Facile method for the synthesis of oseltamivir phosphate

A. I. Kalashnikov, S. V. Sysolyatin, G. V. Sakovich, E. G. Sonina, and I. A. Shchurova*

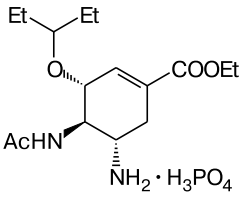
Institute for Problems of Chemical and Energetic Technologies, Siberian Branch of the Russian Academy of Sciences, 1 ul. Sotsialisticheskaya, 659322 Biisk, Russian Federation. Fax: +7 (385) 430 1725. E-mail: admin@ipcet.ru

A ten-step scheme for the preparation of an antiviral agent, ethyl (3*R*,4*R*,5*S*)-4-acetylamino-5-amino-3-(pent-3-yloxy)cyclohex-1-enecarboxylate phosphate, from (−)-shikimic acid was studied. The main parameters of the synthesis were determined and the optimal conditions for the preparation of the intermediate compounds were selected. The total yield of oseltamivir phosphate calculated based on (−)-shikimic acid was 27%.

Key words: oseltamivir phosphate, ethyl (3*R*,4*R*,5*S*)-4-acetylamino-5-amino-3-(pent-3-yloxy)cyclohex-1-enecarboxylate, (−)-shikimic acid, aziridines, azides.

Avian influenza virus H5N1 is a threat to the population as a potential source of the pandemia. The mortality rate of the virus is more than 50%. To date, no cases of transmission of the H5N1 from person to person are known. However, in September 2011 at the Congress in Malta it was reported that the more dangerous versions of the virus A(H5N1) was developed in the medical center of Rotterdam, which can be transmitted through airborne droplets.[1] While there is news from England on the development of universal vaccination against the flu H5N1 of all the modifications, these studies appear as the successful development of biological weapons. Therefore, the problem of development of defense against the pandemia of this dangerous virus becomes very important.

According to the data of World Health Organization, oseltamivir phosphate **1** (marketed under the name Tamiflu)[2] is one of the medicinal agents capable to defend from the pandemia.



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The agent inhibits the virus enzyme neuraminidase, thus preventing the virus from coming out of the human cells and its further reproduction. About 30 approaches and different modifications to the preparation of oseltamivir are described in the literature.[3—9] The yield of the product depends on the number of steps in the synthesis and the starting materials used and ranges from 5 to 57%. For the practical purposes, the methods which use available reagents, give acceptable yields, and guarantee the preparation of the desired stereoisomer are of the largest interest. The approaches based on the use of natural (−)-shikimic acid belong to such methods.[5—9] To date, the major amount of shikimic acid **2** is extracted from the seed shells of star anise grown in the south-west China. Some material is produced by the enzymatic method using *E. coli* bacteria.[10] However, the use of conifers as the raw material can not be excluded.[11] Thus, for example, the dry pine needles of the winter period contain up to 1.5% of shikimic acid.[12] One of the shortest ways of the synthesis of oseltamivir from shikimic acid is given in the present work (Scheme 1). The synthesis consists of 10 step and includes synthesis and isolation of the intermediate products **3**—**11**.

Ethyl shikimate **3** (see Refs 13 and 14) was formed by esterification of (−)-shikimic acid **2** with ethanol in the presence of an acid catalyst. Our studies showed that the conversion of **2** reached 96% after 7 h of reflux when TsOH was used.[14] However, the removal of TsOH from the final product was accompanied by the large losses of compound **3**.

It was found that when thionyl chloride was used as the catalyst and the water-binding agent,[13] the 93.5% conversion was reached only after 15—17 h, whereas the content of the main compound in product **3** was 93% (HPLC data). The best results were obtained when a heterogeneous catalyst, the KU-2-8 cationite in the H^+-form, was used with the gradual removal of water from the reaction mixture by the azeotropic distillation with ethanol with subsequent re-addition of the condensate through the column filled with zeolite NaA. When the ratio shikimic acid : KU-2-8 = 1 : 1, the reaction reached completion within 13—15 h (with 99.5% conversion), the purity of compound **3** was on the 99% level. A decrease in the amount of KU-2-8 used by a half increased the reaction time to 22—24 h. Some of the compound **3** was absorbed on the cationite, therefore, the maximal yield was achieved when KU-2-8 was reused (2—10 cycles). If triethyl orthoformate was used for the removal of water, the purity of compound **3** was within 92—93%.

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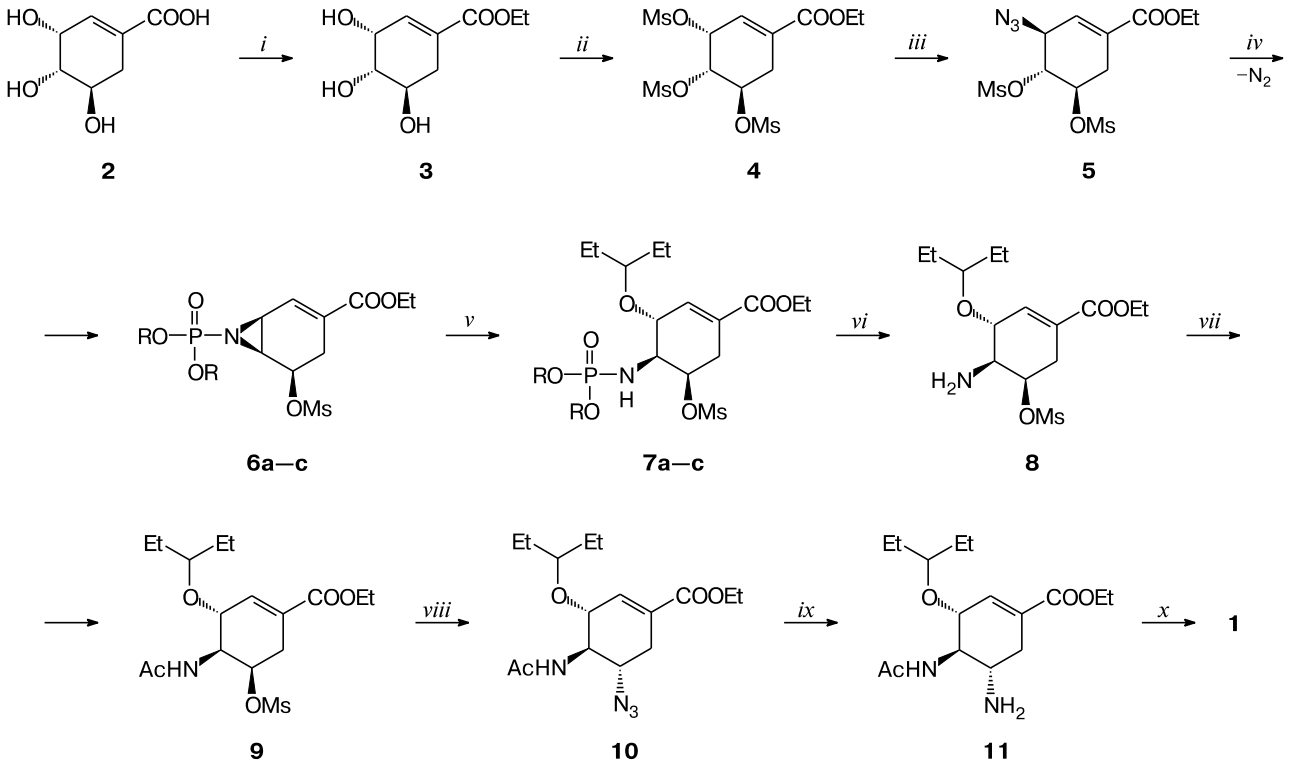
Scheme 1



