Tetrahedron 67 (2011) 7875–7899

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report number 948

Recent synthetic approaches to oseltamivir phosphate (Tamiflu™) for the treatment of influenza

Javier Magano

Pfizer Inc., Eastern Point Road, Groton, CT 06340, USA

ARTICLE INFO

Article history:
Received 24 April 2011
Available online 12 July 2011

Contents

Abbreviations: AAA, asymmetric allylic alkylation; Ac, acetyl; Boc, *tert*-Butoxycarbonyl; *t*-Bu$_3$tPy, 4,4′,4″-Tri-*tert*-butyl-2,2′,6′,2″-terpyridine; Cod, Cyclooctadienyl; CSA, Camphorsulfonic acid; DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene; DCE, 1,2-Dichloroethane; DDQ, 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone; DEAD, Diethyl azodicarboxylate; DIAD, Diisopropyl azodicarboxylate; DIBAL-H, Diisobutylaluminum hydride; DIPEA, Diisopropylethylamine; DMAP, 4-Di(methylamino)pyridine; DMF, *N*,*N*-Dimethylformamide; DMP, Dess-Martin periodinane; DMPU, 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; DMSO, Dimethylsulfoxide; Dppf, 1,1′-Bis(diphenylphosphino)ferrocene; dr, diastereomeric ratio; EDCI, *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; ee, enantiomeric excess; Esp, *α*,*α*,*α*′,*α*′-Tetramethyl-1,3-benzenedipropionic acid; HMDS, Hexamethyldisilazide; HMPA, Hexamethylphosphoramide; HPLC, high performance liquid chromatography; IBX, 2-Iodoxybenzoic acid; IPr, 1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene; LAH, Lithium aluminum hydride; LDA, Lithium diisopropylamide; *m*-CPBA, *m*-Chloroperbenzoic acid; MEIM, *N*-Methylimidazole; Mes, Mesityl; MOM, Methoxymethyl; Ms, Methanesulfonyl; MTBE, *tert*-Butyl methyl ether; MW, microwave; NMO, 4-Methylmorpholine *N*-oxide; Ns, *p*-Nitrobenzenesulfonyl; PCC, Pyridinium chlorochromate; PDC, Pyridinium dichromate; PG, protecting group; PMB, *p*-Methoxybenzyl; PPTS, Pyridine *p*-toluenesulfonate; Py, Pyridine; SES, 2-(Trimethylsilyl)ethanesulfonyl; TBAF, Tetrabutylammonium bromide; TBDMS, *tert*-Butyldimethylsilyl; TBS, *tert*-Butyldimethylsilyl; TCCA, Trichlorocyanuric acid; TEA, Triethylamine; TEMPO, (2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl; Tf, Trifluoromethanesulfonyl; TFA, Trifluoroacetic acid; THF, Tetrahydrofuran; TMS, Trimethylsilyl; Ts, *p*-Toluenesulfonyl.

E-mail address: Javier.Magano@pfizer.com.

0040-4020/$ – see front matter
doi:10.1016/j.tet.2011.07.010

1. Introduction

Influenza, a severe viral infection of the respiratory system, is responsible for substantial morbidity and mortality rates due to annual epidemics and unpredictable pandemics, such as the H1N1 pandemic in 2009.[1] The social implications in the United States are staggering in terms of number of hospitalizations (200,000) and deaths (36,000) per year, with an estimated cost of approximately $12 billion. Worldwide, the virus infects around 20% of the population resulting in 250,000–500,000 deaths.[2,3]

Despite all the research in numerous academic laboratories and pharmaceutical companies to develop new and more efficient drugs, the orally available neuraminidase inhibitor oseltamivir phosphate (**1**, Tamiflu™, Fig. 1) still is the most commonly prescribed treatment to combat the disease. The drug was discovered at Gilead Sciences and is currently manufactured and commercialized by F. Hoffmann-La Roche Ltd. The highly water-soluble phosphate salt is an ester prodrug that is hydrolyzed in the liver by hepatic esterases to the active form oseltamivir carboxylate.[4] The mechanism of action of oseltamivir is by inhibition of neuraminidase, one of the proteins on the surface of the virus, which results in the inability of the virus to spread and infect other cells. Because the active site of this protein is highly conserved, oseltamivir is active against all the neuraminidase subtypes that have been tested so far in vitro.[5] Therefore, the drug can be employed to treat seasonal influenza and avian flu.[2] In addition, during the recent 2009 A/H1N1 swine flu pandemic, oseltamivir played a major role to combat the outbreak by reducing the severity and duration of the symptoms associated with it, such as fever, when the drug was administered shortly after infection. Oseltamivir is well tolerated by most patients and, due to its safety profile, it was also approved in Europe, United States, Canada, and other countries for administration to infants <1 year of age during the pandemic.[6] Oseltamivir has also been proven effective prophylactically if administered before 48 h of infection.[7]

Zanamivir (**2**, Relenza™, Fig. 1), the only other neuraminidase inhibitor approved to treat influenza, has seen limited use despite being highly effective against influenza A and B. This drug, the first neuraminidase inhibitor synthesized from rational drug design using the 3-dimensional structure of the protein neuraminidase,[8] was discovered in 1989 at Biota in Australia and was licensed to GlaxoSmithKline for commercialization in the United States in 1999. Zanamivir has low oral bioavailability and must be administered by inhalation, which may explain why this drug has received less attention than oseltamivir (oral administration).

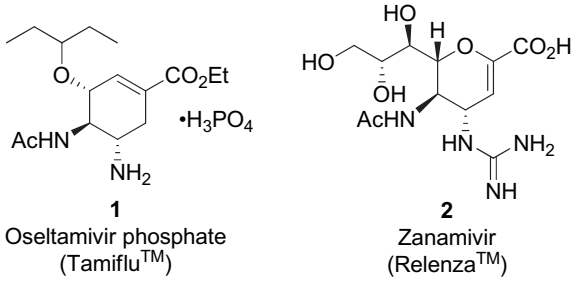


Fig. 1. Structures of neuraminidase inhibitors oseltamivir phosphate (**1**) and zanamivir (**2**).

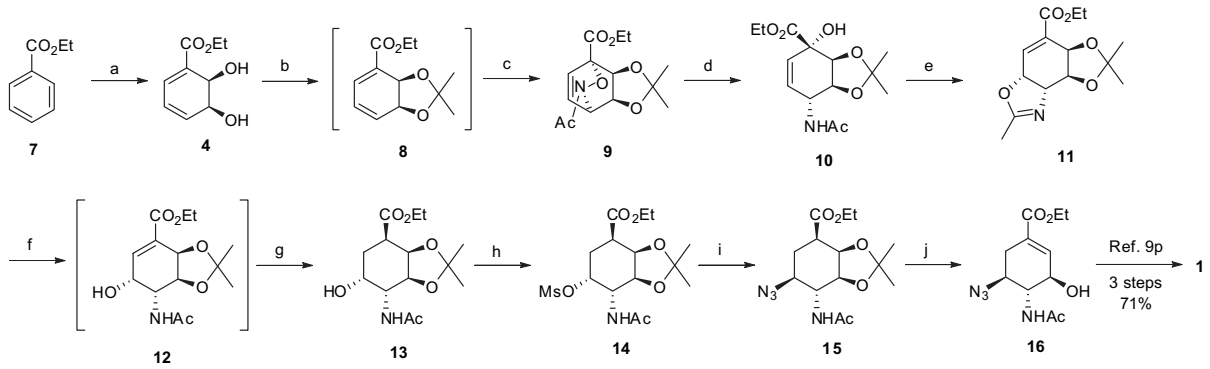
Prior to the routes described in this review, a large number of synthetic approaches to oseltamivir have been reported in the literature[9] and thoroughly reviewed.[10] Since the last comprehensive review on neuraminidase inhibitors syntheses (including publications until May 2009 for both oseltamivir and zanamivir)[10a] several new syntheses as well as a streamlined and greener preparation of a key intermediate in the commercial process for this important drug[11] have been published in the literature. This update will cover these new disclosures from a critical point of view with respect to scalability since, in this reviewer's opinion, the potential for large-scale manufacturing should be one of the most important factors to take into consideration when designing a new chemical route. The patent literature has not been covered. A summary of all the syntheses is provided in Section 5 of this review in table format to serve as a reference for route comparison. Overall yield, number of steps, starting material availability and cost, and the use of protecting group chemistry, halogenated solvents, hazardous and toxic reagents, chromatography, Mitsunobu chemistry (not amenable to scale), and other factors that play a role in the scalability of a process are included.

In contrast to oseltamivir, the number of synthetic routes to zanamivir is very limited[12] and no new total synthesis has been reported since Yao's group publication in 2004.[12d,13] Several reports on the synthesis of oseltamivir and zanamivir analogues have also recently appeared in the literature.[14]

2. Asymmetric syntheses of oseltamivir

2.1. Chemoenzymatic synthesis of oseltamivir from ethyl benzoate by Hudlicky's group

Hudlicky and co-workers at Brock University in Canada have reported a symmetry-based chemoenzymatic synthesis of an advanced intermediate en route to oseltamivir that starts from readily-available ethyl benzoate (**7**, Scheme 1).[15] Bromobenzene has been employed in previous chemoenzymatic approaches to oseltamivir,[9r,t,16] but they later required the introduction of the ester functionality via a carbonylation reaction. Therefore, the selection of ethyl benzoate as starting material avoids this additional step. Taking advantage of the latent symmetry present in oseltamivir (Fig. 2), this research group envisioned that if the configurations of the substituents at the C3, C4, and C5 positions are not specified, then they can perform as an 'enantiomeric switch' that can be controlled by the translocation of the double bond. This latent symmetry would then be used to allow for the flexible introduction of the nitrogen and oxygen functionalities in the order and at the location desired. Approach A has been previously tested.[16] In approach B, the *N*-acyl *anti*-aziridine undergoes ring-opening with a nitrogen nucleophile followed by double bond hydrogenation and elimination of the C6 hydroxy group to regenerate the olefin. The researchers mentioned that since this approach to prepare **5** (R=Ac) was not straightforward, an alternative was pursued that proceeded through an intermediate such as **6**. This new route allowed for the preparation of allylic alcohol **16**, which is an



Reagents and conditions: (a) *E. coli* JM 109 (pDTG601A, ca. 1 g/L). (b) Dimethoxypropane, TsOH, rt. (c) MeCONHOH, $NaIO_4$, MeOH, rt, 70% (from **4**). (d) $[Mo(CO)_6]$, $MeCN/H_2O$ (15:1), Δ, 75%. (e) MsCl, TEA, DMAP, CH_2Cl_2, rt, 54%. (f) $CaCO_3$, $EtOH/H_2O$ (1:1), reflux, 72%. (g) H_2 (60 psig), Rh/Al_2O_3 (5 mol%), 85% aq EtOH, 95%. (h) Ms_2O, TEA, CH_2Cl_2, rt, 73%. (i) NaN_3, acetone/H_2O, rt, 86%. (j) DBU, CH_2Cl_2, rt, 85%.

Scheme 1. Chemoenzymatic synthesis of oseltamivir by Hudlicky's group.

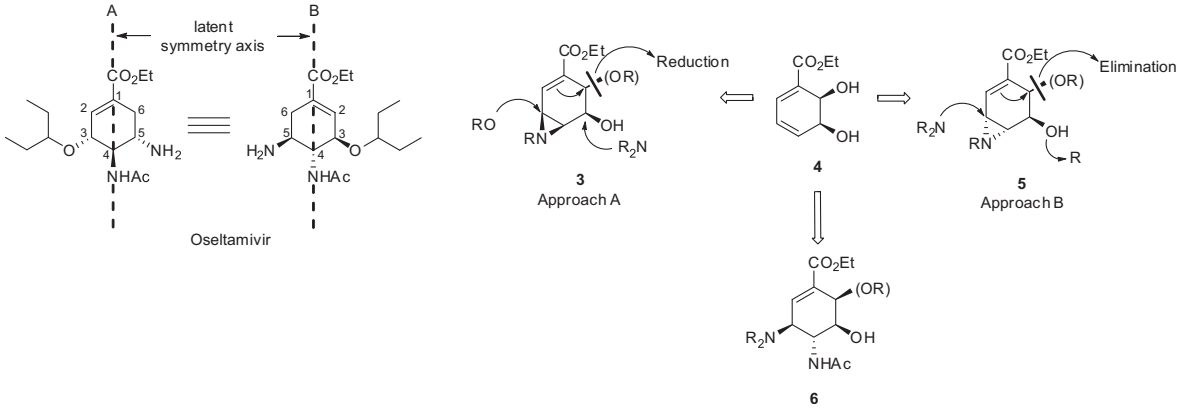


Fig. 2. Hudlicky's group strategies toward oseltamivir.

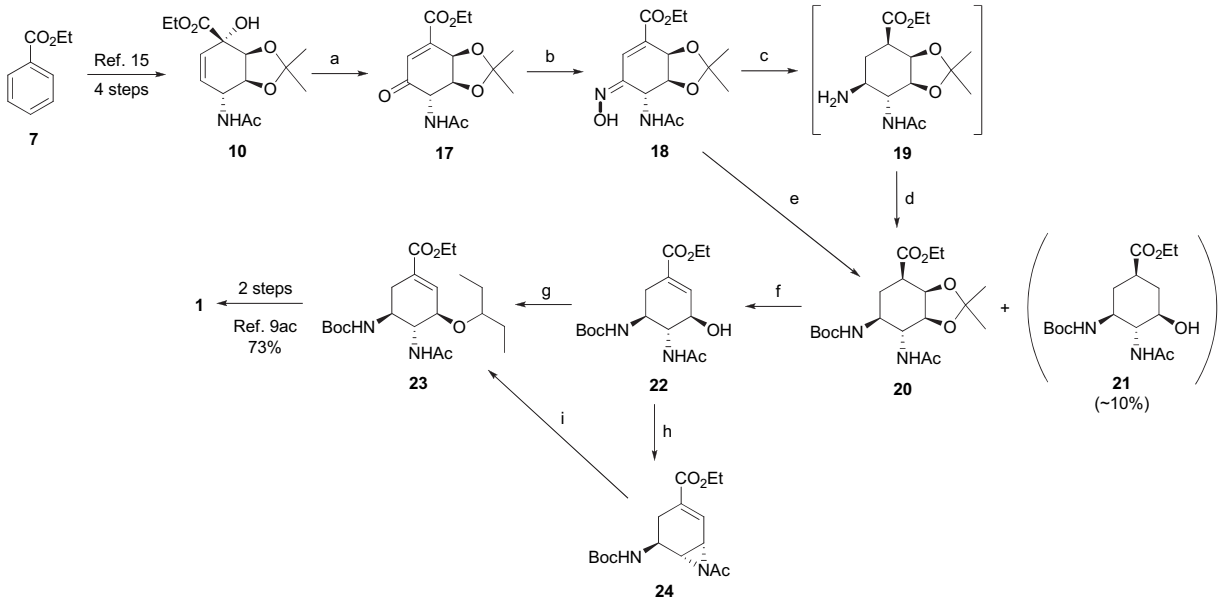
advanced intermediate in Fang's synthesis of oseltamivir from D-xylose.[9p]

The synthesis (Scheme 1) starts with the asymmetric oxidation of ethyl benzoate (**7**) to chiral diol **4** with a recombinant strain of *Escherichia coli* JM109(pDTG601A).[17] After diol protection with dimethoxypropane, crude **8** underwent inverse electron-demand Diels–Alder reaction with *N*-hydroxy acetamide to afford oxazine **9** in 70% yield from **4**.[18] N–O bond reduction with $[Mo(CO)_6]$ in 75% yield followed by mesylation of the resulting alcohol in the presence of TEA provided oxazoline **11** in 54% yield. The oxazoline was cleaved with $CaCO_3$ in aqueous EtOH at reflux to afford hydroxyacetamide **12**. This crude intermediate was subjected to hydrogenation with Rh on alumina as catalyst to generate cyclohexanol **13** in 95% yield. Conversion of this alcohol to the corresponding mesylate and S_N2 displacement with NaN_3 in acetone introduced the nitrogen functionality at C5. The final step involved treating azide **15** with DBU in CH_2Cl_2 to provide advanced intermediate allylic alcohol **16**. Three additional steps from **16** completed the synthesis of oseltamivir phosphate.[9p]

An advantage of this 13-step route to oseltamivir phosphate is the use of very inexpensive ethyl benzoate. The enzymatic oxidation sets the stereochemistry at the C3 position and provides a handle for the introduction of the rest of chirality at the C4 and C5 positions. This route also features a novel Diels–Alder reaction to introduce the amino group at C4. Some of the disadvantages are the very low throughput of the enzymatic oxidation, the use of azide chemistry, and the low overall yield to intermediate **16** (10%). In addition, the scalability of some of the steps (Diels–Alder, N–O bond reduction) would have to be tested. No information was provided in the article on neither the number of chromatographic purifications nor the scale for this route.

2.2. Chemoenzymatic, azide-free synthesis of oseltamivir from ethyl benzoate by Hudlicky's group

Hudlicky and co-workers have recently reported a second chemoenzymatic approach to oseltamivir, which, unlike the previous one shown above, does not resort to azide chemistry with the goal of developing an efficient process that can become practical on commercial scale (Scheme 2).[19] This synthesis also begins from ethyl benzoate (**7**) as a cheap starting material that already contains 9 of the 16 carbon atoms present in oseltamivir. Allylic alcohol **10**, generated in four steps as has been shown in the previous synthesis,[15] underwent [3,3] oxidative rearrangement via reaction with a solution of CrO_3 in Ac_2O in cold CH_2Cl_2 (4 °C) to provide cyclohexenone **17**.[20] The combination CrO_3/Ac_2O performed better than other oxidants, such as PDC, PCC, IBX, Dess–Martin periodinane (DMP) or TEMPO derivatives. For optimal results, the CrO_3 was first dissolved in Ac_2O at 80 °C and this solution was then diluted with CH_2Cl_2 and cooled to 4 °C before the addition of the alcohol. When the oxidation was carried out at higher temperatures, aromatic byproducts were generated. Enone **17** was treated with $NH_2OH\cdot HCl$ to give oxime **18**, which could be hydrogenated with Rh/Al_2O_3 as catalyst to the corresponding amine and protected with Boc_2O in



Reagents and conditions: (a) CrO_3, Ac_2O, CH_2Cl_2, 4 °C, 5 min. (b) NH_2OH•HCl, py, EtOH, rt, 75–82% (2 steps). (c) H_2 (60 psi), 5% Rh/Al_2O_3, EtOH/H_2O (96:4). (d) $(Boc)_2O$, CH_2Cl_2, 50% (2 steps). (e) H_2 (60 psi), 5% Rh/Al_2O_3, $(Boc)_2O$, EtOH/H_2O (96:4), 93%. (f) **20**, 0.05 M NaOEt, EtOH, 94%. (g) 3-Iodopentane, Ag_2CO_3, <10%. (h) $PhMe_2P$, DIAD, CH_2Cl_2, 4 °C, 70–78%. (i) 3-Pentanol, $Cu(OTf)_2$, 60%.

Scheme 2. Azide-free synthesis of oseltamivir by Hudlicky's group.

a two-step sequence to afford intermediate **20** in 50% overall yield. Alternatively, the Boc-protected amine could be produced in a one-pot procedure via oxime reduction in the presence of Boc_2O in 93% yield. About 10% of byproduct **21** was generated during this step most likely as a result of ether elimination at C2 catalyzed by the newly formed amine followed by reduction of the resulting olefin. Cyclohexene **22**, previously reported by Shibasaki during his synthesis of oseltamivir,[9ac] was obtained in 94% yield after treating ketal **20** with dilute NaOEt in EtOH. The direct conversion of alcohol **22** to Boc-protected oseltamivir **23** gave low yields with 3-iodopentane in the presence of Ag_2CO_3.[21] On the other hand, a two-step sequence that involved an intra-molecular Mitsunobu reaction to generate aziridine **24** followed by aziridine ring-opening with 3-pentanol and catalytic $Cu(OTf)_2$ as per Shibasaki's procedure[9ac] provided intermediate **23** in 42–47% overall yield. From **23**, two additional steps completed the synthesis of **1**.[9ac]

As for the previous synthesis by this same group, a clear advantage of this 12- or 13-step route is the choice of inexpensive ethyl benzoate as starting material and provides oseltamivir in 7–12% overall yield from diol **4**. In addition, it avoids the use of NaN_3 for the introduction of one of the amine functionalities, even though the use of $NH_2OH \cdot HCl$ can also pose some safety concerns on scale. Some of the disadvantages are the use of highly toxic CrO_3 and the need for Mitsunobu chemistry for aziridine formation. The researchers mentioned in the text that allylic alcohol **22** can be prepared from diol **4** (Scheme 1) in only five operations and without chromatographic purification on multi-gram scale, even though the yields were lower from losses to the filtrates after recrystallizations compared to chromatography. In contrast, in the experimental section of the article only three intermediates were carried through as crudes (the rest required chromatographic purification) and most of the steps were demonstrated only on mg-scale.

