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Multistep Continuous-Flow Synthesis of (–)-Oseltamivir

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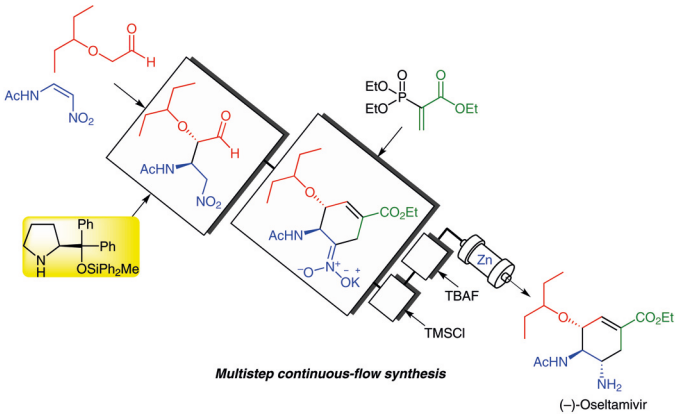
Dedicated to Professor Dieter Enders on the occasion of his 70th birthday



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Abstract A continuous-flow synthesis of (–)-oseltamivir composed of five flow units was accomplished. In each unit, the following reactions proceed efficiently: (1) a diphenylprolinol silyl ether mediated Michael reaction, (2) a domino reaction of Michael and intermolecular Horner–Wadsworth–Emmons reactions, (3) protonation, (4) epimerization, and (5) reduction of a nitro group to an amine. (–)-Oseltamivir was obtained in 13% total yield through a single flow with a residence time of 310 minutes.

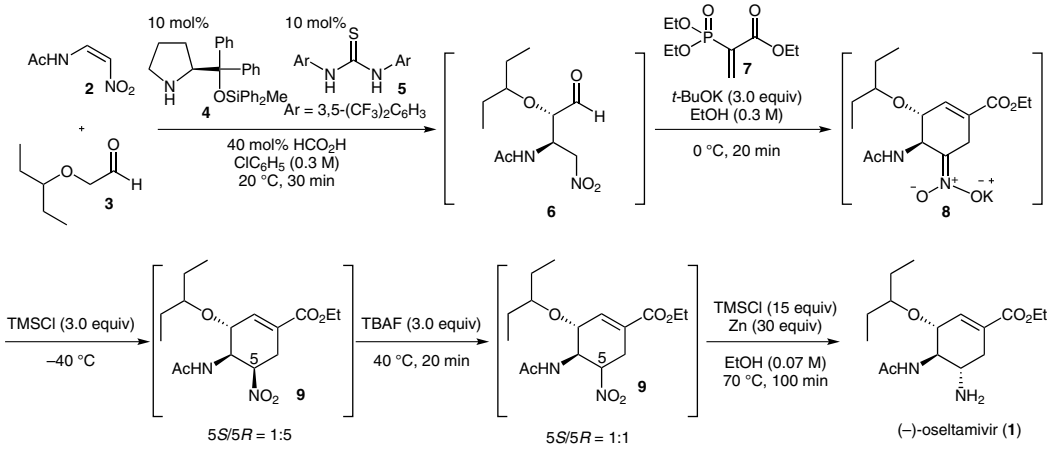
Key words Tamiflu, continuous flow, time economy, total synthesis, organocatalysis

Tamiflu®, or (–)-oseltamivir phosphate, is one of the most effective drugs for the treatment of influenza.[1] Because of its importance, more than 60 different synthetic routes have been developed.[2] Our group has a long-standing interest in the effective synthesis of this drug. On the one hand, we developed three-pot[3] and two-pot[4] syntheses of (–)-oseltamivir (**1**) in 2009 and 2010, respectively, by using an asymmetric Michael reaction of an aldehyde and nitroalkene catalyzed by diphenylprolinol silyl ether[5] as a key step. Ma,[6] Sebesta,[7] and Lu[8] reported the synthesis of (–)-oseltamivir from (*Z*)-nitroalkene **2**, independently. We further accomplished a one-pot procedure in 2013 by using (*Z*)-nitroalkene **2** as a starting material.[9]

