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A new and efficient asymmetric synthesis of oseltamivir phosphate (Tamiflu) from D-mannose

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ABSTRACT

Oseltamivir phosphate (Tamiflu) was synthesized from D-mannose through a short and practical synthetic route. A unique feature of the route is that the bulky 3-pentyloxy group and adjacent acetamide of Tamiflu were introduced at an early stage of the synthesis by copper-catalyzed regioselective ring-opening of the 2,3-pentylidene ketal of D-lyxofuranoside. The D-lyxofuranoside ethylphosphonate precursor was then cyclized via an intramolecular Horner–Wadsworth–Emmons reaction to furnish the Tamiflu skeleton.

Oseltamivir phosphate (Tamiflu, **1**) is a potent inhibitor of viral neuraminidase and is used worldwide as a drug for the treatment and prevention of both type A and type B influenza.[1] The recent spread of the avian virus, H5N1 and the swine flu virus (H1N1 human flu) has prompted many nations to stockpile Tamiflu in the case of a possible influenza outbreak.[2] However, only developing countries can afford to stockpile this drug due to the high cost of the Tamiflu production process.

Currently, Tamiflu is produced and supplied by Roche using (−)-shikimic acid as the starting material, which is not always readily available in consistently pure form.[3] Production of (−)-shikimic acid with a consistent purity, is both time-consuming and costly. Therefore, significant efforts have been made to improve the synthesis of Tamiflu. For example, several new synthetic methods have been developed without using shikimic acid. Commercially available starting materials such as (−)-quinic acid,[3] L-serine,[4] xylose,[5] a mesoaziridine,[6] a substituted cyclohexadiene[7] a lactone,[8] a pyridine,[9] 2,6-dimethoxyphenol,[10] D-mannitol,[11] L-methionine,[12] ethyl benzoate,[13] D-ribose,[14] and diethyl tartrate[15] have been used for the synthesis of Tamiflu. Among those, monosaccharides such as xylose, glucose, ribose, mannose, and arabinose are important chiral raw materials available in nature. They are not only less-expensive, but also possess chiral centers, therefore it is quite easy to find the most appropriate substrate to fit the synthetic plan. Moreover, in order to supply Tamiflu to developing countries where influenza might spread, production costs should be low. This requires that only inexpensive starting materials and reagents be used.

Our group is currently involved in developing alternative synthetic methods for Tamiflu.[14a] In a recent disclosure by us[14b] and other researchers,[14c] D-ribose was used to synthesize the title compound. Our synthesis was based on a metal-mediated domino reaction and ring-closing metathesis to construct the cyclohexene ester core structure, followed by functional group manipulation to afford Tamiflu. Although this synthesis had some merits such as the novel method for constructing the cyclohexene core of the target compound, it used an expensive Ru catalyst which would hamper the large-scale preparation of oseltamivir phosphate. After an extensive study, we have exploited a short, practical synthesis of oseltamivir phosphate starting from D-mannose which is a less-expensive material. Herein, we report the details. The key feature of our new synthetic process is that the bulky 3-pentyloxy group and the adjacent acetamide of Tamiflu were introduced at an early stage of the synthesis by employing catalytic ring-opening of a 2,3-pentylidene ketal of D-lyxofuranoside, derived from D-mannose, and the resulting OH was transformed into an acetamide.

As shown by our retrosynthetic analysis (Fig. 1), we envisioned that construction of the cyclohexene ester **2**, a core of Tamiflu could be accomplished via intramolecular Horner–Wadsworth–Emmons olefination[16] of the phosphoryl ester which in turn could be prepared from the reaction of functionalized 5-aldolyxofuranoside **3** and diethylphosphonoacetate. The functionalized furanoside could be derived from the 2,3-pentylidene ketal of D-lyxofuranoside **6** by

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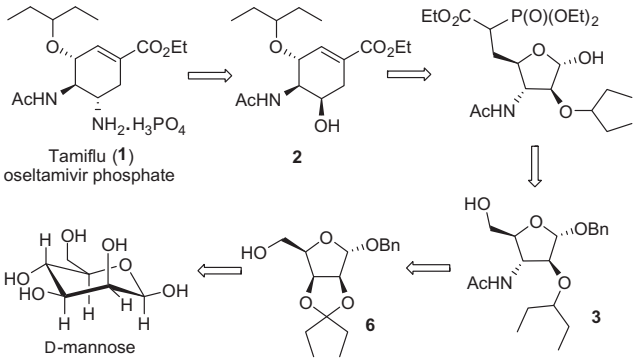
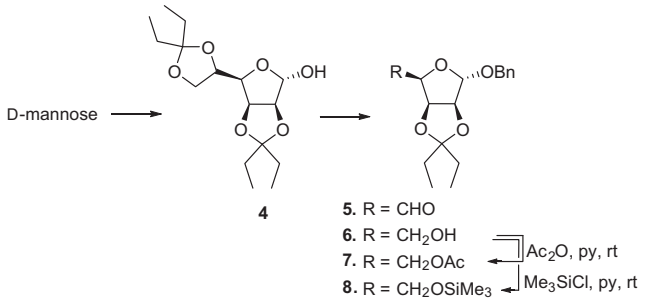


Figure 1. Retrosynthetic analysis of oseltamivir phosphate (**1**) from D-mannose via regioselective ring-opening of a ketal.



