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A Synthesis of Oseltamivir (Tamiflu) Starting from D-Mannitol

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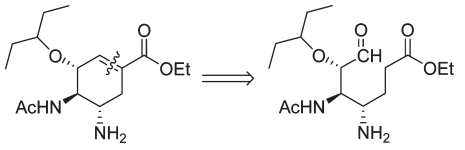

A synthesis of oseltamivir (Tamiflu) was achieved starting from D-mannitol. A unique feature of the synthetic route is that an acyclic precursor was constructed, which was then cyclized in an intramolecular aldol reaction to form the Tamiflu skeleton. Throughout the synthesis, well-established, highly efficient reactions were employed, and no protection/deprotection sequence was needed.

The recent epidemics of the avian influenza in Southeast Asia and the swine influenza in America put a spotlight on oseltamivir (Tamiflu, **1**), one of the two neuraminidase inhibitors currently on the market as anti-influenza drugs and the only orally active one. Worries about future influenza outbreaks turning into a pandemic have prompted governments to stockpile Tamiflu, leading to a shortage—real or feared—of this drug.[1]

The current production of Tamiflu is known to start from shikimic acid, a natural product isolated from Chinese star anise and a limited resource. In order to meet the increasing demand for Tamiflu, therefore, efforts have been directed at three different fronts: (1) to find alternative sources for shikimic acid; (2) to improve synthetic routes from shikimic acid to Tamiflu; and (3) to develop new shikimic (or quinic) acid-independent synthetic routes starting from other readily available materials, the latter two of which being in the domain of synthetic organic chemistry.

The shikimic or quinic acid dependent synthetic routes have been well documented by the scientists at Gilead and at Roche throughout the discovery, development, and production stages of oseltamivir.[2] Recent advances in this area include further optimization of the existing steps,[3] as well as devising new synthetic pathways from shikimic acid to Tamiflu.[4] The search for novel, shikimic acid independent synthetic routes for oseltamivir has been the subject of intensive research efforts at Roche from early on,[2d,e,5] but it is only in the past few years that the subject has received wide attention, and several diverse approaches have been published.[6] Synthetic efforts for both shikimic acid dependent and independent strategies have been reviewed,[1d,7] and an evaluation of the published syntheses based on the material efficiency performances has appeared.[8]

Our own interest in the subject led us to pursue a novel synthetic approach that entailed a construction of an acyclic precursor and its cyclization at a later stage to form the Tamiflu skeleton. Our reasoning was that acyclic intermediates would be more amenable than cyclic ones in the required chemical manipulations such as O→N substitutions.[9] Recently, a synthesis of Tamiflu was reported that employed a

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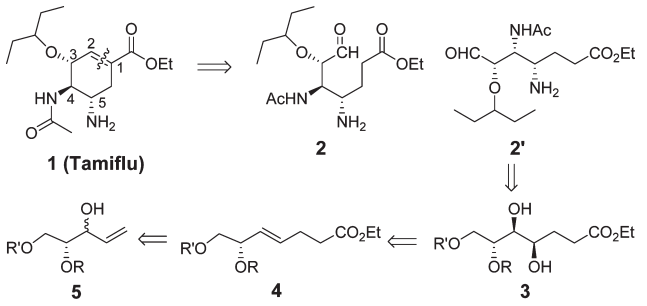
SCHEME 1. Retrosynthesis of Oseltamivir



synthetic strategy quite analogous to our own, although they differ in detailed executions.[6p] Disclosed herein are our efforts.

