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Expeditious access to (−)-shikimic acid derivatives for Tamiflu synthesis

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ABSTRACT

A three-step, one-pot process has been developed for the synthesis of 5-epi-shikimic acid derivative **5** using inexpensive and abundant D-ribose as the starting material. Based on this pivotal intermediate, the syntheses of two key shikimic acid derivatives **6** and **7** for Tamiflu have been achieved in a concise and practical fashion.

Tamiflu (Oseltamivir phosphate, **1**, Fig. 1) is one of the most widely prescribed drugs for the treatment and prevention of various types of influenza including avian flu H1N1 and H5N1 which caused worldwide pandemics in recent years. This anti-influenza drug was initially discovered by Gilead Sciences and subsequently licensed to and marketed by Hoffmann-La Roche Ltd. The commercial manufacturing process of Tamiflu uses (−)-shikimic acid (**2**), a natural product isolated from the star anise fruit, as the raw material.[1] Due to seasonal and geographical constraints, the supply of shikimic acid was of great concern when Tamiflu was in high demand during the avian flu epidemic period.[2] Consequently, synthetic chemists worldwide have devised many ingenious alternative syntheses[3] to this seemingly simple yet challenging molecule.

With an aim to provide a solution to the raw material supply issue, we recently reported a synthetic route to **1** using inexpensive and abundant D-ribose as the starting material.[3b] This new route led to an efficient synthesis of Tamiflu via a late-stage aziridine intermediate **4** derived from 5-*epi*-shikimic acid derivative **5**. To further capitalise on the easily accessible intermediate **5** in alternative routes to **1**, our attention was attracted to two shikimic acid derivatives, ketal **6**[4] and amide **7**,[5] which are the key intermediates for Tamiflu syntheses. Ketal **6** has been obtained from (−)-shikimic acid or (−)-quinic acid and is an early stage intermediate used in the Roche process for Tamiflu manufacturing.[4] Hence, if **5** could be conveniently converted into **6**, it would provide an alternative source for this early stage intermediate. This would be advantageous in the event of urgent need for the drug as it would not require any significant changes to most of the current manufacturing process. Amide **7**, on the other hand, has been obtained from 4-amino-shikimic acid (**3**) produced by fermentation of glucose using genetically engineered amino shikimate dehydrogenase.[5] This compound has been used in a patented route (7 steps only) for Tamiflu synthesis.[6] Herein we describe two concise routes to shikimic acid derivatives **6** and **7** using compound **5** as a common intermediate.

The common intermediate **5** was prepared on a multigram scale based on our previously reported route[3b,16] with significant modifi-

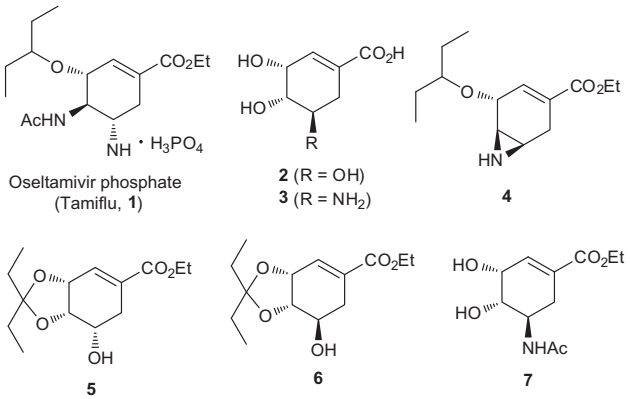

Figure 1. Structures of Tamiflu (**1**) and compounds **2–7**.

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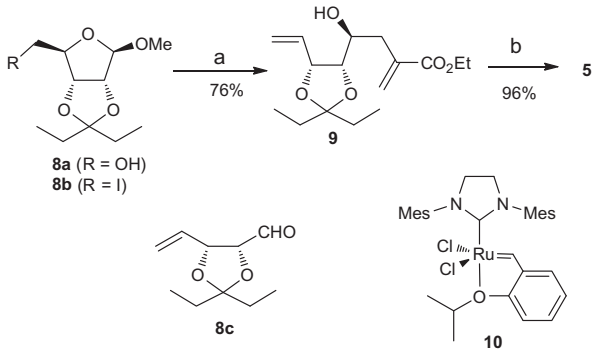


Scheme 1. Improved synthesis of **5**: (a) (i) I_2, imid., PPh_3, THF, reflux, 20 min; (ii) Zn dust, H_2O, reflux, 30 min; (iii) ethyl 2-(bromomethyl)acrylate, reflux, 40 min; (b) 1,2-dichloroethane, **10** (2 mol %), reflux, 4 h.

