Tetrahedron 71 (2015) 2393–2399

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A new and efficient asymmetric synthesis of oseltamivir phosphate (Tamiflu) from D-glucose

Boonsong Kongkathip, Sunisa Akkarasamiyo, Ngampong Kongkathip *

Natural Products and Organic Synthesis Research Unit (NPOS), Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Kasetsart University, Chatuchak, Bangkok 10900, Thailand

ARTICLE INFO

Article history:
Received 22 December 2014
Received in revised form 10 February 2015
Accepted 24 February 2015
Available online 3 March 2015

Keywords:
Oseltamivir phosphate
Tamiflu
Anti-influenza
D-Glucose
Bernet-Vasellar reaction
Ring closing metathesis

ABSTRACT

The *anti*-influenza drug, oseltamivir phosphate (Tamiflu) was synthesized from D-glucose via a novel and efficient synthetic route. A unique feature of the synthesis is that the key intermediate aziridine cyclohexene was synthesized as a mixture of diastereomers, via a metal-mediated domino reaction and ring closing metathesis (RCM). The iodoxylose compound was prepared in 9 steps from D-glucose. Both isomers of aziridine cyclohexene intermediate could be converted into Tamiflu via two pathways. First, both isomers of aziridine cyclohexene underwent aziridine-ring opening yielded diastereomeric of 1,2-amino mesylate cyclohexene esters. The *trans*-1,2-amino mesylate isomer could be transformed to tamiflu by formation of aziridine then regio- and stereoselective nucleophilic substitution of the azide to afford 1,2-amino azido compound whereas the *cis*-isomer could be transformed directly by S_N2 substitution of azide to give the same azido product, which then converted into oseltamivir phosphate.

1. Introduction

Influenza remains a major global human health issue due to the risk of a major pandemic. H5N1 is a particularly virulent subtype of the influenza A virus, which can cause serious illness in humans.[1,2] Therefore, studies of inhibitors or vaccines of H5N1 have attracted interest and worldwide attention.[3]

Oseltamivir phosphate, popularly known as Tamiflu, **1**, is one of the most potent orally active neuraminidase inhibitors used for the treatment of human influenza and H5N1 avian flu infections.[3–7] The commercial manufacturing process of Tamiflu employs (−)-shikimic acid as the raw material, which is not always readily available in consistently pure form.[8] As a consequence, many synthetic groups[9,10] have recently focused on developing alternative synthetic strategies from cheaper, more readily available starting materials. We have recently reported the synthesis of Tamiflu from D-mannose as more efficient and practical synthetic process.[11a,b] Herein, we go further by reporting a novel asymmetric synthesis of Tamiflu using D-glucose, which is a very cheap and abundant starting material.

Carbohydrates have for decades served as chiral pool compounds for the total synthesis of bioactive natural products. In this paper D-glucose, a commercially available starting material, was chosen for the synthesis of Tamiflu. The retrosynthetic analysis is depicted in Fig. 1. We envisioned that the installation of the alkoxy group could be achieved by the opening of the aziridine **8**. It was

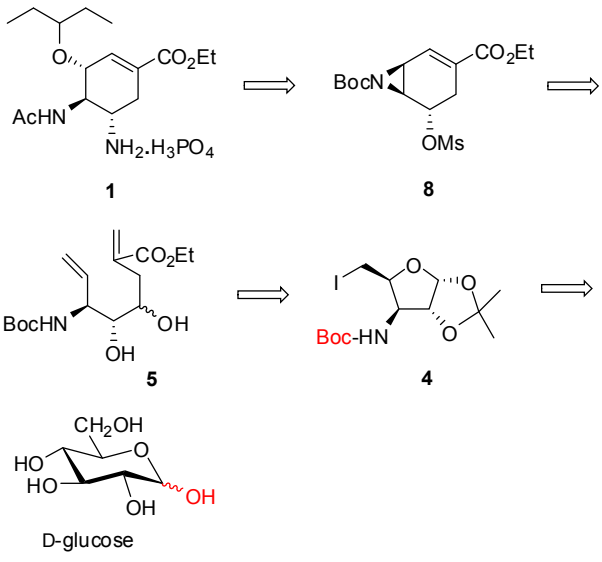


Fig. 1. Retrosynthetic analysis of oseltamivir phosphate (**1**) from D-glucose via aziridine intermediate **8**.

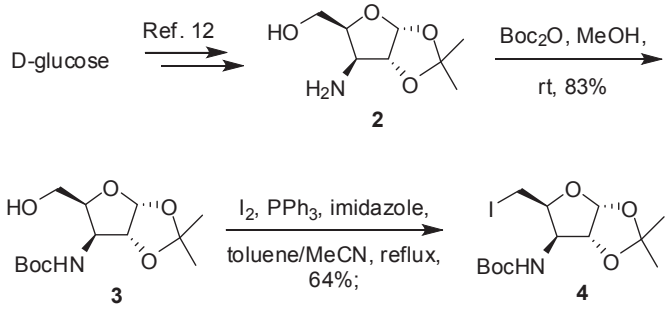
* Corresponding author. Tel.: +662 5625444x2139; fax: +662 5625444x2119; e-mail address: fscinpk@ku.ac.th (N. Kongkathip).

http://dx.doi.org/10.1016/j.tet.2015.02.081
0040-4020/

proposed that **8** could be obtained via ring closing olefin metathesis of a diene **5** generated by metal-mediated reductive elimination of the 3-[(*tert*-butoxycarbonyl)amino]-3,5-dideoxy-5-iodo-1,2-*O*-(1-methylethylidene)-α-D-xylofuranose (**4**) and in situ alkylation of an aldehyde intermediate by a metal allyl reagent. The xylofuranose derivative **4** could be easily prepared from a commercially available D-glucose.[12]

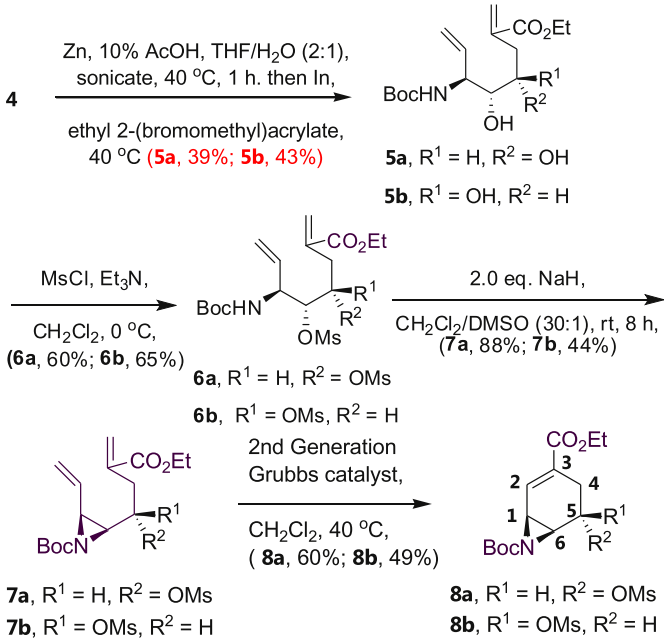
2. Results and discussion

The synthesis began with 3-amino-3-deoxy-1,2-*O*-(1-methylethylidene)-α-D-xylofuranose **2**, obtained from D-glucose following a procedure previously reported.[12] Protection of the amino group of compound **2** as *N*-Boc was accomplished by its treatment with di-*tert*-butyl dicarbonate in methanol to afford compound **3** in 83% yield. Alcohol **3** was converted to the corresponding iodide **4** in 64% yield by treatment with I_2, PPh_3, imidazole and refluxing in a mixed solvent of toluene–acetonitrile (2:1) (Scheme 1).



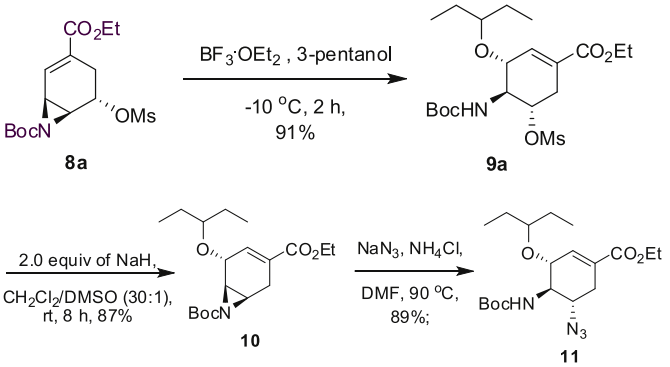
Scheme 1. Synthesis of 3-[(*tert*-butoxycarbonyl)amino]-3,5-dideoxy-5-iodo-1,2-*O*-(1-methylethylidene)-α-D-xylofuranose (**4**).

