JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Two Approaches toward the Formal Total Synthesis of Oseltamivir Phosphate (Tamiflu): Catalytic Enantioselective Three-Component Reaction Strategy and L-Glutamic Acid Strategy

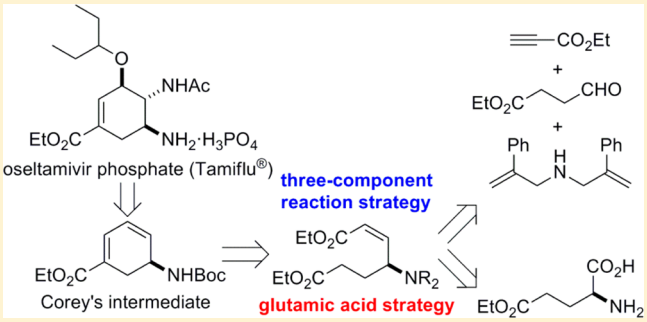
Kaliyamoorthy Alagiri,[†] Makoto Furutachi,[†,‡] Kenzo Yamatsugu,[†] Naoya Kumagai,[†] Takumi Watanabe,*[,†] and Masakatsu Shibasaki*[,†]

[†]Institute of Microbial Chemistry (BIKAKEN), Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

[‡]Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

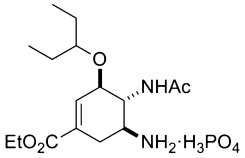
Supporting Information

ABSTRACT: Two independent formal total syntheses of oseltamivir phosphate were successfully achieved: the first utilized a copper-catalyzed asymmetric three-component reaction strategy, and the second utilized L-glutamic acid γ-ester as a chiral source to install the correct stereochemistry. Both strategies used Dieckmann condensation to construct a six-membered ring core, after which manipulation of the functional groups and protecting groups accessed Corey's intermediate for the synthesis of oseltamivir phosphate. While the first synthesis was accomplished via four purification steps in 25.7% overall yield, albeit with moderate optical purity (76% ee), the second strategy achieved the synthesis via six purification steps in 19.8% overall yield with perfect enantiocontrol.



INTRODUCTION

Despite long-standing preventive efforts, influenza continues to be one of the most serious threats to public health. Strains of the influenza virus easily mutate to escape host defense systems (such as the case of the H1N1 subtype in 2009),[1,2] and avian influenza strains sometimes newly acquire infectivity between humans resulting in very high mortality rate. Although immunization is a reliable and established method to prevent human from being infected by the seasonal viruses, the preparation of vaccines against novel strains usually lags behind their detection, allowing for flu outbreaks. Possibilities that highly lethal strains, such as the H5N1 subtype discovered in 1997,[3] will acquire infectivity between humans are of particular concern because of the lack of immunologic warheads. An alternative and powerful means to combat influenza is the use of antivirals, such as viral neuraminidase inhibitors.[4]



oseltamivir phosphate (Tamiflu®), **1**

Neuraminidase is a viral enzyme that catalyzes the cleavage of the sialic acid residue from glycoproteins to liberate proliferated viruses from infected cells. Six years after the report of the first-in-class neuraminidase inhibitor, zanamivir (currently marketed as Relenza),[5] the best-in-class compound, oseltamivir phosphate (Tamiflu), developed by Gilead Science and Roche,[6] was approved as a clinical medicine against influenza A and B viruses by the FDA in 1999. Notably, Tamiflu has demonstrated positive effects against the H5N1 and H1N1 subtypes and is in clinical use. A huge global stockpile of oseltamivir phosphate is needed, however, to prepare for an outbreak of influenza virus, especially newly discovered hazardous strains that can cause serious mortality.

The process of manufacturing Tamiflu used by Roche involves a chemical synthesis beginning with (−)-shikimic acid,[7] which can be isolated from the seeds of Chinese star anise (plant of *Illicium* family). Because the supply of shikimic acid from the plant is susceptible to climate fluctuations, a variety of complementary methods have been developed to secure shikimic acid reserves.[8]

Step-economic synthetic routes employing inexpensive starting materials as well as less costly reaction and purification conditions would be valuable alternative solutions to the supply problem. Since the first reports of asymmetric total syntheses of oseltamivir phosphate in 2006,[9,10] a myriad of synthetic studies have been published.[11,12] Unfortunately, none of these synthetic methods have been developed to the commercial scale due to the high total cost (too many steps, low conversion rates, and costly reagents), impracticality (harsh conditions,

Received: February 18, 2013
Published: March 21, 2013

   dx.doi.org/10.1021/jo400360j | J. Org. Chem. 2013, 78, 4019−4026

malodorous reagents, demands for special equipment, high dilutions, and excessive wastes), and safety issues (flammable or explosive reagents and intermediates). In our continuing efforts toward the development of more practical preparative routes, our group reported several catalytic asymmetric syntheses of oseltamivir phosphate using a yttrium-catalyzed asymmetric ring-opening reaction of *meso*-aziridines with $TMSN_3$ or HOMO-raising barium-catalyzed asymmetric Diels–Alder reaction as key transformations to manipulate the stereochemistry.[13] Despite the improved step-economy, the most recent synthetic route[13d] still requires a potentially explosive azide intermediate, which hinders its technical transfer to industry.

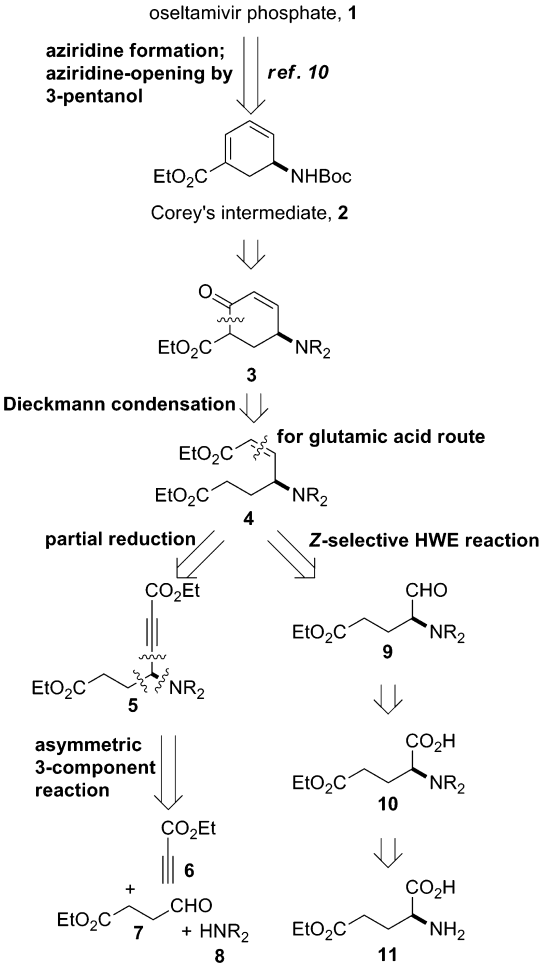
Herein we disclose a formal total synthesis of oseltamivir phosphate by two novel strategies: one using a catalytic asymmetric reaction and the other using enantiopure starting material to install the requisite stereochemistry. Both syntheses were accomplished via the Dieckmann condensation to form the six-membered ring skeleton, after which the identical protocols led to patent-free Corey's synthetic intermediate of oseltamivir phosphate, **2**.[10] The original method reported by Corey takes seven steps to access to **2** and uses the starting material of low boiling point. For other approaches to synthesize Corey's intermediate, Kann et al. produced **2** through a diene-iron carbonyl intermediate and reported its optical resolution,[11a] and Okamura et al. synthesized Corey's intermediate **2** using a Diels–Alder reaction of hydroxy pyridone and ethyl acrylate in a racemic manner.[11e] Trost et al. also produced an intermediate that is different from **2** only in the protective group on the nitrogen atom (phthaloyl group) in an elegant manner using an enantioselective palladium-catalyzed allylic amination reaction as a key transformation.[11f] However, this method includes a step that needs microwave irradiation. Our approaches provide two alternative strategies to access Corey's intermediate in practical manners in terms of total yield and stereocontrol.

