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New, Efficient Synthesis of Oseltamivir Phosphate (Tamiflu) via Enzymatic Desymmetrization of a *meso*-1,3-Cyclohexanedicarboxylic Acid Diester

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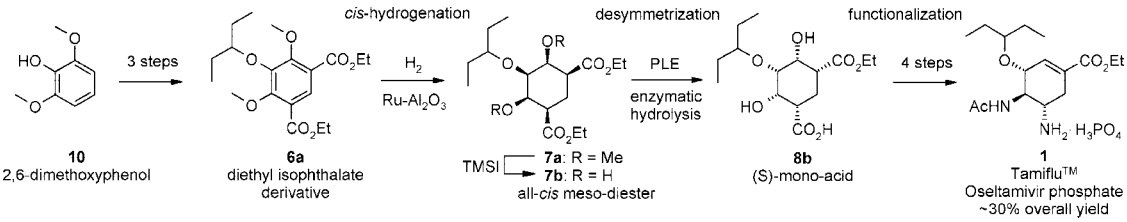
Received February 13, 2008



A new, enantioselective synthesis of the influenza neuraminidase inhibitor prodrug oseltamivir phosphate **1** (Tamiflu) and its enantiomer ***ent*-1** starting from cheap, commercially available 2,6-dimethoxyphenol **10** is described. The main features of this approach comprise the *cis*-hydrogenation of 5-(1-ethyl-propoxy)-4,6-dimethoxy-isophthalic acid diethyl ester (**6a**) and the desymmetrization of the resultant all-*cis meso*-diesters **7a** and **7b**, respectively. Enzymatic hydrolysis of the *meso*-diester **7b** with pig liver esterase afforded the (*S*)-monoacid **8b**, which was converted into cyclohexenol **17** via a Curtius degradation and a base-catalyzed decarboxylative elimination of the Boc-protected oxazolidinone **14**. Introduction of the second amino function via S_N2 substitution of the corresponding triflate **18** with NaN_3 followed by azide reduction, N-acetylation, and Boc-deprotection gave oseltamivir phosphate **1** in a total of 10 steps and an overall yield of ~30%. The enantiomer ***ent*-1** was similarly obtained via an enzymatic desymmetrization of *meso*-diester **7a** with *Aspergillus oryzae* lipase, providing the (*R*)-monoacid ***ent*-8a**.

Introduction

Oseltamivir phosphate **1** is the orally active prodrug of the potent and selective inhibitor **2** of influenza neuraminidases A and B.[1] After its discovery at Gilead Sciences, Foster City (CA), the carboxylic ester **1** was developed in collaboration with Roche as an orally active drug for the treatment and prevention of influenza infections. In 1999, oseltamivir phosphate **1** was successfully launched under the trade name Tamiflu. Process research and development work at Roche aiming at a scalable process was based mainly on the drug discovery route and the kilolaboratory synthesis from Gilead Science, which used either naturally occurring quinic acid **3** or shikimic acid **4** as starting materials (Scheme 1).[2] The resulting commercial manufacturing process commences from shikimic acid **4** and takes advantage of the key epoxide **5** used in the Gilead synthesis.[3,4] Although sufficient quantities of shikimic acid became available either by extraction from Chinese star anise or alternatively by fermentation, further research work at Roche and in academia[5–11] focused on alternative syntheses using cheaper or more readily available starting materials. Meanwhile interesting laboratory-scale syntheses, e.g., via enantioselective Diels–Alder reactions[5,9] or by desymmetrization of *meso*-aziridines[6] have been reported.

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

(2) 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.

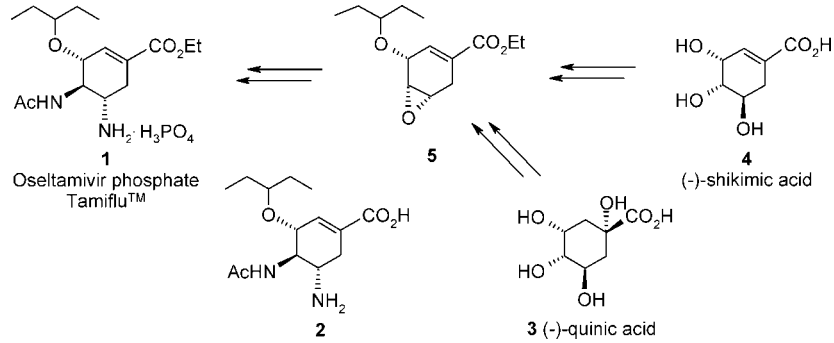
(3) (a) Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Göckel, V.; Götzö, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Röckel-Stäbler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266. (b) Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044, and references therein. (c) Harrington, P. J.; Brown, J. D.; Foderaro, T.; Hughes, R. C. *Org. Process Res. Dev.* **2004**, *8*, 86.

(4) For a summary of process research and development work at Roche, see: (a) Abrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U. *Chimia* **2004**, *58*, 621. (b) Abrecht, S.; Cordon Federspiel, M.; Estermann, H.; Fischer, R.; Karpf, M.; Mair, H.-J.; Oberhauser, T.; Rimmler, G.; Trussardi, R.; Zutter, U. *Chimia* **2007**, *61*, 1, and references therein.

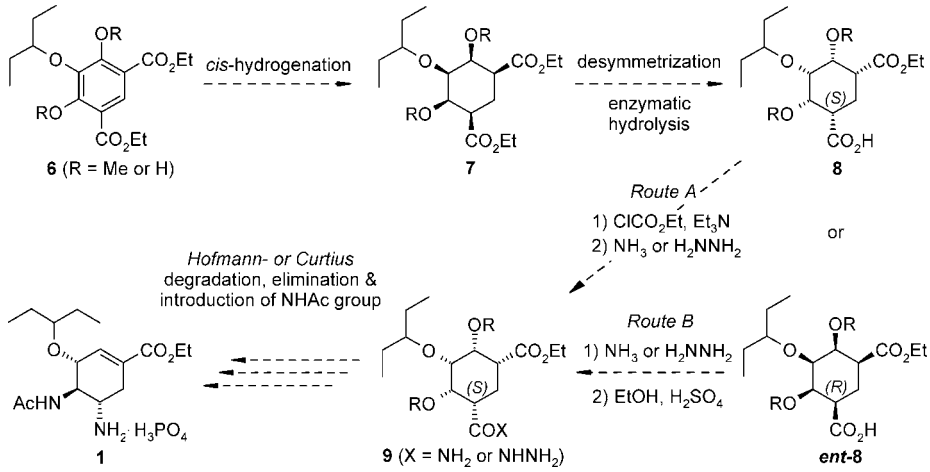
(5) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310.

10.1021/jo800264d CCC: $40.75 © 2008 American Chemical Society
Published on Web 06/03/2008

SCHEME 1. Synthesis of 1 Starting from Quinic Acid 3 and Shikimic Acid 4



SCHEME 2. Desymmetrization Concept



Herein we describe a new efficient synthesis of oseltamivir phosphate **1** and its enantiomer ***ent*-1** starting from cheap 2,6-dimethoxyphenol **10**.[12]

Results and Discussion

Synthetic Strategy. The concept of the synthesis described herein is based on two key transformations: the *cis*-hydrogenation of a trihydroxyisophthalic acid derivative of type **6** and the desymmetrization of the resultant all-*cis meso*-diester **7** by an enzymatic hydrolysis, which was anticipated to afford in potentially quantitative yield either the optically active (*S*)-monoacid **8** or the enantiomeric (*R*)-monoacid ***ent*-8** (Scheme 2). If the preferred (*S*)-monoacid **8** would be formed, introduction of the 5-amino functionality was planned via a Hofmann (or Curtius) degradation of the corresponding amide (or hydrazide) **9** (Route A). Subsequent formation of the cyclohexene double bond via a 1,2-elimination and introduction of the 4-acetyl-amino group under inversion of configuration would complete the synthesis. Should the less favored (*R*)-monoacid ***ent*-8** be produced instead, the required inversion of configuration into the proposed intermediate **9** might be possible via ammonolysis (or hydrazinolysis) of the ester function and esterification of the acid (Route B).

