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Sialidase Inhibitors Related to GG167: Synthesis of Analogues via An Inverse Demand hetero Diels Alder Reaction

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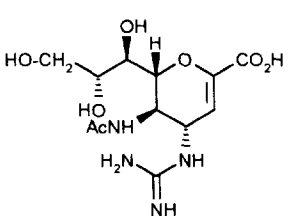
Abstract: An inverse demand hetero Diels Alder strategy has been utilised for the synthesis of novel dihydropyrans as potential inhibitors of influenza virus sialidase. Cyclisation of 1-methoxy-2-acetamido ethene with 2-oxo-4-tButoxycarbonylamino but-3-(Z)-enoic acid t-butyl ester in the presence of tin (IV) chloride afforded a mixture of regio- and stereo-chemical isomers which were further elaborated to analogues of GG167.

GG167 (**1**) is a potent inhibitor of influenza virus sialidase which is currently undergoing phase II clinical trials for the treatment of influenza.[1,2] In several recent reports we and others have described the synthesis and sialidase inhibitory activities of analogues of GG167 which demonstrate that all four of the substituents on the dihydropyran ring make important contributions to its sialidase binding.[3-8] Owing to the stereochemical complexity of GG167, all of these syntheses have utilised sialic acid derivatives as starting materials. Clearly, however, it would be desirable to identify alternative inhibitors which possess fewer chiral centres and would therefore be accessible by alternative chemical strategies. Towards this goal, two groups have recently reported that the trisubstituted benzene **2** is a moderate inhibitor of influenza sialidase.[9,10] An alternative approach towards simpler sialidase inhibitors which we have considered is to retain the core dihydropyran ring, but replace the glycerol sidechain with an achiral substituent. We reasoned that if this achiral substituent were to be attached via an oxygen atom, then the dihydropyran ring could be constructed utilising an inverse demand hetero Diels Alder reaction.[11] Realisation of this chemistry ultimately leads to GG167 analogues of general formula **3**. A similar strategy for the synthesis of dihydropyran derivatives has been described in several recents papers by Tietze et al.[12,13] In this paper we report our model investigations into this chemical approach which have resulted in the preparation of compound ±**4** and some of its isomers as potential inhibitors of influenza virus sialidase.



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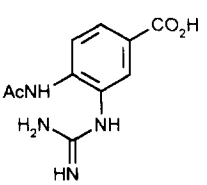

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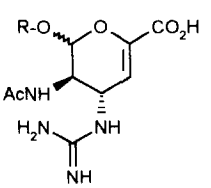

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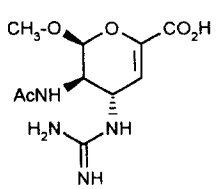
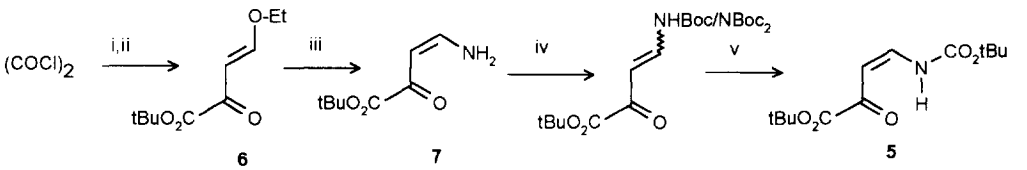