Our retrosynthetic analysis commenced by recognizing the α,β-unsaturated ester function in the target molecule (Scheme 1). Disconnection via intramolecular aldol condensation led to the acyclic precursor **2**, which may be drawn in a more conventional way with the backbone in a zigzag format (**2′**). While the configurations of the three stereocenters do not change during this mental exercise, common notations for their relative stereochemistry do.[10] Thus, what may be commonly referred to as the *anti,anti*-hydroxydiamino function in the Tamiflu structure (at C-3 through C-5, see **1** for numbering) may now be called *syn,syn* in the acyclic precursor **2′**. If the two amino functions were to be introduced via nucleophilic substitutions, the required precursor was then the alkoxy diol **3**, whose *anti,syn*-relative stereochemistry seemed attainable via highly diastereoselective asymmetric dihydroxylation. The γ,δ-unsaturated ester function in the *trans*-alkene substrate **4** pointed to an ortho ester Claisen rearrangement, and the required allylic alcohol starting material **5** was a vinyl Grignard adduct of a protected glyceraldehyde **6**. What remained to be worked out then were ways to differentiate between the two free hydroxyl groups and between the two protected hydroxyl groups (R and R′) in **3** (or its derivatives).

Mannitol is a convenient source for enantiopure glyceraldehyde. We chose the pentylideneketal group for the protection of the terminal diols, as we had planned to turn this ketal protecting group into a part of the 3-pentyl ether moiety at C-3 of Tamiflu (vide infra). Protection and oxidative cleavage produced the protected glyceraldehyde **6** (Scheme 2).[11] Vinyl Grignard reaction and the subsequent ortho ester Claisen rearrangement proceeded uneventfully.[12] When the *trans*-alkene substrate **8** was subjected to the Sharpless asymmetric dihydroxylation protocol with AD-mix-β, the γ-lactone product **9** was isolated as the only product.[13] The stereoselectivity was very high as the reaction represented a matched pair in doubly stereoselective asymmetric reactions.[14a] When achiral OsO_4 reagent was used, the product obtained was a 3:1 mixture of the diastereomeric diols, with the desired *anti,syn*-diastereomer as the major product, which turned into the γ-lactone products upon standing at rt or heating in toluene.[14b]

The completely regioselective in situ lactonization provided a fortuitous way to differentiate between the two free hydroxyl groups. The remaining free hydroxyl group was converted to the azide **10** via the mesylate. One of the nitrogen functions (at C-4 of Tamiflu) had thus been installed. While the second nitrogen function (at C-5) could have been just as easily introduced on the acyclic substrate following a solvolytic opening of the lactone ring, we made a judicious decision to place the intramolecular aldol-type cyclization step before the opening of the lactone ring. The planned cyclization at any point *after* the lactone ring-opening would bring extra issues to deal with: either protection/deprotection steps at the newly released hydroxyl group at C-5, or a way to differentiate between the two nitrogen functions at C-4 and C-5 (Tamiflu numbering). The cyclization before the lactone ring-opening meant that the second O→N substitution at C-5 would be performed on a cyclic substrate, something we had intended to stay away from; however, it was subsequently realized that cyclic substrates would offer a more advantageous situation for this particular substitution (vide infra).

In order to execute the planned aldol-type cyclization, the terminal dioxolane carbon needed to be oxidized to the level of aldehyde. Instead of a complete removal of the ketal protecting group, we sought a regioselective reductive opening of the dioxolane ring which would at once unmask the primary hydroxyl group and install the 3-pentyloxy group at C-3 of Tamiflu (as in **11**). $BH_3\cdot SMe_2$ in the presence of the Lewis acid catalyst TMSOTf was effective for this step when the reaction was performed in an appropriate solvent. When performed in THF at −40 °C, the reaction was completely regioselective for the desired 2-(3-pentyloxy)-1-ol compound, but the reaction was slow and incomplete after 24 h. In dichloromethane, on the other hand, the reaction was fast, but only to show a complete reversal of the regioselectivity. A right balance was struck when the reaction was performed in dichloromethane-THF cosolvent. Thus, when the ketal **10** dissolved in dichloromethane was treated with $BH_3\cdot SMe_2$ in THF followed by TMSOTf (the final solvent: dichloromethane-THF 3.8:1), the desired primary alcohol **11** was obtained in 94% yield, along with a trace of the undesired regioisomer (1%) after 22 h at −20 to −30 °C. These observations are in accord with the published study on the reductive opening of terminal (4-monosubstituted) dioxolanes.[15] Swern oxidation yielded the desired aldehyde **12**, and the stage was then set for the cyclization.

