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A novel and high-yielding asymmetric synthesis of oseltamivir phosphate (Tamiflu) starting from (−)-shikimic acid

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ABSTRACT

A novel and high-yielding asymmetric synthesis of oseltamivir phosphate **1** (Tamiflu®) is described. The target compound **1** was obtained in 55% overall yield via an 11-step asymmetric synthesis starting from the naturally abundant (−)-shikimic acid. The present synthesis is characterized by some advantages such as the easy separation of intermediate **6** from triphenylphosphine oxide by using its large water-solubility, the use of inexpensive reagents throughout the synthesis, the lack of toxic heavy metals, mild reaction conditions and high yields for all steps. The stereochemical structure of the key intermediate **6** was unequivocally confirmed by X-ray crystallographic analysis.

1. Introduction

H5N1 and H1N1 influenzas are both fatal diseases for human beings and if left unchecked could rapidly spread. Oseltamivir phosphate **1** (Tamiflu®) is an active prodrug of the potent neuraminidase inhibitor,[1,2] and has been widely used not only as a frontline therapy for H5N1 influenza[3–5] and H1N1 influenza,[6] but also as a preventive agent against an unpredictable outbreak of pandemic influenza; as a result, there is a tremendous worldwide requirement for this important drug. In order to protect people from an attack of both H5N1 and H1N1 influenza viruses, organic and medicinal chemists have paid great attention to the synthesis of oseltamivir phosphate **1** over the last decade, and thus it has become a very active field of scientific research. To date, extensive efforts have been made by many synthetic chemists[7–62] to tackle the difficult problems associated with the synthesis of oseltamivir phosphate in order to develop more efficient and useful synthetic routes. Recently, we have been engaged in the synthesis of this important compound aiming at practical and industrial processes;[21,37,38] herein we report a novel and high-yielding asymmetric synthesis of oseltamivir phosphate (Tamiflu) starting from (−)-shikimic acid, which is abundant in plant sources.[63–67]

2. Results and discussion

As shown in Scheme 1, our synthetic efforts began with ethyl shikimate **2**, which could be obtained from (−)-shikimic acid according to a known procedure.[61] Cyclic sulfite **3** was prepared by our previously reported procedure in 98% yield from ethyl shikimate **2**.[21] Compound **3** was then treated with 1.5 equiv of methanesulfonyl chloride in the presence of 1.2 equiv of triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP) in ethyl acetate, and *O*-mesylate cyclic sulfite **4** was obtained in 96% yield. Subsequent treatment of compound **4** with 1.6 equiv of sodium azide and 2.0 equiv of ammonium chloride at room temperature in aqueous *N*,*N*-dimethylformamide (DMF/H_2O = 5:1) led to regio- and stereospecific ring opening at the allylic position, affording azide **5** in 95% yield. The presence of ammonium chloride was necessary to allow the reaction to proceed under almost neutral conditions, otherwise the yield of the desired compound **5** would be lowered due to β-elimination. Both cyclic sulfites **3** and **4** were obtained as an epimeric mixture of two epimers with opposite configurations of the sulfur atoms; however separation of the two epimers was unnecessary, because nucleophilic substitution of the two epimers of compound **4** with sodium azide gave the same ring-opening product **5** after removal of the epimeric sulfinyl groups in the next step.

Conversion of azide **5** into aziridine **6** was performed in one step via tandem reactions. Successive treatment of compound **5** successively with 1.0 equiv of triphenylphosphine, 1.0 equiv of powdered potassium carbonate, and a small amount of water in ethanol (H_2O/EtOH = 1:100 v/v) furnished the desired aziridine **6**. During the conversion, triphenylphosphine oxide was obtained as a by-product along with the Staudinger reduction and aziridination. Aziridine **6** has considerable water-solubility, and so can be easily separated from the undesired triphenylphosphine oxide by the following procedure: aziridine **6** was allowed to dissolve in water, and the undissolved amorphous solid triphenylphosphine oxide was thus removed by simple filtration. The aqueous solution of compound **6** was then used as such in the next step. According

