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Graphical Abstract

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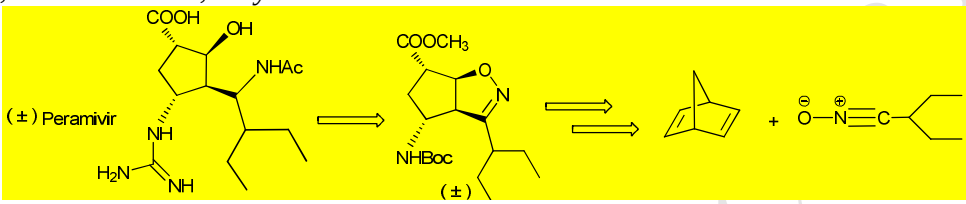

A novel synthetic approach to the racemic Neuraminidase inhibitor Peramivir

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Abstract – An advanced intermediate in the synthesis of the racemic Neuraminidase inhibitor *Peramivir* was synthesised in a new and versatile manner starting from a stereoselective 1,3-dipolar cycloaddition reaction between the nitrile oxide deriving from 2-ethylbutanal and the commercially available and inexpensive bicyclo[2.2.1]hepta-2,5-diene. The reaction mainly afforded the *exo*-isoxazolino-norbornene derivative from which the oxidative cleavage of the carbon-carbon double bond followed by subsequent dehydration led to the corresponding anhydride intermediate. Amines and alcohols were used as nucleophiles for opening the anhydride, with amines providing the better results. Both the monoester-monoacid and the monoester-monoamide were transformed into the monoester-monoamino intermediate from which the synthesis continued using previously published methods. In the best protocol, the total yield of this key intermediate was increased up to 17% from bicyclo[2.2.1]hepta-2,5-diene.

Keywords: Peramivir; Neuraminidase inhibitor; Bicyclo[2.2.1]hepta-2,5-diene; 1,3-Dipolar cycloaddition.

1. Introduction

Influenza viruses infect an enormous number of people each year,[1] and the resulting epidemics lead to substantial costs for the community and a high mortality rate.[2] The infection is particularly dangerous for children, the elderly, and people with immunosuppression.[3]

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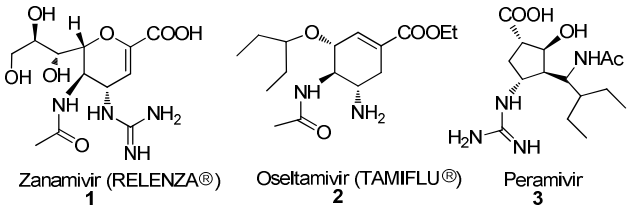
Vaccination remains the primary preventive measure although it provides limited control, partially because influenza viruses mutate very rapidly and there is a continuous emergence of new strains to which even previously vaccinated subjects remain sensitive.[4]

The target of the compounds that have most recently been used in influenza prophylaxis is influenza Neuraminidase, a viral surface enzyme belonging to the family of Glycoside Hydrolases.[5] Neuraminidase catalyses the cleavage of the glycosidic bond between a terminal sialic acid and Hemagglutinin, thus allowing the virion to escape from infected host cells and spread the infection in the respiratory tract.

The first Neuraminidase inhibitors, which prevent the virus from reproducing and therefore slow the spread of the infection, were *Zanamivir*[6] **1** and *Oseltamivir*[7] **2** (Fig. 1).

Figure 1

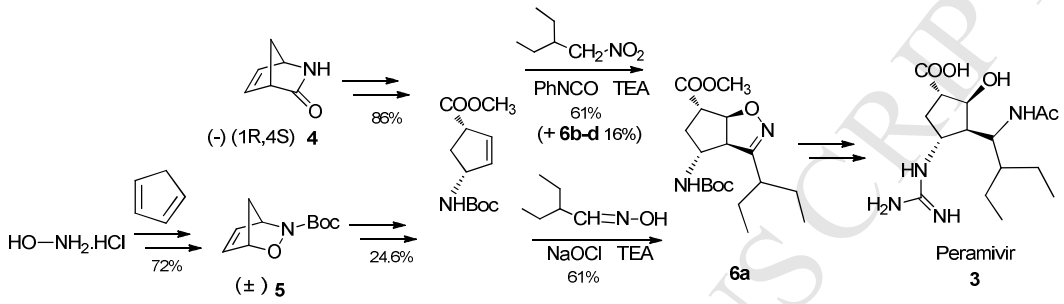


The clinical use of *Zanamivir* is hampered by the fact that its limited oral bioavailability means that it must be administered by oral inhalation, whereas the second-generation Neuraminidase inhibitor *Oseltamivir* has good oral activity as a pro-drug. Both products have side effects: headache and diarrhoea in the case of *Zanamivir*, and nausea and vomiting in the case of *Oseltamivir*. The new *Peramivir*[8] Neuraminidase inhibitor **3** has recently proved to be very potent against a variety of strains of influenza, and more effective than *Zanamivir* or *Oseltamivir*,[9] but its poor bioavailability has aroused considerable interest in designing and synthesising analogous structures.[10] Finding new, versatile and efficient means of synthesis could promote the structure-activity relationship (SAR) studies necessary for the development of new inhibitors.

A number of studies of *Peramivir* synthesis have been published.[11] The starting material in the first studies,[11a,b] and in a recent improvement,[11d] was (-)-(1R,4S)-2-azabicyclo[2.2.1]hept-5-en-3-one **4** (*Vince's* lactam),[12] which is commercially available as an expensive pure enantiomer. Using a different

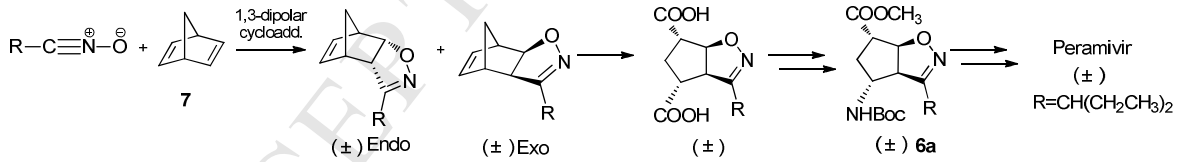
approach, Miller[11c] started with the racemic 2-oxa-3-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylic acid tert-butyl ester **5** obtained from the hetero-Diels-Alder cycloaddition between N-Boc-protected hydroxylamine and cyclopentadiene. Both syntheses have the bicyclic isoxazoline **6a** as a common key intermediate (Scheme 1).

