Domino Reactions

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High-Yielding Synthesis of the Anti-Influenza Neuramidase Inhibitor (−)-Oseltamivir by Three "One-Pot" Operations**

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A great deal of attention has been paid both in the scientific literature and the general media to the high potential risk of a worldwide spread of avian H5N1 influenza virus, the death rate of which is over 50%.[1] Indeed, should this virus acquire the ability to become capable of spreading easily and directly from human to human it could very possibly cause a disastrous pandemic. (−)-Oseltamivir phosphate (Tamiflu), a neuraminidase inhibitor used in the treatment of both type A and type B human influenza,[2] is one of the most promising therapeutics, and many nations have plans to stock a significant amount of this compound in case of a possible influenza outbreak. Moreover, the recent emergence of Tamiflu-resistant virus strains has prompted the chemical community to develop medicines effective against the mutated virus.[3] To meet these demands, intensive efforts have been devoted to the development of efficient preparations of this life-saving drug[1,2,4] and of its derivatives.

For our synthesis of Tamiflu, we set the following objectives, because meeting these requirements would allow a large amount to be prepared in a short time and at low cost: 1) The number of synthetic reactions should be not more than ten, and the number of separate operations should be as few as possible. 2) The overall yield should be over 50%. 3) Only inexpensive reagents should be employed. Preparing a molecule of this complexity, possessing three contiguous chiral centers, in no more than ten synthetic reactions in over 50% overall yield is a very challenging goal. Even if each individual reaction of a sequence proceeds in 90% yield—an excellent yield in organic synthesis—the overall yield falls to 35% after ten reactions ($0.9^{10} = 0.35$). The best yield yet achieved for the total synthesis of Tamiflu is approximately 35%.[4b,d] Moreover, in order to supply Tamiflu to developing countries where influenza might spread, production costs should be kept low. This requires that only inexpensive reagents be used. Although several syntheses of Tamiflu have been reported, previous methods do not meet all these requirements, and developing a method which does so remains a great challenge for the chemical community.

One-pot operations are effective for carrying out several transformations and forming several bonds in a single pot, while at the same time cutting out several purification steps, minimizing chemical waste generation, and saving time. To simplify the synthesis we investigated the preparation of Tamiflu by a small number of one-pot operations. Our strategy was to construct a key, fully functionalized ethyl cyclohexenecarboxylate intermediate in a single-pot operation as the first step; after this, the remainder of the synthesis consists simply of functional group manipulations, also carried out in one-pot operations.

The first key reaction relied on organocatalysis, a relatively new, rapidly developing technology in synthetic organic chemistry.[5] Diphenylprolinol silyl ether **4**,[6] which was developed independently by our group[7] and Jørgensen's group,[8] acts as an effective organocatalyst, promoting many kinds of asymmetric reactions with excellent enantioselectivities. We have already reported the highly enantioselective Michael reactions of aldehydes and nitroalkenes catalyzed by ether **4**,[7a] which was also elegantly employed by Enders and co-workers in a domino reaction with α,β-enals to prepare tetrasubstituted cyclohexenecarbaldehydes.[9] We applied our reaction to the present synthesis using the three simple starting materials alkoxyaldehyde **2**, nitroalkene **3**, and diethyl vinylphosphonate derivative **5**; subsequent treatment with *p*-toluenethiol afforded the heavily functionalized ethyl cyclohexanecarboxylate **6** in good yield (70%) in a single-pot operation (Scheme 1). This crucial reaction requires some comment: The first reaction of **2** and **3**, which is catalyzed by diphenylprolinol silyl ether **4**, provides the Michael adduct **8** (Figure 1) in quantitative yield with excellent enantioselectivity if we quench the reaction at this stage. Only 5 mol% of the catalyst is sufficient to promote the reaction, which makes it highly practical.