It should be noted that the Bernet-Vasella reaction of 5-deoxy-5-iodo derivatives of D-xylose has been reported to be unsuccessful with activated zinc, irrespective of the reaction conditions.[13a,b] Therefore, we examined this reaction with respect to compound **4** and ethyl 2-(bromomethyl)acrylate in THF/H_2O(2:1) and found that it worked very well when 10% AcOH was added into the reaction mixture, affording the corresponding diene **5a** and **5b** as a distereomeric mixture in 1:1 ratio in 82% yield (Scheme 2). The ratio of diastereomers was improved to 1:3 when the reaction was carried out as a two steps sequence where zinc performed the reductive fragmentation of iodide **4** and indium powder promoted the coupling between the aldehyde intermediate and the bromoacrylate ester. The diastereomers **5a** and **5b** were separated by flash column chromatography using hexane–ethyl acetate (2:1) as eluent. The relative stereochemistry of diastereomers **5a** and **5b** was confirmed later when both compounds were transformed to aziridine cyclohexene **8a** and **8b**. Protection of the dihydroxyl group of **5a** and **5b** upon treatment with MsCl provided both mesylate **6a** and **6b** in good yield. When compounds **6a** and **6b** were treated with 2.0 equiv of NaH in a mixed solvent of dichloromethane and dimethyl sulfoxide (CH_2Cl_2/DMSO=30:1) at room temperature, the desired aziridines **7a** and **7b** were obtained in 88% and 44% yield, respectively. Next, by heating dienes **7a** and **7b** to 40 °C in CH_2Cl_2 with the Hoveyda-Grubbs 2nd generation catalyst resulted in ring closing metathesis, providing cyclohexene aziridine **8a** and **8b** in 60% and 49% yield, respectively[10] (Scheme 2). The ^{1}H NMR spectrum of **8a** showed the chemical shift of H_5 at 5.46 as a quintet, which is in agreement with that reported in the literature,[9c] whereas for **8b**, the chemical shift of H_5 appeared at a higher field (δ=5.0) as a doublet of doublet of doublets. Subsequently, *N*-Boc aziridine **8a** and **8b** were immediately exposed to $BF_3\cdot OEt_2$ and a large excess 3-pentanol; ring opening of **8a** and **8b** occurred regio- and stereospecifically to provide compound **9a** and isomer **9b** in 91% and 95%, respectively.[14a,b]

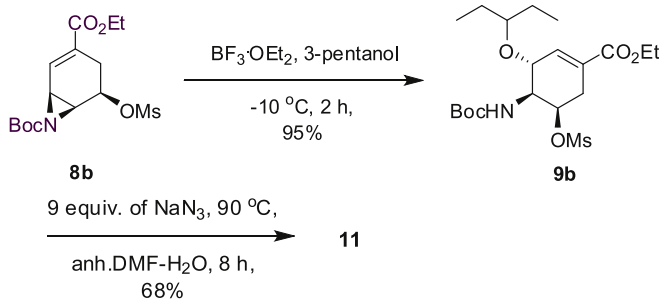


Scheme 2. Synthesis of *N*-Boc aziridine **8a** and **8b**.

Both compounds **9a** and **9b** could be converted into oseltamivir phosphate (**1**). Thus, compound **9a** underwent intramolecular S_N2 type reaction when treated with 2.0 equiv of NaH in CH_2Cl_2-DMSO (30:1) to give *N*-Boc aziridine **10**.[9q] Treatment of **10** with 4.0 equiv of sodium azide in DMF at 90 °C caused the aziridine ring opening reaction to give the azido compound **11** in 77% yield over 2 steps (Scheme 3). The product **11** was obtained in one step, 68% yield from the isomer **9b**, when treated with 2.0 equiv of sodium azide in DMF/H_2O (Scheme 4).[15]

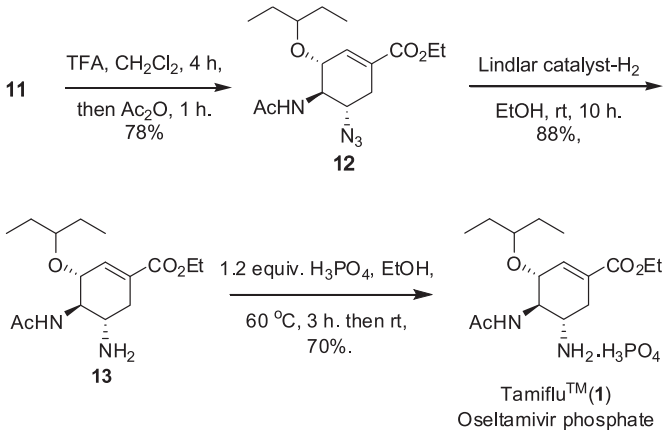


Scheme 3. Synthesis of azido cyclohexene **11** from *N*-Boc aziridine **8a**.



Scheme 4. Synthesis of azido cyclohexene **11** from *N*-Boc aziridine **8b**.

At the end of the synthesis, the *N*-Boc of azido compound **11** was converted into its *N*–Ac derivative by successive treatment with TFA and subsequent acetylation with acetic anhydride to yield *N*–Ac azido **12**.[14] Azide compound **12** was reduced by hydrogenation using the Lindlar catalyst to give the free amine **13**, which was directly reacted with 1.2 equiv H_3PO_4 in EtOH to furnish oseltamivir phosphate (**1**) in 70% yield (Scheme 5).



Scheme 5. Completion of the synthesis of oseltamivir phosphate **1**.

3. Conclusion

In conclusion we have developed an efficient alternative synthesis of Tamiflu from 3-amino-5-hydroxy-1,2-*O*-isopropylidenexylose **2**, which can be prepared from cheap and readily available D-glucose. The strategy requires nine steps from **4** and gives rise to Tamiflu in 7.2% overall yield. The key steps are three consecutive organometallic reactions: zinc-mediated fragmentation of **4**, indium-mediated coupling between the aldehyde intermediate and ethyl 2-(bromomethyl)acrylate, and ruthenium-catalyzed ring closing metathesis of **7**. The synthesis highlights the utility of these organometallic reactions in the synthesis of Tamiflu from carbohydrates.

4. Experimental

4.1. General

Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying reagents immediately prior to use. Tetrahydrofuran was distilled from sodium and benzophenone under nitrogen atmosphere. Triethylamine, pyridine and dichloromethane were distilled from calcium hydride under nitrogen atmosphere. Moisture- and air-sensitive reactions were carried out under an atmosphere of nitrogen. Reaction flasks were oven dried at 105 °C overnight. Unless otherwise stated, concentration under reduced pressure refers to a rotary evaporator at water aspirator pressure. Analytical thin-layer chromatography (TLC) was conducted using MERCK precoated TLC plates (silica gel 60 F-254). Compounds were visualized by ultraviolet light and/or by heating the plate after dipping in a 1% solution of vanillin in 0.1 M sulfuric acid in ethanol. Flash chromatography was carried out using MERCK. silica gel (0.04–0.06 mm particle size). Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using either a VARIAN^{unity} INOVA 400 MHz spectrometer or a Brucker ADVANCE 300 MHz spectrometer. Chemical shifts were recorded as δ values in ppm. Spectra were acquired in $CDCl_3$ unless otherwise stated. The peak due to residual $CHCl_3$ (7.26 ppm for ^1H and 77.23 ppm for ^{13}C) was used as the internal reference. Coupling constant (*J*) values were given in Hertz, and multiplicity was defined as follows: br=broad, s=singlet, d=doublet, dd=double of doublets, ddd=doublet of doublet doublets, dt=doublet of triplets, t=triplet, *t*d=triplet of doublets, q=quartet, *q*d=quartet of doublets and m=multiplet. Optical rotation was measured using a JASCO P-2000 polarimeter. Infrared (IR) spectra were recorded in cm^{-1} on a Parkin-Elmer 2000 Fourier transform infrared spectrophotometer at Chemistry Department, Faculty of Science, Kasetsart University. Samples were analyzed as KBr disks. The high resolution mass spectra (HRMS) were recorded on Q-TOF2 hybrid quadrupole time-of-flight mass spectrometer. Melting points (mp) were determined on Fisher John apparatus and MEI-TEMP capillary melting point apparatus at Chemistry Department, Faculty of Science, Kasetsart University and were reported uncorrected in degrees Celcius (°C).

