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Novel asymmetric synthesis of oseltamivir phosphate (Tamiflu) from (−)-shikimic acid via cyclic sulfite intermediates

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ABSTRACT

A novel asymmetric synthesis of oseltamivir phosphate **1** from the naturally abundant (−)-shikimic acid via 3,4-cyclic sulfite intermediate **3** (Scheme 1) is described. Target compound **1** was obtained in 39% overall yield from this nine-step synthesis, and the characteristic step of the synthesis is the regio- and stereospecific nucleophilic substitution with sodium azide at the allylic (C-3) position of 3,4-cyclic sulfite **3**. Since the yield of the direct-aziridine-formation from the unprotected dihydroxyl azide **4** was not satisfactory, two improved preparations of the established compound **7** via protected 3,4-cyclic sulfites **10** and **13** (Scheme 2) have been developed. In these two improved preparations, compound **7** was obtained from 3,4-cyclic sulfite **3** in 7-steps in 64% or 62% overall yield, respectively.

1. Introduction

Oseltamivir phosphate (Tamiflu®) **1** is an active prodrug of a potent neuraminidase inhibitor,[1,2] which has been widely used for the treatment of H5N1 influenza[3–5] as well as H1N1 influenza.[6] Not only as a reasonable frontline therapy against a possible flu pandemic but also as a preventive agent, Tamiflu has now been stockpiled by many nations to be used strategically when a widespread influenza outbreak occur.[3,4] In order to meet the worldwide requirement for Tamiflu, the synthesis of oseltamivir phosphate **1** has gathered the attention of synthetic chemists, and has become a very active field of research.[1,2,7–56]

Recently, we have been engaged in the synthesis of oseltamivir phosphate, and have reported two practical syntheses[31,32] from (−)-shikimic acid via 3,4-bismesylate[31] or 3,4,5-trimesylate[32] of shikimic acid ethyl ester. Based on the high reactivity and regioselectivity of the cyclic sulfite toward nucleophile azide,[57,58] and due to the wide availability of (−)-shikimic acid,[27,31] we have just finished and herein want to report a novel asymmetric synthesis of oseltamivir phosphate (Tamiflu) **1** from the naturally abundant (−)-shikimic acid, where 3,4-cyclic sulfites derived from ethyl shikimate **2** were used as the key intermediates and were subjected to a highly regioselective and stereoselective nucleophilic replacement by sodium azide at the more active allylic C-3 position.

2. Results and discussion

As shown in the novel synthetic route depicted in Scheme 1, our new synthetic effort began with ethyl shikimate **2**, which could be readily prepared in excellent yield via esterification of (−)-shikimic acid according to a known procedure.[55]

Exposure of ethyl shikimate **2** to 2.5 equiv of thionyl chloride and 2.5 equiv of triethylamine in ethyl acetate at 0 °C to room temperature efficiently produced 3,4-cyclic sulfite **3** in 98% yield. Although 3,4-cyclic sulfite **3** actually occurred as an epimeric mixture of two epimers with different configurations of the sulfur atoms, separation of the two epimers was unnecessary, because the two epimers gave the same ring-opening product **4** in the next step. Treatment of compound **3** with 2.0 equiv of sodium azide at reflux in absolute ethanol led to regio- and stereospecific ring opening at the allylic (C-3) position affording azide **4** in 93% yield, while at the same time the (*R*)-configuration of C-3 was inverted into the (*S*)-configuration via a typical Walden-type inversion.

With dihydroxyl azide **4** in hand, we first attempted to prepare aziridine **5** directly via a Staudinger[59,60] reduction and simultaneous cyclization without protecting the hydroxyl groups. Compound **4** was treated with 1.1 equiv of triphenylphosphine and 0.1 equiv of freshly prepared diethylammonium *p*-toluenesulfonate ($Et_2NH_2^+$*p*-TsO^-) at 60 °C in toluene to generate aziridine **5** in 62% yield. In this transformation, the reduction of the azido group and the aziridination via an intramolecular nucleophilic substitution of the neighboring hydroxyl group at C-4 position took place simultaneously, while the (*R*)-configuration at C-4 of compound **4** was inverted into the (*S*)-configuration at C-6 of compound **5**. We also tried this conversion under other conditions, and the results are summarized in Table 1. An ammonium salt as a catalyst was necessary for the conversion of compound **4** to compound **5** (entry 1), eight ammonium salts and six solvents were tested for the reaction; diethylamonium *p*-toluenesulfonate gave the best yield at 60 °C in toluene (entry 8).

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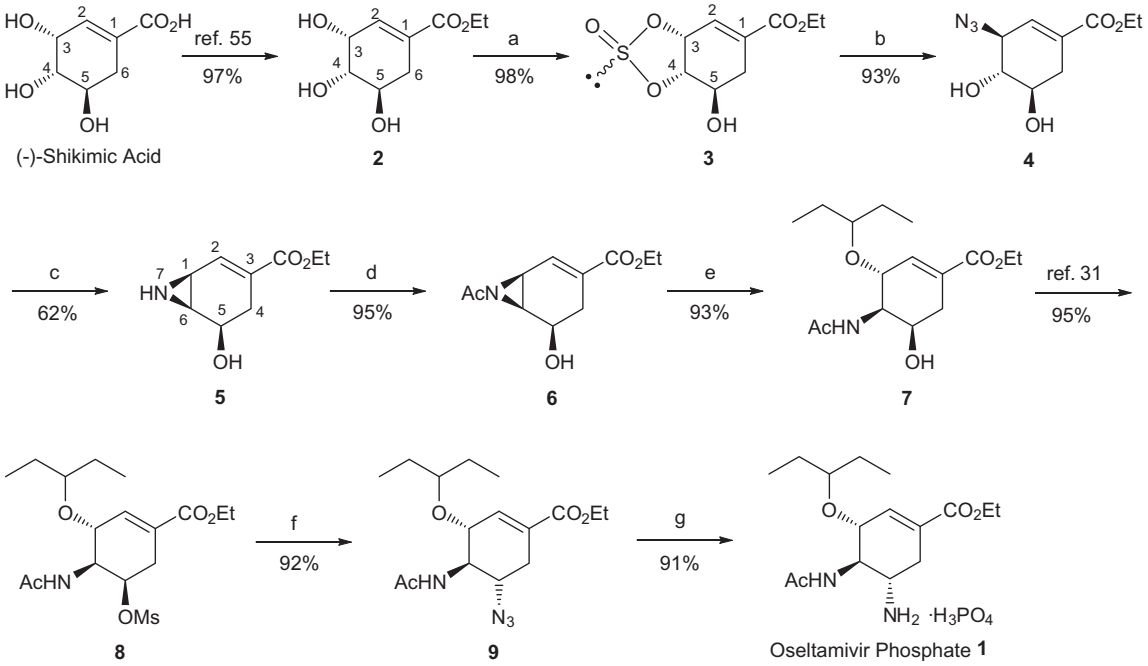