Scheme 1



Given our interest in the stereoselective synthesis of highly functionalised heterocycles using 1,3-dipolar cycloaddition reactions,[13] we here describe a new approach to the synthesis of *Peramivir* in which the isoxazoline ring of intermediate **6a** was generated by a 1,3-dipolar cycloaddition between a suitable nitrile oxide and the commercially available and inexpensive bicyclo[2.2.1]hepta-2,5-diene (2,5-norbornadiene-NBD) **7,** as outlined in Scheme 2.

Scheme 2



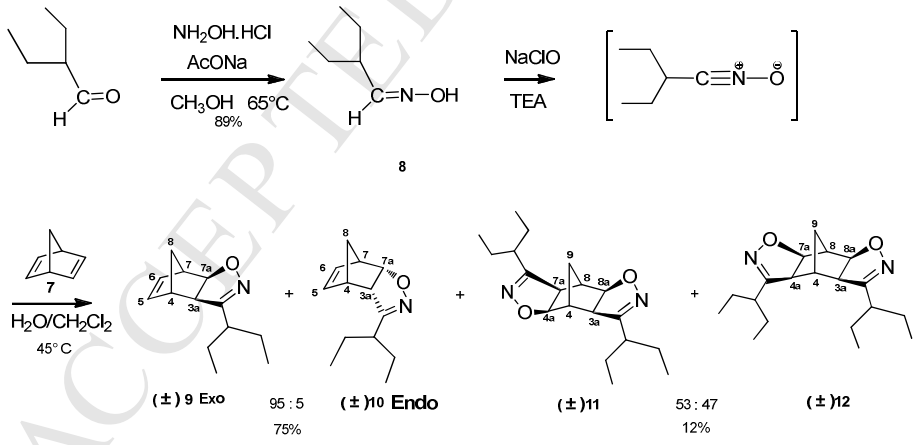
The cycloaddition reaction does not pose any problems of regioselectivity, only stereoselectivity. Only the *exo*-adduct has the cyclopentane ring with the correct steric relationships of the four substituents of *Peramivir*. Furthermore, published data concerning 1,3-dipolar cycloaddition reactions between 2,5-norbornadiene and nitrile oxides have always shown stereo-selectivity in favour of the *exo*-isomer, thus predicting a similar result in our case.[14] The next norbornene opening takes advantage of the presence of the carbon-carbon double bond: the two carboxylic groups can be introduced by means of oxidative cleavage, and appropriately transformed into the acid and substituted amino groups on intermediate **6a** of

Peramivir. This approach should provide greater versatility in synthesising structural analogues of *Peramivir*, particularly in relation to the substitution ($R \neq CH(CH_2CH_3)_2$).

2. Results and discussion

The synthetic scheme was developed for the racemic *Peramivir*. Oxime **8**, the precursor of the nitrile oxide, was prepared from the corresponding commercially available 2-ethylbutanal and hydroxylamine at reflux in MeOH (Scheme 3),[15] and then transformed into the corresponding 1,3-dipole by means of treatment with NaOCl and TEA in a biphasic system, in the presence of an excess of 2,5-norbornadiene **7**. The reaction gave a mixture of the *exo*- and *endo*-adducts **9** and **10** in a 95:5 ratio regardless of the observed yield, which depends on the ratio between 2,5-norbornadiene **7** and oxime **8** is used: total yield was 42% with a ratio of 2:1, but up to 75% with a ratio of 4:1 (the excess 2,5-norbornadiene can be recovered at the end of the reaction by means of distillation). A mixture of the two regioisomers **11** and **12** was also obtained from *exo*-adduct **9** as a result of a double 1,3-dipolar cycloaddition. *Exo*-adduct **9** was easily separated from the other products by means of chromatography on silica gel (Scheme 3).

Scheme 3

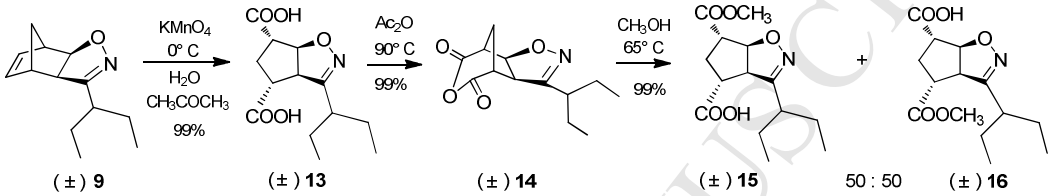


NMR spectroscopy was used to assign *exo* and *endo* to mono-adducts **9** and **10**. In *exo*-adduct **9,** the coupling constant of the bridgehead protons H-3a and H-7a with the adjacent *endo*-protons H-4 and H-7 was 0 Hz ($J_{H3a,H4} = J_{H7a,7} = 0$ Hz) whereas, in *endo*-adduct **10**, the corresponding coupling constant of protons H-3a and H-7a with the adjacent *exo*-protons H-4 and H-7 was 4.0 Hz ($J_{H3a,H4} = J_{H7a,7} = 4.0$ Hz). These values are in line with published findings concerning analogous compounds,[14a,e] and supported by

calculations based on the *Karplus* equation and molecular geometries.[14d] Adducts **11** and **12** were also isolated, and their exact regiochemistry attributed by comparison of the relative NMR spectroscopic data with those of analogous compounds.[14a,d,e]

