Design and Synthesis of a Cyclopentene Scaffold Mimicking Oseltamivir as a Novel Neuraminidase Inhibitor

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The first synthesis of a cyclopentene version of oseltamivir as a novel neuraminidase inhibitor was achieved *via* the key cyclopentenone intermediate **4**, which was prepared *via syn*-elimination from ketone derivative **2**.

Key Words : Neuraminidase inhibitor, Zanamivir, Oseltamivir, Cyclopentene scaffold

Introduction

Despite extensive vaccinations, each year up to 40 million Americans develop the flu, an average of about 300,000 are hospitalized, and 20,000 to 40,000 die from influenza and its complications. Although flu vaccines are used selectively, particularly for the elderly and high-risk groups, the hypermutability of the virus is a major obstacle that limits the extensive application of vaccines to the general public.[1] Currently, new vaccines need to be formulated each year on the basis of the World Health Organization's best guess as to what antigenic determinants are likely to emerge in the next outbreak.

In 1999, the Food and Drug Administration (FDA) approved several anti-influenza neuraminidase inhibitors. Among them, Zanamivir (Relenza™)[2] and Oseltamivir (Tamiflu™)[3] can treat influenza type A and B (Figure 1). However, Zanamivir's effectiveness was demonstrated only in patients who started treatment within two days of symptom onset. Zanamivir, which is taken twice daily for five days using an inhaler,[4] appears less effective in patients who do not have an elevated temperature or severe symptoms.[5] This drug has not been shown to be effective, and may carry additional risks, in patients with severe or decompensated asthma or chronic obstructive pulmonary disease. Oseltamivir is indicated for the treatment of uncomplicated acute illness due to influenza infections in adults who have been symptomatic for no more than two days. The recommended oral dose of Oseltamivir is 75 mg twice daily for five days.[6] Oseltamivir is an orally available anti-influenza drug, which not only makes it convenient, but allows the drug to be distributed throughout the body and reach all key sites of infection, including the upper and lower respiratory tracts. In clinical studies, Oseltamivir showed no interference with the antibody response to influenza infection.

Therefore, as a part of our ongoing search for novel antiviral agents, we designed a novel cyclopentene analogue of Oseltamivir (Figure 1). The structure of the target molecule is a prototype compound with a five-membered ring structure mimicking Oseltamivir. A methylene spacer between C_3 and the hydroxy group is essential to keep the optimum distance for hydrogen bonding.[7] The hydroxy group can be substituted by other hydrogen bond acceptors such as NH_2, guanidine, and urea.[8] Various substituents can be tried at C_5, such as bulky lipophilic groups.[9]

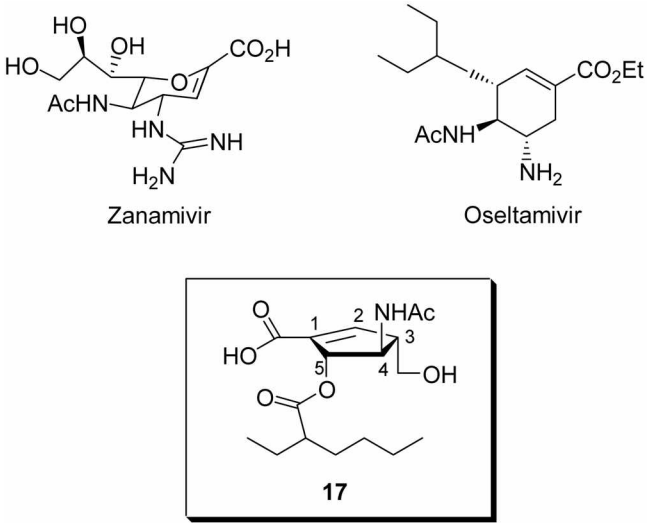
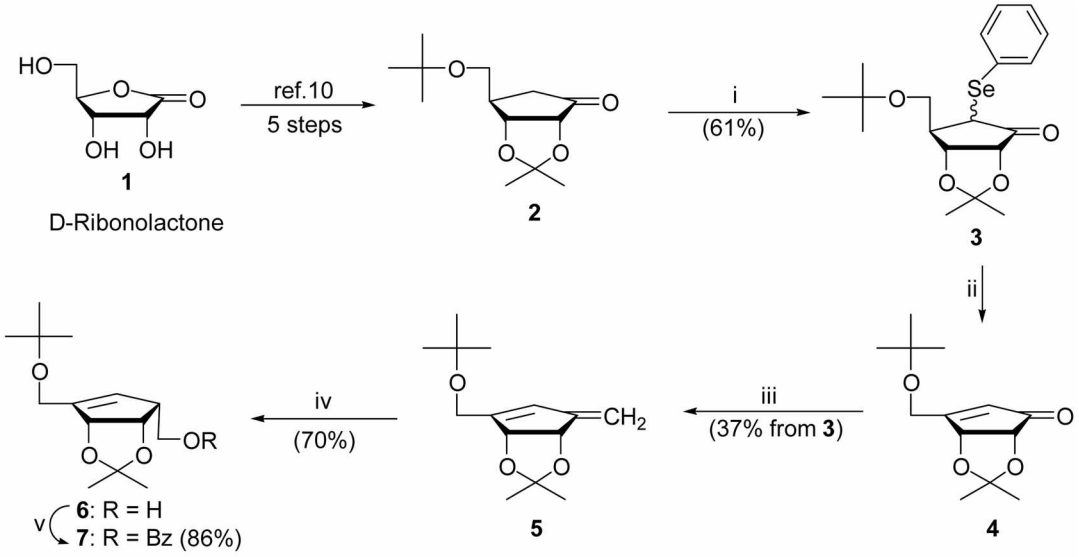


Figure 1. Structures of potent nuraminidase inhibitors and target molecule.