2.3. Ruthenium-catalyzed dihydroxylation route to oseltamivir by Shibasaki's group

Shibasaki and co-workers at the University of Tokyo have reported a thorough study of reaction conditions en route to oseltamivir with the goal of avoiding the use of Mitsunobu chemistry and hazardous reagents.[22] Several strategies were tested for the introduction of the 3-pentyl ether functionality (Fig. 3): (a) opening of epoxides **25**–**27** with 3-pentanol and a Lewis acid ($Al(OTf)_3$, $Yb(OTf)_3$, $BF_3 \cdot OEt_2$, $Sc(OTf)_3$) under basic (NaHMDS) or neutral conditions ($Ni(cod)_2/PBu_3$);[23] (b) S_N2 displacement of the mesylate group in **28** with 3-pentanol; (c) opening of cyclic

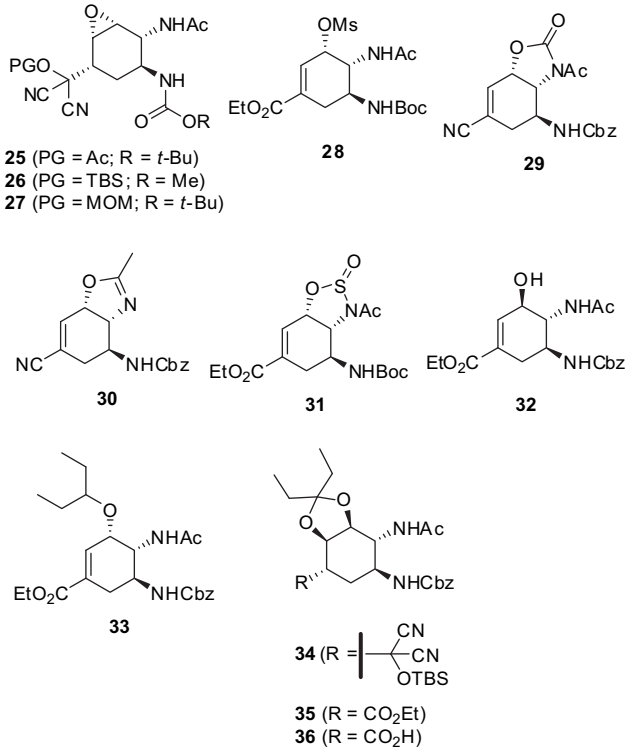
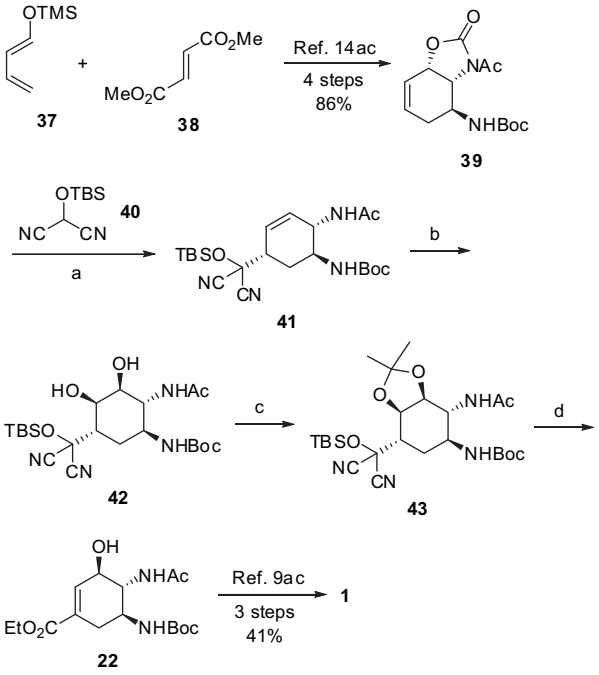


Fig. 3. Substrates tested by Shibasaki's group en route to oseltamivir.

carbamate **29** with 3-pentanol in the presence of Lewis or Brønsted acids ($Sc(OTf)_3$, AgOTf, $Mg(OTf)_2$, TMSOTf, Tf_2NH); (d) generation of a η^3-allyl Pd species from **29** with a Pd catalyst ($Pd(OAc)_2$, $Pd(PPh_3)_4$) and its trapping with 3-pentanol or its Cu or Zn alkoxide; (e) opening of oxazoline **30** with 3-pentanol TMS ether in the presence of a Lewis acid (Et_2AlCl, $BF_3\cdot OEt_2$, $Gd(OTf)_3$, TMSOTf) or Lewis base (CuF, CuI, AgF, *n*-$Bu_4N(Ph_3SiF_2)$); (f) opening of cyclic sulfamidite **31** with Li 3-pentoxide; (g) ether formation from alcohol **32** and a suitable electrophile (3-pentyl trichloroacetimidate, 3-pentylbromide, and the tosylate, nosylate, and 8-quinoline sulfonate derived from 3-pentanol); (h) isomerization of allylic ether **33** at the C3 position, derived from a hemiaminal precursor; and (i) regioselective reductive opening of pentylidene acetals **34**–**36** with a variety of reducing agents (DIBAL-H, Et_3SiH, $BH_3\cdot SMe_2$) in the presence of a Lewis acid (TMSOTf, $BF_3\cdot OEt_2$, $TiCl_4$, $Ti(Oi\text{-}Pr)_2Cl_2$). Unfortunately, none of these approaches provided the desired outcome. This group finally focused on *cis*-diol **42** as a convenient substrate for the preparation of oseltamivir (Scheme 3), since the hydroxy group at C3 has the correct stereochemistry. Therefore, a Mitsunobu reaction would be avoided compared to a previous route that went through epoxide **25** and gave the opposite diastereomer.[9ac] Thus, cyclic carbamate **39**, obtained in four steps from 1-(trimethylsiloxy)-1,3-butadiene (**37**) and dimethyl fumarate (**38**),[9ac] was treated with masked acyl anion equivalent **40**[24] in the presence of $Pd_2(dba)_3\cdot CHCl_3$ (2 mol %) and dppf (8 mol %) to give alkene **41** in 88% yield. This intermediate then underwent dihydroxylation with $NaIO_4$ and catalytic $RuCl_3$ (0.5 mol %) under acidic conditions to afford *cis*-diol **42**, which was protected as the acetonide with 2,2-dimethoxypropane and *p*-$TsOH\cdot H_2O$. The conversion of the TBS-protected hydroxydicyano group to the corresponding ester was carried out with TEA·3HF (0.67 M in EtOH) and DBU in EtOH at rt to give advanced intermediate **22** in 76% yield. Oseltamivir phosphate can be synthesized from **22** in three steps as has been shown in a previous publication from this same group.[9ac]



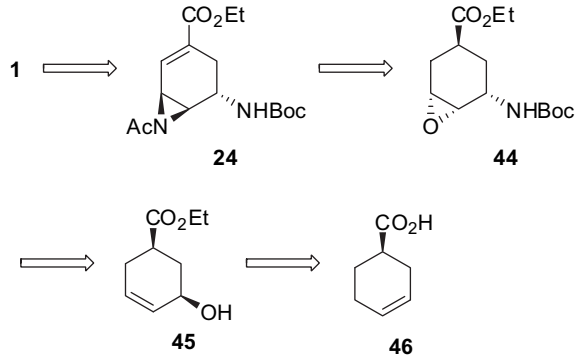
Reagents and conditions: (a) $Pd_2(dba)_3$•$CHCl_3$ (2 mol%), dppf (8 mol%), PhMe, 60 °C, 1 h, 88%. (b) $NaIO_4$, $RuCl_3$ (0.5 mol%), H_2SO_4 (20 mol%), H_2O, 4 °C. (c) 2,2-Dimethoxypropane, *p*-TsOH•H_2O, PhMe, 50 °C, 30 min, 56% (2 steps). (d) TEA•3HF (0.67 M in EtOH), DBU, EtOH, rt, 36 h, 76%.

Scheme 3. Synthesis of oseltamivir by Shibasaki's group.

This synthesis features novel protocols for setting the chirality at C3 via an asymmetric dihydroxylation reaction and introducing the carboxylate through masked acyl anion **40**. As a result, it avoids the inversion step via Mitsunobu reaction at the C3 position but still requires a Curtius rearrangement to install cyclic carbamate **39** from a bis-acyl azide intermediate and an aziridination that resorts to Mitsunobu conditions. In addition, preparative TLC (intermediate **41**) and several chromatographies were employed for the purification of intermediates. This eight-step route to alcohol **22** was demonstrated on mg-scale and the overall yield to oseltamivir phosphate was 13% from diene **37** and dienophile **38**.

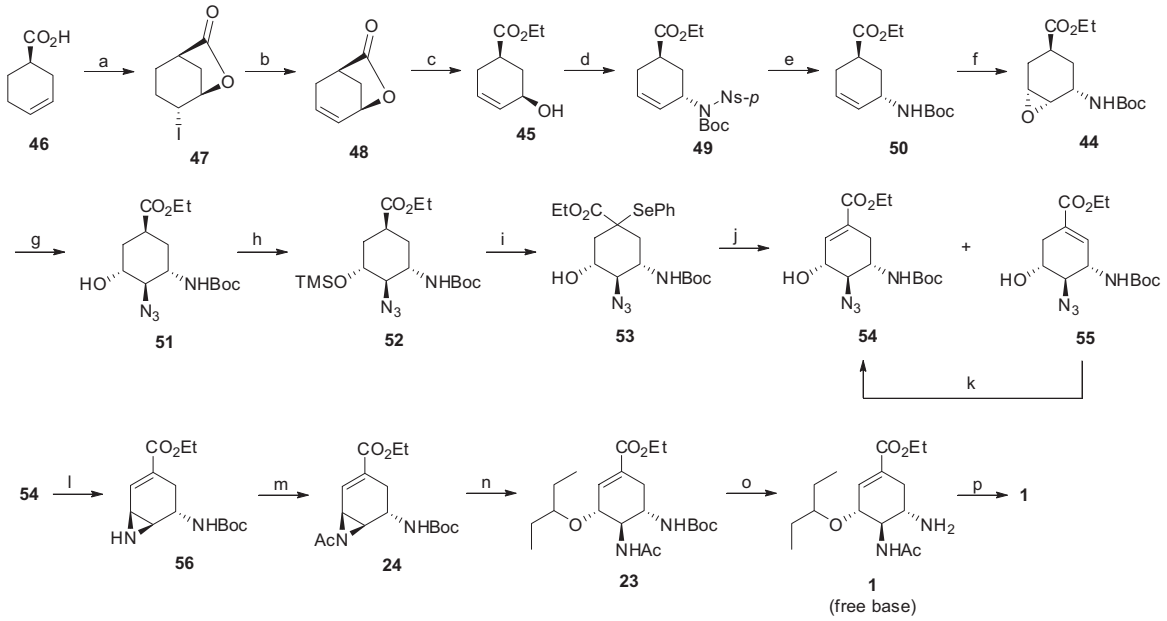
2.4. Enantioselective synthesis of oseltamivir via asymmetric Diels–Alder and carbamate-directed epoxidation reactions by Raghavan's group

Raghavan and co-workers at the Indian Institute of Chemical Technology have recently described an enantioselective synthesis of oseltamivir that relies on three key steps: (a) an asymmetric Diels–Alder reaction to generate cyclohexene carboxylic acid **46**; (b) a Mitsunobu inversion that employs a modified Weinreb reagent; and (c) a carbamate-directed epoxidation.[25] The retrosynthesis is shown in Scheme 4. The ether group is installed via aziridine opening in **24** and this intermediate is derived from epoxide **44**. Allylic alcohol **45** is used as epoxide precursor, which is generated from Diels–Alder adduct **46**.



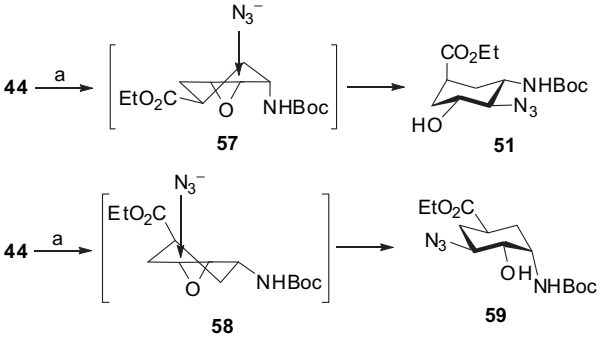
Scheme 4. Retrosynthetic analysis by Raghavan's group.

The synthesis started with acid **46** (Scheme 5), produced in two steps via a previously reported enantioselective Diels–Alder reaction,[26] which underwent iodolactonization to provide intermediate **47** in excellent yield. HI elimination with DBU to give olefin **48**[27] followed by lactone opening with K_2CO_3 in EtOH provided hydroxyester **45** in excellent yield. The amino group at C5 was installed via Mitsunobu reaction between alcohol **45** and Fukuyama-modified Weinreb reagent *N*-Boc-4-nitrobenzenesulfonamide[28] to give sulfonamide **49** in 89% yield. After cleavage of the *p*-nosyl group with 2-mercaptoethanol to provide Boc-protected amine **50**,[29] the double bond was epoxidized with *m*-CPBA to give intermediate **44** as the only product thanks to the directing effect of the carbamate group.[30] The subsequent epoxide-opening step was attempted under several conditions with the goal of optimizing the regioselectivity. Thus, NH_4N_3 in aqueous methanol[31] at 60 °C provided a mixture of **51** and **59** in 2:1 ratio favoring the desired **51** (Scheme 6). The researchers ascribed this result to the presence of a mixture of conformers **57** and **58** under these conditions. However, running the reaction at lower temperature with $TMSN_3$ and $Ti(i\text{-}PrO)_4$ only improved the regioselectivity marginally (3:1).[32] After protecting the hydroxy group as the TMS ether, the introduction of the olefin on the ring was carried out in two steps by first treating ester **52** with LDA followed by quenching the resulting enolate with PhSeBr, prepared in situ from PhSeSePh and Br_2,[33] to give selenide **53** following an acidic, aqueous workup.



Reagents and conditions: (a) I_2, KI, $NaHCO_3$, H_2O, rt, 20 h, 93%. (b) DBU, PhMe, reflux, 6 h, 92%. (c) K_2CO_3, EtOH, rt, 5 h, 90%. (d) BocNHNs-*p*, DEAD, Ph_3P, PhMe, –20 °C, 6 h, 89%. (e) 2-Mercapto ethanol, DBU, acetone, rt, 3 h, 91%. (f) *m*-CPBA, CH_2Cl_2, 0 °C, 6 h, 84%. (g) $TMSN_3$, Ti(O*i*-Pr)$_4$, benzene, 5 to 0 °C, 2 h, 86%, **51**/**59** ratio: 3:1 (Scheme 6). (h) TMSCl, TEA, CH_2Cl_2, 0 °C, 95%. (i) LDA, PhSeSePh, –78 °C, 30 min, 74%. (j) 30% H_2O_2 pyridine, CH_2Cl_2, rt, 30 min, 76%, **54**/**55** ratio: 1:1.5. (k) DBU, PhMe, 36 h, 65%, **54**/**55** ratio: 3:1. (l) Ph_3P, PhMe, reflux, 3 h, 83%. (m) Ac_2O, DMAP, TEA, CH_2Cl_2, 0 °C to rt, 30 min, 87%. (n) 3-Pentanol, BF_3•OEt_2, –20 °C, 30 min, 70%. (o) TFA, CH_2Cl_2, rt, 1 h. (p) H_3PO_4 (1M in EtOH), rt to 50 °C; then 4 °C, 71% (2 steps).

Scheme 5. Synthesis of oseltamivir by Raghavan's group.

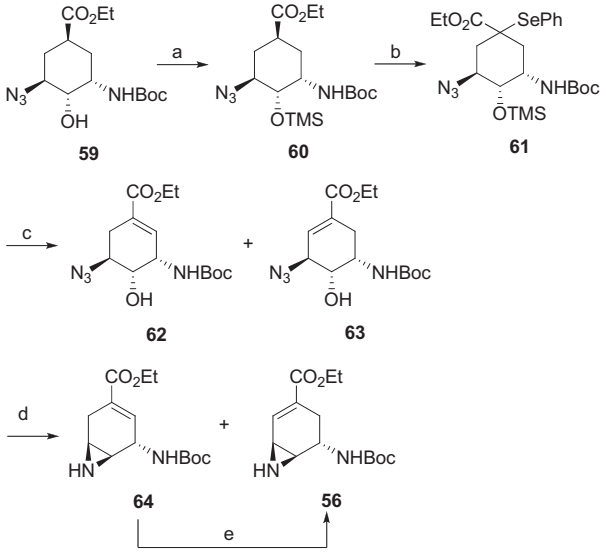


Reagents and conditions: (a) $TMSN_3$, Ti(O*i*-Pr)$_4$, benzene, 5 to 0 °C, 2 h, 86%, **51**/**59** ratio: 3:1.

Scheme 6. Regioselectivity during the opening of epoxide **44** with azide.

Alternatively, double bond formation was attempted by oxidizing alcohol **51** with IBX to the corresponding α,β-unsaturated cyclohexenone but this approach was unsuccessful. Selenide **53** was then oxidized with H_2O_2 and underwent elimination to provide a mixture of α,β-unsaturated esters **54** and **55** in 76% yield and 1:1.5 ratio, respectively, for the two steps. Since the major product from this elimination step was undesired **55** and its separation from regioisomer **54** was difficult, the mixture was treated with DBU in toluene at rt to afford desired **54** in 65% yield (final **54**/**55** ratio after 36 h: 3:1). The next step reduced azide **54** under Staudinger conditions[34] and led to aziridine **56** formation. After acetylating **56** with Ac_2O and TEA with a catalytic amount of DMAP, the acetylaziridine ring was opened up with 3-pentanol in the presence of $BF_3 \cdot OEt_2$ to provide ether **23** in 70% yield. The last steps of the synthesis involved Boc-cleavage with TFA followed by H_3PO_4 salt formation to give **1**.

Due to the low regioselectivity of the epoxide-opening step with azide, this group developed a protocol for the conversion of undesired regioisomer **59** to aziridine **56**, as shown in Scheme 7. Thus, alcohol **59** was protected as the TMS ether and the ester enolate of this intermediate underwent selenylation with PhSeBr to give **61**. After oxidation with H_2O_2, a mixture of inseparable olefins **62** and **63** was obtained in 1:3 ratio, respectively, that was subjected to azide reduction to give a mixture of aziridines **64** and **56**. These two materials could be separated at this stage by chromatography. Alternatively, undesired aziridine **64** was partially converted to desired **56** via treatment with DBU in toluene at rt for 24 h in 58% yield (**64**/**56** ratio 2:3), even though a substantial amount of aromatized product (15%) was also obtained.



Reagents and conditions: (a) TMSCl, TEA, CH_2Cl_2, 0 °C, 94%. (b) LDA, PhSeBr, THF, -78 °C, 58%. (c) H_2O_2, pyridine, CH_2Cl_2, rt, 30 min, 68%. (**67**/**68** ratio: 1:3) (d) PPh_3, PhMe, reflux, 3 h, 71%. (e) DBU, PhMe, rt, 24 h, 58%, **64**/**56** ratio: 2:3.

Scheme 7. Conversion of undesired regioisomer **59** to aziridine **56**.

The synthesis of oseltamivir phosphate was accomplished in 16 steps and 4.3% overall yield. Two additional steps are needed for the preparation of acid **46**, which is a novel approach for introducing the chirality on the molecule. This method suffers from a number of disadvantages since it requires chromatographic purification for every intermediate, employs Mitsunobu and azide chemistry, resorts to highly toxic selenium chemistry for olefin generation, and employs CH_2Cl_2 (several steps) and benzene as solvents. In addition, two of the steps (epoxide opening and double bond introduction) display low regioselectivity. Most of the steps were demonstrated on mg-scale.

2.5. Synthesis of oseltamivir from (−)-shikimic acid via an *O*-trimesylate by F. Hoffmann-La Roche Ltd.

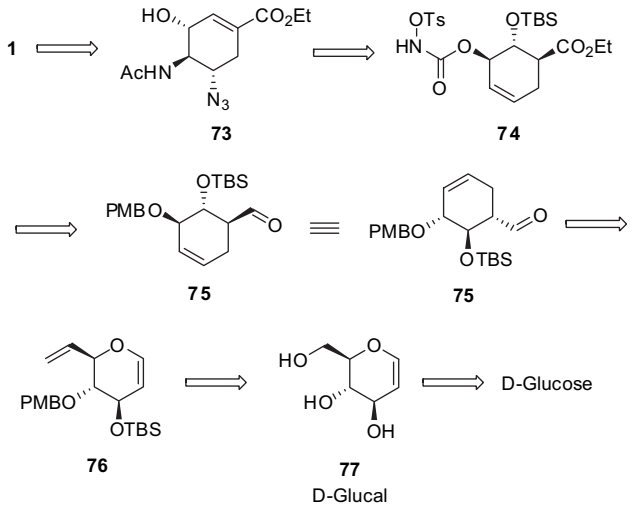
Karpf and Trussardi at F. Hoffmann-La Roche Ltd. in Switzerland have reported an efficient, nine-step route to oseltamivir that starts from now readily available (−)-shikimic acid (**65**, Scheme 8).[35,36] This acid was esterified with thionyl chloride in ethanol at reflux and the resulting ester **66**[9c] was treated with 3 equiv of MsCl to afford trimesylate **67**. Without purification, **67** underwent reaction with NaN_3 in DMSO at rt to regio- and stereoselectively displace the mesylate at C3 position. Crude azide **68** was then treated with triethyl phosphite in toluene at reflux to generate aziridine **69**, an intermediate also found in a previous synthesis by this same group.[9e] The aziridine ring was regioselectively opened at the C3 position with 3-pentanol and a stoichiometric amount of $BF_3 \cdot OEt_2$[9b] to provide ether **70** in 66% yield after crystallization from MTBE. The overall yield up to this stage of the synthesis from (−)-shikimic acid was an excellent 45% yield and none of the previous intermediates required any type of purification beyond standard reaction workups. The treatment of **70** with sulfuric acid in EtOH cleaved the diethylphosphoryl group to give an amine that, without isolation, was acetylated with Ac_2O to afford acetamide **71**. Mesylate displacement with NaN_3 followed by azide reduction with *n*-Bu_3P and salt formation completed the synthesis of oseltamivir phosphate in nine steps, requiring only three workups, and in 20% overall yield (unoptimized).

One of the potential issues with this route is the tendency of some of the intermediates to aromatize. Thus, during the synthesis of trimesylate **67**, aromatization was suppressed by adding the TEA to a solution of triol **66** and MsCl in EtOAc at 0–5 °C. The researchers also mentioned that azide was the only nucleophile that allowed for the introduction of the amino group at the C5 position. More basic nitrogen sources such as allyl amine or tritylamine led to aromatization. Finally, the formation of aziridine **69** required the use of triethyl phosphite as reducing agent under anhydrous conditions. Alternative reagents, such as triaryl and trialkylphosphines via Staudinger iminophosphoranes and subsequent hydrolysis caused aromatization and decomposition.

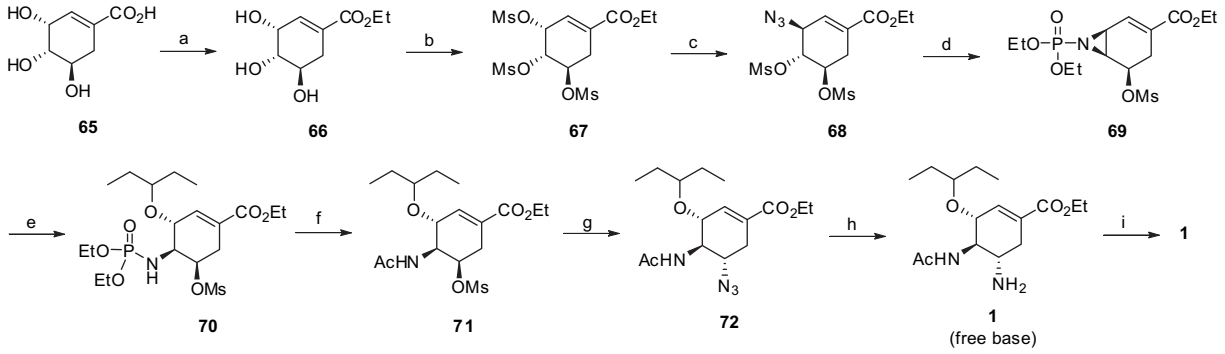
Even though this route employs NaN_3 in two instances to introduce the amino functionalities on the molecule,[37] it has great potential to become an alternative to the current commercial route to oseltamivir[9h] due to its operational simplicity, inexpensive reagents, and lack of protecting group chemistry. It elegantly takes advantage of the chirality present in (−)-shikimic acid to introduce the groups at C3, C4, and C5 with the desired stereochemistry.