*4.1.1. 3-Amino-3-deoxy-1,2-O-(1-methylethylidene)-α-D-xylo-furanose (**2**).* To a solution of azido alcohol (967 mg, 4.50 mmol) in a mixture of THF:water (4:1) (25 mL) was added triphenylphosphine (2.36 g, 8.96 mmol) and stirred at room temperature for 15 h. Then, the solvent was removed by evaporation and the residue was purified by flash column chromatography (silica gel, MeOH:CH_2Cl_2, 10: 90) to give **2** (841 mg, 99%) as a colourless oil. R_f (50% EtOAc/hexane) 0.16; $[\alpha]_D^{25}$ −2.3 (*c* 1.99, $CHCl_3$); FTIR (neat), ν_{max}, cm^{-1}: 3465 (OH), 3373 (NH), 2987, 2937 (C–H), 1217 (C–N), 1071 (C–O); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.89 (d, *J*=3.6 Hz, 1H, H-1), 4.36 (d, *J*=3.6 Hz, 1H, H-2), 4.20 (dt, *J*=5.3, 3.6 Hz, 1H, H-4), 3.91–3.79 (m, 2H, H-5), 3.45 (d, *J*=3.6 Hz, 1H, H-3), 1.47 (s, 3H, CH_3), 1.27 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 111.4 (C-1), 104.2 (C), 86.5 (C-2), 79.5 (C-4), 59.9 (C-5), 57.3 (C-3), 26.4 (CH_3), 26.0 (CH_3); HRMS (ESI$^+$) *m/z* $[M+H]^+$ calcd for $C_8H_{16}NO_4$:190.1079, found: 190.1081.

*4.1.2. 3-[(tert-Butoxycarbonyl)amino]-3-deoxy-1,2-O-(1-methyl-ethylidene)-α-D-xylofuranose (**3**).* To a solution of **2** (643 mg, 3.42 mmol) in MeOH (7 mL) was added Boc_2O (1.49 mg, 6.84 mmol) and stirred at room temperature for 3 h. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane: EtOAc 4:1) to give **3** as a white amorphous solid (816 mg, 83%): mp 155–157 °C. R_f (50% EtOAc/hexane) 0.37; $[\alpha]_D^{25}$ +5.1 (*c* 3.41, $CHCl_3$); FTIR (KBr), ν_{max}, cm^{-1}: 3429 (OH), 3297 (NH), 2984 (C–H), 1708 (C=O), 1062 (C–O); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.84 (d, *J*=3.7 Hz, 1H, H-1), 5.55 (d, *J*=6.4 Hz, 1H, NH), 4.54 (d, *J*=3.7 Hz, 1H, H-2), 4.30–4.24 (m, 1H, H-3), 4.15–4.09 (m, 1H, H-4), 3.85–3.76 (m, 1H, H-5), 1.49 (s, 3H, CH_3), 1.43 (s, 9H, Boc), 1.28 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.2 (C=O), 112.0 ($C(CH_3)_2$), 104.3 (C-1), 84.7 (C-2), 80.3 (C-3), 78.1 ($C(CH_3)_3$), 59.9 (C-5), 57.9 (C-4), 28.3 ($C(CH_3)_3$), 26.6 (CH_3), 26.2

(CH_3); HRMS (ESI^+) *m/z* $[M+Na]^+$, calcd for $C_{13}H_{23}NNaO_6$: 312.1423, found: 312.1424.

*4.1.3. 3-[(tert-Butoxycarbonyl)amino]-3,5-dideoxy-5-iodo-1,2-O-(1-methylethylidene)-α-D-xylofuranose (**4**).* To a solution of **3** (1.98 g, 6.86 mmol) in toluene (32 mL) and acetonitrile (7 mL) was added imidazole (1.40 g, 20.6 mmol) and triphenylphosphine (4.42 g, 16.5 mmol) and then iodine (4.18 g, 16.5 mmol). The reaction mixture was refluxed for 3 h and cooled to room temperature. The reaction mixture was diluted with ethyl acetate (100 mL) and the organic layer was washed with 10% sodium thiosulphate solution (3×100 mL), water (150 mL) and brine (150 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane: ethyl acetate, 2:1) to give **4** (1.48 mg, 64%) as a white amorphous solid, which was recrystallized from hexane to give a colourless needle, mp 114–115 °C; R_f (30% EtOAc/hexane) 0.70; $[\alpha]_D^{25}$ −20.8 (*c* 2.30, $CHCl_3$); FTIR (KBr), ν_{max}, cm^{-1}: 3432, (N–H), 2983, 2930 (C–H), 1714(C=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.85 (d, *J*=3.6 Hz, 1H, H-1), 4.54 (d, *J*=3.6 Hz, 1H, H-2), 4.44 (br, 1H, H-3), 4.32 (d, *J*=9.1 Hz, 1H, H-4), 3.24 (t, *J*=9.1 Hz, 1H, H-5), 3.10 (dd, *J*=10.1, 8.0 Hz, 1H, H-5), 1.51 (s, 3H, CH_3), 1.45 (s, 9H, Boc), 1.28 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.8 (C=O), 112.1 (C), 104.5 (C-1), 84.8 (C-4), 80.3 (C-2), 79.2 ($C(CH_3)$), 57.4 (C-3), 28.2 ($C(CH_3)_3$), 26.5 (CH_3), 26.1 (CH_3), −1.8 (C-5); HRMS (ESI^+) *m/z* $[M+Na]^+$, calcd for $C_{13}H_{22}NNaO_5I$: 422.0440, found: 422.0443.

*4.1.4. Ethyl (4S,5R,6S)-6-[(tert-butoxycarbonyl)amino]-4,5-dihydroxy-2-methylideneoct-7-enoate (**5a**) and ethyl (4R,5R,6S)-6-[(tert-butoxycarbonyl)amino]-4,5-dihydroxy-2-methylideneoct-7-enoate (**5b**).* To a solution of **4** (738 mg, 1.85 mmol) in 2:1 THF:H_2O (60 mL) was added zinc powder (1.78 mg, 27.8 mmol) and 10% acetic acid (0.1 mL). The mixture was sonicated at 40 °C for 30 min and then ethyl 2-(bromomethyl) acrylate (0.52 mL, 3.7 mmol) was added dropwise to the reaction mixture. The sonication was continued for an additional 30 min and the reaction mixture was then filtered. The filtrate was extracted with CH_2Cl_2 (3×70 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane: ethyl acetate, 2:1) to give diene **5a** (238 mg, 39%) and **5b** (260 mg, 43%) as colourless oil; **5a**: R_f (50% EtOAc/hexane) 0.40; $[\alpha]_D^{25}$ +111 (*c* 0.05, $CHCl_3$); FTIR (neat), ν_{max}, cm^{-1}: 3431 br, (N–H, OH), 2981 (C–H), 1690 (C=O), 1507 (C=C); ^1H NMR (400 MHz, $CDCl_3$) δ: 6.23 (d, *J*=1.5 Hz, 1H, H-1), 5.85 (ddd, *J*=17.4, 10.5, 5.2 Hz, 1H, H-7), 5.74 (s, 1H, H-1), 5.22 (dt, *J*=17.4, 1.3 Hz, 1H, H-8), 5.16 (dt, *J*=10.5, 1.3 Hz, 1H, H-8), 4.47 (br, 1H, H-6), 4.17 (q, *J*=7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.52 (br, 1H, H-4), 3.35 (dd, *J*=8.8, 2.0 Hz, 1H, H-5), 2.74 (dd, *J*=14.5, 3.0 Hz, 1H, H-3), 2.45 (dd, *J*=14.5, 7.6 Hz, 1H, H-3), 1.39 (s, 9H, $C(CH_3)_3$), 1.25 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.3 (C=O), 157.0 (C=O), 136.7 (C=C), 136.3 (C-2), 128.2 (C=C), 115.9 (C=C), 79.9 ($C(CH_3)_3$), 75.7 (C-5), 69.9 (C-4), 60.9 ($CO_2CH_2CH_3$), 53.2 (C-6), 35.0 (C-3), 28.1 ($C(CH_3)_3$), 13.9 ($CO_2CH_2CH_3$); HRMS (ESI-TOF) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{27}NNaO_6$: 352.1731, found: 352.1742; **5b**: R_f (50% EtOAc/hexane) 0.31; $[\alpha]_D^{26}$ +8.3 (*c* 0.39, $CHCl_3$); FTIR (neat), ν_{max}, cm^{-1}: 3403 br, (N–H, OH), 2980 (C–H), 1701 (C=O), 1522 (C=C); ^1H NMR (400 MHz, $CDCl_3$) δ: 6.21 (d, *J*=1.4 Hz, 1H, H-1), 5.79 (ddd, *J*=17.1, 6.5, 5.9 Hz, 1H, H-7), 5.69 (d, *J*=0.9 Hz, 1H, H-1), 5.22 (dt, *J*=17.1, 1.2 Hz, 1H, H-8), 5.15 (dt, *J*=10.4, 1.1H, 1H, H-8), 4.23 (br, 1H, H-6), 4.17 (qd, *J*=7.1, 1.1 Hz, 2H, $CO_2CH_2CH_3$), 3.72 (td, *J*=8.6, 4.8 Hz, 1H, H-4), 3.39 (t, *J*=4.8 Hz, 1H, H-5), 2.59 (dd, *J*=14.2, 2.6 Hz, 1H, H-3), 2.47 (dd, *J*=14.2, 8.6 Hz, 1H, H-3), 1.39 (s, 9H, $C(CH_3)_3$), 1.29 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.9 (C=O), 156.1 (C=O), 136.9 (C=C), 136.3(C-2), 128.0 (C=C), 116.2 (C=C), 79.6 ($C(CH_3)_3$), 75.4 (C-5), 71.6 (C-4), 70.6 (C-6), 61.0 ($CO_2CH_2CH_3$), 54.5, (C-6), 36.3 (C-3), 28.2 ($C(CH_3)_3$), 14.0 ($CO_2CH_2CH_3$); HRMS (ESI^+) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{27}NNaO_6$ 352.1731, found 352.1742.

