Organic LETTERS

Letter

pubs.acs.org/OrgLett

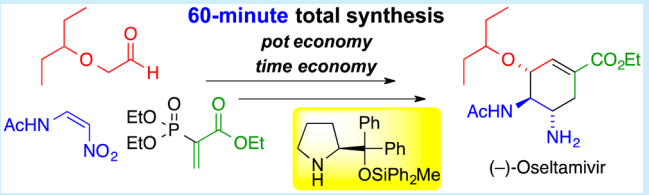
Time Economical Total Synthesis of (−)-Oseltamivir

Yujiro Hayashi* and Shin Ogasawara

Department of Chemistry, Graduate School of Science, Tohoku University, 6-3 Aramaki-Aza Aoba-ku, Sendai, Miyagi 980-8578, Japan

Supporting Information

ABSTRACT: A time economical 60 min total synthesis of (−)-oseltamivir was accomplished in a single reaction vessel over five steps. One of the key issues is reduction in the number of steps by eliminating lengthy reaction steps with substitution of a rapid epimerization step. A catalytic system consisting of three reagents, namely, diphenylprolinol silyl ether, thiourea, and acid, was developed for a rapid asymmetric Michael reaction with excellent diastereo- and enantioselectivities. All reactions were optimized in terms of not only yield and selectivity but also reaction time.



Time is money. This is true not only in our daily life but also in the synthesis of molecules. It is one of the goals for a chemist to synthesize a molecule as quickly as possible. However, this is not easy because some of the single reactions take a long time, and several hours and days are usually necessary to carry out several reactions. For instance, there are more than 60 syntheses[1,2] of (−)-oseltamivir phosphate (Tamiflu),[3] a neuraminidase inhibitor, which is one of the most effective drugs for the treatment of influenza, and the total reaction time for the previous syntheses are more than 30 h. This number only includes the reaction time, and a much longer time is needed, considering the postprocessing operations. It is a great challenge to synthesize a molecule within a short time period in current synthetic organic chemistry. Recently, Jamison reported a remarkable 3 min synthesis of ibuprofen using continuous flow technology.[4]

The most time-consuming operations in the synthesis of organic molecules are those such as quenching, extracting, and purifying after the reaction. To minimize these postprocessing operations, it is synthetically advantageous to carry out several reaction steps in a single reaction vessel sequentially, and we recently proposed the importance of pot economy.[5]

There are several economies[6] in syntheses, such as atom economy,[7] step economy,[8] and redox economy.[9] The selection of a synthetic strategy with a small number of steps according to step economy and redox economy is essential for efficient synthesis as well as performing the reactions in a single vessel, reducing the postprocessing operations according to pot economy. Step, redox, and pot economies are all concerned with reducing the reaction time, but these are not enough for a rapid synthesis. The reaction itself has to be fast, and selection of a rapid reaction and reaction conditions is also essential for the success of time economy. In some cases, new catalytic systems have to be developed. Optimization of reactions is routinely performed mostly in terms of yield, selectivity, and greenness, the last one being especially important in industry. Time should be considered in the optimization. Moreover, not only a single reaction but also all reactions in the complete synthetic scheme should be optimized in view of time. Thus, to realize the ultimate synthesis with time economy, a key is the selection of a synthetic strategy with a small number of rapid reactions under fast reaction conditions using a small number of reaction vessels.

We have been investigating the synthesis of (−)-oseltamivir and reported three-pot and two-pot syntheses in 2009[10] and 2010,[11] respectively, using an asymmetric Michael reaction of aldehyde and nitroalkene catalyzed by diphenylprolinol silyl ether as a key step.[12] Recently, we have accomplished a one-pot synthesis[1a] without solvent swap with a single purification using (*Z*)-nitroalkene **2** developed by Ma,[1b] Sebesta,[1c] and Lu[1d] independently. Even though it is a one-pot procedure, it still takes 57 h for the completion of all of the synthetic transformations. In this communication, we demonstrate the realization of time economy in the very rapid synthesis of (−)-oseltamivir within only 60 min.