Scheme 1. Novel asymmetric synthesis of oseltamivir phosphate **1** from (−)-shikimic acid via a 3,4-cyclic sulfite intermediate. Reagents and conditions: (a) 2.5 equiv of $SOCl_2$, 2.5 equiv of Et_3N, 0–5 °C for 2 h, and then rt for 12 h in EtOAc; (b) 2.0 equiv of NaN_3, reflux for 12 h in absolute EtOH; (c) 1.1 equiv of PhP_3, 0.1 equiv of diethylamonium toluenesulfonate (Et_2NH–TsOH), rt for 1 h, and then 60 °C for 2 h; (d) 1.2 equiv of Ac_2O, 2.0 equiv of Et_3N, 0 °C for 0.5 h in CH_2Cl_2. (e) 1.5 equiv of $BF_3{\cdot}OEt_2$, −8 °C for 1.5 h in 3-pentanol; (f) 2.0 equiv of NaN_3, 90 °C for 8 h in anhydrous DMF; (g) 1.1 equiv of Ph_3P, reflux for 8 h in THF/H_2O (10:1); 1.2 equiv of H_3PO_4, 50 °C for 2 h, then rt for 8 h in EtOAc/EtOH (2:1).

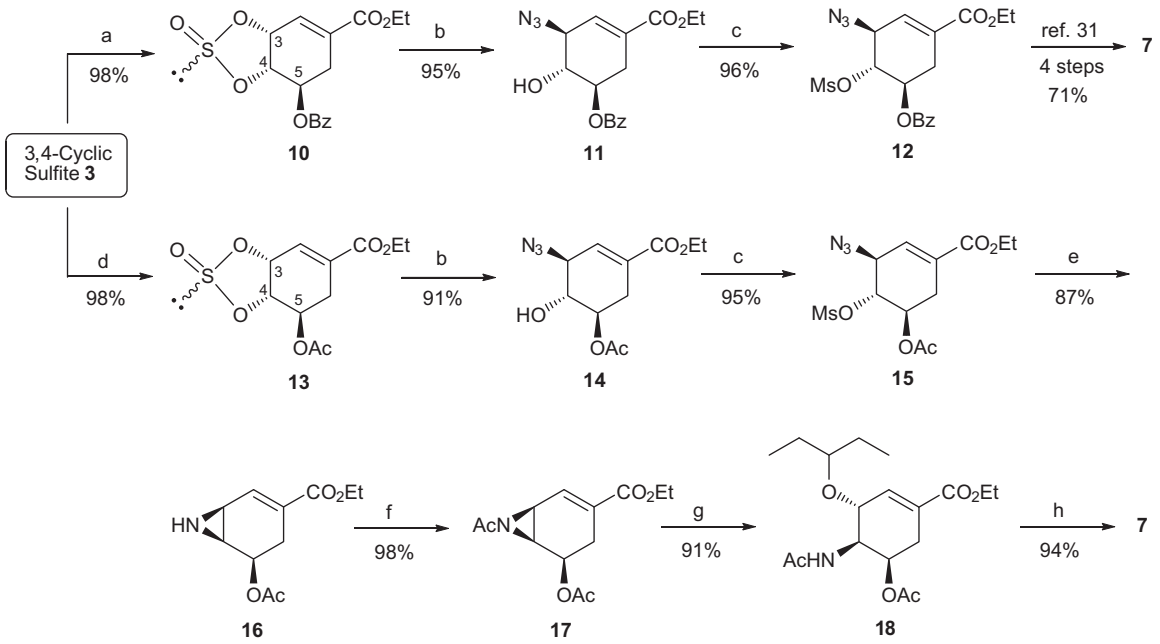
Table 1
Optimization of the reaction conditions for the conversion of compound **4** to compound **5**

Entry	Catalyst[a]	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	None	Toluene	60	3	0
2	Et_3N–*p*-TsOH	Toluene	60	3	38
3	Et_3N–MsOH	Toluene	60	3	40
4	DIPEA[c]–*p*-TsOH	Toluene	60	2	57
5	DIPEA–MsOH	Toluene	60	2	56
6	DIPA[d]–*p*-TsOH	Toluene	60	2	54
7	DIPA–MsOH	Toluene	60	2	56
8	Et_2NH–*p*-TsOH	Toluene	60	2	62
9	Et_2NH–MsOH	Toluene	60	2	60
10	Et_2NH–*p*-TsOH	Toluene	45	4	50
11	Et_2NH–*p*-TsOH	Toluene	70	2	53
12	Et_2NH–*p*-TsOH	Benzene	60	2	55
13	Et_2NH–*p*-TsOH	Chloroform	60	2	10
14	Et_2NH–*p*-TsOH	Dichloromethane	40[e]	6	<5
15	Et_2NH–*p*-TsOH	THF	60	3	<5
16	Et_2NH–*p*-TsOH	EtOAc	60	3	<5

[a] An ammonium salt as catalyst was freshly prepared prior to use, and 0.1 equiv of the ammonium salt were used (entries 2–16).
[b] Isolated yield of compound **5**.
[c] Diisopropylethylamine.
[d] Diisopropylamine.
[e] Reflux.

Aziridine **5** was then exposed to 1.2 equiv of acetic anhydride and 2.0 equiv of triethylamine in dichloromethane to form *N*-acetyl aziridine **6** in 95% yield. Herein it is noteworthy that both the amount of acetic anhydride and the reaction temperature are crucial for the selective acetylation at the N-7 position of the bicyclic molecule while leaving the hydroxyl group at the C-5 position intact. Subsequently, compound **6** was immediately exposed to 1.5 equiv of borontrifluoride etherate ($BF_3{\cdot}OEt_2$) and a large excess 3-pentanol; ring opening of *N*-acetyl aziridine **6** in 3-pentanol solution at −8 °C thus occurred regio- and stereospecifically to generate compound **7** in 93% yield, while the (*S*)-configuration of C-1 of compound **6** was inverted back into the (*R*)-configuration of C-3 of compound **7**.