RESULTS AND DISCUSSION

The two novel approaches to our formal total synthesis of oseltamivir are summarized in Scheme 1. Retrosynthetically, the conjugated diene system of **2** precedes a cyclohexene-derived β-ketoester **3** that can be disconnected to **4** by Dieckmann condensation. The route then branches off to one of two pathways, a catalytic asymmetric synthesis and a chiral pool method. The catalytic asymmetric synthesis takes advantage of a copper-catalyzed enantioselective three-component reaction to give optically active propargylic amines. As reported by Knochel et al.,[14] the reaction proceeds via several events in a stepwise manner. The first step is *in situ* generation of an enamine from aldehyde **7** and secondary amine **8**. Then, the copper(I) catalyst activates the enamine as a Lewis acid, accompanied by concomitant tautomerization into the iminium form, which is followed by copper(I) acetylide formation en route to its nucleophilic addition to the iminium resulting in propargylic amine **5**. Subsequent partial reduction of the triple bond affords **4**.

The chiral pool method utilizes the preinstalled chirality of L-glutamic acid as the origin of the stereochemistry of the target compound **2**. An α-amino aldehyde **9** is readily prepared from a commercially available L-glutamic acid γ-ester, which is followed by a *Z*-selective Horner–Wadsworth–Emmons (HWE) reaction to afford **4**.

Scheme 1. Retrosynthesis of Corey's intermediate 2



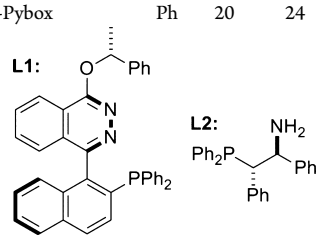
According to Knochel's report, the influence of the substituents of each substrate on the enantioselectivity of the three-component reaction can be summarized as follows: (1) trimethylsilylacetylene is the most preferable, aryl-substituted acetylene decreases the selectivity (never exceeding 90% ee), (2) bisbenzylamine gives excellent selectivity, but simple diallylamine substantially lowers the enantioselectivity, (3) aliphatic aldehydes provide better selectivity compared to aryl congeners, and α-alkyl-branched aliphatic aldehydes are the most preferable. The choice of the secondary amine is important not only because it is a determinant of the selectivity; the substituents should act as a protecting group of the primary amine and must be removed without damaging other functionalities upon exchange with a Boc group. Because removal of the benzyl group was expected to be problematic in the presence of a double bond, which always exists on the intermediates later than **4** bis(4-methoxybenzyl)amine was examined in a preliminary study. Unfortunately, oxidative deprotection did not work. We then decided to use diallylamine, which is removable via allylic substitution using Pd(0) as a catalyst. In addition, the absence of examples of propiolate ester such as **6** in the original reports led us to optimize reaction conditions (Table 1).

Initially, a reaction with **6**, **7**, and **8a** was conducted under the standard conditions reported by Knochel with slight modification: with the catalyst system comprising 5 mol % of CuBr and 5.5 mol % of (*R*)-Quinap,[15] the reactions were

dx.doi.org/10.1021/jo400360j | J. Org. Chem. 2013, 78, 4019–4026

Table 1. Screening for Chiral Ligand in the Catalytic Asymmetric Three-Component Reaction

entry	ligand	R	X	Y	yield (%)[e]	ee (%)[f]
1	(*R*)-Quinap	H	5.5	4	70	7
2[a,c]	**L1**	H	20	12	43	3
3	**L2**	H	5.5	3	73	1
4	(*R*)-Monophos	H	11	12	88	7
5	(*R*)-MOP	H	11	12	6	3
6	(*R*)-Segphos	H	5.5	12	21	4
7	(*R,R*)-*i*-Pr-DuPhos	H	5.5	14	17	7
8	(*S,S*)-Ph-BPE	H	5.5	14	25	2
9	(*R,R*)-Ph-Box	H	5.5	3	88	2[g]
10	(*R,R*)-Ph-Pybox	H	5.5	12	89	43[g]
11	(*S,S*)-4-MeO-C_6H_4-Pybox	H	5.5	14	91	33
12	(*R,R*)-4-F-C_6H_4-Pybox	H	5.5	12	87	46[g]
13	(*R,R*)-2-naphthyl-Pybox	H	5.5	14	94	42[g]
14[a]	(*S,S*)-Ph-Pybox	H	11	12	83	38
15[b]	(*S,S*)-Ph-Pybox	H	11	12	76	47
16[b,c]	(*S,S*)-Ph-Pybox	H	20	24	78	59
17[b,c]	(*S,S*)-Ph-Pybox	Ph	20	24	91	64
18[b,d]	(*S,S*)-Ph-Pybox	Ph	20	24	84	76



[a]10 mol % of CuBr was used. [b]10 mol % of $CuBr_2$ was used. [c]The reaction was performed at 0 °C. [d]The reaction was performed at −15 °C. [e]NMR yield using 2-methoxynaphthalene as an internal standard. [f]Determined by HPLC. [g](*R*)-Isomer predominated.

performed in toluene in the presence of MS 4Å for 3 h at room temperature. The product was obtained in good yield (70%), but the enantioselectivity was as low as 7% ee. This outcome forced us to refine the catalyst system in an ad hoc manner to fit it to our particular system. Toward this end, we performed a broad screening for chiral ligands. Another *P,N*-ligand structurally closely related to Quinap reported by Carreira et al.[16] (**L1**) also afforded similarly unsatisfactory selectivity (entry 2), whereas a different type of *P,N*-ligand, **L2**, afforded an almost racemic adduct, albeit with clean conversion (entry 3, 73% yield, 1% ee). Next, testing of a variety of chiral monodentate and bidentate phosphorus-based ligands (phosphine- and phosphoramidite-based) revealed very poor enantioselectivity (entries 4−8, 6−88% yield, 2−7% ee). We then turned our attention to the use of Box ligands, which are well recognized as privileged chiral ligands containing two oxazoline rings and are commonly used in Lewis acidic copper-catalyzed asymmetric reactions. While a simple (*R,R*)-Ph-Box gave rise to the almost racemic product (entry 9), the tridentate variant (*R,R*)-Ph-Pybox, originally developed by Nishiyama and co-workers,[17] affected the asymmetric induction (entry 10, 89% yield, the antipode of 43% ee). Further tuning of the electronic and steric characteristics of the aryl groups located at oxazoline moieties had almost no beneficial effects on the enantioselectivity (entries 11−13). Notably, a catalyst system comprising Cu(II) and Ph-Pybox ligand (10 mol % of $CuBr_2$ and 20 mol % of (*S,S*)-Ph-Pybox) was slightly more effective compared with the Cu(I) system (entries 14 and 15). Indeed, an improved enantioselectivity up to 59% ee was observed at lower temperature at 0 °C, although an increased loading of the ligand and an extended reaction time (24 h) were required to fulfill reasonable conversions (entry 16, 78%). Encouraged by this result, the effects of a secondary amine were then examined.

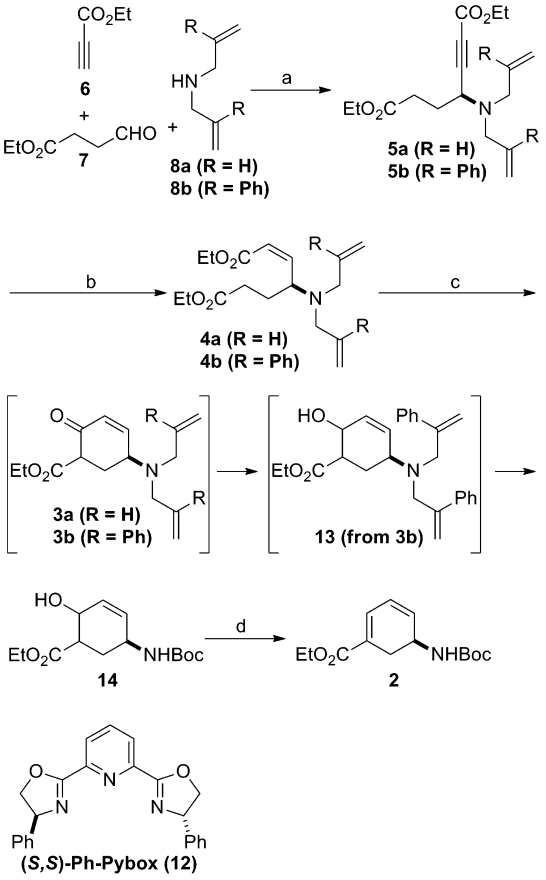
Knochel reported that the use of a secondary amine with additional steric bulk, bis(2-phenylallyl)amine **8b**, improved enantioselectivity in many cases.[18] This embellished allyl functionality can be uneventfully removed by Pd(0)-mediated allylic substitution. Accordingly, **8b** was tested under the conditions optimized for our system, as discussed above, resulting in better chemical yield and stereoselectivity (entry 17, 91% yield, 64% ee). Eventually, 84% yield with 76% ee was attained at a reaction temperature of −15 °C, as demonstrated in entry 18. Further modifications of the conditions, however, failed to improve the enantioselectivity.

