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Efficient Formal Synthesis of Oseltamivir Phosphate (Tamiflu) with Inexpensive D-Ribose as the Starting Material

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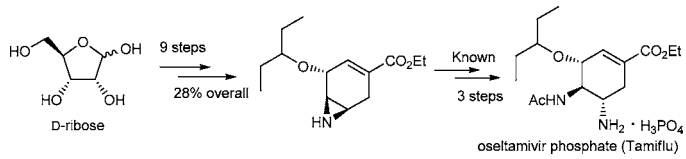
ABSTRACT



An efficient formal synthesis of oseltamivir phosphate (Tamiflu) has been achieved in 12 steps with use of the inexpensive and highly abundant D-ribose as the starting material. This concise alternative route does not utilize protecting groups and features the introduction of 3-pentylidene ketal as the latent 3-pentyl ether, the use of a highly efficient RCM reaction to form the Tamiflu skeleton, and selective functional group manipulations.

The recent global pandemic of AH_1N_1 influenza has resulted in over 480 000 diagnosed infected cases and more than 6 000 recorded related deaths to date.[1] This pandemic highlights the critical importance of the development and manufacture of anti-influenza drugs to safeguard public health in the world. To date, oseltamivir phosphate (Tamiflu, **1**) remains the most widely used antiviral drug for the treatment and prevention of influenzas, with many countries worldwide stockpiling this drug for the treatment of AH_1N_1 infections. This, together with the threat of avian and other seasonal influenzas, has inevitably increased the demand of Tamiflu, putting pressure on the supply of this drug and its raw materials. As a result, unabated efforts have been devoted to the synthesis of **1** and to date, 26 syntheses and/or modifications have been reported.[2] These syntheses, which have been extensively reviewed recently,[3] highlight the ingenuity of synthetic chemists in devising diverse approaches toward this important synthetic target.

Many of the reported synthetic routes[2f−w] focused on the use of alternative starting materials as there was a potential supply issue of (−)-shikimic acid used in the current manufacturing process.[4,5] In line with these efforts, our work has been directed toward the development of an alternative synthetic route using an inexpensive, reliable, and abundant source of starting material. A search of the chiral pool revealed that D-ribose (**2**), produced on a multithousand ton scale at the cost of ca. $30/kg,[6] can be an attractive alternative starting material for the synthesis of **1**. Herein, we report our preliminary results on an efficient formal synthesis of Tamiflu (**1**) via the advanced aziridine intermediate **3**,[2b] using D-ribose (**2**) as the starting material.

Our strategies would (Figure 1) involve the transformation of D-ribose (**2**) to the intermediate aldehyde **4**, which would undergo a known *anti*-selective Reformatsky-type allylation

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(1) Statistics obtained from the World Health Organisation (WHO) website: http://www.who.int/csr/disease/swineflu/updates/en/. The actual infected cases are far more than what have been reported as many countries no longer test and report individual cases. Figures were updated as of Nov 1, 2009.

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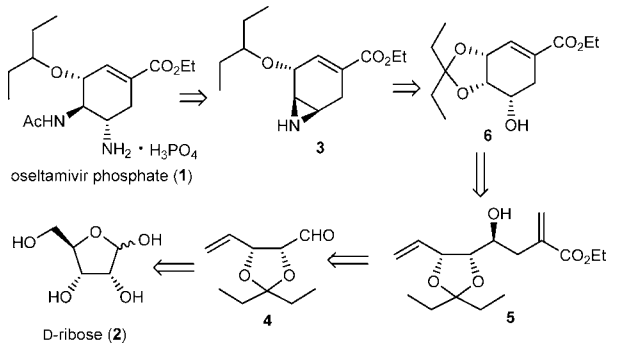
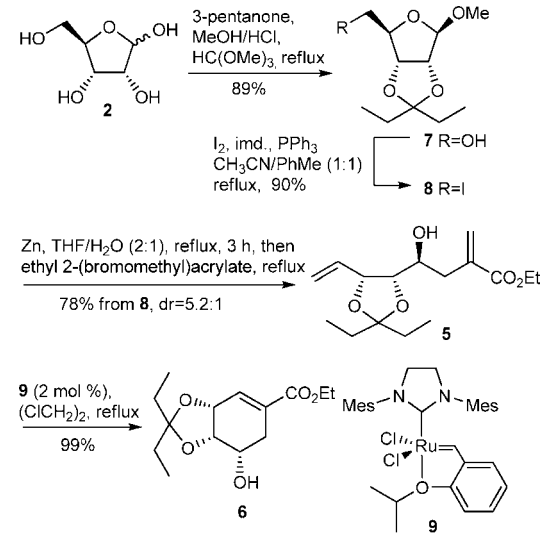


