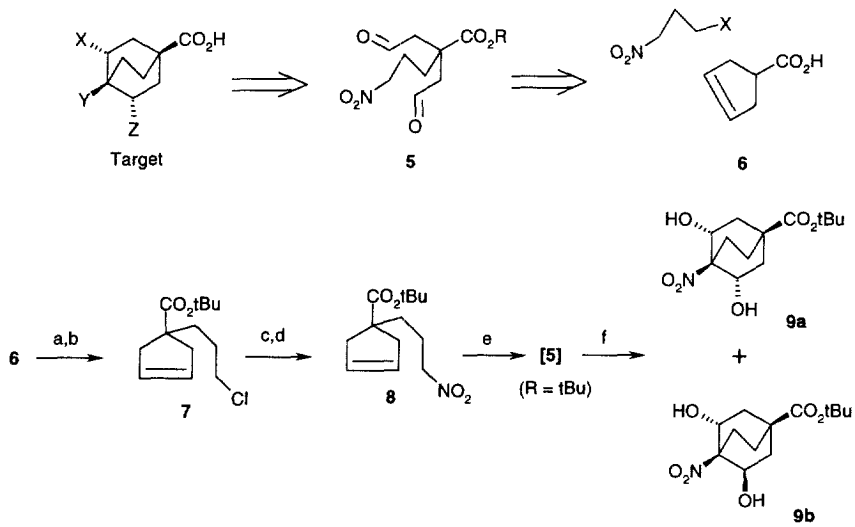


Figure 1: 3-D Comparison of sialic acid **2** in the high energy conformation adopted when binding to influenza A sialidase and the target compound **1**

Synthesis of Racemic **1**

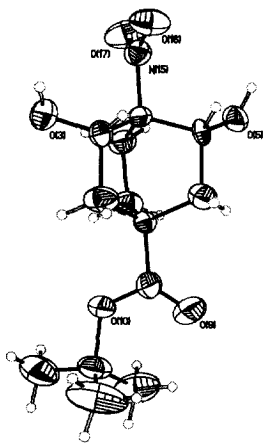
Based upon early studies on the reactions of nitromethane with glutaraldehyde[10] a novel strategy for the tetra-substituted bicyclo-octane skeleton was conceived which involved a tandem Henry reaction on the dialdehyde precursor **5**. Intermediate **5** (R = tBu) was prepared in four stages from cyclopentene-3-carboxylic acid **6**.[11] Thus initial esterification of **6** with DMF-di-tert butyl acetal, and alkylation with chloroiodopropane produced intermediate **7** (quantitative). This was converted in two stages to the required cyclisation precursor nitro-alkene **8**.



Reagents and conditions: a) $(tBuO)_2CHNMe_2$, H^+ b) $Cl(CH_2)_3I$, LDA, DMPU, -78° (100%) c) NaI, acetone, reflux 48h (91%) d) $NaNO_2$, DMSO (63%) e) O_3, CH_2Cl_2, -50°C then Me_2S (91% crude) f) Na_2CO_3, aq MeOH (30% **9a** + 18% **9b**)

Ozonolysis of intermediate **8** and subsequent decomposition of the intermediate ozonide, with dimethyl sulfide, generated crude dialdehyde **5** (R = tBu) (91%). This unstable intermediate was not purified but directly treated with sodium carbonate in aqueous methanol to afford a mixture of the two diastereoisomeric bicyclo [2.2.2] octanes **9a** and **9b** (racemic) (5:3 mixture, 48% yield). These compounds were readily separated by column chromatography and easily distinguished by their

NMR spectra. The structure of the symmetrical isomer **9a** was confirmed by X-ray crystallography (figure 2).



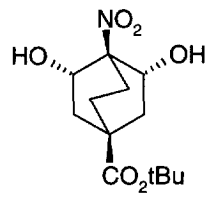
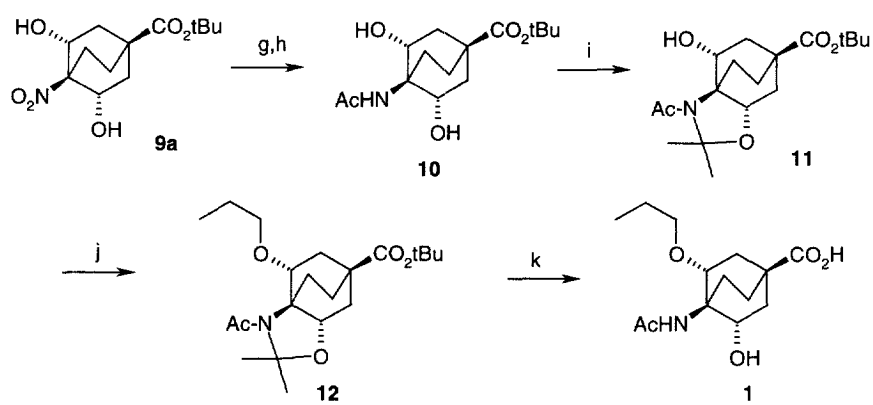


Figure 2: Thermal ellipsoid plot for compound **9a**

Compound **9a** was converted into target **1** in 5 stages. The nitro group was first reduced to the amine with hydrogen over platinum oxide in acetic acid. Acetylation of the amine with acetic anhydride in tetrahydrofuran produced the diol **10**. Treatment of **10** with 2,2-dimethoxypropane and acid produced the acetonide **11**. Alkylation of the remaining free hydroxyl group in **11** with propyl iodide produced the ether **12**. Acid hydrolysis of **12** with trifluoroacetic acid in methanol produced the required compound **1.**



Reagents and conditions: g) PtO_2/H_2/AcOH (100%), h) Ac_2O, THF (90%), i) PPTs, DMP, (75%), j) Propyl iodide, NaI (17%), k) CF_3CO_2H, MeOH (9:1) (57%)

Sialidase inhibitory activity of compound 1.

Compound **1** was evaluated as an inhibitor of influenza virus sialidase by the methods previously reported (Table).[12] It proved to be inactive against both influenza A and B sialidases, suggesting that the bicycloctane is not an appropriate scaffold for achieving optimal display of binding groups to the enzyme.

Compound	IC_{50} Influenza A (μM)	IC_{50} Influenza B (μM)
1	>660	>660*
3	2.8	3.0
4[9]	0.13	-

(* 12% inhibition observed @ 660μM)

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12. Inhibition of influenza sialidase was determined in a fluorimetric assay by measuring the ability of compounds to inhibit the hydrolysis of 2'-(4-methylumbelliferyl)-α-D-N-acetylneuraminic acid (MUN) by whole virus (A/Aichi N2 or B Victoria) grown in hen eggs. The IC_{50} value quoted is the concentration of inhibitor required to reduce the enzymic activity in this preparation by 50%.