The overall process according to the catalytic asymmetric three-component reaction strategy is summarized in Scheme 2. With the optically active propargylamine products in hand, the succeeding partial reduction of the triple bond was examined. When adduct **5a** was subjected to the conditions with poisoned Pd-mediated hydrogenation, such as Lindlar's catalyst, reduction of the allyl group afforded *Z*-olefin **4a** as an inseparable mixture of products. The highest chemoselectivity was realized by the siloxane-based reduction method reported by Trost ($(Me_2HSi)_2O$, AcOH, 2.5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$, and 10 mol % of P(*o*-tol)$_3$),[19] but the reaction continued to suffer from a substantial undesired reduction of allyl groups. The same reaction conditions as above with the phenyl-substituted substrate **5b**, however, escaped the overreduction to give *Z*-olefin **4b** in 84% yield without any trace of reduction of the 2-phenylallyl groups, presumably because of the increased steric bulk.

The stage was set for the second key transformation of the synthesis, Dieckmann condensation. Preliminarily, several bases to promote this reaction were screened with **4a** as the substrate. Use of 3 equiv of LHMDS at −40 °C led to substantially better conversion (ca. 90% yield) compared to the cases using KO*t*-Bu (31%) and NaH (no reaction). The transformation completed in 30 min at a higher temperature (−10 °C) without affecting the reaction course to give cyclization product **3a** (see Scheme 3 also). The same protocol was effective for the synthesis via **4b** to afford **3b**, which was subjected to a 1,2-reduction of the enone moiety employing $NaBH_4$ to give **13**. The two 2-phenylallyl groups of **13** were removed by allylic substitution in the presence of a catalytic amount of $Pd(PPh_3)_4$ and *N,N*-dimethylbarbituric acid as a nucleophile,[20] which was followed by introduction of the Boc group to give **14** as a mixture of diastereomers in 58% yield over four steps. Further efforts to shorten the reaction sequence by introducing the Boc group prior to Dieckmann condensation failed: anion species derived from **4** by deprotonation of carbamate NH attacked at the carbonyl group of ester to give rise to a dead-end byproduct. At the end of the synthesis, mesylation of the

dx.doi.org/10.1021/jo400360j | J. Org. Chem. 2013, 78, 4019−4026

Scheme 2. Formal Total Synthesis of Oseltamivir Phosphate via a Catalytic Asymmetric Three-Component Reaction[a]

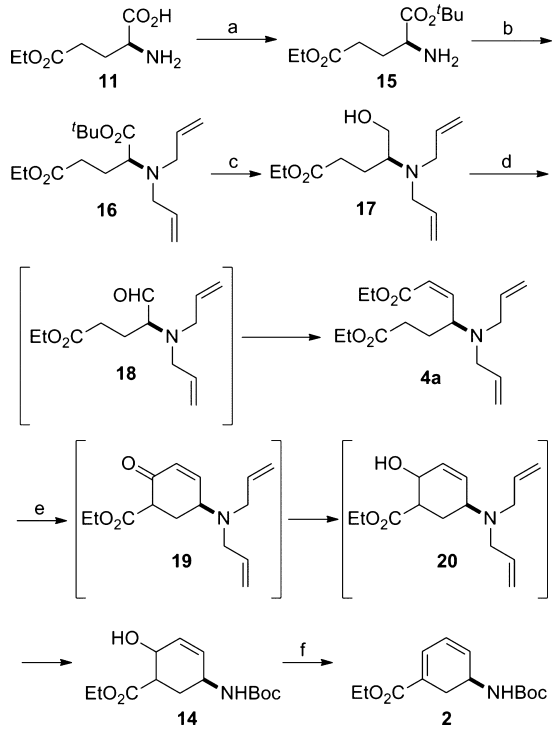


[a]Conditions: (a) See Table 1 (runs 16−18), $CuBr_2$ (10 mol %), (*S*,*S*)-Ph-Pybox (20 mol %), **6** (2 equiv), **7** (1 equiv), **8a** or **8b** (2 equiv), MS 4Å, toluene, −15 or 0 °C, 24 h; (b) $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), P(*o*-tol)$_3$ (10 mol %), $(Me_2HSi)_2O$ (1 equiv), AcOH (1 equiv), toluene, 45 or 40 °C, 19 or 24 h, yield 36% for **4a**, 84% for **4b**; (c) LHMDS (3 equiv), THF, −40 °C, 1 h; $NaBH_4$ (2 equiv), MeOH, −20 °C, 30 min; $Pd(PPh_3)_4$ (10 mol %), *N*,*N*-dimethylbarbituric acid (6 equiv), CH_2Cl_2, rt, 1 h; Boc_2O (5 equiv), $NaHCO_3$ aq, CH_3CN, rt, 1 h, yield 55% for 4 steps; (d) MsCl (1.1 equiv), Et_3N (2 equiv), CH_2Cl_2, 4 °C, 10 min; DBU (3.1 equiv), CH_2Cl_2, rt, 1 h, 87% for 2 steps.

hydroxyl group and subsequent *β*-elimination afforded the target compound of this study, Corey's intermediate **2**, in good yield (87%).

Despite the overall fair efficiency of the synthetic route described above, enhancing the enantioselectivity of the asymmetric three-component reaction would be a formidable task. Therefore, we decided to switch our strategy to the chiral pool method, sharing the same synthetic intermediate **4** with the first synthetic route (Scheme 1). Historically, many asymmetric total syntheses have been accomplished using readily available chiral compounds, especially abundant natural products, as their origin of chirality. Of those, natural amino acids are inexpensive, inexhaustible chiral pools. Among the natural amino acids, L-glutamic acid is one of the least expensive starting materials for asymmetric syntheses. Previously, Saicic and co-workers achieved the synthesis of oseltamivir phosphate by taking advantage of L-glutamic acid as a chiral source, but the synthesis also made use of the Evans oxazolidinone-based diastereoselective aldol reaction to furnish the requisite

Scheme 3. Formal Total Synthesis of Oseltamivir Phosphate via the Glutamic Acid Route[a]



[a]Conditions: (a) 60% $HClO_4$ (1.1 equiv), *t*-BuOAc (excess), rt, 2 d, 77%; (b) allyl bromide (6 equiv), $NaHCO_3$ (4 equiv), EtOH, reflux, 24 h, yield 84%; (c) HCO_2H (excess), 80 °C, 1 h; $ClCO_2Et$ (3 equiv), Et_3N (5 equiv), THF, −10 °C, 15 min, then $NaBH_4$ (6 equiv), MeOH, 0 °C, 30 min, yield 80% for 2 steps; (d) SO_3·pyridine (4 equiv), Et_3N (3.6 equiv), DMSO, 0 °C, 2 h; $(CF_3CH_2O)_2P(=O)CH_2CO_2Et$ (1.1 equiv), 18-crown-6 (5 equiv), KHMDS (1.2 equiv), THF, −78 °C, 2 h, yield 80% for 2 steps; (e) LHMDS (3 equiv), THF, −40 °C, 1 h; $NaBH_4$ (2 equiv), MeOH, −20 °C, 30 min; $Pd(PPh_3)_4$ (10 mol %), *N*,*N*-dimethylbarbituric acid (6 equiv), CH_2Cl_2, rt, 1 h; Boc_2O (5 equiv), CH_3CN, rt, 1 h, yield 55% for 4 steps; (f) MsCl (1.1 equiv), Et_3N (2 equiv), CH_2Cl_2, 4 °C, 10 min; DBU (3 equiv), rt, 1 h, 87% for 2 steps.

stereochemistry.[11z] In our approach, the *α*-carbon of L-glutamic acid is the sole determinant of the stereochemistry of oseltamivir phosphate, which made the overall process more concise and efficient.