*4.1.5. Ethyl(4R,5R,6S)-6-[(tert-butoxycarbonyl)amino]-2-methylidene-4,5 bis[(methylsulfonyl)-oxy]oct-7-enoate (**6b**).* To a solution of **5b** (133 mg, 0.40 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added and Et_3N (0.17 mL, 1.21 mmol) followed by methanesulfonyl chloride (0.10 mL, 1.21 mmol). The reaction mixture was stirred at 0 °C for 1 h then water was added to the solution, and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane: ethyl acetate, 1:1) to give **6b** 126 mg, 65%) as colourless oil. R_f (30% EtOAc/hexane) 0.29; $[\alpha]_D^{25}$ −29.4 (*c* 0.75, $CHCl_3$); FTIR (neat), ν_{max}, cm^{-1}: 3415, (N–H), 2981 (C–H), 1709 (C=O), 1358, 1336 1175(SO_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 6.35 (s, 1H, H-1), 5.93–5.38 (m, 1H, H-7), 5.83 (s, 1H, H-1), 5.34 (d, *J*=16.6 Hz, 1H, H-8), 5.31 (dt, *J*=10.3 H, 1H, H-8), 5.12 (td, *J*=6.9, 5.2 Hz, 1H, H-4), 4.99 (d, *J*=8.6 Hz, 1H, H-6), 4.74 (d, *J*=5.0 Hz, 1H, H-5), 4.20 (q, *J*=7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.12 (s, 3H, SO_2CH_3), 3.04 (s, 3H, SO_2CH_3), 2.92 (dd, *J*=14.5, 5.2 Hz, 1H, H-3), 2.78 (dd, *J*=14.5, 6.9 Hz, 1H, H-3), 1.43 (s, 9H, $C(CH_3)_3$), 1.28 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.3 (C=O), 155.0 (C=O), 134.3 (C-2), 134.1 (C=C), 130.5 (C=C), 118.2 (C=C), 81.2 ($C(CH_3)_3$), 80.4 (C-5), 76.8 (C-4), 61.2 ($CO_2CH_2CH_3$), 52.4 (C-6), 39.1 (SO_2CH_3), 38.8 (SO_2CH_3), 34.4 (C-3), 28.2 ($C(CH_3)_3$), 14.0 ($CO_2CH_2CH_3$); HRMS (ESI^+) *m/z* $[M+H]^+$, calcd for $C_{18}H_{32}NO_{10}S_2$: 486.1462, found: 486.1461.

*4.1.6. Ethyl (4S,5R,6S)-6-[(tert-butoxycarbonyl)amino]-2-methylidene-4,5-bis[(methylsulfonyl) oxy]oct-7-enoate (**6a**).* To a solution of **5a** (240 mg, 0.73 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added and Et_3N (0.30 mL, 2.19 mmol) followed by methanesulfonyl chloride (0.20 mL, 2.19 mmol). The reaction mixture was stirred at 0 °C for 1 h then water was added to the solution, and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane: ethyl acetate, 1:1) to give **6a** (300 mg, 60%) as a colourless oil. R_f (30% EtOAc/hexane) 0.30; $[\alpha]_D^{25}$ +38.2 (*c* 0.21, $CHCl_3$); FTIR (neat), ν_{max}, cm^{-1}: 3432, (N–H), 2989 (C–H), 1701, 1646 (C=O), 1355, 1177(SO_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 6.33 (d, *J*=0.9 Hz, 1H, H-1), 5.86 (ddd, *J*=17.2, 10.4, 6.3 Hz, 1H, H-7), 5.77 (s, 1H, H-1), 5.42 (d, *J*=17.2 Hz, 1H, H-8), 5.35 (dt, *J*=10.4, 1.1 Hz, 1H, H-8), 5.13 (ddd, *J*=9.8, 3.2, 2.5 Hz, 1H, H-4), 5.01 (d, *J*=9.4 Hz, 1H, NH), 4.89 (dd, *J*=7.0, 2.2 Hz, 1H, H-6), 4.55 (br, 1H, H-5), 4.17 (qd, *J*=7.2, 1.7 Hz, 2H, $CO_2CH_2CH_3$), 3.13 (s, 3H, SO_2CH_3), 2.98 (s, 3H, SO_2CH_3), 2.87 (dd, *J*=14.3, 3.2 Hz, 1H, H-3), 2.71 (dd, *J*=14.3, 10.1 Hz, 1H, H-3), 1.43 (s, 9H, $C(CH_3)_3$), 1.29 (t, *J*=7.2 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.1 (C=O), 155.0 (C=O), 134.5 (C-2), 133.0 (C=C), 130.0 (C=C), 119.3 (C=C), 81.5 ($C(CH_3)_3$), 80.2 (C-5), 78.4 (C-4), 61.2 ($CO_2CH_2CH_3$), 52.4(C-6), 38.9 (SO_2CH_3), 38.5 (SO_2CH_3), 32.6 (C-3), 28.2 ($C(CH_3)_3$), 14.1 ($CO_2CH_2CH_3$); HRMS (ESI^+) *m/z* $[M+Na]^+$, calcd for $C_{18}H_{31}NNaO_{10}S_2$: 508.1282, found: 508.1283.