The next step involves a domino reaction as nitroalkane **8** reacts with vinylphosphonate **5** by a Michael reaction, and the phosphonate generated undergoes an intramolecular Horner–Wardsworth–Emmons reaction with the formyl group to generate ethyl cyclohexenecarboxylate **9**. Although this proceeds well, not only the desired **9** but also by-products such as **10** and **11** are obtained. Hydroxy phosphonate **10** can be isolated as a result of the *anti* arrangement of its hydroxy and diethoxyphosphoryl groups, which is unfavorable for elimination; **11** arises from a second Michael reaction, this time of **9** with **5**. We found that the undesired products **10** and **11** can be transformed successfully into the desired cyclohexene **9** by treating the mixture of **9**, **10**, and **11** in situ with

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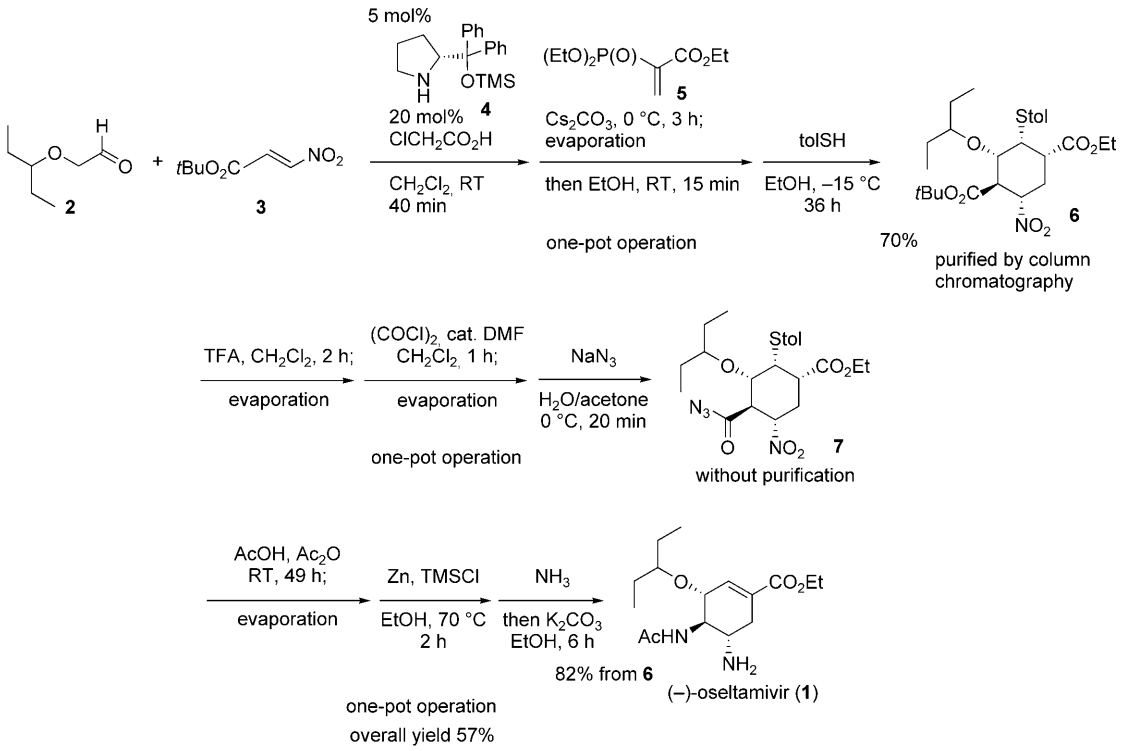

Scheme 1. The total synthesis of (−)-oseltamivir (**1**). TFA = trifluoroacetic acid, TMS = trimethylsilyl, tol = tolyl.

