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Synthetic Strategies for Oseltamivir Phosphate

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Keywords: Oseltamivir phosphate / Influenza / Process chemistry / Asymmetric catalysis / Analogue synthesis / Tamiflu

We review here the synthetic strategies for oseltamivir phosphate, an important orally active anti-influenza drug. The Roche synthesis utilized naturally occurring shikimic acid as a starting material. Introduction of the 1-ethylpropyloxy ("3-pentyloxy") functionality by regioselective reduction of the acetal and iterative ring-opening reactions with azide to introduce nitrogen functionalities were the key steps. Corey and Fukuyama's syntheses utilized catalytic asymmetric Diels–Alder reactions as the starting points, whereas Shibasaki and Kanai's synthesis began with an asymmetric aziridine-opening reaction with $TMSN_3$ catalyzed by a polymetallic gadolinium complex. These three syntheses demonstrate the power of asymmetric catalysis in pharmaceutical synthesis. Although Kann's synthesis required resolution to provide an enantiomerically pure intermediate, the properties of chiral iron–diene complexes were elegantly utilized. Yao and Fang's syntheses started from abundant natural chiral sources: L-serine and D-xylose, respectively. Specifically, Fang's study identified new analogues of oseltamivir with higher potency against several neuraminidases, including oseltamivir-resistant mutants. Despite the relatively small molecular size, oseltamivir synthesis highlights an important frontier in organic synthesis.

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1. Introduction

The potential for an influenza pandemic is a worldwide concern. There were three historical influenza pandemics or epidemics in the twentieth century (Spanish flu in 1918, Asian flu in 1957, and Hong Kong flu in 1968). A pandemic is attributed to a mutation of influenza virus proteins that allows the virus to evade the human immune system. The avian H5N1 influenza virus, which originated in poultry in Hong Kong in 1997, has such characteristics. The lethality rate of the avian influenza is over 50%. Fortunately, the virus currently does not spread from human to human, although there are fears that it will soon gain the infectious ability to do that. Because of today's extensive global transport, a local influenza epidemic cannot be restricted to a specific area. Therefore, the number of patients could increase explosively in several remote places simultaneously.

Because of the high mutation frequency of influenza virus, an effective anti-influenza drug should target fundamental molecular processes that are essential and specific for the lifecycle of the virus. This principle is based on the hypothesis that structures of fundamental proteins (or their domains) are conserved even in mutant viruses. Neuraminidase (NA) belongs among such virus proteins. An influenza virion budding from an infected cell binds to a terminal sialic acid residue (**1**) on the host cell surface glycoprotein with haemagglutinin (HA: Figure 1). NA hydrolytically cleaves the glycosidic bond of sialic acid to release the virus from the host cell surface. This process liberates the budding virion from the infected cell and is essential for spreading the infection. As expected, the active site of NA is highly conserved across the influenza A and B virus strains. Therefore, an NA inhibitor is a prime candidate for broad-spectrum anti-influenza drugs.

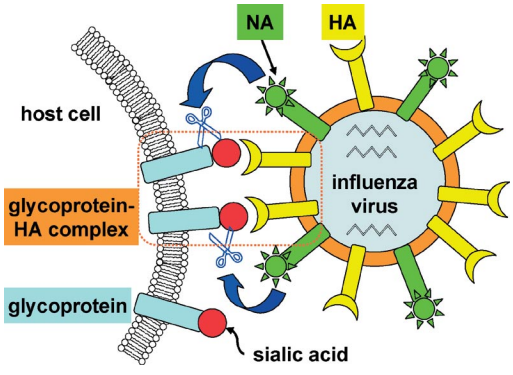

Figure 1. Schematic representation of an influenza virion budding from a host cell.

The X-ray structure of the NA–sialic acid (**1**) complex[1] provides molecular-level structural information for the design of NA inhibitors. Although the stable conformation of the core pyran ring of **1** in water is the chair form with its C-1 carboxylic acid at an axial position, it is converted into a boat conformation **3** when bound to the active site of NA

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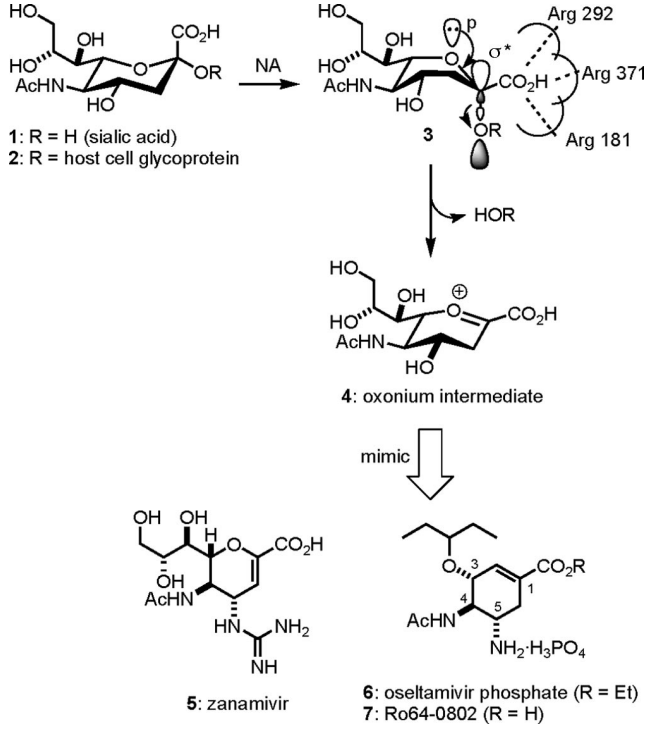
(Scheme 1). The boat conformation is stabilized by acid–base interactions between the C-1 carboxylic acid of **1** (or **2**) and three arginine residues of NA at the active site. This conformational switch is stereoelectronically required for glycoside bond cleavage. In boat conformer **3**, the axial lone pair of the pyran oxygen atom is positioned anti-parallel to the glycoside C–O bond. The glycoside bond is cleaved through a p–σ* orbital overlap, and oxonium intermediate **4** is generated. Two anti-influenza drugs – zanamivir (**5**: GlaxoSmithKlein's Relenza)[2] and oseltamivir phosphate (**6**: Gilead's Tamiflu, marketed by Roche)[3] – inhibit NA by strongly binding to the active site of NA as stable analogues of **4**. The IC_{50} values of these drugs are in the nanomolar range. Oseltamivir phosphate is an orally active prodrug, and its active form is the corresponding carboxylic acid **7**. Zanamivir has low bioavailability and is administered by inhalation. These drugs are considered to be effective to treat H5N1 influenza. According to the World Health Organization, stockpiling of these drugs is currently the only way to guard against a pandemic.



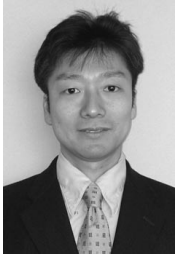
Scheme 1. A closer look at the hydrolysis step of silaic acid by NA and design of NA inhibitors.

Although these molecules are relatively small, the development of a practical synthesis that can provide the quantity required worldwide is highly challenging. These compounds thus offer an urgent but interesting opportunity to develop an ideal synthesis. Here, several reported synthetic strategies for oseltamivir phosphate are reviewed.

2. Gilead's Synthesis

The medicinal chemistry group at Gilead Sciences first synthesized **6** from a natural product, (–)-shikimic acid, as the starting material (Scheme 2).[3a] Treatment of (–)-methyl shikimate (**8**) under Mitsunobu conditions produced an epoxide through selective activation of the least sterically hindered hydroxy group at C-5. After the remaining hydroxy group at C-3 had been protected with a MOM group (**9**), epoxide ring-opening with azide proceeded selectively at the sterically less hindered C-5, affording azido alcohol **10**. *O*-Mesylation, followed by a Staudinger reaction to generate iminophosphorane, aziridinium formation through substitution of the mesyl group, and hydrolysis of the inter-

Masakatsu Shibasaki was born in 1947 in Saitama, Japan, and received his PhD. from the University of Tokyo in 1974 under the direction of the late Professor Shun-ichi Yamada before doing postdoctoral studies with Professor E. J. Corey at Harvard University. In 1977 he returned to Japan and joined Teikyo University as an associate professor. In 1983 he moved to Sagami Chemical Research Center as a group leader, and in 1986 took up a professorship at Hokkaido University, before returning to the University of Tokyo as a professor in 1991. He was a visiting professor at Philipps-Universität Marburg during 1995. He has received the Pharmaceutical Society of Japan Award for Young Scientists (1981), the Inoue Prize for Science (1994), the Fluka Prize (Reagent of the Year, 1996), the Elsevier Award for Inventiveness in Organic Chemistry (1998), the Pharmaceutical Society of Japan Award (1999), the Molecular Chirality Award (1999), the Naito Foundation Research Prize for 2001 (2002), the ACS Award (Arthur C. Cope Senior Scholar Award) (2002), the National Prize of Purple Ribbon (2003), the Toray Science Award (2004), the Japan Academy Prize (2005), the Takamine Memorial Sankyo Award, 2006 (Japan), the Rare Earth Society of Japan Award, 2006 (Japan), the Centenary Medal and Lectureship (Royal Society of Chemistry),2008, the ACS Award: Creative Work in Synthetic Organic Chemistry, 2008, and the Prelog Medal, 2008. Moreover, he has been selected as a Fellow of the Royal Society of Chemistry (1997) and an Honorary Fellow of the Chemical Research Society of India in 2003. His research interests include asymmetric catalysis and medicinal chemistry of biologically significant compounds.