*4.1.7. tert-Butyl(2S,3S)-2-ethenyl-3-{(1R)-3-(ethoxycarbonyl)-1-[(methylsulfonyl)oxy]but-3-en1-yl}aziridine-1-carboxylate (**7b**).* To a solution of **6b** (198 mg, 0.41 mmol) in a mixed solvent of CH_2Cl_2 (40 mL) and DMSO (5.5 mL) was added sodium hydride (60% in oil) (33 mg, 0.82 mmol). The reaction mixture was stirred at room temperature for 1 h, then water was added, and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash

column chromatography (silica gel, hexane: ethyl acetate, 4:1) to give **7b** (70 mg, 44%) as a colourless oil. $[\alpha]_D^{25}$ +20.8 (*c* 0.31, $CHCl_3$). [lit. $[\alpha]_D^{20}$ +25.1 (*c* 1.33, $CHCl_3$)[15]]; FTIR (neat), ν_{max}, cm^{-1}: 3422, (N–H), 2920 (C–H), 1706 (C=O), 1366, 1175 (SO_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 6.33 (d, *J*=1.2 Hz, 1H, H-1), 5.84 (ddd, *J*=16.9, 10.4, 5.9 Hz, 1H, H-7), 5.78 (d, *J*=0.9 Hz, 1H, H-1), 5.39 (ddd, *J*=17.0, 1.5, 1.1 Hz, 1H, H-8), 5.49 (ddd, *J*=10.4, 1.5, 0.7 Hz, 1H, H-8), 4.66 (ddd, *J*=9.4, 7.9, 3.6 Hz, 1H, H-4), 4.26–4.17 (m, 2H, $CO_2CH_2CH_3$), 3.14 (tt, *J*=5.8, 0.8 Hz, 1H, H-6), 3.04 (ddd, *J*=14.7, 3.7, 0.9 Hz, 1H, H-3), 2.93 (s, 3H, SO_2CH_3), 2.76 (dd, *J*=7.9, 6.0 Hz, 1H, H-5), 2.77 (ddd, *J*=14.7, 9.5, 0.6 Hz, 1H, H-3), 1.47 (s, 9H, $C(CH_3)_3$), 1.30 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.3 (C=O), 161.2 (C=O), 135.1 (C-2), 131.1 (C=C), 129.2 (C=C), 120.3 (C=C), 81.0 ($C(CH_3)_3$), 76.6 (C-4), 61.0 ($CO_2CH_2CH_3$), 44.6 (C-5), 43.6 (C-6), 38.6 (SO_2CH_3), 36.8 (C-3), 27.9 ($C(CH_3)_3$), 14.2 ($CO_2CH_2CH_3$); HRMS (ESI^+) *m/z* $[M+Na]^+$, calcd for $C_{17}H_{27}NNaO_7S$: 412.1400, found: 412.1419.

*4.1.8. tert-Butyl (2S,3R)-2-ethenyl-3-{(1S)-3-(ethoxycarbonyl)-1-[(methylsulfonyl) oxy]but-3-en-1-yl}aziridine-1-carboxylate (**7a**).* To a solution of **6a** (208 mg, 0.43 mmol) in a mixed solvent of CH_2Cl_2 (43 mL) and DMSO (5.70 mL) was added sodium hydride (60% in oil) (35 mg, 0.86 mmol). The reaction mixture was stirred at room temperature for 1 h then water was added, and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane: ethyl acetate, 4:1) to give **7a** (148 mg, 88%) as a colourless oil. R_f (30% EtOAc/hexane) 0.59; $[\alpha]_D^{25}$ +28.7 (c 1.03, $CHCl_3$); FTIR (neat), ν_{max}, cm^{-1}: 3438, (N–H), 2980 (C–H), 1720 (C=O), 1366, 1176 (SO_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 6.33 (d, *J*=1.1 Hz, 1H, H-1), 5.75 (d, *J*=0.9 Hz, 1H, H-1), 5.69 (ddd, *J*=17.0, 10.3, 6.6 Hz, 1H, H-7), 5.50 (dt, *J*=17.0, 0.9 Hz, 1H, H-8), 5.37 (d, *J*=10.3 Hz, 1H, H-8), 4.52 (td, *J*=8.9, 4.5 Hz, 1H, H-4), 4.19 (q, *J*=7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.14–3.11 (m, 1H, H-6), 3.12 (s, 3H, SO_2CH_3), 2.73 (dd, *J*=9.3, 6.6 Hz, 1H, H-5), 2.71 (ddd, *J*=13.8, 4.5, 0.9 Hz, 1H, H-3), 2.60 (dd, *J*=14.0, 8.6 Hz, 1H, H-3), 1.43 (s, 9H, $C(CH_3)_3$), 1.28 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.1 (C=O), 160.9 (C=O), 134.1 (C-2), 130.8 (C=C), 129.9 (C=C), 121.0 (C=C), 82.2 ($C(CH_3)_3$), 80.8 (C-4), 60.9 ($CO_2CH_2CH_3$) 45.1 (C-5), 42.9 (C-6), 39.0 (SO_2CH_3), 36.1 (C-3), 27.8 ($C(CH_3)_3$), 14.1 ($CO_2CH_2CH_3$); HRMS (ESI^+) *m/z* $[M+Na]^+$, calcd for $C_{17}H_{27}NNaO_7S$: 412.1400, found: 412.1407.

*4.1.9. 7-tert-Butyl 3-ethyl (1S,5R,6S)-5-[(methylsulfonyl)oxy]-7-azabicyclo[4.1.0] hept-2-ene-3,7-dicarboxylate (**8b**).* To a solution of **7b** (30 mg, 0.06 mmol) in dry CH_2Cl_2 (6 mL) under nitrogen atmosphere was added Hoveyda-Grubbs catalyst (second generation) (4 mg, 0.006 mmol). The reaction mixture was stirred at 40 °C for 16 h, then the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane: ethyl acetate, 4:1) to give **8b** (11 mg, 49%) as a colourless oil: $[\alpha]_D^{25}$ −10.2 (c 0.25, $CHCl_3$). (lit. $[\alpha]_D^{22}$ −8.29 (*c* 1.62, $CHCl_3$);[15] FTIR (neat), ν_{max}, cm^{-1}: 3394, (N–H), 2923 (C–H), 1716 (C=O), 1367, 1175 (SO_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.10 (dd, *J*=4.6, 3.4 Hz, 1H, H-2), 5.00 (ddd, *J*=10.1, 6.6, 2.3 Hz, 1H, H-5), 4.20 (dq, *J*=7.1, 0.7 Hz, 2H, $CO_2CH_2CH_3$), 3.37 (dt, *J*=6.6, 2.0 Hz, 1H, H-4), 3.18 (s, 3H, SO_2CH_3), 3.11 (dd, *J*=6.3, 4.6 Hz, 1H, H-3), 3.05 (ddd, *J*=16.4, 6.6, 1.8 Hz, 1H, H-6), 2.40 (ddd, *J*=16.4, 10.2, 3.4 Hz, 1H, H-6), 1.46 (s, 9H, $C(CH_3)_3$), 1.29 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.9 (C=O), 160.5 (C=O), 132.6 (C-1), 131.3 (C-2), 82.6 ($C(CH_3)_3$), 75.2 (C-5), 61.2 ($CO_2CH_2CH_3$), 40.8 (C-4), 39.4 (SO_2CH_3), 36.1 (C-3), 27.8 ($C(CH_3)_3$), 26.6 (C-6), 14.2 ($CO_2CH_2CH_3$); HRMS(ESI^+) *m/z* $[M+Na]^+$ calcd for $C_{15}H_{23}NNaO_7S$: 384.1087, found: 384.1087.

*4.1.10. 7-tert-Butyl 3-ethyl (1S,5S,6S)-5-[(methylsulfonyl)-oxy]-7-azabicyclo[4.1.0]hept-2-ene-3,7-dicarboxylate (**8a**).* To a solution of **7a** (127 mg, 0.262 mmol) in dry CH_2Cl_2 (26 mL) was added Hoveyda-Grubbs catalyst (second generation) (17 mg, 0.026 mmol). The reaction mixture was stirred at 40 °C for 16 h, then the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane: ethyl acetate, 4:1) to give **8a** (56 mg, 60%) as a colourless oil: R_f (30% EtOAc/hexane) 0.10; $[\alpha]_D^{25}$ +52.2 (*c* 0.17, $CHCl_3$); FTIR (neat), ν_{max}, cm^{-1}: 3369, (N–H), 2923 (C–H), 1716 (C=O), 1364, 1176 (SO_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.19 (dd, *J*=4.7, 3.3 Hz, 1H, H-1), 5.46 (quint, *J*=2.4 Hz, 1H, H-5), 4.19 (dq, *J*=7.1, 1.0 Hz, 2H, $CO_2CH_2CH_3$), 3.28 (dt, *J*=5.8, 2.3 Hz, 1H, H-4), 3.10 (dd, *J*=5.6, 4.9 Hz, 1H, H-3), 3.02 (dt, *J*=17.9, 2.1 Hz, 1H, H-6), 3.01 (s, 3H, SO_2CH_3), 2.39 (ddd, *J*=17.9, 4.5, 3.3 Hz, 1H, H-6), 1.43 (s, 9H, $C(CH_3)_3$), 1.27 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.5 (C=O), 160.1 (C=O), 133.4 (C-2), 128.8 (C-1), 82.7 ($C(CH_3)_3$), 72.2 (C-5), 61.1 ($CO_2CH_2CH_3$), 40.1 (C-4), 38.7 (SO_2CH_3), 33.3 (C-3), 27.8 ($C(CH_3)_3$), 26.9 (C-6), 14.2 ($CO_2CH_2CH_3$); HRMS (ESI^+) *m/z* $[M+Na]^+$ calcd for $C_{15}H_{23}NNaO_7S$: 384.1087, found: 384.1103.