Synthesis of Diethyl Isophthalate 6a and 6b. The first part of the synthesis starts from readily available and cheap 2,6-dimethoxyphenol **10**, which was etherified with 3-pentyl mesylate using KO*t*Bu in DMSO (Scheme 3). To minimize competitive elimination of the mesylate to 2-pentene, KO*t*Bu was added slowly over 4 h to a solution of the phenol **10** and 2 equiv of the mesylate. Bromination of the crude 3-pentylether **11** with 2 equiv of *N*-bromosuccinimide provided the crystalline dibromide **12** with high selectivity (GC <1% dibromo isomer and tribromo side product). Subsequent Pd-catalyzed ethoxycarbonylation with carbon monoxide (10 bar CO, 110 °C) and KOAc in EtOH provided the diethyl isophthalate derivative **6a**, which was distilled to ensure an optimal quality for the ensuing hydrogenation step. Methyl ether cleavage with 2 equiv of $MgBr_2$ in refluxing THF gave the corresponding diphenol **6b** as an alternative substrate for the aromatic ring hydrogenation.

Aromatic Ring Hydrogenation of 6a and 6b. The hydrogenation of the isophthalic acid derivatives **6a** and **6b** was examined with a variety of catalysts such as Rh, Ru, and Pt on Al_2O_3 or charcoal support as well as with Raney-Ni. While Pt and Raney-Ni proved to be inactive, hydrogenation of the dimethoxy derivative **6a** with both Rh and Ru catalysts led to the desired all-*cis meso*-diester **7a**. Best results were obtained with 5% Ru−Al_2O_3 in EtOAc (100 bar H_2, 60 °C),

(6) (a) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312. (b) Mita, T.; Fukuda, N.; Roca, X.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 259.

(7) Yamatsugu, K.; Kamijo, S.; Suto, Y.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 1403.

(8) Bromfield, K. M.; Gradén, H.; Hagberg, D. P.; Olsson, T.; Kann, N. *Chem. Commun.* **2007**, 3183.

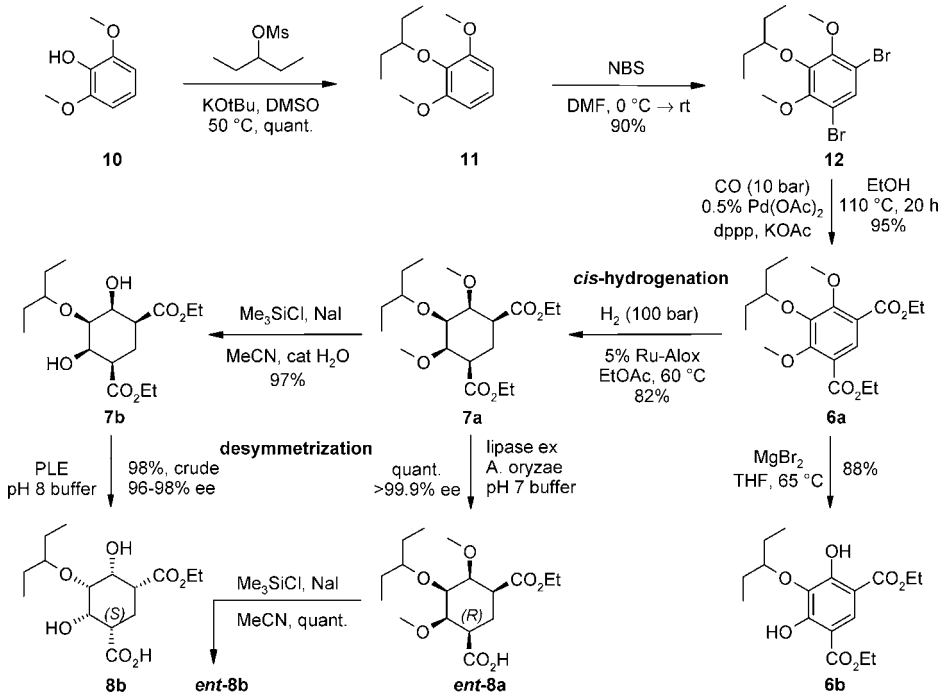
(9) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5734.

(10) 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.

(11) For recent reviews on the synthesis of oseltamivir phosphate **1**, see: (a) Farina, V.; Brown, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7330. (b) Shibasaki, M.; Kanai, M. *Eur. J. Org. Chem.* **2008**, 1839.

(12) Iding, H.; Wirz, B. ; Zutter, U., F. Hoffmann-La Roche AG, EP 1146036-A2 (priority date 10.04.2000).

SCHEME 3. Synthesis of Isophthalate 6a and Hydrogenation and Desymmetrization of Diester 7a and 7b



providing **7a** in over 80% yield after crystallization from hexane. According to GC analysis (area %), the crude reaction mixture consisted of ~90% of the desired **7a** and only small amounts of a few side products whereof the two *des*-methoxy side products were identified (GC <1.5%). Considering that 10 diastereomers (6 racemates + 4 mesoforms) were theoretically possible, the diastereoselectivity of this aromatic ring hydrogenation was quite remarkable.[13] In contrast, no suitable catalyst could be found for the hydrogenation of the corresponding diphenol **6b**. Hydrogenation over 5% Rh−Al_2O_3, (100 bar H_2, EtOAc, 100 °C) afforded a complex product mixture containing only ~10% (GC) of the dihydroxy-*meso*-diester **7b**. Instead, cleavage of the two methyl ether groups in **7a** with TMS−iodide generated in situ (Me_3SiCl, NaI, cat. H_2O) afforded the desired dihydroxy-*meso*-diester **7b** in nearly quantitative yield so that both *meso*-diesters **7a** and **7b** could be readily accessed and the enzymatic monohydrolysis studied.

Enzymatic Desymmetrization of All-*cis* *meso*-Diesters 7a and 7b. The enzymatic desymmetrization of *cis*-1,3-cyclohexanedicarboxylic acid diesters has already been described in the literature.[14] An extensive enzyme screening revealed that the most selective hydrolysis of dihydroxy-*meso*-diester **7b** was effected by pig liver esterase (PLE, Fluka), affording the desired (*S*)-monoacid **8b** with high enantiomeric excess (96−98% ee) and in nearly quantitative yield. Quite remarkably, the enzyme readily tolerated 10% substrate concentration, even at 35 °C, probably owing to the insolubility of the substrate as well as the hydrophilic nature of the product.[15]

On the other hand, hydrolysis of the corresponding dimethoxy-*meso*-diester **7a** with commercial lipases from *Aspergillus oryzae, Thermomyces lanuginosa*, or *Mucor miehei* afforded the monoacid ***ent*-8a** with high selectivity and enantiomeric purity (*A. oryzae* quant yield, >99.9% ee) albeit with the wrong configuration for the further transformation into **1** via direct Curtius degradation. The absolute configuration of ***ent*-8a** was assigned after O-demethylation with TMS−iodide by transformation of the resultant (*R*)-monoacid ***ent*-8b** into the enantiomer ***ent*-1** of oseltamivir phosphate **1** (see Experimental Section).[16]

Transformation of the (*S*)-Mono-Acid 8b into Oseltamivir Phosphate 1. The final part of the synthesis required the introduction of the 1,2-cyclohexene double bond, the 5-amino, and the 4-acetylamino functionalities with the required configuration (Scheme 4). Treatment of the hydroxy-acid **8b** with diphenylphosphoryl azide (DPPA) and Et_3N effected a Curtius degradation, a rearrangement known to proceed with retention of configuration, and provided the crystalline oxazolidinone **13** via intramolecular trapping of the isocyanate intermediate by the adjacent hydroxyl group.[17] The subsequent transformation to the desired cyclohexenol **17** and the corresponding triflate **18** thereof was initially accomplished via Boc-protection, dehydration of the β-hydroxy ester function in **14** with triflic anhydride and DMAP (2.2 equiv Tf_2O, 4.5 equiv DMAP) followed by cleavage of the cyclic carbamate in **15** with catalytic Cs_2CO_3 in ethanol.[18] The moderate overall yield for the stepwise transformation **13** → **18** of 45% prompted us to investigate a more efficient alternative. Above all, the observation that the carbonate **16** was an intermediate in the base-catalyzed ethanolysis of Boc-oxazolidinone **15** encouraged us to test whether

