Drug Synthesis

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A Practical Synthesis of (−)-Oseltamivir**

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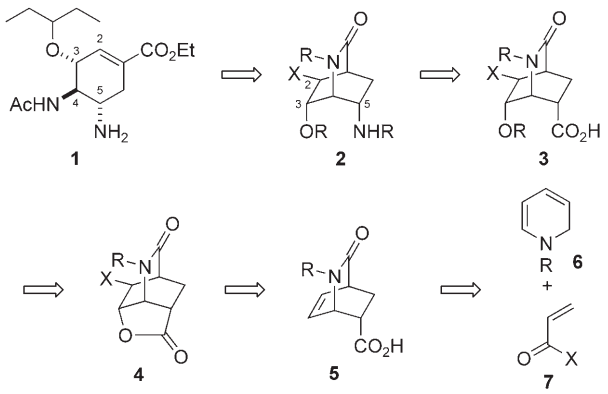
(−)-Oseltamivir phosphate (**1**·H_3PO_4, tamiflu) is a potent inhibitor of neuraminidase and is used worldwide as a drug for influenza of both type A and type B.[1] The recent spread of the avian virus H5N1 has prompted governments to stockpile tamiflu as a precautionary measure against an influenza pandemic. However, the high cost of the drug makes it difficult for developing countries to stockpile tamiflu. The starting material in the current industrial synthesis of oseltamivir is shikimic acid, which is obtained either by the extraction of Chinese star anise or by the fermentation of genetically engineered *E. coli* through tedious purification processes.[2] Furthermore, special production facilities are needed to handle the explosive intermediates and reagents involved. Therefore, intensive efforts have been made to improve the synthesis of oseltamivir.[3] Herein, we report a practical synthesis of oseltamivir.

Our retrosynthesis of oseltamivir (**1**) is outlined in Scheme 1: We proposed the bicyclo[2.2.2] lactam **2** with a



Scheme 1. Retrosynthesis of oseltamivir (**1**).

leaving group X at C2 as a key precursor to **1** and envisaged that **2** could be derived from carboxylic acid **3** by either a Curtius or a Hofmann rearrangement of the corresponding amide. Lactone **4**, a precursor of **3**, could in turn be derived from **5** by halolactonization. Finally, the bicyclic system **5** could best be constructed by an asymmetric Diels–Alder reaction between dihydropyridine **6** and the acrylic acid derivative **7**.

Our synthesis commenced with the reduction of pyridine (**8**) in the presence of benzyl chloroformate to give dihydropyridine **9** (Scheme 2).[4] Asymmetric Diels–Alder reactions between dihydropyridine derivatives and acrylic acid derivatives have not yet been developed to a high enough level to be used practically in synthesis.[5] We therefore turned to a two-step sequence involving the use of acrolein. The treatment of **9** with acrolein in the presence of the MacMillan catalyst (**10**)[6] at room temperature led to a mixture of aldehydes which included the desired Diels–Alder adduct **11**.[7] This mixture was subjected without purification to Kraus oxidation to give the corresponding carboxylic acid **12** among the products.[8] After the removal of basic impurities by washing a solution of the product mixture in ethyl acetate with dilute HCl, the carboxylic acids were extracted into an aqueous solution of sodium bicarbonate. Upon addition of bromine, a facile bromolactonization proceeded to give the desired lactone **13**. As acidic by-products remain in the aqueous phase, simple extraction followed by crystallization from methanol afforded practically pure **13** (>99% *ee*) in 26% yield from benzyl chloroformate. Thus, neither tedious chromatographic separations nor expensive reagents are needed to prepare bromolactone **13**.

Having developed a highly efficient route to this key intermediate, we then focused on the further transformation of **13** into oseltamivir. The Cbz group in **13** was exchanged for a Boc group by hydrogenolysis in the presence of Boc_2O to give **14** (92% yield),[9] which was oxidized with a catalytic amount of $RuO_2 \cdot n H_2O$ (10 mol%) and $NaIO_4$ to furnish imide **15** in 86% yield.[10] Ammonolysis of the lactone followed by mesylation of the resulting alcohol afforded mesylate **17** in 86% yield from **15**. When treated with iodobenzene diacetate and allyl alcohol, amide **17** underwent the Hofmann rearrangement to give allyl carbamate **18** in 88% yield.[11]

As initially anticipated, **18** underwent a series of transformations upon treatment with a slight excess of sodium ethoxide (2.02 equiv) at 0°C: Thus, ethanolysis of the *N*-Boc lactam, dehydrobromination, and aziridine formation provided **19** in 87% yield. The regioselective cleavage of aziridine **19** was effected by treatment with $BF_3 \cdot Et_2O$ in 3-pentanol to give ether **20** in 62% yield.[1,12] Removal of the Boc group and acetylation of the resulting amine afforded **21** in 88% yield. Finally, deprotection of the Alloc-substituted amine with a combination of Pd/C, Ph_3P, and 1,3-dimethylbarbituric acid in ethanol at reflux, removal of the Pd/C catalyst by filtration, concentration in vacuo, and the addition of phosphoric acid[3d] furnished crystalline oseltamivir phosphate (**1**·H_3PO_4) in 76% yield. The spectroscopic data of

