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Formal Total Synthesis of (−)-Oseltamivir Phosphate

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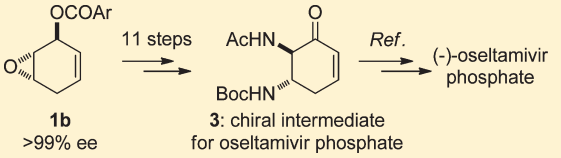
Supporting Information

ABSTRACT: An asymmetric synthesis of chiral intermediate **3** for (−)-oseltamivir phosphate has been accomplished from chiral building block **1**, which was prepared by catalytic asymmetric synthesis.



Multifunctionalized optically active six-membered ring moieties exist widely in natural products and pharmaceutical agents. For example, many kinds of carbasugars possess antiviral, anticancer, and antibiotic activities.[1] Recently, oseltamivir phosphate, a cyclohexene ring bearing three asymmetric centers, has received much attention from various scientific fields (Figure 1). (−)-Oseltamivir phosphate is an anti-influenza drug (Tamiflu) developed by Gilead Science[2] with a proven potency for the H5N1 avian flu virus. Thus, several total asymmetric syntheses of (−)-oseltamivir phosphate have been investigated.[3,4]

Recently, we developed a synthetic method for enantiopure (1*S*,2*S*,3*S*)-3-acyloxy-1,2-epoxycyclohex-4-ene (**1**) via asymmetric desymmetrization of 1,2-epoxycyclohex-4-ene using Kharasch−Sosnovsky allylic oxidation.[5,6] The catalyst derived from chiral *N*,*N*-bidentate Schiff base ligand **2** was the most effective in terms of enantioselectivity, affording **1a** in 84% ee (1*S*,2*S*,3*S*). Furthermore, after exchanging the protecting group of the hydroxy moiety and recrystallization from hexane and ethyl acetate (4:1), the enantiomeric excess of **1b** was improved to >99% ee (1*S*,2*S*,3*S*) (Scheme 1).[6]

Herein, we describe the synthesis of **3**, a key intermediate for Shibasaki's third generation oseltamivir phosphate synthesis,[7] from chiral building block **1b**. In Shibasaki's work, this compound was synthesized in its racemic form and the optically active compound was obtained by chiral HPLC separation. We synthesized the optically active key intermediate **3** from chiral building block **1b** prepared by catalytic asymmetric desymmetrization of 1,2-epoxycyclohex-4-ene using Kharasch−Sosnovsky allylic oxidation.

The first stage of the synthesis involved the preparation of the chiral mesylate **5** (Scheme 2). The O-protecting group of chiral building block **1b** was exchanged to a methoxymethyl (MOM) group, affording methoxymethyl ether **4** in 99% yield (2 steps). Regioselective ring opening of O-protected epoxide **4** with sodium azide in the presence of ammonium chloride generated the β-azido alcohol.[8] The resultant β-azido alcohol was treated with mesyl chloride (MsCl) and diisopropylethylamine (DIPEA)

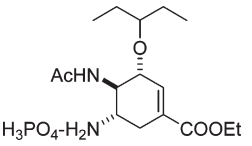
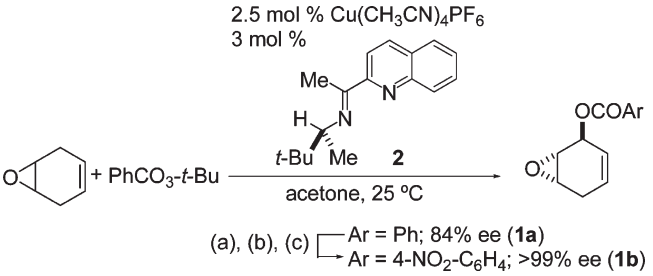


Figure 1. Structure of (−)-oseltamivir phosphate (Tamiflu).

Scheme 1. Asymmetric Desymmetrization of 1,2-Epoxycyclohex-4-ene Using Allylic Oxidation[a]



[a] Conditions: (a) MeONa, (b) 4-$NO_2C_6H_4COCl$, (c) recrystallization.

in CH_2Cl_2 to obtain mesylate **5** in 88% yield (2 steps). In this process, the undesired regioselective product was not obtained.