Synthesis along this line commenced with commercially available L-glutamic acid *γ*-ethyl ester **11** (>99% ee) as shown in Scheme 3. The *α*-carboxyl group of **11** was masked as *tert*-butyl ester **15** under acidic conditions with $HClO_4$ in the presence of *t*-BuOAc (77%).[21] Then, the allyl groups were uneventfully introduced to the amino group of **15** to give a fully protected L-glutamic acid derivative **16** in 84% yield. Subsequent treatment of HCO_2H with **16** unveiled the *α*-carboxyl group, which was converted to the corresponding primary alcohol **17** via the formation of mixed anhydride followed by reduction with $NaBH_4$ in 80% yield over two steps.[22] After thorough investigation of the conditions for the subsequent oxidation of the hydroxyl group (e.g., DMP, Swern, TEMPO), Parikh-Doering oxidation (SO_3·pyridine, Et_3N, DMSO) was found to produce the best conversion. Because the aldehyde product **18** was labile upon purification, the crude material was directly used in the subsequent *Z*-selective HWE reaction.

dx.doi.org/10.1021/jo400360j | J. Org. Chem. 2013, 78, 4019−4026

Toward this end, two well-known *Z*-selective HWE reactions were tested. While Ando's protocol[23] with $(o\text{-tol})_2P(=O)CH_2CO_2Et$, NaI, and DBU gave the *Z*-olefin in 62% yield, accompanied by a substantial amount of the *E*-isomer (*Z*/*E* ratio; 80/20), the procedure reported by Still and Gennari[24] using $(CF_3CH_2O)_2P(=O)CH_2CO_2Et$, KHMDS, and 18-crown-6 achieved good reactivity (80% over 2 steps) and excellent *Z*/*E* selectivity (98/2) to give **4a**. Subsequently, essentially the same reaction scheme developed for the first strategy led to the desired Corey's intermediate **2**. In fact, the four-step procedure to **20** in 55% yield was followed by the two-step transformation into **2** in 87% yield as shown in Scheme 2. The optical purity of the final product **2** obtained by this method was 99% ee, confirming that no racemization occurred during the synthesis.

■ CONCLUSION

In summary, we developed two independent synthetic methods to access the synthetic precursor (**2**) of oseltamivir phosphate reported by Corey. In the first strategy, we took advantage of the copper-catalyzed asymmetric three-component reaction of terminal alkyne, aldehyde, and secondary amine to afford the propargylic amine product from which a substrate for Dieckmann condensation, *Z*-olefin **4b**, was derived. The second strategy used the chirality of a readily available, optically pure L-glutamic acid derivative as the origin of the stereochemistry of target compound **2** and accessed the substrate of Dieckmann condensation **4a** via a *Z*-selective HWE reaction of **18**. The first synthesis was accomplished via five purification steps in 25.7% overall yield albeit with moderate optical purity (76% ee), and the second synthesis was achieved via six purification steps in 19.8% overall yield in optical pure form. Studies to further refine the glutamic acid route to make it more cost-effective by reducing the purification steps and tuning the reaction conditions are underway.

■ EXPERIMENTAL SECTION

All reactions were performed in oven-dried round-bottom flasks and test tubes with a Teflon-coated magnetic stirring bar under Ar atmosphere unless otherwise noted. Air- and moisture-sensitive liquids were transferred via a gastight syringe and a stainless steel needle. All workup and purification procedures were carried out with reagent grade solvents under ambient atmosphere. Flash chromatography was performed using silica gel 60 (230−400 mesh). Infrared (IR) spectra were recorded on a Fourier transform IR spectrophotometer. NMR was recorded on a 400 MHz spectrometer. For ^{1}H NMR (400 MHz), chemical shifts of protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26 ppm). For ^{13}C NMR (100 MHz), chemical shifts are reported in the scale relative to NMR solvent ($CDCl_3$, δ 77.0 ppm) as an internal reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quartet, m: multiplet), coupling constant (Hz), and integration. Optical rotation was measured using a 2-mL cell with a 1.0-dm path length on a polarimeter. High-resolution mass spectra (ESI-Orbitrap) were measured on an ESIMS instrument equipped with an Orbitrap detector. HPLC analysis was conducted on an HPLC system equipped with chiral stationary-phase columns (0.46 cm × 25 cm).

(*S*)-Diethyl 4-(Diallylamino)hept-2-ynedioate (5a, Table 1, entry 16). To a tube containing $CuBr_2$ (4.5 mg, 20 μmol, 10 mol %) and (*S*,*S*)-Ph-Pybox (14.8 mg, 40 μmol, 20 mol %) was added toluene (0.8 mL) with stirring at room temperature. After 30 min, MS 4Å (120 mg), ethyl propiolate **6** (40.5 μL, 0.400 mmol, 2 equiv), aldehyde **7**[25] (25.0 μL, 0.200 mmol, 1 equiv), and diallylamine **8a** (49.2 μL, 0.400 mmol, 2 equiv) were successively added at 0 °C, and the mixture was stirred for 24 h at the same temperature. The reaction mixture was quenched with 1.0 M aqueous HCl. The resulting biphasic mixture was extracted with EtOAc, and the combined organic extract was washed with brine and dried over Na_2SO_4. Evaporation of volatiles under reduced pressure gave the crude mixture, which was used to determine ee (HPLC conditions are described below) and NMR yield (10 mg of 2-methoxynaphthalene was used as an internal standard). To collect physicochemical data, a crude material was purified with silica gel column chromatography (*n*-hexane/AcOEt = 8/1 to 6/1) to afford **5a** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.73 (m, 2H), 5.21 (d, J = 17.0 Hz, 2H), 5.11 (d, J = 10.5 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.11 (q, J = 7.0 Hz, 2H), 3.71 (dd, J = 7.8 Hz, 7.1 Hz, 1H), 3.28 (m, 2H), 2.87 (dd, J = 14.0 Hz, 7.8 Hz, 2H), 2.42 (m, 2H), 1.99 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.9, 153.6, 135.9, 117.7, 85.9, 77.6, 62.0, 60.5, 53.7, 51.3, 30.9, 27.9, 14.3, 14.0; IR (neat, cm^{-1}) 3081, 2981, 2819, 2225, 1740, 1712; ESI-HRMS calcd for $C_{17}H_{25}NO_4Na$ $[M + Na]^+$ 330.1676, found 330.1674; $[\alpha]^{22}_D$ = −40.1 (34% ee, a sample obtained under different conditions, *c* 0.97, $CHCl_3$); HPLC (*n*-hexane/2-propanol = 50/1, CHIRALPAK IC, 0.5 mL/min, 254 nm) t_R = 17.8 min (minor), 19.6 min (major).

(*S*)-Diethyl 4-(Bis(2-phenylallyl)amino)hept-2-ynedioate (5b, Table 1, entry 18). Substrates **6** (40.5 μL, 0.400 mmol, 2 equiv), **7** (25.0 μL, 0.200 mmol, 1 equiv), and bis(2-phenylallyl)amine **8b** (94.1 μL, 0.400 mmol, 2 equiv) were used in the presence of catalyst comprising $CuBr_2$ (4.5 mg, 20 μmol, 10 mol %) and (*S*,*S*)-Ph-Pybox (14.8 mg, 40 μmol, 20 mol %). After stirring for 24 h at −15 °C, the reaction mixture was quenched with 1.0 M aqueous HCl. The resulting biphasic mixture was extracted with EtOAc, and the combined organic extract was washed with brine and dried over Na_2SO_4. Evaporation of volatiles under reduced pressure gave the crude mixture, which was used to determine NMR yield and ee (HPLC conditions are described below), then was purified by silica gel column chromatography (*n*-hexane/AcOEt = 12/1 to 8/1) to give **5b** (86.4 mg, 94%, 76% ee) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28−7.11 (m, 10H), 5.43 (s, 2H), 5.27 (s, 2H), 4.24 (q, J = 7.1 Hz, 2H), 4.07−3.90 (m, 2H), 3.86 (d, J = 13.8 Hz, 2H), 3.72−3.60 (m, 1H), 3.18 (d, J = 13.8 Hz, 2H), 2.00−1.82 (m, 3H), 1.82−1.68 (m, 1H), 1.32 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 1.16 (dd, J = 7.1 Hz, 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 153.5, 144.8, 139.3, 128.0, 127.5, 126.6, 116.5, 85.3, 78.0, 62.0, 60.2, 55.4, 50.6, 30.2, 27.5, 14.1, 14.0; IR (neat, cm^{-1}) 2222, 1733, 1711, 1244, 1182, 908, 779, 752, 696, 407; ESI-HRMS calcd for $C_{29}H_{34}NO_4$ $[M + H]^+$ 460.2482, found 460.2477; $[\alpha]_D^{29}$ = −38.7 (73% ee, a sample obtained under different conditions, *c* 1.02, $CHCl_3$); HPLC (*n*-hexane/2-propanol = 50/1, CHIRALPAK IC, 0.5 mL/min, 254 nm) t_R = 22.3 min (minor), 24.5 min (major).