A flow synthesis, on the other hand, has attracted considerable attention recently because of its efficiency, productivity, safety, and reproducibility.[10] Moreover, continuous-flow techniques have been developed to combine a multistep synthesis with a single, continuous, and uninterrupted reactor network without isolation of the intermediate.[11] Kobayashi recently reported the synthesis of (*R*)- and (*S*)-rolipram with a single chiral center with four flow reactors in a single flow, all using heterogeneous catalysts,[12] while a three minute synthesis of racemic ibuprofen over three flow reactors and one-membrane separation was reported by Jamison.[13] Despite these excellent syntheses, it was a challenge to synthesize (–)-oseltamivir with three continuous chiral centers through a multistep continuous-flow method in a single passage. In comparison with the batch system, the flow system was easy to increase the productivity in the long time operation or directly applicable to a larger scale after optimization on a small scale. We anticipated that a continuous-flow synthesis of (–)-oseltamivir would be more efficient.

In our one-pot synthesis of (–)-oseltamivir in 2013,[9] we simply added the reagents sequentially without evaporation or solvent swap. Thus, we considered that we could apply flow techniques to the synthesis of (–)-oseltamivir. However, one of the most critical issues when our one-pot procedure[9] is applied to a flow method is the total reaction time. As it takes 57 hours for completion of the total synthesis, although it is a one-pot procedure, a very long reaction tube has to be prepared, which is not practical. It was necessary to shorten the reaction time. For this purpose, we have investigated the time-economical synthesis of (–)-oseltamivir through a batch system. Recently, we accomplished a 60-minute total synthesis of (–)-oseltamivir, optimizing the reactions according to time, decreasing the number of reaction steps, and using microwave (MW) irradiation. Even without microwave irradiation, (–)-oseltamivir could be synthesized within 170 minutes (Scheme 1).[2a] As the reaction is completed within a short time, we applied flow techniques to this rapid synthesis of (–)-oseltamivir, which will be described in this communication.

Although we shortened the reaction time, there remained problems to be solved for the application of a flow method. (1) In a flow system, generally all reagents have to be soluble in the solvent except for polymer-supported reagents, but nitroalkene **2** was barely soluble in the reaction