6, **7:** R = Et (**a**), Me (**b**), $CHMe_2$ (**c**)

Reagents: *i.* H^+, EtOH; *ii.* MsCl, Et_3N, AcOEt, *iii.* NH_4N_3; *iv.* $(RO)_3P$; *v.* $BF_3 \cdot Et_2O$, pentan-3-ol; *vi.* H_2SO_4, EtOH; *vii.* Ac_2O; *viii.* NaN_3; *ix.* Ph_3P; *x.* H_3PO_4.

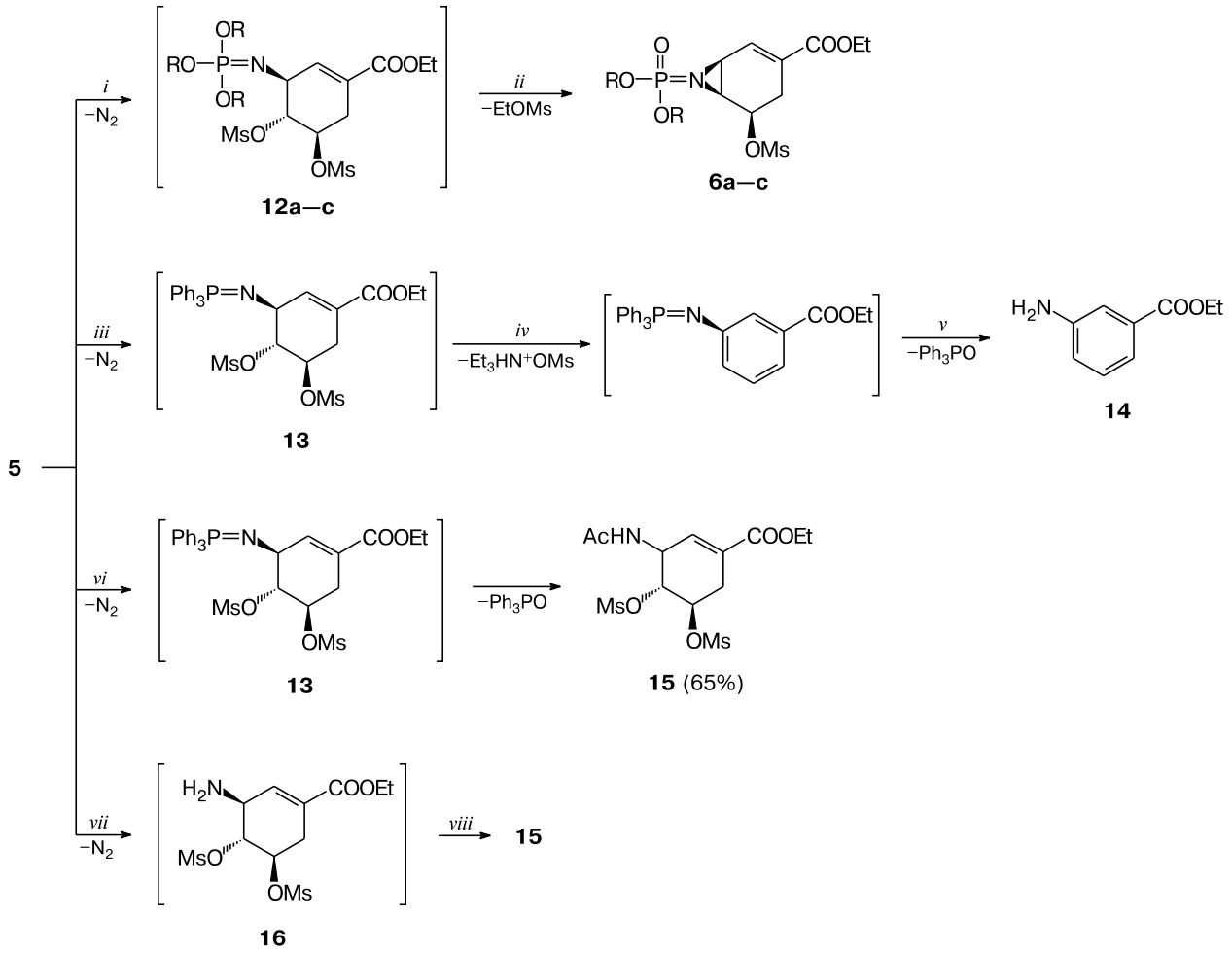
Trimesylate **4** was formed smoothly enough by treatment of triol **3** with MsCl in the presence of triethylamine.[7] The content of impurities in the product obtained did not exceed 5%. However, the use of the crude compound **4** in the subsequent steps of the synthesis led to the accumulation of the impurities and, as a consequence, to a decrease in the yield. Therefore, trimesylate **4** was isolated by the step-wise crystallization. The yield of the crystalline product was 88—89%, whereas the content of the main compound was 98—99%.

