The Second Generation Catalytic Asymmetric Synthesis of Tamiflu: Allylic Substitution Route

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General: Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^1H NMR, 126.65 MHz for ^{13}C NMR. Chemical shifts in CDCl_3 were reported in the scale relative to CHCl_3 (7.26 ppm) for ^1H NMR, and to CDCl_3 (77.0 ppm) for ^{13}C NMR, as internal references. Optical rotations were measured on a JASCO P-1010 polarimeter. ESI mass spectra were measured on Water-ZQ4000. EI Mass spectra were measured on JEOL JMS-BU20 GCmate. FAB mass spectra were measured on JEOL MStation JMS-700. Column chromatographies were performed with silica gel Merck 60 (230-400 mesh ASTM). The enantiomeric excesses (ee's) were determined by HPLC. HPLC analysis was performed on JASCO HPLC systems containing of following: pump, PU-980; detector, UV-970, measured at 254 nm; column, Daicel Chiralpak AD-H or Daicel Chiralcel OD-H; mobile phase, 2-propanol/hexane; flow rate, 1.0 mL/min. In general, reactions were carried out in dry solvents under an argon atmosphere, unless noted otherwise. Dry solvents of tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purchased from Kanto Chemical. Co., Inc. Propionitrile was distilled from calcium hydride. Other reagents were purified by usual methods. $\text{Y}(\text{O}^i\text{Pr})_3$ was purchased from Kojundo Chemical Laboratory Co., Ltd. (Fax: +81-492-84-1351, sales@kojundo.co.jp). Chiral ligand **2** was prepared by a reported method.¹ This ligand is commercially available from Junsei Chemical. Co., Ltd. (Fax: +81-3-3270-5461) **Caution!** Azide compounds are potentially explosive, especially when concentrated to dryness.

(A) Catalytic Enantioselective Ring-Opening Reaction of Aziridine with TMSN_3 on 30 g-Scale²

To a solution of ligand **2** (0.92 g, 2.0 mmol, 2 mol %) in THF (30 mL), $\text{Y}(\text{O}^i\text{Pr})_3$ (0.2 M in THF, 5 mL, 1.0 mmol, 1 mol %) was added at room temperature. The mixture was stirred at 45-60 °C for 1 h, and then the solvent was evaporated. After drying the resulting pre-catalyst under reduced pressure (<5 mmHg) for 2 h, aziridine **3** (28.9 g, 0.10 mol)², 2,6-dimethylphenol (12.2 g, 0.10 mmol, 1 equiv), and propionitrile (500 mL) were added at room temperature. After 10 min, TMSN_3 (19.6 mL, 0.15 mol, 1.5 equiv) was added to start the reaction. After 12 h, water was added followed by the addition of toluene. The organic layer was separated, and washed with 1 M NaOH several times. The solvent was removed under reduced pressure to afford **4** (31.5 g, 0.094 mmol, calculated by ^1H NMR analysis.)² in 94% yield as colorless solid. The enantiomeric excess of the product was determined by HPLC analysis to be 89% ee. Enantiomerically enriched **4** (99% ee) was obtained after recrystallization from 2-propanol (recrystallization yield; 72%).

¹ Kato, N.; Tomita, D.; Maki, K.; Kanai, M.; Shibasaki, M. *J. Org. Chem.* **2004**, *69*, 6128.

² Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312.

(B) Asymmetric Synthesis of Tamiflu®-Preliminary Optimization of the Allylic Substitution Route
(4*S*,5*S*)-4-Azido-5-*tert*-butoxycarbonylaminocyclohexene (11**)²**

To a solution of **4** (11.36 g, 34.2 mmol, 99% ee) in CH₃CN (200 mL), Boc₂O (11.9 g, 54.5 mmol, 1.6 equiv) and DMAP (2.09 g, 17.1 mmol, 50 mol %) were added, and the mixture was stirred at room temperature for 1 h. 4 M NaOH (150 mL) was added and the mixture was stirred at room temperature for 1 h. Water was added, and the product was extracted with AcOEt twice. The combined organic layer was dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography (silica gel, hexane-AcOEt, 5:1) to afford **11** (7.96 g, 33.4 mmol)² as a colorless solid in 98% yield (2 steps).

