Second Generation Catalytic Asymmetric Synthesis of Tamiflu: Allylic Substitution Route

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ABSTRACT

Catalytic asymmetric synthesis of Tamiflu, an important antiinfluenza drug, was achieved. After the catalytic enantioselective desymmetrization of meso-aziridine 3 with TMSN₃ using a Y catalyst (1 mol %) derived from ligand 2, an allylic oxygen function and C1 unit on the C=C double bond were introduced through cyanophosphorylation of enone and allylic substitution with an oxygen nucleophile. This second generation route of Tamiflu is more practical than our previously reported route.

The antiinfluenza drug Tamiflu (1) is extremely important for protecting humans against a potential future pandemic of otherwise lethal flu. Considering the amount of Tamiflu required worldwide, there is an urgent demand to improve the Tamiflu production process. Currently, three groups have reported the asymmetric synthesis of Tamiflu: Roche’s commercial route utilizing naturally occurring shikimic acid as a starting material, Corey’s route using the catalytic asymmetric Diels—Alder reaction developed by his group, and a route using the catalytic desymmetrization of meso-aziridines that was developed by our group. In this Letter, we report an alternative route that significantly improves upon our initial synthesis.

Our previous synthesis of 1 utilized azido amide 4, obtained with high enantioselectivity via catalytic desymmetrization of meso-aziridine 3 as the starting chiral building block. A yttrium complex derived from ligand 2 was used as the asymmetric catalyst. There were two main drawbacks to this route: (1) allylic oxidation to introduce oxygen functionality to a diamine-derivative 10 required a stoichiometric amount of a toxic selenium reagent and (2) to effect this allylic oxidation in a synthetically useful yield, desymmetrized 4 was converted to a C₂ symmetric 1,2-diamine derivative (10: P₁, P₂ = Boc), which resulted in cumbersome protection group shuffling at the later stages of synthesis. Thus, we planned to develop a more practical synthetic route to circumvent these two problems (Scheme 1).

(2) For a recent review of synthetic strategies of Tamiflu, see: Farina, V.; Brown, J. D. Angew. Chem., Int. Ed. 2006, 45, 7330.
The bulky 3-pentyloxy group should be introduced at a late stage with a ring-opening reaction of aziridine 5, which was produced from amido alcohol 6 under Mitsunobu conditions. Compound 6 containing a \( \beta \)-OH group would be obtained via suprafacial allylic rearrangement of cyanophosphate 7,\(^6\) which could be synthesized from enone 8 via cyanophosphorylation. Enone 8 would be synthesized from \( 1,2 \)-trans-diamine derivative 10 through halocyclization followed by elimination, hydrolysis, and oxidation. As reported previously,\(^10\) 10 can be synthesized with excellent enantioselectivity through catalytic enantioselective desymmetrization of \( \text{meso} \)-aziridine 3. To avoid protection group shuffling, two amino groups of 10 should be differentiated, preferably with the protecting group \( P^1 \) to be an acetyl.

On the basis of this synthetic plan, enantiomerically pure 11 was synthesized through catalytic desymmetrization of 3 with TMSN\(_3\) as a key step (Scheme 2). This catalytic reaction led to two new findings. First, the reaction was performed with 1 mol % of catalyst in the presence of 1 equiv of 2,6-dimethylphenol in a 30-g scale. The reaction rate was faster than in the previously reported conditions in the absence of a protic additive, and the enantioselectivity was comparable (89% ee).\(^7\) Second, chiral ligand 2 was recovered in 81% yield after the reaction through extraction with a base. A catalyst prepared from the recovered 2 produced almost comparable results to the first cycle with regard to catalyst activity and enantioselectivity.

Next, reduction of the azide with Ph\(_3\)P and acetylation of the resulting amine produced unsymmetrically protected diamine derivative (10: \( P^1 = \text{Boc} \), \( P^2 = \text{Ac} \). Iodocyclization proceeded selectively on the acetamide carbonyl oxygen atom, and the following elimination of HI with DBU produced dihydrooxazine 12. In the iodocyclization step, the product resulting from the cyclization of \( N \)-Boc urethane carbonyl oxygen while maintaining the acetamide was a more favorable reaction pathway for the Tamiflu synthesis—was produced only as a minor component. The dihydrooxazine moiety was hydrolyzed in the presence of CbzCl,\(^8\) producing acetate 13. Hydrolysis of the acetate followed by Dess–Martin oxidation produced the key enone 14 in high overall yield.