2.6. Synthesis of oseltamivir from D-glucal by Chen's and Liu's groups

Chen, Liu, and coworkers at Nanyang Technological University in Singapore have reported a synthesis of oseltamivir from commercially available D-glucal (**77**),[38] which can also be readily prepared from D-glucose. The retrosynthetic analysis is shown in Scheme 9. Oseltamivir is derived from intermediate **73**, which in turn comes from an aziridine-opening step. *N*-Tosyl carbamate precursor **74** is generated form aldehyde **75** and this material can be produced from glucal derivative **76** via a 3,3-sigmatropic rearrangement. Intermediate **76** comes from D-glucal (**77**), which in turn can be readily synthesized from D-glucose.



Scheme 9. Retrosynthetic analysis by Chen's and Liu's groups.

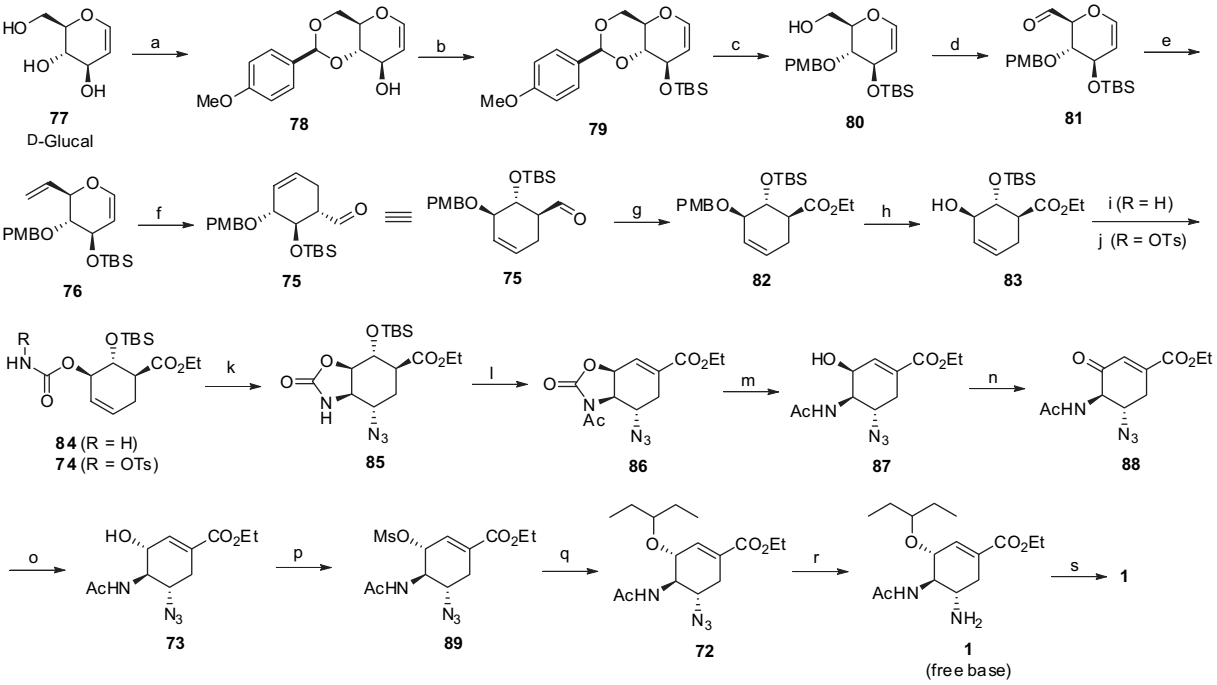


Reagents and conditions: (a) Cl_2SO, EtOH, reflux, 2 h. (b) $MeSO_2Cl$, TEA, EtOAc, 0-5 °C to rt, 20 h. (c) NaN_3, DMSO, rt, 3 h. (d) $(EtO)_3P$, PhMe, reflux, 5 h. (e) 3-Pentanol, $BF_3 \cdot OEt_2$, rt, 16 h, 45% from **65**. (f) (i) H_2SO_4, EtOH, reflux, 16 h; (ii) Ac_2O, EtOAc, rt, 1 h, 73% (2 steps). (g) NaN_3, DMSO, EtOH, 90 °C, 20 h, 66%. (h) *n*-Bu_3P, EtOH, rt, 5 h. (i) H_3PO_4, acetone, 92% (2 steps).

Scheme 8. Synthesis of oseltamivir by F. Hoffmann-La Roche.

The synthesis started with readily available D-glucal (**77**, Scheme 10), which was converted to 4,6-benzylidene acetal **78** with *p*-anisaldehyde diethyl acetal and catalytic PPTS followed by protection of the remaining hydroxy group as the corresponding *tert*-butyldimethylsilyl ether. Reductive cleavage of acetal **79** with DIBAL-H afforded alcohol **80** (65% yield for the three steps combined), which was oxidized to aldehyde **81** with Dess–Martin periodinane (Swern oxidation could also be used as an alternative, even though the yield was not provided). This aldehyde underwent Wittig olefination with methyltriphenylphosphonium bromide to provide alkene **76**. The next step involved a key Claisen rearrangement to form the cyclohexene core. Thus, alkene **76** was heated in diphenyl ether at 210 °C in a sealed tube to provide intermediate **75** in 88% yield. No information was provided on the diastereoselectivity of this transformation, but the stereochemical outcome was explained by resorting to a boat-like transition state as has been previously reported.[39] After aldehyde oxidation with $NaClO_2/NaH_2PO_4$, the resulting acid was esterified with EtI to afford ester **82** in 87% yield for the two steps combined. Alternatively, oxone or I_2/KOH provided lower yields (30%) of the acid. PMB-protecting group removal with DDQ gave alcohol **83** and set the stage for the introduction of the two amine functionalities using the hydroxy group as a handle to control the stereochemistry at the C4 and C5 positions via intra-molecular delivery. Thus, carbamate **84** was prepared by treating alcohol **83** with $Cl_3CCONCO$,[40] but this intermediate did not lead to aziridine formation (not shown) after testing a number of catalysts ($[Cu(MeCN)_4PF_6]$, $(CuOTf)_2\cdot$toluene, $Rh_2(OAc)_4$, and $[Rh_2(CF_3CONH)_4]$). On the other hand, more electrophilic *O*-tosyl carbamate **74**, prepared through the reaction of alcohol **83** with CDI/NH_2OH followed by TsCl/TEA,[41] did provide the desired aziridine intermediate with a catalytic amount of $(CuOTf)_2\cdot$toluene in MeCN, whereas $Rh_2(OAc)_4$ in CH_2Cl_2 at rt led to lower yield (63%). The introduction of the second nitrogen functionality was accomplished via stereo- and regioselective aziridine-opening with $TMSN_3$ and a stoichiometric amount of TBAF in THF to generate azidooxazolidinone **85** in 82% yield. Other nitrogen sources, such as *p*-methoxybenzylamine and allyl amine gave diastereomeric mixtures. Since the direct treatment of **85** with DBU did not produce the desired α,β-unsaturated ester and led to racemization at the C1 position and aromatization at higher temperatures, the researchers opted for acetylating the carbamate nitrogen first with AcCl/NaH followed by reaction with Cs_2CO_3 to provide **87** in 67% yield (two steps). The configuration at the C3 position was inverted by oxidizing alcohol **87** with Dess–Martin periodinane and subsequent stereoselective ketone **88** reduction with bulky LiAlH(*t*-BuO)$_3$ to give alcohol **73** in 70% yield. The synthesis continued with the mesylation of **73** in the presence of TEA to give an aziridine intermediate (not shown) that was opened up with 3-pentanol and $BF_3\cdot Et_2O$ to deliver ether **72**. The synthesis of oseltamivir phosphate was completed by reducing the azido group with Ph_3P followed by salt formation.

The overall yield for this approach was 2.6% after 22 linear steps and provided mg-quantities of oseltamivir phosphate. Extensive chromatography (16 instances) was required for intermediate purification as well as a sealed-tube step at high temperature. In addition, protecting group chemistry as well as oxidation–reduction



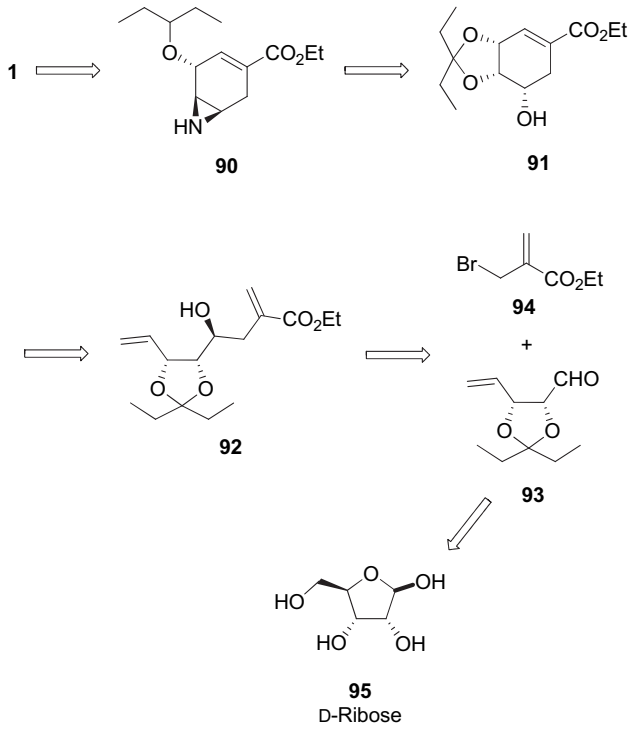
Reagents and conditions: (a) *p*-Anisaldehyde diethyl acetal, PPTS, DMF, 25 °C, 2 h. (b) TBSCl, imidazole, DMAP, DMF, 25 °C, 3 h. (c) DIBAL-H, CH_2Cl_2, −15 to 0 °C, 2 h, 65% (3 steps). (d) Dess-Martin periodinane, CH_2Cl_2, 25 °C. (e) Methyltriphenylphosphonium bromide, *n*-BuLi, THF, −78 to 25 °C, 1 h, 67% (2 steps). (f) Diphenyl ether, 210 °C, 2 h, 88%. (g) (i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 25 °C, 2 h; (ii) EtI, K_2CO_3, DMF, 25 °C, 3 h, 87% (2 steps). (h) DDQ, CH_2Cl_2/H_2O, 92%. (i) $Cl_3CCONCO$, K_2CO_3, CH_2Cl_2/MeOH, 87%. (j) (i) CDI, CH_2Cl_2, 25 °C, 2 h; $NH_2OH\cdot HCl$, pyridine, 25 °C, 3 h; (ii) TsCl, TEA, Et_2O, 25 °C, 12 h, 77% (2 steps). (k) (i) **74**, $(CuOTf)_2\cdot$toluene, K_2CO_3, MeCN, 25 °C, 12 h; (ii) $TMSN_3$, TBAF, THF, 0–25 °C, 3 h, 82%. (l) (i) AcCl, NaH, THF, 0–25 °C, 2 h; (ii) DBU, MeCN, 25 °C, 24 h, 67% (2 steps). (m) Cs_2CO_3 (0.1 equiv), EtOH, 25 °C, 3 h, 72%. (n) Dess-Martin periodinane, CH_2Cl_2, 25 °C, 2 h. (o) LiAlH(*t*-BuO)$_3$, THF, −20 to 25 °C, 3 h, 70% (2 steps). (p) MsCl, TEA, CH_2Cl_2, 0–25 °C, 3 h. (q) $BF_3\cdot Et_2O$, 4 Å mol.sieves, 3-pentanol, −20 °C, 2 h, 52% (2 steps). (r) Ph_3P, THF/H_2O (1:1), reflux, 3 h, 90%. (s) 85% H_3PO_4, EtOH, 55 °C, 30 min, 85%.

Scheme 10. Synthesis of oseltamivir by Chen's and Liu's groups.

steps (stereochemistry inversion at C3) were needed, which makes this route impractical at this stage of development for large-scale manufacturing despite of the fact that it starts from commercially available D-glucal.

2.7. Formal synthesis of oseltamivir from D-ribose via metal-mediated domino reaction and ring-closing metathesis by Chen's and Chai's groups

Chen, Chai, and coworkers at Shionogi & Co., Ltd. in Japan and the Institute of Chemical and Engineering Sciences in Singapore have described a formal synthesis of oseltamivir that starts from readily available and inexpensive D-ribose (**95**).[42] The retrosynthetic analysis is shown in Scheme 11. Oseltamivir is derived from aziridine **90**, which in turn comes from alcohol **91**. This intermediate is the result of a ring-closing metathesis (RCM) reaction[43] on diene **92**, which can be generated from aldehyde **93** via a known *anti*-selective Reformatsky-type allylation reaction with bromoester **94**. Aldehyde **93** is obtained from readily available D-ribose (**95**).



Scheme 11. Retrosynthetic analysis by Chen's and Chai's groups.

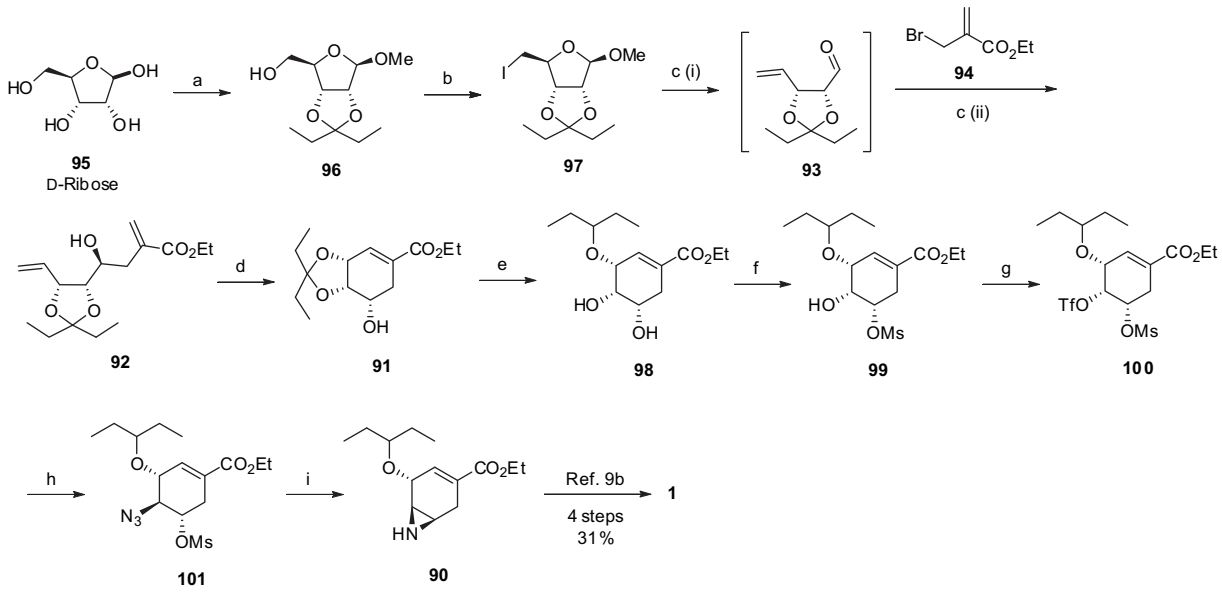
The synthesis started with the protection of the *syn*-diol moiety of D-ribose with 3-pentanone as ketal **96** (Scheme 12), which also served to introduce the 3-pentyl functionality on the molecule with the desired stereochemistry at C3. Trimethyl *ortho*formate was required as dehydrating agent to obtain high yield.[44] The hydroxy group at the 6-position was converted to the corresponding iodide with I_2 and Ph_3P[45] and this intermediate underwent a Bernet–Vasella reaction with Zn in a THF/H_2O mixture (2:1) to give aldehyde **93**,[46] which, without isolation, was subjected to an *anti*-selective Reformatsky-type transformation with ethyl 2-(bromomethyl)acrylate (**94**)[47] to provide alcohol **92** in 5.2:1 dr. The cyclohexyl ring was assembled via a ring-closing metathesis reaction of **92** in the presence of Grubbs–Hoveyda catalyst **102** (2 mol %, Fig. 4) in DCE at reflux to generate 5-*epi*-shikimic acid derivative **91** in excellent yield. The researchers tried the conversion of the 3-pentyledene ketal to the 3-pentyl ether at C3 next by treating **91** with MsCl and pyridine to generate the corresponding mesylate followed by reductive ketal cleavage with $TiCl_4$/Et_3SiH in CH_2Cl_2 at −34 °C, as has been shown for the epimer at the C5 position.[9c] Unfortunately, this protocol showed low selectivity and provided a 1:3 mixture of 3-pentylethers at the C3 and C4 positions, respectively. Other Lewis acids, such as BF_3, $AlCl_3$, and $ZnCl_2$ provided similar results. Based on conformational analysis studies, it was proposed that the possible cause is the fact that the mesylate derivative of alcohol **91** is much more congested than the epimer at the C5 position and this makes the coordination of the Lewis acid on the ketal and mesylate oxygens difficult. On the other hand, unprotected alcohol **91** was successfully converted to ether **98** with $AlCl_3$ and Et_3SiH as reductant in 67% yield and 6:1 regioselectivity.[48] Selective mesylation of the less hindered hydroxy group in diol **98** with 1.05 equiv of MsCl to give **99** followed by the reaction of the remaining hydroxy group with Tf_2O afforded triflate **100**. The exclusive displacement of the triflate group with NaN_3 in an acetone/H_2O mixture (9:1) provided azide **101** in 86% yield from mesylate **99**. The high regioselectivity of this transformation was explained due to the axial orientation of the triflate group that favors its displacement by the azide nucleophile, compared to the mesylate group, which is in an equatorial position (Fig. 5).[9v] The reduction of the azido group via Staudinger reaction[49] and aziridine formation in the presence of TEA provided known intermediate **90**, which can be converted to oseltamivir phosphate in four steps as has been previously shown.[9b]

This route consists of nine steps to aziridine **90** with a 27% overall yield (9% overall yield when the last three steps to oseltamivir phosphate are included) and was demonstrated on mg-scale. Advantages of this route are the use of inexpensive D-ribose as starting material and the lack of protecting group chemistry. Some of the caveats are the need for azide chemistry, the use of highly toxic halogenated solvents, and the need for chromatographic purification for all the intermediates.

2.8. Synthesis of oseltamivir from D-ribose via metal-mediated domino reaction and ring-closing metathesis by Kongkathip's group

Kongkathip and co-workers at Kasetsart University in Thailand have described a preparation of oseltamivir that, as for Chen's and Chai's synthesis,[42] features a metal-mediated elimination–allylation of a D-ribose derivative to form a diene that then undergoes ring-closing metathesis (RCM) to generate the cyclohexene ring.[50] The retrosynthesis, shown in Scheme 13, proceeds through cyclohexene **91**, which is prepared from diene **92** via an RCM reaction. This material is in turn derived from D-ribose (**95**) via iodide **97**.

As, for Chen's and Chai's route,[42] the first four steps lead to alcohol **91** (Scheme 14). Thus, D-ribose (**95**) was converted to iodide **97** by first protecting the *cis*-diol as the ketal with 3-pentanone followed by conversion of the C5 hydroxy group to the corresponding iodide with I_2/Ph_3P.[51] The next step, a Bernet–Vasella domino reaction[47] with ethyl 2-(bromomethyl)acrylate (**94**) in the presence of Zn to prepare RCM precursor diene **92**, was thoroughly investigated. Zn dust in combination with sonication provided the necessary activation for Zn insertion into the iodide leading to elimination to provide a transient γ,δ-unsaturated aldehyde **93** (Scheme 12). Subsequent Barbier-type addition of the acrylate to the carbonyl group gave homoallylic alcohol **92** in 70% yield. These conditions afforded reproducible results and the addition of water resulted in a faster rate of reaction. As a byproduct, lactone **111** (Fig. 6) was obtained in 22% yield. Indium was also tested but a slower reaction rate was observed compared to Zn. Furthermore, byproduct **112** was generated in significant yield, but the addition of HOAc (0.01 equiv) and sonication kept it at low level (7%) and, at



Reagents and conditions: (a) 3-Pentanone, HCl (1 M in MeOH), $HC(OMe)_3$, reflux, 6 h, 89%. (b) I_2, Ph_3P, PhMe/MeCN (1:1), reflux, 5 min, 90%. (c) (i) Zn, THF/H_2O (2:1), reflux, 3 h; (ii) reflux, 4 h, 78%, dr = 5.2:1. (d) **102** (2 mol%), DCE, reflux, 2 h, 99%. (e) (i) $AlCl_3$,$CHCl_3$, sonication, 0 °C; (ii) Et_3SiH, -50 °C, 4 h; then 0 °C, 16 h, 67%. (f) MsCl, TEA, CH_2Cl_2, –20 °C, 40 min; then rt, 1 h, 92%. (g) Tf_2O, py, CH_2Cl_2, -10 °C, 30 min; then 0 °C, 20 min. (h) NaN_3, acetone/H_2O (9:1), rt, 4 h, 86% (2 steps). (i) Ph_3P, TEA, THF, rt, 17 h, 84%.

Scheme 12. Synthesis of oseltamivir by Chen's and Chai's groups.

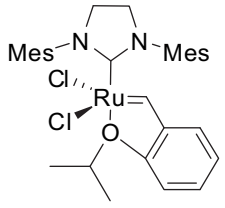


Fig. 4. Grubbs–Hoveyda ring-closing metathesis catalyst.

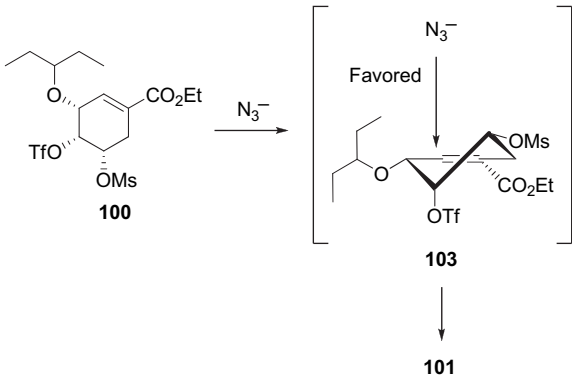
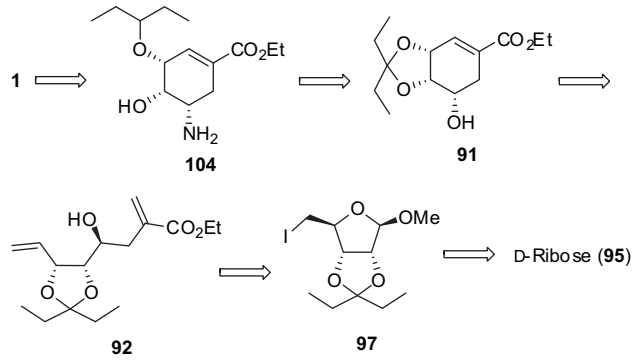


Fig. 5. Rationale for the selective displacement of the triflate group over the mesylate group in **100** by NaN_3 to afford **101**.