(4*S*,5*S*)-4-Acetoamido-5-*tert*-butoxycarbonylaminocyclohexene (30**)**

To a solution of **11** (6.50 g, 27.3 mmol) in THF (150 mL), PPh₃ (7.20 g, 27.3 mmol, 1.0 equiv) was added portion wise, and the mixture was stirred at 60-70 °C. After 2.5 h, additional PPh₃ (0.36 g, 1.37 mmol, 0.05 equiv) was added. After 7.5 h, water (20 mL) was added, and the reaction mixture was stirred at 40 °C for 21 h. After most of THF was removed under reduced pressure, water was removed by azeotropic evaporation with toluene (three times). To the residue, CH₂Cl₂ (80 mL), pyridine (6.6 mL, 81.8 mmol, 3 equiv), and Ac₂O (5.2 mL, 54.6 mmol, 2 equiv) were added, and the resulting mixture was stirred at room temperature. After 2 h, water was added and the product was extracted with CH₂Cl₂ twice, and the combined organic layer was dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane-AcOEt, 4:1 to 0:1) to afford a mixture of P(O)Ph₃ and **30**, which was used for next step without further purification. The yield was calculated by ¹H NMR analysis (6.92 g, 27.2 mmol; 99% yield (2 steps)). The analytically pure **30** was obtained through the purification by column chromatography (silica gel, hexane-acetone, 2:1). IR (KBr): 3322, 2970, 1682, 1647, 1529, 1371, 1308, 1161, 1020, 661 cm⁻¹; ¹H NMR (CDCl₃): δ = 6.33 (d, *J* = 7.4 Hz, 1H), 5.56 (s, 2H), 4.76 (d, *J* = 8.5 Hz, 1H), 3.97-3.86 (m, 1H), 3.74-3.62 (m, 1H), 2.54-2.37 (m, 2H), 2.05-1.89 (m, 5H), 1.41 (s, 9H) ppm; ¹³C NMR (CDCl₃): δ = 170.4, 156.9, 125.2, 124.6, 79.6, 51.4, 50.3, 32.6, 32.4, 28.3, 23.3 ppm; MS (ESI): *m/z* 277 [M+Na⁺]; HRMS (EI): *m/z* calcd for C₁₃H₂₂N₂O₃ [M⁺]: 254.1625. Found: 254.1614; [α]_D²⁶ -73.7 (*c* = 1.410, CHCl₃).

(3*R*,5*S*,6*S*)-3-Acetoxy-5-benzyloxycarbonylamino-6-*tert*-butoxycarbonylaminocyclohexene (13)

To a solution of **30** (804 mg, 3.16 mmol) containing P(O)Ph₃ in CH₂Cl₂ (50 mL), NIS (1.08 g, 4.80 mmol, 1.5 equiv) was added, and the resulting mixture was stirred at room temperature for 72 h. Additional NIS (0.5 g, 2.22 mmol, 0.7 equiv) in CHCl₃ (25 mL) was added, and the resulting mixture was stirred at 40-60 °C for 10 h. After **30** was consumed, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU: 1.5 mL, 10.0 mmol, 3.2 equiv) was added in one portion at room temperature. After 12 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography roughly (silica gel, hexane-AcOEt, 1:1 to 0:1) to afford a mixture of P(O)Ph₃ (12.9 mg, 0.036 mmol), succinimide and **12**, which was used for next step without further purification. Analytical data of **12**: IR (KBr): 3201, 2967, 1705, 1657, 1530, 1250, 1176, 1052, 1021, 816 cm⁻¹; ¹H NMR (CDCl₃): δ = 6.00 (dd, *J* = 5.7, 9.4 Hz, 1H), 5.90 (dd, *J* = 4.6, 9.4 Hz, 1H), 4.63-4.49 (m, 2H), 4.22 (brs, 1H), 3.74 (brs, 1H), 1.90-1.76 (m, 5H), 1.43 (s, 9H) ppm; ¹³C NMR (CDCl₃): δ = 156.6, 154.5, 130.1, 127.3, 79.7, 67.0/65.2 (rotamer), 50.0, 49.1, 28.33/28.28 (rotamer), 22.8, 21.8 ppm; MS (ESI): *m/z* 253 [M+H⁺] and 275 [M+Na⁺]; HRMS (EI): *m/z* calcd for C₁₃H₂₀N₂O₃ [M⁺]: 252.1468. Found: 252.1455. [α]_D²² +183.1 (*c* = 1.230, CHCl₃).

To a solution of NaHCO₃ (598 mg, 7.12 mmol, 2.3 equiv) and **12** in CH₂Cl₂-H₂O (20-10 mL), CbzCl (500 μL, 3.50 mmol, 1.1 equiv) was added dropwise. After 2 h, water was added and the product was extracted with CH₂Cl₂ twice, and the combined organic layer was dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane-AcOEt, 4:1 to 2:1) to afford pure **13** (1.09 g, 2.69 mmol) as a colorless solid in 85% yield (3 steps). In this purification, P(O)Ph₃ and succinimide could be removed completely. IR (KBr): 3336, 2968, 1733, 1675, 1520, 1300, 1239, 1171, 1024, 636 cm⁻¹; ¹H NMR (CDCl₃): δ = 7.33 (brs, 5H), 5.70 (d, *J* = 10.1 Hz, 1H), 5.68 (d, *J* = 10.1 Hz, 1H), 5.46 (brs, 1H), 5.39 (brs, 1H), 5.08 (s, 2H), 4.81-4.67 (m, 1H), 4.29-4.17 (m, 1H), 3.74-3.59 (m, 1H), 2.53-3.37 (m, 1H), 2.04 (s, 3H), 1.73-1.60 (m, 1H), 1.41 (s, 9H) ppm; ¹³C NMR (CDCl₃): δ = 170.3, 156.4, 156.2, 136.4, 130.6, 129.3, 128.5, 128.04, 127.96, 80.1, 68.7, 66.7, 52.7, 51.8, 34.6, 28.2, 21.1 ppm; MS (ESI): *m/z* 427 [M+Na⁺]; HRMS (EI): *m/z* calcd for C₂₁H₂₈N₂O₆ [M⁺]: 404.1942. Found: 404.1943; [α]_D²⁶ +99.4 (*c* = 1.710, CHCl₃).