Ethyl (3*S*,4*R*,5*R*)-3-azido-4,5-bis(methanesulfonyloxy)cyclohex-1-enecarboxylate (**5**) (see Ref. 6) was formed by treatment of product **4** with sodium azide, which resulted in the regioselective substitution for the one of the methanesulfonyl groups (at position 3) and the inversion of configuration of the carbon atom at position 3 from *R* to *S*. Azide **5** is a poorly purifiable liquid, decomposing on standing. For the subsequent steps of the synthesis to be successful, it was important to minimize the amount of impurities in compound **5**. At the same time, the considerable basicity of sodium azide caused the side reactions with elimination of the MsO groups remained and aromatization of the six-membered ring to proceed. In this case, the content of ethyl esters of 3-methanesulfonyloxy- and 3-azidobenzoic acids in the reaction products reached 10%. When the basic DMF was used as the solvent, the aromatization reaction became predominant. The content of impurities was decreased to 3—5% by the use of the less basic ammonium azide (generated *in situ* from NaN_3 and NH_4Cl) and by the carrying out the reaction in MeOH.

The next step included treatment of azide **5** with alkyl phosphite (the Schtaudinger reaction). The liberation of nitrogen and the formation of the intermediate iminophosphites **12a**—**c** started already during mixing the components (Scheme 2), the intermediate were converted to aziridines **6a**—**c** upon heating. The highest rate of formation of compound **12** was observed when trimethyl phosphite was used, the reaction with triisopropyl phosphite was the slowest one. For compounds **6a**—**c** to be formed, it was enough to reflux the solution of iminophosphites **12a**—**c** in toluene for 7 h. The aziridines **6a**—**c** are liquids and can be isolated in the pure form only by preparative chromatography, therefore, products **6a**—**c** were used in the following steps without purification.

For the preparation of ethyl (3*R*,4*S*,5*R*)-4-(dialkoxyphosphorylamino)-5-methanesulfonyloxy-3-(pent-3-yloxy)cyclohex-1-enecarboxylates **7a**—**c**, the solutions of aziridines **6a**—**c** in pentan-3-ol were treated with $BF_3 \cdot Et_2O$

Scheme 2



6, 12: R = Et (**a**), Me (**b**), $CHMe_2$ (**c**)

Reagents: *i*. $(RO)_3P$; *ii*. PhMe, reflux; *iii*. Ph_3P, THF; *iv*. Et_3N, H_2O; *v*. H_2O; *vi*. Ph_3P, AcOH; *vii*. $NaBH_4$ or H_2, Pd/C; *viii*. Ac_2O.

(see Scheme 1). The analysis of the reaction mixtures by HPLC showed that the reactions were almost complete and the content of **7a—c** in the reaction products was within 75—80%. However, the isolation of the products in the pure form with good yields had proved a rather difficult problem. The samples of **7a** and **7b** isolated by preparative chromatography are crystalline compounds with melting points of 102—104 and 97—98 °C, respectively, whereas the product **7c** is a liquid. In the course of our studies, we selected the conditions under which the greater part of compound **7a** (66.2% from the theoretical yield calculated based on azide **5**) was isolated from the reaction mixture in the crystalline form, that is convenient for industrial application. The product obtained had rather high purity (98%, HPLC data). An additional amount of compound **7a** can be isolated by concentration of the reaction mixture and treatment of the residue with water. The pentan-3-ol obtained by evaporation from the reaction mixture contained water, up to 3% of toluene (impurities to compound **5**), up to 2% of pentan-2-ol, esters of pentanol and fluoroboric and difluoroboric acids (GLC data). Such a composition of the evaporated liquid allows one to comparatively easy regenerate the solvent, which includes an alkaline treatment and rectification.

Since the pure dimethylphosphorylamide **7b** and diisopropylphosphorylamide **7c** were successfully isolated only by preparative chromatography, a possibility of their use without purification in the synthesis of ethyl (3*R*,4*S*,5*R*)-4-acetamido-5-methanesulfonyloxy-3-(pent-3-yloxy)cyclohex-1-enecarboxylate (**9**) was tested.

The attempt to synthesize aziridine by the reaction of compound **5** with triphenylphosphine[6] was unsuccessful (see Scheme 2). Initially, a fast formation of iminophosphorane **13** was observed, however, with time the reaction

led (HPLC data) to the formation of triphenylphosphine oxide, ethyl *m*-aminobenzoate **14**, and several more unidentified products.[15] Apparently, the use of rather basic agents, such as triphenylphosphine (the phosphorus analog of triphenylamine) and triethylamine, caused (as in the preceding step) the formation of aromatic compounds. Carrying out the reaction in acetic acid through the hydrolysis and acylation mainly led to ethyl 3-acetamido-4,5-bis(methanesulfonyloxy)cyclohex-1-enecarboxylate (**15**).

The use of reducing agent ($NaBH_4$ or H_2—Pd/C) led to the reduction of the azide group, however, no cyclization of the *o*-aminomesylate **16** obtained to aziridine was observed. After treatment of the reaction products with acetic anhydride, only acetamide **15** was isolated.

The replacement of the dialkoxyphosphoryl group in compounds **7a**—**c** with the acetyl group was carried out in two steps (see Scheme 1). First, compounds **7a**—**c** were treated with a mixture of ethanol and sulfuric acid. Such conditions provided the hydrolysis of the amide group to the amine one, with the ester bond remaining intact. The analysis of the reaction mixture by HPLC showed the virtually complete absence of impurities and the stability of amine **8** formed. For the reaction to reach completion, it was enough 14—16 h of reflux. The acidic solution of amine **8** obtained was neutralized with aqueous $NaHCO_3$ and acetylated with acetic anhydride under heterogeneous conditions. The reaction was easy enough to proceed. For its completion, it was enough to use 1.5 mol of acetic anhydride and 30 min. As in the preceding steps, a strongly alkaline reaction medium caused the side reactions to take place and a decrease in the yield of ethyl (3*R*,4*S*,5*R*)-4-acetamido-5-methanesulfonyloxy-3-(pent-3-yloxy)-cyclohex-1-enecarboxylate **9**. The yield of acetamide **9** calculated based on compound **7a** was 82.8%, its yield calculated based on the starting azide **5** (four steps) was 52.6%. The use of crude products **7b**,**c** with the content of impurities about 25% instead of compound **7a** significantly hindered isolation of the pure acetamide **9**. Thus, when **7c** was used the yield of acetamide **9** calculated on the starting azide **5** was 37.4%.