4

Synthesis of Heterodiene 5

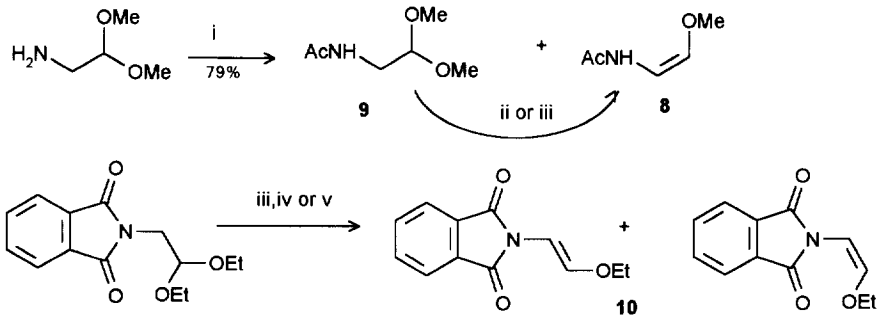
Heterodiene **5** was synthesised in four stages from oxalyl chloride. Initially oxalyl chloride was treated with t-butanol (1 equivalent), and the resulting monoester monoacid chloride isolated by distillation. Treatment of this monoester monoacid chloride with ethyl vinyl ether then triethylamine afforded the butenoate **6**. Ammonolysis of **6** in THF then produced the stable (Z)- **7** (68% over these two stages). Treatment of **7** with an excess of di-t-butyl dicarbonate produced a mixture of mono- and di t-Boc derivatives. These could be cleanly converted into the mono-Boc (Z)-alkene **5** following overnight treatment in THF-methanol with silica gel. Compound **5** is a stable crystalline solid which can be prepared on multigram scale (41% overall yield from oxalyl chloride). It is an ideal intermediate for the preparation of GG167 analogues in that upon cyclisation it efficiently introduces both the 1-acid and 4-amino functionality of GG167 into the dihydropyran products.



i) t-BuOH,pyridine, -78° -> r.t overnight, then distil, (60%); ii) ethyl vinyl ether, then Et_3N: iii) NH_3,THF, 50°, (68% yield from t-butyloxalyl chloride): iv) $(Boc)_2O$, DMAP; v) SiO_2, THF:MeOH (20:1), (100% from **7**)

Synthesis of Diene **8**

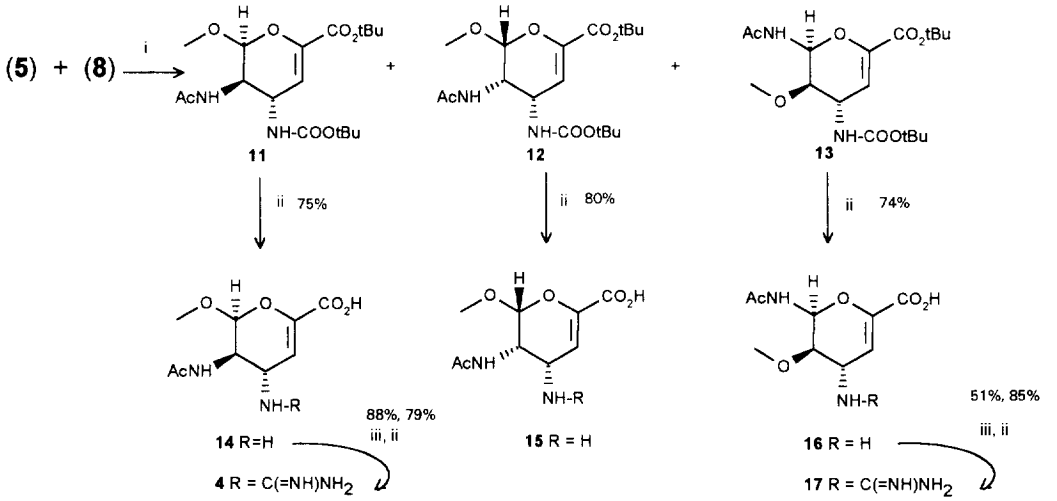
The only synthesis of acetamido-substituted vinyl ethers currently reported was achieved via condensation between acetamide and the appropriate alkoxyacetaldehyde.[14] However, synthesis of 1-methoxy-2-acetamido ethene **8** by this approach proved difficult in our hands with none of the required vinyl ether being produced. In an alternative procedure, a low yield (3-5%) of the pure (Z)- isomer of **8** was isolated by vacuum distillation of the crude dimethyl acetal **9**, which was prepared by acetylation of commercially available aminoacetaldehyde dimethyl acetal. The distillate contained largely the pure acetal **9**, contaminated with a few percent of the enol ether **8** which was detected as a highly mobile uv active component on tlc. **8** was readily separated from **9** using flash chromatography. None of the (E)- vinyl ether appears to be produced under these conditions. Although inefficient, we were able to produce gram quantities of compound **8** by this method since the starting material is commercially available in large quantities. An alternative procedure with 2 equivalents of TMS-triflate using the conditions of Gassman[15] appeared to show significant formation of **8** by tlc together with other minor products. However, following work up we were unable to achieve an isolated yield of **8** >15%. Preparation of enol ethers bearing a vinyl phthalimido group was somewhat easier and may offer an alternative pathway to the required targets. Thus N-phthalimido aminoacetaldehyde diethyl acetal was converted to a mixture of the (E)- and (Z)- vinyl ethers **10** either by refluxing with Dowex acid resin in toluene under Dean Stark conditions, or using TMS-triflate.