(3*R*,5*S*,6*S*)-5-Benzyloxycarbonylamino-6-*tert*-butoxycarbonylaminocyclohexene (31)

To a solution of **13** (6.27 g, 15.5 mmol) in MeOH (400 mL), K₂CO₃ (4.30 g, 31.0 mmol, 2 equiv) was added and the mixture was stirred at room temperature for 2 h. After most of MeOH was removed under reduced pressure, AcOEt and water were added, and the product was extracted with AcOEt twice. The

organic layer was washed with brine, dried over Na₂SO₄, and concentrated to afford **31** (5.57 g, 15.4 mmol) as a colorless solid in 99% yield. IR (KBr): 3344, 2951, 1675, 1525, 1276, 1063, 1025, 994, 700, 623 cm⁻¹; ¹H NMR (*d*₄-MeOH): δ = 7.41-7.22 (m, 5H), 5.71 (dd, *J* = 1.7, 10.2 Hz, 1H), 5.50 (d, *J* = 10.2 Hz, 1H), 5.08 (d, *J* = 12.5 Hz, 1H), 5.04 (d, *J* = 12.5 Hz, 1H), 4.33 (brs, 1H), 4.09-4.02 (m, 1H), 3.61-3.52 (m, 1H), 2.25-2.16 (m, 1H), 1.67-1.53 (m, 1H), 1.40 (s, 9H) ppm; ¹³C NMR (*d*₄-MeOH): δ = 158.55, 158.52, 138.3, 134.0, 130.0, 129.4, 128.9, 128.8, 80.3, 67.5, 67.4, 53.4, 53.1, 39.8, 28.7 ppm; MS (ESI): *m/z* 385 [M+Na⁺]; HRMS (EI): *m/z* calcd for C₁₉H₂₇N₂O₅ [M+H⁺]: 363.1914. Found: 363.1912; [α]_D²⁵ +90.7 (*c* = 0.635, CHCl₃).

(5*S*,6*S*)-5-Benzyloxycarbonylamino-6-*tert*-butoxycarbonylaminocyclohexen-3-one (14)

To a solution of **31** (5.57 g, 15.4 mmol) in CH₂Cl₂ (400 mL), Dess-Martin periodinane (9.9 g, 23.3 mmol, 1.5 equiv) was added, and the mixture was stirred at room temperature. After 16 h, saturated aqueous Na₂S₂O₃ was added and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ twice, and the combined organic layer was washed with saturated aqueous NaHCO₃ once and dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane-AcOEt, 4:1 to 2:1) to afford **14** (5.33 g, 14.8 mmol) as a colorless solid in 96% yield. Enantiomeric excess was determined by chiral HPLC to be 99%. IR (KBr): 3289, 2979, 1688, 1552, 1284, 1251, 1168, 1045, 757, 697 cm⁻¹; ¹H NMR (CDCl₃): δ = 7.39-7.27 (m, 5H), 6.77 (dd, *J* = 1.1, 10.0 Hz, 1H), 6.04 (d, *J* = 10.0 Hz, 1H), 5.50 (d, *J* = 8.5 Hz, 1H), 5.16 (d, *J* = 8.5 Hz, 1H), 5.09 (d, *J* = 12.5 Hz, 1H), 5.06 (d, *J* = 12.5 Hz, 1H), 4.55-4.42 (m, 1H), 4.09-3.96 (m, 1H), 2.83 (dd, *J* = 4.0, 16.4 Hz, 1H), 2.43 (dd, *J* = 13.4, 16.4 Hz, 1H), 1.41 (s, 9H) ppm; ¹³C NMR (CDCl₃): δ = 196.3, 156.2, 150.1, 141.8, 136.1, 130.3, 128.5, 128.2, 128.0, 80.5, 66.9, 53.1, 52.9, 43.8, 28.2 ppm; MS (ESI): *m/z* 383 [M+Na⁺]; HRMS (EI): *m/z* calcd for C₁₉H₂₄N₂O₅ [M⁺]: 360.1680. Found: 360.1671; [α]_D²⁴ +90.3 (*c* = 0.905, CHCl₃, 99% ee). HPLC (Chiralpak AD-H, 2-propanol/hexane 1/9, flow 1.0 mL/min, detection at 254 nm.): *t*_R 20.0 min (major) and 27.6 min (minor).