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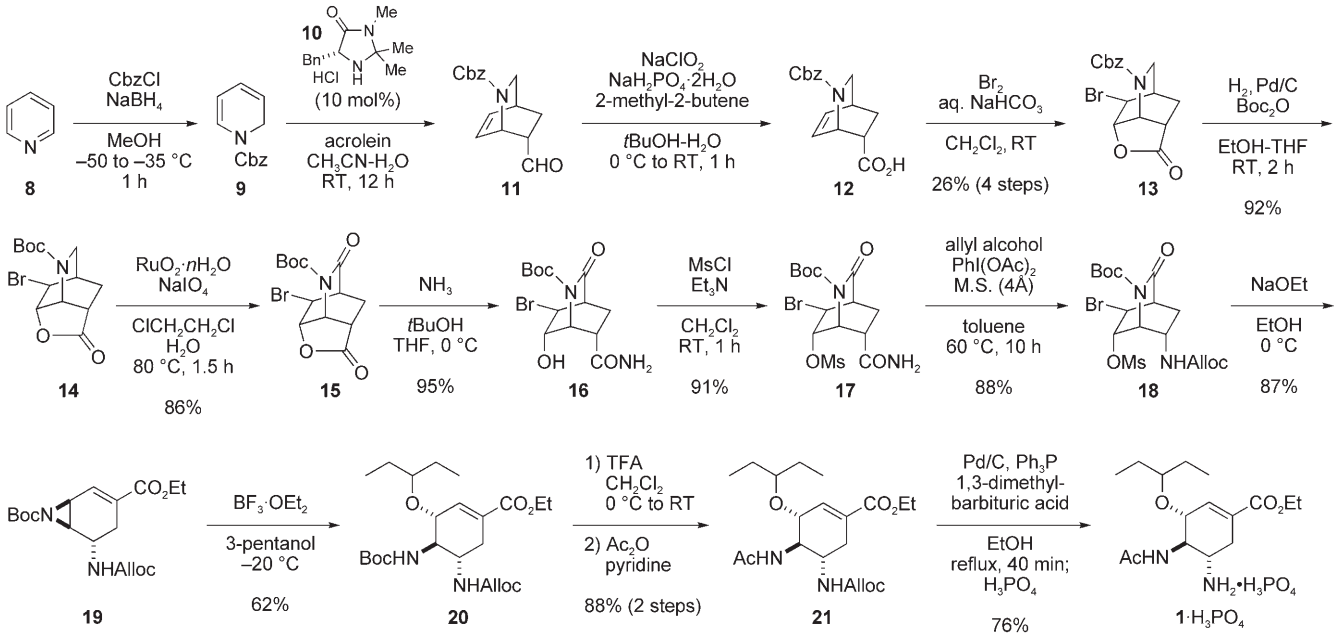
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Synthesis of oseltamivir phosphate (**1**·H_3PO_4). Alloc = allyloxycarbonyl, Bn = benzyl, Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, Ms = methanesulfonyl, M.S. = molecular sieves, TFA = trifluoroacetic acid.

oseltamivir phosphate obtained by this synthetic route are consistent with those reported in the literature.[3a]

We believe that our synthetic route to **1** is highly practical for a number of reasons: First, inexpensive and commonly used reagents are employed. The relatively expensive catalyst $RuO_2 \cdot n\,H_2O$ can be recovered and reused (see reference [8] and the Supporting Information). Furthermore, although the overall yield of lactone **13** from benzyl chloroformate is rather low (26%), this intermediate can be obtained as crystals on a large scale without tedious purification procedures. The other reactions proceed in high yields, and a majority of the intermediates are obtained as crystals. In practice, no chromatographic purifications are required for the conversion of **13** into **17** or for the conversion of **20** into **1**.

In conclusion, we have synthesized oseltamivir phosphate (**1**·H_3PO_4) in 22% yield from the readily available lactone **13** (5.6% yield from benzyl chloroformate) by using an asymmetric Diels–Alder reaction, a bromolactonization, and a Hofmann rearrangement as key transformations. We believe that the overall yield of **1** prepared by the route described would be much improved in a production-scale operation and that our synthesis is thus a viable alternative to the Roche–Gilead synthesis in which shikimic acid is employed as the starting material. Furthermore, our synthetic route has great potential for the generation of a wide range of tamiflu analogues.

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[7] The main by-product was benzyl (5-formylcyclohexa-2,4-dienyl)methylcarbamate, which was isolated as the corresponding alcohol after reduction of the crude mixture of aldehydes (see the Supporting Information). The *exo* isomer was not detected.

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[10] In an experiment with 4.5 g of **14**, 93% of the $RuO_2 \cdot n H_2O$ used could be recovered by the addition of isopropanol to the reaction mixture followed by filtration. The recovered material could be reused and showed no sign of deterioration (see the Supporting Information). Oxone could also be used as a cooxidant (90% over 2 steps). Quite recently, we found that *n*-propyl acetate, a safer solvent than dichloroethane, could be used with similar results.

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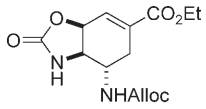
[12] The relatively low yield of **20** was attributed to the concomitant formation of oxazolidinone **22**. The mixture was readily separable by chromatography on silica gel.



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