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Second Generation Catalytic Asymmetric Synthesis of Tamiflu: Allylic Substitution Route

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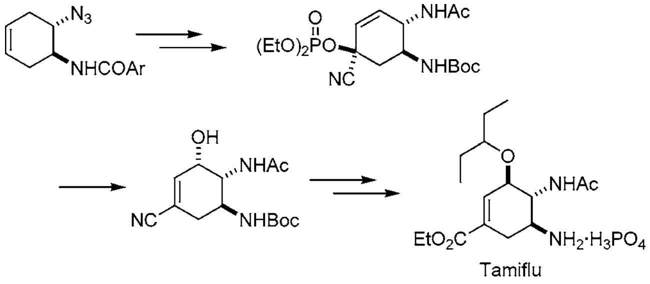
ABSTRACT



Catalytic asymmetric synthesis of Tamiflu, an important antiinfluenza drug, was achieved. After the catalytic enantioselective desymmetrization of *meso*-aziridine 3 with $TMSN_3$, 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**)[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:[2] Roche's commercial route utilizing naturally occurring shikimic acid as a starting material,[3] Corey's route using the catalytic asymmetric Diels−Alder reaction developed by his group,[4] and a route using the catalytic desymmetrization of *meso*-aziridines that was developed by our group.[5] 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 a *meso*-aziridine **3** as the starting chiral building block.[5] 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 C_2 symmetric 1,2-diamine derivative (**10**: P^1, P^2 = 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).

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[1] Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681.

[2] For a recent review of synthetic strategies of Tamiflu, see: Farina, V.; Brown, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7330.

[3] Abrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U. *Chimia* **2004**, *58*, 621.

[4] Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310.

[5] Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.

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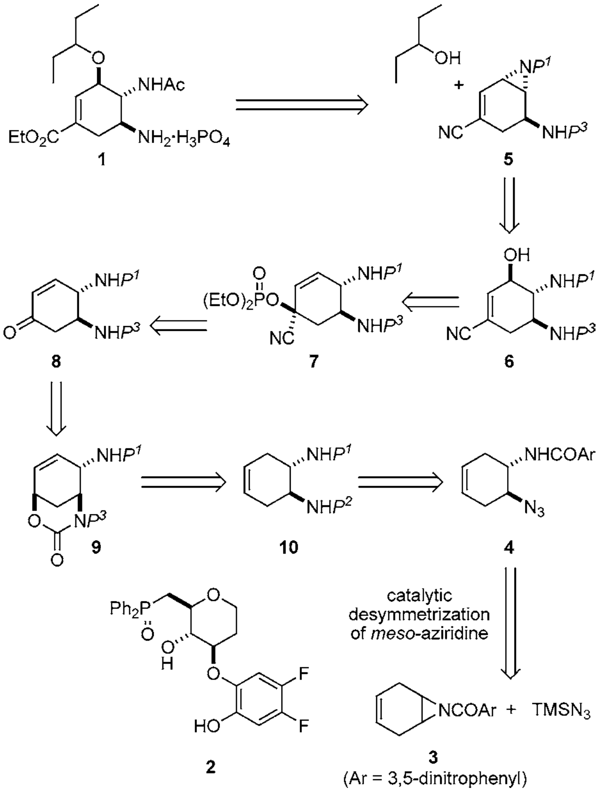
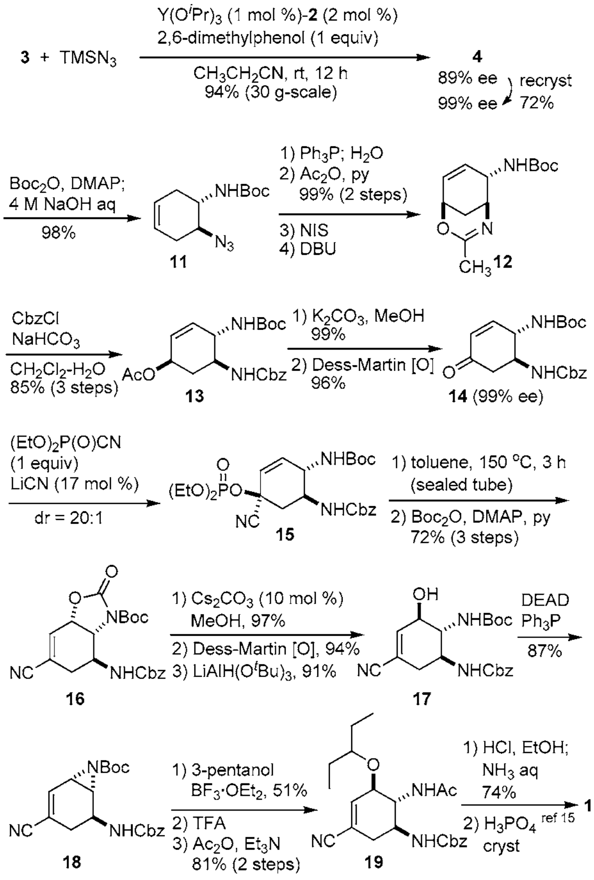
Scheme 1. Synthetic Plan



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.[5] Compound **6** containing a β-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** can be synthesized with excellent enantioselectivity through catalytic enantioselective desymmetrization of *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.

