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An efficient synthesis of oseltamivir phosphate (Tamiflu) via a metal-mediated domino reaction and ring-closing metathesis

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ABSTRACT

An efficient synthesis of the influenza neuraminidase inhibitor prodrug oseltamivir phosphate (Tamiflu) from cheap, commercially available D-ribose is described. The main features of this approach comprise a metal (Zn, In)-mediated domino reaction and ring-closing olefin metathesis (RCM) of the resultant functionalized dienes to produce the Tamiflu skeleton. The synthesis described in this Letter represents a new and efficient transformation of a shikimic acid derivative into a 1,2-diamino compound which involved oxidation of an alcohol followed by reductive amination, regioselective ring opening of an amino pentylidene ketal and stereospecific nucleophilic replacement of a triflate with an azide.

Oseltamivir phosphate (Tamiflu, **1**) (Fig. 1) is used as an orally active drug for the treatment and the prevention of infections due to influenza viruses. Tamiflu is hydrolyzed by an esterase enzyme to the corresponding carboxylic acid, which is a potent inhibitor of neuraminidases A and B.[1] Recently, this compound was found to be active against the swine flu virus (H1N1 human flu) which has become a global influenza pandemic.[2] Many nations now have plans to stock a significant amount of this compound in case of a possible influenza outbreak. As a result, concerns have been raised about the capacity of the existing production process to meet world demand. These arise because the current manufacturing process uses (−)-shikimic acid as the starting compound which is not always readily available in consistently pure form.[3] Consequently, there has been intense effort from the chemical community in developing alternative approaches which start from cheap and readily available substrates.[4] The recent disclosure, by Chen and co-workers, of the synthesis of the title compound from the readily available and inexpensive D-ribose[5] prompts us to report our own efforts in the area.

As shown by our retrosynthetic analysis (Fig. 1), we envisioned installation of the cyclohexene ester core of Tamiflu via ring-closing metathesis of a diene generated by metal-mediated reductive elimination of an iodoribose derivative and in situ alkylation of an aldehyde intermediate by a metal allyl reagent. This diene can then be converted into the cyclohexene ester by ring-closing olefin metathesis (RCM).

The synthesis started from D-ribose with protection of the *syn*-1,2-dihydroxy group as the 3-pentylidene ketal **2** by reaction with 3-pentanone in methanolic saturated HCl solution and trimethyl orthoformate [$HC(OMe)_3$]. The alcohol **2** was then converted into the iodoribose derivative **3** in 79% yield by treatment with PPh_3 and iodine in the presence of imidazole (Scheme 1).[6]

We next examined the Bernet–Vasella domino reaction[7] of iodoribose derivative **3** in the presence of Zn and ethyl 2-(bromomethyl)acrylate. Activated zinc dust in THF under sonication conditions proved to be very reliable and consistently gave full conversion and a very high yield of the desired diene **4**. However, the reaction proceeded slowly in THF alone. The reactivity could be enhanced by addition of H_2O as a co-solvent.

The reaction of **3** with Zn in THF/H_2O (2:1) gave the desired diene **4** along with lactone **5** resulting from cyclization of hydroxy

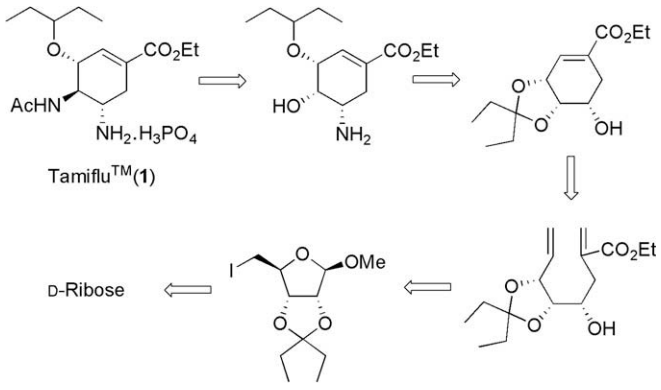

Figure 1. Retrosynthetic analysis of oseltamivir phosphate (**1**) from D-ribose via a 1,2-amino hydroxy intermediate.