(3*aR*,4*S*,7*aS*)-4-Benzyloxycarbonylamino-3-*tert*-butoxycarbonylaminocyclohex-2-en-1-one (16)

To a solution of **14** (148 mg, 0.411 mmol) in THF (2 mL), diethylphosphoryl cyanide (64 μ L, 0.42 mmol, 1 equiv) was added at room temperature. After cooling to -20 $^{\circ}$ C, LiCN (2.5 mg, 0.068 mmol, 17 mol %)³ was added in one portion. After stirring at -20 $^{\circ}$ C for 1 h, THF was removed under reduced pressure. The residue was diluted in toluene (3 mL), and heated at 150 $^{\circ}$ C in a sealed tube. After 3 h, THF was removed under reduced pressure, and the residue was diluted with pyridine (1 mL). After the addition of a catalytic amount of DMAP, Boc₂O (total 190 mg, 0.87 mmol, 2.1 equiv) was added in portionwise for 10 h until **32** was completely consumed. Pyridine was removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexane-AcOEt, 4:1 to 2:1) to afford **16** (122 mg, 0.295 mmol) as a colorless amorphous in 72% yield. The diastereoselectivity of **15** was determined by ¹H NMR analysis to be ca. 20:1. The configuration of the tetrasubstituted carbon of **15** was temporarily assigned. IR (neat): 3353, 2982, 2936, 2224, 1808, 1731, 1538, 1359, 1023, 757 cm^{-1} ; ¹H NMR (CDCl₃): δ = 7.40-7.29 (m, 5H), 6.62 (t, J = 3.3 Hz, 1H), 5.82 (d, J = 4.9 Hz, 1H), 5.12 (d, J = 12.5 Hz, 1H), 5.09 (d, J = 12.5 Hz, 1H), 5.05-4.99 (m, 1H), 4.42 (dd, J = 7.4, 10.4 Hz, 1H), 3.94-3.85 (m, 1H), 3.00 (dd, J = 3.9, 17.4 Hz, 1H), 2.34-2.23 (m, 1H), 1.53 (s, 9H) ppm; ¹³C NMR (CDCl₃): δ = 155.8, 150.5, 149.5, 135.9, 134.9, 128.5, 128.3, 128.1, 117.6, 116.4, 85.8, 69.5, 67.0, 55.5, 49.5, 31.2, 27.7 ppm; MS (ESI): m/z 436 [M+Na⁺] and 336 [M-Boc+H+Na⁺]; HRMS (EI): m/z calcd for C₂₁H₂₃N₃O₆ [M⁺ (minor)]: 413.1581. Found: 413.1574 and m/z calcd for C₁₆H₁₅N₃O₄ [M-Boc+H⁺ (major)]: 313.1057. Found: 313.1060; $[\alpha]_D^{25}$ +7.2 (c = 1.185, CHCl₃).

(3*S*,4*R*,5*S*)-5-Benzoyloxycarbonylamino-4-*tert*-butoxycarbonylamino-1-cyano-3-hydroxycyclohexene
(34)

To a solution of **16** (1.36 g, 3.28 mmol) in MeOH (100 mL), Cs₂CO₃ (107 mg, 0.33 mmol, 10 mol %) was added and the mixture was stirred at room temperature. After 3 h, MeOH was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane-AcOEt, 2:1) to afford **34** (1.24 g, 3.20 mmol) as a colorless solid in 97% yield. IR (KBr): 3324, 2981, 2225, 1697, 1670, 1543, 1281, 1169, 1043, 741 cm^{-1} ; ¹H NMR (CDCl₃): δ = 7.42-7.28 (m, 5H), 6.55 (s, 1H), 5.76 (d, J = 7.9 Hz, 1H), 5.43 (d, J = 8.5 Hz, 1H), 5.07 (s, 2H), 4.37-4.27 (m, 1H), 4.05-3.94 (m, 1H), 3.75-3.64 (m, 1H), 3.10 (d, J = 7.4 Hz, 1H), 2.82 (dd, J = 5.1, 16.5 Hz, 1H), 2.20 (dd, J = 10.8, 16.5 Hz, 1H), 1.41 (s, 9H) ppm; ¹³C NMR (CDCl₃): δ = 157.1, 156.8, 141.6, 136.0, 128.5, 128.2, 127.8, 117.4, 114.1, 80.4, 67.0, 65.3, 52.8, 47.4, 34.5, 28.2 ppm; MS (ESI): m/z 410 [M+Na⁺]; HRMS (EI): m/z calcd for C₂₀H₂₅N₃O₅ [M⁺]: 387.1789. Found: 387.1787; $[\alpha]_D^{26}$ +65.1 (c = 0.625, CHCl₃).

³ Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 3413.

(4*R*,5*S*)-5-Benzyloxycarbonylamino-4-*tert*-butoxycarbonylamino-1-cyano-3-hydroxycyclohexene (35)