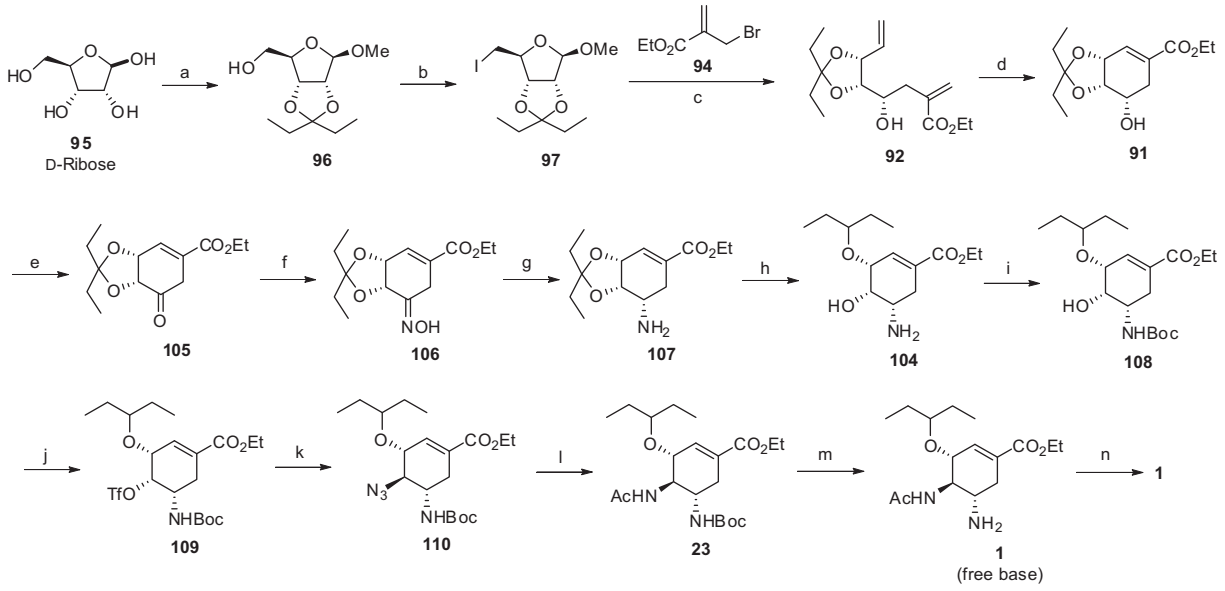


Scheme 13. Retrosynthesis of oseltamivir by Kongkathip's group.

the same time, improved the yield of **92**. The key RCM step to produce the cyclohexene ring was carried out with second-generation Grubbs' catalyst (**113**, 10 mol %; Fig. 7) in CH_2Cl_2 at reflux to give **91** as the only stereoisomer.

From here on, the two routes diverge. Thus, the introduction of the first amino group on the ring was accomplished via oxidation of alcohol **91** with TEMPO and trichloroisocyanuric acid (TCCA) to give the corresponding crude ketone **105**, which underwent reaction with $NH_2OH{\cdot}HCl$ to provide hydroxylamine **106** in 71% yield (two steps). Reduction of this substrate with a large excess of $NaBH_4$ (10 equiv) and stoichiometric MoO_3 gave the desired amine **107** in excellent yield. The 3-pentyl ether moiety was then generated via reductive ketal opening with Et_3SiH and $TiCl_4$ in CH_2Cl_2 at cryogenic temperature[9c] to give aminoalcohol **104**, which was protected as the *N*-Boc derivative for easier purification by chromatography. The introduction of the second amine group at C4 was accomplished by converting alcohol **108** to triflate **109** with Tf_2O/py followed by S_N2 displacement with NaN_3 in a 9:1 acetone/water mixture to generate azide **110**. The reduction of the azido group with thioacetic acid and 2,6-lutidine in $CHCl_3$ at reflux[52] followed by Boc-cleavage with TFA and phosphate salt formation completed the synthesis of oseltamivir phosphate.

This synthesis converts inexpensive and readily available D-ribose into oseltamivir phosphate in 14 steps and 5% overall yield and was demonstrated on mg-scale. It takes advantage of some technologies that have not been widely explored in previous syntheses



Reagents and conditions: (a) 3-Pentanone, $HC(OCH_3)_3$, MeOH saturated with HCl, rt, overnight, 98%. (b) I_2, Ph_3P, imidazole, PhMe/MeCN (5:1), reflux, 3 h, 79%. (c) Zn (powder), THF/H_2O (2:1), sonication, 40 °C, 3 h, 70%. (d) **113** (10 mol%), CH_2Cl_2, reflux, 4 h, 60%. (e) TEMPO, TCCA, CH_2Cl_2, 0 °C to rt, 45 min. (f) NH_2OH•HCl, pyridine, EtOH, rt, 2 h, 71% (2 steps). (g) $NaBH_4$, MoO_3, MeOH, rt, 30 min, 92%. (h) Et_3SiH, $TiCl_4$, CH_2Cl_2, −78 to −10 °C, 7 h. (i) Boc_2O, MeOH, rt, 3 h, 66% (2 steps). (j) Tf_2O, pyridine, CH_2Cl_2, -10 °C to 0 °C, 30 min. (k) NaN_3, acetone/H_2O (9:1), rt, 15 h. (l) AcSH, 2,6-lutidine, $CHCl_3$, reflux, 5 h, 44% (3 steps). (m) TFA, CH_2Cl_2, 0 °C to rt, 1 h. (n) H_3PO_4 (1 M in EtOH), EtOH, 55 °C to 0 °C, 75% (2 steps).

Scheme 14. Synthesis of oseltamivir by Kongkathip's group.

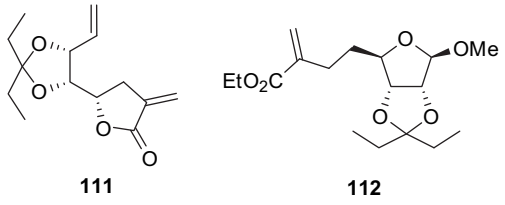


Fig. 6. Byproducts from Zn- and In-mediated elimination–allylation of **97**.

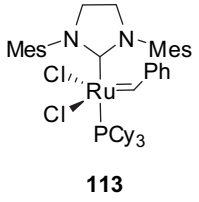
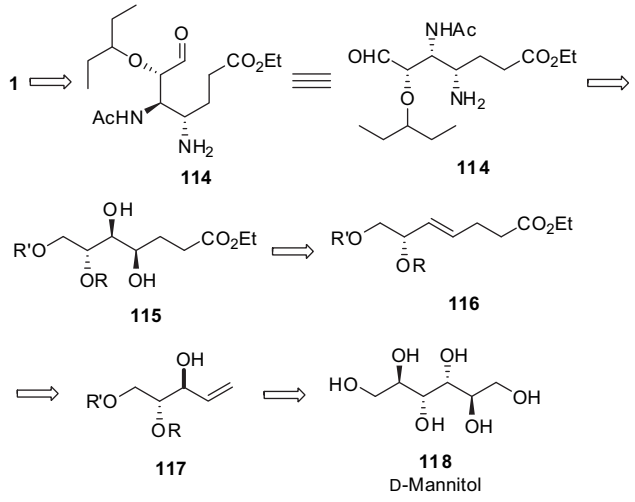


Fig. 7. Second-generation Grubbs' catalyst for the generation of cyclohexene **91**.

of the drug, such as the Zn-catalyzed Bernet–Vasella olefination followed by the stereoselective Barbier-type addition of ethyl 2-(bromomethyl)acrylate to an aldehyde and the RCM reaction to assemble the cyclohexene ring as in Yao's synthesis of oseltamivir.[9k] The use of thioacetic acid as an alternative to the usual Staudinger protocol for azide reduction also represents a different approach for this step. Some of the disadvantages are the use of azide and hydroxylamine chemistry, the heavy use of halogenated solvents (six steps), and the need for chromatographic purification of most intermediates.

2.9. Synthesis of oseltamivir from D-mannitol by Ko's group

D-Mannitol has been employed by Ko and co-workers at Ewha Womans University in Korea for their synthesis of oseltamivir.[53] In their strategy, they prepared a highly-functionalized acyclic intermediate that then underwent cyclization to generate the cyclohexane core with the correct stereochemistry at C3 and C4. Further manipulation installed the double bond on the ring and inverted the stereochemistry at the C5 position. The retrosynthesis path is shown in Scheme 15. The cyclohexane moiety comes from the intra-molecular condensation of aldehyde-ester **114**, whose two amino groups are introduced via S_N2 substitutions on a 1,2-diol, such as **115**. This material can be derived from an alkene precursor **116** via asymmetric dihydroxylation. Alkene **116** can in turn come from a Claisen rearrangement of an allylic alcohol such as **117**, which is derived from D-mannitol (**118**).

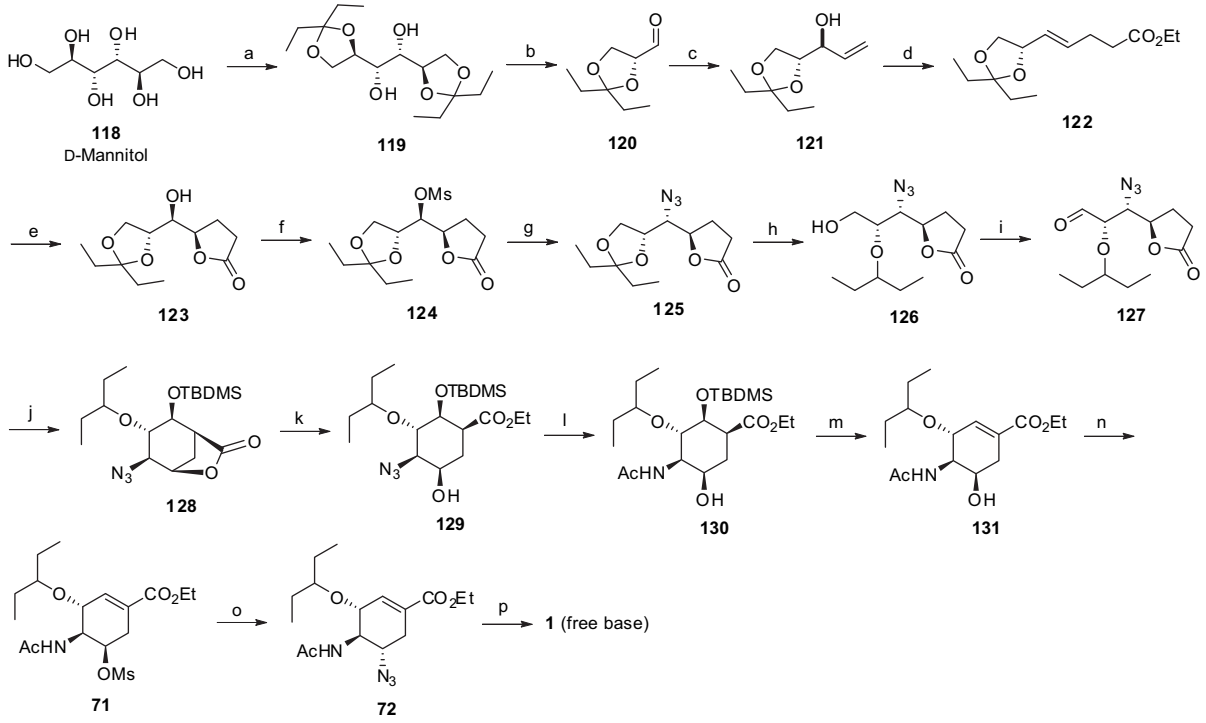


Scheme 15. Retrosynthetic analysis by Ko's group.

The synthesis started with readily available D-mannitol (**118**, Scheme 16), which was converted to allylic alcohol **121** in a three-step sequence that involved ketal formation with 3,3-

dimethoxypentane followed by oxidative cleavage with KIO_4[54] and treatment of the resulting aldehyde **120** with vinylmagnesium bromide (44% yield for the three steps combined). Alcohol **121**, obtained as a 1.5:1 mixture of diastereomers, underwent Claisen rearrangement with triethyl orthoacetate to provide γ,δ-unsaturated ester **122** in 85% yield.[55] No information was provided on the diastereoselectivity of this transformation. Up to this point, the synthesis is identical to the one previously reported by Mandai.[9z] The olefin was dihydroxylated under Sharpless conditions with AD-mix-β to provide lactone **123** as the only product.[56] The perfect diastereoselectivity was ascribed to the fact that the alkene and AD-mix-β are a matched pair in this doubly stereoselective asymmetric reaction.[57] Alternatively, the use of OsO_4 in this dihydroxylation step afforded a 3:1 mixture of diastereomers favoring the desired one. The regioselectivity in lactone formation allowed for the differentiation of the two hydroxy groups and served as a protecting group for the hydroxy group that eventually ended up at C5. Alcohol **123** could then be converted to azide **125** after mesylation and displacement with NaN_3 at high temperature. The regioselective reductive opening of the ketal was then investigated. It was found that the reaction was completely regioselective to give desired **126** with $BH_3 \cdot SMe_2$ and TMSOTf in THF at −40 °C, but did not go to completion after 24 h. Reverse regiochemistry was obtained in CH_2Cl_2 but, at the same time, a faster reaction rate was observed. Based on this information, a mixed solvent system was chosen (CH_2Cl_2/THF 3.8:1), which provided alcohol **126** in 94% yield with less than 1% of the undesired regioisomer. Subsequent Swern oxidation of **126** ($(COCl)_2$, DMSO, TEA, −68 °C) provided cyclization precursor **127** in excellent yield. The cyclization step was attempted based on some literature reports that describe the intra-molecular aldol reaction between lactones as nucleophiles and aldehydes as electrophiles.[58] Thus, when substrate **127** was treated with TBDMSOTf and DIPEA in CH_2Cl_2, bicyclic lactone **128** was obtained in 76% yield as the only diastereomer, whose structure was confirmed by X-ray crystallography. The last steps of the synthesis involved solvolytic lactone opening to form hydroxyester **129**,[59] azide reduction via catalytic hydrogenation followed by acetylation of the resulting amine to give **130**, elimination of TBDMSiOH to generate the double bond in the ring (intermediate **131**), the introduction of the second nitrogen at C5 with inversion of configuration via mesylate **71** using azide chemistry to afford intermediate **72**, and azide reduction to provide oseltamivir as the free base.

This approach to oseltamivir (free base) was accomplished after 16 steps in 7% overall yield and some of the steps were demonstrated on multi-gram scale. It features an asymmetric dihydroxylation reaction to introduce the chirality at C4 and C5. The major advantage is the use of inexpensive D-mannitol as starting material. On the other hand, the long synthetic route, extensive use of chromatographic purification (14 instances), and the need for azide chemistry at high temperature (two instances) makes it impractical for large-scale work at this stage of development.



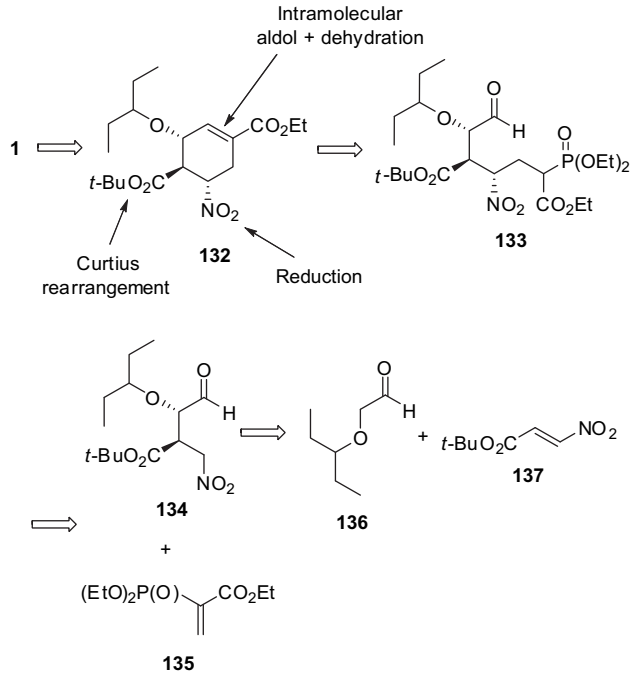
Reagents and conditions: (a) 3,3-Dimethoxypentane, CSA, DMF, 40 °C, 4 h. (b) KIO_4, $KHCO_3$, H_2O/THF (2.5:1), rt, 4 h. (c) Vinylmagnesium bromide (1 M in THF), 0 °C, 5 h, 43% (3 steps). (d) $MeC(OEt)_3$, propionic acid, 132 °C, 25 h, 85%. (e) AD-mix-β, *t*-BuOH/H_2O (1:1), $MeSO_2NH_2$, 0 °C, 6 h, 93%. (f) MsCl, TEA, CH_2Cl_2, 0 °C, 4 h, 100%. (g) NaN_3, DMF, 120 °C, 49 h, 73%. (h) $BH_3 \cdot Me_2S$ (2 M in THF), TMSOTf, CH_2Cl_2, −50 °C, 30 min; then −20 to −30 °C, 22 h, 94%. (i) $(COCl)_2$, DMSO, CH_2Cl_2, TEA, −68 °C, 1 h, 92%. (j) TBDMSOTf, DIPEA, CH_2Cl_2, 0 °C, 25 min; then rt, 2 h, 76%. (k) LiBr, DBU, EtOH, 0 °C, 1 h, 96%. (l) H_2 (balloon), 10% Pd/C, Ac_2O, TEA, EtOAc, rt, 22 h, 96%. (m) DBU, $LiClO_4$, EtOH, reflux, 2.5 h, 62%. (n) MsCl, TEA, CH_2Cl_2, 0 °C, 1.5 h, 97%. (o) LiN_3, DMF, 90 °C, 7 h, 78%. (p) Ph_3P, THF/H_2O (5:1), 50 °C, 19 h, 98%.

Scheme 16. Synthesis of oseltamivir by Ko's group.

2.10. Synthesis of oseltamivir via two 'one-pot' sequences by Hayashi's group

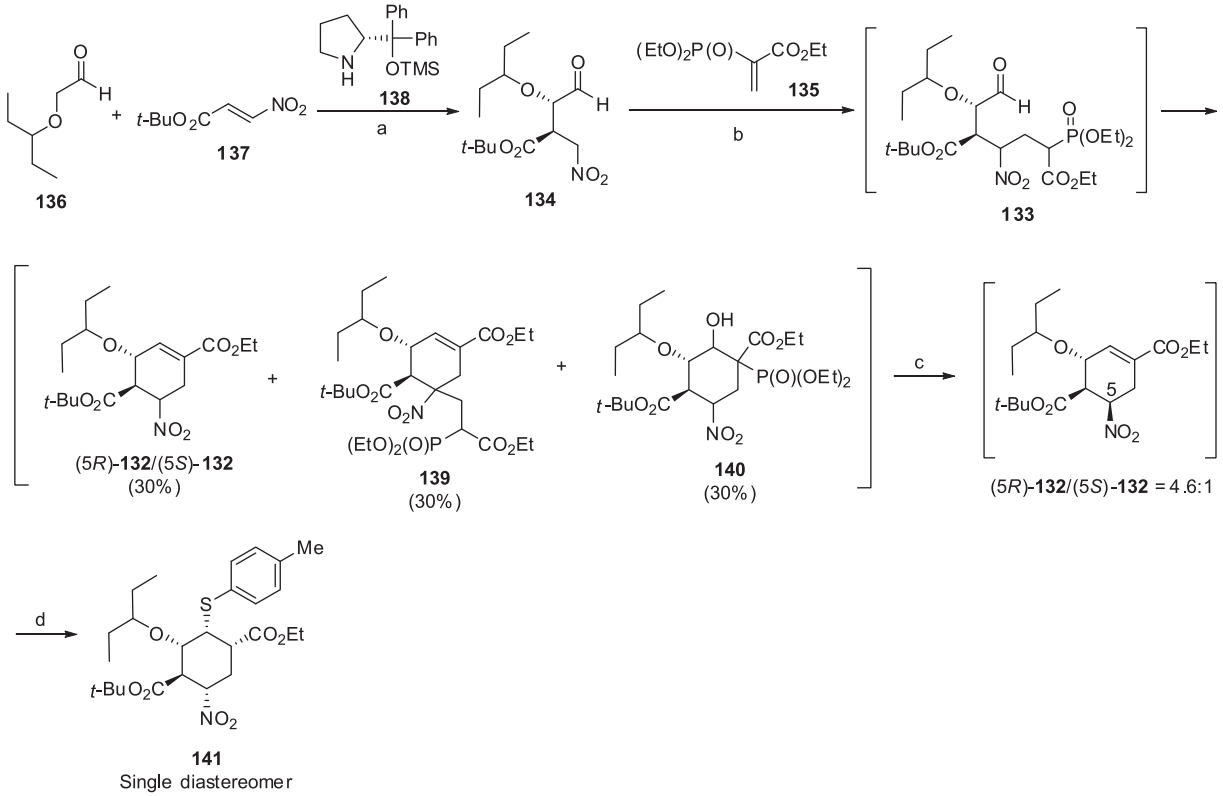
Hayashi and co-workers at Tokyo University of Science and the National Institute of Advanced Industrial Science and Technology in Japan have published their efforts to design a highly efficient synthesis of oseltamivir in two 'one-pot' sequences.[60] This disclosure provides a very detailed account of the process optimization that has been carried out by this group on a previous synthesis that employed three 'one-pot' sequences to give access to oseltamivir.[9y] Hayashi established a very specific set of objectives with the goal of developing a synthetic route that allowed for the preparation of large amounts of drug in a short period of time and at low cost. These objectives were as follows: (a) no more than 10 synthetic steps and as few operations, such as purifications and isolations, as possible; (b) overall yield ≥50%; (c) use of inexpensive reagents exclusively; (d) minimize the use of chromatographic purifications; and (e) avoid the use of metal-containing reagents. By 'one-pot' operation the authors meant several chemical steps that can be performed without workup or any type of purification between steps (telescoping). A simple solvent evaporation is enough to move forward to the next step.

The retrosynthetic analysis is shown in Scheme 17. Oseltamivir can be derived from nitro compound **132**, whose cyclohexene ring comes from an intra-molecular Horner–Wadsworth–Emmons (H–W–E) reaction of acyclic intermediate **133**. This material is assembled via an asymmetric Michael reaction between nitroaldehyde **134** and vinylphosphonate **135**. Nitroaldehyde **134** is generated from the asymmetric Michael addition of aldehyde **136** to nitroolefin **137**.



Scheme 17. Retrosynthetic analysis by Hayashi's group.