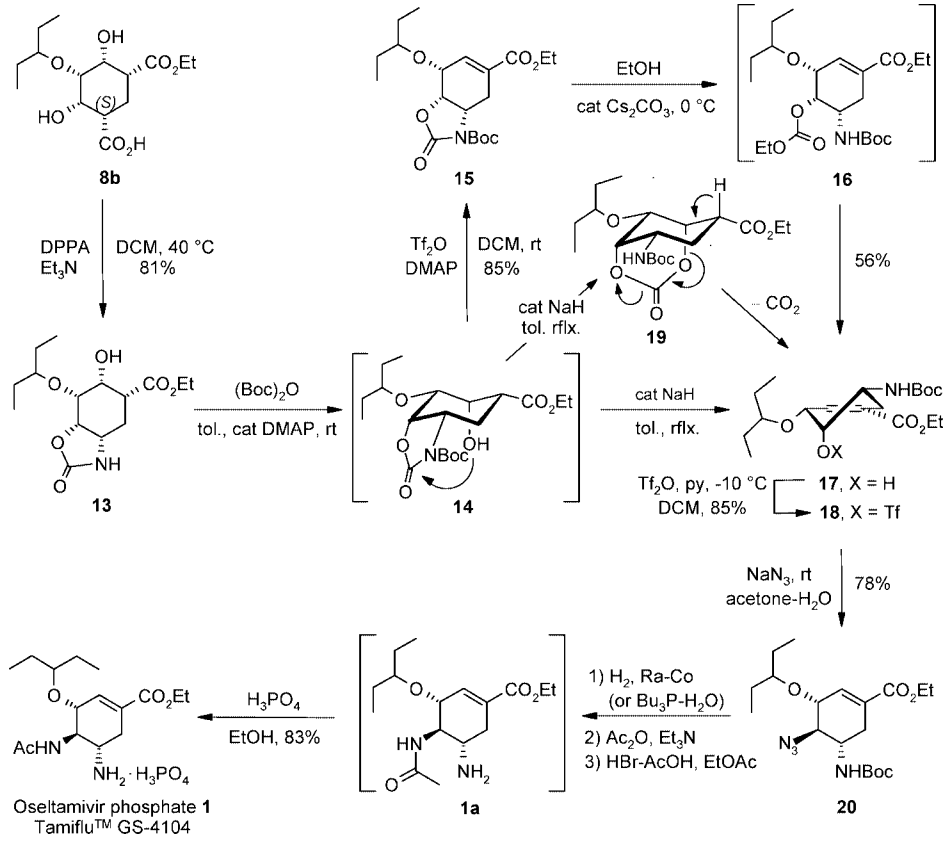
(13) (a) Bailey, W. J.; Economy, J. *J. Org. Chem.* **1957**, *23*, 1002. (b) Gensler, W. J.; Solomon, P. H. *J. Org. Chem.* **1973**, *38*, 1726–1731. (c) Nielsen, A.-T.; Christian, S. L.; Moor, D. W. *J. Org. Chem.* **1987**, *52*, 1656–1662. (d) Burgstahler, A. W.; Bithos, Z. J. *Org. Synth.* **1973**, *3*, 591–595. An examination of the literature revealed that the hydrogenation of unsubstituted isophthalic esters like dimethyl isophthalate[13a] (Ra-Ni, neat, 300 bar, 150 °C) produces *cis*−*trans* mixtures of the corresponding 1,3-cyclohexanedicarboxylic acid diesters. Hydrogenation of substituted isophthalic esters, e.g., dimethyl 5-hydroxyisophthalate[13b] (Rh−Al_2O_3, MeOH, 3.5 bar, 25 °C) or triethyl benzene-1,3,5-tricarboxylate[13c] (PtO_2, AcOH, 3.5 bar, 25 °C) as well as gallic acid[13d] (Rh−Al_2O_3, EtOH, 180 bar, 70 °C) deliver predominantly the all-*cis* isomers.

(14) Boaz, N. E. *Tetrahedron: Asymmetry* **1999**, *10*, 813.

(15) For larger scale experiments a PLE "technical grade" (Roche Diagnostics, cat. no. 11681800103) was successfully employed.

(16) In fact, as the absolute configuration of ***ent*-8a** was unknown and ***ent*-8a** was obtained as the first product of desymmetrization, ***ent*-1** was synthesized before **1**.

SCHEME 4. Conversion of Mono-Acid 8b to Oseltamivir Phosphate 1

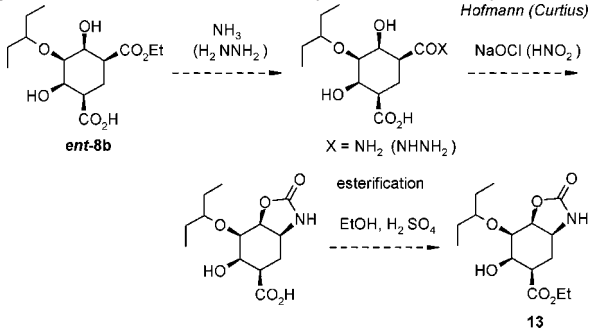


an analogous intramolecular alcoholysis of the Boc-activated cyclic carbamate in **14** would generate the cyclic carbonate intermediate **19** with the α-hydrogen and the *β*-carbonate leaving group optimally set up to undergo a base-induced decarboxylative elimination reaction. Indeed, treatment of **14** with a catalytic amount of NaH or KO*t*Bu in refluxing toluene effected a highly selective transformation affording cyclohexenol **17** with both the double bond and the Boc-protected amino group introduced correctly.

Whereas no intermediate could be detected during this transformation in refluxing toluene, under milder conditions (EtOAc, 10 mol % NaH, 70 °C, 17 h) a trace was seen by TLC that was then isolated by chromatography and identified as the proposed carbonate intermediate **19** (NMR and MS).[19] This decarboxylative elimination shortcut was easily implemented in a "one-pot" procedure for the conversion of the oxazolidinone **13** into the triflate **18**. Thus, treatment of **13** with $(Boc)_2O$ and 2 mol % DMAP in toluene provided Boc-oxazolidinone **14**, which upon heating with 0.5 mol % NaH furnished cyclohexenol **17**. Subsequent esterification of crude **17** with Tf_2O and pyridine gave after crystallization from isopropyl ether the triflate **18** in 85% overall yield starting from **13**, nearly doubling the yield of the previous stepwise protocol.

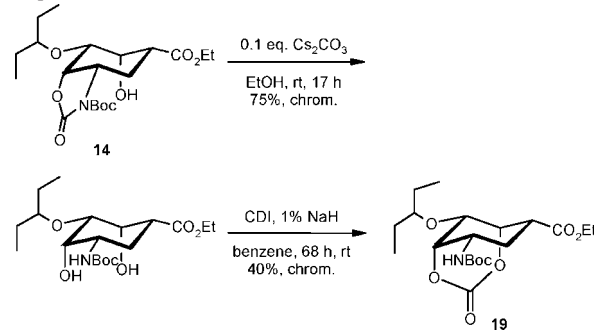
The 4-amino functionality was incorporated via a S_N2 substitution of the triflate **18** with NaN_3 in aqueous acetone at ambient temperature, providing the azide **20** with full inversion of configuration (Scheme 4). Azide substitution of less powerful sulfonate leaving groups such as nosylate or mesylate in DMSO at 50 °C afforded lower yields and more 1,3-cyclohexadiene

(17) The desymmetrization concept discussed at the beginning included a synthesis of **1** via both enantiomeric monoacids **8b** and ***ent*-8b** (Scheme 2). Alternatively, the desired oxazolidinone **13** should be accessible using the (*R*)-monoacid ***ent*-8b** via ammonolysis (or hydrazinolysis) and Hofmann (or Curtius) degradation of the resultant amide (or hydrazide) followed by esterification:



(18) Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185.