Scheme 1. Synthesis of *O*-benzyl-2,3-*O*-isopentylidene-α-D-lyxofuranosides.

regioselective opening of the ketal followed by azide substitution of the resulting hydroxy group, reduction, and acetylation.

The synthesis (Scheme 1) was started with diacetal formation from D-mannose using a modified method described by Whistler[17] to give 2,3:5,6-di-*O*-pentylidene-α-D-mannofuranose (**4**), which was subsequently converted, without isolation into aldehyde **5** and then reduced into alcohol **6**; the overall yield of **6** from D-mannose was 30% (Scheme 1).[18]

Our initial plan was to convert **6** into its acetate **7** followed by cleavage of the ketal group employing a highly selective protocol involving $TiCl_4/Et_3SiH$, as in the shikimic acid route, developed by Mair and co-workers.[3b] Unfortunately, the reaction afforded poor selectivity (**9**:**10** = 1:1) for the desired product **9** either at −78 °C or at 0 °C (Table 1, entries 1 and 2). However improved regioselectivity was observed when the hydroxy parent compound **6** was used (entry 3). These results indicated that the direction of ring-cleavage might be influenced by the hydroxy group at C-5. In order to investigate the effect of the functional group at C-5 in this reaction, the silyl ether **8** and the aldehyde analog **5** were examined. Moreover, $Cu(OTf)_2$, which has been reported to be an effective catalyst for the regioselective ring-opening of 4,6-*O*-benzylidene acetal in hexapyranoside systems,[19] was also tested in our investigation. We found that when using Et_3SiH in the presence of $Cu(OTf)_2$ in acetonitrile, reductive ring-opening of ketal **5** did not proceed, and only starting material was recovered (entry 4). This might be due to $Cu(OTf)_2$ being a weaker Lewis acid than $TiCl_4$. When $Cu(OTf)_2$ was used in combination with BH_3·THF, a stronger reductant, ketal ring-opening proceeded to give diol **11** and alcohol **6** (entry 5). The results indicated that the aldehyde was reduced to an alcohol under these conditions. Similar results were obtained when the acetate and silyl derivatives **7** and **8** were examined (entries 6 and 7). TLC monitoring of the reaction revealed that the acetoxy and silyl groups were removed under the reaction conditions to give the corresponding alcohols which then proceeded to undergo ketal ring-opening. To prove our assumption alcohol **6** was subjected to catalytic ring-opening under the same conditions. Indeed, only isomer **11** was obtained exclusively from the reaction (entry 8).

This regioselectivity is attributed to the preferential complexation of the 5-hydroxy group and the adjacent ketal oxygen with the copper reagent to form a bidentate complex (Fig. 2), which would favor C3–O bond cleavage to give *O*-benzyl-2-*O*-isopentylidene-5-α-D-lyxomannofuranoside (**11**).

Having achieved the crucial regioselective cleavage of the ketal group, selective protection of diol **11** was performed using TBDMSCl to give **13** in good yield (Scheme 2). Treatment of **13** with trifluoromethane sulfonic anhydride in the presence of pyridine at 0 °C afforded the triflate derivative, which was subsequently reacted with sodium azide in acetone-water to give 3-azidofuranose **14**. The azide group of **14** was transformed into an amino moiety by treatment with PPh_3 which was then acetylated to give acetamide **15**. Removal of the silyl protecting group by treatment with