To a solution of **34** (47.6 mg, 0.123 mmol) in CH₂Cl₂ (5 mL), Dess-Martin periodinane (79.2 mg, 0.19 mmol, 1.5 equiv) was added and the mixture was stirred at room temperature. After 19 h, CH₂Cl₂ was removed under reduced pressure, and the residue was purified through short pad column (silica gel, hexane-AcOEt, 2:1) to afford **35** (44.6 mg, 0.116 mmol) as a colorless solid in 94% yield. The purification should be performed quickly because β-cyanoenone **35** was relatively unstable on a silica gel column chromatography. This reaction was also applicable on a 1.24 g scale. (80% yield). IR (KBr): 3311, 2980, 2225, 1717, 1686, 1553, 1528, 1276, 1023, 758 cm⁻¹; ¹H NMR (CDCl₃): δ = 7.41-7.28 (m, 5H), 6.62 (d, *J* = 2.8 Hz, 1H), 6.34 (d, *J* = 6.8 Hz, 1H), 5.50 (d, *J* = 6.2 Hz, 1H), 5.09 (s, 2H), 4.47-4.35 (m, 1H), 4.09-3.97 (m, 1H), 3.12 (dd, *J* = 4.5, 18.1 Hz, 1H), 2.66 (ddd, *J* = 2.8, 10.5, 18.1 Hz, 1H), 1.41 (s, 9H) ppm; ¹³C NMR (CDCl₃): δ = 192.2, 157.4, 156.1, 137.1, 136.1, 129.5, 128.5, 128.1, 127.9, 115.8, 81.3, 66.9, 60.1, 53.8, 35.4, 28.2, 28.0 ppm; MS (ESI): *m/z* 408 [M+Na⁺]; HRMS (EI): *m/z* calcd for C₂₀H₂₃N₃O₅ [M⁺]: 385.1632. Found: 385.1633; [α]_D²⁶ -36.4 (*c* = 0.838, CHCl₃).

(3*R*,4*R*,5*S*)-5-Benzyloxycarbonylamino-4-*tert*-butoxycarbonylamino-1-cyano-3-hydroxycyclohexene (17)

To a solution of LiAlH(O^{*t*}Bu)₃ (1 M in THF, 7.7 mL, 7.70 mmol, 3 equiv) in THF (70 mL), **35** (987 mg, 2.56 mmol) in THF (30 mL) was added, and the resulting mixture was stirred at -20 °C, and then warmed to 0 °C. After 2 h, saturated aqueous NH₄Cl was added to quench the reaction. After removal of insoluble materials through a celite pad, the product was extracted with CH₂Cl₂ three times, and the combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane-AcOEt, 4:1 to 1:1) to afford **17** (900 mg, 2.32 mmol) as a colorless solid in 91% yield. The diastereoselectivity of the product was determined by ¹H NMR analysis to be >20:1. IR (KBr): 3456, 3289, 2976, 2227, 1700, 1561, 1523, 1281, 1037, 994 cm⁻¹; ¹H NMR (CDCl₃): δ = 7.41-7.29 (m, 5H), 6.49 (s, 1H), 5.26 (d, *J* = 8.3 Hz, 1H), 5.16 (d, *J* = 7.9 Hz, 1H), 5.15-5.06 (m, 2H), 4.25 (brs, 1H), 3.93-3.82 (m, 1H), 3.80 (brs, 1H), 3.64-3.53 (m, 1H), 2.70 (dd, *J* = 4.3, 17.4 Hz, 1H), 2.35-2.26 (m, 1H), 1.41 (s, 9H) ppm; ¹³C NMR (CDCl₃): δ = 157.8, 156.7, 144.8, 135.9, 128.6, 128.3, 128.0, 117.2, 110.9, 80.9, 71.5, 67.2, 57.4, 49.1, 33.3, 28.2 ppm; MS (ESI): *m/z* 410 [M+Na⁺]; HRMS (EI): *m/z* calcd for C₂₀H₂₅N₃O₅ [M⁺]: 387.1789. Found: 387.1788; [α]_D²⁴ -63.0 (*c* = 0.825, MeOH).

(3*S*,4*R*,5*S*)-5-Benzoyloxycarbonylamino-3,4-*tert*-butoxycarbonylimino-1-cyanocyclohexene (18)

To a solution of PPh_3 (78.7 mg, 0.30 mmol, 2.5 equiv) in THF (2 mL), DEAD (40% in toluene, 130 μL , 0.30 mmol, 2.5 equiv) and **17** (45.9 mg, 0.118 mmol) in THF (1 mL) were added and the resulting mixture was stirred at 0 °C. After 3 h, mixture was concentrated, and purified by column chromatography (silica gel, hexane-AcOEt, 4:1 to 3:1) to afford **18** (37.9 mg, 0.103 mmol) as a colorless amorphous in 87% yield. IR (neat): 3330, 2979, 2219, 1724, 1531, 1369, 1236, 1152, 1041, 752 cm^{-1} ; ^1H NMR (CDCl_3): δ = 7.44-7.29 (m, 5H), 6.88 (t, J = 3.7 Hz, 1H), 5.13 (d, J = 11.9 Hz, 1H), 5.08 (d, J = 11.9 Hz, 1H), 4.78 (d, J = 8.5 Hz, 1H), 4.62 (brs, 1H), 3.10 (brs, 1H), 2.96 (t, J = 5.1 Hz, 1H), 2.58 (d, J = 16.7 Hz, 1H), 2.36 (d, J = 16.7 Hz, 1H), 1.45 (s, 9H) ppm; ^{13}C NMR (CDCl_3): δ = 159.9, 155.4, 140.3, 135.8, 128.6, 128.4, 128.3, 118.1, 112.3, 82.8, 67.3, 41.8, 41.3, 31.9, 30.0, 27.8 ppm; MS (ESI): m/z 392 $[\text{M}+\text{Na}^+]$; HRMS (EI): m/z calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_4$ $[\text{M}^+]$: 369.1683. Found: 369.1628; $[\alpha]_D^{24}$ -51.9 (c = 0.750, CHCl_3).