*4.1.11. Ethyl (3R,4R,5R)-4—(tert-butoxycarbonyl)-5—(methane-sulfonyloxy)-3-(1-ethylpropoxy)-cyclohex-1-ene-1-carboxylate (**9b**).* To a solution of **8b** (17 mg, 0.05 mmol) in 3-pentanol (1.2 mL) at −10 °C was added $BF_3{\cdot}OEt_2$ (9 μL, 0.07 mmol) in 3-pentanol (0.5 mL). The reaction mixture was stirred for 2 h at −10 °C then the mixture was diluted with EtOAc (10 mL) and 20% aq K_2CO_3 (5 mL). The organic phase was separated and washed with water (5 mL) and brine (5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane: ethyl acetate, 4:1) to give white solid, which was recrystallized from hexane–dichloromethane to give **9b** as a white solid (20 mg, 95%), mp 160–161 °C (lit. Mp 157–158.5 °C).[15] $[\alpha]_D^{25}$ −166.7 (c 0.07, $CHCl_3$). [lit. $[\alpha]_D^{19}$ −75.4 (c 1.52, $CHCl_3$)[15]]; FTIR (KBr), ν_{max}, cm^{-1}: 3364, (N–H), 2929 (C–H), 1721, 1682 (C=O), 1345, 1172 (SO_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 6.85 (dt, *J*=2.9, 1.5 Hz, 1H, H-2), 5.22 (br s,1H, H-5), 4.76 (d, *J*=7.4 Hz, 1H, NH), 4.22 (q, *J*=7.1 Hz, 2H, $CO_2CH_2CH_3$), 4.05–4.00 (m, 1H, H-4), 4.00–3.94 (m, 1H, H-3), 3.40 (quint, *J*=5.8 Hz, 1H, H-7), 3.04 (s, 3H, SO_2CH_3), 2.86–2.68 (m, 2H, H-6), 1.59–1.48 (m, 4H, 2×(CH_2CH_3)), 1.44 (s, 9H, $C(CH_3)_3$), 1.29 (t, *J*=7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.92 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 0.91 (t, *J*=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.6 (C=O), 155.4 (C=O), 136.5 (C-2), 127.8 (C-1), 82.4 ($C(CH_3)_3$), 80.2 (C-3), 72.8 (C-5), 61.1 ($CO_2CH_2CH_3$), 52.8 (C-4), 38.4 (SO_2CH_3), 29.3 (CH_2CH_3), 28.3 (CH_2CH_3), 26.3 ($C(CH_3)_3$), 26.0 (C-6), 14.1 ($CO_2CH_2CH_3$), 9.6 (CH_2CH_3), 9.3 (CH_2CH_3); HRMS (ESI^+) *m/z* $[M+Na]^+$, calcd for $C_{20}H_{35}NNaO_8S$: 472.1976, found: 472.1997.

*4.1.12. Ethyl(3R,4S,5S)-4-[(tert-butoxycarbonyl)amino]-5-[(methyl sulfonyl)oxy]-3-(1-ethylpropoxy)cyclohex-1-ene-1-carboxylate (**9a**).* To a solution of **8a** (45 mg, 0.124 mmol) in 3-pentanol (4 mL) at −10 °C was added $BF_3{\cdot}OEt_2$ (24 μL, 0.19 mmol) in 3-pentanol (1.5 mL). The reaction mixture was stirred for 2 h at −10 °C then the mixture was diluted with EtOAc (10 mL) and 20% aq K_2CO_3 (10 mL). The organic phase was separated and washed with water (5 mL) and brine (5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane: ethyl acetate, 4:1) to give **9a** (51 mg, 91%) as a white solid mp 117–119 °C, R_f (30% EtOAc/hexane) 0.24; $[\alpha]_D^{25}$ +140.5 (*c* 0.05, $CHCl_3$); FTIR (KBr), ν_{max}, cm^{-1}: 3344, (N–H), 2920 (C–H), 1719, 1683 (C=O), 1363, 1179 (SO_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 6.75 (t, *J*=1.8 Hz, 1H, H-2), 5.07–4.97 (m,1H, NH), 4.93 (d, *J*=7.7 Hz, 1H, H-5), 4.39 (d, *J*=7.4 Hz, 1H, H-4), 4.19 (q, *J*=7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.54–3.24 (m, 1H, H-3), 3.29–3.21 (m, 1H), 3.13–3.04 (m, 1H), 3.03 (s, 3H, SO_2CH_3), 2.53 (ddt, *J*=17.5, 9.8, 3.1 Hz, 2H, H-6), 1.53–1.45 (m, 4H, 2×(CH_2CH_3)), 1.41 (s, 9H, $C(CH_3)_3$), 1.26 (t,

J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.89 (t, J=7.3 Hz, 3H, CH_2CH_3), 0.88 (t, J=7.3 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.5 (C=O), 155.4 (C=O), 138.0 (C-2), 127.2 (C-1), 82.6 ($C(CH_3)_3$), 76.1 (C-3), 74.0 (C-5), 61.1 ($CO_2CH_2CH_3$), 56.6 (C-4), 38.3 (SO_2CH_3), 31.8 (CH_2CH_3), 28.3 (CH_2CH_3), 26.3 ($C(CH_3)_3$), 25.7 (C-6), 14.2 ($CO_2CH_2CH_3$), 9.5 (CH_2CH_3), 9.3 (CH_2CH_3); HRMS (ESI$^+$) m/z [M+H]$^+$, calcd for $C_{20}H_{36}NO_8S$: 450.2156, found: 450.2156.

*4.1.13. 7-tert-Butyl 3-ethyl (1R,5R,6R)-5-(1-ethylpropoxy)-7-azabicyclo[4.1.0]hept-3-ene-3,7-dicarboxylate (**10**).* To a solution of **9a** (44 mg, 0.098 mmol) in a mixed solvent of CH_2Cl_2 (6 mL) and DMSO (0.2 mL) was added sodium hydride (60% in oil) (8 mg, 0.196 mmol). The reaction mixture was stirred at room temperature for 30 min then water was added, and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane: ethyl acetate, 8:1) to give **10** (30 mg, 87%) as a colourless oil. R_f (30% EtOAc/hexane) 0.48; $[\alpha]_D^{25}$ −28.0 (c 0.43, $CHCl_3$); FTIR (neat), ν_{max}, cm^{-1}: 3375, (N–H), 2929 (C–H), 1719 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.78 (br s, 1H, H-2), 4.39 (br s,1H, NH), 4.18 (q, J=7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.42 (quint, J=5.9 Hz, 1H, H-7), 2.94 (br d, J=19.2 Hz, 1H, H-4), 2.88–2.78 (m, 2H, H-6), 2.60 (br d, J=19.2 Hz, 1H, H-5), 1.61–1.48 (m, 4H, 2×(CH_2CH_3)), 1.43 (s, 9H, $C(CH_3)_3$), 1.26 (t, J=7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.96 (t, J=7.2 Hz, 3H, CH_2CH_3), 0.89 (t, J=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.5 (C=O), 161.6 (C=O), 133.1 (C-2), 127.8 (C-1), 82.5 ($C(CH_3)_3$), 81.4 (C-7), 68.6 (C-3), 60.8 ($CO_2CH_2CH_3$), 37.5 (C-4), 35.8 (C-5), 27.8 (2×(CH_2CH_3)), 26.6 ($C(CH_3)_3$), 23.5 (C-6), 14.2 ($CO_2CH_2CH_3$), 9.9 (CH_2CH_3), 9.5 (CH_2CH_3); HRMS (ESI$^+$) m/z [M+Na]$^+$, calcd for $C_{19}H_{31}NNaO_5$: 376.2094, found: 376.2100.