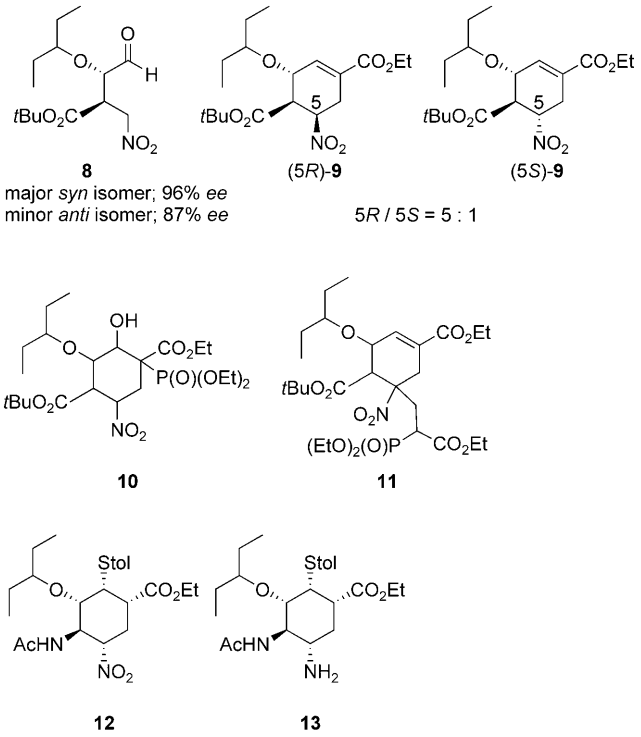

Figure 1. The synthetic intermediates of (−)-oseltamivir (**1**).

Cs_2CO_3 in EtOH. Compound **10** undergoes a retro-aldol reaction followed by Horner–Wardsworth–Emmons reaction, and **11** undergoes a retro-Michael reaction; in both cases target **9** is generated.

As diester **9** is obtained as a mixture of diastereomers in which the undesired (5*R*)-**9** isomer predominates, we examined the isomerization. Although both acid- and base-mediated conversion of (5*R*)-**9** to the desired (5*S*)-**9** was partially successful, we have developed a more efficient transformation, which is the last stage of the first one-pot operation: Treatment of the (5*S*)-**9**/(5*R*)-**9** mixture with *p*-toluenethiol in the presence of Cs_2CO_3 gives the Michael product in excellent yield, with the desired 5*S* isomer predominating. In this reaction, (5*R*)-**9** and (5*S*)-**9** equilibrate, and a thiol-Michael addition reaction proceeds stereoselectively and predominantly from (5*R*)-**9**. Although the Michael adduct (5*R*)-**6** is first formed, it is easily isomerized into (5*S*)-**6**, which is more stable than (5*R*)-**6** under basic conditions. Thus, starting from the mixture of (5*R*)-**9** and (5*S*)-**9**, the desired isomer (5*S*)-**6** is obtained in good yield.

The remaining transformations required are the conversion of a *tert*-butoxycarbonyl group into an acetylamino moiety, and reduction of the nitro group into an amine moiety. Deprotection of the *tert*-butyl ester was successfully performed by treatment of **6** with CF_3CO_2H. Excess reagent was removed under reduced pressure, and the crude carboxylic acid was converted into the acyl azide by addition of first oxalyl chloride, then NaN_3 in aqueous acetone. In this way, acyl azide **7**, which is pure enough to be used directly in the next reactions, was prepared from **6** in a single pot.

The next three reactions were also conducted in one pot. When **7** was treated with AcOH in Ac_2O at room temper-

ature, a domino reaction consisting of a Curtius rearrangement and amide formation proceeded to afford **12**.[10] It is a synthetic merit that the Curtius rearrangement proceeds at room temperature; reaction of the acyl azide does not require heating, which decreases potential hazards. Nitro compound **12** was treated with Zn/HCl in EtOH to provide amine **13**. After ammonia had been bubbled into the reaction mixture to form the Zn^{II}–NH_3 complex, addition of K_2CO_3 promoted the retro-Michael reaction of the thiol to afford oseltamivir (**1**), which was purified by acid/base extraction and obtained in 82% yield from **6**. The properties of synthetic (−)-oseltamivir are identical to those reported in the literature (^{1}H and ^{13}C NMR spectra, IR spectrum, R_f value, optical rotation).[4k,n] It should be noted that all the synthetic transformations from **7** to **1** could be performed in the same reaction vessel. The intermediate **12** is a solid and can be purified by crystallization.