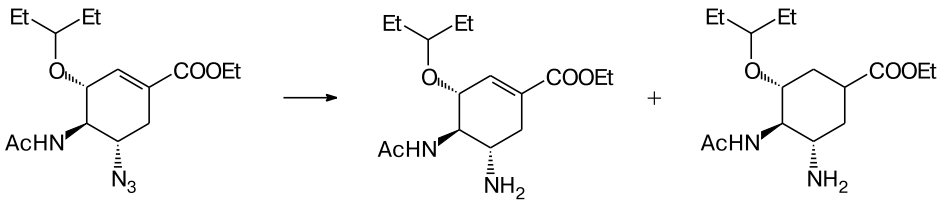
The final steps of the synthesis included the replacement of the MsO group with the azide one and its reduction to the amine. The exchange of the mesyl group with the azide at position 5 was accompanied by the inversion at atom C(5) from *R*- to *S*-configuration and proceeded in EtOH at a considerable rate only at high temperature. For the reaction to reach completion, a large excess of sodium azide was required. Thus, the use of 3 mol of NaN_3 (per 1 mol of acetamide **9**) and carrying out the reaction by reflux in 78% aqueous ethanol led to the 95% conversion of acetamide **9** within 15 h. When the amount of sodium azide was reduced to 2 mol, the same conversion required more than 24 h. The yield of ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-azido-3-(pent-3-yloxy)cyclohex-1-enecarboxylate (**10**) was 72%.

The molecule of compound **10** besides the azide group contains an easily reducible activated double bond, therefore, the choice of reducing agents was limited. When sodium borohydride was used, the reduction at room temperature occurred slowly. The conversion of 70% at the ratio $NaBH_4$: **10** = 1 : 1 was reached within 2 days. The reaction resulted in the formation of a mixture of products (Scheme 3), which contained, besides the expected ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(pent-3-yloxy)cyclohex-1-enecarboxylate (oseltamivir, **11**), the product of the complete reduction, *viz.*, ethyl 4-acetamido-5-amino-3-(pent-3-yloxy)cyclohexane-1-carboxylate (**17**).

The use of catalytic hydrogenation required a thorough control of the reaction. Thus, when the palladium catalyst (5% Pd/C) was used the rate of reduction of the azide group was 6 times as fast as the rate of the reduction of the double bond, and the yield of the product **1** (after purification) was 63%. The Raney nickel[16] and the Lindlar catalyst[5] ($Pd/BaSO_4$) are described to be successfully used in the known methods for the reduction of the azide group.

The highest selectivity of reduction was obtained when triphenylphosphine was used. The mechanism of the process described in the literature includes three steps. The formation of azidophosphorane takes place initially, which rapidly eliminates nitrogen to be converted to iminophosphorane. The following step of the process is the hydrolysis of the iminophosphorane obtained upon the action of water. The process is comparatively long (14 h at the temperature of 45 °C). The unavoidable presence of water and the basicity of the medium (all the products are bases) lead to the side reactions: the hydrolysis of the ester bond and

Scheme 3



10 **11** **17**

the aromatization of the six-membered ring (with the elimination of some groups), therefore, the yield of the reduction products was lower than theoretical. The reaction can take place in aqueous alcohols (methanol, ethanol). The use of *tert*-butyl methyl ether increases the content of impurities. The best results were provided by THF with the sequential dosage of **10** and water to the solution of triphenylphosphine. The addition of a small amount of acetic acid increases the yield of the product by 3—5%. The replacement of AcOH with phosphoric acid does not result in the increase of the yield, whereas the use of H_3PO_4 in the amount of 1 mol per 1 mol of **10** according to the TLC data completely blocks hydrolysis of iminophosphorane. Treatment of compound **11** (see Refs 5 and 16) with phosphoric acid in a mixture of EtOH—AcOEt leads to the preparation of oseltamivir phosphate **1**.

The synthesis of compound **1** under consideration (see Scheme 1) does not require the use of nonstandard appliances, uses the minimum amount of expensive reagents, and can be easily and rapidly accomplished by any chemical production. The total yield of oseltamivir phosphate calculated on shikimic acid for the given ten-step synthesis was 27%.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400.13 (^{1}H) and 100.61 MHz (^{13}C)) in DMSO-d_6, $(CD_3)_2CO$, D_2O, and $CDCl_3$. Chemical shift are given relative to $SiMe_4$. IR spectra of compounds were recorded on a Infralyum FT-801 spectrometer in KBr pellets. HPLC analysis was performed on an Agilent 1200 instrument; a 2.1×15-mm precolumn, Zorbax SB-18 (3 μm) sorbent; a 2.1×150-mm column, Zorbax SB-18 (5 μm) sorbent. Composition and quality of products were determined by an UV detector (λ = 213 nm) using a gradient elution. Eluent A: 0.2% aqueous orthophosphoric acid, eluent B: acetonitrile. Specific optical rotation was determined on a P 3002 KRUSS polarimeter. Shikimic acid containing 99% of the main compound (HPLC data) was prepared by crystallization of the commercial product (SHANGHAI AZ IMPORT & EXPORT CO., LTD) from water. Zeolite NaA was dried for 12 h at 270 °C. Anhydrous ethanol (the content of water 0.8%) was prepared by drying over zeolite NaA. Silica gel 60 Å, 0.06—0.20 mm (Acros Organics) was used for preparative chromatography.

Ethyl shikimate (3). A mixture of shikimic acid **2** (50 g, 0.287 mol), anhydrous ethanol (200 mL), and KU-2-8 cationite (50 g) (reuse) were placed in a flask, the flask was connected to a Sohxlet apparatus, which was preliminary loaded with zeolite NaA (160 g). The mixture was refluxed for 15 h with magnetic stirring. The solution obtained was cooled and filtered, the cationite was washed with anhydrous ethanol (3×100 mL), the solvent was evaporated *in vacuo*. The residue was treated with diethyl ether (350 mL) and filtered to obtain compound **2** (54.0 g, 93.0%), m.p. 97.8—99.0 °C, the content of the main compound was 99.0% (HPLC data); $[\alpha]_D^{22}$ −45.4 (*c* 1.0, H_2O). Found (%): C, 54.00; H, 7.16. $C_9H_{14}O_5$. Calculated (%): C, 53.46; H, 6.98. IR, ν/cm^{-1}: 3354, 2911, 1717, 1654, 1456, 1372, 1238, 1092, 1053, 932, 873, 837, 749. ^{1}H NMR ($(CD_3)_2CO$), δ: 6.77 (s, 1 H, CH); 4.37 (s, 1 H, CH); 4.18 (q, 1 H, CH, *J* = 7.1 Hz); 3.95 (m, 2 H, CH_2); 3.68 (m, 1 H, CH); 2.99 (dd, 1 H, CH_2, *J* = 4.4 Hz, *J* = 12.4 Hz); 2.71 (dd, 1 H, CH_2, *J* = 4.6 Hz, *J* = 12.9 Hz); 1.28 (t, 3 H, CH_3, *J* = 7.0 Hz). ^{13}C NMR ($(CD_3)_2CO$), δ: 166.9 (C=O), 139.5 (CH), 128.8 (C), 66.3 (CH), 60.6 (CH_2), 30.5 (CH_2), 14.4 (CH_3).