Intramolecular aldol reactions of unsymmetrical substrates face a regiochemical problem. Although simple pK_a considerations suggest the planned cyclization in the desired direction would be very daunting, there are literature precedents for this type of cyclization between lactones on one end (providing the nucleophiles) and aldehydes on the other end (for the electrophilic functions), leading to bicyclic compounds consisting of γ-lactone and various medium size

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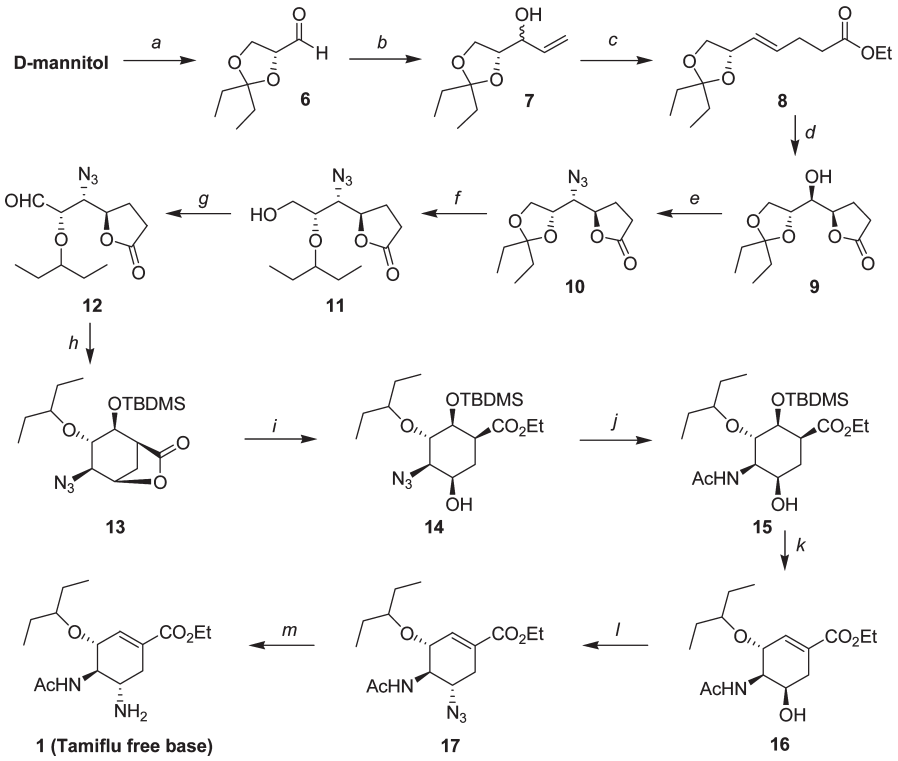
SCHEME 2. Synthesis of Oseltamivir from D-Mannitol



(a) (i) $Et_2C(OMe)_2$, CSA, DMF, (ii) KIO_4, $KHCO_3$, H_2O/THF; (b) vinyl MgBr, THF, 44% (from D-mannitol); (c) $CH_3C(OEt)_3$, $EtCO_2H$, 85%; (d) AD-mix-β, H_2O-t-BuOH, 93%; (e) (i) MsCl, Et_3N, 100%, (ii) NaN_3, DMF, 73%; (f) $BH_3 \cdot SMe_2$, TMSOTf, DCM-THF, 94%; (g) $(COCl)_2$, DMSO, 92%; (h) TBDMSOTf, DIPEA, DCM, 76%; (i) LiBr, DBU, EtOH, 96%; (j) H_2, Pd/C, Ac_2O, Et_3N, 96%; (k) $LiClO_4$, DBU, EtOH, 62%; (l) (i) MsCl, Et_3N, 97%, (ii) NaN_3, DMF, 78%; (m) PPh_3, $THF-H_2O$, 98%.

rings.[16] The reactions have been reported under basic conditions,[16b,c] or more effectively, under the Mukaiyama conditions. When the substrate **12** was treated with TBDMSOTf and Hünig's base, the desired bicyclic product **13** was obtained in 76% yield. Although it is not relevant in the current synthesis of Tamiflu, the product was obtained as a single stereoisomer. The (1*S*,2*S*)-configurations of the newly formed stereocenters were confirmed by X-ray crystallography. A literature search revealed no example of similar intramolecular aldol-type cyclizations between an ester function (nucleophile) on one end and an aldehyde (electrophile) on the other, unless the ester function is further activated or the enolization of the aldehyde function is blocked.[17] It appears that the presence of a lactone ring is crucial in the success of this type of intramolecular aldol-cyclizations. The cyclization might not have been possible after the lactone ring-opening.