i) Ac_2O, TEA ii) Distil crude product then chromatography iii) TMS-OTf, CH_2Cl_2 iv) Dowex H^+, Dean-Stark, toluene h, reflux. v) $KHSO_4$ (cat) 150 - 170°, 5h, N_2 62% overall (~2:1 E:Z)

Hetero Diels Alder Cyclisation of **5** with **8** and elaboration to **4** and its isomers.

The Diels Alder cyclisation between **5** and **8** was carried out in the presence of tin (IV) chloride. The reaction was slow at room temperature, requiring several hours for the starting materials to be consumed. Under these conditions the reaction proceeded with very poor regio- and stereoselectivity, producing three of the four possible isomeric products **11** - **13** (Ratio **11**:**12**:**13** 1.8:1.1:1 35% yield).[16] Intermediates **11** - **13** were separated and the acid labile protecting groups removed using TFA to afford the amino acids **14** - **16**. Two of these products were further converted into the 4-guanidino derivatives **4** and **17** utilising bisBocPCH.[17,18]



i) $SnCl_4$, DCM , (16% **11** + 10% **12** + 9% **13**) ii) TFA iii) BisBocPCH, Et_3N/ MeOH

Sialidase inhibitory activity of compound **4** and **15-17**.

None of the compounds displayed useful levels of sialidase inhibitory activity in our assay.[19] Compounds **4** and **17** showed slight activity (IC_{50} vs Flu A sialidase **4:** 280μM, **17:** 140μM), but all the others were inactive at 500μM.

Conclusion

We have demonstrated that synthesis of analogues of GG167 containing simplified 6-substituents is possible via an inverse demand hetero Diels Alder strategy. Further optimisation of the cyclisation conditions and substituents could potentially lead to novel compounds with useful biological properties.

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16. ^{1}H NMR **11:** ($CDCl_3$) 6.08 (br d, J 8Hz, 5-NH), 5.84 (d, J 2Hz, H-3), 5.04 (d, J 2Hz, H-6equatorial), 4.69 (br d, J 9Hz, 4-NH), 4.54 (br dt, J 9Hz, H-4axial), 4.11 (br dt, H-5axial), 3.49 (s, 3H, OCH_3), 2.00 (s, 3H, $COCH_3$), 1.50, 1.43 (2s, 18H, tBu). **12:** (d_6 DMSO) 7.78 (d, J 9Hz, 4-NH), 5.84 (d, J 4Hz, H-3), 5.80 (d, J 9Hz, 5-NH), 5.02 (d, J 2Hz, H6), 4.32 - 4.2 (m, 2H, H-4,5), 3.38 (s, 3H, OCH_3), 1.86 (s, 3H, $COCH_3$), 1.46, 1.39 (2s, 18H, tBu). **13:** ($CDCl_3$) 6.68 (br d, J 10 Hz, 6-NH), 5.84 (dd, J 6,2 Hz, H-3), 5.55 (br d, J 10Hz, H-6axial), 4.66 (br d, J 6Hz, 4-NH), 4.33 (br t, J 6Hz, H-4equatorial), 3.56 (s, 3H, OCH_3), 3.39 (q, 2Hz, H-5equatorial), 2.08 (s, 3H, $COCH_3$), 1.5-1.4 (2s, 18H, tBu). nOe's observed from H-4 to H-3,5 and OCH_3, and from H-6 to 6-NH, 4-NH and H-5.

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