Motomu Kanai was born in 1967 in Tokyo, Japan, and received his PhD from Osaka University in 1995 under the direction of Professor Kiyoshi Tomioka before doing postdoctoral studies with Professor Laura L. Kiessling at the University of Wisconsin. In 1997 he returned to Japan and joined Professor Shibasaki's group in the University of Tokyo as an assistant professor. He is currently an associate professor in Shibasaki's group. He has received the Pharmaceutical Society of Japan Award for Young Scientists (2001) and the Merck–Banyu Lectureship Award (2005). His research interests center on the design and synthesis of functional molecules.

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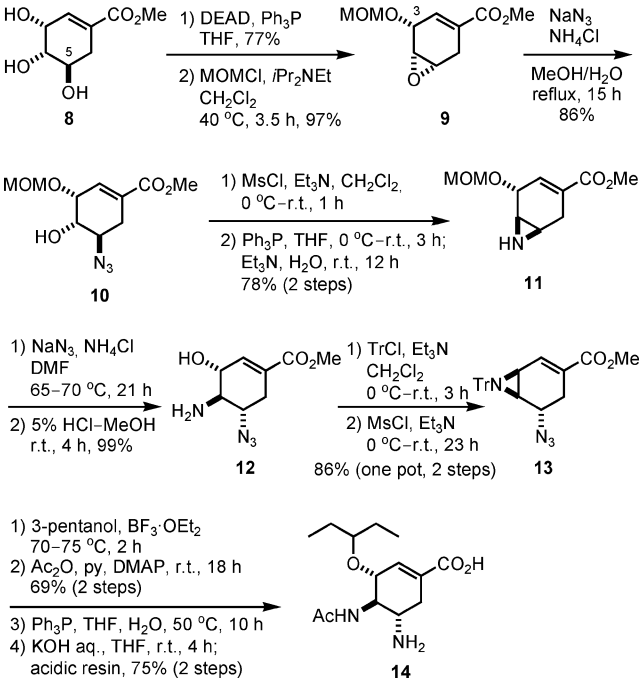
mediate with Et_3N in H_2O, produced aziridine **11**. Regioselective aziridine-opening with azide proceeded at C-5, and cleavage of the MOM group afforded amino alcohol **12**.



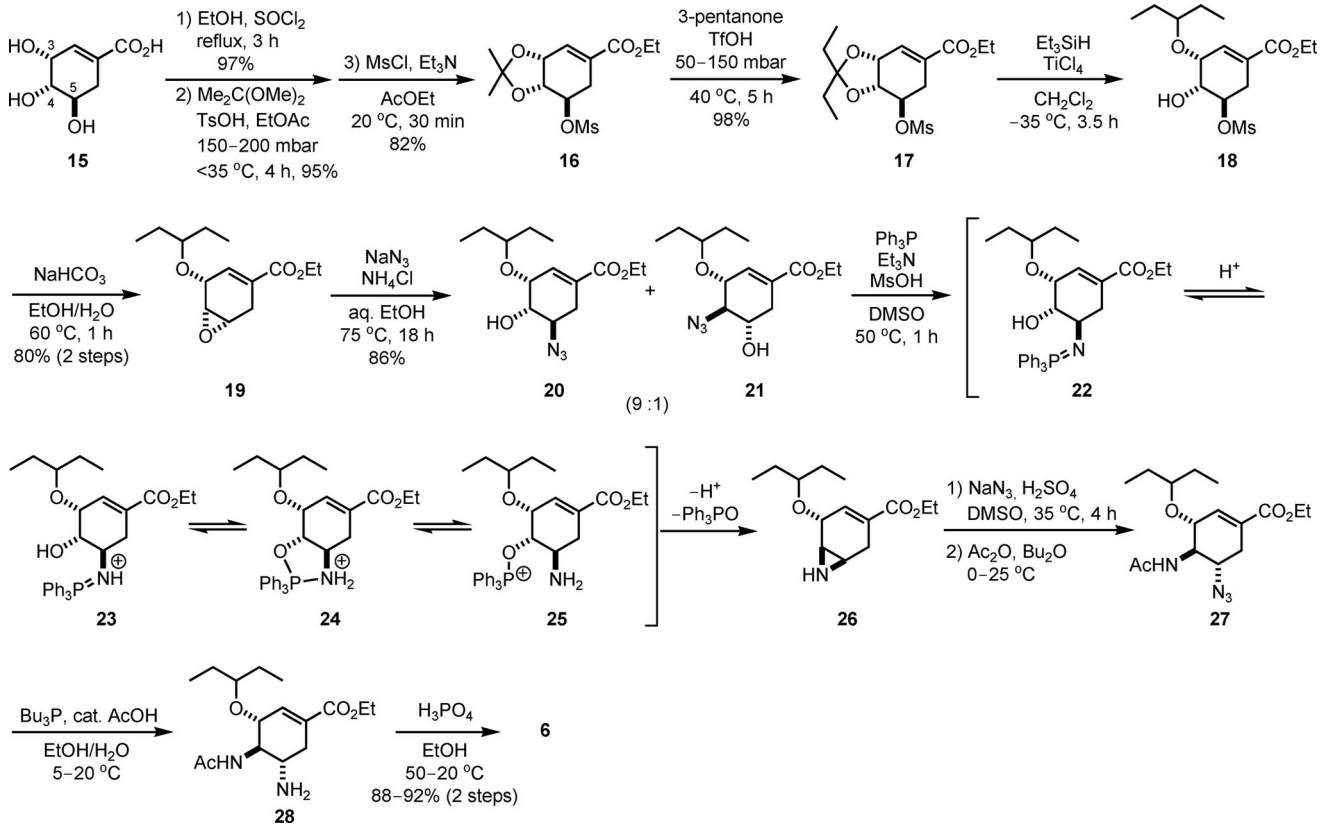
Scheme 2. Gilead Sciences' synthetic route.

Aziridine **13**, which is a precursor for introduction of the C-3 3-pentyloxy group, was synthesized from **12** by a two-step, one-pot process: (1) protection of the amino functionality with a trityl group, and (2) mesylation of the hydroxy group. Site-selective ring-opening of aziridine **13** with pentan-3-ol proceeded in the presence of 1.5 equiv. of $BF_3{\cdot}OEt_2$, and subsequent acetylation of the resulting amine produced the corresponding amido ether. The synthesis of the biologically active form **14** of oseltamivir was completed through reduction of the azide, followed by hydrolysis of the methyl ester under basic conditions.

The characteristics of this synthesis are as follows: (1) the bulky 3-pentyloxy group at the C-3 position is introduced at a late stage through an aziridine-opening reaction, and (2) the *trans* 1,2-diamine moiety is constructed through an aziridine-opening reaction with azide. The late-stage introduction of the C-3 alkoxy group is advantageous in the drug discovery stage, because this part can be easily diversified. Indeed, the 3-pentyloxy group is critically important for potent NA inhibitory activity.[4] The method for constructing the 1,2-diamine moiety is also utilized in Roche's process synthesis of oseltamivir phosphate, discussed in the next section.

3. Roche's Process Synthesis

The purpose of process chemistry is to provide the target compound on a large scale (ton scale) as efficiently as pos-



Scheme 3. Roche's synthesis.