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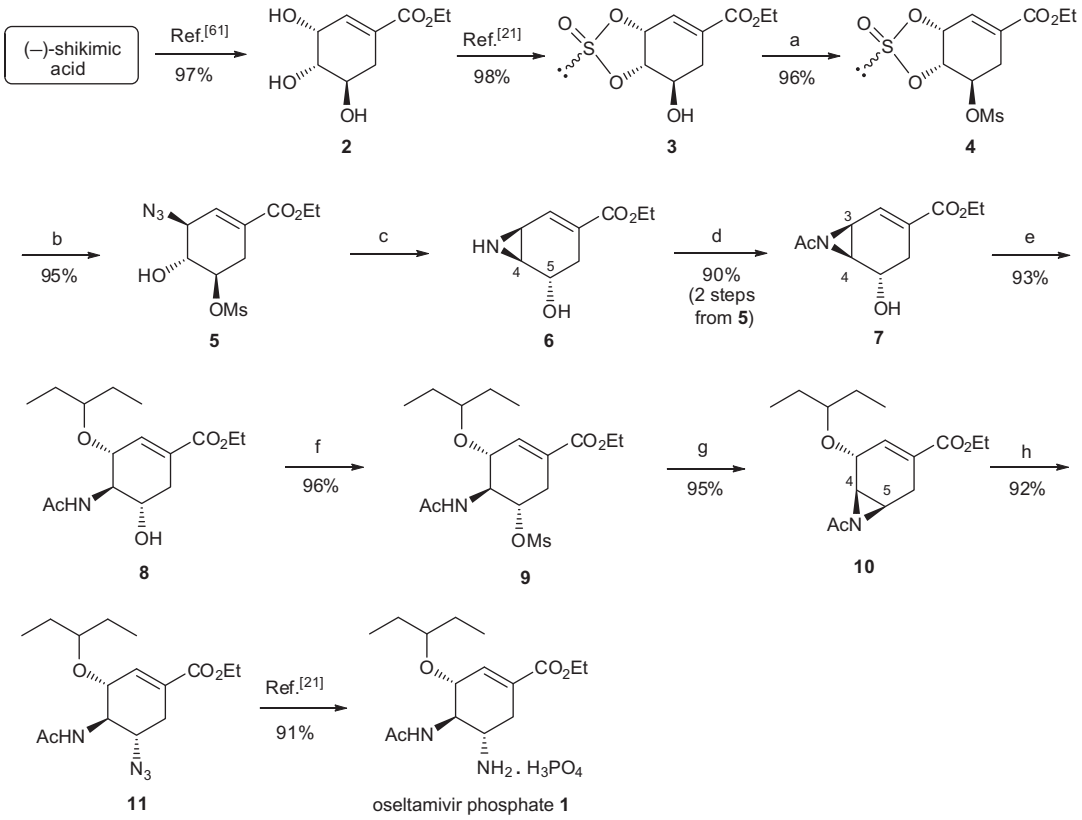
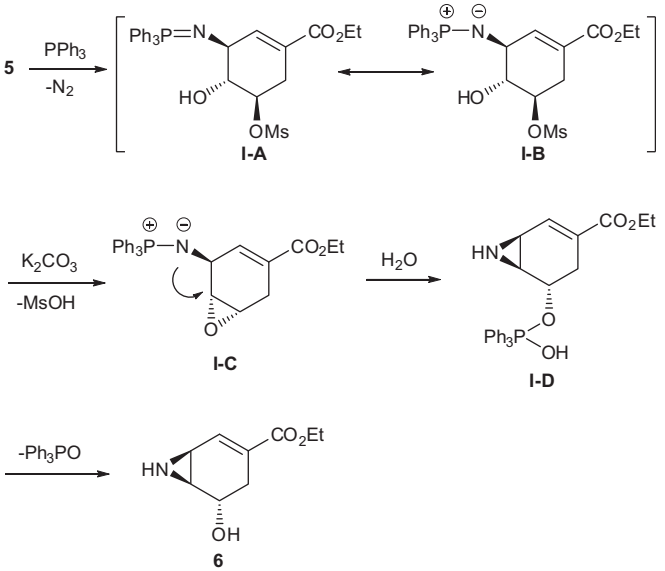