The key intermediate **3** was synthesized from chiral mesylate **5** in seven simple steps (Scheme 3). The chiral aziridine was prepared via Staudinger reduction of the azido group followed by an intramolecular nucleophilic ring-closing reaction.[9] Regioselective ring opening of the resultant O-protected aziridine with sodium azide in the presence of ammonium chloride generated the β-azido amine. The resultant primary amine was treated with acetic anhydride (Ac_2O) and 8% sodium bicarbonate solution

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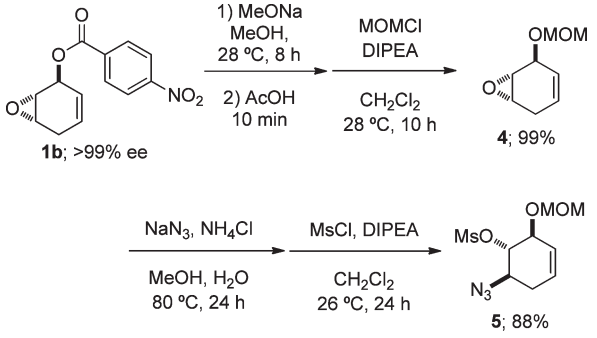
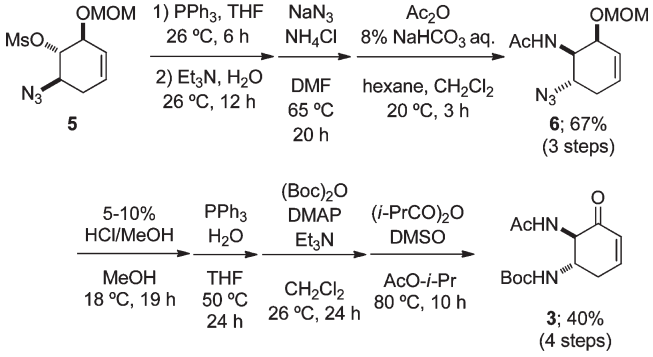
Scheme 2. Synthesis of Chiral Mesylate 5



Scheme 3. Synthetic Route to Key Intermediate 3



(aqueous $NaHCO_3$) in hexane and CH_2Cl_2 to obtain acetamide **6** in 67% yield (3 steps). In this transformation, no undesired regioselective product was observed. MOM ether **6** was deprotected by hydrogen chloride (5−10% in methanol). Then the azido group was converted to a *tert*-butoxycarbonylamino group via Staudinger reduction and ordinary Boc protection. Finally, the allylic alcohol was oxidized by modified Moffat conditions.[7,10] Intermediate **3** was obtained in 40% yield (4 steps). The enantiomeric excess of enone **3** was determined as >99% ee by chiral HPLC analysis (DAICEL Chiralpak AD-H).[7] Compound **3** was obtained from **1b** (>99% ee) in 23% overall yield in 11 steps.

EXPERIMENTAL SECTION

(1*S*,2*S*,3*S*)-3-Methoxymethyl-1,2-epoxycyclohex-4-ene (4): To a solution of **1b** (1.5 g, 5.8 mmol) in MeOH (15 mL) was added a 0.5 M NaOMe solution (0.6 mL, 0.3 mmol). After stirring at rt for 8 h, the complete disappearance of starting material was indicated by TLC and acetic acid (18 mL, 0.3 mmol) was added to quench the reaction. Methanol was removed by rotary evaporation, and the residue was purified by chromatography (hexane/EtOAc = 4/1 to 2/1) to give the deprotected compound as a colorless liquid. To a solution of the deprotected compound in CH_2Cl_2 (30 mL) was added DIPEA (2.9 mL, 17.3 mmol), followed by addition of MOMCl (1.3 mL, 17.3 mmol). The mixture was stirred for 10 h, and H_2O (30 mL) was added to quench the reaction. The aqueous layer was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography (hexane/EtOAc = 5/1) to give MOM-protected compound **4** as a colorless oil (0.88 g, 99%): R_f = 0.28 (hexane/EtOAc = 3/1); $[\alpha]^{17}_D$ +118.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.6 (br s, 2H), 4.78 (d, *J* = 7.2 Hz, 1H), 4.75 (d, *J* = 7.2 Hz, 1H), 4.4 (br s, 1H), 3.40 (s, 3H), 3.2 (br s, 1H), 3.3 (br s, 1H), 2.63−2.51 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 125.3, 122.8, 95.9, 68.7, 55.5, 52.4, 50.3, 25.1; MS (ESI) *m*/*z* 157 $(M + H)^+$. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.25; H, 7.81.