Figure 1. Retrosynthetic analysis of oseltamivir phosphate (**1**) from D-ribose (**2**) via the aziridine intermediate (**3**).

with ethyl 2-(bromomethyl)acrylate,[7] leading to the diene **5**. This would then be cyclized by a ring-closing olefin metathesis (RCM) to provide the 5-*epi*-shikimic acid derivative **6**, which is to be converted to the aziridine **3** that leads to **1** via known methodologies.[2b]

The synthesis started with D-ribose (**2**) whose *syn* diol was converted to its 3-pentylidene ketal (Scheme 1), which served as the latent 3-pentyl ether moiety present in **1**. This was achieved by heating **2** with 3-pentanone in a methanolic hydrochloric solution, providing the ketal **7** in an initial 54% yield. The reaction was significantly improved to 89% yield by the addition of trimethyl orthoformate as a dehydrating reagent.[8] The alcohol **7** was then converted to the iodoribose derivative **8** in 90% yield by a known method (Ph_3P/I_2/imidazole).[9]

Scheme 1. Synthesis of 5-*epi*-Shikimic Acid Derivative **6**



Bernet−Vasella reaction[10] of **8** in THF−H_2O (2:1) under reflux provided the intermediate aldehyde **4**, which was not isolated and underwent an *anti*-selective Reformatsky-type allylation with ethyl 2-(bromomethyl)acrylate in a one-pot fashion,[7] furnishing the diene **5** in 78% yield after separation of the minor diastereomer (dr = 5.2:1). In the presence of the second-generation Grubbs−Hoveyda catalyst (**9**), the diene **5** underwent efficient ring-closing olefin metathesis in 1,2-dichloroethane at reflux, providing 5-*epi*-shikimic acid derivative **6** in nearly quantitative yield. The robustness of catalyst **9** allowed its loading to be as low as 2 mol % and the use of 1,2-dichloroethane (boiling point 81 °C) as the solvent greatly facilitated the reaction, enabling the cyclization of **5** to completion within 2 h.

With the 5-*epi*-shikimic acid derivative **6** in hand, strategies for the transformation of the 3-pentylidene ketal in **6** to the 3-pentyl ether moiety for **1** were explored. Our initial plan was to convert **6** to its mesylate **10**, followed by selective cleavage of the ketal group employing a highly selective protocol ($TiCl_4$, Et_3SiH, −34 °C) reported for the mesylate **11** in the shikimic acid route (Scheme 2).[2c]

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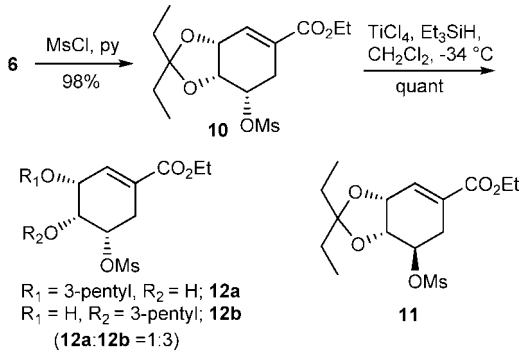
Scheme 2. Reductive Ketal Cleavge of Mesylate **10**



Unfortunately, the reaction afforded a poor selectivity (**12a**:**12b** = 1:3) for the desired product **12a** despite a quantitative combined yield. A variety of other Lewis acids, including BF_3, $AlCl_3$, and $ZnCl_2$, and conditions were investigated, but no significant improvement was observed in terms of desired regioselectivity.

The dramatic difference in the regioselectivity of ketal cleavage between mesylate **10** and **11** promoted us to look into the likely causes. Conformation analysis[11] revealed that the *syn*-mesylate **10** (Figure 2. A) is sterically much more

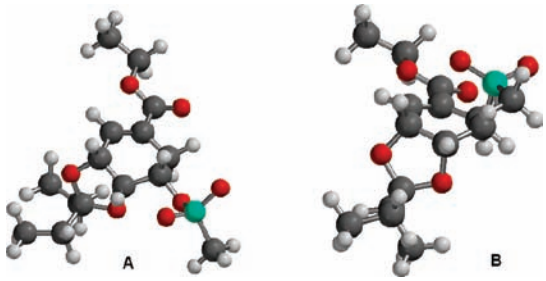
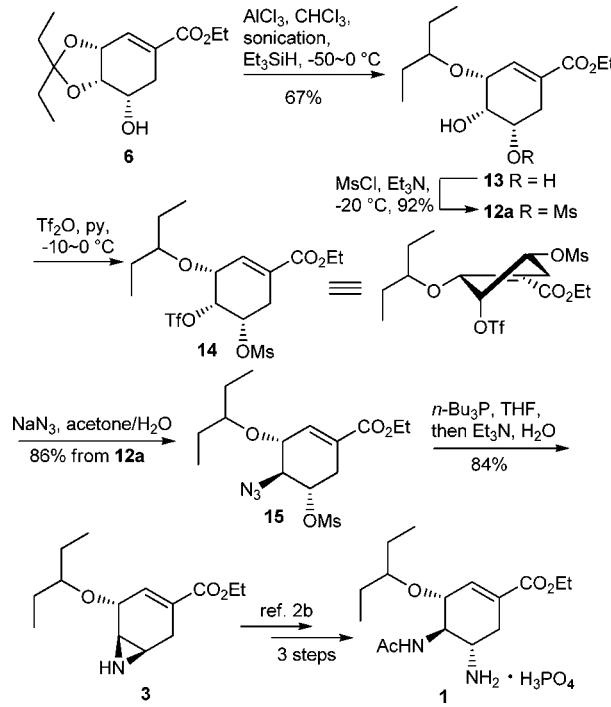