Scheme 1. Synthesis of oseltamivir phosphate **1**. Reagents and conditions: (a) 1.5 equiv of MsCl, 1.2 equiv of Et_3N, 0.1 equiv of DMAP, 0 °C for 1 h in EtOAc; (b) 1.6 equiv of NaN_3, 2.0 equiv of NH_4Cl, rt for 9 h in DMF/H_2O (5:1); (c) 1.0 equiv of Ph_3P, 1.0 equiv of K_2CO_3, rt for 3 h in EtOH, and then 5.0 equiv of H_2O, reflux for 3 h in EtOH; (d) 1.5 equiv of Ac_2O, 2.0 equiv of Et_3N, 0 °C for 0.5 h in CH_2Cl_2/H_2O (1:1); (e) 0.2 equiv of $BF_3{\cdot}OEt_2$, −8 °C for 1 h in 3-pentanol; (f) 1.5 equiv of MsCl, 2.0 equiv of Et_3N, 0.1 equiv of DMAP, 0 °C for 1 h in EtOAc; (g) 4.0 equiv of NaH, rt for 1 h in THF; (h) 4.2 equiv of LiCl, 4.0 equiv of NaN_3, 80 °C for 3 h in DMF.

to a similar procedure,[21] N-acetylation of compound **6** with 1.5 equiv of acetic anhydride and 2.0 equiv of triethylamine in a two-phase reaction system (CH_2Cl_2/H_2O = 1:1) at 0 °C afforded compound **7** in 90% yield (over 2 steps from compound **5**), while leaving the hydroxyl group (at the C-5 position) intact.

A plausible mechanism for the conversion of compound **5** to compound **6** is proposed in Scheme 2. The following cascade reactions were involved in the conversion: Staudinger reduction of compound **5** produced an intermediate aza-ylid **I-A** (or **I-B**), which readily changed to another aza-ylid **I-C** via epoxide-formation under basic conditions. An intramolecular S_N2-type reaction via nucleophilic attack of the nitrogen anion on the vicinal epoxide moiety furnished a complex aziridine **I-D** in the presence of water. Decomposition of the intermediate **I-D** afforded compound **6**, while releasing triphenylphosphine oxide as a by-product. Both configurations of the two stereogenic centers at the C(3) and C(4)-positions were inverted during the conversion of compound **5** to compound **6**, which was unequivocally confirmed by X-ray crystallographic analysis of the single crystal of compound **6** as shown in Figure 1.

Subsequently, the mild $BF_3{\cdot}OEt_2$-catalyzed regioselective and stereospecific ring-opening reaction of *N*-Ac-aziridine **7** produced compound **8** in 93% yield. A similar procedure could be followed for this transformation;[21] herein the reaction was performed in 3-pentanol at −8 °C with 0.2 equiv of $BF_3{\cdot}OEt_2$ as the catalyst. Since the allylic C(3)-position is much more active than the C(4)-position, so 3-pentanol attacked the allylic C(3)-position with very high regioselectivity during the aziridine ring-opening. Following a similar procedure,[37] compound **8** was then exposed to 1.5 equiv of methanesulfonyl chloride and 2.0 equiv of triethylamine in ethyl acetate in the presence of a catalytic amount of DMAP (0.1 equiv),



Scheme 2. Possible mechanism for the conversion of compound **5** to compound **6**.

and methanesulfonate **9** was thus obtained in 96% yield. Next, *N*-acetylaziridine **10** was formed in 95% yield by an S_N2 type intramolecular reaction of mesylate **9** with 4.0 equiv of sodium hydride (60% in mineral oil) in dry tetrahydrofuran. Treatment of compound **10** with 4.2 equiv of lithium chloride and 4.0 equiv of sodium azide in *N*,*N*-dimethylformamide (DMF) at 80 °C caused the

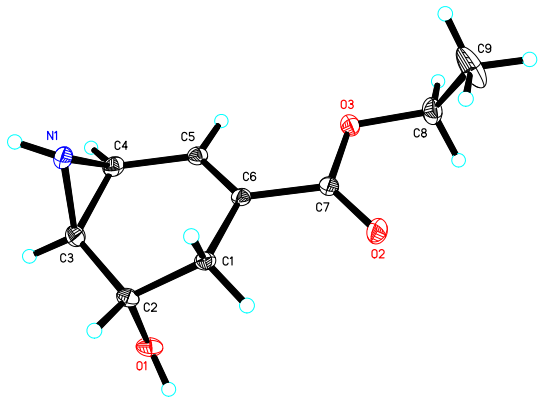


Figure 1. ORTEP drawing of compound **6**.