The first 'one-pot' sequence is shown in Scheme 18. The asymmetric Michael addition of aldehyde **136** to nitroolefin **137** was implemented in the presence of proline-derived catalyst **138** (1 mol %) in toluene at rt for 6 h to give Michael adduct **134** in 7.8:1



Reagents and conditions: (a) **138** (1 mol%), $ClCH_2CO_2H$ (20 mol%), PhMe, rt, 6 h, dr = 7.8:1, ee = 97%. (b) Cs_2CO_3, PhMe, 0 °C to rt, 4 h. (c) EtOH, rt, 10 min. (d) *p*-MeC_6H_4SH, Cs_2CO_3, EtOH, -15 °C, 36 h, 74% (4 steps).

Scheme 18. First 'one-pot' sequence by Hayashi's group.

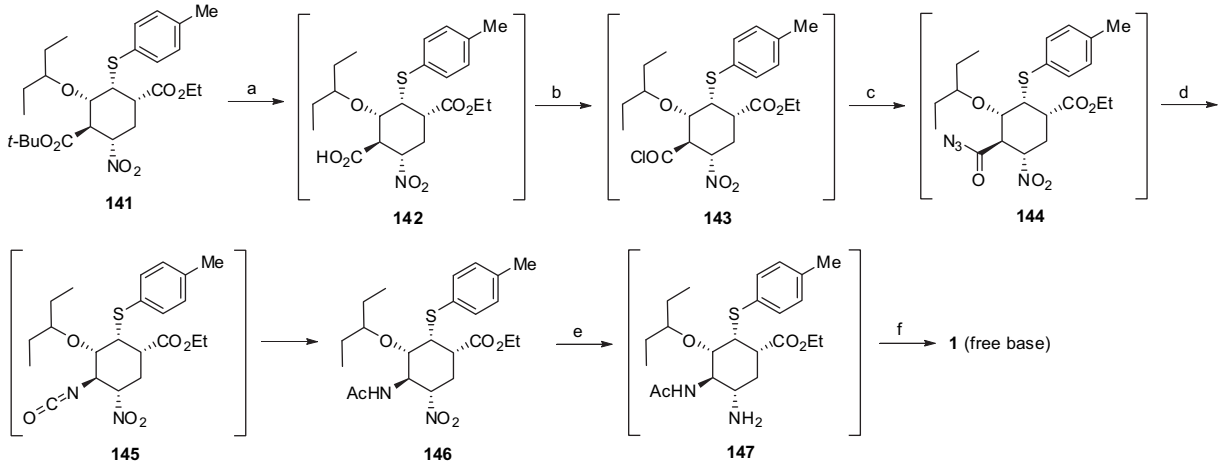
diastereomeric ratio, 97% ee, and quantitative yield. Chloroacetic acid was employed as additive based on some literature reports that described the use of acids to increase the rate of Michael additions.[61] Other acids (CF_3CH_2OH, *p*-NO_2PhOH, $PhCO_2H$, and Cl_3CCO_2H), solvents (hexane, CH_2Cl_2), and higher catalyst loadings gave less satisfactory results. Nitroaldehyde **134** was then subjected to the asymmetric Michael addition with vinylphosphonate **135** followed by an intra-molecular H–W–E reaction via transient intermediate **133** to create the cyclohexene ring. Using Cs_2CO_3 as base in toluene, an equimolecular mixture of products (5*R*)-**132**/(5*S*)-**132**, **139**, and **140** (30% each) was obtained. Since reaction optimization did not succeed in improving the ratio toward desired **132**, a protocol was implemented to convert **139** and **140** into **132** via retroaldol and a combination of retroaldol followed by H–W–E, respectively. Thus, after reaction completion to give the mixture of three products in toluene, EtOH was added and, after only 15 min at rt, complete conversion to a 4.6:1 diastereomeric mixture of (5*R*)-**132** (undesired) and (5*S*)-**132** (desired) was observed. The isomerization of (5*R*)-**132** to (5*S*)-**132** was tried next under basic conditions (K_2CO_3, Cs_2CO_3, or TEA) or in contact with silica, but no change in the ratio (K_2CO_3, Cs_2CO_3) or a ~1:1 mixture (TEA, silica) was obtained, which seemed to indicate that both isomers had similar thermodynamic stability. Based on theoretical calculations, it was rationalized that the epimerization at C5 would occur more readily in a cyclohexane ring since the epimerizable groups would be in equatorial positions. Thus, the (5*R*)-**132**/(5*S*)-**132** mixture was treated with 4-methylthiophenol in EtOH at −15 °C to give Michael-addition product **141** as a single diastereomer in 74% yield from aldehyde **136** and nitroalkene **137** after column chromatography. Under the reaction conditions, the two diastereomers equilibrate to give the desired (5*S*)-**132** predominantly. The Michael addition of 4-methylthiophenol to the acrylate then proceeds stereoselectively and preferentially on the (5*S*)-isomer to give **141**.

Some of the highlights of this first 'one-pot' sequence are: (a) equimolar amounts of **136** and **137** are used in the first step. Since this reaction proceeds to completion, no residual amounts of these two starting materials can interfere with subsequent steps; (b) Cs_2CO_3 is the only base that is employed and it plays several roles; (c) only the intermediates after the H–W–E reaction and **141** are isolated; (d) the purification of intermediate **141** is the only chromatography that is required in this entire synthesis of oseltamivir.

The second 'one-pot' sequence is described in Scheme 19. *tert*-Butyl ester **141** was cleaved with TFA to give carboxylic acid **142**, which was converted to acid chloride **143** via treatment with oxalyl chloride and a catalytic DMF. Crude **143** then underwent reaction with $TMSN_3$ and pyridine in toluene to afford acyl azide **144**. Since this type of intermediate is potentially explosive, it was not isolated but carried directly into the next step (Curtius rearrangement) in a one-pot protocol and treated with Ac_2O in HOAc[62] at rt to give acetamide **146**. Under these conditions, acyl azide **144** (of sufficient purity by ^1H NMR analysis) underwent the Curtius rearrangement at rt to provide isocyanate **145** and, therefore, avoided the harsher conditions usually required for this type of transformation. In contrast, the reaction was sluggish in benzene at rt. Alternatively, NaN_3 in aqueous acetone also provided acyl azide **144**, but an extractive workup was necessary for intermediate isolation. The $TMSN_3$ protocol was operationally simpler and would be clearly preferable on large scale. Nitro group reduction in **146** was initially carried out with Zn and aqueous 2 N HCl to give amine **147** in 86% yield, which was treated with K_2CO_3 in EtOH to provide oseltamivir. With the goal of simplifying this two-pot procedure, a new protocol was developed that called for the reduction of the nitro group with Zn and TMSCl in EtOH (in situ generation of anhydrous HCl). Ammonia gas was then bubbled through the reaction mixture to chelate Zn(II) byproduct[63] followed by the addition of K_2CO_3 to effect 4-methylthiophenol elimination and afford oseltamivir as free base in a remarkable 61% yield for the six steps combined. No information was provided on neither the chiral nor the chemical purity of **1** generated through this route.

Hayashi's synthesis of oseltamivir proceeds in 10 steps with an outstanding 60% overall yield and was demonstrated on gram-scale. Only five isolations are required, in most cases without the need for any type of workup (a simple solvent evaporation is enough to proceed to the next step), and the crudes can be carried forward without any additional purification. Even though one chromatographic purification is mentioned above for the purification of intermediate **141**, the researchers later pointed out that they had developed a chromatography-free synthesis of **141** by removing the H–W–E byproduct $(EtO)_2P(O)OH$ from the reaction mixture via a NH_4OH wash of the organic phase before going into the next step (*tert*-butyl ester cleavage with TFA).

Despite of the fact that this route also employs azide chemistry, the small number of steps from aldehyde **136** and nitroolefin **137** (additional steps are needed for the preparation of these two starting materials), low catalyst loading in the asymmetric Michael



Reagents and conditions: (a) TFA, PhMe, 23 °C, 4 h. (b) $(COCl)_2$, DMF, PhMe, 23 °C, 30 min. (c) $TMSN_3$, pyridine, PhMe, 0 to 23 °C. (d) Ac_2O, HOAc, 0 to 23 °C, 48 h. (e) (i) Zn (powder), TMSCl, EtOH, 70 °C, 2 h; (ii) NH_3 (gas), 0 °C, 10 min. (f) K_2CO_3, EtOH, 23 °C, 9 h, 81% (6 steps).

Scheme 19. Second 'one-pot' sequence by Hayashi's group.

addition of **136** to **137**, lack of protecting group chemistry, absence of halogenated solvents, operationally simple protocols with no purifications, and small number of isolations make it potentially very attractive for large-scale manufacturing.

2.11. Synthesis of oseltamivir via organocatalytic Michael addition of an aldehyde to 2-amino-1-nitroethene by Ma's group

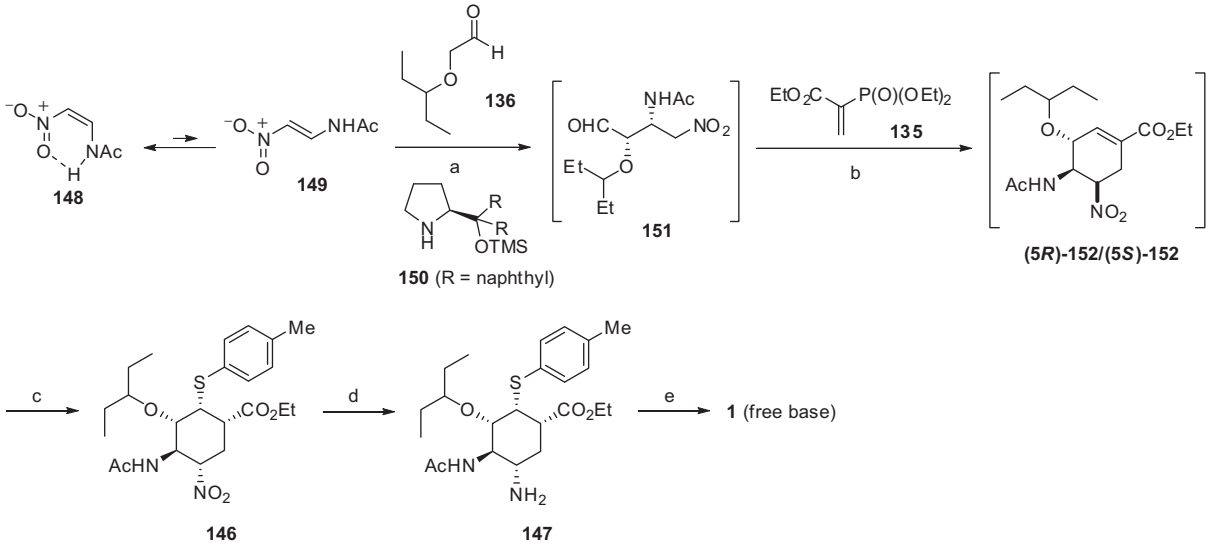
Ma and co-workers at the Shanghai Institute of Organic Chemistry in China have published a new synthesis of oseltamivir that relies on some work carried out within this same group on the asymmetric addition of aldehydes to nitroolefins with an organocatalyst to generate 1,2-diamines.[64] Thus, nitroolefin **148** (Scheme 20) was prepared by acetylation of (*Z*)-2-nitroethenanime as the only product due to intra-molecular hydrogen bonding.[65] Under the reaction conditions, it was hypothesized that **148** would isomerize to **149** and allow the subsequent Michael addition to take place. As expected, **148** underwent reaction with aldehyde **136** in the presence of proline-derived catalyst **150** (10 mol %) and benzoic acid (30 mol %) to give Michael-addition product **151** in ~80% yield and 5:1 *syn*/*anti* ratio. The use of 4 Å molecular sieves and benzoic acid, and running the reaction at −5 °C contributed to improve the selectivity of this step. Without purification, aldehyde **151** was treated with vinylphosphonate **135** and Cs_2CO_3 to give cyclohexene **152** as a mixture of epimers at C5, following a similar strategy as Hayashi and co-workers during their synthesis of oseltamivir.[9y,60] No information was provided about the diastereoselectivity of this step. This crude material was then subjected to the reaction with 4-methylthiophenol to give intermediate **146** and its epimer at C5, which presumably were separated at this stage, even though this point was not clarified in the article. The yield for these three steps combined was 54% and **146** was obtained in 96% ee, whose structure was confirmed by X-ray analysis. Nitro reduction with Zn and TMSCl followed by 4-methylthiophenol elimination with K_2CO_3 in MeOH to regenerate the double bond provided oseltamivir as the free base.

The authors mentioned that this approach only required two separation steps, which makes it attractive as a candidate for the large-scale preparation of **1**. The overall yield for this five-step route was an outstanding 46% from aldehyde **136** and nitroolefin **148**, but additional steps are needed to assemble these two starting materials. Some similarities are found with Hayashi's synthesis of oseltamivir,[9y,60] but Ma's approach has the advantage that both amino groups are incorporated on the carbon skeleton as nitro and acetamido groups following the asymmetric Michael addition, which avoids the use of azide chemistry at a later stage during the synthesis. Even though the use of nitro compounds on scale can pose some safety concerns, the fact that the reactions where this type of functional group is involved are run at low temperatures (−5 to 0 °C) should minimize the risk. This route was demonstrated on 10 mmol scale to produce intermediate **146**. No information on the scale for the rest of the steps was provided in the article.

2.12. Azide-free synthesis of oseltamivir from diethyl D-tartrate by Lu's group

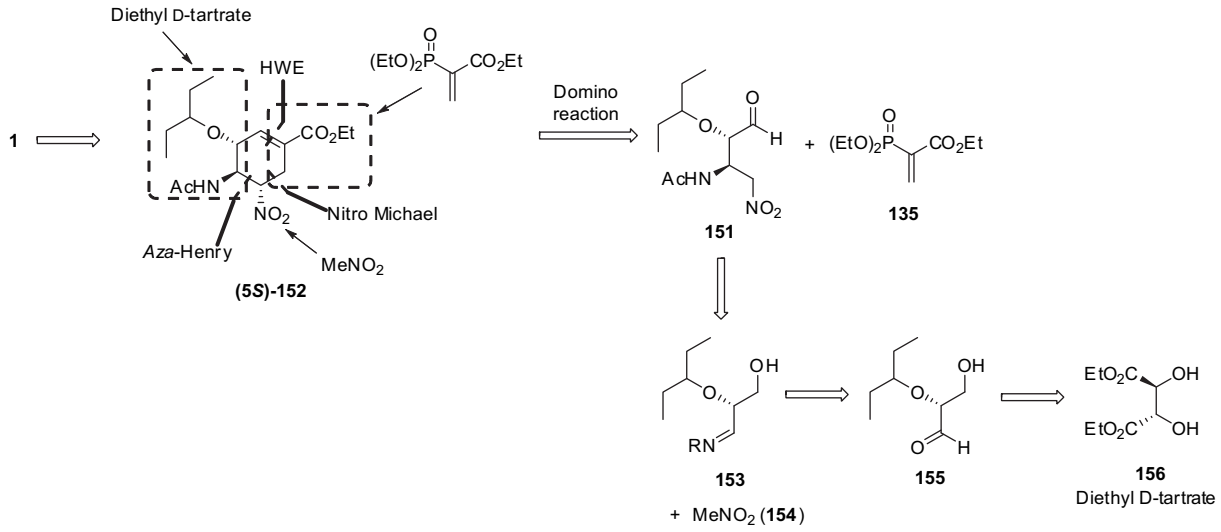
Lu and co-workers at Sun Yat-sen University and the Hong Kong Polytechnic University in China have reported an azide-free synthesis of oseltamivir that employs inexpensive and readily available diethyl D-tartrate (**156**) as starting material.[66] The retrosynthesis designed by this group is shown in Scheme 21. The key steps are: (a) a domino reaction between aldehyde **151** and vinylphosphonate **135** to create the cyclohexene ring as in Hayashi's[60] and Ma's[64] syntheses; (b) an asymmetric aza-Henry reaction between chiral imine **153** and nitromethane (**154**) to produce aldehyde **151**. Imine **153** comes from aldehyde **155**, which can be generated from diethyl D-tartrate (**156**).

The synthesis (Scheme 22) starts with diethyl D-tartrate (**156**), whose diol moiety was protected as the ketal with 3,3-dimethoxypentane and catalytic *p*-TsOH in toluene at reflux to give **157**. The simultaneous ester reduction and reductive opening of the ketal with LAH and $AlCl_3$ generated triol **158** in 88% yield and positioned the 3-pentyl group on the carbon skeleton with the correct stereochemistry. Triol **158** was then oxidized with $NaIO_4$ to produce unstable aldehyde **155** in 95% yield. This material was generated in multi-gram quantities without resorting to chromatographic purification of any of the intermediates. Due to the instability of **155**, the crude material was carried through into the next imine formation step with (*S*)-(−)-*tert*-butanesulfinamide

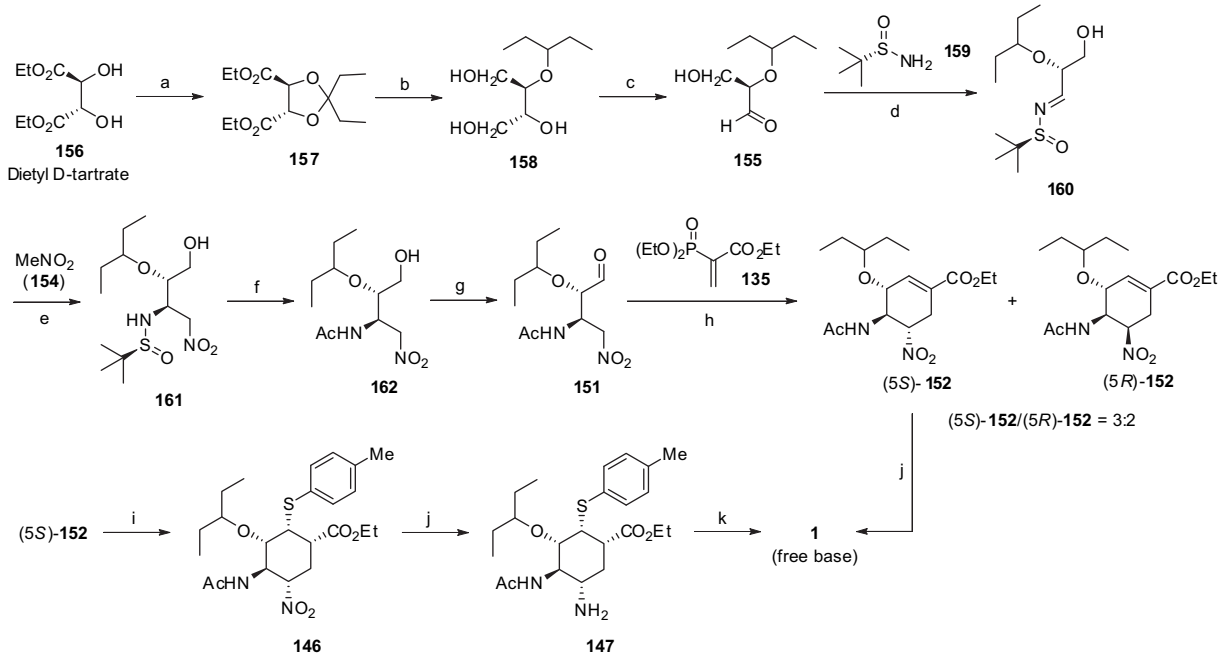


Reagents and conditions: (a) **150** (10 mol%), $PhCO_2H$ (30 mol%), $CHCl_3$, 4 Å molecular sieves, −5 °C, *syn*/*anti* ratio: 5:1. (b) Cs_2CO_3, 0 °C, 3 h. (c) *p*-MeC_6H_4SH, −15 °C, 48 h, 54% (3 steps), 96% ee. (d) Zn, TMSCl, EtOH. (e) K_2CO_3, MeOH, 85% (2 steps).

Scheme 20. Synthesis of oseltamivir by Ma's group.



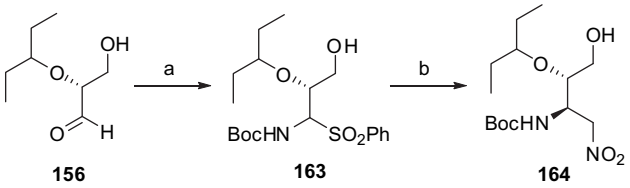
Scheme 21. Retrosynthetic analysis by Lu's group.



Reagents and conditions: (a) 3,3-Dimethoxypentane, *p*-TsOH, PhMe, reflux, 3 h, 96%. (b) (i) LAH, $AlCl_3$, Et_2O/CH_2Cl_2 (1:1), −30 °C, 30 min; then 0 °C; (ii) rt, 1 h; then, reflux, 2 h, 88%. (c) $NaIO_4$, THF/H_2O (1:1), 95%. (d) $CuSO_4$, CH_2Cl_2, rt, 3 days, 73%. (e) $MeNO_2$, NaOH, 4 Å molecular sieves, rt, 24 h, 86%, dr = 10:1. (f) (i) HCl, MeOH, rt, 2 h; (ii) Ac_2O, MeOH, rt, 30 min, 83%. (g) IBX, EtOAc, reflux, 3 h, 100%. (h) DBU, LiCl, MeCN, −15 °C, 14 h; then 0 °C, 2 h, 61%, dr = 3:2. (i) *p*-MeC_6H_4SH, Cs_2CO_3, EtOH, −15 °C, 48 h, 95%. (j) (i) Zn (powder), TMSCl, EtOH, 70 °C, 2 h; (ii) NH_3 (gas), 0 °C, 15 min; (iii) K_2CO_3, rt, 6 h, 86%.

Scheme 22. Synthesis of oseltamivir by Lu's group.

(**159**) and anhydrous $CuSO_4$ to give sulfinyl aldimine **160** in 73% yield on multi-gram scale.[67] With this substrate on hand, the key *aza*-Henry reaction was carried out with $MeNO_2$ as solvent in the presence of NaOH and 4 Å molecular sieves to give intermediate **161** in 86% yield and dr=10:1.[68] The researchers also tried this transformation using sulfone **163** (Scheme 23) as an in situ imine precursor but lower diastereoselectivity (dr=5:1) was observed. The two diastereomers were separated by chromatography and the desired **161** (major component of the mixture) was treated with HCl in methanol to cleave the *tert*-butylsulfinamide followed by acetylation with Ac_2O to afford acetamide **162** in 83% overall yield. The hydroxy group was oxidized to the corresponding aldehyde **151** with IBX in EtOAc at 80 °C without epimerization of the contiguous



Reagents and conditions: (a) $PhSO_2H$, $BocNH_2$, $MgSO_4$, CH_2Cl_2, rt, 48 h, 85%. (b) $MeNO_2$, K_2CO_3, THF, 0 °C to rt, 48 h, 78%, dr = 5:1

Scheme 23. Alternative conditions for the asymmetric *aza*-Henry reaction using sulfone **163**.

chiral center. Aldehyde **151** was then converted to cyclohexene **152** through the reaction with vinylphosphonate **135** via the two-step process seen before.[9y,60,64,69] The diastereoselectivity of this transformation was 3:2 favoring the desired (5*S*)-**152**, which could be purified by chromatography. Nitro reduction with Zn/TMSCl completed the synthesis of oseltamivir (free base).