(19) An independent synthesis of the carbonate intermediate **19** was accomplished as follows:



MS and elemental analysis of compound **19**: ESI-MS (*m*/*z*) 438 ($M + Na^+$, 32), 433 ($M + NH_4^+$, 75), 360 ($M + H^+ - C_4H_8$, 100). Anal. Calcd for $C_{20}H_{33}NO_8$: C, 57.82; H, 8.01; N, 3.37; O, 30.81. Found: C, 57.53; H, 7.87; N, 3.32; O, 30.57. $^1H/^{13}C$ NMR spectra, see Supporting Information.

side product (triflate ~10%, mesylate ~50% 1,3-cyclohexadiene side product). Azide reduction (Bu_3P-H_2O or H_2/Ra−Co) followed by acetylation with Ac_2O, removal of the Boc protecting group with HBr in AcOH and salt formation with H_3PO_4 gave oseltamivir phosphate **1** with ~30% overall yield in 10 steps starting from 2,6-dimethoxyphenol. The enantiomeric purity of **1** determined by chiral HPLC of the Boc-derivative **21** was >99.9% ee (see Experimental Section).

Conclusion

In summary, a new enantioselective synthesis of the anti-influenza neuraminidase inhibitor oseltamivir phosphate **1** starting from cheap 2,6-dimethoxyphenol **10** has been accomplished. Key steps of this approach were the *cis*-hydrogenation of the trihydroxyisophthalic acid derivative **6a** and the desymmetrization of the dihydroxy-*meso*-diester **7b** by enantioselective hydrolysis with pig liver esterase, affording the (*S*)-monoacid **8b**. Subsequent Shioiri−Yamada−Curtius degradation followed by a unique decarboxylative elimination reaction of Boc-oxazolidinone **14** gave cyclohexenol **17**, which was converted to the target molecule **1** by substitution of the corresponding triflate **18** with NaN_3, azide reduction, N-acetylation, and deprotection. This practical and efficient 10-step synthesis provided the enantiomerically pure oseltamivir phosphate **1** in ~30% overall yield without any chromatographic purification and compares favorably with recently published syntheses.[5–11] Hydrolysis of the dimethoxy-*meso*-diester **7a** with *Aspergillus oryzae* lipase followed by demethylation afforded the (*R*)-monoacid ***ent*-8b**, which can be transformed into the enantiomer ***ent*-1** of oseltamivir phosphate in a similar manner to that described above.

Experimental Section

Methanesulfonic Acid 1-Ethyl-propyl Ester. To a stirred solution of 3-pentanol (176.3 g, 2.0 mol) in pyridine (200 mL) at 0 °C was added methanesulfonyl chloride (252.0 g, 2.2 mol) over 1 h. After stirring at room temperature for 1 h, water (100 mL) was added, and stirring was continued for 1 h. The reaction mixture was diluted with EtOAc (1000 mL) and washed with 1 M HCl (1600 mL) and brine (500 mL). The aqueous layers were extracted with EtOAc (500 mL), and the combined organic layers were dried over Na_2SO_4 and filtered. Evaporation of the solvent and drying (50 °C/1 mbar) afforded crude 3-pentylmesylate (313.4 g, 94%) as a yellow oil which was used without purification in the next step. IR (film) ν 2975, 2943, 2884, 1436, 1348, 1176, 912 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 0.98 (t, J = 7.4 Hz, 6H), 1.74 (quint, J = 7.4, 4H), 3.01 (s, 3H), 4.61 (quint, J = 6.0 Hz, 1H). Anal. Calcd for $C_6H_{14}O_3S$: C, 43.35; H, 8.49; S, 19.29. Found: C, 43.18; H, 8.44; S, 19.15.

2-(1-Ethylpropoxy)-1,3-dimethoxybenzene (11). To a stirred solution of 2,6-dimethoxyphenol **10** (38.5 g, 0.25 mol) and 3-pentyl mesylate **9** (83.1 g, 0.50 mol) in DMSO (500 mL) was added at 50 °C a solution of potassium *tert*-butylate (56.1 g, 0.50 mol) in DMSO (500 mL) over 4 h, during which the reaction mixture turned brown and viscous. Additional potassium *tert*-butylate (2.8 g, 0.025 mol) was added, and stirring at 50 °C was continued for 1 h to complete the reaction. The mixture was cooled to room temperature, diluted with EtOAc (500 mL), and washed with 1 M HCl (600 mL). The aqueous layer was extracted with EtOAc (250 mL), and both organic layers were washed with water. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated to give 56.2 g (100%) crude 3-pentyl aryl ether **11** after drying (50 °C/1 mbar) as an orange oil which was used without purification in the next step (crude **11** can be distilled, bp 90 °C/0.03 mbar). IR (film) ν 2836, 1594, 1492, 1252 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 0.97 (t, J = 7.4 Hz, 6H), 1.54−1.70 (m, 4H), 3.81 (s, 6H), 4.02 (quint, J = 6.0 Hz, 1H), 6.56 (d, J = 8.3 Hz, 2H), 6.95 (t, J = 8.3 Hz, 1H). EI-MS (m/z) 224 ($M^{+\bullet}$, 5), 154 ($M^{+\bullet} - C_5H_{10}$, 100). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.60; H, 9.10.

1,5-Dibromo-3-(1-ethylpropoxy)-2,4-dimethoxybenzene (12). Crude 3-pentyl aryl ether **11** (44.9 g, 0.20 mol) dissolved in DMF (60 mL) was added to a stirred solution of NBS (73.4 g, 0.40 mol) in DMF (160 mL) at 0 °C over 1 h. After stirring at room temperature for 18 h, the red-brown reaction mixture was diluted with EtOAc (400 mL) and washed three times with 5% brine (400, 200, 200 mL). All aqueous layers were extracted with EtOAc (200 mL), and the combined organic layers were stirred with charcoal (4 g) for 1 h. Filtration and evaporation gave the crude product (78.7 g) which was dissolved in 80% EtOH/H_2O (400 mL) at 50 °C. After cooling and stirring at −20 °C for 18 h, the suspension was filtered, and the crystalline residue was washed with cold 80% EtOH/H_2O and dried (35 °C/1 mbar/18 h), affording 68.9 g (90%) light yellow dibromide **12**, mp 47−48 °C. IR (nujol) ν 1559, 1271, 1005 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 0.96 (t, J = 7.4 Hz, 6H), 1.50−1.75 (m, 4H), 3.86 (s, 6H), 4.24 (quint, J = 6.0 Hz, 1H), 7.46 (s, 1H). EI-MS (m/z) 380 ($M^{+\bullet}$, 4), 310 ($M^{+\bullet} - C_5H_{10}$, 55). Anal. Calcd for $C_{13}H_{18}Br_2O_3$: C, 40.87; H, 4.75; Br, 41.82. Found: C, 40.61; H, 4.54; Br, 41.52.