ring-opening reaction of compound **10** to give an azido compound **11** in 92% yield. Finally, compound **11** was transformed into oseltamivir phosphate **1** in 91% yield according to our previously reported procedure,[21] and the characterization data of compound **1** obtained from the above synthesis were identical to those of the sample previously obtained.[37,38]

The regioselectivity of the ring opening of compound **10** was found to be very high, with almost no C(4)-attacked by-product being detected. Conformational analysis as portrayed in Figure 2 might explain the above high regioselectivity: compound **10** would most likely adopt a boat conformation (conformer **A**), since the nucleophilic attack of the azide anion (N_3^-) at the C(4)-position of conformer **A** could be exclusively blocked by the neighboring bulky 3-pentoxy group, hence the nucleophile (N_3^-) would favorably attack the much less hindered C(5)-position of conformer **A**, and axial attack at C(5) would first produce an unstable twist chair conformer **B**, which would then flip to a stable twist chair conformer **C** of compound **11**.

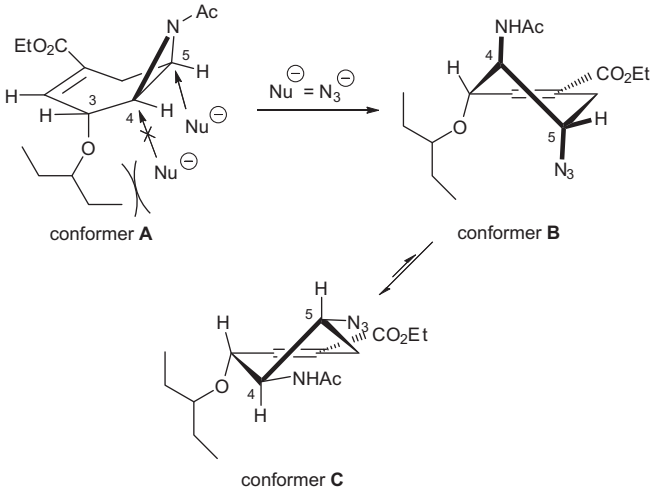


Figure 2. Conformational analysis for the highly regioselective aziridine-opening of compound **10** by favorable N_3^--attack at the C(5)-position.

3. Conclusion

In conclusion, compound **1** was obtained in 55% overall yield via an 11 step synthesis starting from the naturally abundant (−)-shikimic acid. The total yield (55%) of the present synthesis is obviously higher than the best overall yield (47%)[38] of three previous syntheses.[21,37,38] All of the transformations in the present synthesis are quite clean, and the yields for every step are greater than 90%, meaning that the crude products of these transformations can be used directly for the next steps without purification. Some advantages such as the easy separation of intermediate **6** from triphenylphosphine oxide based on its high water-solubility, the use of inexpensive reagents throughout the synthesis, lack of toxic heavy metals, mild reaction conditions, and high yields for all steps, would make the above described synthesis more practical and easy to scale up.

4. Experimental

4.1. General

Melting points were determined on a Mel-TEMP II apparatus. ^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker AM-500 spectrometer at 300 K. Chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. Infrared (IR) spectra were recorded on a Nicolet 6700 instrument. MS spectra were recorded on a Shimadzu GC–MS 2010 or a LC/MSD TOF HR-MS equipment. 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 in 97% yield according to a known procedure.[61] Cyclic sulfite **3** was prepared in 98% yield according to a previously reported method.[21]