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sible without using toxic and hazardous reagents. Because the availability of sufficient amounts of shikimic acid (**15**) was secured by extraction from Chinese star anise (1 kg of **15** from 30 kg of dried plant) or fermentation using genetically modified *E. coli*,[5] Roche selected **15** as the starting material for their large-scale synthesis (Scheme 3).[6] Compound **15** is a reasonable starting material because the oxidation states of all the carbons in **15** are the same as in **6**. Roche's synthesis is characterized by early introduction of the 3-pentyloxy moiety at C-3 by regioselective reduction of acetal **17**.

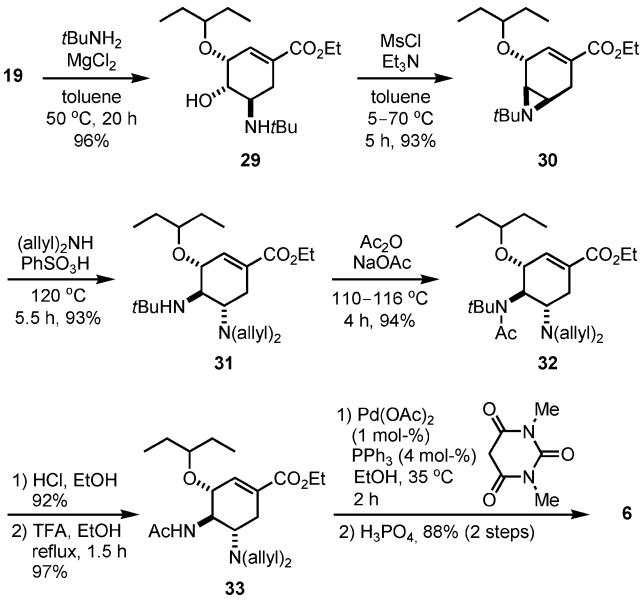
Intermediate **17** was synthesized from **15** indirectly via the crystalline acetonide **16**, due to the fact that the purity of the starting **15** was variable (85 to 99%) with very different impurity profiles. A later key intermediate **19** was not obtained with sufficient quality by a direct route involving the corresponding pentylidene acetal. Ethyl ester formation on **15**, followed by acetonide formation at the C-3,4-*cis* dihydroxy groups and mesylation of the remaining C-5 OH, produced **16** in high yield. This compound was purified by recrystallization from MeOH. Then, acetal exchange in the presence of excess pentan-3-one and a catalytic amount (4.5 mol-%) of triflic acid afforded **17**. Regioselective reductive opening of the acetal was best performed with Et_3SiH and $TiCl_4$ in CH_2Cl_2 at –35 °C. Under these conditions, **18** was obtained predominantly (32:1) in high yield, and was converted to epoxide **19** under basic conditions. Crystallization from hexane afforded pure **19** in 80% yield.

An epoxide-opening reaction with NaN_3 produced a 9:1 mixture of isomeric azido alcohols **20** and **21**, both of which were converted into the same aziridine **26**. Because of the explosive natures of azide compounds, **20** and **21** should be handled below 40 °C when neat and below 70 °C in solution. Aziridine formation from the azido alcohols comprised three steps: Staudinger reaction to afford iminophosphorane **22**, migration of triphenylphosphonium to the oxygen atom at C-4 to give **25**, and S_N2 attack of the nitrogen atom to eliminate phosphane oxide (intermediates from **20** are shown in Scheme 3 for simplification). This process was significantly facilitated in the presence of Et_3N and MsOH, probably because oxazaphospholidine (**24**) formation is accelerated by protonation of the nitrogen atom of **22**.

NaN_3 and H_2SO_4 were added to the reaction mixture containing aziridine **26**, with the temperature being kept below 37 °C, to give the corresponding azido amine in one-pot fashion from **20** and **21**. After *N*-acetylation, **27** was obtained. Staudinger reduction of the azide with Bu_3P followed by salt formation produced oseltamivir phosphate **6**, which was purified to ≥99% quality by recrystallization from EtOH.

Although this synthetic route can produce oseltamivir phosphate at a tonne scale, there are two potential drawbacks: (1) the use of the potentially explosive azide-containing intermediates, and (2) the lack of availability of shikimic acid of consistent purity. Roche's chemists are continuing their research toward developing safer and more efficient synthetic routes. Three alternative routes addressing these drawbacks are shown in Schemes 4, 5, and 6.

To avoid the use of azide, tBuNH$_2$ was used as an alternative amine source (Scheme 4).[7] Epoxide **19** was opened regioselectively by treatment with tBuNH$_2$–$MgCl_2$ complex, producing amino alcohol **29** in 96% yield. Thanks to the presence of a bulky *tert*-butyl group on the nitrogen atom, mesylation occurred selectively at the oxygen atom, and aziridine **30** was formed in one-pot fashion from **29**. After aziridine opening with diallylamine in the presence of $PhSO_3H$, the secondary amine was acetylated under relatively forcing conditions to give **32**, which was purified by precipitation as the corresponding HCl salt. This operation is the only purification required in the sequence between **19** and **6**. Cleavage of the *N*-*tert*-butyl group under acidic (TFA) conditions and deallylation through Pd-catalyzed allyl transfer to 1,3-dimethylbarbituric acid followed by phosphate salt formation afforded **6**.



Scheme 4. Azide-free synthesis of oseltamivir phosphate by the Roche group.

Because of the initial uncertainty with regard to the availability of shikimic acid on a tonne scale, several different strategies independent of this starting material were investigated by the Roche group.[6c,6d] Specifically, a variety of Diels–Alder strategies were attempted. A successful route in this direction is shown in Scheme 5.[6c,6d] This synthesis started with a racemic Diels–Alder reaction between furan and ethyl acrylate. The reaction proceeded in the presence of 1 equiv. $ZnCl_2$ under neat conditions, and the thermodynamically more stable *exo*-**34** was obtained as the major product (9:1). Enzymatic resolution of **34** allowed access to the desired (*R*) isomer **35** with 97% *ee* at 75% conversion (20% yield). Compound **35** was converted into the *endo* aziridine **38** by treatment with diphenylphosphoryl azide (DPPA)[8] at 70 °C through [3+2] cycloaddition, affording a mixture of *exo*-**36** and **37**, which was subjected to inverting thermal extrusion of N_2. No precise stereochemical mechanism for this unprecedented aziridine formation is clear at the moment. After transesterification at the phosphate moi-

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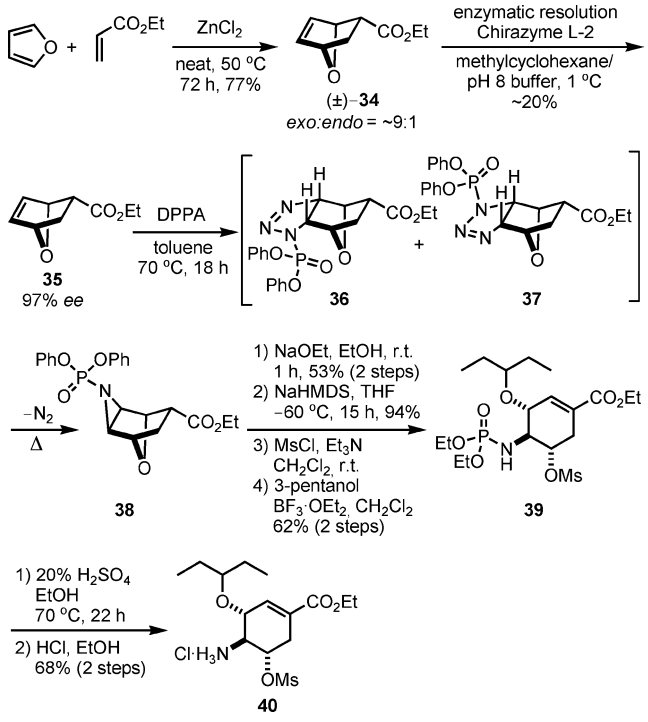
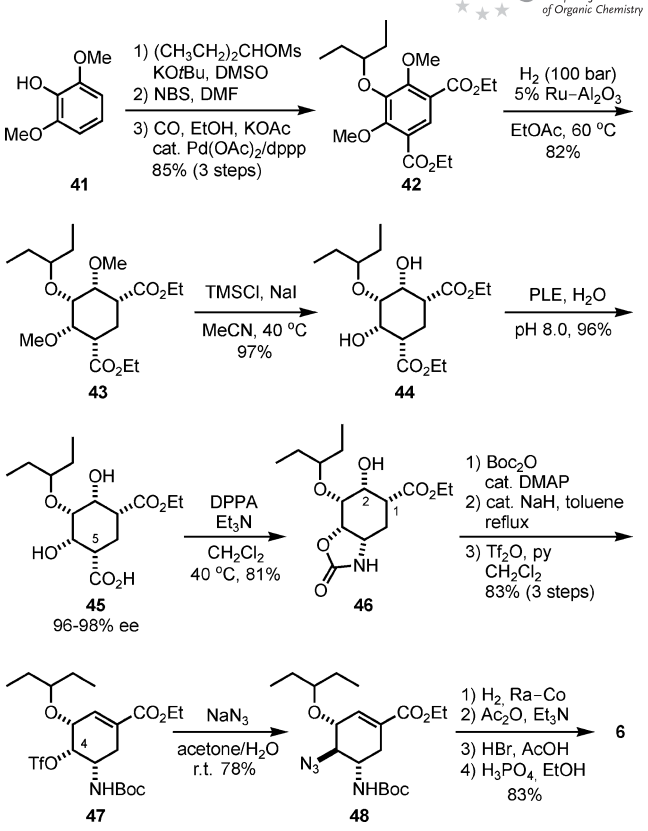
ety, base treatment to open the bicyclic system followed by *O*-mesylation and aziridine-opening with pentan-3-ol produced **39**. Hydrolysis of the phosphoryl amide and hydrochloride formation afforded **40**, which can be converted into **6** by aziridine formation and introduction of an amino functionality at C-5, etc.