(1*R*,2*S*,3*S*)-1-Azido-3-methoxymethyl-2-(methylsulfonyl)-oxycyclohex-4-ene (5): To a solution of **4** (440 mg, 2.8 mmol) in MeOH (15 mL) were added NH_4Cl (450 mg, 8.4 mmol) and NaN_3 (1.27 g, 12.6 mmol) in H_2O (5 mL). The mixture was heated to 80 °C and stirred for 24 h. After cooling to rt, additional H_2O (20 mL) was added to dissolve the solid and MeOH was removed by rotary evaporation. The aqueous solution was extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (15 mL). To the solution were added DIPEA (0.70 mL, 4.2 mmol) and MsCl (0.33 mL, 4.2 mmol) at 0 °C. The mixture was stirred for 24 h, and aqueous ammonium chloride solution (15 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography (hexane/EtOAc = 5/1) to give compound **5** (690 mg, 88%): R_f = 0.17 (hexane/EtOAc = 3/1); mp 57−59 °C; $[\alpha]^{28}_D$ +33.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.72 (m, 2H), 4.81 (d, *J* = 7.2 Hz, 1H), 4.77 (d, *J* = 7.2 Hz, 1H), 4.65 (dd, *J* = 10.4, 7.2 Hz, 1H), 4.32 (dd, *J* = 8.0, 3.6 Hz, 1H), 3.77 (ddd, *J* = 10.4, 10.4, 6.0 Hz, 1H), 3.43 (s, 3H), 3.18 (s, 3H), 2.63 (m, 1H), 2.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 127.3, 125.0, 97.0, 83.5, 76.8, 58.9, 55.9, 39.1, 31.0; MS (ESI) *m*/*z* 300 $(M + Na)^+$. Anal. Calcd for $C_9H_{15}N_3O_5S$: C, 38.98; H, 5.45; N, 15.15. Found: C, 38.98; H, 5.45; N, 14.76.

(1*S*,2*R*,3*S*)-2-(Acetylamino)-1-azido-3-methoxymethyl-cyclohex-4-ene (6): A solution of **5** (430 mg, 1.6 mmol) in THF (10 mL) was stirred at 0 °C. To the solution was added PPh_3 (510 mg, 1.95 mmol) in three portions. The reaction mixture was stirred at room temperature (20 °C) for 3 h. After adding Et_3N (0.43 mL, 2.3 mmol) and H_2O (0.7 mL), the solution was stirred vigorously for 12 h. Organic solvent was removed by rotary evaporation, then the residue was extracted with CH_2Cl_2 (30 mL × 3) and brine (20 mL). The combined organic layers were dried over Na_2SO_4. After evaporation of the solvent, $P(O)Ph_3$ and unreacted PPh_3 were removed by chromatography (EtOAc/MeOH = 10/1) to give the aziridine. To a solution of the aziridine in DMF (15 mL) were added NH_4Cl (150 mg, 2.8 mmol) and NaN_3 (450 mg, 6.9 mmol). The mixture was heated to 65 °C and stirred for 16 h. After cooling to rt, 5% aqueous $NaHCO_3$ (15 mL) was added. The aqueous solution was extracted with hexane (50 mL × 5) and diethyl ether (50 mL × 5). The combined organic layers were dried (Na_2SO_4). After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (1.5 mL) and hexane (1.5 mL). To the solution were added 5% aqueous $NaHCO_3$ (3.0 mL, 2.8 mmol) and Ac_2O (0.13 mL, 1.4 mmol) at 0 °C. The mixture was stirred for 3 h. The aqueous layer was extracted with diethyl ether (30 mL × 3). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography (hexane/EtOAc = 1/2) to give compound **6** (220 mg, 67%): R_f = 0.48 (EtOAc); mp 82−85 °C; $[\alpha]^{28}_D$ +101.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.53 (m, 2H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.80 (d, *J* = 6.8 Hz, 1H), 4.49 (m, 1H), 3.45 (s, 3H), 2.61 (m, 1H), 2.50−2.43 (m, 1H), 2.40−2.31 (m, 2H), 1.26 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 124.9, 124.0, 95.4, 70.7, 55.5, 33.4, 29.1, 24.7; MS (ESI) *m*/*z* 263 $(M + Na)^+$. Anal. Calcd for $C_{10}H_{16}N_4O_3$: C, 49.99; H, 6.71; N, 23.32. Found: C, 50.17; H, 6.85; N, 22.96.

