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Research and Development of a Second-Generation Process for Oseltamivir Phosphate, Prodrug for a Neuraminidase Inhibitor

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Abstract:

A second-generation manufacturing process from a shikimic acid-derived epoxide to oseltamivir phosphate features a magnesium chloride−amine complex-catalyzed ring opening of the epoxide by *tert*-butylamine, a selective O-sulfonylation of the resulting *tert*-butylamino alcohol, a surprisingly efficient cleavage of a *tert*-butyl group from an aliphatic *tert*-butylamide, and the isolation of oseltamivir phosphate from a palladium-catalyzed allyl transfer reaction mixture. The overall yield from the epoxide to oseltamivir phosphate has been increased from 27 to 29% or 35−38% for two previous processes, respectively, to 61%.

Introduction

Oseltamivir phosphate (**1**, Tamiflu, Ro 64-0796, GS 4104) is a prodrug for **2**, a competitive inhibitor of influenza A and B neuraminidase (Figure 1). Oseltamivir phosphate **1** is orally administered for the treatment and prevention of influenza infections.

Our second-generation process parallels previous processes recently described by Gilead[1] and Roche-Basel.[2] The three processes utilize (1) the same starting epoxide, (2) a regioselective ring opening of the epoxide with ammonia equivalent A, (3) a conversion of an amino alcohol to an aziridine, and (4) a regioselective ring opening of an aziridine with ammonia equivalent B. The three processes diverge in the choice of ammonia equivalents A and B, promoters for the epoxide and aziridine openings, and methods for unmasking the ammonia equivalents.

The Gilead route uses azide and Brønsted acid for both ring openings and azide reduction with phosphine to reveal both amino groups (Scheme 1). The result is an efficient process but one requiring expertise in handling two low-molecular weight azides on a production scale. In addition, a competitive conjugate addition of azide results in low levels of β-azido ester associated with a positive Ames test when present in the final drug substance. The Roche-Basel route uses allylamine−magnesium bromide etherate to open epoxide **3** and allylamine−Brønsted acid to open an aziridine. Both amino groups are revealed by heterogeneous palladium-(0)-catalyzed allyl isomerization and in situ enamine hydrolysis (Scheme 2). This route addresses the azide handling and Ames test isues. Our second-generation route uses *tert*-butylamine−magnesium chloride to open epoxide **3** and diallylamine−Brønsted acid to open an aziridine. The first amino group is revealed by acid-mediated *tert*-butyl group

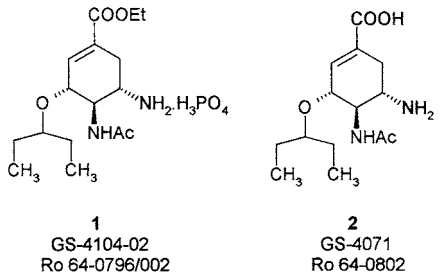
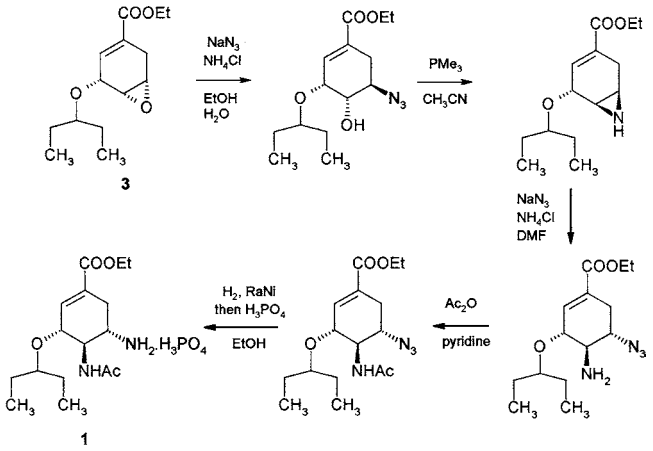
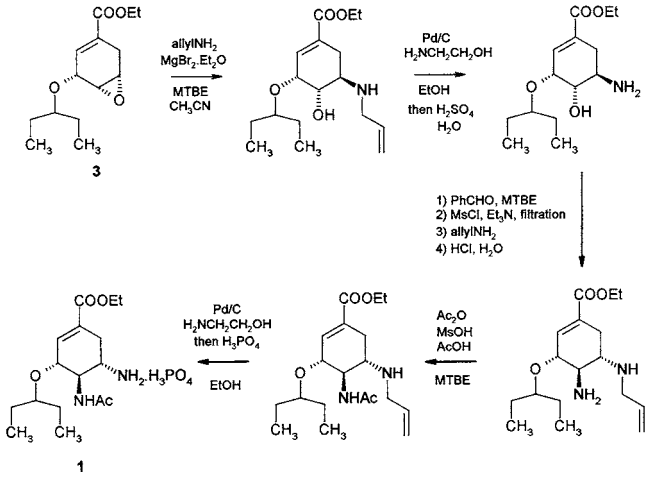