Ethyl (3*R*,4*S*,5*R*)-3,4,5-tri-*O*-methanesulfonylshikimate (4). A suspension of ethyl shikimate **3** (55.0 g) in ethyl acetate (550 mL) and MsCl (94 mL) was cooled to 0 °C, followed by a gradual addition of triethylamine (186 mL) over 2 h with vigorous stirring, keeping the temperature below 3 °C. The mixture was kept for 2 h at 0 °C, diluted with 1 *M* HCl (200 mL), and stirred for 15 min. The organic layer was separated, washed with 2% aqueous Na_2CO_3 (3×100 mL) and 20% aq. NaCl (100 mL). The organic layer was filtered through a paper filter, concentrated to a half volume *in vacuo* at 40 °C, and allowed to stand for 16 h. A precipitated product was filtered off and washed with ethyl acetate. The filtrate was re-concentrated to isolate two more portions of compound **4**. The total yield of compound **4** was 100.0 g (84.2%), m.p. 99—100 °C, $[\alpha]_D^{22}$ −110.3 (*c* 1.0, EtOAc) (*cf.* Ref. 6: m.p. 97.8—99.0 °C, $[\alpha]_D^{25}$ −119.4 (*c* 1.0, EtOAc)). Found (%): C, 32.69; H, 4.57; S, 22.26. $C_{12}H_{20}O_{11}S_3$. Calculated (%): C, 33.02; H, 4.62; S, 22.04. IR, ν/cm^{-1}: 3033, 2942, 1714, 1658, 1348, 1260, 1180, 1105. ^{1}H NMR ($CDCl_3$), δ: 6.76 (s, 1 H, CH); 5.46 (t, 1 H, CH, *J* = 4.1 Hz); 5.04 (m, 1 H, CH); 4.95 (dd, 1 H, CH, *J* = 4.3 Hz, *J* = 3.9 Hz); 4.20 (m, 2 H, CH_2); 3.12 (d, 9 H, 3 CH_3, *J* = 4.3 Hz); 3.07 (s, 1 H, CH_2); 2.67 (dd, 1 H, CH_2, *J* = 6.2 Hz, *J* = 12.8 Hz); 1.26 (t, 3 H, CH_3, *J* = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ: 164.3 (C=O), 132.8 (C), 129.8 (CH), 74.4 (CH_2), 72.8 (2 CH), 61.6 (CH_2), 38.5 (CH_3), 30.2 (CH_2), 13.9 (CH_3).

Ethyl (3*S*,4*R*,5*R*)-3-azido-4,5-bis(methanesulfonyloxy)cyclohex-1-enecarboxylate (5). Sodium azide (14.4 g, 0.22 mol) was added in small portions to suspension of compound **4** (60.0 g, 0.14 mol) and NH_4Cl (22.2 g) in MeOH (210 mL) over 1.5 h with vigorous stirring, maintaining the temperature below 10 °C. The reaction mixture was kept at room temperature for 5 h, diluted with toluene (210 mL), a precipitate was separated by filtration, the filtrate was concentrated *in vacuo* on a rotary evaporator. The residue was dissolved in a mixture of water (60 mL) and toluene (200 mL). The layers were separated, the organic phase was dried with $MgSO_4$, the solvent was evaporated *in vacuo* on a rotary evaporator at 45 °C to obtain compound **5** (52.5 g, 98%), a dense liquid with the content of the main compound 95% (HPLC data). An analytical sample of product **5** was purified by preparative chromatography (eluent ethyl acetate—hexane (1 : 1)), $[\alpha]_D^{22}$ +48.1 (*c* 1.0, EtOAc) (*cf.* Ref. 6: $[\alpha]_D^{25}$ +45.1 (*c* 1.9, EtOAc)). Found (%): C, 34.83; H, 4.47; N, 10.96; S, 16.73. $C_{11}H_{17}N_3O_8S_2$. Calculated (%): C, 34.46; H, 4.47; N, 10.96; S, 16.73. IR, ν/cm^{-1}: 2940, 2108, 1717, 1661, 1446, 1358, 1253, 1176, 1075, 1016. ^{1}H NMR ($CDCl_3$), δ: 6.65 (s, 1 H, CH); 4.80 (m, 1 H, CH); 4.68 (m, 1 H, CH); 4.30 (t, 1 H, CH, *J* = 3.9 Hz); 4.19 (q, 2 H, CH_2, *J* = 7.2 Hz); 3.14 (s, 3 H, CH_3); 3.06 (s, 3 H, CH_3); 2.63 (m, 2 H, CH_2); 1.25 (m, 3 H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 164.08 (C=O), 131.9 (CH), 130.1 (C), 78.9 (CH), 73.8 (CH), 61.6 (CH_2), 60.9 (CH), 39.2 (CH_3), 38.8 (CH_3), 30.9 (CH_2), 14.0 (CH_3).

Ethyl (3*R*,4*S*,5*R*)-4-(diethoxyphosphorylamino)-5-methanesulfonyloxy-3-(pent-3-yloxy)cyclohex-1-enecarboxylate (7a). Triethyl phosphite (23.5 mL, 22.6 g) was added carefully to