4.2. Ethyl (3*R*,4*S*,5*R*)-3,4-*O*-thionyl-5-*O*-methanesulfonyl-shikimate 4

Methanesulfonyl chloride (6.920 g, 60.41 mmol) and DMAP (0.490 g, 4.011 mmol) were added to a solution of cyclic sulfite **3** (10.00 g, 40.28 mmol) in ethyl acetate (200 mL) at 0 °C. Triethylamine (4.890 g, 48.32 mmol) was then added dropwise over 0.5 h. After the addition was finished, the reaction mixture was stirred at 0 °C for another 0.5 h. The reaction was quenched by adding a dilute HCl aqueous solution (1 M, 100 mL), and then the organic phase was separated and washed with dilute potassium carbonate aqueous solution until pH 8–9. The organic solution was dried over anhydrous $MgSO_4$, and then concentrated under vacuum to afford a pale yellow oil that could be used directly for the next step or purified by flash chromatography to furnish compound **4** (12.62 g, 38.67 mmol) in 96% yield. $[\alpha]_D^{20} = +19$ (*c* 1.5, EtOAc). ^{1}H NMR ($CDCl_3$) for major diastereomer: δ 1.33 (t, J = 7.1 Hz, 3H), 2.54–2.64 (m, 1H), 3.09–3.18 (m, 1H), 3.14 (s, 3H), 4.27 (q, J = 7.1 Hz, 2H), 4.72–4.81 (m, 1H), 5.01 (dd, J_1 = 8.2 Hz; J_2 = 5.7 Hz, 1H), 5.65 (dd, J_1 = 5.7 Hz, J_2 = 4.8 Hz, 1H), 6.96–7.01 (m, 1H). ^{13}C NMR ($CDCl_3$) for major diastereomer: δ 164.23, 132.79, 128.87, 78.12, 76.27, 75.58, 61.91, 38.80, 28.97, 14.13. ^{1}H NMR ($CDCl_3$) for minor diastereomer: δ 1.33 (t, J = 7.1 Hz, 3H), 2.58–2.66 (m, 1H), 3.14 (s, 3H), 3.18–3.27 (m, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.81–4.86 (m, 1H), 5.19–5.27 (m, 1H), 5.28–5.35 (m, 1H), 7.01–7.06 (m, 1H). ^{13}C NMR ($CDCl_3$) for minor diastereomer: δ 164.49, 131.53, 130.37, 79.43, 79.24, 77.53, 61.82, 38.20, 29.12, 14.13. HRMS (ESI) calcd for $(C_{10}H_{14}O_8S_2+K)^+$: 364.9767; found: 364.9769. IR (KBr film) 2983, 1716, 1662, 1367, 1257, 1174, 1100, 1005, 830, 526 cm^{-1}.

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

Ammonium chloride (3.280 g, 61.32 mmol) and sodium azide (3.230 g, 49.68 mmol) were added to a solution of compound **4** (10.00 g, 30.64 mmol) in aqueous *N*,*N*-dimethylformamide

(80 mL, DMF/H_2O = 5:1). The mixture was stirred at room temperature for 9 h, and then diluted with ethyl acetate (250 mL) and water (200 mL). The organic phase was separated, and then washed with water (50 mL) and brine (50 mL). The organic solution was dried over anhydrous $MgSO_4$. The solvent was then removed by distillation under vacuum to give the crude product as yellow crystals. The crystals were collected on a Buchner funnel and rinsed with aqueous methanol (CH_3OH/H_2O = 6:4) to afford compound **5** (8.890 g, 29.12 mmol) in 95% yield. Mp 88.9–89.2 °C. $[\alpha]_D^{20} = +31$ (*c* 2.3, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.31 (t, J = 7.1 Hz, 3H), 2.51–2.59 (m, 1H), 3.10 (dd, J_1 = 17.5 Hz; J_2 = 5.9 Hz, 1H), 3.16 (s, 3H), 3.88 (dd, J_1 = 9.0 Hz, J_2 = 9.1 Hz, 1H), 3.97 (br s, 1H), 4.18–4.29 (m, 3H), 4.70–4.79 (m, 1H), 6.64–6.68 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 165.54, 134.57, 129.96, 79.52, 73.44, 63.72, 62.17, 39.24, 31.41, 14.72. HRMS (ESI) calcd for $(C_{10}H_{15}N_3O_6S+NH_4)^+$: 323.1025; found: 323.1026. IR (KBr film) 3604, 3333, 3031, 2104, 1721, 1663, 1253, 1175, 953 cm^{-1}.