(*S*)-Diethyl 4-(Diallylamino)-(*Z*)-hept-2-enedioate (4a). To $Pd_2(dba)_3{\cdot}CHCl_3$ (105 mg, 0.102 mmol, 2.5 mol %) and $P(o\text{-tol})_3$ (124 mg, 0.406 mmol, 10 mol %) dissolved in toluene (10.3 mL) were added $(Me_2HSi)_2O$ (0.718 mL, 4.06 mmol), AcOH (0.232 mL, 4.06 mmol), and toluene solution (10 mL) of **5a** (1.25 g, 4.06 mmol) successively at room temperature. The mixture was stirred at 45 °C for 19 h, then allowed to reach room temperature, and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 9/1 to 7/1) to afford **4a** as a colorless oil (450 mg, 36%). Spectral data are shown later (as a product of the glutamic acid route). NMR spectra are included in Supporting Information.

(*S*)-Diethyl 4-(Bis(2-phenylallyl)amino)-(*Z*)-hept-2-enedioate (4b). To $Pd_2(dba)_3{\cdot}CHCl_3$ (243 mg, 0.235 mmol, 2.5 mol %) and $P(o\text{-tol})_3$ (286 mg, 0.940 mmol, 10 mol %) dissolved in toluene (23.5 mL) were added $(Me_2HSi)_2O$ (1.66 mL, 9.40 mmol), AcOH (0.537 mL, 9.40 mmol), and toluene solution (23.5 mL) of **5b** (4.31 g, 9.39 mmol) successively at room temperature. The mixture was stirred at 40 °C for 24 h, then allowed to reach to room temperature, and quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the organic layers were washed with brine,

dx.doi.org/10.1021/jo400360j | J. Org. Chem. 2013, 78, 4019−4026

dried over Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 12/1 to 8/1) to afford **4b** as a colorless oil (3.65 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29−7.23 (m, 4H), 7.21−7.16 (m, 6H), 6.27 (dd, J = 11.4 Hz, 11.4 Hz, 1H), 5.94 (d, J = 11.4 Hz, 1H), 5.32 (s, 2H), 5.17 (s, 2H), 4.46−4.32 (m, 1H), 4.14−4.04 (m, 2H), 4.03 (q, J = 7.2 Hz, 1H), 3.83 (d, J = 14.1 Hz, 2H), 3.19 (d, J = 14.1 Hz, 2H), 2.08−1.96 (m, 1H), 1.94−1.72 (m, 2H), 1.71−1.58 (m, 1H), 1.21 (dd, J = 7.2 Hz, 7.2 Hz, 3H), 1.19 (dd, J = 7.2 Hz, 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.8, 165.6, 146.0, 145.7, 140.1, 127.9, 127.3, 126.6, 122.7, 115.2, 60.1, 60.0, 55.2, 54.4, 30.8, 27.2, 14.2; IR (neat, cm^{-1}) 2980, 2820, 1721, 1631, 1416, 1186, 1029, 906, 779, 698; ESI-HRMS calcd for $C_{29}H_{36}NO_4$ $[M + H]^+$ 462.2639, found 462.2632; $[\alpha]^{27}_D$ = +82.0 (73% ee, *c* 1.04, $CHCl_3$).

(2*R*,5*S*)-Ethyl 5-(*tert*-Butoxycarbonylamino)-2-hydroxycyclohex-3-enecarboxylate (14). To a stirred solution of diester (**4b**) (3.61 g, 7.83 mmol) in THF (15.7 mL) was slowly added a 1.0 M THF solution of LHMDS (23.5 mL, 23.5 mmol) at −40 °C. The resultant solution was stirred at the same temperature for 1 h, diluted with EtOAc, and quenched with saturated aqueous NH_4Cl. The biphasic mixture was extracted with EtOAc, and combined organic extracts were washed with brine and dried over Na_2SO_4. After evaporation of the organic solvent under reduced pressure, the crude product including **3b** (keto−enol mixture) was obtained as a pale yellow oil, which was used for the next reaction without further purification.

To a stirred solution of the crude material including **3b** (maximum 7.83 mmol) in MeOH (39.2 mL) was added $NaBH_4$ (592 mg, 15.7 mmol) at −20 °C. The resultant solution was stirred at the same temperature for 30 min and then quenched with saturated aqueous NH_4Cl (slowly added). After warming to room temperature, MeOH was removed under the reduced pressure. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the volatiles under reduced pressure, the crude product including **13** was obtained as pale yellow oil, which was used for the next step without further purification.

To a stirred solution of crude ester (**13**, maximum 7.83 mmol) in CH_2Cl_2 (39.2 mL) were successively added $Pd(PPh_3)_4$ (905 mg, 0.783 mmol, 10 mol %) and *N*,*N*-dimethylbarbituric acid (7.34 g, 47.0 mmol) at room temperature. The resulting solution was stirred at the same temperature for 1 h, and CH_2Cl_2 was removed under reduced pressure. To this mixture were successively added a 1.0 M solution of Boc_2O in CH_3CN (39.2 mL, 39.2 mmol) and saturated aqueous $NaHCO_3$ (39.2 mL) at room temperature. The resulting solution was vigorously stirred at the same temperature for 1 h, diluted with EtOAc, and quenched with saturated aqueous $NaHCO_3$. The biphasic mixture was extracted with EtOAc, and combined organic extracts were washed with brine and dried over Na_2SO_4. After evaporation of volatiles under reduced pressure, the crude mixture was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/1) to give the desired product (**14**) (1.23 g, diastereomeric mixture, 55% yield over 4 steps) as a pale yellow solid. The diastereomers could be partially separated upon careful silica gel column chromatography. Usually, the mixture of the isomers was used in the next step without separation.

(1*R*,2*R*,5*S*)-Ethyl 5-(*tert*-Butoxycarbonylamino)-2-hydroxycyclohex-3-enecarboxylate (14, less polar isomer). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.77−5.71 (m, 1H), 5.65−5.59 (m, 1H), 4.53−4.47 (m, 1H), 4.47−4.40 (m, 1H), 4.35 (brs, 1H), 4.24−4.12 (m, 2H), 2.62−2.52 (m, 1H), 2.51−2.38 (m, 1H), 1.43 (s, 9H), 1.27 (dd, J = 4.8 Hz, 4.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.8, 155.2, 131.6, 130.5, 79.6, 67.7, 61.0, 48.0, 47.3, 31.7, 28.3, 14.1; IR (neat, cm^{-1}) 3424, 3361, 2976, 1718, 1682, 1523, 1181, 1053; ESI-HRMS calcd for $C_{14}H_{23}NNaO_5$ $[M + Na]^+$ 308.1468, found 308.1474; $[\alpha]^{28}_D$ = −53.4 (70% ee, *c* 1.04, $CHCl_3$).