The intramolecular aldol-type cyclization provided the Tamiflu skeleton, with all the carbons at the right oxidation states. Solvolytic lactone opening (DBU/LiBr in EtOH) released the hydroxyl group at C-5 (**14**).[18] The azide at C-4 was converted to the acetamido group (**15**). β-Elimination of TBDMSi−OH was realized by DBU/$LiClO_4$. The second O→N substitution (at C-5) via the corresponding mesylate yielded the azide **17**. Due to the *syn*-relationship at C-4/5 on a cyclic substrate, the acetamido group did not interfere in this sequence. A similar conversion on an acyclic substrate would have been complicated by a competing oxazoline formation.[19] The azide was reduced to produce Tamiflu **1** (free base).

In conclusion, a synthesis of Tamiflu was achieved in 16 steps and 7.1% overall yield starting from D-mannitol. A unique feature of the synthetic route is that an acyclic precursor was constructed, which was then cyclized in an intramolecular aldol reaction to form the Tamiflu skeleton. Throughout the synthesis, well-established, highly efficient reactions were employed, and no protection/deprotection sequence was needed.

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Experimental Section

(*R*)-5-((*S*)-((*R*)-2,2-Diethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-dihydrofuran-2(3*H*)-one (9). AD-mix-β (84.6 g) was dissolved in *t*-BuOH and H_2O (1:1 v/v, 600 mL). Methanesulfonamide (5.75 g, 60.4 mmol) was added, and the mixture was cooled at 0 °C. It was added to compound **8** (15.485 g, 60.4 mmol) in a round-bottomed flask. The mixture was cooled at 0 °C and stirred for 6 h. The reaction was quenched by adding Na_2SO_3 (90.6 g). The mixture was stirred for 4 h at rt and then extracted with ethyl acetate. The organic phases were combined, washed with brine, and dried (Na_2SO_4). Flash silica column chromatography (hexane−EtOAc 1:4) yielded the product **9** (13.69 g, 56.042 mmol, 93%): $[\alpha]_D$ = −38.89 (*c* 1.62, EtOH); HRMS (EI) calcd for $C_{12}H_{21}O_5$ $[M + H]^+$ 245.1390, found 245.1391; ^{1}H NMR ($CDCl_3$) δ 4.73 (1H, td, *J* = 7.3, 2.5 Hz), 4.16−4.11 (2H, m), 4.01−3.91 (1H, m), 3.67−3.61 (1H, m), 2.70−2.47 (2H, m), 2.38−2.28 (2H, m), 2.12−2.06 (1H, m), 1.73−1.59 (4H, m), 0.94−0.87 (6H, m); ^{13}C NMR ($CDCl_3$) δ 177.7, 113.5, 80.1, 76.3, 74.2, 67.5, 29.8, 29.3, 28.8, 24.2, 8.5, 8.3; FT IR 3441, 2974, 2941, 2883, 2113, 1767, 1463, 1361, 1198, 1083, 973, 917 cm^{-1}.