4.4. Ethyl (3*S*,4*S*,5*S*)-5-hydroxy-3,4-imino-cyclohex-1-ene-1-carboxylate 6

A solution of compound **5** (2.000 g, 6.551 mmol) in ethanol (40 mL) was cooled to 0 °C by an ice bath. Next, triphenylphosphine (1.720 g, 6.558 mmol) was added in portions over 5 min. After the solution was stirred at 0 °C for 15 min, powdered potassium carbonate (0.910 g, 6.584 mmol) was added. The ice bath was removed, and the mixture was then vigorously stirred for 3 h at room temperature. The resulting suspension was then filtered by suction to remove insoluble inorganic salts, and the cake was rinsed twice with ethanol (2 × 10 mL). The filtrates were combined and water (0.6 mL) was added. The reaction solution was then heated at reflux for 3 h until the reaction was complete. The solvent was removed by distillation under vacuum to give the crude product as a viscous yellow oil. Water (30 mL) was added, and the mixture was stirred vigorously. Triphenylphosphine oxide gradually precipitated, and was separated from the aqueous solution of compound **6** by filtration. After the cake of triphenylphosphine oxide was washed twice with water (2 × 5 mL), the aqueous filtrates were combined and used in the next step without further purification. For spectroscopic characterization, a sample of **6** was extracted from the aqueous solution, and purified by chromatography. Data for **6**: Mp 99.0–99.9 °C. $[\alpha]_D^{20} = -296$ (*c* 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H), 2.20–2.32 (m, 1H), 2.60–2.68 (m, 1H), 2.72–2.85 (m, 2H), 4.18 (q, J = 7.0 Hz, 2H), 4.45–4.55 (m, 1H), 7.25–7.30 (m, 1H). ^{13}C NMR (acetone-d_6) δ 167.12, 138.86, 128.53, 63.85, 60.77, 39.30, 30.76, 28.34, 14.61. HRMS (EI) calcd for $(C_9H_{13}NO_3+H)^+$: 184.0974; found: 184.0964. IR (KBr film) 3290, 2999, 2964, 1691, 1645, 1466, 1409, 1268, 1236, 1096, 777 cm^{-1}.

4.5. Ethyl (3*S*,4*S*,5*S*)-3,4-acetylimino-5-hydroxy-cyclohex-1-ene-1-carboxylate 7

A procedure similar to a previous article[21] was followed herein. The above aqueous solution of aziridine **6** was mixed with dichloromethane (40 mL), and the two-phase mixture was cooled to 0 °C by an ice bath. Triethylamine (1.320 g, 13.04 mmol) was added, and then acetic anhydride (1.000 g, 9.795 mmol) was added dropwise over 15 min. After the addition was finished, the reaction mixture was further stirred for a further 15 min. Two phases were separated, and the aqueous layer was salted with potassium carbonate (0.500 g) and sodium chloride (15.00 g), and then extracted twice with dichloromethane (2 × 30 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, and then concentrated under vacuum to afford a pale yellow oily product that could be used directly for the next step or purified by flash chromatography to furnish compound **7** (1.330 g, 5.905 mmol) in 90% yield over 2-steps (compound **5** to compound **7**). $[\alpha]_D^{20} = -105$ (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.30 (t, J = 7.1 Hz, 3H), 2.14 (s, 3H), 2.20–2.31 (m, 1H), 2.64–2.70 (m, 1H), 2.79–2.89 (m, 1H), 3.10–3.18 (m, 2H), 4.20 (q, J = 7.1 Hz, 2H), 4.55–4.59 (m, 1H), 7.18–7.22 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 181.79, 166.37, 132.99, 129.99, 61.92, 61.02, 41.73, 32.56, 29.21, 23.17, 14.15. HRMS (EI) calcd for $(C_{11}H_{15}NO_4+H)^+$: 226.1079; found: 226.1075. IR (KBr film) 3412, 2979, 1709, 1368, 1263, 1199, 1099, 1053, 753 cm^{-1}.