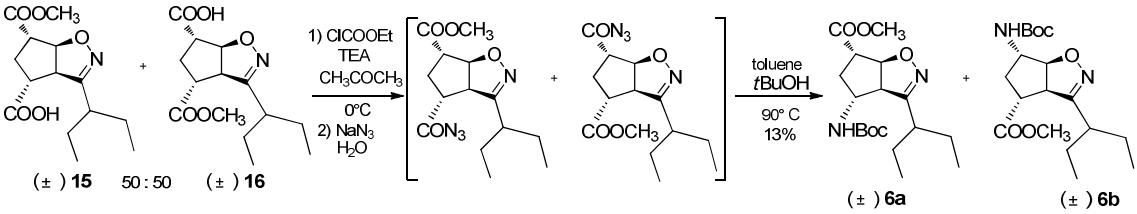
The synthetic approach considered the oxidative cleavage of the carbon-carbon double bond with the insertion of two carboxylic groups, so the *exo*-adduct **9** was transformed into the dicarboxylic acid **13** by treating it with $KMnO_4$ under controlled conditions (Scheme 4).

Scheme 4



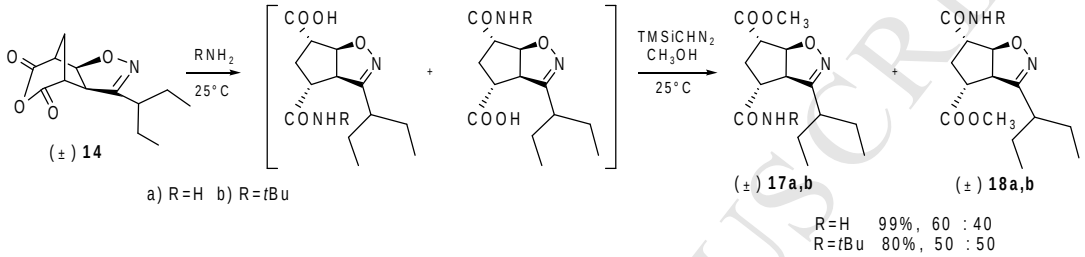
A key point of the synthesis was expected to be the regioselective differentiation of the two carboxylic groups. We decided to synthesise the intermediate cyclic anhydride **14**, which could be opened by a suitable nucleophile to obtain a dicarboxylic acid mono-acyl azide or mono-amide from which to obtain an amino group using *Curtius* or *Hoffmann* rearrangements. We verified both possibilities. Anhydride **14** was prepared in quantitative yield by heating the diacid **13** with acetic anhydride, then turned into a 50:50 mixture of the two mono-ester, mono-acid regioisomers **15** and **16** by heating with MeOH (Scheme 4). This mixture was inseparable, therefore it was used as such in the next step. Numerous ways of carrying out *Curtius* rearrangement were tested,[16] but only activation of the carboxylic group with $ClCO_2Et$ followed by treatment with sodium azide and heating in toluene/*t*BuOH[16e] led to a mixture of the unreacted compounds **15** and **16** and the regioisomeric products **6a** and **6b,**[11b] and then with a total yield of only 13% (Scheme 5).

Scheme 5



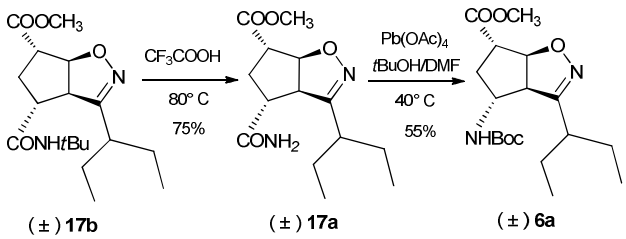
Considering these results unsatisfactory, we turned our attention to *Hoffmann* rearrangement for which it was necessary to prepare the mono-ester, mono-amide derivative. A THF solution of anhydride **14** was first treated with gaseous ammonia in methanol and then with $TMSiCHN_2$ to yield a mixture of the two regioisomeric compounds **17a** and **18a** in a ratio of 60:40, as estimated by integrating the peaks of proton H-6a in the ^1H NMR spectra of the crude reaction mixture (Scheme 6).

Scheme 6



The exact regiochemistry of the two products was established by comparing them with the amides obtained from deprotecting the corresponding *N*-*t*Bu-amides, as described below. The observed regioselectivity of the opening of the anhydride was unsatisfactory, and it was not possible to separate the two mono-amides by means of flash chromatography, not even as mono-acid intermediates. With the aim of improving regioselectivity, anhydride **14** was treated with the more sterically hindered amine *t*Bu-NH_2. Although regioselectivity remained poor, it was possible to separate the mono-amide/mono-ester regioisomers **17b** and **18b** by means of flash chromatography and confirm their structures on the basis of analytical and spectroscopic data (HSQC, HMBC and COSY experiments). Structures **17b** and **18b** were respectively assigned to the regioisomers having the H-6a proton signal at 5.31 and 5.01 δ. Finally the *t*-butyl group was removed by treating compound **17b** with trifluoroacetic acid, thus obtaining amide **17a** (Scheme 7).

Scheme 7

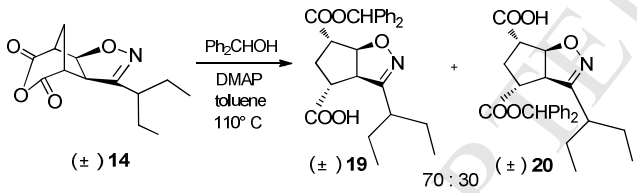


Unsuccessful attempts were made to develop *Hoffmann* rearrangements of **17a** using aqueous $NaOH/Br_2$ or CH_3ONa/Br_2 in methanol.[17a] The protocol that provided the best results was heating amide **17a** with lead tetracetate in a mixture of *t*-butanol and DMF.[17b,c] Under these conditions, the reaction directly afforded the amino *N*-Boc protected derivative **6a** (Scheme 7). The synthesis of *Peramivir* was completed from **6a** using previously reported procedures and with similar results.[11b,d]

By means of this sequence, the isoxazoline intermediate **6a** was obtained from 2,5-norbornadiene in six steps, with a total yield of about 11.5%, which is comparable with that obtained by Miller (10.8% from hydroxylamine hydrochloride in seven steps),[11c] but lower than that reported by Chand (52% from *Vince*'s lactam in two steps).[11b] This was mainly due to the lack of regioselectivity observed when opening the anhydride **14** with *t*Bu-NH_2.