In summary, an efficient, enantioselective total synthesis of (−)-oseltamivir has been accomplished, demonstrating the power of asymmetric reactions catalyzed by organocatalysts, in particular diphenylprolinol silyl ether **4**. The present synthesis has several noteworthy features: 1) A highly functionalized chiral cyclohexane framework of the correct configuration is synthesized in the first one-pot operation, which consists of a succession of reactions, including a diphenylprolinol silyl ether mediated, asymmetric Michael reaction, a domino Michael reaction/Horner–Wardsworth–Emmons reaction combined with retro-aldol and retro-Michael reactions, a thiol-Michael reaction, and a base-catalyzed isomerization. 2) Three reactions occur in the third one-pot operation: a Curtius rearrangement, the reduction of a nitro group to an amine, and a retro-Michael reaction of the thiol. 3) The Curtius rearrangement proceeds at room temperature without heating, decreasing the potential hazards. 4) The domino reaction consisting of a Curtius rearrangement and amide formation is a direct method for the synthesis of **12**.

This synthesis requires nine reactions, a total of three separate one-pot operations, and one purification by column chromatography. The total yield of (−)-oseltamivir from nitroalkene **3** is 57%. All the reagents are inexpensive. The metal-based reagents employed in the present total synthesis contain either alkali-metal ions (Na, K, and Cs) or nontoxic Zn. No special care is needed to exclude water or air. Thus, the present procedure is suitable for large-scale preparation. The synthetic route itself is completely different from previous ones and should enable the synthesis of a wide variety of novel derivatives. This will be valuable in the search for agents effective against Tamiflu-resistant viruses. We hope that further refinement of the present method will make it useful in the prevention of a possibly disastrous influenza pandemic.

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[1] V. Farina, J. D. Brown, *Angew. Chem.* **2006**, *118*, 7488; *Angew. Chem. Int. Ed.* **2006**, *45*, 7330.

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

[3] P. J. Collins, L. F. Haire, Y. P. Lin, J. Liu, R. J. Russell, P. A. Walker, J. J. Skehel, S. R. Martin, A. J. Hay, S. J. Gamblin, *Nature* **2008**, *453*, 1258.

[4] a) J. C. Rohloff, K. M. Kent, M. J. Postich, M. W. Becker, H. H. Chapman, D. E. Kelly, W. Lew, M. S. Louie, L. R. McGee, E. J. Prisbe, L. M. Schultze, R. H. Yu, L. Zhang, *J. Org. Chem.* **1998**, *63*, 4545; b) M. Federspiel, R. Fischer, M. Hennig, H.-J. Mair, T. Oberhauser, G. Rimmler, T. Albiez, J. Bruhin, H. Estermann, C. Gandert, V. Göckel, S. Götzö, U. Hoffmann, G. Huber, G. Janatsch, S. Lauper, O. Röckel-Stäbler, R. Trussardi, A. G. Zwahlen, *Org. Process Res. Dev.* **1999**, *3*, 266; c) P. J. Harrington, J. D. Brown, T. Foderaro, R. C. Hughes, *Org. Process Res. Dev.* **2004**, *8*, 86; d) S. Abrecht, P. Harrington, H. Iding, M. Karpf, R. Trussardi, B. Wirz, U. Zutter, *Chimia* **2004**, *58*, 621; e) Y.-Y. Yeung, S. Hong, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 6310; f) Y. Fukuta, T. Mita, N. Fukuda, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6312; g) X. Cong, Z.-J. Yao, *J. Org. Chem.* **2006**, *71*, 5365; h) S. Abrecht, M. C. Federspiel, H. Estermann, R. Fischer, M. Karpf, H.-J. Mair, T. Oberhauser, G. Rimmler, R. Trussardi, U. Zutter, *Chimia* **2007**, *61*, 93; i) N. Satoh, T. Akiba, S. Yokoshima, T. Fukuyama, *Angew. Chem.* **2007**, *119*, 5836; *Angew. Chem. Int. Ed.* **2007**, *46*, 5734; j) J.-J. Shie, J.-M. Fang, S.-Y. Wang, K.-C. Tsai, Y.-S. E. Cheng, A.-S. Yang, S.-C. Hsiao, C.-Y. Su, C.-H. Wong, *J. Am. Chem. Soc.* **2007**, *129*, 11892; k) T. Mita, N. Fukuda, F. X. Roca, M. Kanai, M. Shibasaki, *Org. Lett.* **2007**, *9*, 259; l) U. Zutter, H. Iding, P. Spurr, B. Wirz, *J. Org. Chem.* **2008**, *73*, 4895; m) J.-J. Shie, J.-M. Fang, C.-H. Wong, *Angew. Chem.* **2008**, *120*, 5872; *Angew. Chem. Int. Ed.* **2008**, *47*, 5788; n) B. M. Trost, T. Zhang, *Angew. Chem.* **2008**, *120*, 3819; *Angew. Chem. Int. Ed.* **2008**, *47*, 3759; o) Review, see: M. Shibasaki, M. Kanai, *Eur. J. Org. Chem.* **2008**, 1839.