(*R*)-5-((1*R*,2*S*)-1-Azido-3-hydroxy-2-(pentan-3-yloxy)propyl)-dihydrofuran-2(3*H*)-one (11). Compound **10** (1.643 g, 6.10 mmol) was dissolved in CH_2Cl_2 (58 mL), and the solution was cooled at −50 °C. $BH_3 \cdot SMe_2$ (2.0 M solution in THF, 15.25 mL, 30.5 mmol) was added, and the mixture was stirred at −50 °C for 30 min. TMSOTf (2.2 mL, 12.20 mmol) was added, and the mixture was stirred at −20 to −30 °C for 22 h. The reaction was quenched by adding saturated aqueous $NaHCO_3$ solution (60 mL), and the resulting mixture was stirred overnight at rt. Extractive workup (DCM) was followed by flash silica column chromatography (hexane−EtOAc 1:1.5) to yield the primary alcohol **11** (1.554 g, 5.73 mmol, 94%): $[\alpha]_D$ = −49.07 (*c* 1.08, EtOH); HRMS (EI) calcd for $C_{12}H_{22}N_3O_4$ $[M + H]^+$ 272.1612, found 272.1607; ^{1}H NMR ($CDCl_3$) δ 4.76 (1H, q, *J* = 6.1 Hz), 3.81−3.64 (4H, m), 3.34 (1H, quint, *J* = 5.5 Hz), 2.72−2.56 (2H, m), 2.39−2.19 (2H, m), 1.80 (1H, t, *J* = 5.4 Hz), 1.64−1.49 (4H, m), 0.95−0.87 (6H, m); ^{13}C NMR ($CDCl_3$) δ 176.8, 81.9, 77.7, 76.7, 65.2, 61.5, 28.5, 26.3, 25.7, 24.3, 9.7, 9.6; FT IR 3463, 2966, 2938, 2879, 2108, 1780, 1461, 1347, 1276, 1185, 1056, 921 cm^{-1}.

Intramolecular Aldol Cyclization of 12. Diisopropylethylamine (1.80 mL, 10.29 mmol) was dissolved in CH_2Cl_2 (20 mL), and the solution was cooled at 0 °C. TBDMSOTf (2.36 mL, 10.29 mmol) was added, and the mixture was stirred for 10 min. The aldehyde **12** (0.924 g, 3.43 mmol) in CH_2Cl_2 (15 mL) was added. The mixture was stirred for 25 min at 0 °C before it was warmed to rt, where it was stirred for further 2 h. The reaction was quenched by adding saturated aqueous NH_4Cl solution (35 mL). Extractive workup (DCM) was followed by flash silica column chromatography (hexane−EtOAc 2:1) to yield the bicyclolactone **13** (1.005 g, 2.62 mmol, 76%): mp 75−76 °C; $[\alpha]_D$ = +2.22 (*c* 1.805, EtOH); HRMS (EI) calcd for $C_{18}H_{33}N_3O_4Si$ $[M]^+$ 383.2240, found 383.2258; ^{1}H NMR ($CDCl_3$) δ 4.75 (1H, d, *J* = 6.2 Hz), 3.83 (1H, dd, *J* = 7.6, 3.3 Hz), 3.76−3.66 (1H, m), 3.58 (1H, t, *J* = 8.1 Hz), 3.34 (1H, dd, *J* = 8.4, 1.1 Hz), 2.69 (1H, dd, *J* = 5.6, 3.4 Hz), 2.49−2.39 (1H, m), 1.79 (1H, d, *J* = 12.6 Hz), 1.72−1.39 (4H, m), 0.96−0.84 (15H, m), 0.17 (3H, s), 0.14 (3H, s); ^{13}C NMR ($CDCl_3$) δ 173.7, 82.3, 80.2, 78.6, 74.4, 66.7, 44.4, 32.2, 25.9, 25.8, 24.5, 18.0, 9.3, 9.1, −4.2, −4.5; FT IR 3433, 2964, 2361, 2103, 1786, 1466, 1260, 1129, 839 cm^{-1}. Annl. Calcd for $C_{18}H_{33}N_3O_4Si$: C, 56.37; H, 8.67; N, 10.96. Found: C, 56.43; H, 8.76; N, 10.87.