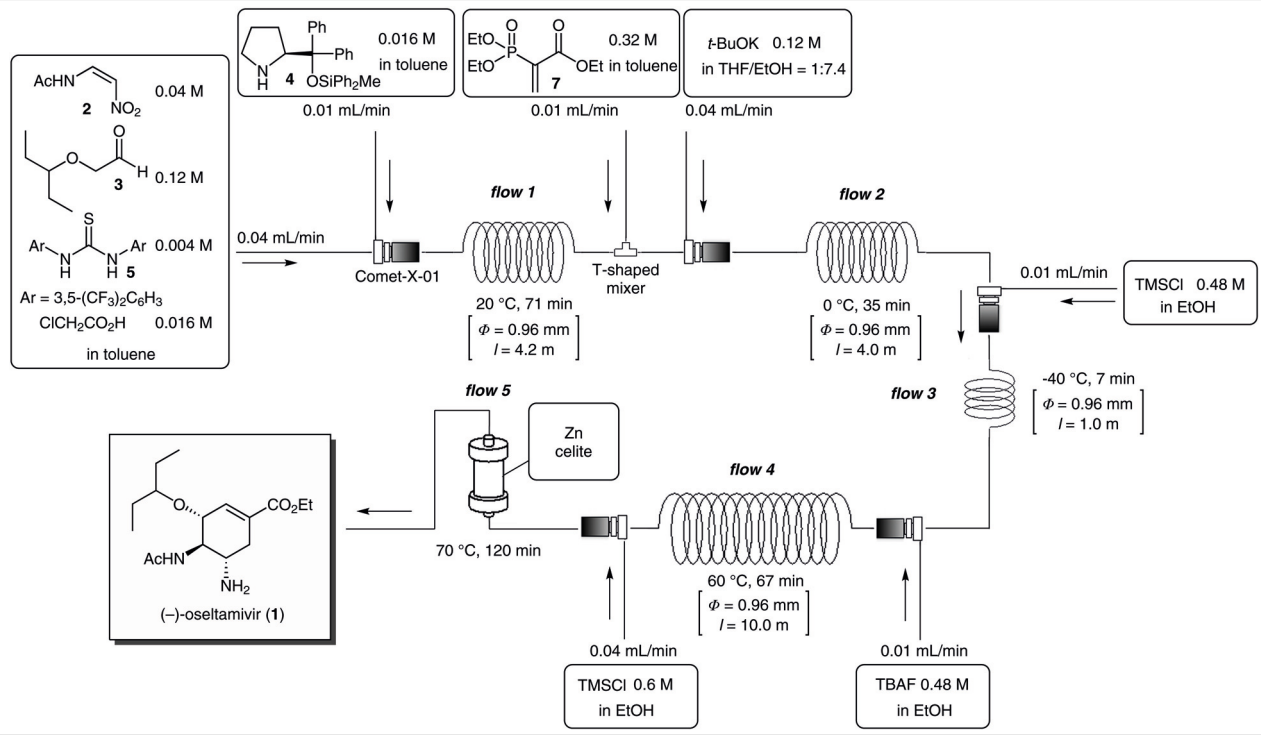


Scheme 1 Time-economical one-pot synthesis of (–)-oseltamivir without microwave irradiation reported in 2016[2a]

solvent. (2) Zinc was employed in the reduction of the nitro group to an amine, and it is problematic to conduct this transformation in a flow system.

To address these problems, we first optimized the synthetic procedure of (–)-oseltamivir by using a batch system. We then applied the optimized procedure to the flow synthesis. After extensive optimization of the reaction conditions, we succeeded in creating a continuous-flow synthesis of (–)-oseltamivir, which is summarized in Scheme 2. This flow synthesis consists of five units, which we will describe in turn.

Flow unit 1 involved the asymmetric Michael reaction of pentan-3-yloxyacetaldehyde (**3**) and (*Z*)-*N*-2-nitroethenylacetamide (**2**). We previously noted that Schreiner's thiourea **5**,[14] with a combination of diphenylprolinol silyl ether **4**, dramatically accelerates the reaction, and that the reaction time was shortened without affecting either the diastereo- or enantioselectivities. As nitroalkene **2** dissolves



Scheme 2 Continuous-flow synthesis of (–)-oseltamivir

only partially in an aromatic solvent, a suspended solution in chlorobenzene (0.3 M) gradually became clear as the reaction proceeded in the batch synthesis.[2a] However, in the flow system, nitroalkene **2** must be soluble in the solvent from the outset. When a polar solvent was employed, nitroalkene **2** dissolved, but an epimerization of the *syn* form to the undesired *anti*-Michael adduct occurs quickly with a corresponding decrease of the chemical yield. After optimizing the solvent and concentration of nitroalkene **2**, we obtained good results by using toluene as the solvent under dilute conditions. The reaction proceeds within 1 hour to afford the Michael product in good yield with high *syn*-selectivity and excellent enantioselectivity (95%, *dr* = 14:1, 97% ee), when a dilute clear toluene solution (0.04 M) of nitroalkene **2** was used (Scheme 2). A toluene solution of nitroalkene **2**, alkoxyaldehyde **3**, thiourea derivative **5**, and $ClCH_2CO_2H$ was mixed with a toluene solution of catalyst **4** by using a Comet-X-01 micromixing device[15,16] at 20 °C. The above mixture was allowed to flow in the tube for 71 minutes to provide Michael adduct **6**. When the reaction was quenched at this stage, the conversion (91%, *dr* = 10:1, 97% ee) was almost same as that of the batch system.