(1*S*,2*R*,5*S*)-Ethyl 5-(*tert*-Butoxycarbonylamino)-2-hydroxycyclohex-3-enecarboxylate (14, more polar isomer). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.00−5.91 (m, 1H), 5.86−5.76 (m, 1H), 4.54−4.42 (m, 1H), 4.40 (dd, J = 4.1 Hz, 4.1 Hz, 1H), 4.32−4.22 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.80−2.67 (m, 1H), 2.30−2.15 (m, 1H), 1.99−1.87 (m, 1H), 1.43 (s, 9H), 1.27 (dd, J = 7.1 Hz, 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.0, 155.0, 131.0, 129.9, 79.6, 63.6, 60.9, 44.4, 41.6, 28.3, 27.0, 14.1; IR (neat, cm^{-1}) 3361, 2979, 2934, 1690, 1517, 1367, 1248, 1170, 1012, 755; ESI-HRMS calcd for $C_{14}H_{23}NNaO_5$ $[M + Na]^+$ 308.1468, found 308.1473; $[\alpha]^{28}_D$ = −133.3 (70% ee, *c* 1.02, $CHCl_3$).

(*S*)-Ethyl 5-((*tert*-Butoxycarbonyl)amino)cyclohexa-1,3-dienecarboxylate (2). To a stirred solution of the residue were successively added **14** (172 mg, 0.603 mmol) in CH_2Cl_2 (3 mL), MsCl (51.3 μL, 0.663 mmol), and Et_3N (167 μL, 1.21 mmol) at 4 °C, and the mixture was stirred for 10 min at the same temperature. DBU (279 μL, 1.87 mmol) was added to the mixture, and the mixture was further stirred for 1 h at room temperature. The mixture was diluted with CH_2Cl_2 and washed with H_2O, and the aqueous layer was back-extracted with CH_2Cl_2. The combined organic layers were washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine successively and dried over Na_2SO_4. The mixture was concentrated to give crude material that was purified with silica gel column chromatography (*n*-hexane/Et_2O = 3/1 to 2/1) to afford **2** (140 mg, 0.523 mmol, 87% yield) as a pale yellow viscous oil. ESI-HRMS calcd for $C_{14}H_{21}NO_4Na$ $[M + Na]^+$ 290.1363, found 290.1361. Physicochemical data was identical to those reported.[10] Other spectral data are shown later (as a product of the glutamic acid route). NMR spectra obtained by this sample are included in Supporting Information.

(*S*)-1-*tert*-Butyl 5-Ethyl 2-Aminopentanedioate (15). L-Glutamic acid γ-ethyl ester (**11**, 10.0 g, 57.1 mmol) was dissolved in aqueous 60% $HClO_4$ (6.9 mL, 62.8 mmol) with stirring in an ice bath. *t*-BuOAc (250 mL) was added, and the stirring was continued until a homogeneous solution was obtained. The mixture was maintained at room temperature for 2 days, then 0.1 N HCl (350 mL) was added to the mixture, and Et_2O was added. The aqueous phase was separated from the organic phase, and the aqueous phase was adjusted to pH = 9 with aqueous Na_2CO_3. The aqueous phase was extracted with EtOAc, and the organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford the desired ester **15** as a colorless oil (10.14 g, 77%). The crude product was NMR pure and was used directly without purification in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.07 (q, J = 7.2 Hz, 2H), 3.28 (dd, J = 8.2 Hz, 5.3 Hz, 1H), 2.38 (dd, J = 7.6 Hz, 7.6 Hz, 2H), 2.02−1.92 (m, 1H), 1.80−1.68 (m, 1H), 1.51 (s, 2H), 1.40 (s, 9H), 1.19 (dd, J = 7.1 Hz, 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.8, 173.2, 81.1, 60.3, 54.2, 30.6, 29.8, 27.9, 14.1; IR (neat, cm^{-1}) 3385, 2979, 2935, 1731; ESI-HRMS calcd for $C_{11}H_{22}NO_4$ $[M + H]^+$ 232.1543, found 232.1546; $[\alpha]^{25}_D$ = 12.4 (*c* 1.04, $CHCl_3$).

(*S*)-1-*tert*-Butyl 5-Ethyl-2-(diallylamino)pentanedioate (16). Diester **15** (9.4 g, 40.6 mmol) was dissolved in EtOH (100 mL), and powdered $NaHCO_3$ (13.65 g, 0.163 mol) and allyl bromide (21.1 mL, 0.244 mol) were added at room temperature. The mixture was stirred under reflux for 20 h, then cooled to room temperature, filtered through a Celite pad using EtOAc, and concentrated to give crude material, which was purified by silica gel column chromatography (*n*-hexane/EtOAc = 32/1) to afford **16** as a colorless oil (10.59 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.78−5.65 (m, 2H), 5.15 (d, J = 17.2 Hz, 2H), 5.07 (d, J = 10.1 Hz, 2H), 4.10 (q, J = 7.1 Hz, 2H), 3.38−3.28 (m, 3H), 3.01 (dd, J = 14.4 Hz, 8.0 Hz, 2H), 2.45−2.26 (m, 2H), 2.00−1.80 (m, 2H), 1.45 (s, 9H), 1.23 (dd, J = 7.1 Hz, 7.1 Hz, 3H; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5, 171.9, 136.7, 116.9, 80.9, 61.1, 60.2, 53.3, 30.9, 28.3, 24.6, 14.2; IR (neat, cm^{-1}): 3078, 2978, 2819, 2934, 2841, 1734; ESI-HRMS calcd for $C_{17}H_{29}NO_4Na$ $[M + Na]^+$ 334.1989, found 334.1987; $[\alpha]^{25}_D$ = −55.7 (*c* 1.1, $CHCl_3$).

(*S*)-Ethyl 4-(Diallylamino)-5-hydroxypentanoate (17). Diester **16** (1.4 g, 4.5 mmol) was dissolved in HCO_2H (15 mL) and stirred at 80 °C for 1 h. The reaction mixture was cooled to room temperature, and HCO_2H was removed by azeotropic distillation with toluene (3 times) and $CHCl_3$ (3 times) under reduced pressure to afford the crude mixture. To the resultant residue in THF (30 mL) at −10 °C was added Et_3N (3.1 mL, 22.5 mmol), followed by ethyl chloroformate (1.28 mL, 13.5 mmol). After 15 min, $NaBH_4$ (1.02 g, 27 mmol) was added in one portion. MeOH (30 mL) was then added dropwise to the mixture at 0 °C. The solution was stirred for an additional 30 min

dx.doi.org/10.1021/jo400360j | J. Org. Chem. 2013, 78, 4019−4026

at the same temperature and then quenched with saturated aqueous NH_4Cl. The organic solvents were evaporated under reduced pressure, and the product was extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford crude material, which was purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/4) to afford **17** as a colorless oil (869 mg, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80−5.67 (m, 2H), 5.21−5.05 (m, 4H), 4.10 (q, J = 7.2 Hz, 2H), 3.47 (dd, J = 10.6, 5.2 Hz, 1H), 3.34−3.21 (m, 3H), 2.96 (dd, J = 14.2 Hz, 7.8 Hz, 2H), 2.90−2.78 (m, 1H), 2.32−2.17 (m, 2H), 1.95−1.83 (m, 1H), 1.48−1.35 (m, 1H), 1.23 (dd, J = 7.1 Hz, 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1, 136.4, 117.4, 60.6, 60.5, 59.2, 52.1, 31.5, 21.0, 14.2; IR (neat, cm^{-1}): 3440, 2978, 2934, 2876, 1733, 1642; ESI-HRMS calcd for $C_{13}H_{24}NO_3$ $[M + H]^+$ 242.1751, found 242.1752; $[\alpha]^{25}_D$ = 23.1 (*c* 1.0, $CHCl_3$).

(*S*)-Ethyl 4-(Diallylamino)-5-oxopentanoate (18). Et_3N (0.21 mL, 1.49 mmol) was added to **17** (100 mg, 0.41 mmol) at 0 °C. Then, SO_3·pyridine (264 mg, 1.66 mmol) in DMSO (1.5 mL) was slowly added at 0 °C. After the addition completed, the mixture was stirred at the same temperature for 2 h. The reaction mixture was then quenched by the addition of cold water (1 mL) and extracted with ether. The combined organic layers were washed with 5% citric acid and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford crude **18** as a colorless oil, which was used for the succeeding reaction without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.66 (s, 1H), 5.75−5.65 (m, 2H), 5.16−5.05 (m, 4H), 4.06 (q, J = 7.1 Hz, 2H), 3.26−3.11 (m, 5H), 2.44−2.37 (m, 1H), 2.31−2.23 (m, 1H), 1.97−1.88 (m, 1H), 1.81−1.72 (m, 1H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.6, 173.2, 136.0, 117.8, 66.9, 60.4, 53.7, 31.0, 19.9, 14.2.