(1*S*,2*S*,3*S*,4*R*,5*R*)-Ethyl 4-Azido-2-(*tert*-butyldimethylsilyloxy)-5-hydroxy-3-(pentan-3-yloxy)cyclohexanecarboxylate (14). The lactone **13** (2.252 g, 5.871 mmol) was dissolved in EtOH (88 mL). LiBr (3.06 g, 35.213 mmol) was added, and the mixture was cooled at 0 °C. DBU (2.63 mL, 17.61 mmol) was added, and the mixture was stirred at 0 °C for 1 h. Quenching with saturated aqueous NH_4Cl solution (100 mL) was followed by extractive workup (DCM) and flash silica column chromatography (hexane−EtOAc 3:1) to yield the compound **14** (2.441 g, 5.61 mmol, 96%): $[\alpha]_D$ = −29.1 (*c* 0.825, EtOH); HRMS (EI) calcd for $C_{20}H_{39}N_3O_5Si$ $[M + H]^+$ 430.2737, found 430.2719; ^{1}H NMR ($CDCl_3$) δ 4.25−4.12 (2H, m), 4.10−4.00 (1H, m), 3.97−3.87 (1H, m), 3.78 (1H, br s), 3.67 (1H, t, *J* = 3.2 Hz), 3.26 (1H, quint, *J* = 5.7 Hz), 2.76 (1H, dt, *J* = 12.0, 3.0 Hz), 2.28−2.01 (2H, m), 1.84 (1H, dt, *J* = 13.0, 4.9 Hz), 1.56−1.42 (4H, m), 1.26 (3H, t, *J* = 7.15 Hz), 0.94−0.88 (15H, m), 0.12 (3H, s), 0.02 (3H, s); ^{13}C NMR ($CDCl_3$) δ 172.6, 82.7, 69.6, 67.8, 63.8, 60.7, 43.7, 26.3, 26.2, 25.9, 25.6, 17.9, 14.1, 9.8, 9.5, −3.9, −5.7; FT IR 3454, 2963, 2930, 2858, 2103, 1729, 1463, 1371, 1257, 1192, 1140, 1080 cm^{-1}.

(3*R*,4*R*,5*R*)-Ethyl 4-Acetamido-5-hydroxy-3-(pentan-3-yloxy)-cyclohex-1-enecarboxylate (16). Compound **15** (0.152 g, 0.340 mmol) was dissolved in EtOH (6 mL). DBU (0.50 mL, 3.40 mmol) and $LiClO_4$ (0.18 g, 1.70 mmol) were added, and the mixture was heated to reflux for 2.5 h. The mixture was then cooled in an ice bath, and saturated aqueous NH_4Cl solution (10 mL) was added. The mixture was extracted with $CHCl_3$. The combined organic phases were washed with brine and dried (Na_2SO_4). Flash silica column chromatography (EtOAc−EtOH 10:1) yielded the product **16** (0.069 g, 0.210 mmol, 62%): mp 129−130 °C; $[\alpha]_D$ = −85.36 (*c* 1.64, EtOH); HRMS (EI) calcd for $C_{16}H_{27}NO_5$ $[M]^+$ 313.1889, found 313.1893; ^{1}H NMR ($CDCl_3$) δ 6.86 (1H s), 5.74 (1H, d, *J* = 6.3 Hz), 4.35 (1H, s), 4.28−4.13 (3H, m), 3.88 (1H, t, *J* = 6.7 Hz), 3.62 (1H, s), 3.42 (1H, quint, *J* = 6.1 Hz), 2.71 (1H, d, *J* = 17.0 Hz), 2.46 (1H, dd, *J* = 18.7, 4.9 Hz), 2.06 (3H, s), 1.59−1.49 (4H, m), 1.32 (3H, t, *J* = 7.1 Hz), 0.94 (6H, t, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 171.8, 166.7, 136.4, 129.5, 82.1, 72.8, 67.3, 61.1, 55.1, 31.8, 26.6, 26.2, 23.7, 14.4, 9.8, 9.7; FT IR 3486, 3318, 2968, 1702, 1643, 1545, 1465, 1373, 1306, 1251, 1214, 1103, 1085 cm^{-1}. Annl. Calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.45; H, 8.75; N, 4.40.

Supporting Information Available: Experimental procedure for compounds **6**−**17** and **1**, ^{1}H and ^{13}C NMR spectra of compounds **8**−**17** and **1**, and crystallographic data for compound **13** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.