4.6. Ethyl (3*R*,4*R*,5*S*)-4-acetamido-3-(1-ethyl-propoxy)-5-hydroxy-cyclohex-1-ene-1-carboxylate 8

A procedure similar to a previous article[21] was followed herein. Compound **7** (1.000 g, 4.440 mmol) was dissolved in 3-pentanol (5 mL), and the resulting solution was cooled to −8 °C by a salt-ice bath. A fresh solution of boron trifluoride-diethyl etherate (0.120 g, 0.846 mmol) solution in 3-pentanol (5 mL) was then added over 30 min. After the addition was finished, the reaction mixture was stirred for a further 1 h at −8 °C. The reaction was quenched by adding an aqueous solution of potassium carbonate (15% w/v, 20 mL), then the aqueous solution was extracted twice with methylene chloride (2 × 30 mL). The organic extracts were combined, and dried over anhydrous $MgSO_4$. Evaporation of the solvents under vacuum gave a yellow solid product, which could be used directly for the next step or purified by flash chromatography to furnish compound **8** (1.300 g, 4.148 mmol) in 93% yield. Mp 104.3–105.4 °C. $[\alpha]_D^{20} = -60$ (*c* 2.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 7.0 Hz, 6H), 1.30 (t, J = 7.1 Hz, 3H), 1.45–1.58 (m, 4H), 2.04 (s, 3H), 2.32–2.42 (m, 1H), 2.75–2.85 (m, 1H), 3.31–3.42 (m, 1H), 3.75–3.85 (m, 1H), 3.92–4.03 (m, 1H), 4.00–4.18 (m, 2H), 4.22 (q, J = 7.1 Hz, 2H), 5.96–6.02 (m, 1H), 6.76–6.81 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 172.11, 166.26, 136.91, 129.07, 81.90, 74.97, 67.87, 60.91, 57.35, 32.92, 26.19, 25.64, 23.48, 14.15, 9.52, 9.22. HRMS (EI) calcd for $(C_{16}H_{27}NO_5+H)^+$: 314.1967; found: 314.1955. IR (KBr film) 3413, 3293, 2973, 2879, 1722, 1642, 1555, 1377, 1248, 1057, 1009 cm^{-1}.

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

A procedure similar to a previous article[37] was followed herein: To a solution of compound **8** (2.000 g, 6.382 mmol) in ethyl acetate (40 mL) was added methanesulfonyl chloride (1.100 g, 9.603 mmol) and DMAP (0.078 g, 0.638 mmol) at 0 °C. Triethylamine (1.290 g, 12.75 mmol) was then dropwise added over 30 min. After the addition was finished, the reaction mixture was stirred at 0 °C for another 0.5 h. The reaction was quenched by adding a dilute HCl aqueous solution (1 M, 100 mL), and then the organic phase was separated and washed with a dilute potassium carbonate aqueous solution until pH 8–9. The organic solution was dried over anhydrous $MgSO_4$, and then concentrated under vacuum to afford a pale yellow solid product, which could be used directly for the next step or purified by flash chromatography to furnish compound **9** (2.400 g, 6.131 mmol) in 96% yield. Mp 102.7–104.0 °C. $[\alpha]_D^{20} = -29$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 0.83–0.95 (m, 6H), 1.30 (t, J = 7.1 Hz, 3H), 1.44–1.59 (m, 4H), 2.03 (s, 3H), 2.53–2.63 (m, 1H), 3.05 (s, 3H), 3.07 (dd, J_1 = 16.8 Hz; J_2 = 5.6 Hz, 1H), 3.29–3.39 (m, 1H), 3.84–3.92 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.36–4.44 (m, 1H), 4.99–5.11 (m, 1H), 6.00–6.05 (m, 1H), 6.78–6.82 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 171.14, 165.47, 138.06, 127.21, 82.46, 75.89, 74.42, 61.19, 55.48, 38.58, 31.55, 26.23, 25.66, 23.54, 14.20, 9.55, 9.26. HRMS (EI) calcd for $(C_{17}H_{29}NO_7S+H)^+$: 392.1743; found: 392.1746. IR (KBr film) 3433, 3270, 2972, 2939, 1717, 1647, 1572, 1362, 1258, 1177, 963, 838 cm^{-1}.