(3*R*,4*R*,5*S*)-5-Benzoyloxycarbonylamino-4-*tert*-butoxycarbonylamino-1-cyano-3-(1-ethylpropoxy)cyclohexene (36)

To a solution of **18** (300 mg, 0.812 mmol) in 3-pentanol (8 mL), $\text{BF}_3 \cdot \text{OEt}_2$ (0.5 M in 3-pentanol, 2.4 mL, 1.20 mmol, 1.5 equiv) was added dropwise, and the resulting mixture was stirred at -20 °C. After 3 h, additional $\text{BF}_3 \cdot \text{OEt}_2$ (0.5 M in 3-pentanol, 0.8 mL, 0.40 mmol, 0.5 equiv) was added dropwise at -20 °C. After 2 h, saturated aqueous NaHCO_3 was added to quench the reaction. The product was extracted with AcOEt twice and CH_2Cl_2 once, and the combined organic layer was dried over Na_2SO_4 . The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane-AcOEt, 7:1 to 5:1 to 0:1) to afford **36** (191 mg, 0.417 mmol) as a colorless solid in 51% yield, along with **32** (71.6 mg, 0.23 mmol) in 28% yield. Cyclic carbamate **32** can be recycled (See S-5). IR (KBr): 3313, 2926, 2223, 1679, 1543, 1288, 1167, 1068, 741, 698 cm^{-1} ; ^1H NMR (CDCl_3): δ = 7.40-7.27 (m, 5H), 6.47 (s, 1H), 5.88 (d, J = 7.4 Hz, 1H), 5.08 (s, 2H), 4.64 (d, J = 7.4 Hz, 1H), 3.91 (brs, 2H), 3.74 (dd, J = 8.5, 17.0 Hz, 1H), 3.34 (t, J = 5.7 Hz, 1H), 2.63 (d, J = 17.3 Hz, 1H), 2.40 (dd, J = 8.5, 17.3 Hz, 1H), 1.55-1.45 (m, 4H), 1.37 (s, 9H), 0.89 (t, J = 7.4 Hz, 6H) ppm; ^{13}C NMR (CDCl_3): δ = 156.4, 156.2, 143.3, 136.3, 128.4, 128.1, 127.9, 117.6, 111.8, 83.2, 80.2, 75.0, 66.8, 54.1, 49.3, 32.6, 28.2, 26.1, 25.8, 9.4, 9.3 ppm; MS (ESI): m/z 480 $[\text{M}+\text{Na}^+]$; HRMS (EI): m/z calcd for $\text{C}_{25}\text{H}_{35}\text{N}_3\text{O}_5$ $[\text{M}^+]$: 457.2571. Found: 457.2588; $[\alpha]_D^{24}$ -48.1 (c = 0.650, CHCl_3).

(3*R*,4*R*,5*S*)-4-Acetylamino-5-benzyloxycarbonylamino-1-cyano-3-(1-ethylpropoxy)cyclohexene (19)

To a solution of **36** (130 mg, 0.284 mmol) in CH₂Cl₂ (5 mL), TFA (420 μ L, 5.65 mmol, 20 equiv) was added at 0 °C. After 1 h, additional TFA (420 μ L, 5.65 mmol, 20 equiv) was added at 0 °C, and the mixture was raised to room temperature. After 2 h, TFA was removed in vacuo. The residue was diluted in CH₂Cl₂ (5 mL), to which Et₃N (200 μ L, 1.43 mmol, 5 equiv) and Ac₂O (40 μ L, 0.43 mmol, 1.5 equiv) were added at 0 °C. The mixture was stirred at room temperature for 16 h. After concentration, the residue was purified by column chromatography (silica gel, hexane-AcOEt, 2:1 to 1:1) to afford **19** (92.2 mg, 0.231 mmol) as a colorless solid in 81% yield. IR (KBr): 3335, 2926, 2222, 1690, 1655, 1544, 1293, 1085, 1065, 700 cm⁻¹; ¹H NMR (CDCl₃): δ = 7.42-7.28 (m, 5H), 6.48 (s, 1H), 5.57 (d, J = 9.1 Hz, 1H), 5.55 (d, J = 9.6 Hz, 1H), 5.12 (d, J = 12.5 Hz, 1H), 5.05 (d, J = 12.5 Hz, 1H), 4.12-4.02 (m, 1H), 4.01-3.94 (m, 1H), 3.93-3.83 (m, 1H), 3.37-3.25 (m, 1H), 2.65 (dd, J = 4.5, 17.6 Hz, 1H), 2.40 (dd, J = 9.1, 17.6 Hz, 1H), 1.87 (s, 3H), 1.54-1.43 (m, 4H), 0.88 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H) ppm; ¹³C NMR (CDCl₃): δ = 171.2, 156.5, 143.4, 136.2, 128.5, 128.2, 127.9, 117.5, 111.7, 82.7, 74.8, 66.9, 53.2, 49.1, 32.7, 26.0, 25.6, 23.1, 9.4, 9.2 ppm; MS (ESI): m/z 422 [M+Na⁺]; HRMS (EI): m/z calcd for C₂₂H₂₉N₃O₄ [M⁺]: 399.2153. Found: 399.2147; [α]_D²⁵ -68.5 (c = 0.900, CHCl₃).