Scheme 2. Preliminary Optimization of the Allylic Substitution Route of Tamiflu



Next, reduction of the azide with Ph$_3$P and acetylation of the resulting amine produced unsymmetrically protected diamine derivative (**10**: P^1 = Boc, P^2 = 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—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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(6) (a) Bartlett, P. A.; McQuaid, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7854. (b) Kurihara, T.; Miki, M.; Yoneda, R.; Harusawa, S. *Chem. Pharm. Bull.* **1986**, *34*, 2747.

(7) Previously, **4** was produced in 96% yield with 91% ee, using 2 mol % of the catalyst in the absence 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.

(8) Dalko, P. I.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 2107.

(9) Yamada, S.; Kasai, Y.; Shioiri, T. *Tetrahedron Lett.* **1973**, 1595.

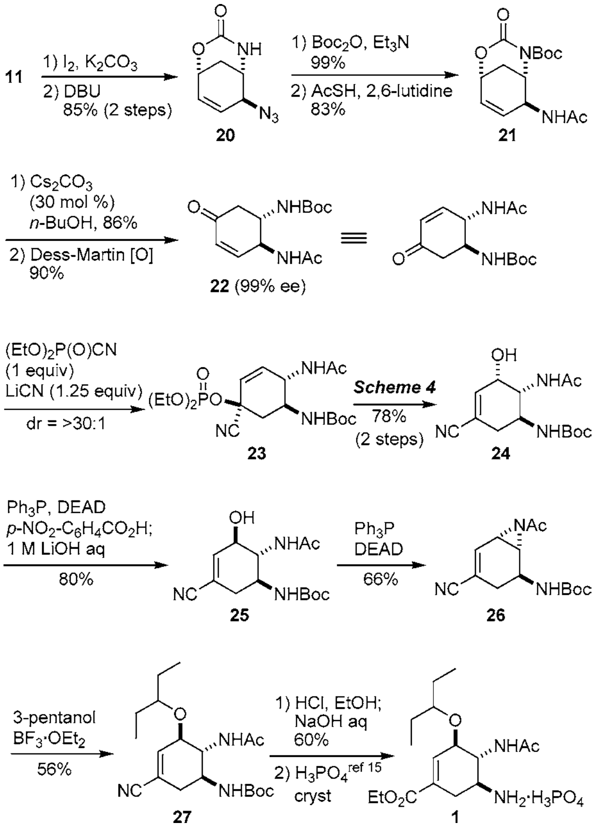
(10) Harusawa, S.; Yoneda, R.; Kurihara, T.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 427.

attempted under thermal conditions.[6b,12] Unexpectedly, a cyclic carbamate was cleanly produced via intramolecular S_N2' 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 Cs_2CO_3 in MeOH, producing the corresponding α-OH allylic alcohol. The stereochemistry of the allylic position was inverted through an oxidation−stereoselective reduction[5] sequence, affording trans amido alcohol **17** containing the suitable stereo-requirement for the following aziridine formation via the Mitsunobu reaction.[13] 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 $BF_3{\cdot}OEt_2$,[14] 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 H_3PO_4 salt formation[15] completed the synthesis of Tamiflu (**1**).

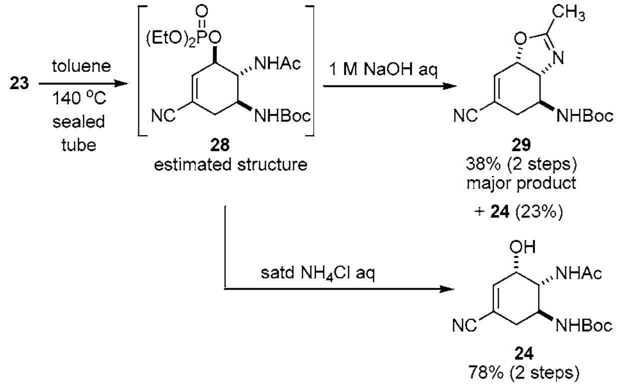
Although this preliminary synthetic route avoided allylic oxidation with the toxic selenium reagent, protection group manipulation was still cumbersome and the synthesis was lengthy due to undesired iodocyclization with the acetamide group at the initial stage of the synthesis. To address this problem, we investigated a modified route involving iodocyclization of azido amide **11** (Scheme 3). Ttreatment of **11** with I_2 in the presence of K_2CO_3, 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[16] 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.[17] 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 S_N2 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,[18] a synthetically useful yield (78%) of α-allylic alcohol **24** was produced by the addition of saturated aqueous NH_4Cl solution to **28**.

Scheme 3. Optimized Allylic Substitution Route



Scheme 4. Allylic Rearrangement−Substitution Sequence



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.

(13) Ho, M.; Chung, J. K. K.; Tang, N. *Tetrahedron Lett.* **1993**, *34*, 6513.

(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.

(15) Harrington, P. J.; Brown, J. D.; Foderaro, T.; Hughes, R. C. *Org. Process Res. Dev.* **2004**, *8*, 86.

(16) Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754.

(17) The stereochemistry of the allylic position of **28** was temporarily assigned based on Bartlett and Kurihara'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**[5] in 56% yield. Ethanolysis of the cyanide and cleavage of the Boc group under acidic ethanol, followed by basification and H_3PO_4 treatment,[15] produced **1**. This route solves the two main problems (allylic oxidation and protection group shuffling) of the previously reported synthetic route.[5] In addition, the synthetic scheme is shorter than that of the previously reported synthesis[5] (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.[5] 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.

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