Compound **7** was converted to mesylate **8** in 95% yield according to the same procedure as described in our previous article.[31] Compound **8** was then treated with 2.0 equiv of sodium azide in anhydrous *N*,*N*-dimethylformamide (DMF) to afford azido compound **9** in 92% yield, while the (*R*)-configuration of C-5 was inverted into the (*S*)-configuration via an S_N2 mechanism. The same conversion of compound **8** to compound **9** has been described twice in our previous articles,[31,32] but herein the yield of compound **9** was increased by using anhydrous DMF as the



Scheme 2. Improved preparations of compound **7** from 3,4-cyclic sulfite **3**. Reagents and conditions: (a) 2.0 equiv of Et_3N, 0.1 equiv of 4-dimethylaminopyridine (DMAP), 1.2 equiv of benzoyl chloride, 0 °C to rt for 5 h in CH_2Cl_2; (b) 2.5 equiv of NaN_3, rt for 24 h in DMF/H_2O (5:1); (c) 1.5 methanesulfonyl chloride, 1.2 equiv of Et_3N, 0.1 equiv of DMAP, 0 °C for 1 h in EtOAc; (d) 2.0 equiv of Et_3N, 0.1 equiv of DMAP, 1.5 equiv of Ac_2O, rt for 2 h in CH_2Cl_2; (e) 1.1 equiv of Ph_3P, 3.0 equiv of Et_3N (in portions), rt for 10.5 h in THF/H_2O (10:1); (f) 2.0 equiv of Et_3N, 1.5 equiv of Ac_2O, 0 °C for 0.5 h in EtOAc; (g) 1.5 equiv of $BF_3{\cdot}OEt_2$, −5–0 °C for 1.5 h in 3-pentanol; (h) 1.1 equiv of K_2CO_3, rt for 6 h in absolute EtOH.

solvent instead of aqueous DMF, and a lesser amount of sodium azide was used. It was found that the anhydrous condition was obviously better than aqueous conditions[31,32] for the conversion, because hydrolysis of the ester group was diminished as much as possible in anhydrous DMF.

At the end of the synthesis, azido compound **9** was treated successively with 1.1 equiv of triphenylphosphine in aqueous tetrahydrofuran (THF/H_2O = 10:1) and then with 1.2 equiv of phosphoric acid in a mixed solvent of ethyl acetate and ethanol (EtOAc/EtOH = 2:1) to furnish oseltamivir phosphate **1** in 91% yield. In order to avoid the use of an expensive and poisonous palladium catalyst (Lindlar's catalyst), we employed the less expensive triphenylphosphine as the reducing agent to reduce the azido group instead. Since the process is free of toxic transition metals, it should be beneficial to the pharmaceutical industry.[9]

It should be noted that during the four-step conversion from cyclic sulfite **3** to compound **7** in the synthesis described above, the direct transformation of dihydroxyl azido compound **4** to aziridine **5** without protecting the hydroxyl groups, only gave a moderate yield (62%). However, our further attempts showed that the overall yield of the conversion from cyclic sulfite **3** to compound **7** could be greatly increased by protecting the C-5 hydroxyl group with a benzoyl (Bz) or acetyl (Ac) group and by masking the C-4 hydroxyl group with a methanesulfonyl (Ms) group.

As shown in Scheme 2, treatment of 3,4-cyclic sulfite **3** with 1.2 equiv of benzoyl chloride, 2.0 equiv of triethylamine and 0.1 equiv of 4-dimethylaminopyridine (DMAP) in dichloromethane generated the Bz-protected 3,4-cyclic sulfite **10** in an almost quantitative yield. Compound **10** was then exposed to 2.5 equiv of sodium azide in aqueous *N*,*N*-dimethylformamide (DMF/H_2O = 5:1) at room temperature to afford the ring-opening product **11** in 95% yield. Reaction of compound **11** with 1.5 equiv of methanesulfonyl chloride in the presence of 1.2 equiv of triethylamine and 0.1 equiv of DMAP in ethyl acetate produced the vicinal azido mesylate **12** in 96% yield. Compound **12** could be converted to compound **7** over four steps in 71% overall yield by following the same sequence as described in our previous article.[31]

As shown in Scheme 2, treatment of 3,4-cyclic sulfite **3** with 1.5 equiv of acetic anhydride, 2.0 equiv of triethylamine and 0.1 equiv of DMAP in dichloromethane generated the Ac-protected 3,4-cyclic sulfite **13** in an almost quantitative yield. Compound **13** was then exposed to 2.5 equiv of sodium azide in aqueous *N*,*N*-dimethylformamide (DMF/H_2O = 5:1) at room temperature to afford the ring-opening product **14** in 91% yield. The reaction of compound **14** with 1.5 equiv of methanesulfonyl chloride in the presence of 1.2 equiv of triethylamine and 0.1 equiv of DMAP in ethyl acetate produced the vicinal azido mesylate **15** in 95% yield. A Staudinger reduction of azide **15** with 1.1 equiv of triphenylphosphine and simultaneous cyclization under basic conditions in aqueous tetrahydrofuran (THF/H_2O = 10:1) afforded aziridine **16** in 87% yield. Exposure of aziridine **16** to 1.5 equiv of acetic anhydride and 2.0 equiv of triethylamine in ethyl acetate formed *N*-Ac-aziridine **17** in an excellent yield. *N*-Acetyl aziridine **17** was then treated with 1.5 equiv of boron trifluoride etherate in 3-pentanol to furnish a ring-opening product **18** in 91% yield. Alcoholysis of compound **18** in absolute ethanol in the presence of 1.1 equiv of potassium carbonate gave the desired compound **7** in 94% yield.

Both the Bz and Ac-protected 3,4-cyclic sulfites **10** and **13** occurred as epimeric mixtures with different configurations at the sulfur atoms, but these epimeric mixtures do not need separation and could be used as such in the next step similar to the unprotected 3,4-cyclic sulfite **3**, since the epimeric sulfinyl groups are lost during the subsequent ring-opening reactions, and diastereomerically pure compounds **11** and **14** are obtained in high yields.

3. Conclusion

In conclusion, we have successfully developed a novel asymmetric synthesis of oseltamivir phosphate **1** from the naturally abundant (−)-shikimic acid via 3,4-cyclic sulfite **3** (Scheme 1). A total of nine steps are involved in the synthesis, and the overall yield of the whole synthesis from (−)-shikimic acid to the target compound **1** is 39%. The disadvantage of this synthesis is the low

yield of compound **5** in the aziridine-formation step, that is the conversion of unprotected dihydroxyl azide **4** to aziridine **5**. In order to overcome such an obvious drawback, two improved preparations of compound **7** from 3,4-cyclic sulfite **3** have also been developed (Scheme 2). In the first improved preparation, Bz was used as a protecting group for the hydroxyl group at the C-4 position of cyclic sulfite **3**, and compound **7** was obtained in 7-steps in 64% overall yield. In the second improved preparation, Ac was used as a protecting group for the hydroxyl group at the C-4 position of cyclic sulfite **3**, and compound **7** was obtained in 7-steps in 62% overall yield. In both improved preparations, Ms was used to mask the hydroxyl groups at the C-5 positions of compounds **11** and **14**.