Scheme 5. Synthesis of oseltamivir phosphate without using shikimic acid as the starting material−Diels–Alder strategy.

A more promising route, also without using shikimic acid, is shown in Scheme 6.[6c,6d] Starting from inexpensive dimethoxyphenol **41**, *O*-alkylation and subsequent dibromination and ethoxycarbonylation afforded symmetrical **42**, which was hydrogenated over Ru/Al_2O_3 to provide the *meso*-diester **43**. After selective *O*-demethylation with TMSI, the resulting **44** was enzymatically hydrolyzed with pig liver esterase (PLE), affording the enantiomerically enriched monoacid **45** with high enantioselectivity (96–98% *ee*) and in almost quantitative yield. Curtius rearrangement of **45** by treatment with DPPA introduced a C-5 nitrogen atom as a cyclic carbamate **46**, which was protected with a Boc group. The resulting *N*-Boc-oxazolidinone was treated with a catalytic amount of NaH in toluene at reflux, providing the corresponding Δ(1,2)-α,β-unsaturated ester. This formal dehydration proceeded through intramolecular attack of the C-2 hydroxide at the Boc-activated oxazolidinone carbonyl carbon, producing the intermediate cyclic carbonate, followed by β-elimination. The resulting C-4 hydroxy group was then activated as a triflate, giving **47**. S_N2 attack of NaN_3 produced azide **48**, which was reduced with Raney cobalt, followed by acetylation, Boc cleavage with HBr/AcOH, and phosphate salt formation produced **6**.



Scheme 6. Synthesis of oseltamivir phosphate without using shikimic acid as the starting material–desymmetrization strategy.

4. Corey's Synthesis

In 2006, Corey et al. reported a concise azide-free synthesis of **6** starting from the catalytic enantioselective Diels–Alder reaction developed in his group (Scheme 7).[9] The Diels–Alder reaction between butadiene (**49**) and trifluoroethyl acrylate (**50**) proceeded at room temperature without solvent (sealed tube) in the presence of 10 mol-% triflimide-activated oxazaborolidine catalyst **51**,[10] giving the product **53** in 97% yield and with 97% *ee*. The excellent enantioselectivity was explained by a transition state model **52**, in which diene **49** approached the activated dienophile from the *Re*-face opposite to the shielding phenyl group of the catalyst. The chiral ligand was recovered efficiently.

Ammonolysis of **53** produced amide **54**, which was converted into *N*-Boc-imide **55** through successive treatment with oxalyl chloride (forming the *N*-acyl isocyanate) and *t*BuOH.[11] Bromolactamization of **55** was performed in the presence of Li*O*t*Bu* and NBS, affording **56**. After elimination of HBr with DBU, allylic bromination followed by ethanolysis under basic conditions produced dienyl ester **59**. Regio- and stereoselective bromoamidation of the $C^3{=}C^4$ double bond was achieved by the originally developed method using *N*-bromoacetamide (NBA) in the presence of a catalytic amount of $SnBr_4$ as an activator of the Br^+ donor in CH_3CN solvent.[12] The reaction proceeded through bromonium ion (**60**) formation with attractive interactions between the carbonyl oxygen of the Boc group and Br^+, nucleophilic attack of CH_3CN at the allylic position (C-3)

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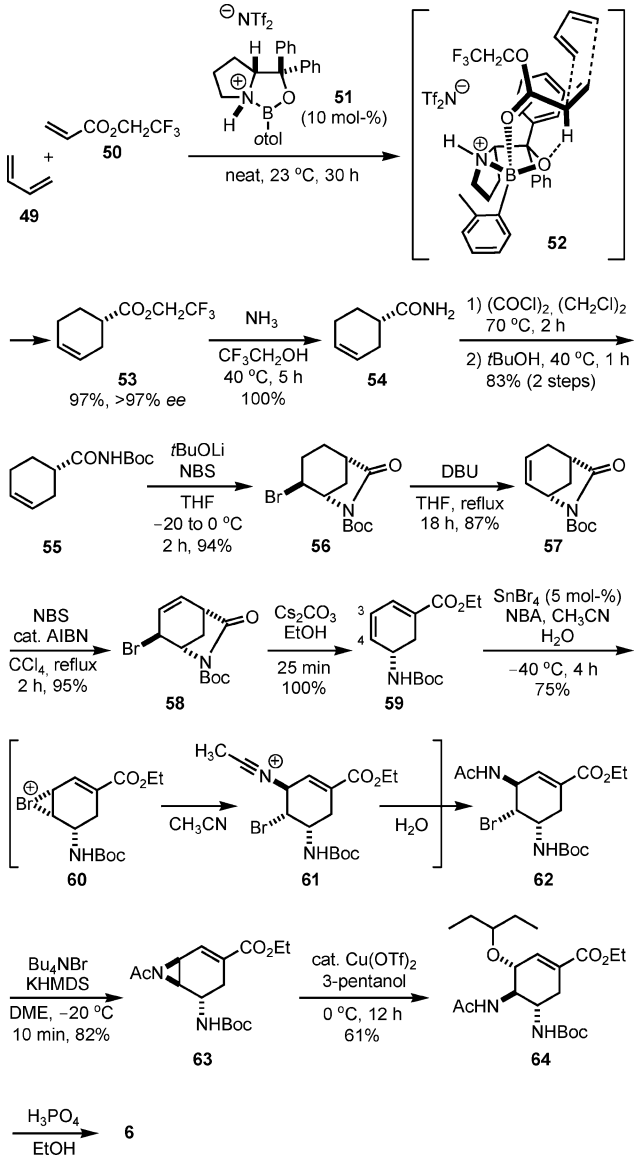


Scheme 7. Corey's synthesis.

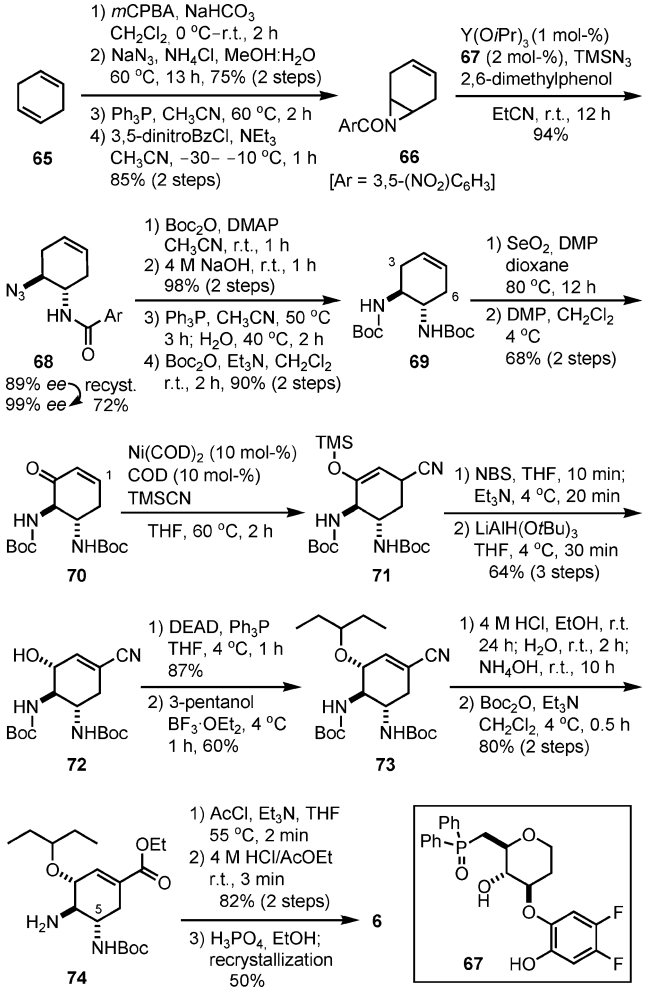
of the bromonium ion, giving **61**, and the addition of H_2O to **61**.