Flow unit 2 involved a domino reaction of Michael and intermolecular Horner–Wadsworth–Emmons reactions. We already optimized this step in a batch system, in which soluble *t*-BuOK was selected as a base[2a] instead of insoluble Cs_2CO_3 at 0 °C.[9] We conducted the reactions in a flow system as follows: phosphoryl acrylate **7** and *t*-BuOK were added separately through the use of a T-shaped mixer and a Comet-X-01 device to avoid the Michael addition of EtOH to phosphoryl acrylate **7**. After a toluene solution of phosphoryl acrylate **7** was added to the reaction mixture, an EtOH solution of *t*-BuOK was added by using the next mixer. Although the reaction proceeded smoothly, a solid appeared in the second mixer and clogged the flow path over time. THF was premixed with *t*-BuOK in EtOH to prevent the precipitation. As a result, after a 35-minute residence time at 0 °C, cyclohexene **9** was obtained in approximately 60% yield[17] when the reaction was quenched at this stage, in which the undesired 5*R*-isomer was predominantly generated (5*S*/5*R*=1:5).

Flow unit 3 protonated the nitronate anion. At the end of the domino reaction, potassium nitronate **8** (Scheme 1) was formed, which needed to be protonated before an epimerization. Protonation was accomplished by the addition of TMSCl in EtOH, which produced HCl in situ, with a residence time of 7 minutes at –40 °C.

Flow unit 4 effected an epimerization from the 5*R*-isomer to the 5*S*-isomer. In the previous report of the batch synthesis,[2a] we optimized the rapid epimerization and found that tetrabutylammonium fluoride (TBAF) is effective, although complete epimerization could not be achieved (5*S*/5*R* = 1:1). The appropriate flow rates and residence times were optimized for epimerization by using a flow system. After a protonation occurred in the flow system at –40 °C, the reaction mixture was combined with an EtOH solution of TBAF in the next Comet-X-01. The combination was allowed to flow for 67 minutes at 60 °C, and equal amounts of *R*- and *S*-isomers were formed.

Flow unit 5 effected the reduction of the nitro group to an amine. In the batch system, it took 2 hours for this reduction using Zn and TMSCl. Because Zn is a solid, we used a column system for this reduction. A column (Biotage, SNAP Empty cartridge 10 g)[18] was packed with zinc (5 g) and Celite (8 g), and was attached to the flow system. Celite was used to avoid clogging.

First we added TMSCl then the reaction mixture was flowed through the column. Partial undesired epimerization of the 5*S*-isomer **9** to 5*R*-isomer **9** was observed after the addition of TMSCl. We found that the concentration of TMSCl was crucial to suppress this epimerization. After optimizing the reaction conditions for a flow system, a mixture of TMSCl in EtOH (0.6 M) was introduced from the bottom of the column, which effectively reduced the nitro group in the flow system without epimerization. The reduction was conducted at 70 °C and the residence time was 120 minutes. The column was replaced every 5 hours because Zn activity gradually decreased over a long period. On the other hand, the column was found to be stable for 5 hours. When three columns were continuously employed for 15 hours, the conversions of several exiting solutions showed almost same value.

(–)-Oseltamivir was isolated by using an acid–base extraction and purified by column chromatography. The total residence time through the five flow units was 310 minutes. Except for unit 5, a reaction tube with a bore size of 0.96 mm was used, and the flow rate and concentration of the nitroalkene **2** were 0.04 mL/min and 0.04 M, respectively. A column packed with Zn and Celite was employed in unit 5. Under these conditions, we obtained 58 mg of (–)-oseltamivir per 15 hours (13% yield).

In summary, a continuous-flow synthesis of (–)-oseltamivir with five flow units was accomplished. All reagents except for Zn were dissolved in solvent. The multistep continuous-flow synthesis for (–)-oseltamivir with three continuous chiral centers was successfully realized without isolating any intermediates by using a single flow.

All reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F254 plates (0.25 mm thickness). Compounds were visualized by UV, $KMnO_4$ or sulfuric acid molybdenum. A Comet-X-01 micromixing device was obtained from Techno Applications Co., Ltd.[15] Syringe pumps (PHD2000 or Catamaran HII-10B) were obtained from Harvard Apparatus or Techno Applications Co., Ltd. 'SNAP Empty cartridge' was purchased from Biotage Japan Co., Ltd.[18] ^1H and ^{13}C NMR spectra were recorded with an Agilent-400 MR (400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR) instrument. High-resolution ESI-TOF mass spectra were measured with a Thermo Orbitrap instrument.