4. Experimental

4.1. General methods

Melting points are uncorrected. ^{1}H NMR spectra were acquired on Bruker AM-500. Chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on Nicolet Magna IR-550. Mass spectra were recorded on HP5989A. Column chromatography was performed on silica gel. Optical rotations of chiral compounds were measured on a WZZ-1S automatic polarimeter at room temperature. All chemicals were analytically pure. (−)-Ethyl shikimate **2** was prepared according to a known procedure.[55]

4.2. Ethyl (3*R*,4*S*,5*R*)-3,4-cyclic sulfite-shikimate 3

(−)-Ethyl shikimate **2** (10.00 g, 49.46 mmol) and triethylamine (12.46 g, 123.13 mmol) were dissolved in ethyl acetate (200 mL) and cooled to 0 °C with an ice bath. A solution of thionyl chloride (14.71 g, 123.64 mmol) in dichloromethane (30 mL) was then dropwise added over 1 h, and the temperature of the reaction mixture was kept below 10 °C during the addition. After the dropwise addition was finished, the ice bath was removed, and the mixture was warmed to room temperature. The reaction mixture was then further stirred at room temperature for 12 h. The reaction was quenched by adding water (60 mL) and an aqueous solution of potassium carbonate (20% w/v, 110 mL) until pH 8–9. The organic phase was separated and dried over anhydrous $MgSO_4$, and then concentrated under vacuum to afford a pale yellow oil that could be directly used for the next step or purified by flash chromatography to furnish cyclic sulfite **3** (12.05 g, 48.54 mmol) in 98% yield. $[\alpha]_D^{20} = +52.0$ (*c* 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$) for major diastereomer δ 1.33 (t, J = 7.1 Hz, 3H), 2.34 (dd, J_1 = 18.1 Hz; J_2 = 8.5 Hz, 1H), 2.80 (br s, 1H), 2.88 (dd, J_1 = 18.0 Hz; J_2 = 4.8 Hz, 1H), 3.91–3.99 (m, 1H), 4.26 (q, J = 7.1 Hz, 2H), 4.86 (dd, J_1 = 7.9 Hz; J_2 = 6.4 Hz, 1H), 5.57 (dd, J_1 = 4.9 Hz, J_2 = 4.8 Hz, 1H), 6.90–6.94 (m, 1H). ^{13}C NMR ($CDCl_3$) for major diastereomer δ 165.26, 133.40, 129.09, 81.31, 75.79, 67.25, 61.64, 29.67, 14.11. ^{1}H NMR ($CDCl_3$) for minor diastereomer δ 1.32 (t, J = 7.1 Hz, 3H), 2.38 (dd, J_1 = 18.2 Hz; J_2 = 8.1 Hz, 1H), 2.80 (br s, 1H), 2.93 (dd, J_1 = 17.8 Hz; J_2 = 4.7 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.43–4.52 (m, 1H), 4.65 (dd, J_1 = 7.6 Hz; J_2 = 6.9 Hz, 1H), 5.27 (dd, J_1 = 5.1 Hz, J_2 = 5.0 Hz, 1H), 6.98–7.03 (m, 1H). ^{13}C NMR ($CDCl_3$) for minor diastereomer δ 165.54, 132.09, 130.70, 83.35, 79.14, 68.20, 61.56, 29.75, 14.11. HRMS (EI) calcd for $(C_9H_{12}O_6S+H)^+$: 249.0433. Found: 249.0438. IR (KBr film) 3490, 2981, 1758, 1719, 1257, 1210, 1100, 984, 854, 768 cm^{-1}.

4.3. Ethyl (3*S*,4*R*,5*R*)-3-azido-4,5-dihydroxycyclohex-1-ene-1-carboxylate 4

The cyclic sulfite **3** (10.00 g, 40.28 mmol) was dissolved in absolute ethanol (100 mL) at room temperature, after which sodium azide (5.24 g, 80.60 mmol) was added. The mixture was stirred and heated at reflux, and then refluxing was continued for around 12 h. After the reaction was complete, ethanol was distilled off under reduced pressure, after which the residue was partitioned between ethyl acetate (200 mL) and water (100 mL). Two layers were separated, and the aqueous layer was extracted with ethyl acetate (100 mL) once again. The organic extracts were combined and dried over anhydrous $MgSO_4$, and then was concentrated under vacuum to afford a yellow oil that could be directly used for the next step or purified by flash chromatography to furnish compound **4** (8.51 g, 37.45 mmol) in 93% yield. $[\alpha]_D^{20} = +67.7$ (*c* 4.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 2.21–2.33 (m, 1H), 2.92 (dd, J_1 = 17.8 Hz; J_2 = 4.9 Hz, 1H), 3.56–3.67 (m, 1H), 3.75–3.86 (m, 1H), 3.91 (br s, 1H), 4.07–4.17 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.29 (br s, 1H), 6.64 (dd, J_1 = 2.5 Hz, J_2 = 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 165.72, 133.95, 130.63, 75.71, 69.53, 63.55, 61.38, 32.13, 14.10. HRMS (EI) calcd for $(C_9H_{13}N_3O_4+NH_4)^+$: 245.1250. Found: 245.1253. IR (KBr film) 3427, 2104, 1716, 1657, 1374, 1252, 1100, 1068, 742 cm^{-1}.

4.4. Ethyl (1*S*,5*R*,6*S*)-5-hydroxy-7-azabicyclo[4.1.0]hept-2-ene-3-carboxylate 5

To a vigorously stirred solution of Et_2NH (1.46 g, 19.96 mmol) in ethyl acetate (15 mL), was added dropwise a solution of $TsOH{\cdot}H_2O$ (3.80 g, 19.98 mmol) in ethyl acetate (15 mL) at room temperature. White crystals formed and precipitated during the addition. After the addition was finished, stirring was continued for one hour. Diethylammonium *p*-toluenesulfonate (4.82 g, 19.65 mmol) was collected on Büchner funnel by suction, and was then dried under vacuum for 3 h at 45 °C.

