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A concise synthesis of Tamiflu: third generation route via the Diels–Alder reaction and the Curtius rearrangement

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Abstract—Our third generation synthesis of Tamiflu was achieved in 12 steps from commercially available starting materials, using the Diels–Alder reaction and Curtius rearrangement as key steps.

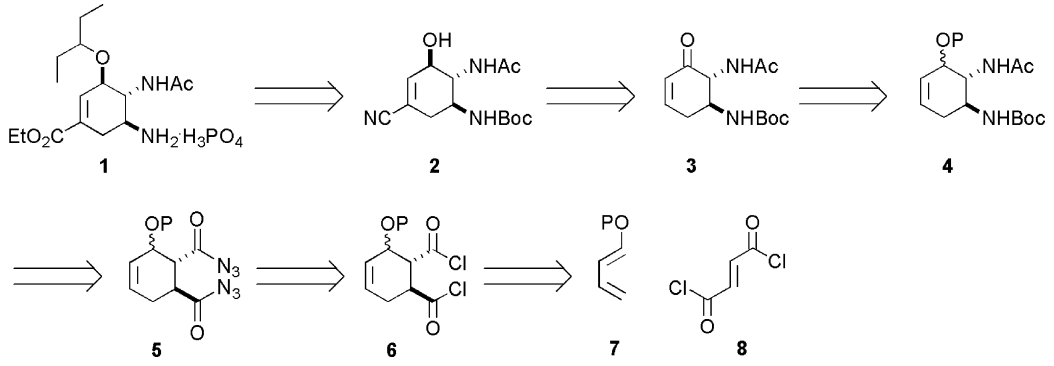
1. Introduction

Avian influenza (H5N1) is caused by a particularly lethal strain of the influenza virus. With increasing fear of a potential new influenza pandemic, the anti-influenza drug Tamiflu (**1**)[1] has become extremely important for protecting humans against this lethal flu. Considering the worldwide demand for Tamiflu, an improved production process is urgently needed.

Currently, three asymmetric syntheses of Tamiflu have been reported; Roche's commercial route utilizing naturally-occurring shikimic acid as the starting material,[2] Corey's route using the catalytic asymmetric Diels–Alder reaction developed by his group,[3] and the route using the catalytic desymmetrization of *meso*-aziridines developed by our group.[4] In this Letter, we report a conceptually different third generation short synthesis of Tamiflu that utilizes the Diels–Alder reaction and Curtius rearrangement as key steps.

2. Synthesis

Our synthetic plan is shown in Scheme 1. The 3-pentyloxy group can be introduced stereoselectively with a ring-opening reaction of aziridine prepared from **2**.[4] Compound **2** should be obtained via the $Ni(cod)_2$-catalyzed 1,4-addition of TMSCN to enone **3**, followed by oxidation,[4] and subsequent stereoselective 1,2-reduction



Scheme 1. Synthetic plan.

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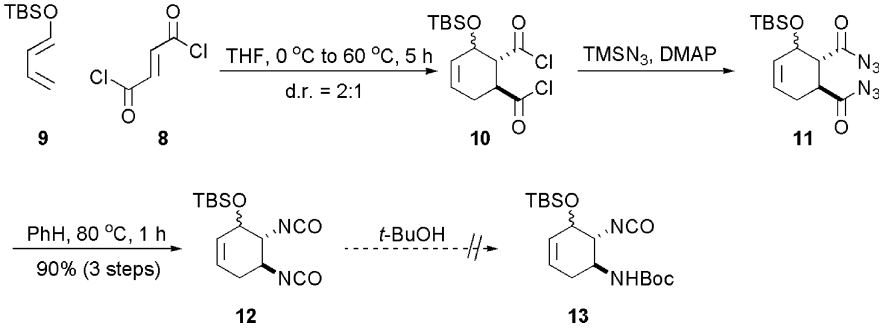
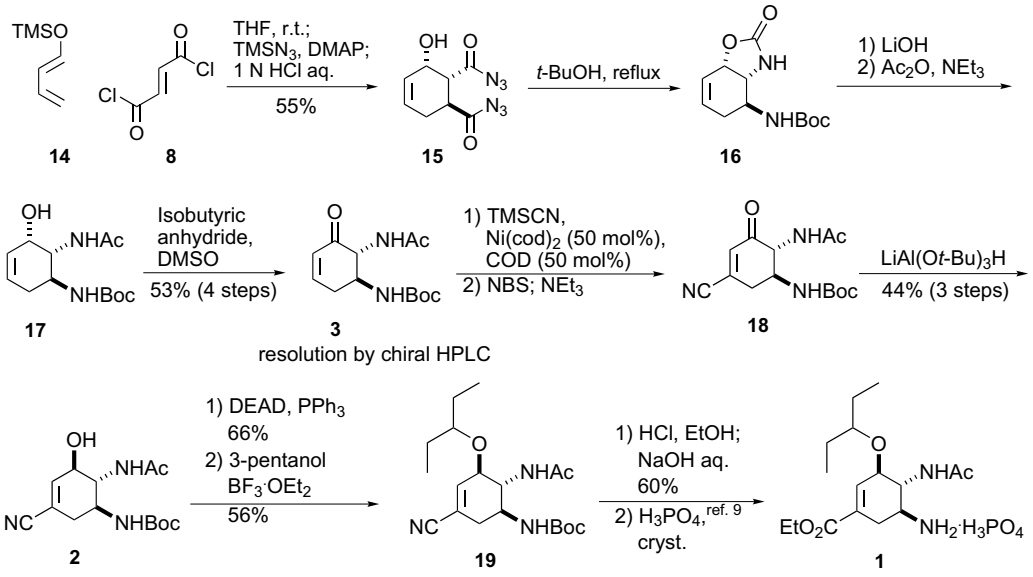
of the resulting β-cyanoenone. Enone **3** would be synthesized from **4** through O-deprotection and oxidation. The key 1,2-*trans*-diamide moiety of **4** would be introduced from diacid chloride **6** through acyl azide formation and Curtius rearrangement. Functionalized cyclohexene **6** would be obtained via the Diels–Alder reaction between diene **7** and dienophile **8**. To quickly establish this synthetic route, we started our synthesis without chirality control. We planned to obtain enantiomerically pure Tamiflu by resolution of an intermediate using chiral HPLC.