cation (Scheme 1). The conversion of the known ketal **8a** into diene **9** was previously carried out in two separate steps via the formation of iodide **8b**, followed by a one-pot Bernet–Vasella reaction. In this process, the intermediate iodide **8b** had to be isolated. After optimisation, it was found that this series of three-step transformations could be carried out in a more efficient one-pot operation. Thus, alcohol **8a** was converted into the corresponding iodide **8b** (Ph_3P/I_2/imidazole) in refluxing THF. The resultant iodide then underwent the Bernet–Vasella reaction[7] to form the intermediate aldehyde **8c** in the presence of zinc dust. Aldehyde **8c** was further reacted with ethyl 2-(bromomethyl)acrylate in the presence of excess zinc dust (present from the previous step), providing the desired diene alcohol **9** in 76% yield after chromatographic separation of the minor diastereomer. This improved procedure, without the need to isolate the intermediates, greatly simplifies the procedure for scalable operation. The diene **9b** was then cyclised, as described previously,[3b] via ring-closing olefin metathesis using the Grubbs-Hoveyda second generation catalyst (**10**) to provide 5-*epi*-shikimic acid derivative **5** in multigram quantity in 96% yield.

With the establishment of a scalable route to **5**, we set out to investigate the inversion of 5-hydroxy group. Since conformational analysis[8] revealed that 5-hydroxy group adopts an axial orientation, (Fig. 2) we envisioned that its inversion would be favourable although β-elimination reactions might occur.

The first attempted inversion via the Mitsunobu reaction resulted in the formation of elimination products[9] instead of the required inversion product (Table 1, entry 1). An alternative displacement via mesylate **11** was then investigated. Whilst reactions of **11** with either $CaCO_3$/H_2O–THF[10] at reflux (entry 2) or CsOAc[11] in DMF at room temperature (entry 3) returned the starting material, an increase in the reaction temperature to 80 °C in the latter case led to the formation of elimination products. However, it was reasoned that the use of triflate as a better leaving group might favour the displacement. Nevertheless, treatment of triflate

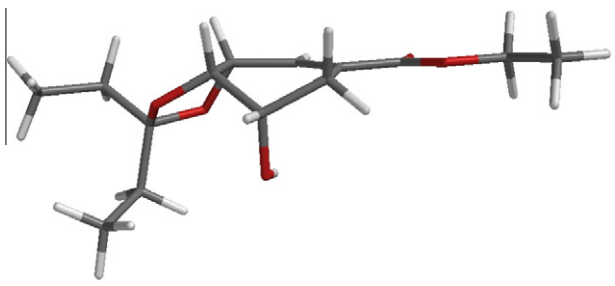


Figure 2. Energy minimised conformation of **5.**

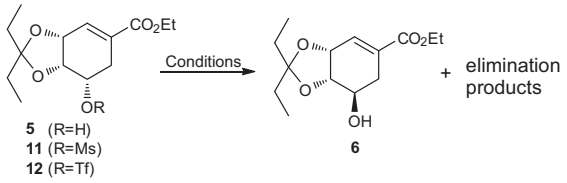


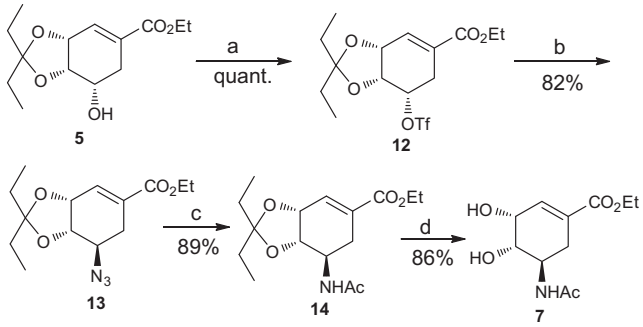
Table 1
Investigation of the conditions for inversion of the 5-hydroxy group

Entry	Substrate	Conditions	Result
1	**5**	Ph_3P, DIAD, $PhCO_2H$, 0 °C to rt	Elimination[9]
2	**11**	$CaCO_3$, H_2O/THF (1:1), reflux	Recovered **5**
3	**11**	CsOAc, DMF, rt	Recovered **5**
4	**11**	CsOAc, DMF, 80 °C	Elimination[9]
5	**12**	CsOAc, DMF, rt	Elimination[9]
6	**12**	$NaNO_2$, DMF, 0 °C–rt	**6** (75%) + elimination[9]

12 with CsOAc also resulted in the formation of elimination products. At this point our attention was turned to a less known method for the inversion of triflate with sodium nitrite.[12] Gratifyingly, treatment of **12** with sodium nitrite at room temperature in DMF led to successful inversion, providing alcohol **6**[13] in 75% yield with <10% of elimination products being formed. This direct inversion is more convenient than the Mitsunobu conditions or using CsOAc as it negates the ester hydrolysis step.