Compound **4** (2.05 g, 9.02 mmol) was dissolved in toluene (100 mL). Diethylamonium *p*-toluenesulfonate (223 mg, 0.91 mmol) was added, and then PPh_3 (2.60 g, 9.90 mmol) was slowly added in portions at room temperature. Upon completion of the addition, the reaction mixture was further stirred at room temperature for 1 h. Next, the reaction mixture was warmed to 60 °C and stirred for 2 h. Toluene was removed by vacuum distillation to give a crude oil, which was then subjected to direct chromatography to give aziridine **5** (1.03 g, 5.62 mmol) as pale yellow crystals in 62% yield. Mp 145.0–145.9 °C, $[\alpha]_D^{20} = -219.8$ (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.1 Hz, 3H), 1.98–2.11 (m, 1H), 2.66–2.72 (m, 1H), 2.80–2.86 (m, 1H), 2.88–2.95 (m, 1H), 4.10–4.25 (m, 3H), 7.13 (dd, J_1 = 4.7 Hz; J_2 = 3.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 165.98, 136.40, 130.13, 66.47, 60.76, 38.27, 29.51, 29.20, 14.21. HRMS (EI) calcd for $(C_9H_{13}NO_3+H)^+$: 184.0974. Found: 184.0970. IR (KBr film) 3281, 3190, 1700, 1375, 1322, 1257, 1047, 852, 731 cm^{-1}.

4.5. Ethyl (1*S*,5*R*,6*S*)-7-acetyl-5-hydroxy-7-azabicyclo[4.1.0]-hept-2-ene-3-carboxylate 6

Compound **5** (0.80 g, 4.37 mmol) and triethylamine (0.88 g, 8.70 mmol) were dissolved in methylene chloride (16 mL), and the resulting solution was cooled to 0 °C. Acetic anhydride (0.54 g, 5.29 mmol) was then added dropwise over 15 min. After the addition was finished, the reaction mixture was further stirred at 0 °C for 15 min. The reaction was then immediately quenched by adding an aqueous solution of potassium carbonate (15% w/v, 10 mL). After the organic and aqueous phases were separated, the aqueous layer and brine (10 mL) were mixed and extracted twice with methylene chloride (2 × 15 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$, and then concentrated under vacuum to give a yellow oil that could be directly used for the next step or purified by flash chromatography to furnish compound **6** (0.94 g, 4.17 mmol) in 95% yield. $[\alpha]_D^{20} = -90.7$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3H), 2.06–2.16 (m, 1H), 2.21 (s, 3H), 2.94 (dd, J_1 = 16.5 Hz;

J_2 = 6.6 Hz, 1H), 3.17–3.24 (m, 2H), 3.92 (br s, 1H), 4.03–4.12 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 7.04–7.14 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 182.82, 165.73, 132.60, 132.45, 65.54, 61.03, 42.96, 35.06, 29.41, 23.42, 14.15. HRMS (EI) calcd for $(C_{11}H_{15}NO_4+K)^+$: 264.0638. Found: 264.0641. IR (KBr film) 3406, 2981, 1705, 1369, 1252, 1200, 1099, 1054, 741 cm^{-1}.

4.6. Ethyl (3*R*,4*R*,5*R*)-4-acetamido-3-(1-ethyl-propoxy)-5-hydroxy-cyclohex-1-ene-1-carboxylate 7

Compound **6** (0.90 g, 4.00 mmol) was dissolved in 3-pentanol (4.5 mL), and the resulting solution was cooled to −8 °C with a salt-ice bath. Then a solution of boron trifluoride diethyl etherate (0.85 g, 5.99 mmol) in 3-pentanol (4.5 mL) was added dropwise over 30 min. After the addition was finished, the reaction mixture was further stirred at −8 °C for 1 h. The mixture was diluted with methylene chloride (20 mL), and the reaction was quenched by adding an aqueous solution of potassium carbonate (15% w/v, 20 mL). The two phases were separated, and the aqueous phase was extracted twice with methylene chloride (2 × 10 mL). The organic extracts were combined and dried over anhydrous $MgSO_4$. The organic solution was concentrated under vacuum to give a residue as yellow crystals that could be directly used for the next step or purified by flash chromatography to furnish compound **7** (1.17 g, 3.73 mmol) in 93% yield. The characterization data of compound **7** were identical with those obtained in our previous article.[31]

4.7. Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-azido-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxylate 9

To a solution of compound **8** (1.20 g, 3.06 mmol) in anhydrous *N*,*N*-dimethylformamide (8 mL), was added sodium azide (0.40 g, 6.15 mmol). The mixture was heated to 90 °C for 8 h and monitored by TLC. After the reaction was complete, the mixture was cooled down to room temperature. The mixture was then partitioned between ethyl acetate (80 mL) and water (45 mL). The organic phase was separated and washed with brine (20 mL). The organic solution was dried over anhydrous Na_2SO_4, and then concentrated under vacuum to produce a crude oil which was purified by chromatography to give compound **9** (0.955 g, 2.82 mmol) in 92% yield. The characterization data of compound **9** were identical with those obtained in our previous articles.[31,32]

4.8. Oseltamivir phosphate 1

Compound **9** (0.90 g, 2.66 mmol) was dissolved in aqueous tetrahydrofuran (20 mL, THF/H_2O = 10:1). Triphenylphosphine (0.77 g, 2.94 mmol) was added in portions at room temperature. After the mixture was heated at reflux and stirring was continued for 8 h. Solvents were removed by vacuum distillation, and the residue was cooled down to room temperature. The residue was then dissolved in a mixed solvent of ethyl acetate (3.5 mL) and ethanol (1.5 mL). After aqueous phosphoric acid (368 mg, 85% w/w, 3.19 mmol) was added, the mixture was warmed to 50 °C, and stirring was continued for 2 h at 50 °C. The reaction mixture was cooled down to room temperature and stirred for a further 8 h. White crystals were formed and precipitated. After suction and twice rinsing with ethyl acetate, the white crystals were dried under vacuum at 50 °C overnight to furnish the title compound oseltamivir phosphate **1** (997 mg, 2.43 mmol) in 91% yield. The characterization data of compound **1** were identical with those of the sample obtained in our previous articles.[31,32]