Figure 2. Energy minimized conformations of mesylate **10** (A) and **11** (B).

congested than the *anti* compound **11** (Figure 2. B) between the mesyloxy and the ketal group. This steric hindrance imposed by the *syn* alignment of mesylate in relation to the ketal moiety in **10** would have hampered the coordination of the Lewis acid to the adjacent oxygen atoms of the mesylate and the ketal, resulting in the poor selectivity.

In light of this conclusion, it was postulated that the cleavage of the ketal moiety could be better controlled with alcohol **6**, which is sterically less hindered than **10**, and the hydroxy group is likely to react with the Lewis acid, facilitating its desired coordination to the adjacent ketal oxygen thus leading to better selectivity. After screening several Lewis acids including $TiCl_4$, $BF_3{-}OEt_2$, BH_3, and $AlCl_3$, it was found that anhydrous aluminum trichloride in combination with triethylsilane[12] afforded a 6:1 regioisomeric ratio of products, in favor of the desired diol **13** in 67% yield (Scheme 3).

Scheme 3. Completion of the Synthesis of Azirdine **3**



Having achieved the crucial regioselective cleavage of the ketal group, selective mesylation of the diol **13** was examined. Although the formation of the dimesylate is a potential competing reaction,[2x−z] we envisioned that it would be possible to selectively mesylate the least sterically hindered 5-hydroxy group of **13**. To our delight, mesylation of **13** carried out at −20 °C with 1.05 equiv of methanesulfonyl chloride with triethylamine as the base provided the monomesylate **12a** as the sole product in 92% yield. Treatment of **12a** with trifluoromethanesulfonic anhydride in the presence of pyridine at −10 °C afforded the mesyloxy triflate **14**, which was used in the next step of the synthesis without purification due to its instability.

To transform **14** to the aziridine **3** requires the selective displacement of the more reactive but also more hindered 4-triflate in the presence of the 5-mesylate group. This was achieved by treatment of **14** with sodium azide in acetone−water (9:1) providing the 4-azidomesylate **15** without noticeable formation of either the 5-azide or diazide. This high regioselectivity is attributed to the orientation of the trifloxy and mesyloxy groups in the preferred conformation[2o] in which the 4-trifloxy adopts a favored axial position for the azide substitution reaction whereas the 5-mesyloxy occupies a disfavored equatorial position (Scheme 3).

(11) The energy minimized conformations were obtained by using the MMFF94 force field, Spartan 04 version for Windows; Wavefunction, Inc.

(12) Crimmins, M. T.; Rafferty, S. W. *Tetrahedron Lett.* **1996**, *37*, 5649.

To complete the synthesis, a final two-step, one-pot sequential transformation of the azide **15** to **3** was carried out by reduction of the azide to the corresponding amine via a Staudinger reaction[13] followed by a triethylamine-mediated cyclization to form the aziridine **3** in 84% yield. This concluded an efficient synthesis of this advanced intermediate in nine steps in 28% overall yield from **2**. As the conversion of **3** to **1** has been reported previously in three steps,[2b] this work constitutes a concise formal synthesis of **1** in 12 steps (Scheme 3).

In summary, we have accomplished an efficient synthesis of the key aziridine intermediate **3** for the synthesis of Tamiflu, **1**, using the inexpensive and abundant D-ribose as the starting material. This concise alternative route *does not utilize protecting groups* and features the introduction of 3-pentylidene ketal as the latent 3-pentyl ether present in **1**, a highly efficient RCM reaction to form the cyclohexene skeleton, and selective functional group manipulations. This route demonstrates the potential of D-ribose as an alternative, inexpensive, and renewable raw material for the synthesis of Tamiflu, **1**.

(13) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353, and references cited therein.

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Note Added after ASAP Publication. An error was corrected in Scheme 1 in the version published ASAP December 7, 2009.

Supporting Information Available: Experimental procedures and full spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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