Ethyl (3*R*,4*R*,5*S*)-4-Acetylamino-5-amino-3-(1-ethylpropoxy)cyclohexene-1-carboxylate (37: Tamiflu-Free)

A solution of **19** (21.2 mg, 0.053 mmol) in conc. HCl/EtOH (5 mL) was stirred at room temperature for 24 h. After concentration of the mixture in vacuo, H₂O (100 μ L) in EtOH (2 mL) were added in order to decompose the imino ester. After 2 h, 25% aqueous NH₃ (2 mL) and EtOH (4 mL) were added to the mixture. After 10 h, solvent was removed under reduced pressure. To the residue, CH₂Cl₂ and saturated aqueous NaHCO₃ were added slowly, and organic layer was separated. The product in water layer was extracted with CH₂Cl₂ twice. The combined organic layer was dried over Na₂SO₄. Filtration and removal of solvent gave the Tamiflu-free **37** (12.2 mg, 0.039 mmol) as a colorless oil in 74% yield. IR (neat): 3283, 2963, 2930, 2876, 1715, 1652, 1556, 1373, 1259, 1061, 802 cm⁻¹; ¹H NMR (CDCl₃): δ = 6.73 (t, J = 2.0 Hz, 1H), 5.61 (d, J = 7.9 Hz, 1H), 4.25-4.15 (m, 3H), 3.52 (qlike, J = 10.2 Hz, 1H), 3.34 (quintet, J = 5.7 Hz, 1H), 3.24 (td, J = 5.4, 10.2 Hz, 1H), 2.75 (dd, J = 5.4, 18.1 Hz, 1H), 2.20-2.11 (m, 1H), 2.04 (s, 3H),

1.58-1.44 (m, 4H), 1.29 (t, $J = 7.4$ Hz, 3H), 0.904 (t, $J = 7.4$ Hz, 3H), 0.895 (t, $J = 7.4$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3): $\delta = 170.9, 166.3, 137.5, 129.5, 81.6, 74.8, 60.8, 59.0, 49.2, 33.6, 26.2, 25.7, 23.7, 14.2, 9.5, 9.3$ ppm; MS (ESI): m/z 313 [$\text{M}+\text{H}^+$] and 335 [$\text{M}+\text{Na}^+$]; HRMS (EI): m/z calcd for $\text{C}_{16}\text{H}_{28}\text{N}_2\text{O}_4$ [M^+]: 312.2044. Found: 312.2043; $[\alpha]_D^{24} -52.9$ ($c = 0.610, \text{CHCl}_3$). [lit. $[\alpha]_D^{24} -56.2$ ($c = 0.566, \text{CHCl}_3$)⁴]

Further conversion from **37** to Tamiflu[®] (**1**) was reported in some literatures.^{5,6,7} According to these methods, we performed the H_3PO_4 salt formation followed by crystallization to obtain Tamiflu[®] (**1**)². All analytical data completely matched with the reported one.⁵

(C) Asymmetric Synthesis of Tamiflu[®]-Optimized Allylic Substitution Route

(1*R*,5*S*,6*S*)-6-Azido-2-oxo-4-azabicyclo[3.3.1]non-7-en-3-one (**20**)

To a solution of **11** (1.35 g, 5.67 mmol) in chloroform (68 ml), potassium carbonate (2.35 g, 17.02 mmol), iodine (4.32 g, 17.02 mmol), and potassium iodide (0.94 g, 5.67 mmol) were added at 4 °C, and the reaction mixture was warmed to 60 °C. After stirred for 14 h, saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (50 ml) was added to quench the reaction. The product was extracted with CH_2Cl_2 (20 ml) twice. The combined organic layer was washed with brine (50 ml) and dried over Na_2SO_4 . The solvent was concentrated in vacuo.

To a solution of the residue in chloroform (68 ml), 1,8-diazabicyclo[5.4.0]undec-7-ene (1.7 ml, 11.34 mmol) was added at 4 °C, and the reaction mixture was warmed to room temperature. After stirred for 4 h, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography ($\text{EtOAc}:\text{hexane}$ 2:1 $\rightarrow$ 4:1 $\rightarrow$ EtOAc) to afford **20** (870.5 mg, 4.83 mmol) as a white solid in 85% yield. IR (neat) $\nu_{\text{max}} = 3371, 2946, 2100, 1704, 1671, 1460 \text{ cm}^{-1}$; ^1H NMR (d_6 -DMSO): $\delta = 7.52$ (brs, 1 H), 6.28 (dd, $J = 6.3, 9.8$ Hz, 1 H), 6.05 (dd, $J = 5.2, 9.8$ Hz, 1 H), 4.73-4.69 (m, 1 H), 3.97 (brs, 1 H), 3.61 (brs, 1 H), 3.33 (s, 2 H) ppm; ^{13}C NMR (d_6 -DMSO): $\delta = 151.3, 129.8, 126.1, 65.9, 58.0, 47.1, 22.2$ ppm; MS (ESI): m/z 203 [$\text{M}+\text{Na}^+$]; HRMS (EI): m/z calcd for $\text{C}_7\text{H}_8\text{N}_4\text{O}_2$ [M^+]: 180.0642. Found: 180.0673; $[\alpha]_D^{26} +494.8$ ($c = 1.02, \text{CHCl}_3, 99\% \text{ ee}$).