5-(1-Ethylpropoxy)-4,6-dimethoxyisophthalic Acid Diethyl Ester (6a). An autoclave (380 mL) charged with the dibromide **12** (38.2 g, 100 mmol), potassium acetate (39.3 g, 400 mmol), ethanol (200 mL), palladium(II) acetate (0.11 g, 0.5 mmol), and 1,3-bis(diphenylphosphino)propane (0.25 g, 0.6 mmol) was pressurized and vented four times with carbon monoxide (CO, 10 bar) and then heated to 110 °C. After stirring (600 rpm) at 110 °C for 15 h under a CO pressure of 10 bar, the autoclave was cooled to room temperature and vented. The reaction mixture was poured into a stirred mixture of hexane (100 mL) and aqueous 5% $NaHCO_3$ (200 mL), and the aqueous layer was extracted with hexane (100 mL). Both organic layers were washed with 1 M HCl (100 mL), combined, and dried (Na_2SO_4). After filtration and evaporation of the solvent, the oily residue (35.7 g) was vacuum-distilled providing the diethyl ester **6a** (34.9 g, 95%) as a colorless oil, bp 140 °C/0.02 mbar. IR (film) ν 1729, 1594, 1230, 1040 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 0.95 (t, J = 7.5 Hz, 6H), 1.39 (t, J = 7.1 Hz, 6H), 1.50−1.80 (m, 4H), 3.95 (s, 6H), 4.23 (quint, J = 6.0 Hz, 1H), 4.37 (q, J = 7.1 Hz, 4H), 7.99 (s, 1H). EI-MS (m/z) 368 (M^+, 10), 323 ($M^{+\bullet} - C_2H_5O$, 40), 298 ($M^{+\bullet} - C_5H_{10}$, 100). Anal. Calcd for $C_{19}H_{28}O_7$: C, 61.94; H, 7.66. Found: C, 61.89; H, 7.50.

All-*cis*-5-(1-ethylpropoxy)-4,6-dimethoxycyclohexane-1,3-dicarboxylic Acid Diethyl Ester (7a). The autoclave (500 mL) was charged with the diethyl ester **6a** (36.8 g, 100 mmol), 5% Ru−Al_2O_3 catalyst (36.8 g, Heraeus no. 1738), and EtOAc (250 mL). The reaction mixture was stirred (1000 rpm) and heated to 60 °C under a pressure of 100 bar H_2 for 24 h. After cooling to room temperature, the autoclave was vented and flushed with Ar, and the black suspension was filtered. Evaporation of the solvent and drying (50 °C/1 mbar) afforded a white, crystalline residue (35.1 g) which was dissolved in hexane (530 mL) at 50 °C. Crystallization was effected at −20 °C for 6 h, and after filtration, washing with cold hexane, and drying (50 °C/1 mbar/6 h), the all-*cis*-diester **7a** (30.8 g, 82%) was isolated as white needles, mp 108−109 °C. IR (nujol) ν 1734, 1465, 1190, 1087 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ 0.93 (t, J = 7.5 Hz, 6H), 1.27 (t, J = 7.1 Hz, 6H), 1.50−1.68 (m, 4H), 1.90−2.01 (m, 1H), 2.17−2.41 (m, 3H), 3.27 (t, J = 3 Hz, 1H), 3.41 (quint, J = 6.0 Hz, 1H), 3.53 (s, 6H), 4.02 (br s, 2H), 4.18 (m, 4H). ESI-MS (m/z) 375 ($M + H^+$, 100), 305 ($M + H^+ - C_5H_{10}$, 50). Anal. Calcd for $C_{19}H_{34}O_7$: C, 60.94; H, 9.15. Found: C, 60.79; H, 9.30.

All-*cis*-5-(1-ethylpropoxy)-4,6-dihydroxycyclohexane-1,3-dicarboxylic Acid Diethyl Ester (7b). To a suspension of NaI (60.0 g, 400 mmol) in acetonitrile (200 mL) was added water (0.36 g, 20 mmol), and after 30 min of stirring at 40 °C trimethylchlorosilane

(43.5 g, 400 mmol) was added all at once. Stirring was continued at 40 °C for 30 min, then the all-*cis*-diester **7a** (37.4 g, 100 mmol) was added in one portion, and the reaction was completed at 40 °C for 14 h. The orange reaction mixture was cooled to room temperature, diluted with EtOAc (500 mL), and washed with water (250 mL). Following decolorization with $Na_2S_2O_3$ (2.5 g), the organic layer was washed with 10% brine (2 × 100 mL), and all three aqueous layers were extracted sequentially with EtOAc (100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The crystalline residue (34.9 g) was dissolved in refluxing methylcyclohexane (200 mL) and recrystallized with stirring at −20 °C for 16 h. Filtration, washing with cold methylcyclohexane and drying (50 °C/1 mbar/6 h) gave the all-*cis*-dihydroxy diester **7b** (33.6 g, 97%) as a white powder, mp 115−116.5 °C. IR (nujol) ν 3410, 1730, 1252, 1105 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, J = 7.6 Hz, 6H), 1.29 (t, J = 7.2 Hz, 6H), 1.53−1.65 (m, 4H), 2.00−2.07 (m, 1H), 2.28−2.45 (m, 3H), 3.21 (t, J = 2.8 Hz, 1H), 3.42 (quint, J = 6.0 Hz, 1H), 3.52 (d, J = 5.6 Hz, 2H), 4.22 (m, 4H), 4.46 (br s, 2H). ESI-MS (*m*/*z*) 347 (M + H^+, 100), 277 (M + H^+ − C_5H_{10}, 50). Anal. Calcd for $C_{17}H_{30}O_7$: C, 58.94; H, 8.73. Found: C, 58.73; H, 8.55.

All-*cis*-(1*R*,3*S*,4*S*,5*S*,6*R*)-5-(1-ethylpropoxy)-4,6-dihydroxycyclohexane-1,3-dicarboxylic Acid 1-Ethyl Ester (8b). To a vigorously stirred suspension of the all-*cis*-dihydroxy diester **7b** (34.4 g, 100 mmol) in TRIS buffer pH 8.0 (390 mL, 10 mM; prepared from tris(hydroxymethyl)-aminomethane and deionized water, adjusted to pH 8.0 with 0.1 M HCl) was added at 35 °C pig liver esterase (3.4 mL PLE suspension, Fluka no. 46063). Stirring at 35 °C was continued at pH 8.0, which was controlled by the addition of 1.0 M NaOH with a pH-stat (during the course of the reaction the suspension became an opaque solution). After 46 h of stirring with a total consumption of 103.3 mL of 1.0 M NaOH (103.3 mol = 1.04 equiv), the pH of the reaction mixture was adjusted to 2.0 with 25% HCl (ca. 13 mL), and the reaction mixture extracted with dichloromethane (3 × 330 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated, affording after drying (40 °C/5 mbar) 31.2 g (98.2%) of crude monoacid **8b** as a colorless gum, which was used without purification in the next step. Enantiomeric ratio (er) = 98.2:1.8, determined by chiral GC of the methyl ester derivative (CH_2N_2) with a BGB-172 column (15 m × 0.25 mm). $[\alpha]^{20}_D$ = +7.2 (*c* 1.0; $CHCl_3$). IR (film) ν 3600−2450 (br), 1729, 1270, 1195, 1114 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 0.89 (t, J = 7.2 Hz, 6H), 1.19 (t, J = 6.8 Hz, 6H), 1.40−1.56 (m, 4H), 1.67 and 2.00 (ABX_2, J_{AB} = 14 Hz, J_{AX} = 2 Hz, J_{BX} = 13.2 Hz, $1H_{eq}$ + $1H_{ax}$), 2.38−2.58 (m, 2H), 3.28 (t, J = 2.0 Hz, 1H), 3.34 (quint, J = 6.0 Hz, 1H), 4.08 (m, 2H), 4.24 (br d, 2H), 5.14 (br s, 2H), 12.0 (br s, 1H). ESI-MS (*m*/*z*) 317 (M − H^-, 100), 271 (M − H^- − EtOH, 50). Anal. Calcd for $C_{15}H_{26}O_7$: C, 56.59; H, 8.23. Found: C, 56.45; H, 8.26.