Results and Discussion

Compound **2**, which is readily synthesized from the commercially available D-ribonolactone **1** using a previously reported method,[10] was used to produce the target molecule. α,β-Unsaturated cyclopentenone **4** could readily be obtained from the ketone derivative **2** *via syn*-elimination using LDA/PhSeBr and oxidation. Owing to its instability, the enone **4** was passed through a short silica gel column and used in the next reaction without further purification, and only a small amount was purified for characterization purposes. *Exo*-olefin analogue **5** was synthesized from enone **4** by a Wittig-olefination procedure by the condition of $CH_3(Ph)_3PBr$/*n*-BuLi.[11] Regio- and stereoselective hydroboration of compound **5** with 9-BBN and oxidation[12] with H_2O_2 of corresponding organoborane gave the desired alcohol derivative **6** in 70% yield. Protection of the hydroxyl functional group of **6** with BzCl in py/CH_2Cl_2 at 0 °C provided **7** in 86% yield (Scheme 1).

Simultaneous deprotection of the *t*-butyl and isoprop-



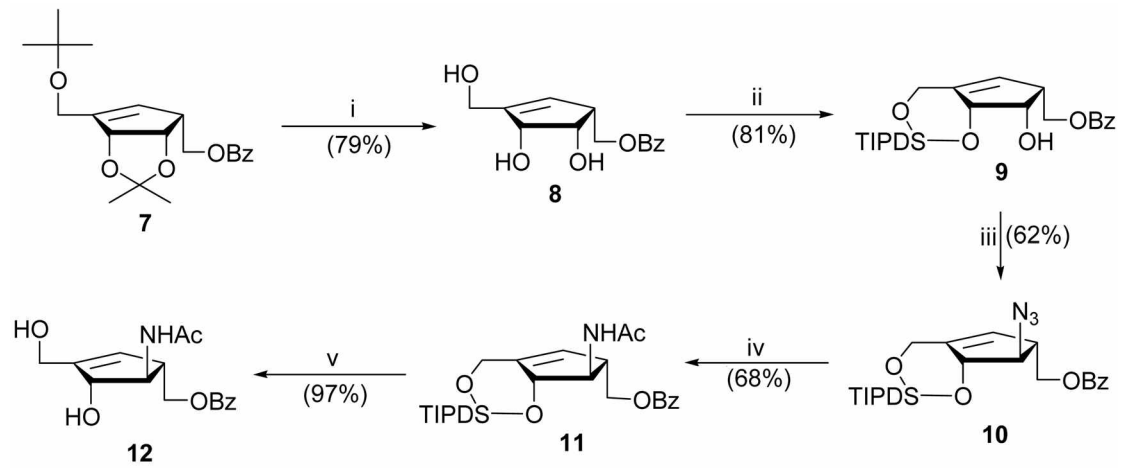
Scheme 1. Synthesis of benzoyl intermediate **7**. Reagents: i) PhSeBr, LDA; ii) H_2O_2, Py; iii) $CH_3(Ph)_3PBr$, *n*-BuLi; iv) (a) 9-BBN; (b) $NaOH/H_2O_2$; v) BzCl, Py.

ylidene groups of the intermediate **7** by use of $TiCl_4$ in CH_2Cl_2 at 0 °C gave triol derivative **8** in 79% yield.[13] Selective protection of the 5,6-hydroxyl groups by $TIPDSCl_2$ in pyridine[14] yielded the alcohol derivative **9** in 81% yield, which was reacted under Mitsunobu conditions to obtain the azide derivative **10**. The azide functional group **10** was reduced to the amino group by a Staudinger type condition[15] using triphenylphosphine in THF/H_2O, followed by acetyl protection using Ac_2O in pyridine to provide compound **11** in 68% yield for two steps. Deprotection of the TIPDS group by TBAF yielded diol **12** in 97% yield (Scheme 2). Selective protection of the primary hydroxyl group of **12** with TBDPSCl in pyridine/DMAP gave **13** in 57% yield. Also, the benzoyl protection group of **13** was replaced with a TBDPS to yield compound **14** in 68% two-step yield. Esterification of **14** with 2-ethyl-hexanoyl chloride in pyridine/DMAP gave **15**, which is a diastereomeric mixture. Both of the silyl protection groups of **15** were removed by TBAF to provide the diol derivative **16** in 95% yield. Chemoselective oxidation of the allylic hydroxyl was successfully accomplished using manganese dioxide (MnO_2), which was further oxidized by use of $NaClO_2$/KH_2PO_4 to yield the desired compound **17** in 86% two-step yield (Scheme 3).