With the aim of testing regioselectivity when opening the anhydride with other nucleophiles, **14** was treated with the sterically hindered alcohol benzhydrol. The reaction required a long time at high temperatures, but provided a mixture of the two ester regioisomers **19** and **20** in a 70:30 ratio (Scheme 8).

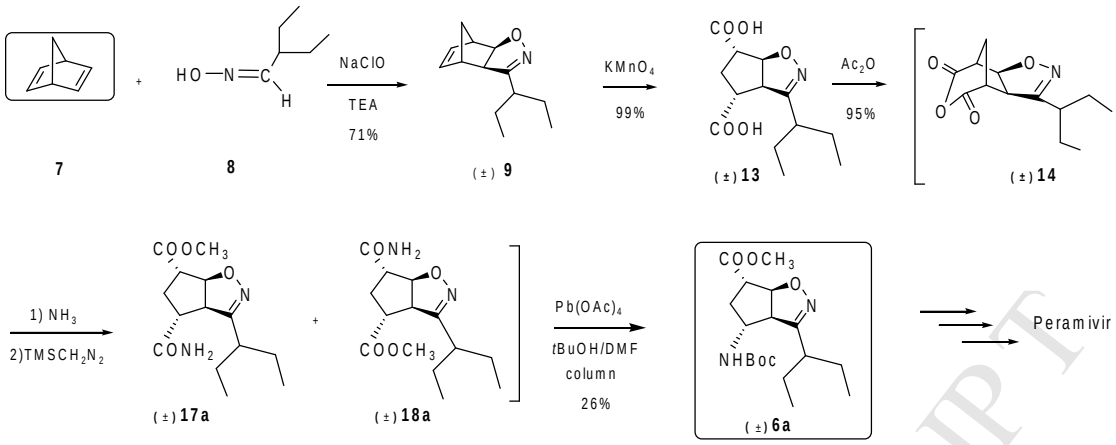
Scheme 8



Compound **19** was easily separated from the other product by means of chromatography on silica gel, but the yield was only 23%.

Given the difficulty in obtaining the regioselective opening of anhydride **14** with alcohols or sterically hindered amines, we reconsidered using ammonia. As intermediate **6a** can be separated chromatographically from its regioisomer **6b**,[11b] the anhydride was opened with ammonia, and the subsequent reactions were carried out on the mixture of the two amides **17a** and **18a**. In this way, the desired bicyclic isoxazoline **6a** was isolated, from 2,5-norbornadiene **7** in five steps, with an overall yield of 17% (Scheme 9).

Scheme 9



3. Conclusions

We describe new strategy for obtaining racemic *Peramivir*, a potent Neuraminidase inhibitor approved by FDA as an anti-influenza drug. In order to synthesise the tricyclic system from which to obtain the cyclopentane nucleus, we used a 1,3-dipolar cycloaddition reaction of the appropriate nitrile oxide on 2,5-norbornadiene. In this way, intermediate **6a** was synthesised using inexpensive, commercially available reagents, and simple reactions. This approach represents an improvement of the previously reported processes, and makes it possible to obtain potential Neuraminidase inhibiting analogues of *Peramivir* by varying the alkyl group of the nitrile oxide used.

4. Experimental Section

4.1. General methods

Melting points were determined on a *Büchi* B-540 apparatus . ^{1}H and ^{13}C NMR spectra were recorded using a *Varian-Gemini 200 MHz* spectrometer. Chemical shifts (δ) are given in ppm in relation to TMS; the solvent was $CDCl_3$ unless otherwise specified. All of the coupling constants (J) are in Hertz. Elemental analyses were performed by the Microanalytical Laboratory of the Department. The MS spectra were recorded with a *Thermo-Finnigan LCQ* advantage AP electrospray/ion trap equipped instrument using a syringe pump device to directly inject sample solutions. Bicyclo[2.2.1]hepta-2,5-diene and 2-ethylbutanal were obtained from commercial sources. Oxime **8**[15] was prepared following the reported method.

4.2. 1,3-Dipolar cycloaddition of 2,5-norbornadiene 7 with 2-ethyl-butanenitrile oxide. A 4.5% aqueous solution of NaClO (229.4 mL) was added dropwise to a solution of bicyclo[2.2.1]hepta-2,5-diene **7** (25.61 g, 278.4 mmol, 4 equiv.), oxime **8** (8.0 g, 69.6 mmol, 1 equiv.) and TEA (0.64 mL, 4.64 mmol, 0.06 equiv.) in CH_2Cl_2 (100 mL). The mixture was stirred for 20 h at 45°C, and then cooled to room temperature, the phases were separated and the aqueous phase was extracted using CH_2Cl_2 (3x30 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated at reduced pressure. Compounds **9**, **10**, **11** and **12** were separated by means of column chromatography on silica gel (from hexane/ethyl acetate=95/5 to hexane/ethyl acetate=75/25).