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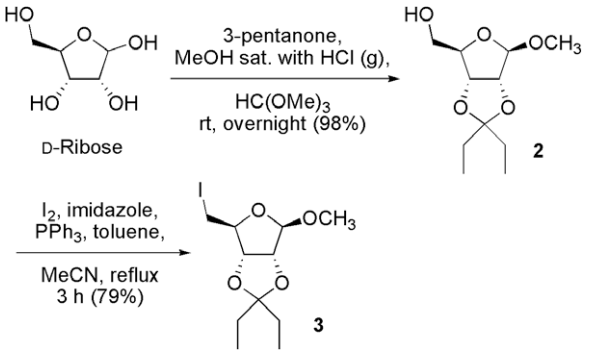
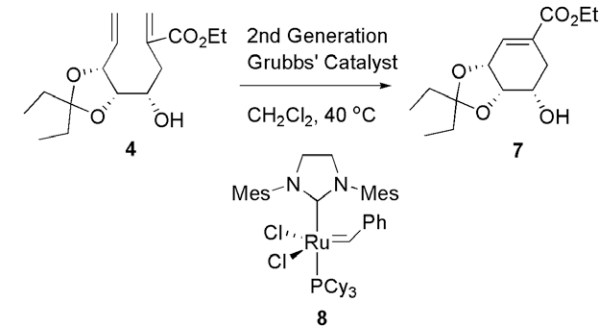


Scheme 1. Preparation of methyl 5-deoxy-5-iodo-2,3-*O*-isopentylidene-β-D-ribofuranose (**3**).

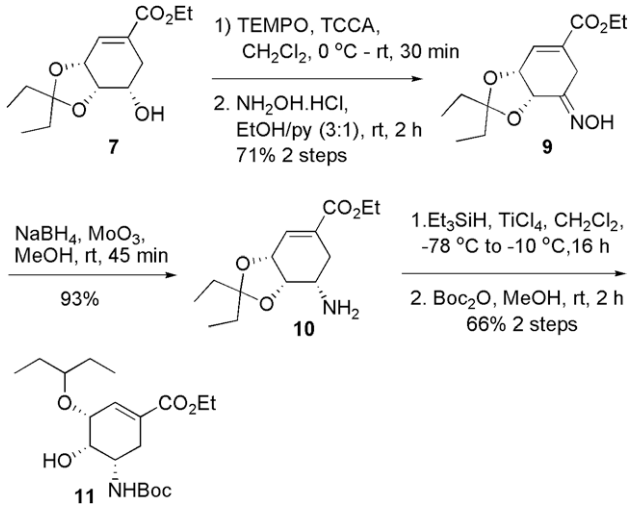
ester **4** (Table 1, entry 1). Besides zinc, the reaction with indium was also investigated. This reaction proceeded significantly slower than with zinc under the same conditions to give the desired diene and a substantial amount of the alkylated by-product **6** (entry 2). However the amount of by-product **6** could be reduced and the yield of **4** was improved significantly to 70% by the addition of acetic acid (0.01 equiv) and sonication until the intermediate aldehyde was formed (monitoring by TLC) before the introduction of ethyl 2-(bromomethyl)acrylate (entry 3).

Using the second-generation Grubbs' catalyst (**8**), the diene **4** underwent ring-closing metathesis to provide 5-*epi*-shikimic acid derivative **7** in 60% yield (Scheme 2). The ^{1}H and ^{13}C NMR spectra of **7** were in agreement with those reported by Chen and co-workers,[5] and hence the stereochemistry of **4** could be assigned (see Supplementary data). Moreover, we did not detect the other isomeric shikimic acid derivative during the RCM reaction, and thus compound **4** is a single stereoisomer.

Our strategy for the transformation of 5-*epi*-shikimic acid derivative **7** into the 1,2-diamino derivative was different from reports in the literature.[3a–d,8] The secondary hydroxy group of **7** was converted into an amino group by oxidation with TEMPO and trichloroisocyanuric acid (TCCA) to provide the corresponding ketone, followed by oxime formation and then reduction of the oxime with $NaBH_4$ catalyzed by MoO_3 to give 5-amino ketal **10**. Regioselective reductive ring opening of the 5-amino ketal was best performed employing a highly selective protocol (Et_3SiH and $TiCl_4$ in CH_2Cl_2 at −78 °C to −10 °C) as reported by scientists at Roche in their shikimic acid route.[3b] However, the hydroxy amino product was difficult to separate by column chromatography. Protection of the amino group with Boc anhydride made chromatographic separation of the protected product **11** much easier (Scheme 3).



Scheme 2. Ring-closing metathesis (RCM) of diene **4**.