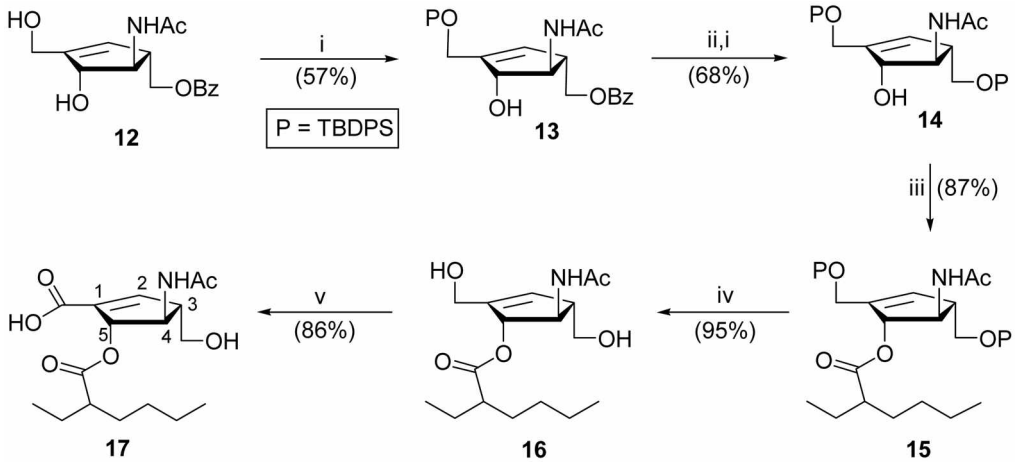
In summary, we have designed and successfully synthesized a novel cyclopentene scaffold mimicking Oseltamivir as a neuraminidase inhibitor. Based on this method, we are synthesizing a number of cyclopentene derivatives in our laboratory. The activity tests of synthesized compounds are currently underway and will be reported in due course.

Experiments

Melting points were determined on a Mel-temp II labora-



Scheme 2. Synthesis of key intermediate **12**. Reagents: i) $TiCl_4$, CH_2Cl_2; ii) TIPDSCl, Py; iii) DEAD, Ph_3P, DPPA; iv) (a) Ph_3P, THF/H_2O; (b) Ac_2O, Py; v) TBAF/THF.



Scheme 3. Synthesis of cyclopentenyl target compound 17. Reagents: i) TBDPSCl, Py; ii) 1% NaOH, MeOH; iii) 2-Ethyl-hexanoyl-Cl, Py; iv) TBAF, THF; v) (a) MnO_2, CH_2Cl_2; (b) $NaClO_2$, KH_2PO_4.

tory device and are uncorrected. NMR spectra were recorded on a JEOL 300 Fourier transform spectrometer. Chemical shifts are reported in parts per million (δ), and signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet), dm (doublet of multiplet), dq (doublet of quartet), and dd (doublet of doublets). Optical rotations were measured on Autopol-IV digital polarimeter. The elemental analyses were performed using an Elemental Analyzer System (EA1112). TLC was performed on Uniplates (silica gel) purchased from Analtech Co. All reactions were carried out under an atmosphere of nitrogen unless otherwise specified. Dry dichloromethane, benzene, and pyridine were obtained by distillation from CaH_2. Dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

(4*R*,5*R*)-4,5-(Isopropylidenedioxy)-3-(*tert*-butoxymethyl)-2-phenylseleno-cyclopentan-1-one (3). A solution of lithium diisopropylamide mono(tetrahydrofuran) (1.50 M in cyclohexane, 1.64 mL, 2.47 mmol) in dry THF (80 mL) was stirred under nitrogen at −78 °C and compound **2** (0.50 g, 2.06 mmol) in 2.5 mL of dry THF was added dropwise while keeping the reaction temperature at −78 °C. The reaction mixture was stirred for 10 min at −78 °C, and phenylselenyl bromide (0.58 g, 2.47 mmol) in THF (2.50 mL) was added rapidly. The reaction mixture was allowed to warm to room temperature while monitoring by TLC. After completion of the reaction (about 20 min after it reached room temperature) the mixture was cooled in an ice bath, and 1 mL of H_2O was slowly added. The reaction mixture was neutralized with HOAc, washed with brine, and the phases separated. The organic phase was dried over Na_2SO_4, evaporated to dryness, and purified by silica gel column chromatography (5% EtOAc:hexanes) to give **3** (0.5 g, 1.25 mmol, 61%) as an orange semisolid mixture of two unseparable anomers (11:1), which were crystallized in hexanes. mp 77-79 °C; ^{1}H NMR ($CDCl_3$) δ 7.68 (m, 2H), 7.57 (m, 1H), 7.29 (m, 2H), 4.72-4.63 (dd, J = 5.7, 5.5 Hz, 1H), 4.37-4.30 (dd, J = 7.2, 5.5 Hz, 1H), 3.56-3.45 (m, 3H), 2.71 (m, 1H), 1.60 (s, 3H), 1.35 (s, 3H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 210.5, 137.8, 133.9, 133.4, 131.0, 129.3, 129.2, 127.9, 127.5, 111.8, 111.3, 81.1, 80.8, 79.5, 77.7, 74.0, 73.6, 63.1, 60.4, 49.2, 46.3, 45.1, 42.4, 27.3, 27.1, 26.6, 26.3, 24.6, 24.4; Anal. Calcd. for $C_{19}H_{26}O_4Se$: C, 57.43; H, 6.60. Found: C, 57.40; H, 6.68.