Figure 1. **Oseltamivir phosphate and the neuraminidase inhibitor.**

Scheme 1. **Gilead route to oseltamivir phosphate 1**



Scheme 2. **Roche-Basel route to oseltamivir phosphate 1**



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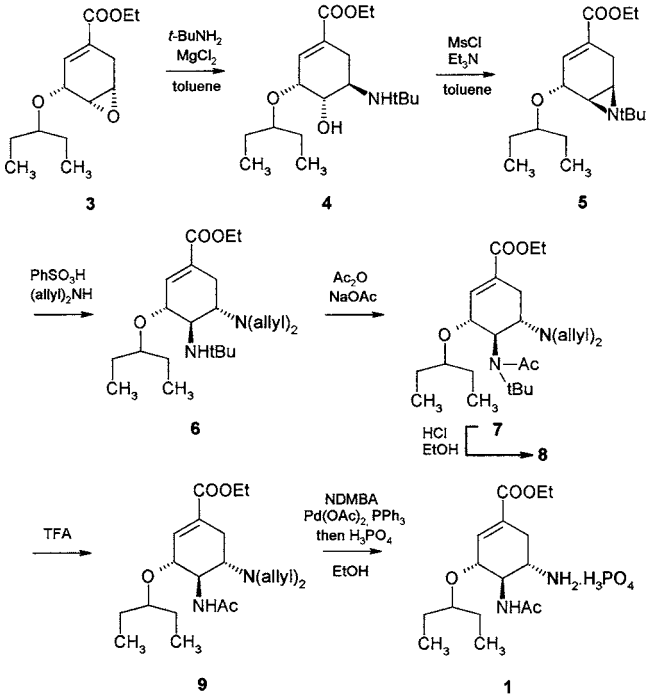
Scheme 3. **Second-generation route to oseltamivir phosphate 1**



cleavage after acetylation. The second amino group is revealed by allyl group transfer to 1,3-dimethylbarbituric acid catalyzed by a homogeneous palladium(0)-phosphine catalyst (Scheme 3). This route addresses the azide handling and Ames test issues and has the highest overall yield from expensive epoxide **3** to final drug substance.

Epoxide Opening using Magnesium Chloride. The addition of nitrogen nucleophiles to epoxides has been extensively exploited in synthesis. Since epoxide **3** is prone to aromatization on reaction with strong bases, ring opening with a metal amide was not an option.[2] Karpf and Trussardi demonstrated catalysis (0.15−0.25 equiv) of the reaction of epoxide **3** with allylamine using "magnesium halide derivatives". These are defined as anhydrous or hydrated magnesium chloride, magnesium bromide or magnesium iodide, or an etherate, in particular a dimethyl etherate, a diethyl etherate, a dipropyl etherate, or a diisopropyl etherate thereof.

We confirmed magnesium bromide diethyl etherate catalysis of epoxide **3** opening with *tert*-butylamine. We also pursued magnesium chloride catalysis in an effort to reduce catalyst cost and eliminate the ethyl ether byproduct. The rate of formation of the amino alcohol **4** is slow when the order of reagent addition is magnesium chloride, epoxide, then amine. We suggest that magnesium chloride quickly converts epoxide **3** to a chlorohydrin and that the chlorohydrin only slowly reverts to epoxide **3** under the reaction conditions.[3] The rate of formation of the amino alcohol **4** is faster when the order of reagent addition is magnesium chloride, amine, and then epoxide. The addition of *tert*-butylamine to anhydrous magnesium chloride produced a sparingly soluble *tert*-butylamine−magnesium chloride complex. Much less chlorohydrin is formed in the conversion of epoxide **3** to amino alcohol **4** using this preformed *tert*-butylamine−magnesium chloride complex.[4]

Aziridine Formation. The Roche-Basel process relies on an efficient protection−deprotection strategy to achieve selective O-sulfonylation of the amino alcohol. Selective O-sulfonylation can be accomplished without protection−deprotection when an amino alcohol has an electron-withdrawing (sulfonyl, acyl, phosphoryl) or bulky (trityl,[5] diphenylmethyl,[6] even α-methylbenzyl[7]) nitrogen subsitituent. Mesylation and cyclization of *tert*-butylamino alcohol **4** is simple and efficient (93%).