The conversion of **62** into oseltamivir phosphate (**6**) was straightforward. Treatment of **62** with tetrabutylammonium hexamethyldisilazide (generated in situ from KHMDS and Bu_4NBr) produced aziridine **63**, which was converted into **64** through a Lewis acid-catalyzed (Cu^{2+}) ring-opening reaction with pentan-3-ol. Cleavage of the Boc group was conducted with H_3PO_4, giving **6**.

Corey's synthesis is characterized by the linear increase in the oxidation state of the intermediates, starting from the low-oxidation state material **53**, generated in an enantiomerically enriched form by the catalytic enantioselective Diels–Alder reaction. Specifically, the development of stereoselective bromoamidation (from **59** to **62**) was the key to a shortening of the synthesis (12 steps).

5. Shibasaki and Kanai's Synthesis

Concurrently with Corey's report, our group reported an alternative synthesis of **6** after developing a general catalytic asymmetric ring-opening reaction of *meso*-*N*-3,5-dinitrobenzoylaziridines with $TMSN_3$ as a platform methodology (Scheme 8).[13] This general reaction was useful for the synthesis of *trans*-1,2-diamines, versatile chiral building blocks for pharmaceuticals and chiral ligands, in enantiomerically enriched forms.[14] Aziridine **66** was synthesized in four steps from cyclohexa-1,4-diene (**65**): (1) monoepoxidation, (2) epoxide opening with azide, (3) aziridine formation, and (4) *N*-acylation.



Scheme 8. Shibasaki and Kanai's first-generation synthesis.

Through the use of a complex (1 mol-%) generated from $Y(OiPr)_3$ and chiral ligand **67** mixed in a 1:2 ratio as an asymmetric catalyst,[15] an asymmetric ring-opening reaction of **66** with $TMSN_3$ proceeded at room temperature in the presence of 2,6-dimethylphenol (1 equiv.). The product **68** was obtained with 89% *ee* and in 94% yield. The enantiomeric purity was enriched to 99% *ee* through one recrystallization from *i*PrOH. The active catalyst was determined to be a polymetallic complex (Y/**67** = 2:3 or 4:5 complex),[16] and the reaction proceeded through intramolecular azide transfer from a yttrium azide (generated through

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transmetalation from $TMSN_3$) to an activated aziridine coordinating to another yttrium acting as a Lewis acid (Figure 2).[17] This reaction was performed on a relatively large scale (30 g scale) without difficulty. After the reaction, ligand **67** was recovered in 81% yield by extraction with a base. The recovered ligand can be reused without any decrease in catalyst activity and enantioselectivity.

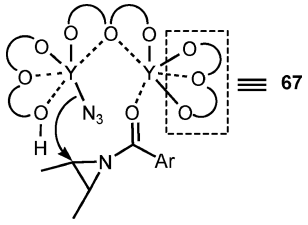
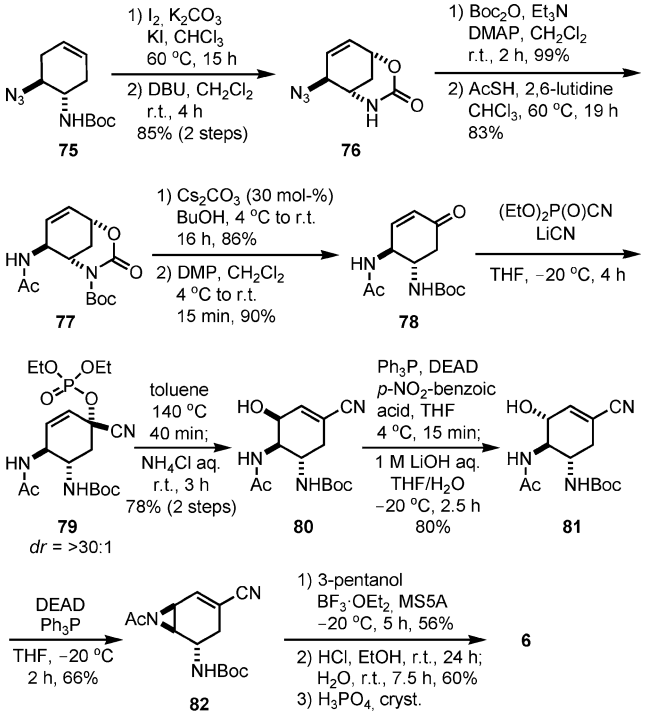


Figure 2. Schematic representation showing the mechanism of the catalytic asymmetric aziridine-opening reaction (Y/**67** = 2:3 complex is shown as a representative catalyst).

Synthesis of **6** from **68** required introduction of the oxygen functionality at C-3 and the ethoxycarbonyl group at C-1. To introduce the oxygen functionality at C-3, **68** was first converted into the C_2-symmetric diBoc **69** through Boc imide formation, hydrolysis of the benzoyl group, Staudinger reduction, and *N*-Boc protection. Allylic oxidation was performed with SeO_2[18] in the presence of Dess–Martin periodinane (DMP). The addition of DMP efficiently prevented over-oxidation to give the 3,6-diol by converting the produced allylic monoalcohol into the corresponding enone **70** in the reaction mixture. After complete conversion of the remaining allylic alcohol into the enone through DMP oxidation, CN was introduced at C-1 by our original method with the Ni–COD complex catalyst.[19] α-Bromination of the thus generated silyl enol ether **71** with NBS, followed by the elimination of HBr by use of Et_3N as a base, produced the corresponding β-cyano enone. This enone was not very stable during silica gel purification, and so it was immediately reduced without purification with the bulky reducing reagent $LiAlH(OtBu)_3$ to give α-allylic alcohol **72** with excellent stereoselectivity (>20:1). Aziridine formation under Mitsunobu conditions[20] and subsequent regioselective aziridine-opening with pentan-3-ol at the allylic (C-3) position produced **73**. Ethanolysis of the nitrile proceeded with concomitant Boc cleavage on treatment with acidic ethanol, and the resulting diamine was selectively monoprotected with a Boc group at the C-5 nitrogen, giving **74**. *N*-Acetylation followed by Boc cleavage and phosphate salt formation afforded **6**.[21]

Our first-generation route relied on the practical catalytic asymmetric aziridine-opening reaction with $TMSN_3$. However, the use of a toxic selenium reagent in the allylic oxidation and the necessary shuffling of the protecting group were two major drawbacks.

These drawbacks were overcome in our second-generation synthesis (Scheme 9).[22] After the catalytic asymmetric aziridine-opening reaction, *N*-Boc azide **75** was synthesized by the same procedure as described in Scheme 8 (steps 1 and 2 of the conversion from **68** to **69**). Iodolactamization followed by elimination of HI by treatment with DBU produced bicyclic carbonate **76**. Protection of the carbamate nitrogen atom with a Boc group and reductive acetylation of the azide with AcSH[23] afforded **77**, which was selectively hydrolyzed and oxidized with DMP to produce enone **78**. Cyanophosphorylation of **78** with DEPC proceeded in the presence of LiCN,[24] and cyanophosphate **79** was obtained as a single detectable isomer. Allylic rearrangement of the phosphate under thermal conditions[25] produced the corresponding allylic α-phosphate, which was treated with aqueous NH_4Cl to provide β-alcohol **80** through S_N2 substitution of the phosphate with H_2O. After inversion of the allylic stereochemistry by means of a Mitsunobu reaction with *p*-nitrobenzoic acid, followed by benzoate hydrolysis under basic conditions, azidirine **82** was synthesized through a Mitsunobu reaction. Aziridine-opening with pentan-3-ol, Boc cleavage with concomitant nitrile ethanolysis, and phosphate salt formation produced **6**.



Scheme 9. Shibasaki and Kanai's second-generation synthesis.

Although the two drawbacks of the first-generation synthesis had been eliminated, the second-generation route was still long (20 steps from **65**). In 2007, we developed a completely different synthetic route using the Diels–Alder reaction and Curtius rearrangement as key steps (Scheme 10).[26] Although the third-generation route depended on resolution by chiral HPLC, it required significantly fewer steps (12 steps) than the first- and second-generation syntheses.