(4*R*,5*R*)-4,5-(Isopropylidenedioxy)-3-(*tert*-butoxymethyl)-2-cyclopenten-1-one (4). H_2O_2 (24.7 mL, dissolved in 205 mL of H_2O) was added dropwise to a solution of **3** (11.9 g, 30.0 mmol) in 625 mL of CH_2Cl_2 and 20 mL of pyridine, while keeping the reaction temperature between 20 and 25 °C. The reaction mixture was stirred at room temperature for 30 min, then washed with H_2O (200 mL). The organic layer was dried (Na_2SO_4) and evaporated to dryness. The reaction mixture was eluted on a short silica gel pad (6 cm height) with 20% EtOAc:hexanes to obtain an orange oil, of which only an small amount was purified by silica gel due to its instability. The remaining crude mixture was used directly in the next reaction. mp 70-71 °C; $[\alpha]_D^{25}$ −12.1 (c 0.43, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 6.17 (d, J = 1.3 Hz, 1H), 5.10 (d, J = 5.6 Hz, 1H), 4.50 (d, J = 5.6 Hz, 1H), 4.32 (dq, J = 17.7, 1.6 Hz, 2H), 1.41 (s, 6H), 1.25 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 202.3, 176.1, 128.7, 115.8, 78.5, 78.3, 74.6, 60.6, 27.8, 27.8, 26.6; Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.96; H, 8.49.

(5*R*,6*R*)-5,6-(Isopropylidenedioxy)-4-(*tert*-butoxymethyl)-3,1-exo-cyclopentadiene (5). BuLi (1.60 M solution in hexanes, 24.6 mL, 39.4 mmol) was added to a suspension of methyltriphenylphosphonium bromide (14.8 g, 41.5 mmol) in THF (76.6 mL) at −78 °C. The reaction mixture was stirred for 1 h allowing the yellowish mixture to warm to room temperature. Upon recooling to −78 °C, the crude ketone **4** in 32 mL of dry THF was added dropwise to the stirring mixture. The reaction mixture, allowed to warm to room temperature, was stirred for 2 h. Upon completion by TLC, the resulting mixture was cooled to 0 °C and neutralized with saturated NH_4Cl. The mixture was extracted with EtOAc (250 mL) and the organic layer was dried over $NaSO_4$. The crude product was concentrated *in vacuo* and purified by silica gel column chromatography (5% EtOAc:

hexanes) to give **5** (2.65 g, 11.1 mmol, 37% from **3**) as a clear oil. $[\alpha]_D^{25}$ −111.5 (c 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 6.10 (s, 1H), 5.08 (d, J = 13.4 Hz, 2H), 4.98 (d, J = 5.8 Hz, 1H), 4.86 (d, J = 5.8 Hz, 1H), 4.06 (dd, J = 30.3, 14.5 Hz, 2H), 1.33 (s, 6H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 149.0, 148.2, 128.5, 110.5, 108.1, 81.8, 78.7, 72.5, 57.9, 28.7, 26.5, 25.2; Anal. Calcd. for $C_{14}H_{22}O_3$·1.0 EtOAc: C, 66.23; H, 9.26. Found: C, 66.18; H, 8.87.

(4*R*,5*R*)-4,5-(Isopropylidenedioxy)-3-hydroxymethyl-1-(*tert*-butoxymethyl)-1-cyclopentene (6). 9-BBN (0.50 M solution in THF, 26.7 mL, 13.3 mmol) was added to a solution of **5** (2.65 g, 11.14 mmol) in dry THF (2.50 mL) at −10 °C. The reaction was permitted to proceed for 48 h at room temperature, then cooled to 0 °C in an ice-water bath. Water was added (1 mL) in order to quench the residual hydride. The organoborane formed was oxidized for 1 h by adding 3.71 mL of 3 N NaOH followed by dropwise addition of 30% hydrogen peroxide (3.71 mL) at 0 °C. The reaction mixture was stirred for 1 h at room temperature and then partitioned between brine (100 mL) and EtOAc (100 mL). The organic phase was separated, dried (Na_2SO_4), evaporated to dryness, and purified by silica gel column chromatography (25% EtOAc:hexanes) to obtain **6** (2.00 g, 7.80 mmol, 70%) as a clear oil. $[\alpha]_D^{26}$ 38.2 (c 0.34, EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.61 (s, 1H), 5.08 (d, J = 5.8 Hz, 1H), 4.86 (t, J = 5.8 Hz, 1H), 4.08-3.98 (m, 2H), 3.91-3.75 (m, 2H), 2.91 (s, 1H), 2.34 (s, 1H, D_2O exchangeable), 1.42 (s, 3H), 1.37 (s, 3H), 1.23 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 143.1, 128.1, 111.1, 84.77, 80.3, 73.8, 62.1, 58.5, 48.7, 27.5, 27.2, 25.7; Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 66.76; H, 9.54.

(4*R*,5*R*)-4,5-(Isopropylidenedioxy)-3-benzoyloxymethyl-1-(*tert*-butoxymethyl)-1-cyclopentene (7). BzCl (1.30 mL, 11.2 mmol, dissolved in 1.40 mL of pyridine) was added dropwise to a solution of **6** (2.35 g, 9.16 mmol) in pyridine (10 mL) and CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then water (1 mL) was added to quench the remaining BzCl. The reaction mixture was evaporated to dryness, dissolved in EtOAc (100 mL), washed with sat $NaHCO_3$ (100 mL), and dried (Na_2SO_4). Evaporation of the solvent gave an orange syrup, which was purified using silica gel column chromatography (5% EtOAc: hexanes) to obtain **7** (2.85 g, 7.91 mmol, 86%) as a yellowish oil. $[\alpha]_D^{25}$ 10.9 (c 0.61, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 8.07 (d, J = 7.5 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.3 Hz, 2H), 5.69 (s, 1H), 5.10 (d, J = 5.4 Hz, 1H), 4.85 (t, J = 5.4 Hz, 1H), 4.58-4.36 (m, 2H), 4.10-4.00 (m, 2H), 3.13 (s, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 1.24 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 165.4, 142.7, 131.8, 129.4, 128.6, 127.3, 125.7, 109.9, 83.8, 77.6, 72.3, 62.8, 57.4, 45.3, 26.4, 25.3; Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.73; H, 7.87.