(3a*S*,5*R*,6*R*,7*R*,7a*S*)-7-(1-Ethylpropoxy)-6-hydroxy-2-oxooctahydrobenzooxazole-5-carboxylic Acid Ethyl Ester (13). To a stirred solution of the monoacid **8b** (31.2 g, from 100 mmol of all-*cis*-dihydroxy diester **7b**) in dichloromethane (200 mL) was added Et_3N (10.1 g, 100 mmol) followed by diphenylphosphoryl azide (29.0 g, ca. 100 mol; assay ∼95%) in one portion. After refluxing at ∼41 °C for 16 h, the clear reaction mixture was diluted with dichloromethane (200 mL) and washed with 1 M HCl (300 mL), 5% $NaHCO_3$ (300 mL), and 5% brine (3 × 300 mL). All aqueous layers were extracted sequentially with dichloromethane (200 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. The white, crystalline residue (34.6 g) was dissolved in refluxing *n*BuOAc (300 mL) and crystallized with stirring at −20 °C for 16 h. Filtration, washing with cold *n*BuOAc, and drying (50 °C/10 mbar/16 h) gave white, crystalline oxazolidinone **13** (25.4 g, 80% over two steps), mp 180−181 °C. $[\alpha]^{20}_D$ = +31.2 (*c* 1.0; $CHCl_3$). IR (nujol) ν 3423, 3307, 1750, 1711, 1462, 1224 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.94 and 0.95 (t, J = 7.6 Hz, 3H each), 1.29 (t, J = 6.8 Hz, 3H), 1.50−1.68 (m, 4H), 2.04−2.22 (m, 2H), 2.28−2.37 (m, 1H), 2.75 (s, 1H), 3.47 (quint, J = 6.0 Hz, 1H), 3.54 (t, J = 4.0 Hz, 1H), 3.71 (m, 1H), 4.21 (m, 2H), 4.45 (s, 1H), 4.67 (t, J = 5.2 Hz, 1H), 5.65 (s, 1H). ESI-MS (*m*/*z*) 316 (M + H^+, 10), 246 (M + H^+ − C_5H_{10}, 100). Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.19; H, 7.86; N, 4.49.

(3*R*,4*S*,5*S*)-5-*tert*-Butoxycarbonylamino-3-(1-ethylpropoxy)-4-hydroxycyclohex-1-enecarboxylic Acid Ethyl Ester (17). (a) Boc protection. A suspension of the oxazolidinone **13** (15.77 g, 50 mmol), di-*tert*-butyl dicarbonate (12.0 g, 55 mmol), and 4-dimethylaminopyridine (0.12 g, 1 mmol) in toluene (250 mL) was stirred at room temperature for 4 h. After 2 h, the suspension became a colorless solution, and after 3 h, full conversion was indicated by TLC. A sample was worked up for analysis of Boc-oxazolidinone **14** (ca. 2 mL was washed with 2 mL of 0.5 M HCl and 2 mL of 10% brine. Evaporation of the organic layer gave 0.15 g of viscous oil). $[\alpha]^{20}_D$ = +60.8 (*c* 1.0; $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 and 0.93 (t, J = 7.6 Hz, 3H each), 1.30 (t, J = 7.2 Hz, 3H), 1.55 (s, 9H), 1.55−1.65 (m, 4H), 2.11 ("q", 1H), 2.35 ("d", 1H), 2.38−2.47 (m, 1H), 2.59 (s, 1H), 3.44 (quint, J = 6.0 Hz, 1H), 3.52 (t, 1H), 4.17−4.30 (m, 3H), 4.46 (s, 1H), 4.57 (t, 1H). Anal. Calcd for $C_{20}H_{33}NO_8$: C, 57.82; H, 8.01; N, 3.37. Found: C, 57.97; H, 8.12; N, 3.05. **(b) Decarboxylative elimination.** To the colorless solution of **14** was added NaH (10 mg 60% NaH dispersion in oil, ∼0.25 mmol), and the reaction mixture was refluxed for 1.5 h (during which CO_2 was evolved). Evaporation of the solvent gave crude, semicrystalline cyclohexenol **17** (19.6 g) which was used without purification in the next step. Purified sample: $[\alpha]^{20}_D$ = −52.5 (*c* 1.0; $CHCl_3$). IR (nujol) ν 3557, 3365, 1717, 1680, 1653, 1523, 1248 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, J = 7.6 Hz, 6H), 1.45 (s, 9H), 1.50−1.65 (m, 4H), 2.34 and 2.60 (ABX, J_{AB} = 17.5 Hz, J_{AX} = 10 Hz, J_{BX} = 5.6 Hz, $1H_{eq}$ + $1H_{ax}$), 2.54 (s, 1H), 3.43 (quint, J = 6.0 Hz, 1H), 3.87 (q, J = 6.0 Hz, 1H), 4.04 (s, 1H), 4.15 (s, 1H), 4.20 (q, J = 7.2 Hz, 2H), 5.18 (d, J = 9.2 Hz, 1H), 6.67 (s, 1H). ESI-MS (*m*/*z*) 372 (M + H^+, 10), 272 (M + H^+ − C_4H_8 − CO_2, 100). Anal. Calcd for $C_{19}H_{33}NO_6$: C, 61.43; H, 8.95; N, 3.77. Found: C, 61.30; H, 8.88; N, 3.80.

(3*R*,4*S*,5*S*)-5-*tert*-Butoxycarbonylamino-3-(1-ethylpropoxy)-4-trifluoromethanesulfonyloxy-cyclohex-1-enecarboxylic Acid Ethyl Ester (18). To a solution of crude cyclohexenol **17** (19.6 g, 50 mmol) and pyridine (8.05 mL, 100 mmol) in dichloromethane (250 mL) at −10 °C was added trifluoromethanesulfonic anhydride (8.66 mL = 14.81 g, 52.5 mmol) over 15 min, and stirring was continued for 2.5 h. To the cold reaction mixture was added under stirring 1 M HCl (50 mL), and then the organic layer was separated and washed with 10% brine (2 × 50 mL). The aqueous layers were extracted with dichloromethane (50 mL), and the combined organic layers were dried (Na_2SO_4). Evaporation of the solvent afforded a yellow, crystalline residue (24.9 g) which was dissolved in hot isopropyl ether (375 mL, 60 °C). Small amounts of insoluble, brown particles adhering to the glass wall were removed by decanting the yellow solution. Crystallization at room temperature and then −20 °C gave after filtration and drying 21.4 g (85%) of yellowish, crystalline triflate **18**, mp 119−120 °C (dec.). $[\alpha]^{20}_D$ = −79.4 (*c* 1.0; $CHCl_3$). IR (nujol) ν 3379, 1711, 1689, 1525, 1413, 1211 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.90 and 0.93 (t, J = 7.6 Hz, 3H each), 1.31 (t, J = 7.2 Hz, 3H), 1.45 (s, 9H), 1.50−1.68 (m, 4H), 2.32 and 2.69 (ABX, J_{AB} = 18.0 Hz, J_{AX} = 10.0 Hz, J_{BX} = 6.0 Hz, $1H_{eq}$ + $1H_{ax}$), 3.48 (quint, J = 5.6 Hz, 1H), 4.04 (m, 1H), 4.23 (q, J = 7.2 Hz, 2H), 4.33 (s, 1H), 4.93 (d, J = 6.2 Hz, 1H), 5.35 (s, 1H), 6.77 (s, 1H). ESI-MS (*m*/*z*) 504 (M + H^+, 20), 448 (M + H^+ − C_4H_8, 90), 404 (M + H^+ − C_4H_8 − CO_2, 100). Anal. Calcd for $C_{20}H_{32}F_3NO_8S$: C, 47.71; H, 6.41; N, 2.78; S, 6.37; F, 11.32. Found: C, 47.69; H, 6.43; N, 2.81; S, 6.32; F, 11.45.