Scheme 1 summarizes our 60 min time economical total synthesis of (−)-oseltamivir. An asymmetric Michael reaction of nitroalkene **2** and *α*-alkoxyaldehyde **3** proceeds smoothly in the presence of three catalysts, such as diphenylprolinol silyl ether **4**, Schreiner's thiourea **5**,[13] and formic acid at 20 °C for 30 min to afford the Michael product **6**. The product was isolated with excellent *syn*- and enantioselectivity when the reaction was quenched at this step (Table 1, entry 1). If any one of these catalysts is lacking, the reaction does not proceed well in terms of reaction speed, yield, and selectivity (entries 2 and 3). Diphenylprolinol silyl ether **4** is key for the generation of enamine,[12,14] the reactive intermediate, while thiourea **5** activates nitroalkene **2** via hydrogen bonding.[13] The acid is for suppression of side reactions, such as the generation of an unreactive cyclobutane intermediate.[15] These three catalysts

Received: June 2, 2016

DOI: 10.1021/acs.orglett.6b01595
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. 60 Minute Time Economical Synthesis of (−)-Oseltamivir

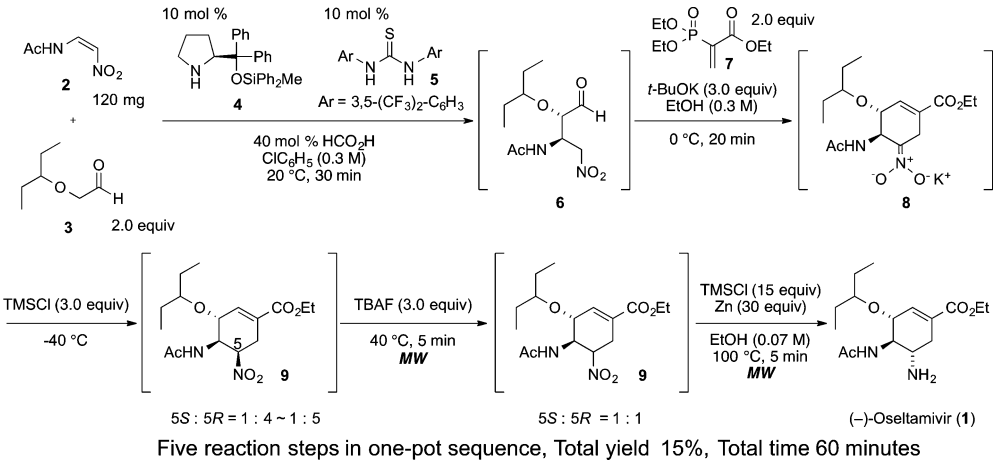
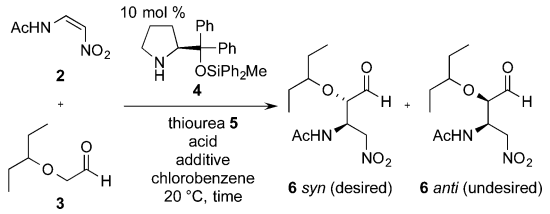


Table 1. Asymmetric Michael Reaction of 2 and 3 Catalyzed by Diphenylprolinol Silyl Ether 4[a]



entry	acid[b]	thiourea[c]	time (min)	yield (%)[d]	*syn*/*anti*[e]	ee[f]
1	yes	yes	30	>95	6:1	97
2	yes	no	90	80	7:1	99
3	no	yes	90	<5		

[a]Unless noted otherwise, reactions were performed by employing **2** (0.15 mmol) and **3** (0.3 mmol) in chlorobenzene (0.5 mL) at 20 °C for the indicated time. [b]Formic acid (0.06 mmol, 40 mol %) was employed. [c]Thiourea **5** (0.015 mmol, 10 mol %) was employed. [d]Conversion yield from the ^{1}H NMR of the reaction mixture. [e]Determined by ^{1}H NMR analysis. [f]See the Supporting Information for determination of enantioselectivity.

work in different ways in good harmony to achieve a dramatic acceleration of the reaction.

Domino Michael and Horner−Wardsworth−Emmons reactions proceed smoothly by addition of ethyl acrylate derivative **7**, *t*-BuOK, and EtOH in the same vessel at 0 °C for 20 min to provide cyclohexene **8**, while this transformation took 3.5 h using Cs_2CO_3 in chlorobenzene followed by the addition of EtOH in the previous synthesis.[1a] The base is essential for the rapid reaction. Changing the base to *t*-BuOK greatly reduced the reaction time.

Next, protonation occurs on the nitronate ion instantly at −40 °C by reaction with HCl, which was generated from trimethylsilyl chloride in situ. A mixture of 5*R* and 5*S* isomers of nitrocyclohexene **9** was obtained with predominant formation of undesired 5*R* isomer (5*S*/5*R* = 1:4−5). Epimerization from the 5*R* to 5*S* isomer is the next step.