Based on the synthetic plan mentioned above, diacid chloride **10** was synthesized using the Diels–Alder reaction between 1-(*tert*-butyldimethylsiloxy)-1,3-butadiene (**9**)[5] and fumaryl chloride (**8**) (Scheme 2). The reaction proceeded at 0–60 °C, and product **10** was obtained as a diastereomixture (*endo*:*exo* = 2:1) in an excellent yield. After evaporation of the solvent, crude **10** was treated with $TMSN_3$[6] in the presence of a catalytic amount of DMAP to afford diacyl azide **11**. The Curtius rearrangement proceeded by heating **11** in benzene at 80 °C, and unexpectedly stable **12** was obtained in a high overall yield (90%) through three steps from **9** and **8**. Diisocyanate **12** was pure enough to be used for the next reaction without further purification. We then attempted to convert **12** to **13** via *t*-BuOH addition. Complex mixtures were produced, however, and neither mono-*tert*-butylcarbamate nor di-*tert*-butylcarbamate was obtained under the various conditions examined. The main reaction pathway might be Boc-protected urea formation through an intermolecular *t*-BuOH attack to less sterically hindered isocyanate, followed by an intramolecular addition of the resulting *tert*-butylcarbamate to the other neighboring isocyanate.

Thus, an alternative substrate **15** containing a free hydroxy group that can trap the intermediate isocyanate in the Curtius rearrangement was designed. Hydroxydiacyl azide **15** was synthesized through the Diels–Alder reaction between commercially available 1-(trimethylsiloxy)-1,3-butadiene (**14**) and fumaryl chloride (**8**), followed by $TMSN_3$ addition[6] in the presence of a catalytic amount of DMAP, and acidic cleavage of trimethylsilyl ether (Scheme 3). Although this Diels–Alder reaction afforded a 2:1 (*endo*/*exo*) mixture of diastereoisomers, undesired *exo* isomer selectively decomposed during the acidic cleavage of trimethylsilyl ether. The key Curtius rearrangement of **15** proceeded cleanly in distilled *t*-BuOH under refluxing conditions, and the



Scheme 2. Unsuccessful preparation of 1,2-*trans*-diamide.



Scheme 3. Successful synthetic route to Tamiflu.

oxazolidin-2-one **16** was produced exclusively. The success of this step was due to the rapid intramolecular trap of the intermediate isocyanate by the neighboring α-allyl alcohol, followed by the intermolecular addition of *t*-BuOH to the other isocyanate. The intramolecular isocyanate trap was so fast that neither di-*tert*-butylcarbamate derived from double intermolecular addition of *t*-BuOH nor the intramolecular addition of *tert*-butylcarbamate to the other isocyanate (protected urea formation) was detected. Hydrolysis of the cyclic carbamate moiety of **16**, followed by N-acetylation, proceeded uneventfully to afford **17**. Oxidation of **17** was, however, unexpectedly problematic. After intensive studies, modified Moffat conditions using bulky isobutyric anhydride[7,8] as an activator of DMSO were determined to be optimum. Under the optimized conditions, enone **3** was obtained in a 53% yield via four steps from acyl azide **15**.

At this stage, the resolution of intermediate **3** using chiral HPLC [Daicel Chiralpak AD-H, 2-propanol/hexane 1/9, flow 0.6 mL/min, detection at 254 nm: t_R 15.4 min (desired, $[\alpha]_D^{26}$ −149.2 (*c* 0.313, $CHCl_3$)) and 18.4 min (undesired, $[\alpha]_D^{27}$ +140.9 (*c* 0.313, $CHCl_3$)) was performed, and enantiomerically pure **3** was obtained.