*4.1.14. Ethyl (3R,4R,5S)-5-azido-4-[(tert-butoxycarbonyl)amino]-3-(1-ethylpropoxy)cyclohex-1-ene -1-carboxylate (**11**)*

Procedure 1. To a solution of **10** (5 mg, 0.014 mmol) in anhydrous DMF (2 mL) was added sodium azide (16 mg, 0.21 mmol) and ammonium chloride (3 mg, 0.05 mmol). The reaction mixture was heated and stirred at 90 °C for 6 h. Then the reaction was cooled down to room temperature, EtOAc (10 mL) and water (5 mL) were added. The organic phase was separated and washed with water (5 mL). The organic layers was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane: ethyl acetate, 8:1) to give **11** (5 mg, 89%) as a white solid, mp 127–128 °C; R_f (30% EtOAc/hexane) 0.63; $[\alpha]_D^{25}$ −35.0 (c 0.86, $CHCl_3$); FTIR (KBr), ν_{max}, cm^{-1}: 3341, (N–H), 2978 (C–H), 2103(N=N=N), 1719, 1687 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.77 (d, J=2.2 Hz, 1H, H-2), 4.91 (br s,1H, H-3), 4.48 (br s, 1H, H-4), 4.20 (q, J=7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.34 (quint, J=5.7 Hz, 1H, H-7), 3.12 (br s, 1H, H-5), 2.83 (dd, J=17.7, 5.7 Hz, 1H, H-6), 2.20 (br s, 1H, H-6), 1.56–1.47 (m, 4H, 2×(CH_2CH_3)), 1.45 (s, 9H, $C(CH_3)_3$), 1.26 (t, J=7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.91 (t, J=7.3 Hz, 6H, 2×(CH_2CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.7 (C=O), 155.2 (C=O), 138.1 (C-2), 127.9 (C-1), 82.1 (C-7), 79.6 ($C(CH_3)_3$), 73.5 (C-3), 60.8 ($CO_2CH_2CH_3$), 58.1 (C-5), 57.5 (C-4), 30.6 (C-6), 28.2 ($C(CH_3)_3$), 26.1 (CH_2CH_3), 25.5 (CH_2CH_3), 14.0 ($CO_2CH_2CH_3$), 9.5 (CH_2CH_3), 9.2 (CH_2CH_3); HRMS (ESI$^+$) m/z [M+Na]$^+$, calcd for $C_{19}H_{32}N_4O_5Na$: 419.2265, found: 419.2276.

Procedure 2. To a solution of **9b** (12 mg, 0.026 mmol) in a mixed solvent of DMF (2 mL) and water (0.4 mL) was added sodium azide (14 mg, 0.214 mmol). The reaction mixture was heated and stirred at 90 °C for 8 h. Then the reaction mixture was cooled down to room temperature, EtOAc (10 mL) and water (5 mL) were added. The organic phase was separated and washed with water (5 mL). The organic layers was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane: ethyl acetate, 8:1) to give **11** (7 mg, 68%) as a white solid.

*4.1.15. Ethyl (3R,4R,5S)-4-(acetylamino)-5-azido-3-(1-ethylpropoxy) cyclohex-1-ene-1-carboxylate (**12**).* To a solution of **11** (82 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added trifluoro acetic acid (0.32 mL, 4.14 mmol). The reaction mixture was warmed to room temperature and stirred for 4 h. Saturated aq $NaHCO_3$ was added to neutralize the mixture and then extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in pyridine (0.23 mL), acetic anhydride was then added. The reaction mixture was stirred at room temperature for 1 h and quenched with MeOH (0.23 mL). The trace Ac_2O was removed by coevaporattion with toluene (10 mL). The crude product was purified by flash column chromatography (silica gel, hexane:ethyl acetate, 2:1) to give **12** (55 mg, 78%), which was recrystallized from hexane/CH_2Cl_2 to give a colourless needle, mp 137–139 °C (lit. Mp 138–139 °C);[14] $[\alpha]_D^{23}$ −33.1 (c 0.40, $CHCl_3$) [lit. $[\alpha]_D^{21}$ −44.7 (c 0.83, $CHCl_3$)];[15] FTIR (KBr), ν_{max}, cm^{-1}: 3278, (N–H), 2967 (C–H), 2101(N=N=N), 1719, 1656 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.76 (d, J=2.3 Hz, 1H, H-2), 6.28 (d, J=6.9 Hz, 1H, NH), 4.50 (d, J=8.8 Hz, 1H, H-4), 4.19 (q, J=7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.19–4.13 (m, 1H, H-3), 3.40 (td, J=10.4, 8.1 Hz, 1H, H-5), 3.31 (quint, J=5.7 Hz, 1H, H-7), 2.83 (dd, J=17.6, 5.7 Hz, 1H, H-6), 2.21 (ddt, J=17.6, 10.4, 2.9 Hz, 1H, H-6), 2.01 (s, 3H, C(O)CH_3), 1.55–1.43 (m, 4H, CH_2CH_3), 1.27 (t, J=7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.92–0.84 (m, 6H, 2×(CH_2CH_3)); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.2 (C=O), 165.7 (C=O), 138.0 (C-2), 128.0 (C-1), 82.0 (C-7), 73.7 (C-3), 61.0 ($CO_2CH_2CH_3$), 58.0 (2) (C-4, C-5), 30.4 (C-6), 26.2 (CH_2), 25.5 (CH_2), 23.4 (C(O)CH_3), 14.1 ($CO_2CH_2CH_3$), 9.5 (CH_3), 9.2 (CH_3); HRMS (ESI$^+$) m/z: [M+Na]$^+$ calcd for $C_{16}H_{26}N_4O_4Na$: 361.1854, found: 361.1858.

*4.1.16. Ethyl (3R,4R,5S)-4-(acetylamino)-5-amino-3-(1-ethylpropoxy) cyclohex-1-ene-1-carboxylate (**13**).* To a solution of **12** (55 mg) in EtOH (10 mL) was treated with Lindlar catalyst (55 mg) and the resulting suspension was stirred under atmosphere of hydrogen gas for 10 h. The mixture was then filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2:MeOH, 4:1) to give **13** (45 mg, 88%) as a colourless oil, $[\alpha]_D^{23}$ −41.7 (c 0.92, CH_2Cl_2) [lit. $[\alpha]_D^{25}$ −55.8 (c 2.05, $CHCl_3$)];[16] FTIR (neat), ν_{max}, cm^{-1}: 3412, (N–H), 2966 (C–H), 1714, 1651 (C=O), 1559 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) 6.74 (s, 1H, H-2), 6.69 (d, J=8.4 Hz, 1H, NH), 4.22–4.12 (m, 3H, H-3, $CO_2CH_2CH_3$), 3.65 (td, J=10.0, 8.9 Hz, 1H, H-4), 3.39–3.24 (m, 2H, H-5, H-7), 2.78 (dd, J=18.2, 5.0 Hz, 1H, H-6), 2.28–2.16 (m, 1H, H-6), 2.01 (s, 3H, Ac),1.53–1.42 (m, 4H, CH_2CH_3), 1.26 (t, J=7.0 Hz, 3H, $CO_2CH_2CH_3$), 0.87 (t, J=7.2 Hz, 3H, CH_3), 0.85 (t, J=7.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.8 (C=O), 166.1 (C=O), 138.0 (C-2), 128.8 (C-1), 81.9 (C-7), 74.9 (C-3), 60.9 ($CO_2CH_2CH_3$), 57.2 (C-4), 49.2 (C-5), 32.4 (C-6), 26.1 (CH_2), 25.6 (CH_2), 23.6 (C(O)CH_3), 14.1 ($CO_2CH_2CH_3$), 9.5 (CH_3), 9.2 (CH_3); HRMS (ESI$^+$) m/z [M+H]$^+$ calcd for $C_{16}H_{29}N_2O_4$: 313.2122, found: 313.2121.