Aziridine Opening. The acid-catalyzed addition of nucleophiles to aziridines has been extensively exploited in synthesis. Clean inversion of stereochemistry is typically observed, indicative of an S_N2 mechanism. The mechanism may vary, depending on the specific acid catalyst, nucleophile, nitrogen substituent, and carbon substituents.[8]

There is good precedent for the acid-catalyzed ring opening of *N*-alkylaziridines by aliphatic amines. Ring opening of 7-azabicyclo[4.1.0]heptane with ammonia or an amine yields the *trans*-1,2-diaminocyclohexane.[9] Ring opening of a 7-azabicyclo[4.1.0]heptane by an amine in water containing ammonium chloride is the preferred method for construction of the *trans*-diaminocyclohexane portion of many κ-opioid analgesics.[10] Ring opening of *N*-benzyl-7-azabicyclo[4.1.0]heptane by benzylamine is catalyzed by ytterbium triflate (20 mol %) or lithium bis-trifluoromethanesulfonimidate (20−50 mol %).[11,12] Lithium perchlorate (1 equiv) facilitates the ring opening of *N*-[(*S*)-α-phenylethyl]-cyclohexene aziridine by (*S*)-α-phenylethylamine.[7]

Karpf and Trussardi used methanesulfonic acid for ring opening of an aziridine by allylamine as part of their four-step domino sequence.[2] We have demonstrated the sulfonic acid-promoted opening of aziridine **5** by diallylamine (93% yield using 1.24 equiv of $PhSO_3H$ and 1.35 equiv of diallylamine at 120 °C for 5.5 h). Comparable results can be achieved using a Lewis acid catalyst (10−20 mol %) such as copper (II) chloride, bromide, or triflate, zinc chloride, zinc triflate, or boron trifluoride etherate.

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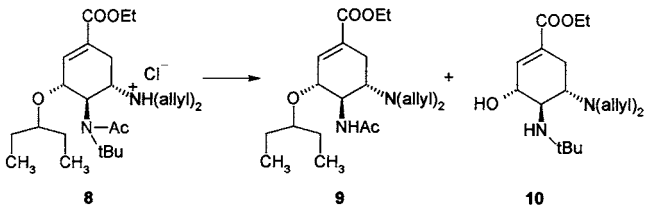
Acetylation. The efficient acetylation of secondary amines with acetic anhydride is well documented. However, the acetylation we intended to accomplish is uniquely difficult. In fact, heating a mixture of diamine **6** and two equivalents of acetic anhydride at 90 °C for 1 h resulted in low conversion. While pyridine does catalyze the acetylation, the high water solubility and teratogenicity of pyridine complicate recovery/recycle or disposal on a production scale. We demonstrated that pyridine can be replaced by calcium oxide, magnesium oxide, lithium carbonate, sodium carbonate, potassium acetate, sodium acetate, dipotassium hydrogen phosphate, or tripotassium phosphate.[13]

Cleavage of the *tert*-Butyl Acetamide. The efficient cleavage of the *tert*-butyl group from the nitrogen of *aliphatic* acetamide **7** was a key observation. While *tert*-butyl cleavage from the oxygen of ethers, carbamates, and esters has been extensively exploited in synthetic protection-deprotection strategies for many years, *tert*-butyl cleavage from the nitrogen of amines, carbamates, and amides has received less attention. The *tert*-butyl group of a cyclopropylamine can be cleaved upon prolonged heating in acid (aqueous 2 N HCl at reflux for 3−5 days).[14] Reaction of an N-substituted-N-*tert*-butyl carbamate with triflic acid at 25 °C afforded a carbamate-protected primary amine.[15] Acid hydrolysis of N-*tert*-amyl and N-*tert*-octyl acetamides produced the corresponding alkene, ammonia, and acetic acid.[16] Researchers at Lederle Labs concluded that the removal of a *tert*-butyl group from an amide nitrogen "was too difficult for practical application to peptide synthesis." [17] Encouraging results have been reported for *aromatic* amides: reaction of N-*tert*-butyl benzamide with 98% sulfuric acid for 5 min at 25 °C afforded benzamide (99%). *tert*-Butyl cleavage with trifluoroacetic acid at reflux was a key step in a short synthesis of lunularic acid, a growth inhibitor found in *Lunularia cruciata*.[18]

We found reaction of *tert*-butyl acetamide **7** with one equivalent of hydrogen chloride in ethanol at < 25 °C produces a precipitate of the hydrochloride salt **8**. Isolation of salt **8** is the only cleanup required in the sequence between epoxide **3** and oseltamivir phosphate **1**. The *tert*-butyl group of salt **8** is then cleaved with trifluoroacetic acid at 25−50 °C or with hydrogen chloride in ethanol at reflux.