(–)-Oseltamivir (1); Flow Synthetic Procedure

A toluene solution of nitroalkene **2** (0.04 M), alkoxyaldehyde **3** (0.12 M), thiourea derivative **5** (0.004 M), $ClCH_2CO_2H$ (0.016 M) and 1,3,6-trimethoxybenzene (0.002 M, internal standard) were mixed and loaded into a syringe. A toluene solution of diphenylproninol silyl ether **4** (0.016 M) was loaded into a second syringe. The syringe pumps were then switched on at a flow rate of 0.04 mL/min and 0.01 mL/min, respectively. These solutions were united at a micromixer (Comet-X-01) at the same time, and the reaction mixture was allowed to flow for 71 minutes through a Teflon reactor tube (φ 0.96 mm, l = 4.2 m) at 20 °C. The Michael adduct was united with a solution of ethyl acrylate derivative **7** (0.32 M) in toluene through the T-shaped mixer by using a third syringe pump at a flow rate of 0.01 mL/min at 0 °C. *t*-BuOK in THF and EtOH solution (0.12 M, 1:7.4) was injected into the next micromixer (Comet-X-01) by using a fourth syringe pump at a flow rate of 0.04 mL/min and mixed with the reaction mixture. After the reaction mixture was allowed to flow for 35 min through a Teflon reactor tube (φ 0.96 mm, l = 4.0 m) at 0 °C, the nitronate anion was protonated by another flow of TMSCl in EtOH (0.48 M) by using a fifth syringe pump at a flow rate of 0.01 mL/min. It took 7 minutes through a Teflon reactor tube (φ = 0.96 mm, l = 1.0 m) at –40 °C. A EtOH solution of 1 M TBAF in THF (0.48 M) was injected into the next micromixer (Comet-X-01) by using a sixth syringe pump at a flow rate of 0.01 mL/min and the reaction mixture was allowed to flow for 67 minutes through a Teflon reactor tube (φ 0.96 mm, l = 10 m) at 60 °C.

Zn reduction was conducted as follows. Celite® 545 (8 g) and an activated Zn powder (5 g) were charged into a SNAP Empty cartridge (10 g). After a solution of TMSCl in EtOH (0.6 M) was injected to the next micromixer (Comet-X-01) by using a seventh syringe pump at a flow rate of 0.04 mL/min and united with the reaction mixture, the solution was introduced into the column from the bottom to the top, which was heated at 70 °C. The reaction mixture was allowed to flow for 2 h through the column. This package of column was replaced every 5 h. The exiting solution was collected and concentrated in vacuo. 1 M HCl was added to the residue at 0 °C. The aqueous layer was washed with EtOAc. To the aqueous layer was added 28% NH_4OH to adjust to pH 11. The aqueous layer was extracted three times with 10% MeOH/$CHCl_3$. The combined organic layer was concentrated in vacuo. The residue was dissolved in 10% MeOH/EtOAc, and washed with 10% NaCl in H_2O to remove TBAF, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2; $CHCl_3$/MeOH, 10:1) to afford (–)-oseltamivir (**1**) (58 mg / 15 h) in 13% yield as a pale-yellow oil; R_f = 0.3 ($CHCl_3$/MeOH, 4:1). Spectroscopic data corresponded with the published data.[2a]

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588899.

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(15) A micromixing device, 'Comet X-01', is available from Techno Applications Co., Ltd., 34-16-204, Hon, Denenchofu, Oota, Tokyo, 145-0072, Japan (e-mail: yukio-matsubara@nifty.com).

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(17) The yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

(18) 'SNAP Empty cartridge' is available from Biotage Japan Co., Ltd., 1-4-14, Kameido, koto-ku, Tokyo, 136-0071, Japan (e-mail: japan-info@biotage.com).