Having achieved the synthesis of **6**, we turned our attention to the transformation of **5** into **7** (Scheme 2). Nucleophilic displacement of triflate **12** with sodium azide proceeded smoothly to provide **13**. It is worth noting that control of the temperature was crucial for the reaction. While the reaction proceeded sluggishly at <−20 °C, significant amounts of elimination products were formed when it was raised to ambient temperature (~25 °C). The optimal temperature range for this reaction was found to be between −10 and 0 °C at which **13** was obtained in 82% yield. The azide **13** was subsequently reduced to the corresponding amine at room temperature under atmospheric pressure of hydrogen using Lindlar catalyst. These conditions left the less reactive double bond intact.[14] Without isolation, the crude amine was acetylated to provide amide **14**[15] in 89% yield over two steps. Final removal of the ketal-protecting group (1.0 M aq HCl in methanol) furnished the desired amide **7** in 62% overall yield from **5**.

In summary, we have developed a scalable, three-step, one-pot process for the synthesis of 5-*epi*-shikimic acid derivative **5** using inexpensive and abundant D-ribose as the starting material. Using **5** as a common intermediate, the syntheses of two key shikimic



Scheme 2. Synthesis of **7**: (a) Tf_2O, Py; (b) NaN_3, DMF, −10 to 0 °C; (c) (i) H_2 (1 atm), Lindlar catalyst (5 mol % Pd); (ii) Ac_2O, Et_3N; (d) 1.0 M aq HCl, MeOH, rt.

acid derivatives **6** and **7** for Tamiflu syntheses have been achieved, providing alternative routes for the syntheses of this antiviral drug.

Acknowledgements

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Supplementary data

Supplementary data (complete experimental procedures, characterization and spectral data of all key compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.035.

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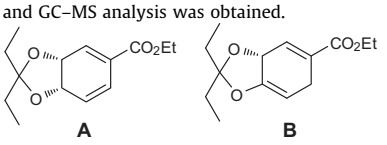
8. The energy minimized conformation was obtained using the MMFF94 force field, SPARTAN'04 version for Windows, Wavefunction, Inc.
9. An inseparable mixture of two products **A** and **B** identified by ^{1}H NMR spectroscopy and GC–MS analysis was obtained.



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13. Shikimic acid derivative **6**: colorless oil; R_f = 0.43 (EtOAc/PE = 2:3); $[\alpha]_D^{24}$ −74.92 (*c* 1.08, $CHCl_3$); ν_{max} (EF)/cm^{-1} 3460, 2975, 2938, 1713, 1653, 1462, 1364, 1248, 1172, 1067, 1037, 934, 873, 751, 726, 644, 519; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94–6.93 (m, 1H) 4.78–4.73 (m, 1H), 4.22 (q, *J* = 8.0 Hz, 2H), 4.09 (t, *J* = 8.0 Hz, 1H), 3.94–3.87 (m, 1H), 2.81–2.76 (m, 1H), 2.28–2.21 (m, 1H), 2.04 (br s, 1H), 1.70–1.64 (m, 4H), 1.30 (t, *J* = 8.0 Hz, 3H), 0.92 (t, *J* = 8.0 Hz, 3H), 0.89 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 134.0, 130.4, 113.6, 77.9, 72.2, 68.9, 61.1, 29.7, 29.3, 29.1, 14.2, 8.6, 7.9; HRMS (ESI-TOF): *m*/*z* found 293.1359 $[M+Na]^+$; $C_{14}H_{22}NaO_5$ requires 293.1365.
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15. Amide **7**: amorphous solid; R_f = 57 (EtOAc/PE = 9:1); $[\alpha]_D^{24}$ −103.3 (*c* 1.2, MeOH); ν_{max} (EF)/cm^{-1} 3289, 2976, 2941, 1716, 1654, 1550, 1371, 1172, 1073, 1059, 927, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (m, 1H), 4.31 (t, *J* = 4.2 Hz, 1H), 4.25–4.18 (m, 3H), 3.74 (dd, *J* = 9.0, 4.1 Hz, 1H), 2.82 (dd, *J* = 18.1, 5.2 Hz, 1H), 2.23–2.08 (m, 1H), 2.00 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.5, 168.7, 139.2, 132.2, 72.2, 67.9, 62.8, 49.0, 31.1, 23.5, 15.3; HRMS (ESI-TOF): *m*/*z* found 244.1812 $[M+H]^+$; $C_{11}H_{18}NO_5$ requires 244.1815.
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