Cleavage of the pentyl group is competitive using hydrogen chloride in ethanol at reflux. Cleavage to an alcohol, intramolecular transfer of the acetyl group from nitrogen to oxygen, then transesterification to ethanol produces diamino alcohol **10** (eq 1).



Cleavage of the acetyl group back to diamine **6** followed pentyl ether cleavage is unlikely: no diamino alcohol **10** is produced from diamine **6** and hydrogen chloride in ethanol after 4 h at reflux.

Deallylation. Two general methods are available for amine deallylation: metal catalyzed double bond isomerization and enamine hydrolysis or palladium(0) catalyzed allyl transfer to a nucleophilic allyl scavenger. Deallylation by isomerization/hydrolysis with $(PPh_3)_3RhCl$ in aqueous acetonitrile was the key step in the synthesis of anticapsin from L-tyrosine.[19] Alternative conditions for isomerization and enamine hydrolysis are Pd/C and methanesulfonic acid in water.[20] Since oseltamivir is prone to acetyl migration under acidic conditions or in the presence of salts, Karpf and Trussardi developed new conditions for the isomerization and enamine cleavage: Pd/C and ethanolamine in refluxing ethanol (70% yield for deallylation and phosphate salt formation).[2]

The removal of allyl protecting groups by η^3-allyl palladium-mediated transfer to a nucleophilic scavenger has recently been reviewed.[21] Amine deallylation by allyl transfer to 1,3-dimethylbarbituric acid (NDMBA) was reported by Guibé in 1993.[22] More recently, α-allyl-α-amino acid esters were produced by allylation of an amino acid ester, [2,3]-Stevens rearrangement, and amine deallylation with NDMBA.[23] 2-Mercaptobenzoic acid[24] and *p*-toluenesulfinic acid[25] are also effective scavengers. Deallylation of *N*-allyl histidine derivatives was demonstrated with both NDMBA and, under milder conditions, with phenylsilane/acetic acid.[26] We developed a palladium-catalyzed allyl group transfer to NDMBA in ethanol which allowed us to carry the allyl transfer reaction mixture directly into the phosphate salt formation (88% yield for deallylation and phosphate salt formation).

The key features of the second-generation process are a magnesium chloride−amine complex catalyzed ring opening of epoxide **3**, a selective O-sulfonylation of the resulting *tert*-butylamino alcohol **4**, a surprisingly efficient cleavage of the *tert*-butyl group from aliphatic amide **8**, oseltamivir phosphate **1** isolation from a palladium-catalyzed allyl

(13) While there is little precedent for the use of tripotassium phosphate as an acetylation catalyst, we found that *tert*-butyl acetamide yields using this base nearly matched yields obtained using sodium acetate. Leppänen, S.; Strandman, L.; Takala, S.; Pajunen, P.; Koskikallio, J. *Acta Chem. Scand.* **1973**, *27*, 3572. (b) Jpn. Kokai Tokkyo Koho 58074639, 1983; *Chem Abstr.* **1983**, *99*, 159009a.
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transfer reaction mixture. The overall yields from epoxide **3** for the three processes are: Gilead 27−29%, Roche-Basel 35−38%, and second-generation 61%.

Experimental Section

Ethyl (3*R*,4*S*,5*R*)-5-*N*-(1,1-Dimethylethyl)amino-3-(1-ethylpropoxy)-4-hydroxy-1-cyclohexene-1-carboxylate (4). A magnesium chloride−amine complex was first prepared by adding 65 mL (45.2 g, 0.619 mol, 1.50 equiv) of *tert*-butylamine to a suspension of 35.7 g (0.375 mol, 0.90 equiv) of magnesium chloride in 200 mL of dry toluene at 25 °C. The colorless slurry was stirred at 25 °C for 6 h. A solution of 105.0 g (0.413 mol) of epoxide **3**[27] in 250 mL of dry toluene was added via an 18-gauge stainless steel cannula to the magnesium chloride−amine complex suspension at 20−25 °C. The resulting suspension was heated at 50 °C for 8 h. More *tert*-butylamine (52 mL, 36.2 g, 0.495 mol, 1.20 equiv) was added, and the solution was heated for an additional 12 h.