(4*R*,5*R*)-4,5-(Dihydroxy)-3-benzoyloxymethyl-1-(hydroxymethyl)-1-cyclopentene (8). $TiCl_4$ (1 M solution in CH_2Cl_2, 21.9 mL, 21.9 mmol) was added to a solution of **7** (3.94 g, 10.9 mmol) in CH_2Cl_2 (80.7 mL) at 0 °C. The reaction mixture was stirred for 1 min at 0 °C, then MeOH (5 mL) was added to quench the remaining $TiCl_4$. The reaction mixture was evaporated to dryness, coevaporated with toluene, and directly purified by silica gel column chromatography (5% MeOH:$CHCl_3$) to obtain **8** (2.30 g, 8.70 mmol, 79%) as a clear oil. $[\alpha]_D^{25}$ 61.6 (c 0.72, MeOH); ^{1}H NMR (DMSO-d_6) δ 7.98 (d, J = 7.5 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 4.73 (s, 1H, D_2O exchangeable), 4.54 (d, J = 3.8 Hz, 1H, D_2O exchangeable), 4.46 (q, J = 6.8 Hz, 1H), 4.30 (d, J = 8.0 Hz, 2H, D_2O exchangeable), 4.19 (q, J = 8.1 Hz, 2H), 4.03 (q, J = 14.8 Hz, 2H), 2.90 (d, J = 6.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 166.2, 147.9, 133.6, 130.4, 129.51, 129.1, 124.6, 74.5, 71.7, 65.9, 58.8, 46.1; Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.43; H, 6.08.

(4*R*,5*R*)-5,6-(Tetraisopropyldisiloxane-1,3-diyl)-4-hydroxy-3-benzoyloxymethyl-1-cyclopentene (9). Compound **8** (2.30 g, 8.70 mmol) was dissolved in dry pyridine (86.7 mL), and then 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (2.26 mL, 10.4 mmol) was added dropwise at 0 °C. The mixture was stirred at room temperature for 1 h, quenched with MeOH (1 mL), and evaporated to dryness. The residue was dissolved in EtOAc (100 mL), washed with water (50 mL) and brine (50 mL), and dried with $NaSO_4$. The solvent was removed by evaporation and the residue was purified by silica gel column chromatography (5% EtOAc:hexanes) to obtain **9** (3.60 g, 7.10 mmol, 81%) as a clear oil. $[\alpha]_D^{26}$ −16.2 (c 0.77, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 8.06 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 5.71 (s, 1H), 4.94 (d, J = 5.4 Hz, 1H), 4.59 (dd, J = 10.7, 7.5 Hz, 1H), 4.49-4.31 (m, 4H), 3.13 (d, J = 6.0 Hz, 1H), 3.01 (s, 1H, D_2O exchangeable), 1.12-1.05 (m, 28H); ^{13}C NMR (DMSO-d_6) δ 166.6, 143.8, 132.9, 130.4, 129.6, 128.3, 127.6, 74.8, 70.9, 63.9, 58.6, 47.06, 17.5, 17.5, 17.3, 17.3, 17.2, 17.2, 17.1, 16.9, 13.2, 12.8, 12.6; Anal. Calcd. for $C_{26}H_{42}O_6Si_2$·0.6 H_2O: C, 60.33; H, 8.41. Found: C, 60.66; H, 8.65.

(4*R*,5*R*)-5,6-(Tetraisopropyldisiloxane-1,3-diyl)-4-azido-3-benzoyloxymethyl-1-cyclopentene (10). Diphenylphosphorylazide (2.42 mL, 11.2 mmol) was added dropwise to a solution of **9** (1.13 g, 2.24 mmol), triphenylphosphine (2.94 g, 11.2 mmol), and DEAD (1.77 Ml, 11.2 mmol) in dry THF (42.0 mL) at 0 °C. The reaction mixture was warmed to 60 °C and stirred for 24 h. The mixture was evaporated to dryness and purified by silica gel column chromatography (2% EtOAc:hexanes) to obtain **10** (0.75 g, 1.41 mmol, 62%) as an amorphous solid. mp 68-70 °C; $[\alpha]_D^{25}$ 8.2 (c 0.60, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 8.05 (d, J = 7.5 Hz, 2H), 7.57 (t, J = 7.3 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 5.60 (s, 1H), 4.91 (d, J = 5.5 Hz, 1H), 4.43 (m, 4H), 4.21 (d, J = 12.4 Hz, 1H), 3.00 (d, J = 5.5 Hz, 1H), 1.14-1.03 (m, 28H); ^{13}C NMR (DMSO-d_6) δ 165.4, 144.4, 132.2, 128.7, 127.4, 124.9, 124.8, 78.8, 71.8, 64.5, 57.2, 46.21, 16.4, 16.4, 16.3, 16.2, 16.2, 16.1, 12.2, 12.2, 11.7, 11.5; Anal. Calcd. for $C_{26}H_{41}N_3O_5Si_2$·0.2 hexanes: C, 59.50; H, 7.65; N, 7.65. Found: C, 59.21; H, 7.84; N, 7.24.