The Diels–Alder reaction between siloxy diene **83** and fumaroyl chloride (**84**) proceeded at room temperature over 2 h. After the reaction was complete, $TMSN_3$ and DMAP were added to the mixture, and the corresponding acyl

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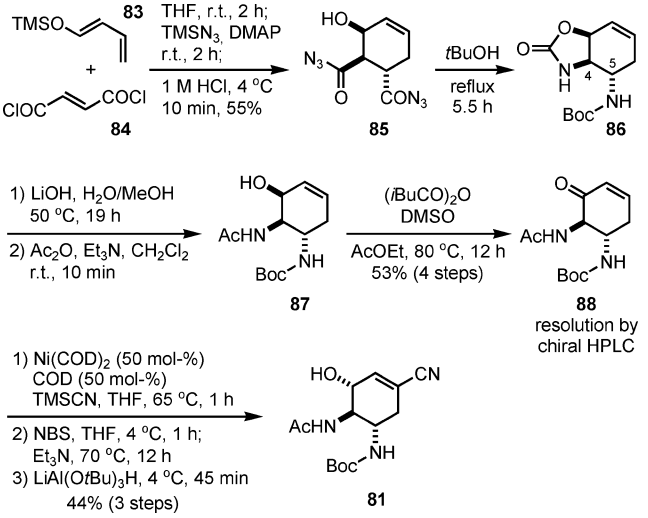
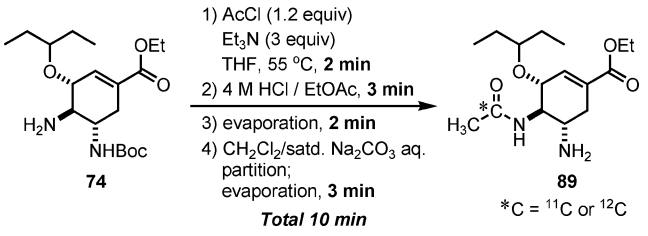


Scheme 10. Shibasaki and Kanai's third-generation synthesis.

azide was formed. On quenching of the reaction with HCl (1 M), desilylation took place and **85** was obtained in 55% yield over three operations. Although the Diels–Alder reaction afforded a 2:1 (*endo*/*exo*) mixture of diastereomers, the undesired *exo* isomer selectively decomposed during the acidic cleavage of the TMS ether. A Curtius rearrangement was conducted by heating a *t*BuOH solution of acyl azide **85** at reflux. In this process, two nitrogen atoms at C-4 and C-5 were differentiated, affording **86**. Selective hydrolysis of the cyclic carbonate with LiOH and subsequent *N*-acetylation produced **87**, which was oxidized to enone **88** under modified Moffat conditions with isobutyric anhydride.[27] Use of the sterically bulky anhydride in this step was essential in order to avoid *O*-acylation. At this stage, the enantiomers were separated by chiral HPLC. The Ni-mediated conjugate addition of TMSCN, followed by α-bromination, elimination of HBr, and stereoselective reduction with LiAl(O*t*Bu)$_3$H, afforded **81**, the same intermediate as in our second-generation synthesis. Extension of this synthetic route to an asymmetric variant through the development of a catalytic asymmetric Diels–Alder reaction is currently ongoing.

Our group has also developed a protocol based on our third-generation approach for the synthesis of an oseltamivir positron emission tomography (PET) tracer.[21] PET is a non-invasive method for identification of the distributions of molecules of interest in living systems. Because possible side effects of oseltamivir phosphate on the nervous system are a serious concern, especially for young flu patients,[28] it is critical to clarify whether or not oseltamivir crosses the blood–brain barrier. PET is a suitable method to address this point.[29] We designed an oseltamivir PET tracer containing ^{11}C in the acetamide portion at C-4. Because of the short half-life of ^{11}C (20.3 min), conditions were optimized to complete the synthesis in approximately 10 min after the introduction of the ^{11}C. As a result, we developed a method starting from **74** to **89** (Scheme 11). Although this study utilized normal (^{12}C-containing) AcCl, it can be extended to the synthesis of the radioactive PET tracer by using CH$_3$^{11}COCl. Studies to clarify the distribution of oseltamivir with the aid of PET are ongoing.



Scheme 11. Protocol for the synthesis of an oseltamivir PET probe.

6. Yao's Synthetic Study

In 2006, Yao and Cong reported a synthetic route for a potential intermediate (**100**) for oseltamivir production, starting from L-serine and using ring-closing metathesis (RCM) as a key step (Scheme 12).[30] L-Garner aldehyde (**90**), obtained in five steps from L-serine, was condensed with *N*-(*p*-methoxybenzyl)hydroxylamine (PMBNHOH), giving nitrone **91**. The addition of allylmagnesium bromide in the presence of a stoichiometric amount of $ZnBr_2$ produced the desired 5α-hydroxylamine **92** as a major isomer (87%), possibly through a cyclic transition state.[31] After reductive hydroxylamine cleavage, followed by protection of the nitrogen atom with a Cbz group to give **93**, dihydroxylation of the terminal double bond, hydrogenolytic cleavage of the Cbz and PMB groups, and reprotection of the C-5 nitrogen atom with Cbz produced diol **94**. Selective protection of the primary hydroxy group with a TBDPS group, Swern oxidation of the remaining secondary alcohol to a ketone, and a Wittig reaction afforded olefin **95**, which acted as a handle for the later-stage RCM.

The other C=C double bond for RCM was introduced through acetal cleavage in the presence of catalytic $BiBr_3$, Swern oxidation, and vinyl metal addition, giving **97**, with the desired stereochemistry at C-3, as the major isomer (*dr* = 3:1). Protection of the C-3 hydroxy group with a MOM group, followed by RCM in the presence of Grubbs' second-generation catalyst, produced **98**, containing the cyclohexene core of oseltamivir. The primary hydroxy group, generated by desilylation, was oxidized in two steps with PCC and $NaClO_2$. The resulting carboxylic acid was then converted into the corresponding ethyl ester to afford **99**. Both MOM and Boc groups were cleaved with acidic ethanol and the resulting amine was acetylated to give **100**.

Although Yao's route utilizes abundant L-serine as the starting material, the synthesis is rather lengthy and the C-3 stereoinduction is not efficient. Moreover, it is doubtful that **100** could be a precursor of **6**.[32]

7. Fukuyama's Synthesis

Fukuyama's synthesis of **6**, reported in 2007,[33] started with a novel asymmetric Diels–Alder reaction between the