After cooling the yellow solution to 25 °C, 200 mL of 10% w/w aqueous citric acid solution was added and the solution stirred at 25 °C for 30 min. The layers were separated. The organic layer was concentrated in vacuo (rotary evaporator at 40 °C and 25 mmHg and then vacuum pump at 25 °C and 1 mmHg for 17 h) to afford 135.3 g of orange oil (LC assay 96.0 wt % **4**, 96.1% yield).

An analytical sample was prepared by radial chromatography on silica gel; ^{1}H NMR ($CDCl_3$) δ 6.84−6.82 (m, 1H), 4.23 (t, 1H, J = 4.0 Hz), 4.20 (q, 2H, J = 7.0 Hz), 3.6−3.0 (br, 1H, NH or OH), 3.55 (p, 1H, J = 6.0 Hz), 3.37 (dd, 1H, J = 4.0 Hz, J = 9.5 Hz), 3.12−3.08 (m, 1H, J = 5.0 Hz), 2.91 (dd, 1H, J = 5.5 Hz, J = 17 Hz), 1.97−1.91 (m, 1H, J = 8.0 Hz, J = 17 Hz), 1.59−1.54 (m, 4H), 1.29 (t, 3H, J = 7.0 Hz), 1.13 (s, 9H), 0.95 (t, 3H, J = 7.5 Hz), 0.91 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 166.9, 135.7, 131.7, 82.8, 72.6, 71.3, 61.0, 51.3, 48.9, 34.3, 30.5, 26.8, 26.7, 14.5, 10.4, 9.5; IR (neat) 3600−3300, 2970, 2940, 2880, 1720, 1660, 1470, 1400, 1370, 1240, 1110, 1080, 1060, 670 cm^{-1}. HRFABMS found *m*/*z* 328.2481 (M + H$^+$), calcd for $C_{18}H_{34}NO_4$ 328.2488.

Ethyl (3*R*,4*S*,5*R*)-4,5-(1,1-Dimethylethyl)imino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (5). Methanesulfonyl chloride (32.9 mL, 48.7 g, 0. 425 mol, 1.07 equiv) was added to a solution of 135.3 g (0.397 mol at 96.0 wt %) of the crude alcohol **4** in 500 mL of dry toluene at 5 °C (cool H_2O bath) over 30 min. The solution was warmed to 10 °C and stirred for 60 min. Triethylamine (112 mL, 81.3 g, 0.804 mol, 2.03 equiv) was added dropwise at <5 °C over 45 min. The resulting suspension was stirred at 5 °C for 20 min, heated to 70 °C (bath) over 2 h, and then held at 70 °C for an additional 3 h.

After cooling the suspension to <15 °C, a solution of anhydrous potassium carbonate (55.6 g, 0.402 mol) in 200 mL of water was added. The suspension was stirred for 15 min, and the layers were separated. The organic layer was concentrated in vacuo (rotary evaporator at 40 °C and 25 mmHg) to afford 132.2 g of orange oil with trace solids (LC assay 86 wt % **5**, 93% yield).

An analytical sample was prepared by radial chromatography on silica gel; ^{1}H NMR ($CDCl_3$) δ 6.80−6.78 (m, 1H), 4.17 (dq, 2H, J = 7.5 Hz, J = 1.5 Hz), 4.15−4.14 (m 1H), 3.39 (p, 1H, J = 6.0 Hz), 2.62−2.52 (m, 2H), 2.13−2.11 (m, 1H), 2.00 (d, 1H, J = 6.0 Hz), 1.61−1.51 (m, 4H), 1.26 (t, 3H, J = 7.5 Hz), 1.00 (s, 9H), 0.98 (t, 3H, J = 7.5 Hz), 0.92 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 167.3, 134.4, 128.6, 82.4, 70.9, 60.7, 53.3, 33.2, 29.9, 27.0, 26.9, 26.8, 25.0, 14.5, 10.2, 9.9; IR (neat) 3575, 2970, 2930, 2875, 1720, 1650, 1460, 1370, 1250, 1230, 1215, 1080, 1070, 1050, 670 cm^{-1}. HRFABMS found *m*/*z* 310.2378 (M + H$^+$), calcd for $C_{18}H_{32}NO_3$ 310.2382.