(3*R*,4*R*,5*S*)-4-Azido-5-*tert*-butoxycarbonylamino-3-(1-ethylpropoxy)-cyclohex-1-enecarboxylic Acid Ethyl Ester (20). To a stirred suspension of the triflate **18** (10.1 g, 20 mmol) in 90% acetone−water (50 mL) was added NaN_3 (1.43 g, 22 mmol), and the reaction mixture was stirred at room temperature for 15 h. The

yellowish clear solution was concentrated, and the oily residue was dissolved in EtOAc (50 mL) and washed with 5% brine (2 × 25 mL). The aqueous layers were extracted with EtOAc (25 mL), and the combined organic layers were dried (Na_2SO_4). After evaporation of solvent, the yellow, oily residue (8.00 g) was dissolved in hot hexane (80 mL) at 55 °C, filtered, and crystallized at −20 °C. Filtration and washing with cold hexane gave after drying the white, crystalline azide **20** (15.0 g, 78%), mp 92−93 °C. $[\alpha]^{20}_D = -61.2$ (*c* 1.0; $CHCl_3$). IR (nujol) ν 3336, 2113, 1714, 1688, 1533 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 and 0.94 (t, $J = 7.2$ Hz, 3H each), 1.29 (t, $J = 7.2$ Hz, 3H), 1.46 (s, 9H), 1.48−1.66 (m, 4H), 2.34 and 2.78 (ABX, $J_{AB} = 18.0$ Hz, $J_{AX} = 8.4$ Hz, $J_{BX} = 5.6$ Hz, $1H_{eq} + 1H_{ax}$), 3.46 (quint, $J = 5.6$ Hz, 1H), 3.55 (dd, $J = 9.2$, 7.2 Hz, 1H), 3.82 (br s, 1H), 4.01 (m, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 4.90 (br s, 1H), 6.77 (s, 1H). ESI-MS (*m*/*z*) 397 ($M + H^+$, 10), 297 ($M + H^+ - C_4H_8 - CO_2$, 100). Anal. Calcd for $C_{19}H_{32}N_4O_5$: C, 57.56; H, 8.14; N, 14.13. Found: C, 57.43; H, 8.02; N, 13.84.

(3*R*,4*R*,5*S*)-4-Acetylamino-5-amino-3-(1-ethylpropoxy)-cyclohex-1-enecarboxylic Acid Ethyl Ester Phosphoric Acid Salt (1:1) (Oseltamivir Phosphate, 1). (a) Hydrogenolysis. To a solution of the azide **20** (3.96 g, 10 mmol) in EtOAc (50 mL) was added Raney-cobalt catalyst (2.0 g water wet catalyst, washed with EtOH and EtOAc), and the suspension was stirred at room temperature for 20 h under 1 bar H_2 at 500 rpm. Due to the formation of N_2 during the hydrogenation, the reaction flask was evacuated and refilled with H_2 three times. The catalyst was removed by filtration and a sample (ca. 100 μL) was evaporated for analysis. ^1H NMR ($CDCl_3$, 250 MHz) δ 0.93 (t, $J = 7.5$ Hz, 6H), 1.29 (t, $J = 7.2$ Hz, 3H), 1.45 (s, 9H), 1.48−1.69 (m, 4H), 2.22 and 2.81 (ABX, $J_{AB} = 18$ Hz, $J_{AX} = 9$ Hz, $J_{BX} = 6$ Hz, $1H_{eq} + 1H_{ax}$), 2.87 (dd, $J = 10$, 7 Hz, 1H), 3.41 (quint, $J = 5.6$ Hz, 1H), 3.71 (br s, 1H), 3.83 (m, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 5.02 (br s, 1H), 6.82 (s, 1H). **(b) Acetylation.** To the stirred filtrate were added at room temperature triethylamine (1.11 g, 11 mmol) and then acetic anhydride (1.07 g, 10.5 mmol) in one portion. The colorless solution was stirred at room temperature for 1 h, and a sample was worked up for analysis of **21** (ca. 100 μL in 2 mL of EtOAc was washed with 2 mL of 0.5 M HCl and 2 mL of 10% brine. The organic layer was evaporated). $[\alpha]^{20}_D = -90.1$ (*c* 1.0; $CHCl_3$). ^1H NMR ($CDCl_3$, 250 MHz) δ 0.88 and 0.90 (t, $J = 7.2$ Hz, 3H each), 1.29 (t, $J = 7.1$ Hz, 3H), 1.42 (s, 9H), 1.45−1.60 (m, 4H), 1.98 (s, 3H), 2.30 and 2.75 (ABX, $J_{AB} = 18$ Hz, $J_{AX} = 10$ Hz, $J_{BX} = 5$ Hz, $1H_{eq} + 1H_{ax}$), 3.37 (quint, $J = 5.6$ Hz, 1H), 3.70−3.90 (m, 1H), 3.90−4.12 (m, 2H), 4.21 (q, $J = 7.1$ Hz, 2H), 5.12 (d, $J = 10$ Hz, 1H), 5.82 (d, $J = 10$ Hz, 1H), 6.79 (s, 1H). Anal. Calcd for $C_{21}H_{36}N_2O_6$: C, 61.14; H, 8.80; N, 6.79. Found: C, 61.23; H, 8.82; N, 6.80. **(c) Deprotection.** 5.7 M HBr−AcOH (5.26 mL, 30 mmol HBr) was added to the clear reaction mixture, and stirring at room temperature was continued for 20 h. The resulting suspension was washed with 2 M NaOH (55 mL, pH ≅ 9.5) and 20% brine (2 × 30 mL). All three aqueous layers were extracted with EtOAc (2 × 30 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated. **(d) Salt formation.** The resulting yellow, viscous free base **1a** (3.47 g) was dissolved in EtOH (20 mL) and added under stirring to a warm solution (50 °C) of orthophosphoric acid (0.98 g, 10 mmol) in EtOH (40 mL) over 30 min. After seeding with pure **1**, the white suspension was cooled and stirred at 0 °C for 3 h. The suspension was filtered, washed with acetone, and dried, affording 3.41 g (83%) of white, crystalline oseltamivir phosphate **1**, mp ca. 199−200 °C (dec). $[\alpha]^{20}_D = -31.7$ (*c* 1.0; H_2O). IR (nujol) ν 3352, 3300−2400 (br), 1724, 1663, 1551, 1463, 1377, 1263 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 0.79 and 0.84 (t, $J = 7.2$ Hz, 3H each), 1.23 (t, $J = 7.2$ Hz, 3H), 1.30−1.54 (m, 4H), 1.88 (s, 3H), 2.22 and 2.74 (ABX, $J_{AB} = 18$ Hz, $J_{AX} = 12$ Hz, $J_{BX} = 5$ Hz, $1H_{eq} + 1H_{ax}$), 3.18 (m, 1H), 3.36 (quint, $J = 5.6$ Hz, 1H), 3.69 ("q", $J \cong 10$ Hz, 1H), 4.15 (m, 3H), 6.65 (s, 1H), 8.15 (br s, ∼5H), 8.32 (d, $J = 9.2$ Hz, 1H). ESI-MS (*m*/*z*) 313 ($M + H^+$, 100). Anal. Calcd for $C_{16}H_{31}N_2O_8P$: C, 46.83; H, 7.61; N, 6.83; P, 7.55. Found: C, 46.61; H, 7.74; N, 6.78; P, 7.58.

Boc-Protection of Oseltamivir Phosphate 1 for Determination of Optical Purity. (3*R*,4*R*,5*S*)-4-Acetylamino-5-*tert*-butoxycarbonylamino-3-(1-ethylpropoxy)-cyclohex-1-enecarboxylic Acid Ethyl Ester (21). A solution of oseltamivir phosphate **1** (ca. 100 mg, 0.25 mmol), di-*tert*-butyl dicarbonate (65 mg, 0.3 mmol), and triethylamine (200 μL, 1.5 mmol) in dichlormethane (4 mL) was stirred at room temperature for 30 min. The reaction mixture was washed with 1 M HCl (2 mL) and 10% brine (2 × 2 mL), and the organic layer was evaporated. The semicrystalline residue was dissolved in hot hexane (4 mL, ca. 60 °C), and the solvent was evaporated, yielding white, crystalline **21** (ca. 100 mg). The optical purity of **21** was determined by HPLC on a Chiralpak AD column (250 mm × 4.6 mm, Daicel) with the eluent EtOH/Et_2NH/heptane = 20:0.4:1000 (220 nm; $t_R = 10.9$ min ***ent*-21**, 15.1 min **21**). Enantiomeric excess: >99.9% ee. For spectral data, see procedure for the synthesis of **1**.