Cyanophosphorylation of enone 14 proceeded stereoselectively with use of diethylphosphoryl cyanide (DEPC)\(^9\) in the presence of a catalytic amount of LiCN,\(^10\) affording cyanophosphate 15.\(^11\) The crucial allylic rearrangement was

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(7) Previously, 4 was produced in 96% yield with 91% ee, using 2 mol % of the catalyst in the presence of 2,6-dimethylphenol (reaction time = 48 h). For beneficial effects of a protic additive in a catalytic asymmetric conjugate addition of an azide, see: Guerin, D. J.; Miller, S. J. J. Am. Chem. Soc. 2002, 124, 2134.


attempted under thermal conditions. Unexpectedly, a cyclic carbamate was cleanly produced via intramolecular SN2′ allylic substitution. After reprotection of the nitrogen atom of the cyclic carbamate with a Boc group to afford 16, the less sterically hindered carbamate was cleaved by a catalytic amount of Cs2CO3 in MeOH, producing the corresponding α-OH allylic alcohol. The stereochemistry of the allylic position was inverted through an oxidation—stereoselective reduction sequence, affording trans amido alcohol 17 containing the suitable stereo-requirement for the following aziridine formation via the Mitsunobu reaction. The Mitsunobu reaction proceeded in high yield. The resulting aziridine 18 was subjected to a ring-opening reaction with 3-pentanol in the presence of BF3·OEt2 and the successive cleavage of the N-Boc group followed by N-acetylation afforded 19 in 81% yield. Hydrolysis of the N-Cbz group and ethanolysis of the nitrile proceeded concomitantly in acidic ethanol. Basification and H3PO4 salt formation completed the synthesis of Tamiflu (1).

Although this preliminary synthetic route avoided allylic oxidation with the toxic selenium reagent, protection group manipulation was still cumbersome and the synthesis was lengthy due to undesired iodocyclization with the acetamide group at the initial stage of the synthesis. To address this problem, we investigated a modified route involving iodocyclization of azido amide 11 (Scheme 3). Treatment of 11 with I2 in the presence of K2CO3, followed by subjecting the resulting cyclic carbamate to an elimination reaction of HI with DBU, produced 20 in 85% yield. Protection of the carbamate nitrogen atom with a Boc group and reductive acetylation of the azide with AcSH produced 21, which was selectively hydrolyzed and oxidized with Dess–Martin periodinane to produce enone 22. Cyanophosphorylation of enone 22 proceeded with DEPC in the presence of LiCN, and cyanophosphate 23 was obtained as a single detectable isomer. The key allylic rearrangement of 23 was studied under thermal conditions (Scheme 4). Heating a toluene solution of 23 to 140 °C in a sealed tube produced a labile and unisolatable β-allyl phosphate 28 as an initial product, whose structure was estimated by ESI-MS without isolation. Addition of 1 M NaOH solution to the reaction mixture produced stable oxazoline 29 as a major product in 38% yield, together with allylic alcohol 24 (23%) produced through an SN2 attack of a hydroxide anion to the phosphate. Because we could not find any conditions that affect the oxazoline opening of 29 with 3-pentanol, we next turned our attention to an intermolecular nucleophilic substitution of the allylic phosphate of 28. After several trials, a synthetically useful yield (78%) of α-allylic alcohol 24 was produced by the addition of saturated aqueous NH4Cl solution to 28.

On the basis of the above findings, asymmetric synthesis of Tamiflu was completed from 24 as follows (Scheme 3).

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(11) Configuration of the tetrasubstituted carbon of 15 was temporarily assigned as shown based on the structure of 29 (see Scheme 4).
(12) Pd(II)-catalyzed allylic rearrangement (ref 6a) did not afford the desired product.
(14) Ring-opening reaction of cyclic carbamate 16 with 3-pentanol was intensively studied in the presence of a variety of Lewis acids. The desired product, however, was not produced in these reactions.
(17) The stereochemistry of the allylic position of 28 was temporarily assigned based on Bartlett and Kurinjika’s previous findings (ref 6), in which allylic rearrangement of α-cyanophosphate proceeded in a suprafacial fashion.
(18) Neither direct addition of 3-pentanol to 28 nor aziridine formation from 28 proceeded under various conditions.
After the α-allyl alcohol of 24 was inverted via the Mitsunobu reaction with p-nitrobenzoic acid followed by hydrolysis of the p-nitrobenzoate in one pot, the resulting β-allylic alcohol 25 was subjected to aziridine formation through Mitsunobu conditions, producing 26. Introduction of 3-pentanol was conducted with an aziridine opening reaction to produce 27 in 56% yield. Ethanalysis of the cyanide and cleavage of the Boc group under acidic ethanol, followed by basification and H$_3$PO$_4$ treatment, produced 1. This route solves the two main problems (allylic oxidation and protection group shuffling) of the previously reported synthetic route. In addition, the synthetic scheme is shorter than that of the previously reported synthesis (15 steps from aziridine 3).

In summary, we developed our second generation synthesis of Tamiflu. This route utilizes a catalytic enantioselective desymmetrization of meso-aziridine 3 with TMSN$_3$ as the initial key step. The reaction was performed with 1 mol % of chiral Y catalyst derived from ligand 2 at room temperature. Careful optimization of the synthetic scheme made it possible to avoid protection group shuffling, which was a drawback in our first generation synthesis. The allylic oxygen functionality required for 3-pentyl ether formation was introduced by rearrangement of an allylic phosphate followed by substitution with a hydroxyl group. Thus, the other drawback of our previous synthesis—i.e., the use of a toxic selenium reagent in the allylic oxidation—was also overcome. Further improvement of the synthetic efficacy by using a completely different strategy is currently under investigation.

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**Supporting Information Available:** Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.