Ethyl (3*R*,4*R*,5*S*)-5-*N*,*N*-Diallylamino-4-(1,1-dimethylethyl)amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (6). Benezensulfonic acid (72.0 g, 0.454 mol, 1.24 equiv) was added to a mixture of 132.2 g (0.367 mol at 86 wt %) of the aziridine **5** and 61.2 mL (48.16 g, 0.496 mol, 1.35 equiv) of diallylamine. The suspension was heated at 120 °C (bath) for 5.5 h.

The solution was cooled to <90 °C, and 150 mL of toluene was added. The solution was cooled to 10 °C, and a solution of 18.5 g (0.463 mol) sodium hydroxide in 250 mL of water was added. After stirring the suspension for 30 min, the layers were separated. The aqueous layer was extracted with 50 mL of toluene twice. The combined organic layers were concentrated in vacuo (40 °C and 25 mmHg) to afford 157.2 g of brown oil (LC assay 88.1 wt % **6**, 92.8% yield).

An analytical sample was prepared by radial chromatography on silica gel; ^{1}H NMR ($CDCl_3$) δ 6.87 (t, 1H, J = 2.5 Hz), 5.79 (m, 2H), 5.17 (d, 2H, J = 17.5 Hz), 5.11 (d, 2H, J = 10.5 Hz), 4.22 (q, 2H, J = 7.0 Hz), 3.94−3.92 (m, 1H), 3.41−3.36 (m, 1H), 3.31−3.27 (dm, 2H, J = 14 Hz), 2.92 (dd, 2H, J = 14 Hz, J = 8.0 Hz), 2.81 (dd, 1H, J = 10.5 Hz, J = 6.5 Hz), 2.69 (dt, 1H, J = 10.5 Hz, J = 4.5 Hz), 2.56 (dd, 1H, J = 17.0 Hz, J = 4.5 Hz), 2.19 (dt, 1H, J = 17.0 Hz, J = 3 Hz), 1.82−1.74 (m, 1H), 1.64−1.56 (m, 1H), 1.51−1.38 (m, 2H), 1.31 (t, 3H, J = 7.0 Hz), 1.15 (s, 9H), 0.91 (t, 3H, J = 7.5 Hz), 0.87 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 167.1, 137.9, 136.9, 130.3, 117.7, 80.1, 78.8, 60.9, 58.5, 55.3, 52.6, 50.7, 31.1, 26.7, 25.3, 22.5, 14.5, 10.5, 9.87; IR (neat) 3590, 3640−3000, 2980, 2930, 2875, 2820, 1720, 1665, 1640, 1230, 675 cm^{-1}. HRFABMS found *m*/*z* 407.3280 (M + H$^+$), calcd for $C_{24}H_{43}N_2O_3$ 407.3274.

Ethyl (3*R*,4*R*,5*S*)-4-*N*-Acetyl(1,1-dimethylethyl)amino-5-*N*,*N*-diallylamino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (7). Acetic anhydride (158.5 mL, 171.5 g, 1.68 mol, 4.94 equiv) was added to a mixture of 157.1 g (340 mmol at 88.1 wt % assay) of diamine **6** and 41.35 g (504 mmol, 1.48 equiv) of anhydrous sodium acetate. The resulting suspension was heated at 110−116 °C and 200 rpm for 4 h.

(27) An industrial synthesis of epoxide **3** has been described: 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.; Rockel-Stäbler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266.

The suspension was cooled to 50 °C, diluted with 600 mL of heptane, cooled to 25 °C, and then left standing overnight. The suspension was cooled to 0 °C and then quenched by dropwise addition of a solution of 121.0 g (3.03 mol) of sodium hydroxide in 485 mL of H_2O over 190 min at 0−5 °C. The suspension was stirred and warmed to 25 °C over 40 min. The layers were separated, and the aqueous layer was extracted with 100 mL of heptane. The combined organic layers were washed with 100 mL of H_2O and then concentrated in vacuo (rotary evaporator at 30 °C and 40−10 mmHg) to afford 175.35 g of brown syrup with trace solids (LC assay 82.1 wt % **7**, 94.4% yield).