As an alternative to the chromatographic separation of (5*R*)-**152** and (5*S*)-**152**, the strategy devised by Hayashi and co-workers was employed,[9y,60] which treated the (5*R*)-**152**/(5*S*)-**152** mixture with 4-methylthiophenol and Cs_2CO_3 in EtOH at −15 °C to give exclusively diastereomer **146**, as has been previously shown in Hayashi's synthesis.[60] After nitro reduction with Zn and TMSCl in EtOH, amine **147** was treated with ammonia gas to form a Zn(II)–NH_3 complex followed by reaction with K_2CO_3 to eliminate 4-methylthiophenol and generate oseltamivir in 82% yield for the three steps combined.

Lu's synthesis of oseltamivir (free base) involves 11 steps from diethyl D-tartrate and proceeds in an excellent 21% overall yield. Even though this route employs unsafe reagents, such as IBX and $MeNO_2$, and requires chromatographic separation for some of the intermediates, it has the potential to become a scalable route to produce large quantities of drug due to use of inexpensive diethyl D-tartrate, the small number of steps, and lack of protecting group chemistry. The early steps of the synthesis up to intermediate **161** were demonstrated on multi-gram scale.

2.13. Synthesis of oseltamivir via a novel palladium-catalyzed asymmetric allylic alkylation reaction by Trost's group

Trost and Zhang at Stanford University have recently published a full account of their synthetic efforts toward oseltamivir[70] that describes in considerably more detail the route that they had previously disclosed in 2008.[9s] Since this publication has already been described in a previous review,[10a] this section will only focus on the two key steps of the synthesis: (a) a novel palladium-catalyzed asymmetric allylic alkylation reaction (Pd-AAA) to desymmetrize lactone **165**; (b) a rhodium-catalyzed aziridination to install the acetamido group on the ring.

The Pd-AAA step was implemented on commercially available lactone **165**,[71] since it contained the cyclohexene backbone and the *cis*-disubstituted stereochemistry (Scheme 24). A number of nitrogen nucleophiles were tested for the asymmetric introduction of the first amino group, such as $HN(Boc)_2$,[72] $HN(Cbz)_2$,[73] $NaN(CHO)_2$,[74] phthalimide,[75] and sodium phthalimide[76] in combination with $[Pd_2(dba)_3]\cdot CHCl_3$ or $[\{Pd(C_3H_5)Cl\}_2]$ as catalyst, several bases (NaH, Cs_2CO_3, CsOAc, $(n\text{-Hex})_4NBr$), and chiral ligand **175** (Fig. 8) but no desired product was obtained. As a possible explanation, the authors proposed that the attack by the incoming nucleophile is disfavored by the negatively-charged carboxylate leaving group on the ring due to charge repulsion (complex **177**; Fig. 9). On the other hand, the Pd-AAA performed on racemic ester **179** was successful and provided desired **167** in 96% yield and 99% ee. Based on this experimental information, TMS–phthalimide was tested since it was rationalized that the TMS group would be transferred to the carboxylate thus avoiding the electrostatic repulsion and, as a result, more nucleophilic phthalimide would be generated. This approach provided desired product **167** in very good yield (84%) and optical purity (98% ee) after esterification in the presence of p-TsOH·H_2O in EtOH on 20 mmol scale. In addition to its novelty, the importance of this first step in the synthesis comes from the fact that the stereochemistry that it generates serves as the basis for the introduction of the rest of the chirality in the molecule.

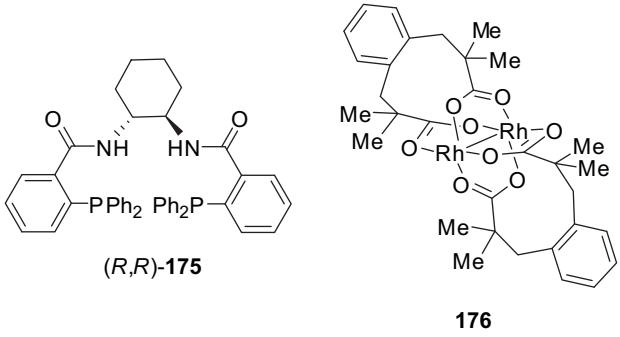
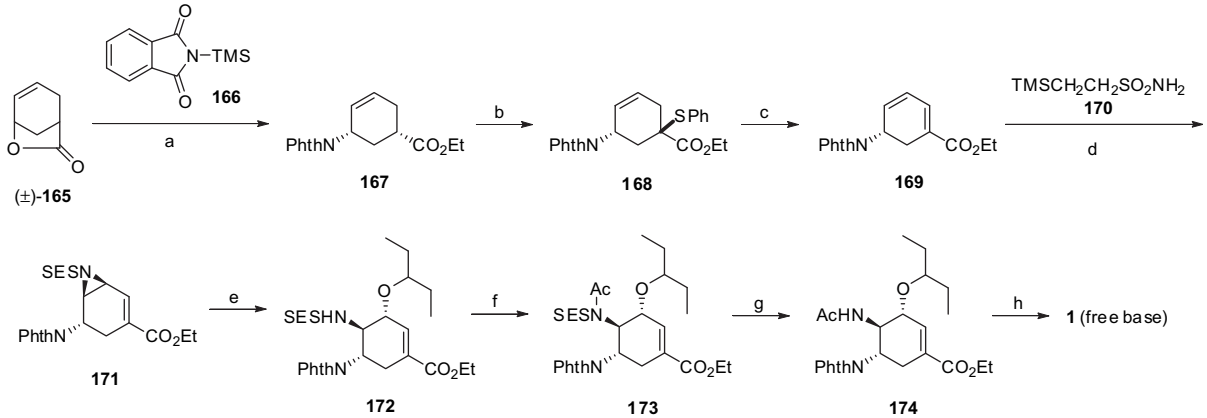


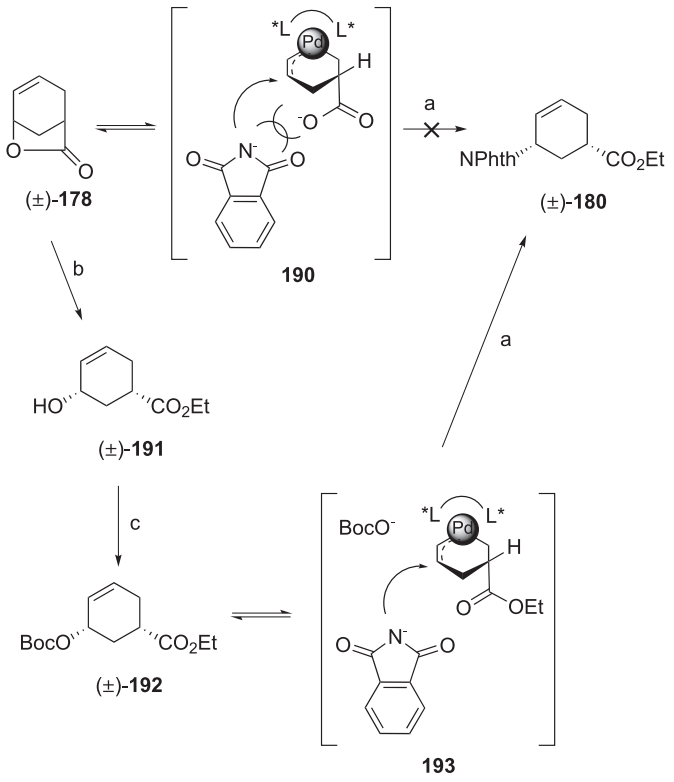
Fig. 8. Ligand and catalyst for the Pd-catalyzed AAA and Rh-catalyzed aziridine opening, respectively.

The second amine group on the molecule was installed via an aziridination reaction on diene **169**.[77] 4-Nitrobenzenesulfonyl and benzenesulfonyl as easily-removed protecting groups were investigated for the amine. Unfortunately, decomposition during the aziridination step and during the protecting group cleavage was observed, respectively. On the other hand, 2-(trimethylsilyl)ethanesulfonyl (SES) was a good compromise between stability and ease of removal with fluoride sources. The regio- and stereoselectivity of the



Reagents and conditions: (a) (i) $[\{Pd(C_3H_5)Cl\}_2]$ (2.5 mol%), **175** (7.5 mol%), THF, 40 °C; (ii) TsOH•H_2O, EtOH, reflux, 84%, 98% ee. (b) KHMDS, $PhSSO_2Ph$, THF, -78 °C to rt, 94%. (c) (i) *m*-CPBA, $NaHCO_3$, 0 °C; (ii) DBU, PhMe, 60 °C, 85%. (d) **176** (2 mol%), $PhI(O_2CCMe_3)_2$, MgO, PhCl, 0 °C to rt, 86%. (e) 3-Pentanol, BF_3•Et_2O, 75 °C, 65%. (f) DMAP, py, Ac_2O, MW, 150 °C, 1 h, 84%. (g) TBAF, THF, rt, 95%. (h) NH_2NH_2, EtOH, 68 °C, 100%.

Scheme 24. Synthesis of oseltamivir by Trost's group.



Reagents and conditions: (a) Phthalimide, [{(C_3H_5)PdCl}$_2$] (2.5 mol%), (*R*,*R*)-**188** (7.5 mol%), Cs_2CO_3, THF, rt, 96%, 99% ee. (b) K_2CO_3, MeOH. (c) Boc_2O, MEIM, CCl_4, 86% (2 steps).

Fig. 9. Rationale for the different reactivities between lactone **165** and ester **179** in the Pd-AAA reaction with phthalimide.

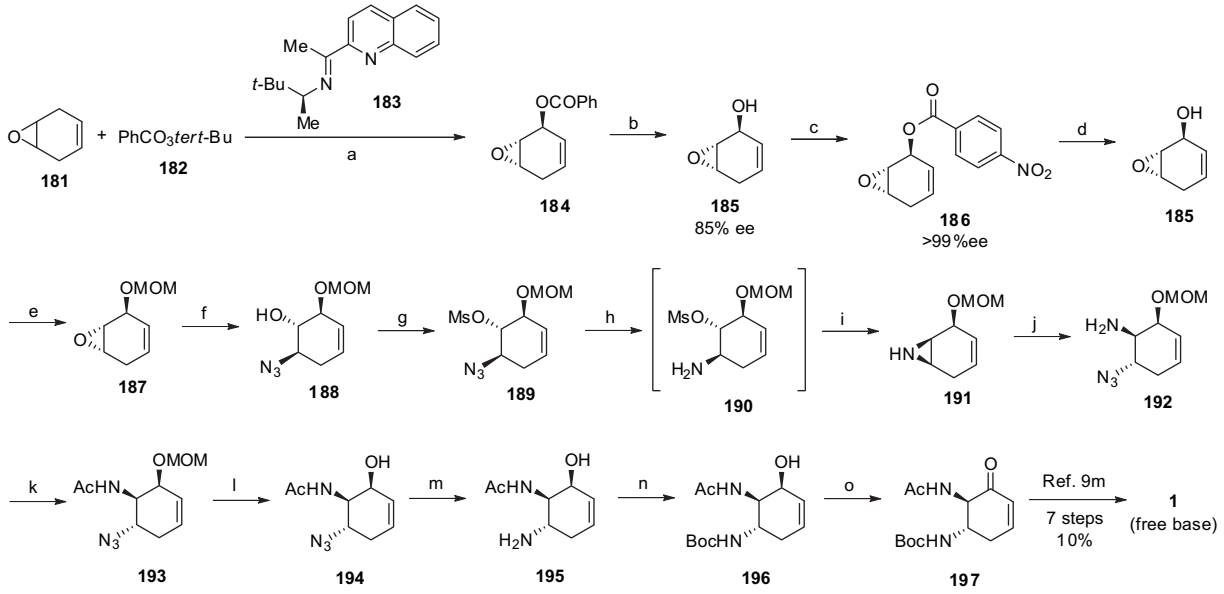
aziridination reaction was tested with (trimethylsilyl)ethanesulfonamide (**170**) and a number of metal catalysts. Thus, Cu catalysts ([Cu(CH_3CN)$_4$]PF_6 and [Cu(IPr)Cl]) by themselves showed no regioselectivity, whereas Ag ([Ag_2(*t*-Bu_3tPy)$_2$(NO_3)$_2$]) or Au ([Au(*t*-Bu_3tPy)OTf]) catalysts gave better regioselectivity but low reactivity. The desired balance was found when Rh catalyst **176** (Rh_2(esp)$_2$)[78] was employed (Fig. 8), which provided aziridine **171** in 86% yield as the only product. Other Rh catalysts, such as [Rh_2($OCOCPh_3$)$_4$], [Rh_2($OCOCMe_3$)$_4$] or [Rh_2(CF_3CONH)$_4$] gave lower conversions but equally good regioselectivity.

Trost's synthesis of oseltamivir (free base) involved eight steps from lactone **165**, proceeded in 30% overall yield despite of the fair yield of the aziridine-opening step, and was demonstrated on mg-scale. The introduction of the absolute stereochemistry on the molecule is elegantly accomplished via a novel Pd-catalyzed asymmetric allylic alkylation reaction with TMS–phthalimide and represents an unusual approach for the synthesis of the drug. Even though this route is azide-free, the use of MW radiation (acylation of intermediate **172**) and hydrazine as well as the cost of goods are potential caveats when the scalability is brought into consideration.

2.14. Formal total synthesis of oseltamivir via asymmetric desymmetrization of 1,2-epoxycyclohex-4-ene by Hayashi's group

Hayashi and co-workers at Kobe University and Asahi Kasei Chemicals Corporation in Japan have recently reported the asymmetric synthesis of enantiopure cyclohexenone **197**, an advanced intermediate en route to oseltamivir (Scheme 25).[79] This material has been previously synthesized by Shibasaki and co-workers in racemic form and resolved via chiral HPLC during one of their approaches to oseltamivir.[9m]

Hayashi's route to **197** relies on a synthetic methodology developed in this same group for the asymmetric desymmetrization of 1,2-epoxycyclohex-4-ene (**181**)[80] by means of a Kharasch–Sosnovsky allylic oxidation.[81] Thus, **181** was treated with *tert*-



Reagents and conditions: (a) **183** (3 mol%), Cu(CH_3CN)$_4PF_6$ (2.5 mol%), acetone, 25 °C, 16 h, 85% ee. (b) NaOMe, MeOH, rt, 2 h. (c) 4-Nitrobenzoyl chloride, TEA, CH_2Cl_2, rt, overnight, 23% (3 steps), >99% ee. (d) NaOMe, MeOH, 28 °C, 8 h. (e) MOMCl, DIPEA, CH_2Cl_2, rt, 10 h, 99% (2 steps). (f) NaN_3, NH_4Cl, MeOH/H_2O (3:1), 80 °C, 24 h. (g) MsCl, DIPEA, CH_2Cl_2, 0 °C, 24 h, 88% (2 steps). (h) PPh_3, THF, 0 to 20 °C, 3 h. (i) TEA, H_2O, 12 h. (j) NaN_3, NH_4Cl, DMF, 65 °C, 16 h. (k) Ac_2O, $NaHCO_3$, CH_2Cl_2/hexane (1:1), 0 °C, 3 h, 67% (4 steps). (l) 5-10% HCl, MeOH, 20 °C, 20 h. (m) (i) PPh_3, THF, 20 °C, 1 h; (ii) H_2O, 50 °C, 24 h. (n) Boc_2O, TEA, DMAP, CH_2Cl_2, 26 °C, 24 h. (o) (*i*-PrCO)$_2$O, DMSO, *i*-PrOAc, 80 °C, 5 h, 40% (4 steps).

Scheme 25. Synthesis of oseltamivir from epoxide **181** by Hayashi and co-workers.

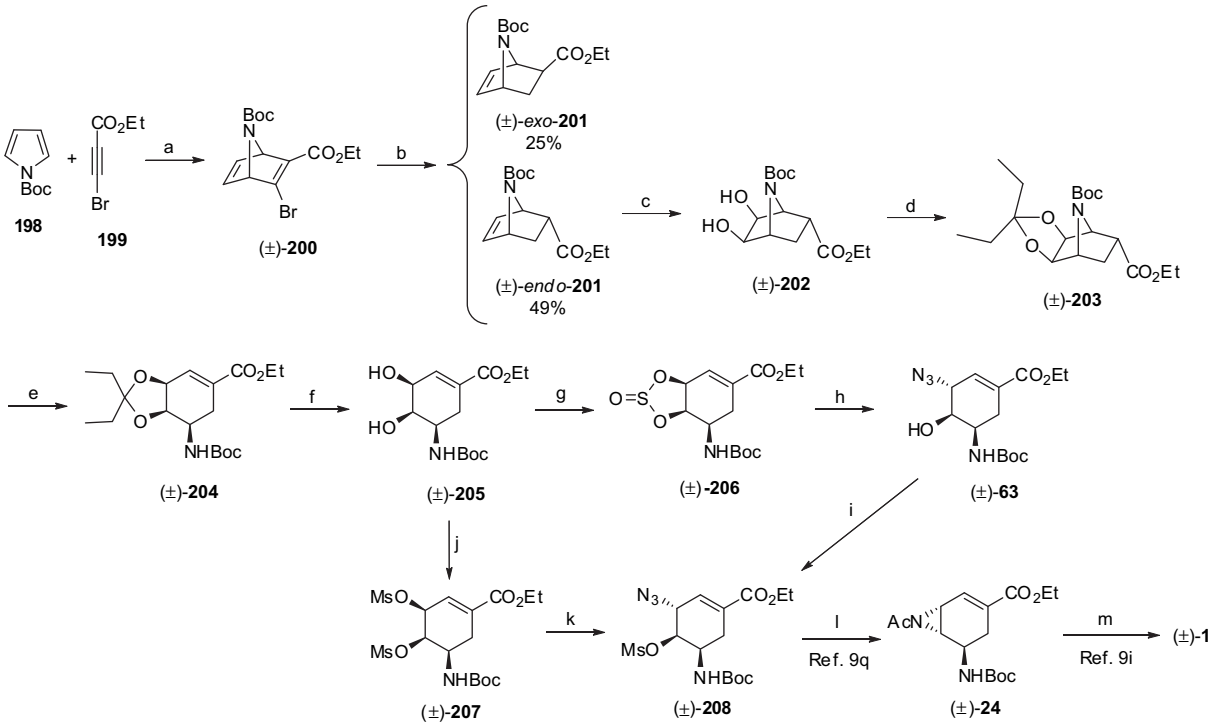
butyl perbenzoate (**182**) in the presence of a catalytic amount of *N*,*N*-bidentate chiral Schiff base ligand **183** (3 mol %) and $Cu(CH_3CN)_4PF_6$ (2.5 mol %) in acetone to afford ester **184** in 85% ee and less than 1% of the undesired diastereomer. With the goal of improving the ee, the benzoic ester was converted to the 4-nitrobenzoate (**186**) in a two-step sequence in 23% yield from **181** and >99% ee after recrystallization from hexane/EtOAc (4:1). When *tert*-butyl *p*-nitroperbenzoate was employed instead of *tert*-butyl perbenzoate in the reaction with **181**, the crude material was obtained in 82% ee and >99% ee after recrystallization but the chemical yield was only 15%.[81b] The ester group in **186** was cleaved with NaOMe to give enantioenriched alcohol **185**, which was protected as the MOM ether in quantitative yield (two steps). The epoxide ring was opened up with NaN_3 in MeOH at reflux and the resulting alcohol was converted to mesylate **189** with MsCl and DIPEA in 88% yield for the two steps combined. After Staudinger reduction of the azido group, the intermediate amine was in situ treated with aqueous TEA to provide aziridine **191**.[34a] As for the epoxide ring, the aziridine ring was opened up with NaN_3 to install the second amino group on the molecule followed by treatment with Ac_2O to afford acetamide intermediate **193** with complete regioselective control in 67% yield from **189**. After alcohol deprotection with dilute HCl, the azido group underwent reduction as before with PPh_3 and the resulting amino group was protected with Boc_2O to give carbamate **196**. The last step of the synthesis involved the modified Moffat oxidation of allylic alcohol **196** with $(i\text{-PrCO})_2O$ and DMSO in *i*-PrOAc at 80 °C to provide cyclohexenone **197** in 40% yield from **193**. Seven additional steps completed the synthesis of oseltamivir (free base) as has been shown before.[9m]

Hayashi's synthesis of oseltamivir (free base) involves 21 steps and proceeds in 0.5% yield from 1,2-epoxycyclohex-4-ene (**181**). The introduction of the stereochemistry is accomplished via a novel technology that employs an allylic oxidation to desymmetrize **181** and provides enantiopure *p*-nitrobenzoate **186** after recrystallization on multi-gram scale. Some of the drawbacks of this route are the large number of steps, the use of protecting group chemistry in several instances, azide and Mitsunobu (during a subsequent step reported in Ref. 9m) chemistry, numerous chromatographies, and the very low overall yield (0.05%).

3. Racemic syntheses of oseltamivir

3.1. Synthesis of racemic oseltamivir via a Diels–Alder reaction by Wu's group

Wu and co-workers at the Shanghai Institute of Organic Chemistry and Jilin University in China have reported the synthesis of racemic oseltamivir via a Diels–Alder reaction to generate the cyclohexane ring (Scheme 26).[82] Adduct **200** was formed through the reaction between Boc-protected pyrrole (**198**)[83] and bromoester **199**[84] in 60% yield based on some literature reports.[85] Subsequent reduction with $NaBH_4$ in DMSO[86] effected debromination and double bond reduction to afford a mixture of *endo*-**201** and *exo*-**201** in 49% and 25% isolated yields, respectively. After purification via chromatography, *endo*-**201** was dihydroxylated with OsO_4 and NMO to afford diol **202** in excellent yield. After protecting the diol moiety as the ketal and treatment with LiHMDS, ring opening led to the formation of racemic ester **204**. The ketal protecting group was cleaved with *p*-$TsOH\cdot H_2O$ in MeOH to provide diol **205** in 80% yield. With **205** on hand, two alternative routes were explored for the generation of azide **208**.[9q] In the first route, diol **205** was treated with Cl_2SO and TEA to provide cyclic sulfite **206**, which was ring-opened with NaN_3 in DMF to give hydroxyazide **63**. This intermediate was mesylated with MsCl and TEA in CH_2Cl_2 to provide the desired **208**.