(1*S*,2*R*,3*S*)-2-(Acetylamino)-1-(*tert*-butoxycarbonylamino)-4-cyclohexen-3-one (3): A solution of **6** (230 mg, 0.9 mmol) in

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MeOH (1 mL) was stirred at 0 °C. To the solution was added slowly 5−10% HCl in MeOH (5 mL). The reaction mixture was stirred at room temperature (20 °C) for 20 h. Organic solvent was removed by rotary evaporation. Further removal of HCl gas was carried out by passing air over the solution for 1 h. The residue was dissolved in THF (10 mL). To this solution was added PPh_3 (370 mg, 1.4 mmol) in three portions. The reaction mixture was stirred at room temperature (20 °C) for 1 h. After adding H_2O (1 mL), the solution was stirred vigorously at 50 °C for 24 h. Organic solvent was removed by rotary evaporation and the residue was dissolved in CH_2Cl_2 (10 mL). To the solution were added Boc_2O (210 mg, 0.9 mmol) and Et_3N (0.66 mL, 4.8 mmol). After adding 4-dimethylaminopyridine (6.1 mg, 0.05 mmol), the solution was stirred at 26 °C for 24 h. Saturated aqueous NH_4Cl (2 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by chromatography (EtOAc) to give the crude allylic alcohol. This allylic alcohol was dissolved in *i*-PrOAc (1.5 mL) and DMSO (135 mL) to which was added isobutyric anhydride (150 mL). The reaction mixture was stirred at 80 °C for 5 h. The mixture was diluted with 10 mL of EtOAc. The organic solution was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The combined organic layers were dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by chromatography (hexane/EtOAc = 1/1) to give compound **3** (96.7 mg, 40%): R_f = 0.50 (EtOAc); mp 142−144 °C; $[\alpha]^{28}_D$ −119.6 (*c* 0.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.98 (ddd, *J* = 10.0, 6.4, 2.0 Hz, 1H), 6.36 (br d, *J* = 6.4 Hz, 1H), 6.15 (dd, *J* = 10.0, 3.6 Hz, 1H), 5.72 (br d, *J* = 7.2 Hz, 1H), 4.61 (dd, *J* = 13.2, 6.8 Hz, 1H), 3.98−3.87 (m, 1H), 2.97 (ddd, *J* = 19.2, 6.4, 4.8 Hz, 1H), 2.48−2.40 (m, 1H), 2.10 (s, 3H), 1.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 194.8, 172.4, 148.7, 132.1, 128.5, 79.5, 59.7, 53.6, 34.2, 28.4, 23.9; MS (ESI) *m*/*z* 291 $(M + Na)^+$. ^{1}H NMR data of **3** were completely consistent with the reported one.[7] Melting points and optical rotation value were not described in ref 7.

■ ASSOCIATED CONTENT

Supporting Information. Full experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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