(*S*)-Diethyl 4-(Diallylamino)-(*Z*)-hept-2-enedioate (4a). A solution of $(CF_3CH_2O)_2P(=O)CH_2CO_2Et$ (151 mg, 0.455 mmol) and 18-crown-6 (547 mg, 2.07 mmol) in THF (4 mL) was cooled to −78 °C and treated with KHMDS (0.5 M in toluene, 0.95 mL, 0.476 mmol). The mixture was stirred at −78 °C for 45 min, and then **18** (maximum 0.414 mmol) in THF (3 mL) was slowly added at −78 °C. After the addition was completed, the mixture was stirred at −78 °C for 2 h. Then, the reaction mixture was quenched with saturated aqueous NH_4Cl. After the mixture was warmed to room temperature, the solvent was evaporated under reduced pressure and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford crude material as a colorless oil (Z/E = 98/2), which was purified by silica gel column chromatography (*n*-hexane/EtOAc = 11.5/1) to afford *Z*-olefin **4a** as a colorless oil (103 mg, 80% over 2 steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.12 (dd, J = 11.4 Hz, 10.3 Hz, 1H), 5.89 (d, J = 11.4 Hz, 1H), 5.80−5.70 (m, 2H), 5.13−5.04 (m, 4H), 4.45 (m, 1H), 4.15−4.07 (m, 4H), 3.26 (m, 2H), 2.91 (dd, J = 14.4 Hz, 7.4 Hz, 2H), 2.46 (m, 1H), 2.30 (m, 1H), 1.93 (m, 1H), 1.73 (m, 1H), 1.28−1.21 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 165.8, 147.4, 136.5, 122.1, 116.7, 60.2, 60.1, 56.0, 52.5, 31.1, 27.3, 14.2; IR (neat, cm^{-1}) 2980, 2936, 1734, 1732; ESI-HRMS calcd for $C_{17}H_{28}NO_4$ $[M + H]^+$ 310.2013, found 310.2015; $[\alpha]^{25}_D$ = 138.5 (*c* 0.91, $CHCl_3$).

(5*S*)-Ethyl 5-((*tert*-Butoxycarbonyl)amino)-2-hydroxycyclohex-3-enecarboxylate (14). To a stirred solution of **4a** (340 mg, 1.10 mmol) in THF (5.49 mL) was slowly added a 1.0 M THF solution of LHMDS (3.30 mL, 3.30 mmol) at −40 °C, and the mixture was stirred for 30 min at the same temperature. EtOAc and saturated aqueousNH_4Cl were added to quench the reaction, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give crude **19** (keto−enol mixture) as a pale yellow oil, which was used for the next reaction without further purification.

To a stirred solution of crude **19** (maximum 1.10 mmol) in MeOH (5.49 mL) was added $NaBH_4$ (83.2 mg, 2.20 mmol) at −20 °C, and the mixture was stirred for 30 min at the same temperature. After the addition of saturated aqueous NH_4Cl, MeOH was removed under reduced pressure. EtOAc was added, and the resulting aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give crude **20**, which was partially purified by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) to afford a sample including **20** (180 mg, 0.680 mmol at maximum, diastereomeric mixture) as a pale yellow oil.

To a stirred solution of partially purified **20** (180 mg, maximum 0.680 mmol) in CH_2Cl_2 (3.39 mL) were successively added $Pd(PPh_3)_4$ (78.4 mg, 67.8 μmol, 10 mol %) and *N*,*N*-dimethylbarbituric acid (636 mg, 4.07 mmol) at room temperature, and the mixture was stirred for 1 h. After removing CH_2Cl_2 under the reduced pressure, a 0.82 M solution of Boc_2O in CH_3CN (4.13 mL, 3.39 mmol) and saturated aqueous $NaHCO_3$ were successively added at room temperature, and the mixture was vigorously stirred for 3 h at the same temperature. The mixture was diluted with EtOAc and saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give a crude mixture, which was purified with silica gel column chromatography (*n*-hexane/AcOEt = 1/1) to afford **14** (175 mg, 0.613 mmol, diastereomeric mixture, 56% yield for 4 steps) as a pale yellow solid. NMR and IR data were identical to those described above. ESI-HRMS calcd for $C_{14}H_{23}NO_5Na$ $[M + Na]^+$ 308.1468, found 308.1468. NMR spectra obtained by this sample (diastereomeric mixture) are included in Supporting Information.

(*S*)-Ethyl 5-((*tert*-Butoxycarbonyl)amino)cyclohexa-1,3-dienecarboxylate (2). The same protocol described above was applied to **14** synthesized via the glutamic acid route. Physicochemical data were identical to those reported[10] as follows. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03 (d, J = 3.9 Hz, 1H), 6.18−6.09 (m, 2H), 4.61 (m, 1H), 4.42 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.76−2.61 (m, 2H), 1.42 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 154.9, 132.7, 131.7, 127.0, 124.8, 79.5, 60.6, 43.5, 28.8, 28.4, 14.3; IR (neat, cm^{-1}) 3352, 2978, 1705; ESI-HRMS calcd for $C_{14}H_{21}NO_4Na$ $[M + Na]^+$ 290.1363, found 290.1361; $[\alpha]^{25}_D$ = −205.5 (98.9% ee, *c* 1.1, $CHCl_3$), lit. $[\alpha]^{20}_D$ = −217 (>99% ee, *c* 1.1, $CHCl_3$);[14a] HPLC (*n*-hexane/2-propanol = 50/1, CHIRALPAK AD-H, 1.0 mL/min, 254 nm) t_R = 16.4 min (minor), 19.3 min (major).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: twatanabe@bikaken.or.jp; mshibasa@bikaken.or.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

M.S, K.A, and M.F. are grateful to Adaptable and Seamless Technology Transfer Program through target-driven R&D, JST for financial support. M.F. thanks JSPS predoctral fellowship. The authors thank Ms. Chiharu Sakashita for her technical assistance. The authors are thankful to Dr. Ryuichi Sawa, Ms. Yumiko Kubota, and Ms. Yuko Takahashi for spectroscopic analysis.

■ REFERENCES

(1) Neumann, G.; Chen, H.; Gao, G. F.; Shu, Y.; Kawaoka, Y. *Cell Res.* **2010**, *20*, 51.

(2) Oseltamivir-resistant strains have been already discovered: van der Vries, E.; Stelma, F. F.; Boucher, C. A. B. *N. Engl. J. Med.* **2010**, *363*, 1381.

(3) (a) Moscona, A. *N. Engl. J. Med.* **2005**, *353*, 1363. (b) Boltz, D. A.; Aldridge, J. R., Jr.; Webster, R. G.; Govorkova, E. A. *Drugs* **2010**, *70*, 1349.

(4) (a) Dawood, F. S.; Jain, S.; Finelli, L.; Shaw, M. W.; Lindstrom, S.; Garten, R. J.; Gubareva, L. V.; Xu, X.; Bridges, C. B.; Uyeki, T. M. *N. Engl. J. Med.* **2009**, *360*, 2605. (b) Garten, R. J.; Davis, C. T.; Russell, C. A.; Shu, B.; Lindstrom, S.; Balish, A.; Sessions, W. M.; Xu, X.; Skepner, E.; Deyde, V.; Okomo-Adhiambo, M.; Gubareva, L.; Barnes, J.; Smith, C. B.; Emery, S. L.; Hillman, M. J.; Rivailler, P.; Smagala, J.; de Graaf, M.; Burke, D. F.; Fouchier, R. A. M.; Pappas, C.; Alpuche-Aranda, C. M.; Lopez-Gatell, H.; Olivera, H.; Lopez, I.; Myers, C. A.; Faix, D.; Blair, P. J.; Yu, C.; Keene, K. M.; Dotson, P. D., Jr.; Boxrud, D.; Sambol, A. R.; Abid, S. H.; George, K. S.; Bannerman, T.; Moore, A. L.; Stringer, D. J.; Blevins, P.; Demmler-Harrison, G. J.; Ginsberg, M.; Kriner, P.; Waterman, S.; Smole, S.; Guevara, H. F.; Belongia, E. A.; Clark, P. A.; aBeatrice, S. T.; Donis, R.; Katz, J.; Finelli, L.; Bridges, C. B.; Shaw, M.; Jernigan, D. B.; Uyeki, T. M.; Smith, D. J.; Klimov, A. I.; Cox, N. J. *Science* **2009**, *325*, 197. (c) Smith, G. J. D.; Vijaykrishna, D.; Bahl, J.; Lycett, S. J.; Worobey, M.; Pybus, O. G.; Ma, S. K.; Cheung, C. L.; Raghwani, J.; Bhatt, S.; Peiris, J. S. M.; Guan, Y.; Rambaut, A. *Nature* **2009**, *459*, 1122.