An analytical sample was prepared by radial chromatography on silica gel; ^{1}H NMR ($CDCl_3$) δ 6.87 (m, 1H), 5.81−5.73 (m, 2H), 5.12 (d, 2H, J = 17 Hz), 5.07 (d, 2H, J = 10.5 Hz), 5.02−4.85 (br), 4.22 (dt, 2H, J = 7 Hz), 3.85−3.75 (br), 3.58−3.46 (br), 3.28 (br), 3.24 (br d, 2H, J = 14 Hz), 2.88 (dd, 2H, J = 14 Hz, J = 8 Hz), 2.46−2.38 (m, 2H), 2.28−2.18 (br, 3H), 1.88 (br), 1.63−1.54 and 1.44−1.34 (m, m, 4H), 1.51 (s, 9H), 1.31 (t, 3H, J = 7 Hz), 0.93 (t, 3H, J = 7.5 Hz), 0.81 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 172.5, 166.8, 140.5, 137.2, 130.7, 117.1, 79.5, 73.2, 62.2, 60.9, 56.0, 53.2, 32.2, 31.8, 27.2, 26.6, 25.4, 23.6, 14.5, 10.0, 9.9; IR (neat) 3570, 3090, 2975, 2940, 2880, 2820, 1720, 1625, 1475, 1450, 1370, 1240, 1120, 1060, 675 cm^{-1}. HRFABMS found m/z 449.3368 (M + H$^+$), calcd for $C_{26}H_{45}N_2O_4$ 449.3379.

Ethyl (3*R*,4*R*,5*S*)-4-*N*-Acetyl(1,1-dimethylethyl)amino-5-*N*,*N*-diallylamino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate·HCl (8). A solution of crude *tert*-butyl acetamide **7** (175.3 g, 321 mmol at 82.1 wt %) in 295 mL of anhydrous ethanol was prepared at 300 rpm. A solution of dry hydrogen chloride (14.94 g HCl, 410 mmol, 1.28 equiv) in 50 mL of anhydrous ethanol was prepared at < 25 °C and then added to the crude *tert*-butyl acetamide solution at 13−20 °C over several minutes. Ethanol (5 mL) was used to complete the transfer. The suspension was then cooled to 0−5 °C at 150 rpm. Heptane (350 mL) was added dropwise over 27 min, and then the suspension was cooled to −15 °C and stirred for 60 min. The precipitate was suction filtered, washed with 50 mL of 1:1 ethanol−heptane at −15 °C, washed with 100 mL of heptane at −5 °C, and then dried in vacuo (vacuum oven at 50 °C and 15 mmHg for 40 h) to afford 142.96 g of a fluffy beige-tan solid (LC assay 100.7 wt % **8**, 91.9% yield).

A satisfactory elemental analysis could not be obtained for this salt; ^{1}H NMR ($CDCl_3$) δ 6.97 (br, 1H), 6.61−6.51 (m, 1H), 6.35−6.25 (m, 1H), 5.53−5.39 (m, 4H), 5.01−4.98 (br d, 1H), 4.77−4.70 (m, 1H), 4.26 (q, 2H, J = 7 Hz), 4.24−4.18 (br, 1H), 4.06−3.99 (br, 1H), 3.88 (br t, 1H), 3.51−3.44 (m, 1H), 3.41−3.33 (m, 1H), 3.33−3.27 (m, 1H), 2.80−2.73 (br d, 1H), 2.66−2.58 (m, 1H), 2.62 (m, 1H), 2.54 (s, 3H), 1.68 (s, 9H), 1.68−1.54 (m, 2H), 1.46−1.34 (m, 2H), 1.34 (t, 3H, J = 7 Hz), 0.96 (t, 3H, J = 7.5 Hz), 0.82 (t, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 175.9, 165.5, 140.0, 128.3, 127.4, 127.0, 125.1, 124.0, 79.7, 71.0, 61.4, 59.3, 58.9, 58.2, 55.4, 53.0, 32.5, 28.1, 26.6, 25.1, 24.2, 14.3, 10.1, 10.0.

Ethyl (3*R*,4*R*,5*S*)-4-*N*-Acetylamino-5-*N*,*N*-diallylamino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate (9). A mixture of 142.94 g (295 mmol at 100.0 wt %) of the hydrochloride salt **8** and 200 mL of trifluoroacetic acid was heated at 50 °C for 1.5 h.