(4*R*,5*R*)-5,6-(Tetraisopropyldisiloxane-1,3-diyl)-4-acetamido-3-benzoyloxymethyl-1-cyclopentene (11). Water (0.03 mL, 1.34 mmol) and tripheylphosphine (0.44 g, 1.68

mmol) were added to a solution of **10** (0.59, 1.12 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 5 h, and then evaporated to dryness. The residue was dissolved in anhydrous pyridine, cooled to 0 °C, and then Ac_2O (0.23 mL, 2.24 mmol) was added dropwise under nitrogen. The reaction was monitored by TLC and after the reaction completion (3 h) it was quenched with water (0.10 mL), evaporated to dryness, purified by silica gel column chromatography (25% EtOAc:hexanes), and crystallized in EtOAc:hexanes (1:1) to obtain **11** (0.41 g, 0.76 mmol, 68%) as white crystals. mp 136-137 °C; $[\alpha]_D^{25}$ 21.5 (c 1.17, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.32 (d, J = 8.9 Hz, 1H, D_2O exchangeable), 7.93 (d, J = 7.7 Hz, 2H), 7.65 (t, J = 7.1 Hz, 1H), 5.71 (s, 1H), 4.90 (d, J = 6.0 Hz, 1H), 4.34-4.07 (m, 5H), 2.83 (d, J = 5.7 Hz, 1H), 1.77 (s, 3H), 1.03-0.84 (m, 28H); ^{13}C NMR (DMSO-d_6) δ 168.2, 164.8, 143.7, 132.5, 128.9, 128.3, 127.8, 126.4, 77.7, 64.7, 59.5, 56.9, 46.5, 21.9, 16.5, 16.3, 16.3, 16.3, 16.3, 16.2, 15.9, 15.9, 11.8, 11.5, 11.3, 10.9; Anal. Calcd. for $C_{28}H_{45}NO_6Si_2$: C, 61.39; H, 8.28; N, 2.56. Found: C, 61.26; H, 8.33; N, 2.51.

(4*R*,5*R*)-5,6-Dihydroxy-4-acetamido-3-benzoyloxymethyl-1-cyclopentene (12). TBAF (1 M solution in THF, 2.90 mL, 2.90 mmol) was added to a solution of **11** (1.45 g, 2.28 mmol) in THF (25 mL) at room temperature. The reaction mixture was stirred for 1 h, evaporated to dryness, and purified by silica gel column chromatography (7.5% MeOH: $CHCl_3$) to obtain **12** as a white solid (0.79 g, 2.58 mmol, 97%), which was crystallized in EtOAc:MeOH (3:1). mp 142-144 °C; $[\alpha]_D^{26}$ 58.8 (c 0.44, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.17 (d, J = 8.0 Hz, 1H, D_2O exchangeable), 7.96 (d, J = 7.6 Hz, 2H), 7.65 (t, J = 7.2 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 5.55 (s, 1H), 5.13 (d, J = 6.3 Hz, 1H, D_2O exchangeable), 4.73 (t, J = 5.3 Hz, 1H, D_2O exchangeable), 4.43 (t, J = 5.3 Hz, 1H), 4.33-4.16 (m, 2H), 4.04-3.89 (m, 3H, D_2O exchangeable), 2.72 (s, 1H), 1.80 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 69.7, 166.0, 148.4, 133.7, 130.1, 129.5, 129.1, 123.0, 79.9, 66.8, 61.7, 58.4, 48.1, 23.1; Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.84; H, 6.34; N, 4.67.

(4*R*,5*R*)-6-(*tert*-Butyldiphenylsilyl)-5-hydroxy-4-acetamido-3-benzoyloxymethyl-1-cyclopentene (13). DMAP (3.90 μg, 32.0 μmol) and TBDPSCl (0.09 mL, 0.33 mmol) were added to a stirred solution of **12** (100 mg, 0.32 mmol) in pyridine (4.50 mL) at 0 °C. The mixture was stirred at room temperature for 2 h, quenched with water at 0 °C, and evaporated to dryness. The clear oil obtained was dissolved in EtOAc (50 mL) and washed with H_2O. The organic phase was separated, evaporated to dryness, and purified by silica gel column chromatography (60% EtOAc:hexanes) to give **13** (100 mg, 0.18 mol, 57%) as a white foam. mp 40-42 °C; $[\alpha]_D^{26}$ 39.6 (c 0.20, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.03 (d, J = 7.4 Hz, 2H), 7.66 (m, 4H, D_2O exchangeable), 7.59 (t, J = 7.2 Hz, 1H), 7.47-7.34 (m, 9H), 6.12 (d, J = 4.0 Hz, 1H), 5.71 (s, 1H), 4.62 (d, J = 5.1 Hz, 1H, D_2O exchangeable), 4.44-4.27 (m, 4H), 3.94-3.90 (m, 1H), 2.91 (m, 1H), 1.99 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 172.3, 166.4, 146.1, 135.5, 133.3, 129.8, 129.7, 129.5, 129.4, 128.5, 127.7, 122.9, 82.5, 66.6, 65.0, 61.1, 47.6, 26.8, 22.9, 21.0; Anal. Calcd. for $C_{32}H_{37}NO_5Si$: C, 70.69; H, 6.86; N, 2.58. Found: C, 70.39; H, 6.96; N, 2.50.