A previous ab initio calculation study of the similar compound **10** (Figure 1) in our second-generation synthesis of (−)-oseltamivir indicated that the 5*R* and 5*S* isomers are energetically similar.[11a] That is why a three-step procedure was developed for the complete epimerization from the 5*R* to the 5*S* isomer[1] (Scheme 2): the Michael reaction of thiol to **9**, followed by the epimerization from 5*R* to 5*S* (48 h). After

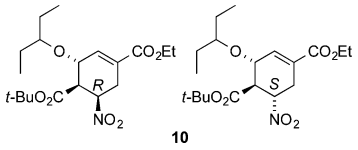


Figure 1. Structure of **10**.

reduction of the nitro group (**11** → **12**), the retro-Michael reaction of thiol proceeded to provide (−)-oseltamivir (14 h). These steps need long reaction times, although the yield and the 5*R*/5*S* selectivity are excellent. In terms of a rapid synthesis, these slow Michael and retro-Michael reactions of thiol should be removed. As this step is for the epimerization from 5*R* to 5*S*, an additional rapid and efficient epimerization step is necessary. After intensive screening, we found that equilibrium was reached within 20 min in the presence of TBAF to provide a 1:1 mixture of 5*R* and 5*S* isomers **9**, although complete epimerization cannot be achieved. Time for the equilibrium was further reduced to 5 min under microwave (MW) irradiation.

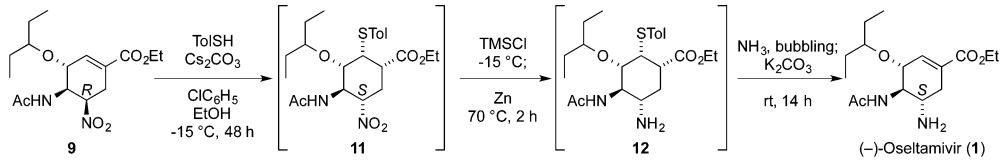
The last step is reduction of the nitro group to an amine using Zn, which took 100 min at 70 °C, but the reaction was greatly accelerated under MW irradiation.[16] The reduction was completed within only 5 min.

Overall, (−)-oseltamivir was obtained in 15% total yield via a one-pot procedure starting from 120 mg of nitroalkene **2**. The procedure is very simple, adding the reagents successively without solvent swap. The total reaction time is just 60 min. As MW irradiation was used in Scheme 1, the scale is limited to the apparatus.[17] A gram-scale synthesis was investigated without MW irradiation (Scheme 3). MW was employed in the last two steps: epimerization and reduction of the nitro group. As described previously, it takes 20 and 100 min for each step without MW irradiation. (−)-Oseltamivir can be prepared still within a short time period (170 min) in similar yield (14%) in a gram-scale experiment without MW irradiation.

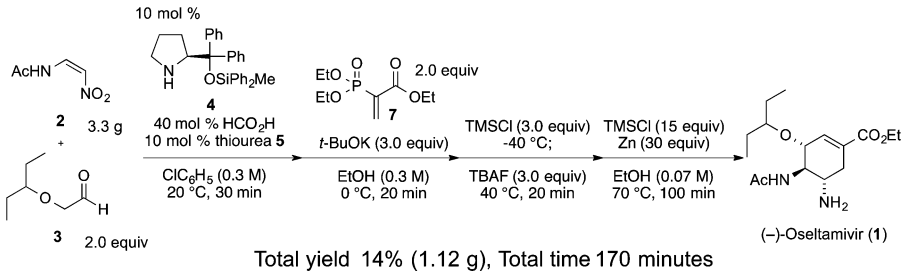
In summary we have accomplished a 60 min time economical total synthesis of (−)-oseltamivir in a single reactor over five steps: (1) asymmetric Michael reaction (**2** + **3** → **6**), (2) domino Michael and Horner−Wardsworth−Emmons reaction (**6** + **7** → **8**), (3) protonation (**8** → **9**), (4) epimerization (5*R* isomer → 5*S* isomer), and (5) reduction of a nitro group (**9** → **1**). There are several noteworthy features

DOI: 10.1021/acs.orglett.6b01595
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Epimerization of 5*R* to 5*S* in the Previous Synthesis



Scheme 3. Gram-Scale Synthesis of (−)-Oseltamivir without Using MW Irradiation



Total yield 14% (1.12 g), Total time 170 minutes

in the synthesis. In the synthetic design, the total number of steps is reduced to five, in line with step economy, and only a single reactor was employed throughout the five steps, which satisfies pot economy. The reaction was optimized in view of not only yield and selectivity but also reaction time. A new catalyst cocktail, in which three catalysts act cooperatively, was developed for the rapid asymmetric Michael reaction in excellent yield with excellent diastereo- and enantioselectivities. To consider the efficiency in the ideal organic synthesis,[18] there are several factors to consider, such as yield, selectivity, and greenness. We propose that time economy should be considered in the synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01595.

Experimental procedures and analytical data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yhayashi@m.tohoku.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. T. Uchimaru at National Institute of Advanced Industrial Science and Technology (AIST) for the ab initio calculation. This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Molecular Transformations by Organocatalysts” from The Ministry of Education, Culture, Sports, Science and Technology, Japan.