The solution was cooled to 25 °C and 200 mL of toluene was added. The solution was concentrated on a rotary evaporator at 48 °C (bath) and 80−50 mmHg. This dilution−concentration procedure was repeated twice more. The solution was then diluted with 400 mL of toluene, cooled to 0−2 °C, and diluted further with 60 mL of H_2O. A solution of 44.46 g (1.11 mol) sodium hydroxide in 87.7 g H_2O was prepared then added portionwise at 0 to 2 °C until the aqueous layer was pH 12−13. The layers were separated. The aqueous layer was extracted with 75 mL toluene. The combined organic layers were washed with 50 mL of H_2O and then concentrated in vacuo (rotary evaporator at 35 °C and 40−30 mmHg) to afford 165.52 g of brown syrup with trace solids (LC assay 67.5 wt % **9**, 96.6% yield).

After precipitation with heptane, an analytical sample was prepared by recrystallization from heptane−ethyl acetate, mp 101.8−102.3 °C; ^{1}H NMR ($CDCl_3$) δ 6.73 (m, 1H), 5.76−5.68 (m, 2H), 5.35 (d, 1H), 5.16 (d, 2H, J = 16.5 Hz), 5.07 (d, 2H, J = 10 Hz), 4.21 (q, 2H, J = 7 Hz), 4.08 (dm, 1H, J = 9 Hz), 3.91 (dt, 1H, J = 11.5 Hz, J = 9 Hz), 3.32 (p, 1H, J = 5.5 Hz), 3.28 (dm, 2H, J = 14.5 Hz), 3.05 (dt, 1H, J = 11.5 Hz, J = 5 Hz), 2.92 (dd, 2H, J = 14.5 Hz, J = 7.5 Hz), 2.58 (dd, 1H, J = 17 Hz, J = 5 Hz), 2.17 (ddt, 1H, J = 17 Hz, J = 10.5 Hz, J = 3.5 Hz), 2.00 (s, 3H), 1.54−1.47 (m, 4H), 1.30 (t, 3H, J = 7 Hz), 0.91 (t, 3H, J = 7 Hz), 0.87 (t, 3H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 170.4, 166.9, 138.5, 137.3, 129.9, 116.9, 82.4, 77.7, 61.1, 56.5, 53.5, 52.5, 26.3, 25.8, 23.9, 23.7, 14.5, 9.8, 9.5; IR (KBr) 3270, 3110, 2980−2960, 2930, 2880, 2810, 1720, 1650, 1580, 1470, 1450, 1380, 1270, 1235, 1120, 1075, 1055, 925 cm^{-1}. HRFABMS found m/z 393.2756 (M + H$^+$), calcd for $C_{22}H_{37}N_2O_4$, 393.2753. Anal. Calcd for $C_{22}H_{36}N_2O_4$: C, 67.32; H, 9.24; N, 7.14. Found: C, 67.00; H, 9.42; N, 7.03.

Ethyl (3*R*,4*R*,5*S*)-4-*N*-Acetylamino-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylate phosphate [1:1] (1). 1,3-Dimethylbarbituric acid (NDMBA) (15.17 g, 97.2 mmol), 0.8493 g (3.24 mmol, 4.0 mol %) of triphenylphosphine, 0.1817 g (0.809 mmol, 1.0 mol %) of palladium acetate, and 58 mL of absolute ethanol were charged to a solution of 43.06 g of diallylamino acetamide **9** (81.0 mmol at 73.8 wt %) in 133 mL of absolute ethanol. The flask was sealed and the mixture stirred under a nitrogen sweep for 10 min. The solution was heated at 35 °C for 2 h.

The resulting solution of oseltamivir **2** was cooled and then transferred to a 250-mL addition funnel. Absolute ethanol (25 mL) was used to complete the transfer. A 500-mL flask was charged with 9.40 g of 85% phosphoric acid and 120 mL of absolute ethanol. The phosphoric acid−ethanol mixture was heated to 50 °C, and then 160 mL (∼two-thirds of the total volume) of the solution of oseltamivir **2** was added. Seed crystals of oseltamivir phosphate **1** (102 mg) were added to initiate crystallization. The resulting suspension was stirred at 50 °C for 45 min, and then the

remaining solution of oseltamivir **2** was added dropwise over 30 min. The addition funnel was rinsed with 8 mL of absolute ethanol. The suspension was cooled to −17 to −18 °C over 15 h and then maintained at that temperature for an additional 2 h. The precipitate was suction filtered using a jacketed fritted funnel, washed with 50 mL of acetone five times, washed with 50 mL of heptane three times, and then dried in vacuo (<50 °C and 15−20 mmHg with nitrogen sweep) to afford 29.38 g of colorless solid (LC assay 99.9 wt %**1**, 88.4% yield).

Supporting Information Available

Analytical methods (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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