(4*R*,5*R*)-6-(*O*-*tert*-Butyldiphenylsilyl)-5-hydroxy-4-acetamido-3-[methyl-*O*-(*tert*-butyldiphenylsilyl)]-1-cyclopentene (14). A solution of **13** (0.55 g, 1.01 mmol) in 1% NaOH/MeOH (6.0 mL) was stirred for 30 min. The reaction mixture was neutralized with 0.20 M HCl at 0 °C. The solvent was evaporated to dryness, and the residue was dissolved in EtOAc (50 mL), washed with water (25 mL) and brine (25 mL), and dried (Na_2SO_4). The organic phase was separated and evaporated to dryness. The clear oily residue was taken-up in anhydrous pyridine and cooled to 0 °C in an ice bath. DMAP (0.24 g, 2.02 mmol) and TBDPSCl (0.34 mL, 1.31 mmol) were added to this solution. The reaction mixture was stirred at room temperature for 3 h, cooled to 0 °C, quenched with H_2O (0.5 mL), and evaporated to dryness. The residue was dissolved in EtOAc (50 mL), washed with water (25 mL) and brine (25 mL), and dried (Na_2SO_4). The organic phase was separated, evaporated to dryness, and purified by silica gel column chromatography (20% EtOAc:hexanes) to obtain **14** (466 mg, 0.68 mmol, 68%) as a white foam. $[\alpha]_D^{26}$ 24.6 (c 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.66-7.62 (m, 9H), 7.48-7.31 (m, 11H), 6.20 (s, 1H, D_2O exchangeable), 5.53 (d, J = 1.3 Hz, 1H), 5.08 (s, 1H, D_2O exchangeable), 4.57 (d, J = 5.3 Hz, 1H), 4.40 (d, J = 15.5 Hz, 1H), 4.25 (d, J = 15.4 Hz, 1H), 3.94-3.91 (m, 1H), 3.72-3.56 (m, 2H), 2.71 (m, 1H), 1.94 (s, 3H), 1.08 (s, 9H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 172.2, 145.9, 135.5, 133.4, 132.9, 129.9, 129.6, 127.9, 127.6, 121.9, 81.7, 67.4, 67.3, 61.0, 50.4, 26.9, 26.8, 22.9, 19.2; Anal. Calcd. for $C_{41}H_{51}NO_4Si_2$: C, 72.63; H, 7.58; N, 2.07. Found: C, 72.59; H, 7.64; N, 2.20.

(4*R*,5*R*)-6-(*O*-*tert*-Butyldiphenylsilyl)-5-*O*-(2-ethylhexanoate)-4-acetamido-3-[methyl-*O*-(*tert*-butyldiphenylsilyl)]-1-cyclopentene (15). 2-Ethylhexanoyl chloride (0.03 mL, 0.18 mmol) was added to a solution of **14** (0.10 g, 0.14 mmol) in pyridine (1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h, cooled to 0 °C in an ice bath, and quenched with water. The resulting mixture was evaporated to dryness, taken-up in EtOAc (20 mL), and washed with water (10 mL) and brine (10 mL). The organic phase was evaporated to dryness and the residue was purified by silica gel column chromatography (10% EtOAc: hexanes) to obtain **15** (0.10 mg, 0.12 mmol, 87%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.67-7.64 (m, 9H), 7.43-7.33 (m, 11H), 5.96 (s, 1H, D_2O exchangeable), 5.68 (d, J = 4.6 Hz, 1H), 5.61 (d, J = 7.8 Hz, 1H), 4.21-4.18 (m, 3H), 3.82-3.71 (m, 3H), 2.66 (m, 1H), 2.19-2.12 (m, 1H), 1.65-1.55 (m, 2H), 1.53-1.38 (m, 2H), 1.37-1.22 (m, 2H), 1.17-1.14 (m, 2H), 1.06 (s, 18H), 0.80-0.71 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 176.3, 176.2, 169.7, 141.3, 135.6, 135.5, 135.4, 133.7, 133.5, 133.4, 133.3, 129.7, 129.6, 129.2, 127.7, 127.7, 127.6, 82.0, 65.1, 60.6, 58.7, 52.3, 47.2, 47.1, 31.4, 31.3, 29.5, 29.4, 26.9, 26.8, 25.2, 25.1, 23.3, 22.5, 22.4, 19.3, 19.2, 13.9, 13.8, 11.7, 11.6; Anal. Calcd. for $C_{49}H_{65}NO_5Si_2$:

C, 73.18; H, 8.15; N, 1.74. Found: C, 74.02; H, 7.99; N, 1.83.