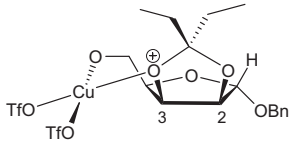
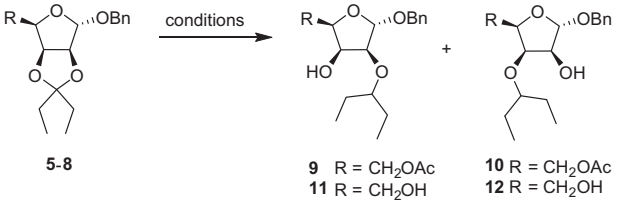
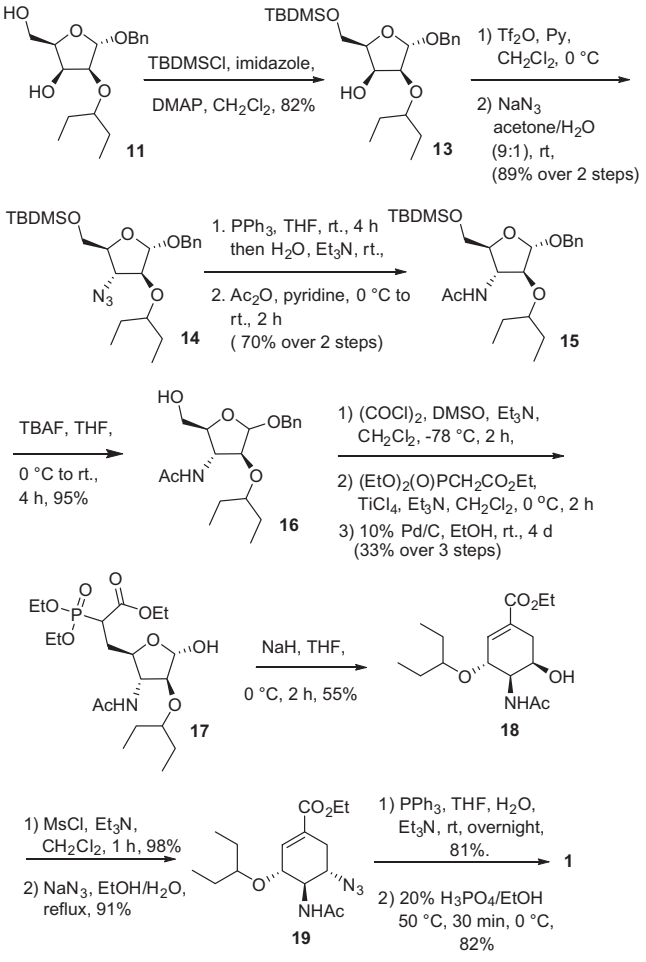


Figure 2. Transition state during ketal cleavage mediated by $Cu(OTf)_2$.

Table 1
Reductive ring-opening of the pentylidene ketals **5–8**



Entry	Substrate	Conditions	Yield (%) **9**	Yield (%) **10**	Yield (%) **11**	Yield (%) **12**	Yield (%) **6**
1	**7**: R = CH_2OAc	$TiCl_4$, Et_3SiH, CH_2Cl_2, −78 °C, 5 min	20	20	—	—	—
2	**7**: R = CH_2OAc	$TiCl_4$, Et_3SiH, CH_2Cl_2, 0 °C, 5 min	18	20	—	—	—
3	**6**: R = CH_2OH	$TiCl_4$, Et_3SiH, CH_2Cl_2, −78 °C, 5 min	—	—	40	15	—
4	**5**: R = CHO	$Cu(OTf)_2$, Et_3SiH, MeCN, rt, 2 h	Starting material was recovered				
5	**5**: R = CHO	$Cu(OTf)_2$, BH_3·THF, rt, 2 h	—	—	60	—	20
6	**7**: R = CH_2OAc	$Cu(OTf)_2$, BH_3·THF, rt, 10 min	—	—	55	—	30
7	**8**: R = CH_2OSiMe_3	$Cu(OTf)_2$, BH_3·THF, rt, 10 min	—	—	59	—	31
8	**6**: R = CH_2OH	$Cu(OTf)_2$, BH_3·THF, rt, 2 h	—	—	75	—	10



Scheme 2. Completion of the synthesis of oseltamivir phosphate **1**.

TBAF gave the hydroxy compound **16** in excellent yield. Oxidation of **16** using Swern conditions yielded the corresponding aldehyde, Knoevenagel condensation of which with ethyl dimethoxyphosphoryl acetate followed by hydrogenation gave the C1-elongated phosphonate **17** in 33% yield over the three steps.

Intramolecular Horner–Wadsworth–Emmons olefination of **17** using sodium hydride in THF afforded 4β-acetamido shikimate **18** in moderate yield. The second amino group was introduced into **18** by activation of the 5β-hydroxy group as the mesylate followed by azide substitution with sodium azide to give azido acetamido shikimate **19**. Finally, azide **19** was reduced by treatment with triphenylphosphine and water to form an amine, which was directly exposed to 1.2 equiv of phosphoric acid in ethanol at 50 °C to afford Tamiflu (**1**) in 82% yield.

In summary, we have achieved a new asymmetric synthesis of Tamiflu in 13 steps and 5% overall yield from cheap and abundant D-mannose. The unique feature of this route is that the bulky 3-pentyloxy group and the adjacent acetamide of Tamiflu were introduced at an early stage of the synthesis by regioselective ketal ring-opening of D-lyxofuranoside using $Cu(OTf)_2$ as the catalyst. Condensation with diethylphosphonoacetate and then cyclization by Horner–Wadsworth–Emmons olefination afforded the Tamiflu skeleton. Throughout the synthesis, well-established, highly efficient reactions were employed.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.143.

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