*4.2.1 (±)-exo-Cycloadduct (**9**)*: Colorless oil (R_f 0.55, hexane/ethyl acetate=90/10, I_2), (10.1 g, 71%). ^{1}H NMR: δ 0.90 (t, *J*=7.3, 6H, $2CH_3$); 1.43-1.79 (m, 6H, 2H-8 + $2CH_2$); 2.16-2.28 (m, 1H, CH); 2.98 (broad s, 1H, H-4); 3.17 (broad s, 1H, H-7); 3.26 (d, *J*=8.1, 1H, H-3a); 4.75 (d, *J*=8.1, 1H, H-7a); 6.00-6.05, 6.20-6.24 (2m, 2H, H-5 + H-6). ^{13}C NMR: δ 11.6, 12.3 ($2CH_3$); 24.7, 26.1 ($2CH_2$); 41.7 (CH); 43.4 (C-8); 44.9, 49.7 (C-4, C-7); 59.3 (C-3a); 87.9 (C-7a); 135.9, 140.1 (C-5, C-6); 160.2 (C-3). IR (nujol): 705 ($\delta_{C\text{-}H}$, CH=CH), 1604 ($\nu_{C=N}$, C=N), 1706 ($\nu_{C=C}$, C=C). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.01; H 9.29; N, 6.78. MS-ESI$^+$ (m/z): 206 $[M+H]^+$, 228 $[M+Na]^+$.

*4.2.2 (±)-endo-Cycloadduct (**10**)*: Colorless oil (R_f 0.40, hexane/ethyl acetate=90/10, I_2), (0.57 g, 4%). ^{1}H NMR: δ 0.88, 0.89 (2t, *J*=7.4, 6H, $2CH_3$); 1.44-1.69 (m, 6H, 2H-8 + $2CH_2$); 2.07-2.17 (m, 1H, CH); 3.10 (broad s, 1H, H-4); 3.29 (broad s, 1H, H-7); 3.64 (dd, *J*=9.5, 4.0, 1H, H-3a); 5.20 (dd, *J*=9.5, 4.0, 1H, H-7a); 6.02-6.13, 6.15-6.20 (2m, 2H, H-5 + H-6). ^{13}C NMR: δ 11.4, 12.3 ($2CH_3$); 23.8, 25.2 ($2CH_2$); 41.3 (CH); 43.4 (C-8); 46.6, 47.7 (C-4, C-7); 58.5 (C-3a); 85.9 (C-7a); 134.3, 135.3 (C-5, C-6); 160.9 (C-3). IR (nujol): 726 ($\delta_{C\text{-}H}$, CH=CH), 1602 ($\nu_{C=N}$, C=N), 1727 ($\nu_{C=C}$, C=C). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.02; H 9.28; N, 6.77. MS-ESI$^+$ (m/z): 206 $[M+H]^+$, 228 $[M+Na]^+$.

*4.2.3 (±)-Cycloadduct (**11**)*: Colorless amorphous glass (R_f 0.20, hexane/ethyl acetate=90/10, I_2), (0.7 g, 6.4%). ^{1}H NMR: δ 0.86 (t, *J*=7.3, 12H, 4CH_3); 1.46-1.60 (m, 10H, 2H-9 + 4CH_2); 2.22-229 (m, 2H, 2CH); 2.69 (broad s, 2H, H-4, H-8); 3.00 (d, *J*=8.4, 2H, H-3a, H-7a); 4.47 (d, *J*=8.1, 2H, H-4a, H-8a). ^{13}C NMR: δ 11.5, 12.2 (4CH_3); 24.7, 26.1 (4CH_2); 27.0 (C-9); 41.5 (2CH); 45.5 (C-4, C-8); 54.4 (C-3a, C-7a); 85.1 (C-4a, C-8a); 160.0 (C-3, C-7). IR (nujol): 1614 ($\nu_{C=N}$, C=N). Anal. Calcd for $C_{19}H_{30}N_2O_2$: C, 71.66; H, 9.50; N, 8.80. Found: C, 71.62; H 9.45; N, 8.71. MS-ESI$^+$ (m/z): 319 $[M+H]^+$, 341 $[M+Na]^+$.

*4.2.4 (±)-Cycloadduct (**12**)*: Colorless amorphous glass (R_f 0.10, hexane/ethyl acetate=90/10, I_2), (0.62 g, 5.6%). ^{1}H NMR: δ 0.91 (t, *J*=7.3, 12H, 4CH_3); 1.53-1.69 (m, 10H, 2H-9 + 4CH_2); 2.22-2.29 (m, 2H, 2CH); 2.46 (broad s, 1H, H-4); 2.94 (broad s, 1H, H-8); 3.13 (d, *J*=8.1, 2H, H-3a + H-4a); 4.46 (d, *J*=8.1, 2H, H-7a + H-8a).^{13}C NMR: δ 11.4, 12.3 (4CH_3); 24.6, 26.0 (4CH_2); 27.2 (C-9); 41.2 (2CH); 41.3 (C-4); 50.3 (C-8); 58.4 (C-3a, C-4a); 82.1 (C-7a, C-8a); 159.9 (C-3, C-5). IR (nujol): 1609 ($\nu_{C=N}$, C=N). Anal. Calcd for $C_{19}H_{30}N_2O_2$: C, 71.66; H, 9.50; N, 8.80. Found: C, 71.59; H 9.37; N, 8.68. MS-ESI$^+$ (m/z): 319 $[M+H]^+$, 341 $[M+Na]^+$.

*4.3. (±)-3-(1-Ethyl-propyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-4,6-dicarboxylic acid (**13**)*. A solution of (±) *exo*-cycloadduct **9** (4.3 g, 21.0 mmol) in acetone (38 mL) was added dropwise to a solution of $KMnO_4$ (11.0 g, 69.6 mmol) in H_2O (38 mL) and cooled to 0°C, while maintaining the temperature between 0 and 5° C. The mixture was stirred for 3 h at room temperature, cooled to 0°C and treated with $Na_2S_2O_5$ (13.22 g, 69.6 mmol), stirred for 0.5 h at room temperature, and then acidified to pH 2 with concentrated HCl and extracted using ethyl acetate. The organic phase was separated and dried over anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo*. Compound **(±)-13** was obtained as a colourless solid, (5.6 g, 99%); (R_f 0.25, toluene/dioxane/AcOH=4.5/1/0.1, bromocresol green); m.p. 133-35 °C (diisopropyl ether). ^{1}H NMR (CD_3OD): δ 0.89, 0.93 (2t, *J*=6.9, 6H, 2CH_3); 1.53-1.70 (m, 4H, 2CH_2); 2.17-2.42 (m, 3H, CH + 2H-5); 2.89-3.01 (m, 2H, H-4 + H-6); 4.09 (dd, *J*=9.9, 5.5, 1H, H-3a); 5.21 (dd, *J*=9.9, 4.8, 1H, H-6a). ^{13}C NMR (CD_3OD): δ 10.2, 11.4 (2CH_3); 24.0, 25.4 (2CH_2); 32.2 (C-5);