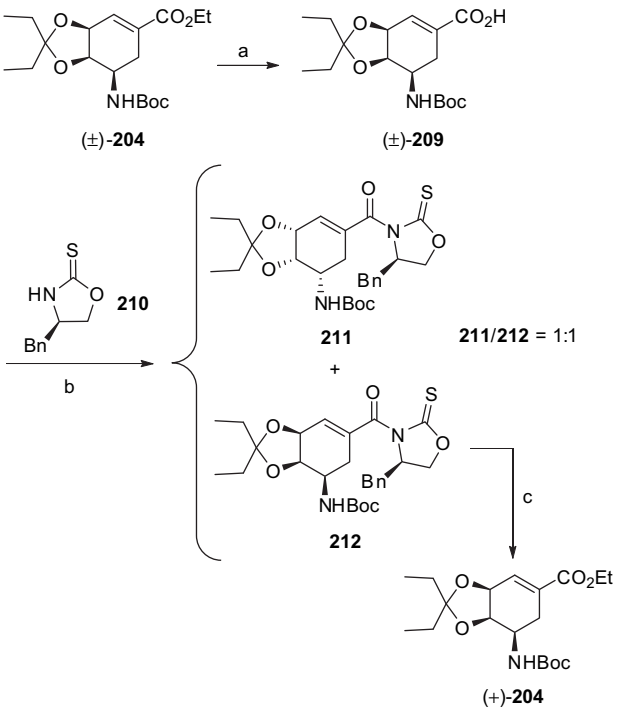


Reagents and conditions: (a) 90 °C, 60%. (b) $NaBH_4$, DMSO, 74%. (c) OsO_4, NMO, *t*-BuOH/H_2O, 96%. (d) 3-Pentanone, *p*-TsOH•H_2O, 94%. (e) LiHMDS, THF, −78 to 0 °C, 80%. (f) TsOH•H_2O, MeOH, 80%. (g) Cl_2SO, TEA, 100%. (h) NaN_3, DMF, 95%. (i) MsCl, TEA, CH_2Cl_2, 97%. (j) MsCl, TEA, 60%. (k) NaN_3, DMF, 67%. (l) (i) Ph_3P, TEA; (ii) Ac_2O, py, 65% (2 steps). (m) (i) 3-Pentanol, $Cu(OTf)_2$, 61%; (ii) H_3PO_4, EtOH, 85%.

Scheme 26. Synthesis of oseltamivir by Wu's group.

Alternatively, diol **205** was transformed into dimesylate **207** under standard conditions followed by regio- and stereoselective displacement of the mesylate group at the C3 position with NaN_3 to give **208**. The completion of the synthesis of oseltamivir was implemented following literature procedures in four additional steps.[9i,q]

Since the previous synthesis generated racemic oseltamivir, this group devised a strategy to provide the desired enantiomer of the drug by preparing optically pure ketal (+)-**204** (Scheme 27). Thus, the ester group in racemic **204** was cleaved by treatment with LiOH in aqueous THF to give acid **209**, which underwent reaction with oxazolidinethione **210** to provide a 1:1 diastereomeric mixture of **211** and **212**. After separation by column chromatography, desired **212** was converted to (+)-**204** via treatment with DMAP in EtOH[87] in 73% yield.



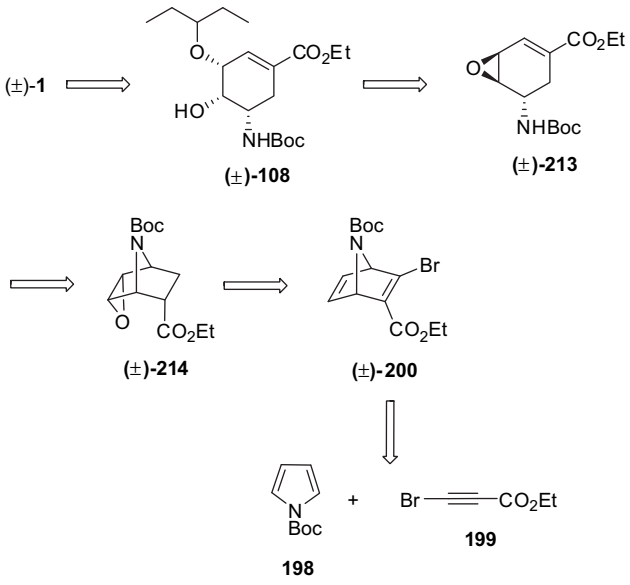
Reagents and conditions: (a) LiOH, THF/H_2O, 91%. (b) EDCI, DMAP, 1:1 mixture of diastereoisomers, 96%. (c) DMAP, EtOH, CH_2Cl_2, 73%.

Scheme 27. Preparation of optically pure ketal (+)-**204**.

This route to racemic oseltamivir phosphate consists of 12 steps, proceeds in 12% overall yield from Boc-protected pyrrole (**198**) and ester **199**, and was demonstrated on mg-scale. Additional steps are needed for the preparation of these two starting materials and the preparation of optically pure oseltamivir brings the yield down to 4%. The researchers mentioned that only one chromatography is needed up to intermediate (±)-**204**. Another advantage is the limited use of protecting groups. Some of the caveats are the need for additional steps for the resolution of (±)-**204** (no diastereoselectivity in the coupling between (±)-**209** and **210**), and the use of azide chemistry.

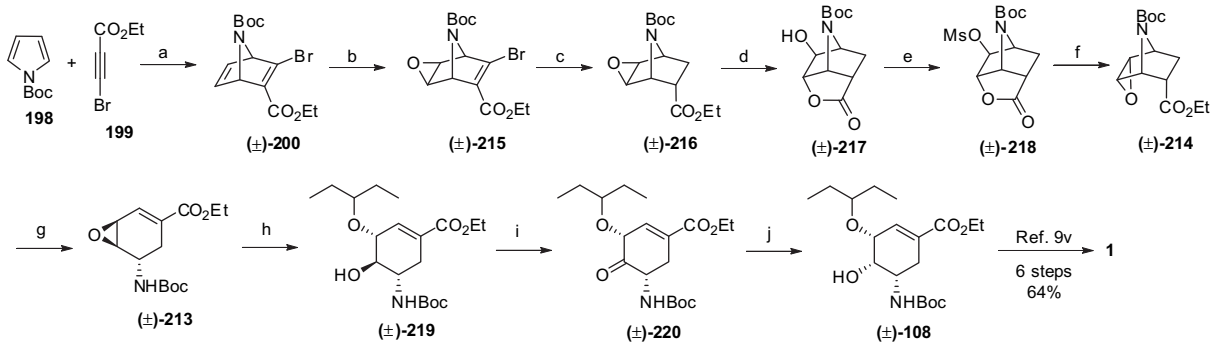
3.2. Formal synthesis of racemic oseltamivir via a Diels–Alder reaction by Kamimura's group

Kamimura and Nakano at Yamaguchi University in Japan have reported a new approach to racemic known intermediate **108** en route to oseltamivir that, as for Wu's synthesis,[82] builds the cyclohexane ring via a Diels–Alder reaction between a pyrrole and an acetylene.[88] The retrosynthesis is shown in Scheme 28. Oseltamivir is derived from (±)-**108**, which comes from epoxide **213**. This epoxide is in turn generated from tricyclic intermediate **214** via β-elimination. The epoxide is obtained from diene **200**, which comes from the Diels–Alder reaction between Boc-protected pyrrole (**198**) and propargylic ester **199**.



Scheme 28. Retrosynthetic analysis by Kamimura's group.

The synthesis started from Boc-protected pyrrole (**198**), a much better partner in Diels–Alder reactions than pyrrole itself, which underwent reaction with **199** at 90 °C for 39 h to give adduct **200** in 57% yield (Scheme 29). Stereoselective epoxidation of the more electron-rich olefin with *m*-CPBA[89] provided exclusively epoxide **215** in fair yield (46%) due to low conversion, whereas other oxidizing reagents such as oxone provided mixtures of isomers. Also, a step-wise approach using NBS followed by base treatment gave no desired epoxide. Simultaneous double bond reduction and debromination was accomplished via catalytic hydrogenation in the presence of 10% Pd/C to give ester **216** in a 4:1 *endo*/*exo* ratio. The addition of a base, such as 2-methylpyridine was necessary to neutralize the HBr produced during the reaction and prevent Boc-cleavage, which led to substrate decomposition. After purifying *endo*-**216** via chromatography, ester saponification followed by epoxide opening afforded lactone **217** in 89% yield, which was converted to the corresponding mesylate **218** with MsCl/TEA in CH_2Cl_2 in almost quantitative yield. The stereochemistry of this intermediate was confirmed by X-ray crystallography. Lactone hydrolysis with KOH resulted in mesylate displacement and epoxide formation and the carboxylate group was subsequently converted to the ethyl ester with EtI in a one-pot procedure to give intermediate **214** in 85% yield. With this intermediate on hand, the ring-opening step under basic conditions to generate the cyclohexene ring was then investigated. KO^{t}Bu, either at −50 °C or reflux gave no desired product and *t*-BuLi or LDA at −50 °C gave low yield of **213** (20 and 24%, respectively) and some recovered starting material. However, LDA in combination with HMPA (1.5 equiv)[90] at −78 °C afforded **213** in 62% yield with only 2% of recovered unreacted stating material. A larger amount of HMPA (3 equiv) gave slightly lower yield (60%), whereas the use of DMPU (1.5 equiv) as a less toxic alternative provided a considerably lower yield (22%). The synthesis continued with the opening of the epoxide moiety in **213** with 3-pentanol and a stoichiometric amount of $BF_3 \cdot OEt_2$ to afford alcohol **219** in 54% yield.[9k] With the goal of introducing the remaining acetamido group with the correct



Reagents and conditions: (a) 90 °C, 39 h, 57%. (b) *m*-CPBA, Et_2O, 0 °C, 1 h; then 49 h, rt, 46%. (c) H_2, 10% Pd/C, 2-methylpyridine, rt, 50 h, 71%, *endo*/*exo* = 4:1. (d) 10% aq. NaOH, 0 °C, 30 min; then rt, 40 h, 89%. (e) MsCl, TEA, CH_2Cl_2, rt, 24 h, 95%. (f) (i) KOH, DMF, rt, 30 h; (ii) EtI, rt, 24 h, 85%. (g) (i) LDA (*i*-Pr_2NH, *t*-BuLi), HMPA, THF; (ii) (±)-**214**, –50 °C, 16 h, 62%. (h) 3-Pentanol, BF_3•OEt_2, –20 °C, 20 min, 54%. (i) Dess-Martin periodinane, CH_2Cl_2, rt, 2 h, 87%. (j) $NaBH_4$, MeOH, –50 °C, 30 min, 91%, dr = 3:1.

Scheme 29. Synthesis of oseltamivir by Kamimura's group.

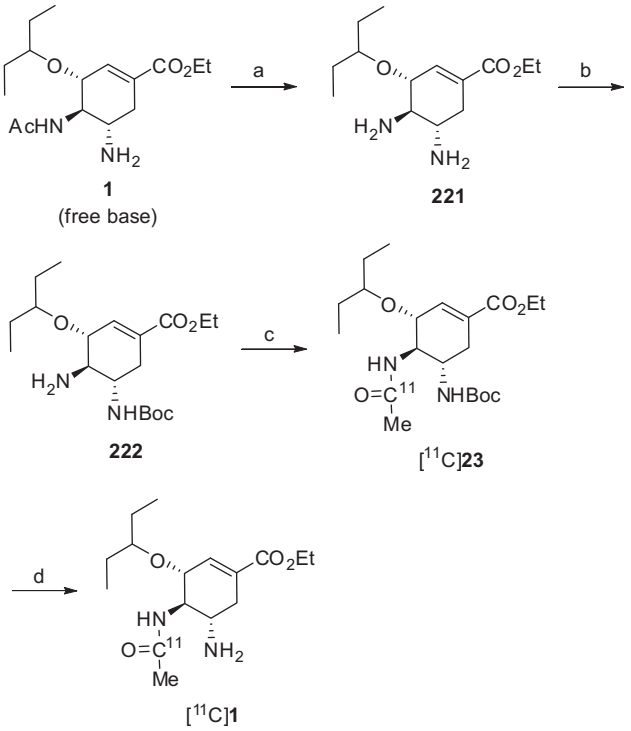
stereochemistry, the configuration at the C4 position had to be inverted and this was accomplished through the oxidation of alcohol **219** with Dess–Martin periodinane followed by stereoselective reduction of the resulting ketone with $NaBH_4$ to generate the desired and known (*S*)-alcohol **108** in dr=3:1.[9v] Oseltamivir can be prepared in six additional steps from this intermediate as has been previously shown.[9v]

This route was demonstrated on mg-scale and the overall yield for this approach to intermediate (±)-**108** was 5% but the actual yield is only 3.3% when the stereoselectivity of some of the steps is factored in. The additional six steps to oseltamivir result in a 2% overall yield from **198** and **199** for 16 steps (additional steps needed to prepare **198** and **199**). The very low throughput, use of highly toxic HMPA, and unsafe reagents (*m*-CPBA, *t*-BuLi, Dess–Martin periodinane; NaN_3 is also employed later on in the synthesis), very long reaction times for several steps, and need for extensive chromatographic purification of intermediates (eight instances) make this route difficult to implement on scale at this stage of development.

4. Synthesis of [^{11}C]oseltamivir by Arai's group

Arai and co-workers at the National Institute of Radiological Sciences in Japan have reported the first synthesis of [^{11}C]oseltamivir with the goal of studying some adverse effects, such as suicide attempts, delirium, and self-injury, observed upon administration of the drug to younger patients in this country.[91] Positron Emission Tomography (PET), which employs radiotracers labeled with short-lived positron emitters, such as ^{11}C, ^{13}N, ^{15}O, and ^{18}F, was the technique of choice to study drug distribution and its interaction with target proteins. However, one of the limitations of this technique is that the generation of radiotracers must be fast since the positron-emitting radionuclide are short-lived.

The synthesis of [^{11}C]oseltamivir, shown in Scheme 30 and carried out in an automated system, started from oseltamivir free base, whose acetyl group was cleaved with concentrated HCl in EtOH at 90 °C to give diamine **221** in 35% yield. Monoprotection of the amine at the C5 position with Boc_2O provided carbamate **222** in 78% yield. This step was necessary prior to acetylation since, during preliminary experiments, it was observed that the reaction of **221** with acetyl chloride provided mostly acetylation at the 5-position. This material was then subjected to an expeditious, two-step sequence that started with the [^{11}C]acetylation of **222** with [1-^{11}C]acetyl chloride,[92] to give [^{11}C]**23** followed by Boc-cleavage to give [^{11}C]oseltamivir. These last two steps were completed in only 36–39 min after the production of [^{11}C]CO_2 by bombardment of dry N_2 gas containing 0.01% O_2 with a beam of high-energy protons.



Reagents and conditions; (a) Conc. HCl, EtOH, 90 °C, 5h, 35%. (b) Boc_2O, CH_2Cl_2, rt, 1 h, 78%. (c) [1-^{11}C]AcCl, TEA, THF, 30 °C, 3 min. (d) 4 M HCl, 120 °C, 3 min.

Scheme 30. Synthesis of [^{11}C]oseltamivir by Arai's group.

5. Summary of synthetic approaches to oseltamivir

Table 1 summarizes the syntheses described in this review. The academic or industrial group, number of steps, overall yield, starting material(s), and some synthetic route highlights are provided. When the synthesis of an intermediate en route to oseltamivir is reported, the additional steps and yields for those steps have been factored in for the production of **1**.

Table 1
Summary of synthetic approaches to oseltamivir

Source	Steps	Overall yield (%)	Starting material	Synthetic route highlights
Hudlicky[15]	13	7	Ethyl benzoate (**7**)	Inexpensive starting material; minimal protecting group chemistry; very low throughput enzymatic oxidation to introduce stereochemistry; novel Diels–Alder reaction to introduce amino group at C4; azide chemistry; no information on chromatographic purifications or scale.
Hudlicky[19]	12–13	7	Ethyl benzoate (**7**)	Inexpensive starting material; minimal protecting group chemistry; azide-free chemistry; very low throughput enzymatic oxidation; highly toxic chromium chemistry; Mitsunobu chemistry; limited use of chromatography; mg-scale.
Shibasaki[22]	11	13	1-(Trimethylsiloxy)-1,3-butadiene (**37**) and dimethyl fumarate (**38**)	Readily available starting materials; novel approach for the introduction of chirality at C3; minimal protecting group chemistry; Curtius rearrangement; Mitsunobu chemistry; preparative TLC; several chromatographies; azide chemistry; mg-scale.
Raghavan[25]	16	4.3	(*R*)-3-Cyclohexene carboxylic acid (**46**)	Minimal protecting group chemistry; new substrate (acid **46**) for the introduction of chirality; two additional steps to prepare **46**; highly toxic Se chemistry; Mitsunobu chemistry; azide chemistry; extensive chromatography; two low-regioselectivity steps; mg-scale.
F. Hoffmann-La Roche Ltd.[35]	8	20	(−)-Shikimic acid (**65**)	Very efficient route; readily available starting material; only three workups; no protecting group chemistry; halogenated solvent-free synthesis; chromatography-free; inexpensive reagents; azide chemistry at high temperature; g-scale.
Chen, Liu[38]	22	2.6	D-Glucal (**77**)	Commercially available starting material; some protecting group chemistry; extensive chromatography; sealed-tube step; oxidation-reduction steps for stereochemical inversion at C3; heavy use of halogenated solvents; mg-scale.
Chen, Chai[42]	12	9	D-Ribose (**95**)	Inexpensive starting material; RCM to generate cyclohexene ring; no protecting group chemistry; use of halogenated solvents in four-steps; azide chemistry; extensive chromatography; mg-scale.
Kongkathip[50]	14	5	D-Ribose (**95**)	Inexpensive starting material; limited protecting group chemistry; RCM to generate cyclohexene ring; azide and hydroxylamine chemistry; heavy use of halogenated solvents (six-steps); extensive chromatography; mg-scale.
Ko[53]	16 (free base)	7	D-Mannitol (**118**)	Inexpensive starting material; highly stereoselective asymmetric dihydroxylation reaction to introduce stereochemistry at C4 and C5; limited protecting group chemistry; extensive chromatography; azide chemistry at high temperature (two instances); multi-g scale for some steps.
Hayashi[60]	10	60	Aldehyde **136** and nitroolefin **137**	Highly efficient process; no protecting group chemistry; minimal isolations and workups; only one chromatography but also chromatography-free conditions developed; no halogenated solvents; Curtius rearrangement at rt; azide chemistry; additional steps for the preparation of **136** and **137**; mg-scale.
Ma[64]	5 (free base)	46	Aldehyde **136** and nitroolefin **148**	Azide-free chemistry; only 2 separation steps; no protecting group chemistry; nitro group chemistry; additional steps for the preparation of **136** and **148**; 10 mmol scale to intermediate **148**; no information on scale or chromatographic separations.
Lu[66]	11	21	Diethyl D-tartrate (**156**)	Inexpensive starting material; no protecting group chemistry; use of IBX and $MeNO_2$; chromatography for several intermediates; mg- to g-scale.
Trost[70]	8 (free base)	30	6-Oxabicyclo[3.2.1]oct-3-en-7-one (**165**)	Elegant introduction of chirality on the molecule; no protecting group chemistry; azide-free chemistry; MW chemistry step; hydrazine chemistry; mg-scale.
Hayashi[79]	21 (free base)	0.05	1,2-Epoxycyclohex-4-ene (**181**)	Introduction of chirality via a novel, chiral Schiff base-catalyzed asymmetric desymmetrization of **181** (g-scale); very low overall yield; extensive chromatography, azide and Mitsunobu chemistry; protecting group chemistry; mg-scale.
Wu[82]	12–13 (additional steps to optically pure **1**)	5–13 (3–8 to optically pure **1**)	Boc-pyrrole (**198**) and ethyl 3-bromopropynoate (**199**)	Racemic synthesis; limited protecting group chemistry; azide chemistry; additional steps for the preparation of **198** and **199**; use of highly toxic Os chemistry; very low overall yield; extensive chromatography; mg-scale.
Kamimura[88]	16	2	Boc-pyrrole (**198**) and ethyl 3-bromopropynoate (**199**)	Racemic synthesis; minimal protecting group chemistry; additional steps for the preparation of **198** and **199**; use of highly toxic and hazardous reagents (DMP, HMPA, *m*-CPBA, azide, *t*-BuLi); extensive chromatography; very low overall yield; mg- to g-scale.

6. Conclusions

The synthesis of neuraminidase inhibitors, and oseltamivir in particular, continues to be a very active area of research.[93] The fear that a highly aggressive strain of the influenza virus such as the H5N1 (avian influenza)[94] can mutate to become easily transmitted from human to human and spark a deadly global pandemic is a major concern. Roche has stepped up the manufacturing capacity of oseltamivir and, as of 2007, it was expected that the production would reach 400 million treatment courses per year (each consisting of 10 capsules),[95] which translates into several hundred metric tons of material.[35] Many countries around the world have stockpiled the drug, which is estimated to amount to 350 million courses between 2004 and 2009.[6]

However, the emergence of oseltamivir-resistant strains of the virus reminds us of the need for continued research to discover new drugs to keep the disease at bay.[96] As an alternative to oseltamivir, the development of new synthetic routes to zanamivir would also be desirable since, as was mentioned in the introduction to this review, this drug is highly effective against the disease.[97] A new approach currently under investigation is the combination of antiviral agents such as oseltamivir and peramivir[98] with the goal of improving efficacy as well as controlling the appearance of drug-resistant viruses.[99]

The new approaches to oseltamivir presented in this review are definitive proof of the ingenuity of the organic chemistry community to solve a difficult synthetic problem. Even though many of them are not amenable to scale at this stage of development, they suggest alternative paths to this drug that, eventually, may lead to the implementation of new commercial processes. Since a number of routes share common intermediates, it is possible that a new large-scale methodology will be derived from a combination of chemistries from several of those routes.

The awareness about the disease that the emergence of the H5N1 and H1N1 strains spurred in the public opinion, governments around the world, and scientific community ensures that the quest for new and better treatments will continue in the future.

Acknowledgements

The author thanks Dr. Joshua R. Dunetz for reviewing this manuscript and providing valuable comments and suggestions to improve it.