(4*R*,5*R*)-6-Hydroxy-5-*O*-(2-ethylhexanoate)-4-acetamido-3-hydroxymethyl-1-cyclopentene (16). TBAF (1 M solution in THF, 0.90 mL, 0.90 mmol) was added to a solution of **15** (0.37 g, 0.46 mmol) in dry THF (5 mL). The reaction mixture was stirred at room temperature for 1 h and evaporated to dryness. The residue was purified by silica gel column chromatography (5% MeOH:$CHCl_3$) to obtain **16** (0.14 mg, 0.44 mmol, 95%) as a clear oil. ^{1}H NMR ($CDCl_3$) δ 6.77 (d, J = 7.0 Hz, 1H), 5.81 (d, J = 5.5 Hz, 1H), 5.70 (s, 1H, D_2O exchangeable), 4.27 (s, 1H, D_2O exchangeable), 4.16-4.11 (m, 2H), 4.04 (s, 1H, D_2O exchangeable), 3.74-3.51 (m, 2H), 2.67 (m, 1H), 2.36-2.28 (m, 1H), 2.01 (s, 3H), 1.92-1.36 (m, 4H), 1.34-1.17 (m, 4H), 0.90-0.85 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 177.5, 171.8, 141.3, 130.1, 81.9, 81.6, 60.9, 58.7, 54.2, 47.3, 31.7, 31.6, 29.6, 29.5, 25.5, 25.4, 23.0, 22.5, 13.9, 11.8, 11.7; Anal. Calcd. for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.11; H, 7.09; N, 4.36.

(5*R*,6*R*)-6-*O*-(2-Ethylhexanoate)-5-acetamido-4-hydroxymethyl-2-cyclopentene-1-carboxylic acid (17). MnO_2 (0.12 g, 1.43 mmol) was added to a solution of **16** (0.02 g, 0.06 mmol) in CH_2Cl_2 (10.0 mL). The reaction mixture was stirred for 24 h, filtered through a celite pad, and evaporated to dryness. The residue was dissolved in THF/H_2O/DMSO (0.40/0.40/0.03 mL). KH_2PO_4 (0.01 g, 0.10 mmol) and $NaClO_2$ (0.02 g, 0.24 mmol) were added to this solution. The reaction mixture was stirred for 3 h, then HCl (2 N solution, 0.23 mL) was added to the reaction mixture, and the resulting solution was extracted with EtOAc (2 × 10 mL). The combined organic phases were evaporated to dryness and purified by a C_{18} silica gel column chromatography to obtain **17** (0.12 g, 0.05 mmol, 86%) as a white solid. mp 141-145 °C; ^{1}H NMR (DMSO-d_6) δ 8.40 (d, J = 8.0 Hz, 1H), 5.94 (s, 1H, D_2O exchangeable), 6.02 (s, 1H), 5.13 (s, 1H), 4.01 (m, 1H, D_2O exchangeable), 3.63-3.59 (m, 1H), 3.44-3.39 (m, 1H), 2.72 (m, 1H), 2.23 (m, 1H), 1.86 (s, 3H), 1.54-1.44 (m, 4H), 1.30 (m, 4H), 0.92-0.86 (m, 6H); ^{13}C NMR (DMSO-d_6) δ 174.4, 169.2, 164.5, 148.3, 134.4, 79.9, 57.7, 53.5, 46.9, 31.6, 29.3, 29.1, 25.4, 22.9, 22.4, 14.1, 11.8; Anal. Calcd. for $C_{17}H_{27}NO_6 \cdot 1.0H_2O$: C, 56.81; H, 8.13; N, 3.89. Found: C, 56.71; H, 8.15; N, 4.02.

References

1. Palache, A. M.; Beyer, W. E.; Luchters, G.; Volker, R.; Sprenger, M. J.; Masurel, N. *Vaccine*. **1993**, *11*, 892.
2. Miller, J. L. *Am. J. Health Syst. Pharm*. **1999**, *56*, 1696.
3. Hayden, F. G.; Treanor, J. J.; Fritz, R. S.; Lobo, M.; Betts, R. F.; Miller, M.; Kinnersley, N.; Mills, R. G.; Ward, P.; Straus, S. E. *Jama*. **1999**, *282*, 1240.
4. Cass, L. M. R.; Efthymiopoulos, C.; Bye, A. *Clin. Phamacokinet*. **1999**, *36*, *Suppl. 1*, 1.
5. Schilling, M.; Povinelli, L.; Krause, P.; Gravenstein, M.; Ambrozaitis, A.; Jones, H. H.; Drinka, P.; Shult, P.; Powers, D.; Gravenstein, S. *Vaccine*. **1998**, *16*, 1771.
6. Hayden, F. G.; Atmar, R. L.; Schilling, M.; Johnson, C.; Poretz, D.; Paar, D.; Huson, L.; Ward, P.; Mills, R. G. *N. Engl. J. Med*. **1999**, *341*, 1336.
7. Taylor, N. R.; von Itstein, M. *J. Med. Chem*. **1994**, *37*, 616.
8. Bossart-Whitaker, P.; Carson, M.; Babu, Y. S.; Smith, C. D.; Laver, W. G.; Air, G. M. *J. Mol. Biol*. **1993**, *232*, 1069.
9. Varghese, J. N.; McKimm-Breschkin, J. L.; Cald, J. B.; Kortt, A. A.; Colman, P. M. *Proteins* **1992**, *14*, 327.
10. Liu, P.; Chu, C. K. *Can. J. Chem*. **2006**, *84*, 748.
11. Lancelin, J. M.; Pougny, J. R.; Sinay, P. *Carbohydr. Res*. **1985**, *136*, 369.
12. Brown, H. C.; Chen, J. C. *J. Org. Chem*. **1981**, *46*, 3978.
13. Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc*. **1982**, *104*, 1116.
14. Tekenaka, K.; Tsuji, T.; Muraoka, M. *Nucleos. Nucleot. Nucleic Acids* **1998**, *17*, 869.
15. Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahdron* **1981**, *37*, 437.