a solution of compound **5** (47.5 g) in toluene (124 mL). The reaction mixture was kept at room temperature for 1 h, then refluxed for 7 h, and cooled. The solvent was evaporated *in vacuo* on a rotary evaporator to obtain the residue (54.9 g) mainly containing compound **6a**. The residue was dissolved in pentan-3-ol (120 mL), followed by the addition of $BF_3 \cdot Et_2O$ (17.3 mL) in small portions over 1 h at 0—3 °C. The reaction mixture was kept for 16 h at room temperature, then diluted with water (50 mL). The organic layer was separated, washed with 5% aq. $NaHCO_3$ (2×30 mL), water (2×30 mL), and placed into a refrigerator (4 °C). After 1—2 days, a precipitate formed was filtered off and washed with Et_2O (50 mL) to obtain compound **7a** (35.5 g), a white crystalline product with m.p. 102—104 °C (*cf.* Ref. 7: m.p. 99.5—102.8 °C). The filtrate was concentrated *in vacuo* on a rotary evaporator at 55 °C (bath temperature), the residue was dissolved in Et_2O (50 mL) and let to stand for several days. Then, the second portion of the product was filtered off. The total yield of compound **7a** was 40.0 g (66.2%); $[\alpha]_D^{22}$ −54° (*c* 1.0, EtOAc). Found (%): C, 46.53; H, 7.35; N, 3.01; S, 7.03. $C_{19}H_{38}NO_9PS$. Calculated (%): C, 47.00; H, 7.47; N, 2.88; S, 6.60. IR, ν/cm^{-1}: 3238, 1714, 1356, 1175, 1101, 1032. ^{1}H NMR ($CDCl_3$), δ: 6.75 (s, 1 H, CH); 4.98 (s, 1 H, CH); 4.13 (q, 2 H, CH_2, J = 7.2 Hz); 4.00 (m, 5 H, 2 CH_2, CH); 3.61 (m, 1 H, CH); 3.33 (m, 2 H, CH, NH); 3.03 (s, 3 H, CH_3); 2.68 (s, 2 H, CH_2); 1.47 (m, 4 H, 2 CH_2); 1.26 (m, 9 H, 3 CH_3); 0.86 (q, 6 H, 2 CH_3, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$), δ: 165.4 (C=O), 135.1 (CH), 128.2 (C), 81.2 (CH), 77.7 (CH_3), 77.2 (CH_2), 73.3 (2 CH), 62.4 (CH_2), 60.8 (CH_2), 53.3 (CH), 38.0 (CH_3), 28.5 (CH_2), 25.9 (CH_2), 25.5 (CH_2), 15.9 (CH_3), 15.8 (CH_3), 9.4 (CH_3), 9.1 (CH_3).

Ethyl (3*R*,4*S*,5*R*)-4-(dimethoxyphosphorylamino)-5-methanesulfonyloxy-3-(pent-3-yloxy)cyclohex-1-enecarboxylate (7b) was obtained similarly to compound **7a** from trimethyl phosphite (20.4 g) and compound **5** (47.5 g). The evaporation of the washed reaction mixture gave a dense product (65.3 g), with the content of compound **7b** being 83% (HPLC data). An analytical sample was purified by preparative chromatography (eluent ethyl acetate) to obtain compound **7b** as colorless crystals, m.p. 97—98 °C. Found (%): C, 44.72; H, 6.98; N, 2.94; S, 7.11. $C_{17}H_{32}NO_9PS$. Calculated (%): C, 44.63; H, 7.05; N, 3.06; S, 7.01. IR, ν/cm^{-1}: 3196, 2963, 1712, 1660, 1466, 1359, 1340, 1306,1264, 1234, 1178, 1105, 971, 909. ^{1}H NMR ($CDCl_3$), δ: 6.85 (s, 1 H, CH); 5.01 (s, 1 H, CH); 4.22 (q, 2 H, CH_2, J = 6.9 Hz); 4.04 (s, 1 H, CH); 3.75, 3.79 (both, 6 H, 2 CH_3); 3.50 (q, 1 H, CH, J = 6.7 Hz); 3.41 (t, 1 H, CH, J = 5.6 Hz); 3.25 (t, 1 H, CH, J = 10.1 Hz); 3.10 (s, 3 H, CH_3); 2.73 (dd, 1 H, CH_2, J = 7.4 Hz, J = 10.6 Hz); 1.55 (m, 4 H, 2 CH_2); 1.33 (t, 3 H, CH_3, J = 8.3 Hz); 0.96 (q, 6 H, 2 CH_3, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ: 165.5 (C=O), 135.3 (CH), 128.6 (C), 81.6 (CH), 77.8 (CH), 73.7 (CH), 61.1 (CH_2), 53.6 (CH), 38.4 (CH_3), 28.8 (CH_2), 26.2 (CH_2), 25.9 (CH_2), 25.5 (CH_2), 14.2 (CH_3), 9.7 (CH_3), 9.4 (CH_3).

Ethyl (3*R*,4*S*,5*R*)-4-(diisopropoxyphosphorylamino)-5-methanesulfonyloxy-3-(pent-3-yloxy)cyclohex-1-enecarboxylate (7c) was obtained similarly to compound **7a** from triisopropyl phosphite (26.0 g) and compound **5** (47.5 g). The evaporation of the washed reaction mixture gave a dense product (67.5 g), with the content of compound **7c** being 81% (HPLC data). An analytical sample was purified by preparative chromatography (eluent ethyl acetate) to obtain compound **7c** as a light yellow liquid. Found (%): C, 49.21; H, 7.75; N, 2.75; S, 6.13. $C_{21}H_{40}NO_9PS$. Calculated (%): C, 49.11; H, 7.85; N, 2.73; S, 6.24. IR, ν/cm^{-1}: 2978, 2937, 1715, 1658, 1464, 1356, 1233, 1174, 1142, 1102, 982, 907, 836, 798, 749. ^{1}H NMR ($CDCl_3$), δ: 6.71 (s, 1 H, CH); 5.08 (t, 1 H, CH, J = 10.2 Hz); 4.87 (m, 1 H, CH); 4.51 (m, 2 H, 2 CH); 4.18 (q, 2 H, CH_2, J = 7.0 Hz); 3.99 (m, 1 H, CH); 3.40 (s, 1 H, NH); 3.32 (m, 1 H, CH); 3.24 (m, 3 H, CH_3); 2.71 (dd, 1 H, CH_2, J = 5.9 Hz, J = 13.5 Hz); 2.65 (dd, 1 H, CH_2, J = 5.9, J = 11.8); 1.48 (m, 4 H, 2 CH_2); 1.24 (m, 15 H, 5 CH_3); 0.86 (q, 6 H, 2 CH_3, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ: 166.2 (C=O), 135.0 (CH), 129.1 (C), 81.1 (CH), 74.4 (CH), 71.1 (CH), 70.1 (2 CH), 60.9 (CH_2), 53.6 (CH), 38.1 (CH_3), 28.5 (CH_2), 25.6 (2 CH_2), 24.1 (CH_3), 14.5 (4 CH_3), 9.7 (CH_3), 9.4 (CH_3).