4.9. Ethyl (3*R*,4*S*,5*R*)-5-*O*-benzoyl-3, 4 -cyclic sulfite-shikimate 10

To a solution of cyclic sulfite **3** (5.00 g, 20.14 mmol) in dichloromethane (50 mL), triethylamine (4.08 g, 40.32 mmol), and DMAP (0.25 g, 2.05 mmol) were added, and the resulting solution was then cooled to 0 °C with an ice bath. Benzoyl chloride (3.40 g, 24.19 mmol) was added dropwise over 10 min. The ice bath was removed, and the mixture was then further stirred for 5 h until the reaction was complete (TLC). The reaction solution was concentrated under vacuum to remove dichloromethane, after which the residue was dissolved in ethyl acetate (100 mL), and the organic solution was washed successively with a dilute hydrochloric aqueous solution (2 M, 25 mL), potassium carbonate aqueous solution (10% w/v, 15 mL), and brine (15 mL). The organic solution was dried over anhydrous $MgSO_4$ and evaporated to give a crude oil, which could be used directly for the next step or purified by flash chromatography to furnish compound **10** (6.95 g, 19.72 mmol) in 98% yield. $[\alpha]_D^{20} = +17.2$ (c 9.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$) for major diastereomer δ 1.25 (t, J = 7.1 Hz, 3H), 2.38–2.52 (m, 1H), 2.98 (dd, J_1 = 18.1 Hz; J_2 = 4.9 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 5.07 (dd, J_1 = 7.5 Hz; J_2 = 6.4 Hz, 1H), 5.26–5.38 (m, 1H), 5.52–5.61 (m, 1H), 6.91 (dd, $J_1 = J_2$ = 1.8 Hz, 1H), 7.31–7.45 (m, 2H), 7.47–7.57 (m, 1H), 7.95 (d, J = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) for major diastereomer δ 165.47, 164.81, 133.64, 132.82, 129.80, 129.75, 129.19, 128.56, 77.61, 75.70, 69.03, 61.70, 27.28, 14.14. ^{1}H NMR ($CDCl_3$) for minor diastereomer δ 1.24 (t, J = 7.1 Hz, 3H), 2.66 (dd, J_1 = 18.3 Hz; J_2 = 4.7 Hz, 1H), 2.89–2.94 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.78 (dd, $J_1 = J_2$ = 6.0 Hz, 1H), 5.26–5.38 (m, 1H), 5.73–5.80 (m, 1H), 6.97–7.03 (m, 1H), 7.31–7.45 (m, 2H), 7.47–7.57 (m, 1H), 7.91 (d, J = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) for minor diastereomer δ 165.32, 165.18, 133.64, 131.13, 130.42, 129.80, 129.75, 128.56, 78.89, 77.52, 69.45, 61.51, 25.76, 14.14. HRMS (EI) calcd for $(C_{16}H_{16}O_7S+Na)^+$: 375.0514. Found: 375.0512. IR (KBr film) 2981, 1721, 1453, 1253, 1100, 989, 710 cm^{-1}.

4.10. Ethyl (3*S*,4*R*,5*R*)-3-azido-5-benzoyloxy-4-hydroxy-cyclohex-1-ene-1-carboxylate 11

Compound **10** (5.00 g, 14.19 mmol) was dissolved in aqueous *N*,*N*-dimethylformamide (50 mL, DMF/H_2O = 5:1) at room temperature, after which sodium azide (2.31 g, 35.53 mmol) was added. The mixture was stirred at room temperature for 24 h. Toluene (100 mL) and water (100 mL) were added, and the mixture was vigorously stirred for 15 min. The organic phase was separated, and then washed with water (30 mL) and brine (20 mL). The organic solution was dried over anhydrous $MgSO_4$. The solvent was then removed off by vacuum distillation to give the crude product as yellow crystals. The crystals were collected on a Buchner funnel by suction and rinsed with hexane/ethyl acetate = 10:1 to afford compound **11** (4.47 g, 13.49 mmol) in 95% yield. Mp 78.5–78.9 °C, $[\alpha]_D^{20} = -4.7$ (c 3.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3H), 2.40–2.47 (m, 1H), 3.09 (dd, J_1 = 17.7 Hz; J_2 = 5.8 Hz, 1H), 3.21 (br s, 1H), 4.00 (dd, $J_1 = J_2$ = 9.0 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.18–4.32 (m, 1H), 5.15–5.30 (m, 1H), 6.63–6.74 (m, 1H), 7.44 (dd, $J_1 = J_2$ = 7.7 Hz, 2H), 7.58 (dd, $J_1 = J_2$ = 7.4 Hz, 1H), 8.04 (d, $J_1 = J_2$ = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 166.95, 165.82, 134.54, 134.08, 130.60, 130.37, 130.08, 129.10, 74.09, 72.09, 72.53, 63.91, 61.96, 30.32, 14.57. MS m/z (%) 331 (M^+, 0.1%), 274 (2), 257 (2), 198 (2), 154 (11), 135 (4), 124 (8), 105 (100), 77 (26). HRMS (EI) calcd for $(C_{16}H_{17}N_3O_5+NH_4)^+$: 349.1512. Found: 349.1523. IR (KBr film) 3542, 2114, 1726, 1702, 1304, 1268, 1089, 1026, 710 cm^{-1}.

4.11. Ethyl (3*S*,4*R*,5*R*)-3-azido-5-benzoyloxy-4-methanesulfonyloxy-cyclohex-1-ene-1-carboxylate 12

To a solution of compound **11** (5.00 g, 15.09 mmol) in ethyl acetate (100 mL) was added methanesulfonyl chloride (2.59 g, 22.61 mmol). The resulting solution was cooled to 0 °C by an ice bath, and DMAP (0.18 g, 1.47 mmol) was added. Triethylamine (1.83 g, 18.08 mmol) was then dropwise added over 15 min. After the addition was finished, the reaction mixture was stirred at 0 °C for a further 1 h to allow the reaction to complete. The reaction was quenched by adding water (20 mL). The organic phase was separated and washed successively with potassium carbonate aqueous solution (10% w/v, 20 mL) and brine (20 mL). The organic solution was dried over anhydrous $MgSO_4$, and then concentrated under vacuum to give a pale yellow oily residue that gradually became solid upon standing at room temperature. The crude solid product was then triturated with hexane to give compound **12** as pale yellow crystals (5.93 g, 14.48 mmol) in 96% yield. The characterization data of compound **12** were identical with those we obtained in our previous article.[31]