The remaining steps from enantiomerically pure enone **3** to Tamiflu were (1) introduction of the ethoxy carbonyl group at the β-position of the enone and (2) introduction of the 3-pentyloxy group. The first step was accomplished with 1,4-addition of TMSCN to the enone, followed by the oxidation of the resulting TMS-enol ether. Thus, compound **3** was treated with TMSCN in the presence of $Ni(cod)_2$ (50 mol %) and 1,5-cyclooctadiene (50 mol %). The resulting enol silyl ether was subjected to α-bromination, and the subsequent HBr elimination with triethylamine afforded β-cyanoenone **18**.[4] Stereoselective reduction of the ketone with $LiAl(O\textit{t}\text{-}Bu)_3H$ proceeded cleanly to produce **2** in 44% yield in three steps. Aziridine formation under Mitsunobu conditions, followed by the ring-opening reaction of the resulting aziridine with 3-pentanol, afforded compound **19**.[4] Ethanolysis of the cyanide and cleavage of the Boc group proceeded in one pot under acidic ethanol. The free amine form of **1** was formed after basification. Treatment of the free amine with H_3PO_4[9] produced **1**.

In summary, we developed a third generation synthesis of Tamiflu. An appropriately functionalized cyclohexene skeleton was synthesized through the Diels–Alder reaction between commercially available diene and dienophile. The unsymmetrically protected 1,2-*trans*-diamine derivative **16** was constructed via Curtius rearrangement and subsequent intramolecular trapping of the resulting isocyanate. These two key reactions allowed for rapid (12 steps) access to the core structure of Tamiflu. As a preliminary study, we separated enantiomers using chiral HPLC at the stage of **3**. Asymmetric synthesis of Tamiflu utilizing the catalytic asymmetric Diels–Alder reaction and investigation of the more efficient conversion of enone **3** to β-cyanoenone **18** are currently ongoing.

3. Experimental

3.1. (1*S**,2*R**,3*S**)-3-Hydroxy-cyclohex-4-ene-1,2-dicarbonyl diazide (15)

Fumaryl chloride (**8**: 7.5 ml, 69.6 mmol) was added slowly to a stirred solution of 1-(trimethylsilyloxy)-1,3-butadiene (**14**: 12.3 ml, 70.3 mmol) in THF (352 ml) at room temperature, and the mixture was stirred at the same temperature for 2 h. $TMSN_3$ (19.6 ml, 148 mmol) and DMAP (800 mg, 7.0 mmol) were carefully added at room temperature, and the mixture was stirred at the same temperature for additional 2 h. After cooling to 4 °C, 1 N HCl aq (70.3 ml, 70.3 mmol) was carefully added, and the mixture was stirred at the same temperature for 10 min. The organic layer was separated and the aqueous layer was extracted twice with AcOEt (500 ml). The combined organic layers were washed with saturated $NaHCO_3$ solution (150 ml) and brine (150 ml), dried over Na_2SO_4, and concentrated to give crude **15**, which was purified by silica gel column chromatography (SiO_2 200 g, hexane/AcOEt = 4/1 to 2/1) to give **15** (9.1 g, 38.5 mmol; 55% yield) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz) δ 6.92–5.86 (m, 2 H), 4.48 (m, 1 H), 2.96 (ddd, *J* = 5.3, 11.6, 12.0 Hz, 1H), 2.87 (dd, *J* = 4.0, 12.0 Hz, 1H), 2.49 (ddd, *J* = 5.2, 5.3, 17.7 Hz, 1H), 2.10–2.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 181.9, 179.3, 128.7, 127.0, 63.8, 49.6, 37.9, 28.7; IR (neat, cm^{-1}) 3412, 2260, 2146, 1710; FAB-HRMS calcd for $C_8H_9N_6O_3$ $[M+H]^+$: 237.0731, found: 237.0726.

3.2. (2-Oxo-2,3,3aβ,4α,5,7aβ-hexahydro-benzoxazol-4-yl)-carbamic acid *tert*-butyl ester (16)

The solution of **15** (8.7 g, 36.8 mmol) in distilled *t*-BuOH (74 ml) was stirred at refluxing temperature for 5.5 h. Removal of the solvent under reduced pressure gave crude **16** (9.4 g, 36.8 mmol) as a white solid, which was used for the next reaction without further purification. ^1H NMR (CD_3OD, 500 MHz) δ 6.10 (m, 1H), 5.88–5.86 (m, 1H), 5.04–5.03 (m, 1H), 3.77–3.73 (m, 1H), 3.55–3.50 (m, 1H), 2.37 (ddd, *J* = 5.2, 5.5, 17.2 Hz, 1H), 2.01–1.96 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (CD_3OD, 125 MHz) δ 161.4, 158.1, 132.7, 123.7, 80.5, 75.3, 56.4, 51.0, 29.8, 28.7; IR (KBr, cm^{-1}) 3370, 3243, 1747, 1683; ESI-MS *m*/*z* 277 $[M+Na]^+$; FAB-HRMS calcd for $C_{12}H_{19}N_2O_4$ $[M+H]^+$: 255.1339, found: 255.1332.

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