Ethyl 3-acetamido-4,5-bis(methanesulfonyloxy)cyclohex-1-enecarboxylate (15). Triphenylphosphine (2.4 g) was added to a solution of compound **5** (2.7 g) in glacial acetic acid (20 mL) at room temperature. The reaction mixture was kept for 1.5 h, then triethylamine (3 mL) was added, and after 30 min water (5 mL) was added. The mixture was kept at room temperature for 12 h. The solvent was evaporated *in vacuo* on a rotary evaporator. The residue obtained was dissolved in a mixture of ethyl acetate—hexane (1 : 2, 20 mL) and separated by preparative chromatography (eluent ethyl acetate—hexane, 1 : 2). The fraction 1 (0.45 g) contained triphenylphosphine, ethyl *m*-aminobenzoate, and an unidentified product (HPLC data), the fraction 2 (1.9 g) contained ester (**15**), m.p. 145—146 °C. Found (%): C, 38.95; H, 5.35; N, 3.62; S, 16.15. $C_{13}H_{21}NO_9S_2$. Calculated (%): C, 39.09; H, 5.30; N, 3.51; S, 16.06. IR, ν/cm^{-1}: 3204, 2984, 2944, 1710, 1658, 1353, 1267, 1222, 1174, 1035, 963. ^{1}H NMR (DMSO-d_6), δ: 8.34 (s, 1 H, CH); 6.45 (d, 1 H, CH, J = 12.3 Hz); 5.07 (s, 1 H, CH); 4.76 (s, 2 H, CH_2); 4.11 (s, 2 H, CH_2); 3.18 (m, 8 H, 2 CH_3, CH_2); 1.83 (d, 3 H, CH_3, J = 14.3 Hz); 1.17 (s, 3 H, CH_3). ^{13}C NMR (DMSO-d_6), δ: 168.9 (C=O), 167.5 (C=O), 139.0 (CH), 132.4 (C), 128.0 (CH), 83.3 (CH), 83.2 (CH), 61.7 (CH_2), 53.8 (CH), 38.9 (CH_3), 38.6 (CH_3), 26.6 (CH_2), 23.4 (CH_3), 14.3 (CH_3).

Ethyl (3*R*,4*S*,5*R*)-4-acetamido-5-methanesulfonyloxy-3-(pent-3-yloxy)cyclohex-1-enecarboxylate (9). A solution of compound **7a** (40.0 g) in a mixture of H_2SO_4 (conc.) (36.5 mL) and EtOH (190 mL) was heated at 78 °C for 16 h. The reaction mixture was diluted with AcOEt (380 mL) and water (80 mL), neutralized with 20% aq. Na_2CO_3 to pH 6.5—7.0, followed by the addition of Ac_2O (7.7 mL). The mixture was kept for 30 min at room temperature, maintaining pH 6.5—7.0 by the addition of aq. Na_2CO_3. After addition of Ac_2O (3.8 mL) and keeping for 30 min, the organic layer was separated, the aqueous layer was extracted with AcOEt (240 mL). The combined organic layers were washed with 5% aq. $NaHCO_3$ (90 mL), dried with Na_2SO_4 and the solvent was evaporated *in vacuo* on a rotary evaporator until a dense suspension was formed. The suspension was diluted with *tert*-butyl methyl ether (35 mL), the product was filtered off, washed with Bu^tOMe to obtain compound **9** (19.1 g). The filtrate was re-concentrated, treated with Bu^tOMe to isolate a second portion of the product (2.6 g). The filtrate was concentrated, the residue was recrystallized from a mixture of Bu^tOMe—EtOAc (5.5 : 1). The total yield of product **9** was 26.5 g (82.1%), m.p. 138—139 °C, $[\alpha]_D^{22}$ −85 (*c* 1.0, $CHCl_3$) (*cf.* Ref. 7: m.p. 129.8—31.9 °C, $[\alpha]_D^{25}$ −85 (*c* 0.7, EtOAc)). Found (%): C, 52.53; H, 7.96; N, 3.22; S, 7.83. $C_{17}H_{29}NO_7S$. Calculated (%): C, 52.16; H, 7.47; N, 3.58; S, 8.19. IR, ν/cm^{-1}: 3307, 1716, 1656, 1536, 1346, 1255, 1177, 1098, 1051. ^{1}H NMR ($CDCl_3$), δ: 6.77 (s, 1 H,

CH); 6.75 (m, 1 H, NH); 5.00 (s, 1 H, CH); 4.12 (m, 3 H, CH, CH_2); 3.99 (d, 1 H, CH, J = 5.4 Hz); 3.28 (q, 1 H, CH, J = 6.2 Hz); 2.97 (s, 3 H, CH_3); 2.69 (s, 2 H, CH_2); 1.90 (s, 3 H, CH_3); 1.42 (m, 4 H, 2 CH_2); 1.20 (t, 3 H, CH_3, J = 6.9 Hz); 0.78 (t, 6 H, 2 CH_3, J = 6.2 Hz). ^{13}C NMR ($CDCl_3$), δ: 171.8 (C=O), 165.0 (C=O), 136.1 (CH), 127.6 (C), 78.2 (2 CH), 75.1 (2 CH), 61.2 (CH_2), 50.1 (CH_3), 48.7 (CH_2), 47.8 (CH_2), 38.3 (CH_3), 38.0 (CH_3), 30.0 (CH_2), 22.0 (CH_3), 13.6 (CH_3).

Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-azido-3-(pent-3-yloxy)-cyclohex-1-enecarboxylate (10). A solution of NaN_3 (17.7 g) in water (36 mL) was added to a solution of compound **9** (23.5 g) in EtOH (260 mL) and the mixture was refluxed for 24 h. The solvent was evaporated *in vacuo*, followed by the addition of AcOEt (200 mL) and water (20 mL). The organic layer was separated, washed with 20% aq. NaCl (15 mL), and dried with $MgSO_4$. The solvent was evaporated *in vacuo* until a dense suspension was formed. The suspension was filtered and washed with Bu^{t}OMe (3×25 mL) to isolate the first portion of the product (12.1 g). The filtrate was re-concentrated to obtain the second portion of the product (2.1 g). Then, the filtrate was concentrated to dryness, the residue was recrystallized from Bu^{t}OMe to additionally obtain 1.1 g of compound **10**. The portions of the product (15.3 g) were combined and recrystallized from a mixture of Bu^{t}OMe—AcOEt (6.5 : 1, v/v, 75 mL) to obtain product **10** (14.6 g, 72.0%), m.p. 137—138 °C, $[\alpha]_D^{22}$ −51.5 (*c* 1.0, $CHCl_3$) (*cf.* Refs 5 and 7: m.p. 137—138 °C, $[\alpha]_D^{20}$ −44 (*c* 1.0, $CHCl_3$)). Found (%): C, 56.54; H, 7.52; N, 16.62. $C_{16}H_{26}N_4O_4$. Calculated (%): C, 56.79; H, 7.74; N, 16.56. IR, ν/cm^{-1}: 3270, 2972, 2105, 1716, 1660, 1563, 1375, 1332, 1254, 1079. ^{1}H NMR ($CDCl_3$), δ: 7.15 (d, 1 H, CH, J = 8.4 Hz); 6.69 (s, 1 H, CH); 4.03 (d, 1 H, CH, J = 8.0 Hz); 3.91 (m, 1 H, CH, J = 5.2 Hz); 3.80 (q, 2 H, CH_2, J = 7.0 Hz); 3.65 (dd, 1 H, CH, J = 10.5 Hz, J = 9.0 Hz); 3.29 (t, 1 H, NH, J = 5.5 Hz); 2.78 (dd, 1 H, CH_2, J = 5.5 Hz, J = 12.5 Hz); 2.18 (m, 1 H, CH_2); 1.97 (s, 3 H, CH_3); 1.44 (m, 4 H, 2 CH_2); 1.24 (t, 3 H, CH_3, J = 7.2 Hz); 0.83 (m, 6 H, 2 CH_3). ^{13}C NMR ($CDCl_3$), δ: 171.2 (C=O), 165.7 (C=O), 138.1 (CH), 127.8 (C), 82.1 (CH), 74.3 (CH), 60.9 (CH_2), 58.0 (CH), 56.3 (CH), 30.2 (CH_2), 26.0 (CH_2), 25.4 (CH_2), 23.3 (CH_3), 14.0 (CH_3), 9.3 (CH_3), 9.0 (CH_3).

Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-amino-3-(pent-3-yloxy)-cyclohex-1-enecarboxylate phosphate (oseltamivir phosphate, 1). ***A.*** Compound **10** (14.2 g) and water (12 mL, acidified with two drops of AcOH) were sequentially added to a suspension of triphenylphosphine (13.0 g) in tetrahydrofuran (100 mL) at room temperature. The mixture was stirred until the temperature ceased to rise and heated at 45 °C for 16 h. The reaction mixture was concentrated to dryness *in vacuo* on a rotary evaporator. The residue was dissolved in EtOH (20 mL) and re-concentrated. Then the residue, containing oseltamivir **11** and triphenylphosphine oxide, was dissolved in a mixture of EtOH—AcOEt (48 mL, 1 : 1). A solution obtained was slowly added dropwise to the solution of 85% aq. H_3PO_4 (2.84 mL, 6.12 g) in a mixture of EtOH—AcOEt (140 mL, 1 : 1) heated to 50—55 °C. A suspension of the product was slowly cooled (4—5 h), the product was filtered off and washed with acetone (4×10 mL). After drying in air, compound **1** (14.4 g, 83.6%) was obtained, m.p. 201—202 °C, the content of the main compound was 98.8% (HPLC data). The filtrate was concentrated on a rotary evaporator *in vacuo*, the residue was dissolved with vigorous stirring in acetone left after washing. The suspension obtained was filtered off, the residue was washed with acetone (4×10 mL). After drying in air, an additional portion of compound **1** (1.4 g, 7.3%) was obtained, the content of the main compound was 90.0% (HPLC data), $[\alpha]_D^{22}$ −34.2 (*c* 1.0, H_2O) (*cf.* Refs 5 and 7: m.p. 203—204 °C, $[\alpha]_D^{20}$ −39 (*c* 1.0, H_2O). Found (%): C, 47.21; H, 7.42; N, 6.76. $C_{16}H_{31}N_2O_8P$. Calculated (%): C, 46.94; H, 7.39; N, 6.84. IR, ν/cm^{-1}: 3351, 3160, 2967, 2939, 2878, 1721, 1660, 1552, 1374, 1337, 1294, 1246, 1129, 1069, 1032, 951, 875, 731. ^{1}H NMR (D_2O), δ: 8.34 (d, 1 H, CH, J = 9.0 Hz); 6.65 (s, 1 H, CH); 4.18 (q, 2 H, CH_2, J = 6.5 Hz); 3.73 (m, 1 H, CH); 3.38 (m, 1 H, CH_2); 3.02 (m, 1 H, CH_2); 2.50 (s, 4 H, CH, CH_3); 2.26 (m, 1 H, CH); 1.88 (s, 3 H, CH_3); 1.46 (m, 4 H, 2 CH_2); 1.24 (t, 3 H, CH_3, J = 7.0 Hz); 0.94 (m, 6 H, 2 CH_3). ^{13}C NMR (D_2O), δ: 174.8 (C=O), 166.5 (C=O), 139.0 (CH), 128.0 (C), 83.3 (CH), 75.3 (CH), 61.7 (CH_2), 53.8 (CH), 49.4 (CH), 29.3 (CH_2), 26.6 (CH_2), 26.0 (CH_2), 23.4 (CH_3), 14.3 (CH_3), 9.6 (CH_3), 9.3 (CH_3).

B. A mixture of compound **10** (5.0 g), the catalyst (6% Pd/C, 0.5 g), and EtOH (100 mL) was placed into a 500-mL flask. The air was thrice vacuum-evacuated, filling the flask with hydrogen. The reduction was carried out with stirring (3 h, 24 °C). Then, the mixture was filtered from the catalyst, a 85% aq. H_3PO_4 (1.1 mL) was added to the filtrate, and the solvent was evaporated *in vacuo* on a rotary evaporator until a solid product was obtained. The residue was dissolved in anhydrous ethanol (35 mL) with heating, diluted with AcOEt (35 mL). After cooling, oseltamivir phosphate (3.9 g, 63%) was filtered off, m.p. 200—201 °C, the content of the main compound was 97.5% (HPLC data). The filtrate, according to the HPLC data, contained mixture of products **1** and **17**.

C. The carrying out the synthesis by similar method with the increase in the hydrogenation time to 12 h and refilling the flask with hydrogen (to remove the liberated nitrogen) led to the consumption of 340 mL of hydrogen and the formation of product **17**. A prolonged concentration of the solution obtained (after the addition of H_3PO_4) on a rotary evaporator *in vacuo* gave a crystalline product (6.3 g), m.p. 216—217 °C. ^{13}C NMR ($CDCl_3$), δ: 173.6 (C=O), 171.0 (C=O), 80.7 (CH), 75.5 (CH), 60.7 (CH_2), 55.7 (CH), 51.2 (CH), 37.8 (CH), 35.0 (CH_2), 31.8 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 23.8 (CH_3), 14.5 (CH_3), 9.9 (CH_3), 9.3 (CH_3).

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