4.12. Ethyl (3*R*,4*S*,5*R*)-5-*O*-acetyl-3,4-cyclic sulfite-shikimate 13

To a solution of cyclic sulfite **3** (5.00 g, 20.14 mmol) in dichloromethane (50 mL), triethylamine (4.08 g, 40.32 mmol) and DMAP (0.25 mg, 2.05 mmol) were added at room temperature. Acetic anhydride (3.08 g, 30.17 mmol) was dropwise added over 10 min. The mixture was then stirred for 2 h until the reaction was complete (TLC). The reaction solution was concentrated under vacuum to remove dichloromethane. The residue was dissolved in ethyl acetate (100 mL), and the resulting solution was washed successively with dilute hydrochloric aqueous solution (2 M, 20 mL), potassium carbonate aqueous solution (15% w/v, 30 mL), and brine (10 mL). The organic solution was dried over anhydrous $MgSO_4$ and evaporated under vacuum to give a crude oil, which could be directly used for the next step or purified by flash chromatography to furnish compound **13** (5.73 g, 19.74 mmol) in 98% yield. $[\alpha]_D^{20} = +62.9$ (*c* 2.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$) for major diastereomer δ 1.32 (t, J = 7.1 Hz, 3H), 2.12 (s, 3H), 2.33–2.42 (m, 1H), 2.92 (dd, J_1 = 18.0 Hz; J_2 = 4.9 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 4.92–5.01 (m, 1H), 5.03–5.16 (m, 1H), 5.57 (dd, $J_1 = J_2$ = 5.8 Hz, 1H), 6.93 (dd, $J_1 = J_2$ = 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) for major diastereomer δ 169.90, 164.77, 132.81, 129.08, 77.63, 75.57, 68.42, 61.65, 27.17, 20.93, 14.12. ^{1}H NMR ($CDCl_3$) for minor diastereomer δ 1.32 (t, J = 7.1 Hz, 3H), 2.09 (s, 3H), 2.57 (dd, J_1 = 18.2 Hz; J_2 = 4.7 Hz, 1H), 2.86–2.97 (m, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.69 (dd, $J_1 = J_2$ = 6.1 Hz, 1H), 5.27–5.35 (m, 1H), 5.58 (dd, $J_1 = J_2$ = 5.0 Hz, 1H), 6.97–7.04 (m, 1H). ^{13}C NMR ($CDCl_3$) for minor diastereomer δ 169.64, 165.29, 131.03, 130.42, 78.90, 77.49, 69.01, 61.46, 25.70, 20.93, 14.12. MS *m*/*z* (%) 245 (17), 184 (12), 166 (67), 155 (12), 138 (100), 110 (56), 43 (29). HRMS (EI) calcd for $(C_{11}H_{14}O_7S+Na)^+$: 313.0358. Found: 313.0355. IR (KBr film) 2987, 1748, 1717, 1374, 1256, 1230, 1047, 991, 839, 772 cm^{-1}.

4.13. Ethyl (3*S*,4*R*,5*R*)-3-azido-5-acetoxy-cyclohex-1-ene-1-carboxylate 14

Compound **13** (5.00 g, 17.22 mmol) was dissolved in aqueous *N*,*N*-dimethylformamide (50 mL, DMF/H_2O = 5:1) at room temperature, after which sodium azide (2.80 g, 43.07 mmol) was added. The mixture was stirred at room temperature for 24 h. Toluene (100 mL) and water (100 mL) were added, and the mixture was vigorously stirred for 15 min. The organic phase was separated, and then washed with water (30 mL) and brine (20 mL). The organic solution was dried over anhydrous $MgSO_4$. The solvent was then removed by vacuum distillation to give a crude oil, which could be directly used for the next step or purified by flash chromatography to furnish compound **14** (4.22 g, 15.67 mmol) in 91% yield. $[\alpha]_D^{20} = +24.2$ (*c* 1.2, EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3H), 2.14 (s, 3H), 2.24–2.38 (m, 1H), 2.98 (dd, J_1 = 17.7 Hz; J_2 = 5.8 Hz, 1H), 3.19 (br s, 1H), 3.85 (dd, $J_1 = J_2$ = 9.0 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.14–4.28 (m, 1H), 4.93–5.04 (m, 1H), 6.59–6.71 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 171.50, 165.81, 134.29, 130.62, 73.62, 71.80, 63.64, 61.91, 30.00, 21.59, 14.69. HRMS *m*/*z* calcd for $(C_{11}H_{15}N_3O_5+Na)^+$: 292.0909. Found: 292.0908. IR (KBr film) 3479, 2979, 1753, 1720, 1447, 1368, 1256, 1092, 1041 cm^{-1}.

4.14. Ethyl (3*S*,4*R*,5*R*)-3-azido-5-acetoxy-4-methanesulfonyloxy-cyclohex-1-ene-1-carboxylate 15

To a solution of compound **14** (4.00 g, 14.86 mmol) in ethyl acetate (80 mL) was added methanesulfonyl chloride (2.55 g, 22.26 mmol). The resulting solution was cooled to 0 °C in an ice bath, and DMAP (0.18 g, 1.47 mmol) was added. Triethylamine (1.80 g, 17.79 mmol) was then dropwise added over 15 min. After the addition was finished, the reaction mixture was further stirred at 0 °C for 1 h to allow the reaction to complete (TLC). The reaction was quenched by adding water (20 mL). The organic phase was separated and washed successively with potassium carbonate aqueous solution (10% w/v, 20 mL) and brine (20 mL). The organic solution was dried over anhydrous $MgSO_4$, and then concentrated under vacuum to give a pale yellow oily residue, which could be directly used for the next step or purified by flash chromatography to furnish compound **15** (4.90 g, 14.11 mmol) in 95% yield. $[\alpha]_D^{20} = +51.5$ (*c* 4.3, EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 3H), 2.14 (s, 3H), 2.39–2.52 (m, 1H), 3.02 (dd, J_1 = 18.0 Hz; J_2 = 6.0 Hz, 1H), 3.17 (s, 3H), 4.24 (q, J = 7.1 Hz, 2H), 4.28–4.40 (m, 1H), 4.78 (dd, $J_1 = J_2$ = 8.9 Hz, 1H), 5.20 (dd, J_1 = 9.4 Hz; J_2 = 6.3 Hz, 1H), 6.69–6.80 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 171.60, 165.10, 134.45, 131.49, 80.37, 67.88, 62.12, 61.64, 39.69, 30.14, 21.47, 14.69. HRMS *m*/*z* calcd for $(C_{12}H_{17}N_3O_7S+Na)^+$: 370.0685. Found: 370.0687. IR (KBr film) 2983, 2919, 2104, 1757, 1716, 1358, 1232, 1179, 1043, 967, 841 cm^{-1}.