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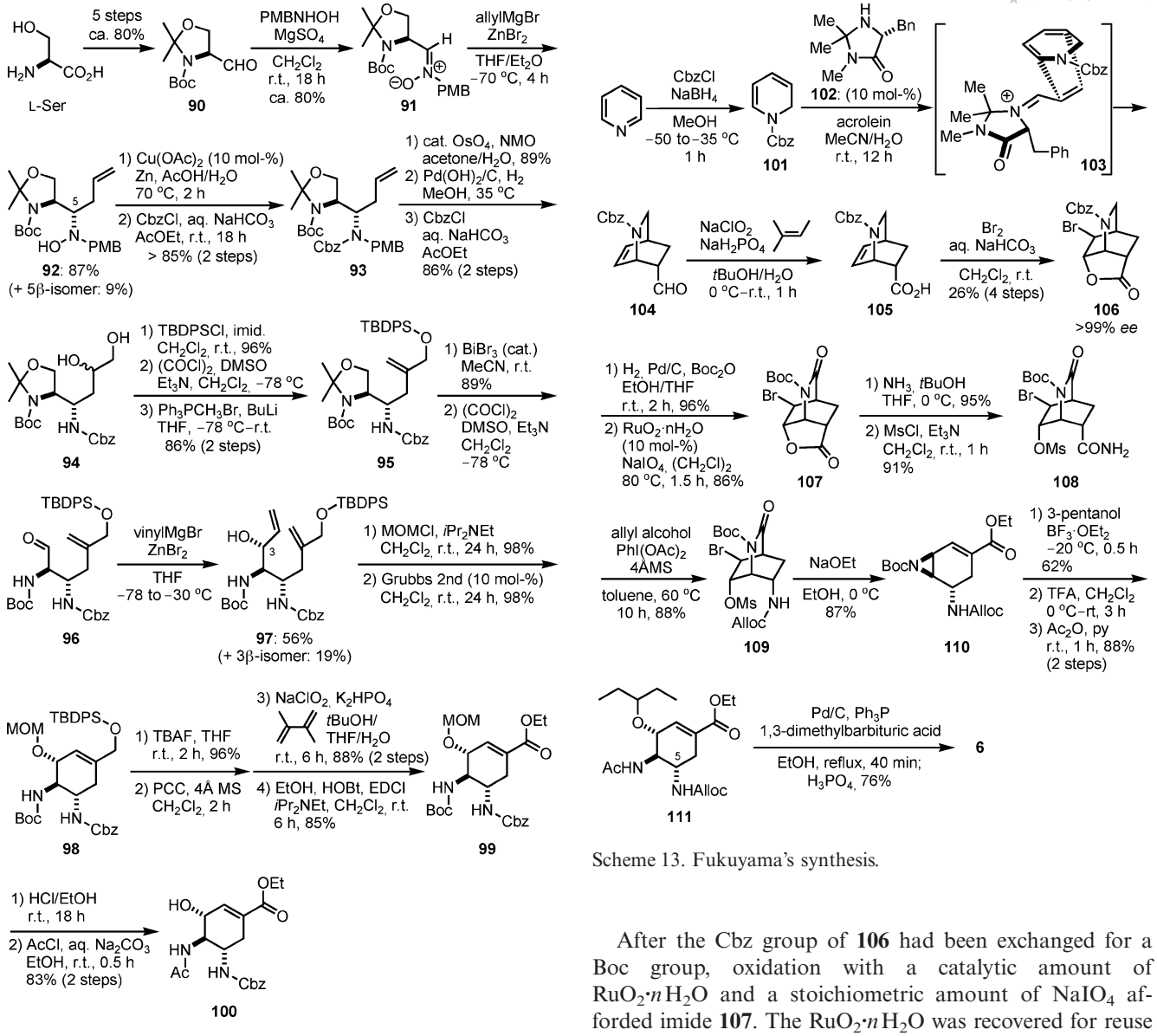

Scheme 12. Yao's synthetic approach.

Scheme 13. Fukuyama's synthesis.

dihydropyridine derivative **101** and acrolein, promoted by MacMillan catalyst **102**[34] (Scheme 13). Dihydropyridine **101** was synthesized from pyridine by $NaBH_4$ reduction in the presence of CbzCl. An asymmetric Diels–Alder reaction between **101** and acrolein proceeded in the presence of 10 mol-% of **102**, affording bicyclic **104**. Kraus oxidation followed by bromolactonization produced **106** in 26% yield from pyridine (4 steps). The moderate yield was attributed to the asymmetric Diels–Alder reaction (<30%), but **106** was easily purified through aqueous acid/base partition and crystallization. Chemically and enantiomerically pure **106** was obtained without column chromatography. The excellent enantioselectivity in the Diels–Alder reaction can be explained by consideration of model **103**, originally proposed by MacMillan: diene **101** would approach the activated dienophile from the side opposite to the steric bulkiness (benzyl group) represented by the catalyst.[34]

After the Cbz group of **106** had been exchanged for a Boc group, oxidation with a catalytic amount of $RuO_2{\cdot}nH_2O$ and a stoichiometric amount of $NaIO_4$ afforded imide **107**. The $RuO_2{\cdot}nH_2O$ was recovered for reuse by quenching of the reaction with *i*PrOH and filtration. In addition, the solvent $(CH_2Cl)_2$ can be substituted with the more environmentally benign AcOPr without decreasing the efficiency. Ammonolysis of the lactone followed by *O*-mesylation produced amide **108**, which was subjected to Hofmann rearrangement in the presence of $PhI(OAc)_2$ and allyl alcohol[35] to give allyl carbamate **109**. Treatment of **109** with NaOEt afforded aziridine **110** through ethanolysis of the imide, aziridination, and elimination of HBr in one-pot fashion. An aziridine-opening reaction with pentan-3-ol, cleavage of the Boc group with TFA, *N*-acetylation, deprotection of C-5 amine, and phosphate salt formation produced **6**.

Although the yield of the catalytic asymmetric Diels–Alder reaction requires further improvement, Fukuyama's 14-step synthesis is within the practical range thanks to the following points: (1) the starting material is the inexpensive pyridine, (2) the number of column purifications is minimal, and (3) safe and commonly used reagents are used for the synthesis.

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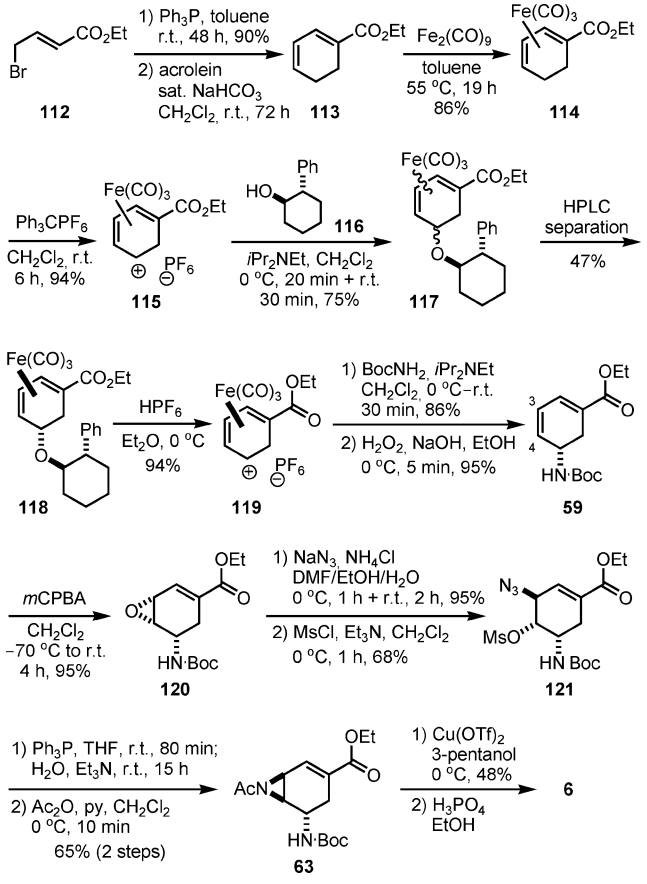
8. Kann's Synthesis

Kann's synthesis utilized stereoselective amination of cationic iron carbonyl complex **119**, which was obtained in an enantiomerically pure form by resolution (Scheme 14).[36] The synthesis started from cyclohexadiene **113**, generated through a tandem Michael/Wittig reaction between the ylide derived from **112** and acrolein.[37] After formation of a diene–iron complex (**114**), an allylic hydrogen atom was abstracted with Ph_3CPF_6, producing **115** in 94% yield. Cation **115** was then trapped with chiral alcohol **116** to afford **117** as a diastereomeric mixture. Enantiomerically pure **119** was obtained through HPLC separation to give the desired diastereomer **118** (47% yield), followed by regeneration of the allylic cation by treatment with HPF_6.

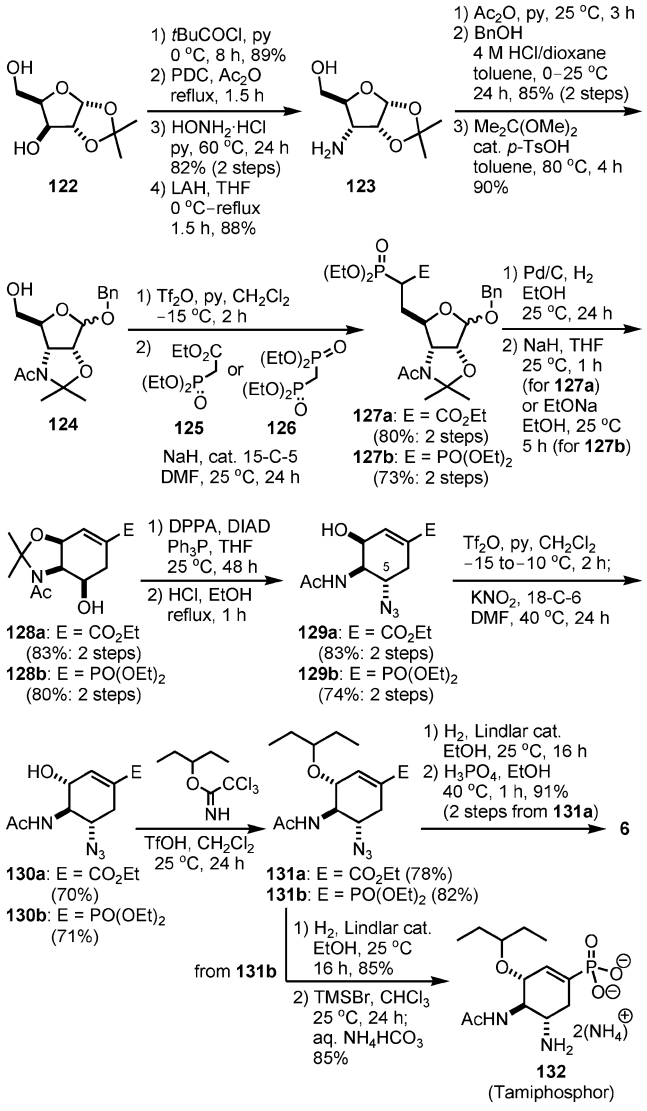


Scheme 14. Kann's synthesis.