References and notes

1. http://www.cdc.gov/h1n1flu/general_info.htm (accessed June 19, 2011).
2. Edmonds, M. K. *Chem. New Zealand* **2009**, *73*, 140.
3. Widmer, N.; Meylan, P.; Ivanyuk, A.; Aouri, M.; Decosterd, L. A.; Buclin, T. *Clin. Pharmacokinet.* **2010**, *49*, 741.
4. (a) He, G.; Massarella, J.; Ward, P. *Clin. Pharmacokinet.* **1999**, *37*, 471; (b) Graul, A.; Leeson, P. A.; Castañer, J. *Drugs Future* **1999**, *24*, 1189.
5. Davies, B. E. *J. Antimicrob. Chemother.* **2010**, *65*, ii5.
6. Reddy, D. *J. Antimicrob. Chemother.* **2010**, *65*, ii35.
7. Sharma, P. P.; Roy, R. K.; Anurag. *J. Pharm. Res.* **2010**, *3*, 1602.
8. 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.; Woods, J. M.; Bethell, R. C.; Hotham, V. J.; Cameron, J. M.; Penn, C. R. *Nature* **1993**, *363*, 418.
9. (a) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; 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) 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. Org. Chem.* **1998**, *63*, 4545; (c) Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Göckel, V.; Götzö, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Röckel-Stäbler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266; (d) Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044; (e) Abrecht, S.; Karpf, M.; Trussardi, R.; Wirz, B. EP 1127872 A1, 2001; *Chem. Abstr.* **2001**, *135*, 195452; (f) Zutter, U.; Iding, H.; Wirz, B. EP 114603 A2, 2001; *Chem. Abstr.* **2001**, *135*, 303728; (g) Harrington, P. J.; Brown, J. D.; Foderaro, T.; Hughes, R. C. *Org. Process Res. Dev.* **2004**, *8*, 86; (h) Abrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U. *Chimia* **2004**, *58*, 621; (i) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310; (j) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312; (k) Cong, X.; Yao, Z.-J. *J. Org. Chem.* **2006**, *71*, 5365; (l) Mita, T.; Fukuda, N.; Roca, F. X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259; (m) Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 1403; (n) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5734; (o) Abrecht, S.; Federspiel, M. C.; Estermann, H.; Fischer, R.; Karpf, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Trussardi, R.; Zutter, U. *Chimia* **2007**, *61*, 93; (p) 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; (q) Bromfield, K. M.; Gradén, H.; Hagberg, D. P.; Olsson, T.; Kann, N. *Chem. Commun.* **2007**, 3183; (r) Shie, J.-J.; Fang, J.-M.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5788; (s) Trost, B. M.; Zhang, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 3759; (t) Matveenko, M.; Banwell, M. G.; Willis, A. C. *Tetrahedron Lett.* **2008**, *49*, 7018; (u) Kipassa, N. T.; Okamura, H.; Kina, K.; Hamada, T.; Iwagawa, T. *Org. Lett.* **2008**, *10*, 815; (v) Zutter, U.; Iding, H.; Spurr, P.; Wirz, B. *J. Org. Chem.* **2008**, *73*, 4895; (w) Nie, L.-D.; Shi, X.-X. *Tetrahedron: Asymmetry* **2009**, *20*, 124; (x) Nie, L.-D.; Shi, X.-X.; Ko, K. H.; Lu, W.-D. *J. Org. Chem.* **2009**, *74*, 3970; (y) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304; (z) Mandai, T.; Oshitari, T. *Synlett* **2009**, 783; (aa) Oshitari, T.; Mandai, T. *Synlett* **2009**, 787; (ab) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Tetrahedron* **2009**, *65*, 3239; (ac) Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1070.
10. (a) Magano, J. *Chem. Rev.* **2009**, *109*, 4398; For other reviews see: (b) Shibasaki, M.; Kanai, M.; Yamatsugu, K. *Isr. J. Chem.* **2011**, *51*, 316; (c) Gong, J.; Xu, W. *Curr. Med. Chem.* **2008**, *15*, 3145; (d) Shibasaki, M.; Kanai, M. *Eur. J. Org. Chem.* **2008**, 1839; (e) Farina, V.; Brown, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7330; (f) Behera, M. *Chemtracts* **2006**, *19*, 38.
11. For a greener preparation of intermediate (3*R*,4*R*,5*S*)-ethyl 4-acetamido-5-amino-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate that eliminates the use of Cl_2SO, see: Carr, R.; Ciccone, F.; Gabel, R.; Guinn, M.; Johnston, D.; Mastriona, J.; Vandermeer, T.; Groaning, M. *Green Chem.* **2008**, *10*, 743.
12. For synthetic routes to zanamivir, see: (a) von Itzstein, M.; Wu, W.-Y.; Jin, B. *Carbohydr. Res.* **1994**, *259*, 301; (b) Scheigetz, J.; Zamboni, R.; Bernstein, M. A.; Roy, B. *Org. Prep. Proced. Int.* **1995**, *27*, 637; (c) Chandler, M.; Bamford, M. J.; Conroy, R.; Lamont, B.; Patel, B.; Patel, V. K.; Steeples, I. P.; Storer, R.; Weir, N. G.; Wright, M.; Williamson, C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1173; (d) Liu, K.-G.; Yan, S.; Wu, Y.-L.; Yao, Z.-J. *Org. Lett.* **2004**, *6*, 2269.
13. For a report on the synthesis of peracetylated Neu5Ac2en methyl ester, an intermediate en route to zanamivir, see: Horn, E. J.; Gervay-Hague, J. *J. Org. Chem.* **2009**, *74*, 4357.
14. For oseltamivir analogues see: (a) Mohan, S.; McAtamney, S.; Haselhost, T.; von Itzstein, M.; Pinto, B. M. *J. Med. Chem.* **2010**, *53*, 7377; (b) Carbain, B.; Hitchcock, P. B.; Streicher, H. *Tetrahedron Lett.* **2010**, *51*, 2717; (c) D'Souza, C.; Kanyalkar, M.; Joshi, M.; Coutinho, E.; Srivastava, S. *Biochim. Biophys. Acta* **2009**, *1788*, 1740; (d) Carbain, B.; Martin, S. R.; Collins, P. J.; Hitchcock, P. B.; Streicher, H. *Org. Biomol. Chem.* **2009**, *7*, 2570; (e) Carbain, B.; Collins, P. J.; Callum, L.; Martin, S. R.; Hay, A. J.; McCauley, J.; Streicher, H. *Chem Med Chem* **2009**, *4*, 335; (f) Rungrotmongkol, T.; Frecer, V.; De-Eknamkul, W.; Hannonghua, S.; Miertus, S. *Antiviral Res.* **2009**, *82*, 51; (g) Kimura, Y.; Yamatsugu, K.; Kanai, M.; Echigo, N.; Kuzuhara, T.; Shibasaki, M. *Tetrahedron Lett.* **2009**, *50*, 3205; (h) Kraus, G. A.; Goronga, T. *Synthesis* **2007**, 1765; For zanamivir analogues, see: (i) Soulé, J.-F.; Mathieu, A.; Norsikian, S.; Beau, J.-M. *Org. Lett.* **2010**, *12*, 5322; (j) Xiong, R. S.; Zhao, Q. J.; Zhu, H. H.; Liu, Z.; Wei, Y. B.; Shen, J. S. *Chin. Chem. Lett.* **2010**, *21*, 1338; (k) Honda, T.; Kubo, S.; Masuda, T.; Arai, M.; Kobayashi, Y.; Yamashita, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2938; (l) Wen, W.-H.; Lin, M.; Su, C.-Y.; Wang, S.-Y.; Cheng, Y.-S. E.; Fang, J.-M.; Wong, C.-H. *J. Med. Chem.* **2009**, *52*, 4903.
15. (a) Sullivan, B.; Carrera, I.; Drouin, M.; Hudlicky, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 4229; (b) Hudlicky, T. *Pure Appl. Chem.* **2010**, *82*, 1785.
16. Hudlicky, T. U.S. Patent 61/052,435, 2008 (provisional).
17. Zylstra, G. J.; Gibson, D. T. *J. Biol. Chem.* **1989**, *264*, 14940.
18. Fabris, F.; Collins, J.; Sullivan, B.; Leisch, H.; Hudlicky, T. *Org. Biomol. Chem.* **2009**, *7*, 2619.
19. Werner, L.; Machara, A.; Hudlicky, T. *Adv. Synth. Catal.* **2010**, *352*, 195.
20. (a) Luzzio, F. A. *Org. React.* **1998**, *53*, 1; (b) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.
21. Morel, A. F.; Larghi, E. L.; Selvero, M. M. *Synlett* **2005**, 2755.
22. Yamatsugu, K.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2009**, *65*, 6017.
23. Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076.
24. (a) Nemoto, H.; Kubota, Y.; Yamamoto, Y. *J. Org. Chem.* **1990**, *55*, 4515; (b) Nemoto, H.; Li, X.; Ma, R.; Suzuki, I.; Shibuya, M. *Tetrahedron Lett.* **2003**, *44*, 73.
25. Raghavan, S.; Babu, V. S. *Tetrahedron* **2011**, *67*, 2044.
26. Acid **46** can be prepared in two-steps from pantolactone acrylate and butadiene. See: (a) Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem.* **1985**, *97*, 116; (b) Poll, T.; Sebezak, A.; Hartmann, H.; Helmchen, G. *Tetrahedron Lett.* **1985**, *26*, 3095; (c) Corey, E. J.; Huang, H.-C. *Tetrahedron Lett.* **1989**, *30*, 5235.
27. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.
28. (a) Fukuyama, T.; Cheung, M.; Kan, T. *Synlett* **1999**, 1301; (b) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.
29. Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301.
30. (a) Kocovsky, P.; Stary, I. *J. Org. Chem.* **1990**, *55*, 3236; (b) Berkowitz, D. B.; Pedersen, M. L. *J. Org. Chem.* **1995**, *60*, 5368; (c) Jenmalm, A.; Berts, W.; Luthman, K.; Csoreg, I.; Hacksell, U. *J. Org. Chem.* **1995**, *60*, 1026; (d) Jenmalm, A.; Luthman, K. *Tetrahedron Lett.* **1998**, *39*, 3213.

31. Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.
32. Sinou, D.; Emziane, M. *Tetrahedron Lett.* **1986**, *27*, 4423.
33. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.
34. (a) Ittah, Y.; Sasson, Y.; Shahak, I.; Isaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271; (b) Tanner, D.; Somfai, P. *Tetrahedron Lett.* **1987**, *28*, 1211.
35. Karpf, M.; Trussardi, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 5760.
36. Shikimic acid has recently become available in multi-hundred ton quantities either by extraction from the Chinese star anise or by a fermentation process that employs a genetically engineered *E. Coli* strain. See: Raghavendra, T. R.; Vaidyanathan, P.; Swathi, S. K.; Ramesha, B. T.; Ravikanth, G.; Ganeshaiah, K. N.; Srikrishna, A.; Shaanker, R. U. *Curr. Sci.* **2009**, *96*, 771 and references therein.
37. The researchers mentioned that F. Hoffmann-La Roche Ltd. has established partnerships with companies that have experience in azide chemistry on large scale to safely scale up this type of transformation.
38. Ma, J.; Zhao, Y.; Ng, S.; Zhang, J.; Zeng, J.; Than, A.; Chen, P.; Liu, X.-W. *Chem. Eur. J.* **2010**, *16*, 4533.
39. Büchi, G.; Powell, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 4559.
40. Pawda, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377.
41. Liu, R.; Herron, S. R.; Fleming, S. A. *J. Org. Chem.* **2007**, *72*, 5587.
42. Osato, H.; Jones, I. L.; Chen, A.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 60.
43. Ring-closing metathesis has been employed in previous syntheses of oseltamivir. See Ref. 9k.
44. Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937.
45. (a) Verheyden, J. P. K.; Moffatt, J. G. *J. Am. Chem. Soc.* **1964**, *86*, 2093; (b) Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 3853; (c) Gallos, J. K.; Goga, E. G.; Koumbis, A. E. *J. Chem. Soc., Perkin Trans. 1* **1994**, 611; (d) Paquette, L. A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849.
46. (a) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990; (b) Nakane, M.; Hutchinson, C. R.; Gollman, H. *Tetrahedron Lett.* **1980**, *21*, 1213; (c) Fürstner, A.; Jumbam, D.; Teslic, J.; Weidmann, H. *J. Org. Chem.* **1991**, *56*, 2213.
47. Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444.
48. Crimmins, M. T.; Rafferty, S. W. *Tetrahedron Lett.* **1996**, *37*, 5649.
49. Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353.
50. Wichienukul, P.; Akkarasamiyo, S.; Kongkathip, N.; Kongkathip, B. *Tetrahedron Lett.* **2010**, *51*, 3208.
51. Classon, B.; Liu, Z. *J. Org. Chem.* **1988**, *53*, 6126.
52. Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754.
53. Ko, J. S.; Keum, J. E.; Ko, S. Y. *J. Org. Chem.* **2010**, *75*, 7006.
54. Schmid, C. R.; Bradley, D. A. *Synthesis* **1992**, 587.
55. (a) Kametani, T.; Suzuki, T.; Sato, E.; Nishimura, M.; Unno, K. *J. Chem. Soc., Chem. Commun.* **1982**, 123; (b) Merrer, Y. L.; Gravier-Pelletier, C.; Micas-Languin, D.; Mestre, F.; Duréault, A.; Depezay, J.-C. *J. Org. Chem.* **1989**, *54*, 2409.
56. (a) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483; (b) Noe, M. C.; Letavic, M. A.; Snow, S. L. *Org. React.* **2006**, *66*, 109.
57. Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.
58. (a) For a review see: Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, 1525; (b) Rassu, G.; Auzzas, L.; Pinna, L.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Org. Lett.* **1999**, *1*, 1213; (c) Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2000**, *65*, 6307; (d) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Battistini, L.; Zanardi, F.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2001**, *66*, 8070; (e) Zanardi, F.; Battistini, L.; Marzocchi, L.; Acquitti, D.; Rassu, G.; Pinna, L.; Auzzas, L.; Zambrano, V.; Casiraghi, G. *Eur. J. Org. Chem.* **2002**, 1956; (f) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Marzocchi, L.; Acquotti, D.; Casiraghi, G. *J. Org. Chem.* **2002**, *67*, 5338; (g) Rassu, G.; Auzzas, L.; Zambrano, V.; Burreddu, P.; Battistini, L.; Curti, C. *Tetrahedron: Asymmetry* **2003**, *14*, 1665; (h) Rassu, G.; Auzzas, L.; Pinna, L.; Zambrano, V.; Zanardi, F.; Battistini, L.; Gaetani, E.; Curti, C.; Casiraghi, G. *J. Org. Chem.* **2003**, *68*, 5881; (i) Battistini, L.; Curti, C.; Zanardi, F.; Rassu, G.; Auzzas, L.; Casiraghi, G. *J. Org. Chem.* **2004**, *69*, 2611; (j) Zanardi, F.; Curti, C.; Sartori, A.; Rassu, G.; Roggio, A.; Battistini, L.; Burreddu, P.; Pinna, L.; Pelosi, G.; Casiraghi, G. *Eur. J. Org. Chem.* **2008**, 2273; (k) Liu, S.-L.; Shi, X.-X.; Xu, Y.-L.; Xu, W.; Dong, J. *Tetrahedron: Asymmetry* **2009**, *20*, 78.
59. Seebach, D.; Thaler, A.; Blaser, D.; Ko, S. Y. *Helv. Chim. Acta* **1991**, *74*, 1102.
60. Ishikawa, H.; Suzuki, T.; Orita, H.; Uchimaru, T.; Hayashi, Y. *Chem. Eur. J.* **2010**, *16*, 12616.
61. (a) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527; (b) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966; (c) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599.
62. Barnum, E. R.; Hamilton, C. S. *J. Am. Chem. Soc.* **1942**, *64*, 540.
63. Unless the ammonia treatment was performed prior to the addition of K_2CO_3, no 4-methylthiophenol elimination occurred even at 80 °C due, presumably, to chelation of the Zn(II) to the amine group.
64. Zhu, S.; Yu, S.; Wang, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4656.
65. Krówczyński, A.; Kozerski, L. *Synthesis* **1983**, 489.
66. 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.
67. For reviews on the subject see: (a) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869; (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.
68. Garcia Ruano, J. L.; Topp, M.; Lopez-Cantarero, J.; Aleman, J.; Remuinan, M. J.; Cid, M. B. *Org. Lett.* **2005**, *7*, 4407.
69. Kraus, G. A.; Goronga, T. *Synthesis* **2007**, 1765.
70. Trost, B. M.; Zhang, T. *Chem. Eur. J.* **2011**, *17*, 3630.
71. Lactone **165** can be prepared in two steps via iodocyclization of 3-cyclohexene-1-carboxylic acid followed by DBU-induced elimination in 84% yield. See: Barlett, P. A.; McQuaid, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7854.
72. (a) Grehn, L.; Ragnarsson, U. *Synthesis* **1987**, *275*; (b) For a Pd-catalyzed AAA with $HN(Boc)_2$ see: Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagne, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905.
73. (a) For Pd-catalyzed stereospecific allylic alkylations with $HN(Cbz)_2$ see: Fairhurst, R. A.; Taylor, R. J. WO Patent 2008006563, 2008. (b) For Pd-catalyzed AAA with $HN(Cbz)_2$ see: Fandrick, D. R. Ph.D. Thesis, Stanford University, 2006.
74. For Pd-catalyzed AAA with $NaN(CHO)_2$ see: Zhang, R.; Yu, L.; Xu, L.; Wang, Z.; Ding, K. *Tetrahedron Lett.* **2001**, *42*, 7659.
75. For Pd-catalyzed AAA examples with phthalimide, see: (a) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089; (b) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968; (c) Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520; (d) Trost, B. M.; Jiang, C.; Hammer, K. *Synthesis* **2005**, 3335; (e) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5987; (f) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Chem. Eur. J.* **2006**, *12*, 6607; (g) Trost, B. M.; Aponick, A. *J. Am. Chem. Soc.* **2006**, *128*, 3931; (h) Trost, B. M.; Aponick, A.; Stanzl, B. N. *Chem. Eur. J.* **2007**, *13*, 9547; (i) Trost, B. M.; O'Boyle, B. M. *Org. Lett.* **2008**, *10*, 1369.
76. For Pd-catalyzed AAA with sodium phthalimide, see: Trost, B. M.; Radinov, R. *J. Am. Chem. Soc.* **1997**, *119*, 5962.
77. Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657.
78. (a) Espino, C. G.; Fiori, K. W.; Kim, J.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378; (b) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562.
79. Tanaka, T.; Tan, Q.; Kawakubo, H.; Hayashi, M. *J. Org. Chem.* **2011**, *76*, 5477.
80. Epoxide **181** was prepared via oxidation of 1,4-cyclohexadiene with *m*-CPBA in 80% yield.
81. (a) Tan, Q. T.; Hayashi, M. *Adv. Synth. Catal.* **2008**, *350*, 2639; (b) Tan, Q. T.; Hayashi, M. *Org. Lett.* **2009**, *11*, 3314.
82. Sun, H.; Lin, Y.-J.; Wu, Y.-L.; Wu, Y. *Synlett* **2009**, 2473.
83. Salman, H.; Abraham, Y.; Tal, S.; Meltzman, S.; Kapon, M.; Tessler, N.; Speiser, S.; Eichen, Y. *Eur. J. Org. Chem.* **2005**, 2207.
84. Andersen, N.-G.; Maddaford, S.-P.; Keay, B.-A. *J. Org. Chem.* **1996**, *61*, 2885.
85. (a) Weeresakare, G.-M.; Xu, Q.; Rainier, J.-D. *Tetrahedron Lett.* **2002**, *43*, 8913; (b) Zhang, C.-M.; Trudell, M. L. *J. Org. Chem.* **1996**, *61*, 7189.
86. Singh, S.; Basmadjian, G. P. *Tetrahedron Lett.* **1997**, *38*, 6829.
87. (a) Wu, Y.-K.; Sun, Y.-P.; Yang, Y.-Q.; Hu, Q.; Zhang, Q. *J. Org. Chem.* **2004**, *69*, 6141; (b) Su, D.-W.; Wang, Y.-C.; Yan, T.-H. *Tetrahedron Lett.* **1999**, *40*, 4197.
88. Kamimura, A.; Nakano, T. *J. Org. Chem.* **2010**, *75*, 3133.
89. Hodgson, D. M.; Maxwell, G. M.; Miles, T. J.; Paruch, E.; Matthews, I. R.; Witherington, J. *Tetrahedron* **2004**, *60*, 3611.
90. Carlier, P. R.; Lo, C. W. S.; Lo, M. M.-C.; Wan, N. C.; Williams, I. D. *Org. Lett.* **2000**, *2*, 2443.
91. Arai, T.; Konno, F.; Ogawa, M.; Zhang, M.-R.; Suzuki, K. *J. Labelled Compd. Radiopharm.* **2009**, *52*, 350.
92. [1-^{11}C]Acetyl chloride was prepared by treating [^{11}C]CO_2 with MeMgBr followed by reaction with $(COCl)_2$.
93. (a) De Clercq, E. *Nat. Rev. Drug Discovery* **2006**, *5*, 1015; (b) von Itzsein, M. *Nat. Rev. Drug Discovery* **2007**, *6*, 967; (c) Uchide, N.; Toyoda, H. *Mini-Rev. Med. Chem.* **2008**, *8*, 491; (d) Mitrasinovic, P. M. *Curr. Drug Targets* **2010**, *11*, 315.
94. http://www.nature.com/avianflu/index.html (accessed June 19, 2011).
95. Enserink, M. *Science* **2006**, *312*, 382.
96. (a) McKimm-Breschkin, J. L. *Antiviral Res.* **2000**, *47*, 1; (b) Gubareva, L. V.; Webster, R. G.; Hayden, F. G. *Antimicrob. Agents Chemother.* **2001**, *45*, 3403; (c) de Jong, M. D.; Thanh, T. T.; Khanh, T. H.; Hien, V. M.; Smith, G. J. D.; Chau, N. V.; Cam, B. V.; Qui, P. T.; Ha, D. Q.; Guan, Y.; Peiris, J. S. M.; Hien, T. T.; Farrar, J. *N. Engl. J. Med.* **2005**, *353*, 2667.
97. GSK is expected to increase its annual production capacity of zanamivir to 190 million treatment courses by the end of 2009. See: http://www.gsk.com/media/pressreleases/2009/2009_pressrelease_10077.htm (accessed June 19, 2011).
98. Peramivir is a neuraminidase inhibitor manufactured by BioCryst Pharmaceuticals and currently undergoing Phase III clinical trials.
99. Smee, D. F.; Hurst, B. L.; Wong, M.-H.; Tarbet, E. B.; Babu, Y. S.; Klumpp, K.; Morrey, J. D. *Antiviral Res.* **2010**, *88*, 38.

Biographical sketch

Javier Magano was born in Madrid, Spain in 1964. He received his Bachelor's Degree in organic chemistry from Complutense University in Madrid in 1987 and his Master's Degree in chemistry from the University of Michigan in 1990. After working for the oil industry in Spain for 3 years, he obtained a Master's Degree in rubber and polymer science from the School of Plastics and Rubber at the Center for Advanced Scientific Research in Madrid. In 1995 he moved back to the United States to carry out graduate work at the University of Michigan. In 1998 he joined Pfizer Inc. to work in the Early Process group in Ann Arbor, MI, and currently in Groton, CT as senior scientist developing scalable processes for the production of drug candidates. He has also worked in the area of biologics for 1.5 years, during which time he has developed technologies for the manufacture of linkers and for their use in conjugation processes with peptides.