4.15. Ethyl (1*S*,5*R*,6*S*)-5-acetoxy-7-azabicyclo[4,1,0]hept-2-ene-3-carboxylate 16

A solution of compound **15** (2.00 g, 5.76 mmol) in THF (50 mL) was cooled to 0 °C in an ice bath. Triphenylphosphine (1.66 g, 6.33 mmol) was then added in portions. After stirring was continued at 0 °C for 0.5 h, the ice bath was removed, and the reaction mixture was allowed to warm to room temperature. Triethylamine (0.58 g, 5.73 mmol) and water (5 mL) were then added. After stirring was continued at room temperature for 0.5 h, more triethylamine (1.16 g, 11.46 mmol) was added in four portions over 2 h. The resulting mixture was stirred at room temperature for a further 8 h. The reaction solution was concentrated below 40 °C under vacuum to remove the THF, and the residue was partitioned between ethyl acetate (60 mL) and water (30 mL). The organic phase was separated and dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by flash chromatography to give compound **16** (1.13 g, 5.02 mmol) as a pale yellow oil in 87% yield. $[\alpha]_D^{20} = -139.7$ (*c* 1.4, EtOAc). ^{1}H NMR (acetone-d_6) δ 1.26 (t, J = 7.1 Hz, 3H), 2.01–2.09 (m, 1H), 2.07 (s, 3H), 2.09–2.17 (m, 1H), 2.59–2.82 (m, 2H), 3.12 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 4.90–5.30 (m, 1H), 7.09–7.21 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 170.69, 165.25, 136.52, 129.45, 69.82, 60.75, 35.12, 31.53, 28.08, 21.21, 14.17. HRMS *m*/*z* calcd for $C_{11}H_{15}NO_4$: 225.1001. Found:

225.1002. IR (KBr film) 3479, 3296, 2979, 1742, 1642, 1553, 1442, 1367, 1258, 1100, 1032, 742 cm^{-1}.

4.16. Ethyl (1*S*,5*R*,6*S*)-5-acetoxy-7-acetyl-7-azabicyclo[4,1,0]-hept-2-ene-3-carboxylate 17

To a solution of compound **16** (2.00 g, 8.88 mmol) in ethyl acetate (40 mL) was added triethylamine (1.80 g, 17.79 mmol), after which the solution was cooled to 0 °C in an ice bath. Acetic anhydride (1.36 g, 13.32 mmol) was added, and stirring was continued at 0 °C for 30 min., after which TLC showed that the reaction was complete. The reaction was immediately quenched by adding an aqueous solution of potassium carbonate (15% w/v, 20 mL). The organic phase was separated and washed with brine (5 mL). After the organic solution was dried over anhydrous $MgSO_4$, the solvent was evaporated under vacuum to give a crude oil, which could be directly used for the next step or purified by flash chromatography to furnish compound **17** (2.32 g, 8.68 mmol) in 98% yield. $[\alpha]_D^{20} = -36.5$ (*c* 1.9, EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3H), 1.90–2.34 (m, 7H), 2.89–3.08 (m, 1H), 3.15–3.32 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 5.03–5.14 (m, 1H), 7.03–7.16 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 181.67, 170.58, 165.28, 132.51, 131.75, 68.43, 61.07, 40.10, 34.60, 25.74, 23.18, 21.09, 14.16. HRMS *m*/*z* calcd for $C_{13}H_{17}NO_5$: 267.1107. Found: 267.1096. IR (KBr film) 2979, 1742, 1710, 1421, 1374, 1237, 1201, 1090, 1033 cm^{-1}.

4.17. Ethyl (3*R*,4*R*,5*R*)-4-acetamido-5-acetoxy-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxylate 18

A solution of compound **17** (2.00 g, 7.48 mmol) in 3-pentanol (10 mL) was cooled to −5 °C in a salt-ice bath. A freshly prepared solution of boron trifluoride etherate (1.59 g, 11.20 mmol) in 3-pentanol (10 mL) was added dropwise over 10 min, and stirring was further continued at −5–0 °C for around 1.5 h. The reaction mixture was diluted with ethyl acetate (50 mL), and an aqueous solution of potassium carbonate (15% w/v, 12 mL) was added to adjust the pH to 9–10. The organic phase was separated and washed with brine (10 mL). The aqueous solution was extracted once more with ethyl acetate (20 mL). The extracts were combined and dried over anhydrous $MgSO_4$. The organic solution was evaporated under vacuum to give the crude product, which could be directly used for the next step or purified by flash chromatography to furnish compound **18** (2.42 g, 6.81 mmol) in 91% yield. $[\alpha]_D^{20} = -76.4$ (*c* 2.0, EtOAc). ^{1}H NMR ($CDCl_3$) δ 0.85–1.00 (m, 6H), 1.30 (t, J = 7.1 Hz, 3H), 1.45–1.62 (m, 4H), 2.00 (s, 3H), 2.06 (s, 3H), 2.43 (dd, J_1 = 18.9 Hz; J_2 = 6.5 Hz, 1H), 2.79 (dd, J_1 = 18.9 Hz; J_2 = 5.0 Hz, 1H), 3.41–3.49 (m, 1H), 4.00–4.09 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.31–4.43 (m, 1H), 5.24–5.36 (m, 1H), 5.51–5.36 (m, 1H), 6.79–6.81 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 170.29, 170.16, 166.01, 135.96, 129.17, 82.03, 73.02, 68.85, 61.03, 50.16, 27.71, 26.23, 26.16, 23.32, 21.13, 14.15, 9.63, 9.27. HRMS (EI) calcd for $C_{18}H_{29}NO_6$: 355.1995. Found: 355.1993. IR (KBr film) 3042, 2973, 2875, 1742, 1719, 1653, 1543, 1376, 1239, 1099, 1053 cm^{-1}.

4.18. Ethyl (3*R*,4*R*,5*R*)-4-acetamido-3-(1-ethyl-propoxy)-5-hydroxy-cyclohex-1-ene-1-carboxylate 7

To a solution of compound **18** (2.00 g, 5.63 mmol) in absolute ethanol (30 mL) was added powdered potassium carbonate (0.86 g, 6.23 mmol). The mixture was then stirred at room temperature for around 6 h. After TLC showed that the reaction was complete, ethanol was removed by distillation under vacuum. The residue was then partitioned between ethyl acetate (100 mL) and water (30 mL). The organic phase was separated and washed with brine (10 mL). The organic solution was dried over anhydrous $MgSO_4$. Removal of the solvent by vacuum distillation gave the crude product as off-white crystals, which were collected on a Büchner funnel and rinsed with a mixed solvent of ethyl acetate and hexane (4:1) to furnish compound **7** (1.66 g, 5.30 mmol) in 94% yield. The characterization data of compound **7** were identical with those obtained in our previous article.[31]

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