40.9 (CH); 48.0, 52.3 (C-4, C-6); 57.2 (C-3a); 87.4 (C-6a); 162.8 (C-3); 173.8, 174.9 (2C=O). The assignments of the signals was made based on the HSQC NMR spectra. IR (nujol): 2970 (ν_{O-H}, O-H), 1726 ($\nu_{C=O}$, C=O), 1612 ($\nu_{C=N}$, C=N). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.92; H 7.05; N, 5.11. MS-ESI$^+$ (m/z): 270 $[M+H]^+$, 292 $[M+Na]^+$.

*4.4. (±)-5-(1-Ethyl-propyl)-3,9-dioxa-4-aza-tricyclo[5.3.1.0^{2,6}]undec-4-ene-8,10-dione (**14**).* A solution of diacid (±)-**13** (1.0 g, 3.72 mmol) in acetic anhydride (8 mL) was stirred for 18 h at 90°C. The acetic anhydride was evaporated *in vacuo* to afford the compound **(±)-14** as a light brown solid that was used without further purification, (0.92 g, 99%); m.p. 124-26 °C. ^{1}H NMR: δ 0.92 (t, *J*=7.3, 6H, $2CH_3$); 1.59-1.68 (m, 4H, $2CH_2$); 1.92-2.09 (m, 1H, CH); 2.28-2.36 (m, 2H, 2H-11); 3.31 (d, *J*=3.2, 1H, H-7); 3.58 (d, *J*=3.2, 1H, H-1); 3.88 (d, *J*=8.2, 1H, H-6); 5.13 (d, *J*=8.2, 1H, H-2).

*4.5. (±)-3-(1-Ethyl-propyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-4,6-dicarboxylic acid 6-methyl ester (**15**) and (±)-3-(1-Ethyl-propyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-4,6-dicarboxylic acid 4-methyl ester (**16**).* A solution of anhydride (±)-**14** (0.92 g, 3.67 mmol) in anhydrous CH_3OH (5 mL) was stirred for 18 h at 65°C. The solvent was evaporated *in vacuo* to afford an inseparable 50:50 mixture of the two mono-ester, mono-acid regioisomers **(±)-15** and **(±)-16** as shown by the ^{1}H NMR spectrum, (1.03 g, 99%); (R_f 0.5, $CHCl_3/CH_3OH$/AcOH=97/2/1, bromocresol green). ^{1}H NMR: δ 0.89, 0.90 (2t, *J*=6.9, 6H, $2CH_3$); 1.54-1.67 (m, 4H, $2CH_2$); 2.27-2.37 (m, 3H, CH + 2H-5); 2.91-2.95, 3.08-3.14 (m, 2H, H-4 + H-6); 3.70, 3.72 (2s, 3H, OCH_3); 4.08 (dd, *J*=9.2, 4.0, 1H, H-3a); 5.29 (dt, *J*=9.5, 3.3, 1H, H-6a); 8.40 (broad s, 1H, COOH). ^{13}C NMR: δ 11.1, 12.3 ($2CH_3$); 24.2, 25.7 ($2CH_2$); 32.0 (C-5); 40.9 (CH); 47.9, 52.3 (C-4, C-6); 52.0, 52.7 (OCH_3); 56.9, 57.1 (C-3a); 87.1, 87.3 (C-6a); 161.9, 162.0 (C-3); 173.1, 173.5 (C=O); 177.5, 177.8 (C=O). IR (nujol): 2964 (ν_{O-H}, O-H), 1737 ($\nu_{C=O}$, C=O), 1612 ($\nu_{C=N}$, C=N). MS-ESI$^+$ (m/z): 284 $[M+H]^+$.

*4.6. (±)-4-Carbamoyl-3-(1-ethyl-propyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-6-carboxylic acid methyl ester (**17a**) and (±)-6-Carbamoyl-3-(1-ethyl-propyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-4-carboxylic acid methyl ester (**18a**).* NH_3 (7N in CH_3OH) (3.0 mL, 21.0 mmol) was added to a solution of anhydride (±)-**14** (0.92 g, 3.67 mmol) in anhydrous THF (10 mL). The mixture was stirred for 18 h at room temperature, and then the solvent was evaporated *in vacuo*. The residue was treated with H_2O, acidified to pH 2 with concentrated HCl, and extracted using ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was evaporated off. The residue was then dissolved in anhydrous THF (10 mL) and treated with $TMSiCHN_2$ 2N in hexane (5.5 mL, 11.0 mmol). The mixture was stirred for 18 h at room temperature, after which CH_3OH (3.0 mL) was added and the solvent was evaporated *in vacuo* to afford an inseparable 60:40 mixture of the two mono-ester, mono-amide regioisomers **(±)-17a** and **(±)-18a**, as shown by the ^{1}H NMR spectrum, (1.02 g, 99%); (R_f 0.35, hexane/ethyl acetate =25/75, I_2). ^{1}H NMR: δ 0.89, 0.91 (2t, *J*=7.6, 6H, $2CH_3$); 1.52-1.82 (m, 4H, $2CH_2$); 2.2-2.34 (m, 3H, CH + 2H-5); 2.74- 3.12 (m, 2H, H-4 + H-6); 3.73, 3.74 (2s, 3H, OCH_3); 4.12 (dd, *J*=9.9, 5.9, 1H, H-3a); 5.07 (dd, *J*=10.3, 5.5, 1H (40%), H-6a); 5.31 (dd, *J*=10.3, 4.4, 1H (60%), H-6a); 5.61-5.86 (broad m, 2H, NH_2). The products were fully characterised after being obtained pure (see below).