4.8. Ethyl (3*R*,4*R*,5*R*)-4,5-acetylimino-3-(1-ethyl-propoxy)-cyclohex-1-ene-1-carboxylate 10

Compound **9** (2.000 g, 5.109 mmol) was dissolved in tetrahydrofuran (60 mL), after which sodium hydride (0.820 g, 60%, 20.50 mmol) was added portionwise. The reaction mixture was allowed to stir at room temperature for 1 h, and then was quenched by adding ethanol (2 mL). The resulting suspension was filtered by suction to remove insoluble salts, and the filtrate was concentrated under vacuum to remove tetrahydrofuran. The residue was partitioned between ethyl acetate (40 mL) and water (10 mL). The organic solution was separated, dried over anhydrous $MgSO_4$, and then concentrated under vacuum to afford a pale yellow oily product, which could be used directly for the next step or purified by flash chromatography to furnish compound **10** (1.430 g, 4.841 mmol) in 95% yield. $[\alpha]_D^{20} = -46$ (*c* 1.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.4 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.48–1.64 (m, 4H), 2.14 (s, 3H), 2.58–2.68 (m, 1H), 2.85–3.00 (m, 3H), 3.38–3.48 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.35–4.40 (m, 1H), 6.81–6.85 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 182.54, 166.45, 133.03, 127.72, 82.41, 68.50, 60.87, 37.11, 34.76, 26.62, 26.56, 23.78, 23.44, 14.15, 9.89, 9.44. HRMS (EI) calcd for $(C_{16}H_{25}NO_4)^+$: 295.1784; found: 295.1785. IR (KBr film) 2969, 2875, 1710, 1426, 1368, 1248, 1063, 743 cm^{-1}.

4.9. Ethyl (3*R*,4*R*,5*S*)-4-acetamido-5-azido-3-(1-ethylpropoxy)-cyclohex-1-ene-1-carboxylate 11

Compound **10** (1.000 g, 3.386 mmol) was dissolved in DMF (10 mL) at room temperature, after which sodium azide (0.880 g, 13.54 mmol) and lithium chloride (0.600 g, 14.15 mmol) were added. The mixture was stirred at 80 °C for 3 h. After the mixture was cooled down to room temperature, toluene (40 mL) and water (30 mL) were added. The organic phase was separated, and then washed successively with water (10 mL) and brine (10 mL). The organic solution was dried over anhydrous $MgSO_4$. The solvent was then removed by distillation under vacuum to give a yellow solid product, which could be used directly for the next step or purified by flash chromatography to furnish compound **11** (1.060 g, 3.132 mmol) in 92% yield. Mp 136.6–137.7 °C. $[\alpha]_D^{20} = -43$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.42–1.58 (m, 4H), 2.04 (s, 3H), 2.18–2.28 (m, 1H), 2.85 (dd, J_1 = 17.6 Hz; J_2 = 5.5 Hz, 1H), 3.29–3.39 (m, 1H), 3.46–3.56 (m, 1H), 4.08–4.18 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.45–4.50 (m, 1H), 6.51–6.56 (m, 1H), 6.75–6.79 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 171.25, 165.82, 138.11, 128.07, 82.13, 73.89, 61.05, 57.65, 57.31, 30.46, 26.22, 25.58, 23.49, 14.16, 9.55, 9.24. HRMS (EI) calcd for $(C_{16}H_{26}N_4O_4+K)^+$: 377.1591; found: 377.1589. IR (KBr film) 3271, 2975, 2106, 1717, 1659, 1563, 1378, 1254, 1079 cm^{-1}.

4.10. Determination of the absolute configurations of compound 6 by X-ray analysis

A clear solution of compound **6** (0.250 g) in ether (20 mL) was placed into a flask. The flask was then sealed with a thin film of polyvinyl chloride (PVC), and left to stand overnight at room temperature. As the ether gradually evaporated, pieces of single crystals of compound **6** were formed on the bottom of the flask.

Crystal data for compound **6**: $C_9H_{13}NO_3$, M_r = 183.20, Monoclinic, space group *P*2(1), *a* = 5.5993(2), *b* = 10.1717(4), *c* = 8.2421(3) Å, α = 90.000°, β = 100.925(2)°, γ = 90.000°, *V* = 460.92(3) Å^3, *Z* = 2, D_C = 1.320 Mg/m^3, μ (CuKα) = 0.826 mm^{-1}, *F* (000) = 196, colorless block, dimensions: 0.15×0.10×0.08 mm. *R* = 0.0266, *wR* = 0.0751, goodness-of-fit on F^2 = 1.151 for 1503 observed reflections with $I > 2\sigma(I)$.

Diffraction intensities were collected on a Bruker APEX2 CCD diffractometer using graphite monochromated Cu Kα radiation (λ = 1.54178 Å) at 133 K. The absorption was corrected *via* multi-scan. The structure was solved by direct methods using SHELXS-97 and refined on F^2 by full-matrix least-squares methods using SHELXL-97. All non-H atoms were refined anisotropically and H-atoms isotropically.

Crystallographic data for the structure herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 848662. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033, e-mail: deposit@ccdc.cam.ac.uk, or internet: www.ccdc.cam.ac.uk/data_request/cif.].

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