All-*cis*-(1*S*,3*R*,4*R*,5*R*,6*S*)-5-(1-ethylpropoxy)-4,6-dimethoxycyclohexane-1,3-dicarboxylic Acid 1-Ethyl Ester (*ent*-8a). To a vigorously stirred suspension of the all-*cis*-diethyl ester **7a** (74.9 g, 0.20 mol) in cyclohexane (240 mL) were added 0.1 M glucose (1.1 L) and 0.1 M sodium phosphate buffer pH 7 (60 mL). Lipase from *Aspergillus oryzae* (0.56 g; Fluka 62285) was added at 35 °C, and the pH was maintained at 7.0 by controlled addition of 1.0 M NaOH (pH-stat). After 20 h and a total consumption of 187.5 mL of 1.0 M NaOH (187.5 mol), the reaction mixture was acidified with 1 M HCl (ca. 200 mL) to pH 2.0 and extracted with dichloromethane (1.5 L). The whole emulsion was filtered through a bed of dicalite (150 g), and the aqueous layer was extracted with dichloromethane (2 × 1.5 L). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated affording 69.4 g (100%) of white, crystalline monoacid ***ent*-8a**, mp 147−148 °C. Enantiomeric excess: >99.9% ee, determined by chiral GC of the methyl ester derivative (CH_2N_2) with a BGB-172 column (30 m × 0.25 mm). $[\alpha]^{20}_D = +7.4$ (*c* 1.0; $CHCl_3$). IR (nujol) ν 3400−2450 (br), 1735, 1707, 1463, 1376, 1280 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.92 and 0.93(t, $J = 7.6$ Hz, 3H each), 1.27 (t, $J = 6.8$ Hz, 3H), 1.52−1.68 (m, 4H), 1.93−2.02 (m, 1H), 2.20−2.46 (m, 3H), 3.28 (t, $J = 2.8$ Hz, 1H), 3.42 (quint, $J = 5.6$ Hz, 1H), 3.54 and 3.60 (s, 3H each), 4.03 (m, 2H), 4.10−4.27 (m, 2H), 11.10 (br s, 1H). ESI-MS (*m*/*z*) 345 ($M - H^-$, 100). Anal. Calcd for $C_{17}H_{30}O_7$: C, 58.94; H, 8.73. Found: C, 58.93; H, 8.60.

All-*cis*-(1*S*,3*R*,4*R*,5*R*,6*S*)-5-(1-ethylpropoxy)-4,6-dihydroxycyclohexane-1,3-dicarboxylic Acid 1-Ethyl Ester (*ent*-8b). To NaI (30.0 g, 200 mmol) in acetonitrile (100 mL) was added trimethylchlorosilane (21.7 g, 200 mmol) in one portion, and the suspension was stirred at room temperature for 30 min. After the addition of the dimethoxy acid ***ent*-8a** (17.3 g, 50 mmol), the reaction mixture was stirred at room temperature for 12 h. The orange suspension was diluted with dichloromethane (250 mL) and washed with an aqueous $Na_2S_2O_3$ solution (0.3 g in 250 mL) and with 10% brine (2 × 100 mL). The aqueous layers were extracted with dichloromethane (100 mL), and the combined organic layers dried (Na_2SO_4), and the solvent was evaporated producing 15.8 g (99.4%) of crude dihydroxy acid ***ent*-8b** as a colorless gum which was used without purification in the next step. $[\alpha]^{20}_D = -7.2$ (*c* 1.0; $CHCl_3$). The following spectral data are identical with those for the enantiomer **8b**. IR (film) ν 3600−2450 (br), 1729, 1270, 1195, 1114 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ 0.89 (t, $J = 7.2$ Hz, 6H), 1.19 (t, $J = 6.8$ Hz, 6H), 1.40−1.56 (m, 4H), 1.67 and 2.00 (ABX_2, $J_{AB} = 14$ Hz, $J_{AX} = 2$ Hz, $J_{BX} = 13.2$ Hz, $1H_{eq} + 1H_{ax}$), 2.38−2.58 (m, 2H), 3.28 (t, $J = 2.0$ Hz, 1H), 3.34 (quint, $J = 6.0$ Hz, 1H), 4.08 (m, 2H), 4.24 (br d, 2H), 5.14 (br s, 2H), 12.0 (br s, 1H). ESI-MS (*m*/*z*) 317 ($M - H^-$, 100), 271 ($M - H^- - EtOH$, 50). Anal. Calcd for $C_{15}H_{26}O_7$: C, 56.59; H, 8.23. Found: C, 56.31; H, 8.05.

All-*cis*-(1*S*,3*R*,4*R*,5*R*,6*S*)-7-(1-ethylpropoxy)-6-hydroxy-2-oxooctahydrobenzooxazole-5-carboxylic Acid Ethyl Ester (*ent*-13).

Synthesized from ***ent*-8b** according to the preparation of its enantiomer **13** in 80% yield. $[\alpha]^{20}_D = -31.1$ (*c* 1.0; $CHCl_3$). For spectral data, see enantiomer **13**.

(3*S*,4*R*,5*R*)-5-*tert*-Butoxycarbonylamino-3-(1-ethylpropoxy)-4-trifluoromethanesulfonyloxy-cyclohex-1-enecarboxylic Acid Ethyl Ester (*ent*-18). Synthesized from **13** according to the preparation of its enantiomer **18** in 82% yield. $[\alpha]^{20}_D = +78.3$ (*c* 1.0; $CHCl_3$). For spectral data, see enantiomer **18**.

(3*S*,4*S*,5*R*)-4-Azido-5-*tert*-butoxycarbonylamino-3-(1-ethylpropoxy)-cyclohex-1-enecarboxylic Acid Ethyl Ester (*ent*-20). Synthesized from triflate ***ent*-18** according to the preparation of its enantiomer **20** in 77% yield. $[\alpha]^{20}_D = +60.1$ (*c* 1.0; $CHCl_3$). For spectral data, see enantiomer **20**.

(3*S*,4*S*,5*R*)-4-Acetylamino-5-amino-3-(1-ethylpropoxy)-cyclohex-1-enecarboxylic Acid Ethyl Ester Phosphoric Acid Salt (1:1) (*ent*-1). Synthesized from azide ***ent*-20** according to the preparation of oseltamivir phosphate **1** in 80% yield. $[\alpha]^{20}_D = +31.3$ (*c* 1.0; $CHCl_3$). For spectral data, see oseltamivir phosphate **1**.

Acknowledgment. The authors thank Karl Bolliger, Jens Gallert, Christof Sparr, and Patrick Stocker for their skillful experimental work and Sophie Brogly and Willy Walther for providing analytical support. We are grateful to Michelangelo Scalone and Josef Stadelmann for the use of their autoclaves and for their support received during the carbonylation experiments. We also thank the members of the Analytical Services of F. Hoffmann-La Roche Ltd., Basel, for providing and interpreting the physical data of all compounds described. The careful reading of the manuscript by Rudolf Schmid and Jean-Michel Adam is gratefully acknowledged.

Supporting Information Available: General remarks and copies of ^{1}H NMR spectra for compounds **11**, **12**, **6a**, **7a**, **7b**, **8b**, **13**, **14**, **17**, **18**, **20**, **21**, **1**, ***ent*-8a**, ***ent*-8b**, and **19** and the ^{13}C NMR spectrum for compound **19**. This material is available free of charge via Internet at http://pubs.acs.org.

JO800264D