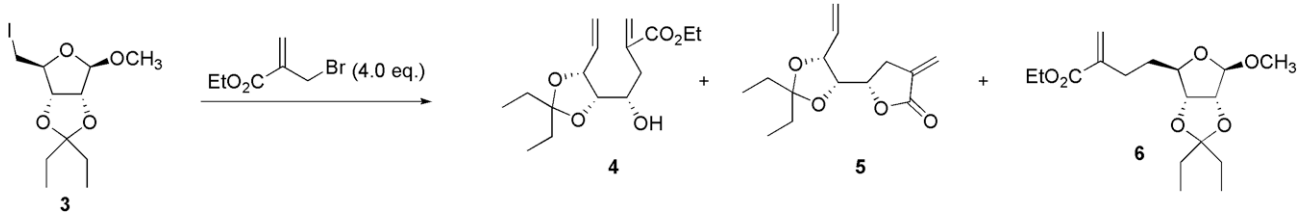


Scheme 3. Synthesis of amino alcohol **11**.

It is interesting to note that when the amino group of ketal **10** was *N*-Boc protected (**10a**), cleavage of the ketal group under the same reaction conditions gave the other regioisomer **11a** (Scheme 4).

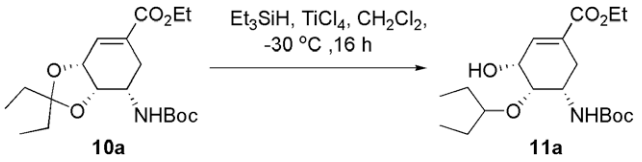
To transform the hydroxy amino compound **11** into the 1,2-diamino carboxylate **13**, the hydroxy group was activated as the triflate which was used in the next step without purification due to its instability (Scheme 5). The triflate underwent S_N2 displacement with sodium azide in acetone/water (9:1) to provide the azido amine **12** in good yield. The azide group of **12** was transformed directly into an acetamide by treatment with thioacetic acid and 2,6-

Table 1
Zinc- and indium-mediated elimination–allylation of **3**

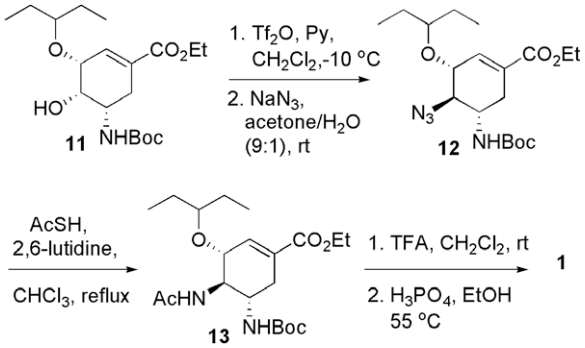


Entry	Metal	Reagents	Yield of **4**[b] (%)	Yield of **5**[b] (%)	Yield of **6**[b] (%)
1	Zn	THF/H_2O (2:1), sonicate, 50 °C, 3 h	71	22	—
2	In	THF/H_2O (2:1), sonicate, 50 °C, 3 h	45	—	30
3	In	THF/H_2O (2:1), AcOH sonicate, 50 °C, 1 h [a]	70	—	7

[a] AcOH (0.01 equiv) was added, the mixture was sonicated until the aldehyde intermediate formed (monitoring by TLC) then ethyl 2-(bromomethyl)acrylate was added and the reaction was sonicated for another 2 h.
[b] Isolated yield.



Scheme 4. Reductive opening of pentylidene ketal **10a**.



Scheme 5. Completion of the synthesis of oseltamivir phosphate (**1**).

lutidine in chloroform at reflux to afford **13** (44% yield, three steps from **11**).[9] Finally, the Boc protecting group of **13** was removed with TFA in CH_2Cl_2 to form an amine, which was directly exposed to 1.2 equiv of phosphoric acid in EtOH at 55 °C to afford oseltamivir phosphate (**1)** in 75% yield (two steps).

In summary, we have accomplished an efficient synthesis of oseltamivir phosphate in 14 steps and 5% overall yield, using cheap and abundant D-ribose as the starting material. The key features of the synthesis include the formation of an *epi*-shikimic acid ester by combining a metal-mediated domino reaction with ring-closing olefin metathesis (RCM). Moreover, transformation of the *epi*-shikimic acid derivative into a 1,2-diamino compound represents a new and efficient synthetic route for the synthesis of Tamiflu which has the potential to be developed as an industrial process in the future.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.044.

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