[5] Reviews on organocatalysis, see: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; b) *Asymmetric Organocatalysis* (Eds.: A. Berkessel, H. Groger), Wiley-VCH, Weinheim, **2005**; c) Y. Hayashi, *J. Syn. Org. Chem. Jpn.* **2005**, *63*, 464; d) B. List, *Chem. Commun.* **2006**, 819; e) M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, 2001; f) M. J. Gaunt, C. C. C. Johnsson, A. McNally, N. T. Vo, *Drug Discovery Today* **2007**, *12*, 8; g) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**; h) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44; *Angew. Chem. Int. Ed.* **2008**, *47*, 42; i) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; j) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138.

[6] Reviews, see: a) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876; b) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922.

[7] a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; b) H. Gotoh, R. Masui, H. Ogino, M. Shoji, Y. Hayashi, *Angew. Chem.* **2006**, *118*, 7007; *Angew. Chem. Int. Ed.* **2006**, *45*, 6853; c) H. Gotoh, Y. Hayashi, *Org. Lett.* **2007**, *9*, 2859; d) Y. Hayashi, T. Okano, S. Aratake, D. Hazelard, *Angew. Chem.* **2007**, *119*, 5010; *Angew. Chem. Int. Ed.* **2007**, *46*, 4922; e) H. Gotoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2007**, *9*, 5307; f) Y. Hayashi, H. Gotoh, R. Masui, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4076; *Angew. Chem. Int. Ed.* **2008**, *47*, 4012; g) Y. Hayashi, S. Samanta, H. Gotoh, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 6736; *Angew. Chem. Int. Ed.* **2008**, *47*, 6634; h) Y. Hayashi, T. Itoh, M. Ohkubo, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 4800; *Angew. Chem. Int.*

Ed. **2008**, *47*, 4722; i) Y. Hayashi, T. Okano, T. Itoh, T. Urushima, H. Ishikawa, T. Uchimaru, *Angew. Chem.* **2008**, *120*, 9193; *Angew. Chem. Int. Ed.* **2008**, *47*, 9053.

[8] a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794; b) M. Marigo, D. Fielenbach, A. Braunton, A. Kjasgaard, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 3769; *Angew. Chem. Int. Ed.* **2005**, *44*, 3703. Recent report, see; c) P. T. Franke, R. L. Johansen, S. Bertelsen, K. A. Jørgensen, *Chem. Asian J.* **2008**, *3*, 216.

[9] D. Enders, M. R. M. Huttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861.

[10] a) C. Naegeli, A. Tyabji, *Helv. Chim. Acta* **1934**, *17*, 931; b) E. R. Barnum, C. S. Hamilton, *J. Am. Chem. Soc.* **1942**, *64*, 540; c) J. B. Press, C. M. Hofmann, S. R. Safir, *J. Org. Chem.* **1979**, *44*, 3292.