(5) (a) von Itzstein, M.; Wu, W. Y.; Kok, G. B.; Pegg, M. S.; Dyason, J. C.; Jin, B.; Phan, T. V.; Smythe, M. L.; White, H. F.; Oliver, S. W.; Colman, P. M.; Varghese, J. N.; Ryan, D. M.; Woods, J. M.; Bethell, R. C.; Hotham, V. J.; Cameron, J. M.; Penn, C. R. *Nature* **1993**, *363*, 418. (b) von Itzstein, M. *Nat. Rev. Drug Discovery* **2007**, *6*, 967.

(6) (a) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H. T.; Zhang, L. J.; 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. (b) Kim, C. U.; Lew, W.; Williams, M. A.; Wu, H. W.; Zhang, L. J.; Chen, X. W.; Escarpe, P. A.; Mendel, D. B.; Laver, W. G.; Stevens, R. C. *J. Med. Chem.* **1998**, *41*, 2451.

(7) (a) Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044. (b) Rohloff, J. C.; Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang, L. J. *J. Org. Chem.* **1998**, *63*, 4545. (c) Abrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U. *Chimia* **2004**, *58*, 621.

(8) (a) Draths, K. M.; Knop, D. R.; Frost, J. W. *J. Am. Chem. Soc.* **1999**, *121*, 1603. (b) Ghosh, S.; Chisti, Y.; Banerjee, U. C. *Biotechnol. Adv.* **2012**, *30*, 1425 and references therein. See also: (c) Farina, V.; Brown, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7330.

(9) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.

(10) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310.

(11) (a) Bromfield, K. M.; Graden, H.; Hagberg, D. P.; Olsson, T.; Kann, N. *Chem.Commun.* **2007**, 3183. (b) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5734. (c) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Tetrahedron* **2009**, *65*, 3239. (d) Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892. (e) Kipassa, N. T.; Okamura, H.; Kina, K.; Hamada, T.; Iwagawa, T. *Org. Lett.* **2008**, *10*, 815−816. (f) Trost, B. M.; Zhang, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 3759. (g) Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, *73*, 4895. (h) Shie, J.-J.; Fang, J.-M.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5788. (i) Matveenko, M.; Willis, A. C.; Banwell, M. G. *Tetrahedron Lett.* **2008**, *49*, 7018. (j) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304. (k) Ishikawa, H.; Suzuki, T.; Orita, H.; Uchimaru, T.; Hayashi, Y. *Chem.—Eur. J.* **2010**, *16*, 12616. (l) Zhu, S.; Yu, S.; Wang, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4656. (m) Sullivan, B.; Carrera, I.; Drouin, M.; Hudlicky, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 4229. (n) Werner, L.; Machara, A.; Hudlicky, T. *Adv. Synth. Catal.* **2010**, *352*, 195. (o) Mandai, T.; Oshitari, T. *Synthesis* **2009**, 783. (p) Oshitari, T.; Mandai, T. *Synlett* **2009**, 787. (q) Sun, H.; Lin, Y.-J.; Wu, Y.-L.; Wu, Y. *Synlett* **2009**, 2473. (r) Osato, H.; Jones, I. L.; Chen, A.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 60. (s) Wichienukul, P.; Akkarasamiyo, S.; Kongkathip, N.; Kongkathip, B. *Tetrahedron Lett.* **2010**, *51*, 3208. (t) Ma, J.; Zhao, Y.; Ng, S.; Zhang, J.; Zeng, J.; Than, A.; Chen, P.; Liu, X.-W. *Chem.—Eur. J.* **2010**, *16*, 4533. (u) Weng, J.; Li, Y.-B.; Wang, R.-B.; Li, F.-Q.; Liu, C.; Chan, A. S. C.; Lu, G. *J. Org. Chem.* **2010**, *75*, 3125. (v) Kamimura, A.; Nakano, T. *J. Org. Chem.* **2010**, *75*, 3133. (w) Ko, J. S.; Keum, J. E.; Ko, S. Y. *J. Org. Chem.* **2010**, *75*, 7006. (x) Ishikawa, H.; Bondzic, B. P.; Hayashi, Y. *Eur. J. Org. Chem.* **2011**, 6020. (y) Trost, B. M.; Zhang, T. *Chem.—Eur. J.* **2011**, *17*, 3630. (z) Trajkovic, M.; Ferjancic, Z.; Saicic, R. N. *Org. Biomol. Chem.* **2011**, *9*, 6927. (aa) Werner, L.; Machara, A.; Sullivan, B.; Carrera, I.; Moser, M.; Adams, D. R.; Hudlicky, T.; Andraos, J. *J. Org. Chem.* **2011**, *76*, 10050. (ab) Oh, H.-S.; Kang, H.-Y. *J. Org. Chem.* **2012**, *77*, 8792. (ac) Rehak, J.; Hut'ka, M.; Latika, A.; Brath, H.; Almassy, A.; Hajzer, V.; Durmis, J.; Toma, Š.; Šebesta, R. *Synthesis* **2012**, *44*, 2424. For alternative approaches using (−)-shikimic acid as starting materials, see: (ad) Karpf, M.; Trussardi, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 5760−5762. (ae) Nie, L.-D.; Shi, X.-X. *Tetrahedron Asymmetry* **2009**, *20*, 124−129. (af) Nie, L.-D.; Shi, X.-X.; Ko, K. H.; Lu, W.-D. *J. Org. Chem.* **2009**, *74*, 3970−3973.

(12) For reviews, see: (a) Shibasaki, M.; Kanai, M. *Eur. J. Org. Chem.* **2008**, 1839. (b) Farina, V.; Brown, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7330−7334. (c) Magano, J. *Chem. Rev.* **2009**, *109*, 4398. (d) Andraos, J. *Org. Process. Res. Dev.* **2009**, *13*, 161. (e) Magano, J. *Tetrahedron* **2011**, *67*, 7875.

(13) (a) Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259. (b) Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *46*, 1403. (c) Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1070. (d) Yamatsugu, K.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2009**, *65*, 6017.

(14) (a) Gommermann, N.; Koradin, X.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (b) Gommermann, N.; Knochel, P. *Chem.—Eur. J.* **2006**, *12*, 4380. (c) Gommermann, N.; Knochel, P. *Tetrahedron* **2005**, *61*, 11418.

(15) Valk, J. M.; Claridge, T. D. W.; Brown, J. M.; Hibbs, D.; Hursthouse, M. B. *Tetrahedron: Asymmetry* **1995**, *6*, 2597.

(16) Knopfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971.

(17) (a) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846. (b) Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119.

(18) Gommermann, N.; Knochel, P. *Chem. Commun.* **2005**, 4175.

(19) Trost, B. M.; Braslau, R. *Tetrahedron Lett.* **1989**, *30*, 4657.

(20) Garrohelion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109.

(21) Hu, J.; Miller, M. J. *J. Am. Chem. Soc.* **1997**, *119*, 3462.

(22) Ishizumi, K.; Koga, K.; Yamada, S.-i. *Chem. Pharm. Bull.* **1968**, *16*, 492.

(23) (a) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406. (b) Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. *J. Org. Chem.* **2000**, *65*, 4745.

(24) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

(25) Izquierdo, J.; Rodriguez, S.; Gonzalez, F. V. *Org. Lett.* **2011**, *13*, 3856.