*4.7. (±)-4-tert-Butylcarbamoyl-3-(1-ethyl-propyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-6-carboxylic acid methyl ester (**17b**) and (±)-6-tert-Butylcarbamoyl-3-(1-ethyl-propyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-4-carboxylic acid methyl ester (**18b**).* *tert*$BuNH_2$ (1.6 mL, 14.9 mmol) was added to a solution of anhydride (±)-**14** (1.87 g, 7.43 mmol) in anhydrous THF (15 mL). The mixture was stirred for 18 h at room temperature, after which the solvent was evaporated *in vacuo*. The residue was treated with H_2O, acidified to pH 2 with concentrated HCl, and extracted using ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4, and the solvent was evaporated off. The residue was then dissolved in anhydrous THF (10 mL) and treated with $TMSiCHN_2$ 2N in hexane (11.15 mL, 22.3 mmol). The mixture was stirred for 18 h at room temperature, after which CH_3OH (6.0 mL) was added and the solvent was evaporated *in vacuo* to give a 50:50 mixture of the two mono-ester, mono-amide

regioisomers **(±)-17b** and **(±)-18b**, as shown by the NMR spectrum. The products were separated by means of flash chromatography (silica gel, hexane/ethyl acetate =65/35), and their exact regiochemistry was assigned by HSQC, HMBC and COSY experiments.

(±)-17b (1.0 g, 40%); colourless solid, m.p. 108-111 °C; (R_f 0.35, hexane/ethyl acetate =65/35, I_2). ^{1}H NMR: δ 0.90, 0.92 (2t, *J*=7.3, 6H, $2CH_3$); 1.36 (s, 9H, $C(CH_3)_3$); 1.50-1.65 (m, 4H, $2CH_2$); 2.18-2.29 (m, 3H, C-H + 2H-5); 2.53-2.60 (m, 1H, H-4); 2.96-3.06 (m, 1H, H-6); 3.73 (s, 3H, OCH_3); 4.09 (dd, *J*=10.2, 6.4, 1H, H-3a); 5.31 (dd, *J*=10.2, 4.6, 1H, H-6a); 5.53 (broad s, 1H, NH). ^{13}C NMR: δ 11.4, 12.5 ($2CH_3$); 24.3, 25.7 ($2CH_2$); 29.1 ($C(CH_3)_3$); 34.9 (C-5); 41.3 (CH); 51.1 (C-4); 51.9 ($C(CH_3)_3$); 52.6 (OCH_3); 53.1 (C-6); 57.1 (C-3a); 87.8 (C-6a); 162.7 (C-3); 171.2 (N-C=O); 173.0 (O-C=O). Anal. Calcd for $C_{18}H_{30}N_2O_4$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.81; H 8.85; N, 8.19. MS-ESI$^+$ (m/z): 339 $[M+H]^+$, 361 $[M+Na]^+$.

(±)-18b (1.0 g, 40%); colourless solid, m.p. 85-88 °C; (R_f 0.5, hexane/ethyl acetate =65/35, I_2). ^{1}H NMR: δ 0.86, 0.89 (2t, *J*=7.3, 6H, $2CH_3$); 1.32 (s, 9H, $C(CH_3)_3$); 1.47-1.68 (m, 4H, $2CH_2$); 2.20, 2.21 (2t, *J*=7.8, 2H, 2H-5); 2.28-2.35 (m, 1H, C-H); 2.55-2.63 (m, 1H, H-6); 2.78-2.89 (m, 1H, H-4); 3.73 (s, 3H, OCH_3); 4.10 (dd, *J*=10.1, 5.9, 1H, H-3a); 5.01 (dd, *J*=10.1, 5.5, 1H, H-6a); 5.60 (broad s, 1H, NH). ^{13}C NMR: δ 11.2, 12.5 ($2CH_3$); 24.3, 25.7 ($2CH_2$); 29.1 ($C(CH_3)_3$); 32.4 (C-5); 40.9 (CH); 47.7 (C-4); 51.8 ($C(CH_3)_3$); 52.7 (OCH_3); 54.4 (C-6); 57.4 (C-3a); 87.9 (C-6a); 162.8 (C-3); 171.0 (N-C=O); 173.5 (O-C=O). Anal. Calcd for $C_{18}H_{30}N_2O_4$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.79; H 8.84; N, 8.18. MS-ESI$^+$ (m/z): 339 $[M+H]^+$, 361 $[M+Na]^+$.

*4.8. (±)-4-Carbamoyl-3-(1-ethyl-propyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-6-carboxylic acid methyl ester (**17a.**)* A solution of (±)-**17b** (0.2 g, 0.6 mmol) in anhydrous TFA (3 mL) was heated to 80°C for 24 h. The mixture was cooled on ice, and a saturated solution of Na_2CO_3 was added until pH=7. The solution was extracted using ethyl acetate, after which the extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated off to give compound **(±)-17a** as an amorphous glass (0.125 g, 75%). ^{1}H NMR: δ 0.89, 0.90 (2t, *J*=7.3, 6H, $2CH_3$); 1.48-1.62 (m, 4H, $2CH_2$); 2.20-2.31 (m, 3H, CH +

2H-5); 2.74-2.84 (m, 1H, H-4); 3.01-3.11 (m, 1H, H-6); 3.73 (s, 3H, OCH_3); 4.12 (dd, *J*=9.9, 5.5, 1H, H-3a); 5.31 (dd, *J*=10.3, 4.4, 1H, H-6a); 5.61 (broad s, 2H, NH_2). ^{13}C NMR: δ 11.1, 12.3 ($2CH_3$); 24.1, 25.6 ($2CH_2$); 34.1 (C-5); 41.0 (CH); 49.2 (C-4); 52.5 (OCH_3); 52.9 (C-6); 56.9 (C-3a); 87.5 (C-6a); 162.3 (C-3); 173.0 (N-C=O); 174.7 (O-C=O). Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.48; H 7.76; N, 9.84. MS-ESI$^+$ (m/z): 305 $[M+Na]^+$.