The cation **119** was then trapped with $BocNH_2$ from the opposite side of the iron carbonyl group, and a subsequent oxidative decomplexation with basic hydrogen peroxide afforded dienyl ester **59**. Selective epoxidation of the more electron-rich C=C double bond between C-3 and C-4 with *m*CPBA afforded epoxide **120**. The mesyl azide **121** was then synthesized from **120** through an epoxide-opening reaction with NaN_3, followed by mesylation. A Staudinger reduction of the azide with Ph_3P and subsequent hydrolysis produced the aziridine, which was acetylated to produce Corey's intermediate **63**. Oseltamivir was then synthesized from **63** by Corey's procedure.

9. Fang's Synthesis

Fang's group developed a new synthetic route for **6**, directed toward analogue synthesis (Scheme 15).[38] Specifically, a phosphonate analogue (**132**: Tamiphosphor) and the guanidine-containing compounds **134** and **135** were synthesized. These analogues exhibit significantly higher potency than **6** in neuraminidase inhibitory activity.



Scheme 15. Fang's synthesis.

The synthesis started from D-xylose derivative **122**. After selective protection of the primary hydroxy group with a pivaloyl moiety, the secondary hydroxy group was converted into an α-amino group (**123**) through oxidation, oxime formation, and reduction. *N*-Acetylation, introduction of a benzyloxy group at the anomeric position under acidic conditions, and acetal formation produced **124**. The phosphonate part was introduced through activation of the primary hydroxy group as a triflate, followed by substitution by a phosphonate anion derived from **125** or **126**, affording **127a** and **127b**, respectively. The anomeric benzyl group was hydrogenetically cleaved, and the cyclohexene core of the

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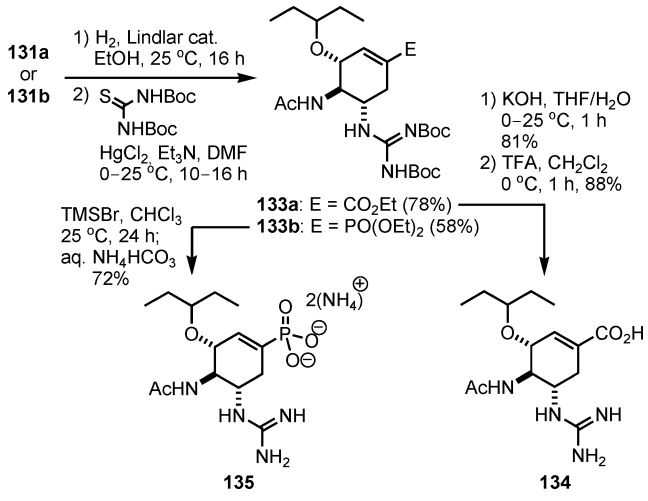
target compounds was constructed through an intramolecular Horner–Wadsworth–Emmons reaction, giving **128**. The tasks remaining at this stage were: (1) conversion of C-5 OH into an amino functionality, and (2) introduction of the C-3 3-pentyloxy group. The conversion of C-5 OH into an amino functionality was achieved by Mitsunobu inversion of the C-5 β-hydroxy group with DPPA, diisopropyl azodicarboxylate (DIAD), and Ph_3P.[39] After hydrolysis of the acetal under acidic conditions, the C-3 hydroxy group was inverted by triflate formation followed by S_N2 attack of KNO_2. The 3-pentyl group was then introduced through substitution of the 3-pentyloxy imidate by the C-3 oxygen in the presence of TfOH. Finally, hydrogenolysis of the azide in the presence of the Lindlar catalyst and subsequent phosphate salt formation produced **6**.

A phosphonate group is a bioisostere of a carboxylate group with a higher acidity. Ionic interactions between phosphonates and basic residues of target proteins are generally stronger than those of carboxylates. The phosphonate analogue **132** was synthesized from **131b** by hydrogenolysis of the azide followed by deprotection of the phosphonate using TMSBr (Scheme 15). In addition, analogues **134** and **135** containing a guanidine group, instead of the C-5 amino group, were synthesized from **131** (Scheme 16). Thus, hydrogenolysis of the azide and subsequent guanidine formation and deprotection afforded carboxylate analogue **134** from **131a**, and phosphonate analogue **135** from **131b**.



Scheme 16. Fang's analogue synthesis.

Comparisons of the inhibitory activities of **7**, **132**, **134**, and **135** in targeting neuraminidases of wild-type influenza viruses (H1N1 and H5N1) and neuraminidase inhibitor-resistant mutant viruses (H274Y) are shown in Table 1. Analogue **135**, containing phosphonate and guanidine groups, exhibited significantly higher potency than **7**. Analogue **135** also inhibited mutant enzymes at low nanomolar concentrations. Although the synthetic efficiency was not necessarily high, this work is remarkable because new potent nueraminidase inhibitors were identified during the development of a new synthetic route.

Table 1. Inhibitory activities against wild-type (Wt) and mutant (Mut) influenza virus neuraminidases.

Compound	Neuraminidase inhibition, IC_{50} [nM]			
	Wt (H1N1)	Mut (H274Y-H1N1)	Wt (H5N1)	Mut (H274Y-H5N1)
7	5.90	295	62.9	971
132	0.30	526	13.3	1210
134	4.10	252	160	1150
135	0.12	7.39	1.82	19.5

Conclusions

Although oseltamivir is a relatively small molecule, developing a practical synthesis that can satisfy worldwide demand in an environmentally friendly and safe way is quite challenging. Roche's current process synthesis relies on naturally occurring shikimic acid as the starting material. There is no doubt, however, that artificial asymmetric catalysts can provide potentially more straightforward starting materials. The synthetic routes developed by three academic groups (the Corey, Shibasaki and Kanai, and Fukuyama groups) support this viewpoint. New synthetic methodologies allow synthetic chemists to design conceptually new synthetic strategies that are otherwise impossible to implement. In this sense, improvement in synthetic efficiency is intimately related to progress in synthetic methodologies.

Another important research vector is to identify molecules with improved pharmacological effects. Like other drugs, oseltamivir phosphate is not perfect. The emergence of an oseltamivir-resistant influenza virus and possible side effects on the human nervous system are two major concerns relating to oseltamivir. Flexible synthetic routes should allow for the synthesis of analogues in order to address these problems. The latest work from Fang's group is an example of such an approach. In addition, organic synthesis can actively contribute to answering biologic questions. The development of a synthetic method for an oseltamivir PET tracer by our group is one such example. Importantly, the discovery of one molecule by chemists has brought a tremendous benefit to human health and welfare, together with emerging vast research interests, part of which are discussed in this review. Discovery of new functional molecules is an extremely important task for synthetic chemists.

Note Added in Proof (February 15, 2008): During the printing process of this review, the following three important contributions appeared. (a) Trost and Zhang reported a short (8 steps, overall yield ~30%) catalytic asymmetric synthesis of oseltamivir phosphate by using a Pd–Trost ligand complex-catalyzed deracemization of a lactone with a nitrogen nucleophile and a $Rh_2(esp)_2$-catalyzed aziridination as key steps: B. M. Trost, T. Zhang, *Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.200800282; (b) Okamura et al. reported a short racemic synthesis of Corey's intermediate **59** by using a base (aqueous NaOH)-mediated Diels–Alder reaction between a hydroxypyridone and ethyl acrylate: N. T. Kipassa, H. Okamura, K. Kina, T. Hamada, T. Iwagawa, *Org. Lett.*, DOI: 10.1021/ol7029646; (c) radioactive PET tracer of oseltamivir was synthesized, and its distribution in rat brain was evaluated: F. Konno, T. Arai, M.-R. Zhang,

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