■ REFERENCES

(1) (a) Mukaiyama, T.; Ishikawa, H.; Koshino, H.; Hayashi, Y. *Chem. - Eur. J.* **2013**, *19*, 17789 and references cited therein. (b) Zhu, S.; Yu, S.; Wang, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4656. (c) Rehak, J.; Hut'ka, M.; Latika, A.; Brath, H.; Almassy, A.; Hajzer, V.; Durmis, J.; Toma, S.; Sebesta, R. *Synthesis* **2012**, *44*, 2424. (d) Weng, J.; Li, Y.-B.; Wang, R.-B.; Lu, G. *ChemCatChem* **2012**, *4*, 1007.

(2) For Tamiflu syntheses published after ref 1, see; (a) Chen, C.-A.; Fang, J.-M. *Org. Biomol. Chem.* **2013**, *11*, 7687. (b) Chavan, S. P.; Chavan, P. N.; Khairnar, L. B. *RSC Adv.* **2014**, *4*, 11417. (c) Furutachi, M.; Kumagai, N.; Watanabe, T.; Shibasaki, M. *Tetrahedron* **2014**, *70*, 9113. (d) Kongkathip, B.; Akkarasamiyo, S.; Kongkathip, N. *Tetrahedron* **2015**, *71*, 2393. (e) Tisovsky, P.; Penaska, T.; Meciarova, M.; Sebesta, R. *ACS Sustainable Chem. Eng.* **2015**, *3*, 3429.

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

(4) Snead, D. R.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2015**, *54*, 983.

(5) (a) Hayashi, Y.; Umemiya, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 3450. (b) Hayashi, Y.; Sakamoto, D.; Okamura, D. *Org. Lett.* **2016**, *18*, 4. (c) Hayashi, Y. *Chem. Sci.* **2016**, *7*, 866.

(6) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.

(7) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.

(8) (a) Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505. (b) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (c) Wender, P. A. *Nat. Prod. Rep.* **2014**, *31*, 433.

(9) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.

(10) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304.

(11) (a) Ishikawa, H.; Suzuki, T.; Orita, H.; Uchimaru, T.; Hayashi, Y. *Chem. - Eur. J.* **2010**, *16*, 12616. (b) Ishikawa, H.; Bondzic, B. P.; Hayashi, Y. *Eur. J. Org. Chem.* **2011**, *2011*, 6020.

(12) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.

(13) (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187.

(14) (a) Hayashi, Y.; Okamura, D.; Yamazaki, T.; Ameda, Y.; Gotoh, H.; Tsuzuki, S.; Uchimaru, T.; Seebach, D. *Chem. - Eur. J.* **2014**, *20*, 17077. (b) Gotoh, H.; Uchimaru, T.; Hayashi, Y. *Chem. - Eur. J.* **2015**, *21*, 12337.

(15) (a) Patora-Komisarska, K.; Benohoud, M.; Ishikawa, H.; Seebach, D.; Hayashi, Y. *Helv. Chim. Acta* **2011**, *94*, 719. (b) Seebach, D.; Sun, X.; Sparr, C.; Ebert, M.-O.; Schweizer, W. B.; Beck, A. K. *Helv. Chim. Acta* **2012**, *95*, 1064. (c) Seebach, D.; Sun, X.; Ebert, M.-O.; Schweizer, W. B.; Purkayastha, N.; Beck, A. K.; Duschmalé, J.; Wennemers, H.; Mukaiyama, T.; Benohoud, M.; Hayashi, Y.; Reiher, M. *Helv. Chim. Acta* **2013**, *96*, 799. (d) Burés, J.; Armstrong, A.;

DOI: 10.1021/acs.orglett.6b01595
Org. Lett. XXXX, XXX, XXX−XXX

Blackmond, D. G. *J. Am. Chem. Soc.* **2011**, *133*, 8822. (e) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 6741. (f) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 14264. (g) Burés, J.; Armstrong, A.; Blackmond, D. G. *Pure Appl. Chem.* **2013**, *85*, 1919. (h) Sahoo, G.; Rahaman, H.; Madaràsz, A.; Pàpai, I.; Melarto, M.; Valkonen, A.; Pihko, P. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 13144; *Angew. Chem.* **2012**, *124*, 13321.

(16) Kamal, A.; Reddy, K. S.; Prasad, B. R.; Babu, A. H.; Ramana, A. V. *Tetrahedron Lett.* **2004**, *45*, 6517.

(17) Microwave irradiations were performed in Biotage Initiator^{+}. The largest volume of a reaction mixture is about 20 mL.

(18) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657.

DOI: 10.1021/acs.orglett.6b01595
Org. Lett. XXXX, XXX, XXX−XXX