*4.9. (±)-6-Carbamoyl-3-(1-ethyl-propyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-4-carboxylic acid methyl ester (**18a**).* Compound **(±)-18a** was obtained as described for compound **(±)-17a**. Amorphous glass (80%). ^{1}H NMR: δ0.88, 0.91 (2t, *J*=7.3, 6H, $2CH_3$); 1.52-1.66 (m, 4H, $2CH_2$); 2.24 (t, *J*=8.4, 2H, 2H-5); 2.29-2.35 (m, 1H, CH); 2.74-2.95 (m, 2H, H-4 + H-6); 3.74 (s, 3H, OCH_3); 4.06-4.16 (m, 1H, H-3a); 5.07 (dd, *J*=10.3, 5.5, 1H, H-6a); 5.85 (broad s, 2H, NH_2). ^{13}C NMR: δ 11.0, 12.3 ($2CH_3$); 24.1, 25.5 ($2CH_2$); 32.3 (C-5); 40.8 (CH); 47.6 (C-4); 52.7 (OCH_3); 53.0 (C-6); 57.2 (C-3a); 87.7 (C-6a); 162.6 (C-3); 173.4 (N-C=O); 174.3 (O-C=O). Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.46; H 7.79; N, 9.88. MS-ESI$^+$ (m/z): 305 $[M+Na]^+$.

*4.10. (±)-4-tert-Butoxycarbonylamino-3-(1-ethyl-propyl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-6-carboxylic acid methyl ester (**6a**).* A solution of (±)-**17a** (0.244 g, 0.77 mmol) in a mixture of *t*BuOH (4 mL) and DMF (2 mL) was heated to 40°C. After the addition of $Pb(OAc)_4$ (1.7 g, 2.31 mmol), the mixture was heated to 80°C for 8 h. The solvent was evaporated, and the residue was treated with water and extracted using ethyl acetate (3x15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated by means of rotary evaporation. The resulting residue was purified by means of column chromatography (silica gel, hexane/ethyl acetate =85/15) to give compound **(±)-6a** as a white solid (0.169 g, 55%), m.p. 108-109 °C. ^{1}H NMR: δ0.88, 0.91 (2t, *J*=7.3, 6H, $2CH_3$); 1.43 (s, 9H, *t*Bu); 1.57-1.73 (m, 4H, $2CH_2$); 2.02-2.11 (m, 2H, 2H-5); 2.43-2.53 (m, 1H, CH); 3.18 (broad d, 1H, *J*=6.6, H-6); 3.57 (d, 1H, *J*=9.2, H-3a); 3.75 (s, 3H, OCH_3); 4.21 (m, 1H, H-4); 5.19 (d,

J=9.2, 1H, H-6a); 5.58 (broad d, *J*=7.7, 1H, NH). Anal. Calcd for $C_{18}H_{30}N_2O_5$: C, 61.00; H, 8.53; N, 7.90. Found: C, 60.89; H 8.47; N, 7.83. MS-ESI$^+$ (m/z): 377 $[M+Na]^+$.

*4.11. (±)-3-(1-Ethyl-propyl)-4,5,6,6a-tetrahydro-3a H-cyclopenta[d]isoxazole-4,6-dicarboxylic acid 6-benzhydryl ester (**19**).* Benzhydrol (0.68 g, 3.67 mmol) and DMAP (0.05 g, 0.37 mmol) were added to a solution of anhydride (±)-**14** (0.92 g, 3.67 mmol) in anhydrous toluene (10 mL), and the mixture was stirred at reflux temperature for 10 h. After the solvent had been distilled, the residue was treated with brine and extracted using ethyl acetate (3x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated by means of rotary evaporation. Distillation of the solvent afforded a 70:30 mixture of the two mono-ester, mono-acid regioisomers **(±)-19** and **(±)-20**, as shown by the ^{1}H NMR spectrum. Compound **(±)-19** was purified by means of column chromatography (silica gel, hexane/ethyl acetate =65/35). Its exact regiochemistry was assigned by HMBC and COSY experiments. Colourless solid (0.37 g, 23%), m.p. 130-133 °C; (R_f 0.55, hexane/ethyl acetate =50/50, bromocresol green). ^{1}H NMR: δ 0.90, 0.92 (2t, *J*=7.3, 6H, $2CH_3$); 1.51-1.72 (m, 4H, $2CH_2$); 2.28-2.40 (m, 3H, C-H + 2H-5); 2.89-2.99 (m, 1H, H-4); 3.21-3.26 (m, 1H, H-6); 4.08 (dd, *J*=9.7, 5.0, 1H, H-3a); 5.30 (dd, *J*=9.7, 3.9, 1H, H-6a); 6.90 (s, 1H, $CHPh_2$); 7.36 (s, 10H, 2Ph); 8.7 (broad s, 1H, OH). ^{13}C NMR: δ 11.3, 12.5 ($2CH_3$); 24.4, 25.9 ($2CH_2$); 32.2 (C-5); 41.1 (CH); 48.0 (C-4); 52.5 (C-6); 57.1 (C-3a); 78.1 (CPh_2); 87.5 (C-6a); 127.4-140.1 (Ph); 162.1 (C-3); 171.8 (O-C=O); 178.2 (HO-C=O). Anal. Calcd for $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.58; H 6.66; N, 3.15. MS-ESI$^+$ (m/z): 458 $[M+Na]^+$.

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Caption Figure 1

Figure 1. Structure of three Neuraminidase inhibitors.