*4.1.17. Oseltamivir phosphate (**1**).* To a solution of **13** (10 mg) in ethanol (1 mL) and added a hot (60 °C) solution of phosphoric acid (3 mg) in ethanol (1 mL). The reaction mixture was heated and stirred at 60 °C for 3 h. After cooling to 0 °C, the precipitates were collected by filtration and rinsed with cold acetone (2×1 mL) to afford oseltamivir phosphate (**1**) (9 mg, 70%) as a white crystal. Mp 203–204 °C (lit. Mp 202–203 °C) [15]; $[\alpha]_D^{23}$ −31.7 (c 0.22, H_2O) [lit. $[\alpha]_D^{29}$ −30.8 (c 0.7, H_2O)];[17] FTIR (KBr), ν_{max}, cm^{-1}: 3422, (N–H),

3233 (NH_3^+) 2874 (C–H), 1719, 1629 (C=O), 1553 (C=C), 1355, 1177; ^{1}H NMR (400 MHz, D_2O) δ: 6.88 (s,1H, *H-2*), 4.35 (d, J=8.8 Hz, 1H, H-3), 4.28 (q, J=7.3 Hz, 2H, OCH_2), 4.08 (dd, J=11.7, 9.2 Hz, 1H, H-4), 3.62 (td, J=10.5, 5.7 Hz, 1H, H-5), 3.58 (quint, J=7.5 Hz, 1H, CH), 2.99 (dd, J=17.5, 5.6 Hz, 1H, H-6), 2.55 (dt, J=17.5, 10.5 Hz, 1H, H-6), 2.11 (s, 3H, Ac), 1.65–1.45 (m, 4H, CH_2), 1.31 (t, 3H, J=7.3 Hz, CH_3), 0.91 (t, 3H, J=7.4 Hz, CH_3), 0.87 (t, 3H, J=7.4 Hz, CH_3); ^{13}C NMR (75 MHz, D_2O) δ: 175.2 (C=O), 167.4 (C=O), 137.9 (2), 127.6 (1), 84.3 (7), 75.0 (OCH_2), 62.3 (3), 52.6 (4), 49.1 (5), 28.1 (6), 25.4 (CH_2), 25.0 (CH_2), 22.3 (Ac), 13.2 (CH_3), 8.5 (CH_3), 8.4 (CH_3).

Acknowledgements

S.A. is a Ph.D. student under the Royal Golden Jubilee Program, the Thailand Research Fund (TRF) and PERCH-CIC. We are grateful for financial support from the TRF and Kasetsart University, through the Royal Golden Jubilee Program. Financial support from the Center of Excellence for Innovation in Chemistry (PERCH-CIC), Commission on Higher Education, Ministry of Education and Kasetsart University Research and Development Institute (KURDI) are also gratefully acknowledged.

Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for all new and important known compounds) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.02.081.

References and notes

1. Webster, R. G.; Monto, A. S. T.; Braciale, J.; Lamb, R. A. *Textbook of Influenza*; Blackwell Science: Oxford, UK, 1998; pp 219–264.
2. For information on H5N1 avian flu and H5N1 virus, visit: http://www.nature.com/avianflu/index.html. For information on H1N1 flu and H1N1 virus, visit: http://www.cdc.gov/h1n1flu/.
3. Moscona, A. *New. Engl. J. Med.* **2005**, *353*, 1363–1373.
4. Hurt, A. C.; Selleck, P.; Komadina, N.; Shaw, R.; Brown, L.; Barr, I. G. *Antivir. Res.* **2007**, *73*, 228–231.
5. Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, W. G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681–690.
6. Kim, C. U.; Lew, W.; Williams, M. A.; Wu, H.; Zhang, L.; Chen, X.; Escarpe, P. A.; Mendel, D. B.; Laver, W. G.; Stevens, R. C. *J. Med. Chem.* **1998**, *41*, 2451–2460.
7. Abbott, A. *Nature* **2005**, *435*, 407–409.
8. (a) Rohloff, J. C.; Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultzw, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998**, *63*, 4545–4550; (b) Federspiel, M.; Fisher, R.; Henning, M.; Mair, H. J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Gockel, V.; Gotzo, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Rockel-Stabler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev.* **1999**, *3*, 266–274; (c) Karpf, M.; Trussardi, R. *J. Org. Chem.* **2001**, *66*, 2044–2051; (d) Harrington, P. J.; Brown, J. D.; Foderaro, T.; Hughes, R. C. *Org. Process Res. Dev.* **2004**, *8*, 86–91.
9. For recent synthetic studies, see: (a) Magano, J. *Chem. Rev.* **2009**, *109*, 4398–4438; (b) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem.* **2009**, *121*, 1330–1333 Angew. Chem., Int. Ed. 2009, 48, 1304-1307;; (c) Nie, L.-D.; Shi, X.-X.; Ko, K. H.; Lu, W.-D. *J. Org. Chem.* **2009**, *74*, 3970–3973; (d) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Tetrahedron* **2009**, *65*, 3239–3245; (e) Weng, J.; Li, Y.-B.; Wang, R.-B.; Li, F.-Q.; Liu, C.; Chan, A. S. C.; Lu, G. *J. Org. Chem.* **2010**, *75*, 3125–3128; (f) Kamimura, A.; Nakano, T. *J.Org. Chem.* **2010**, *75*, 3133–3136; (g) Ma, J.; Zhao, Y.; Ng, S.; Zhang, J.; Zeng, J.; Than, A.; Chen, P.; Liu, X.-W. *Chem.—Eur. J.* **2010**, *16*, 4533–4540; (h) Osato, H.; Jones, I. L.; Chen, A.; Chai, C. L. L. *Org. Lett.* **2010**, *12*, 60–63; (i) Nakano, H.; Osone, K.; Takeshita, M.; Kwon, E.; Seki, C.; Matsuyama, H.; Takano, N.; Kohari, Y. *Chem. Commun.* **2010**, 4827–4829; (j) Zhu, S.; Yu, S.; Wang, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4656–4660; (k) Ko, J. S.; Keum, J. E.; Ko, S. Y. *J. Org. Chem.* **2010**, *75*, 7006–7009; (l) Ishikawa, H.; Suzuki, T.; Orita, H.; Uchimaru, T.; Hayashi, Y. *Chem.—Eur. J.* **2010**, *16*, 12616–12626; (m) Tanaka, T.; Tan, Q.; Kawakubo, H.; Hayashi, M. *J. Org. Chem.* **2011**, *76*, 5477–5479; (n) Ishikawa, H.; Bondzic, B. P.; Hayashi, Y. *Eur. J. Org. Chem.* **2011**, 6020–6031; (o) Rawat, V.; Dey, S.; Sudalai, A. *Org. Biomol. Chem.* **2012**, *10*, 3988–3990; (p) Bhowmik, S.; Batra, S. *Eur. J. Org. Chem.* **2013**, 7145–7151; (r) Nie, L.-D.; Wang, F.-F.; Ding, W.; Shi, X.-X.; Lu, X. *Tetrahedron: Asymmetry* **2013**, *24*, 638–642; (q) Alagiri, K.; Furutachi, M.; Yamatsugu, K.; Kumagai, N.; Watanabe, T.; Shibasaki, M. *J. Org. Chem.* **2013**, *78*, 4019–4026; (s) Kalashnikov, A. I.; Sysolyatin, S. V.; Sakovich, G. V.; Sonina, E. G.; Shchurova, I. A. *Russ. Chem. Bull. Int. Ed.* **2013**, *62*, 163–170.
10. Wichienukul, P.; Akkarasamiyo, S.; Kongkathip, N.; Kongkathip, B. *Tetrahedron Lett.* **2010**, *51*, 3208–3210.
11. (a) Chuanopparat, N.; Kongkathip, N.; Kongkathip, B. *Tetrahedron Lett.* **2012**, *53*, 6209–6211; (b) Chuanopparat, N.; Kongkathip, N.; Kongkathip, B. *Tetrahedron* **2012**, *68*, 6803–6809.
12. Raluy, E.; Pamies, O.; Diieguez, M. *Adv. Synth. Catal.* **2009**, *351*, 1648–1670.
13. (a) Bercier, A.; Plantier-Royon, R.; Portella, C. *Carbohydr. Res.* **2007**, *342*, 2450–2455; (b) He'non, E.; Bercier, A.; Plantier-Royon, R.; Harakat, D.; Portella, C. *J. Org. Chem.* **2007**, *72*, 2271–2278.
14. (a) Nie, L.-D.; Shi, X.-X. *Tetrahedron: Asymmetry* **2009**, *20*, 124–129; (b) Nie, L.-D.; Ding, W.; Shi, X.-X.; Quan, N.; Lu, X. *Tetrahedron: Asymmetry* **2012**, *23*, 742–747.
15. Oh, H.-S.; Kang, H.-Y. *J. Org. Chem.* **2012**, *77*, 8792–8796.
16. Mandai, T.; Oshitari, T. *Synlett* **2009**, 783–786.
17. Werner, L.; Machara, A.; Sullivan, B.; Carrera, I.; Moser, M.; Adams, D. R.; Hudlicky, T. *J. Org. Chem.* **2011**, *76*, 10050–10067.