⁴ This is an optical rotation value of authentic sample of **37**, which was obtained after extraction from commercial “Tamiflu[®] capsule 75 (Roche’s product)” under basic condition.

⁵ 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.; Schultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998**, *63*, 4545.

⁶ Iding, H.; Wirz, B.; Zutter, U. EP Patent 1,146,036, 2001.

⁷ Harrington, P. J.; Brown, J. D.; Foderaro, T.; Hughes, R. C. *Org. Process Dev.* **2004**, *8*, 86.

***tert*-Butyl (1*R*,5*S*,6*S*)-6-Azido-3-oxo-2-oxa-4-azabicyclo[3.3.1]non-7-en-4-carboxyl (38)**

To a solution of **20** (869.7 mg, 4.83 mmol) in dichloromethane (30 ml), triethylamine (1.3 ml, 9.66 mmol), 4-dimethylaminopyridine (59 mg, 0.483 mmol), and di-*tert*-butyl dicarbonate (1.58 g, 7.24 mmol) in dichloromethane (18 ml) were added at 4 °C, and the reaction mixture was warmed to room temperature. After stirred for 2 h, water (40 ml) was added to quench the reaction. The product was extracted with CH_2Cl_2 (20 ml) twice. The combined organic layer was washed with brine (50 ml), dried over Na_2SO_4 , and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc:hexane 1:2 $\rightarrow$ 1:1) to afford **38** (1.34 g, 4.78 mmol) as a white solid in 99% yield. IR (neat) ν_{max} = 2980, 2101, 1793, 1747 cm^{-1} ; ^1H NMR (CDCl_3): δ = 6.28 (dd, J = 6.3, 9.7 Hz, 1 H), 6.01 (dd, J = 4.6, 9.7 Hz, 1 H), 4.71-4.67 (m, 1 H), 4.54-4.49 (m, 1 H), 4.09-4.04 (m, 1 H), 2.25-2.20 (m, 1 H), 2.16-2.10 (m, 1 H), 1.54 (s, 9 H) ppm; ^{13}C NMR (CDCl_3): δ = 151.1, 147.6, 129.0, 126.9, 84.6, 67.0, 56.9, 52.2, 27.8, 23.1 ppm; MS (ESI): m/z 303 [$\text{M}+\text{Na}^+$] and 203 [$\text{M}-\text{Boc}+\text{H}+\text{Na}^+$]; HRMS (FAB): m/z calcd for $\text{C}_{12}\text{H}_{17}\text{N}_4\text{O}_4$ [$\text{M}+\text{H}^+$]: 281.1244. Found: 281.1247; $[\alpha]_{\text{D}}^{25} +361.0$ (c = 0.97, CHCl_3 , 99% ee).

***tert*-Butyl (1*R*,5*S*,6*S*)-6-(Acetylamino)-3-oxo-2-oxa-4-azabicyclo[3.3.1]non-7-en-4-carboxylate (21)**

To a solution of **38** (1.25 g, 4.46 mmol) in chloroform (25 ml), 2,6-lutidine (5.2 ml, 44.58 mmol) and thioacetic acid (3 ml, 44.58 mmol) were added at room temperature, and the reaction mixture was warmed to 60 °C. After stirred for 19 h, the reaction mixture was concentrated in vacuo, and the residue was purified by flash column chromatography (EtOAc:hexane 2:1 $\rightarrow$ EtOAc $\rightarrow$ EtOAc:MeOH 10:1) to afford **21** (1.10 g, 3.71 mmol) as a white solid in 83% yield. IR (neat) ν_{max} = 3336, 2979, 1776, 1735, 1675, 1541 cm^{-1} ; ^1H NMR (CDCl_3): δ = 6.22 (d, J = 8.6 Hz, 1 H), 6.14 (dd, J = 6.3, 9.5 Hz, 1 H), 5.91 (dd, J = 4.6, 9.5 Hz, 1 H), 4.72-4.67 (m, 1 H), 4.60-4.55 (m, 1 H), 4.52-4.48 (m, 1 H), 2.27-2.21 (m, 1 H), 2.12-2.06 (m, 1 H), 1.97 (s, 3 H), 1.56 (s, 9 H) ppm (Its chemical shifts depend on the substrate concentration); ^{13}C NMR (CDCl_3): δ = 169.3, 150.6, 148.7, 129.7, 127.1, 84.8, 67.3, 52.4, 47.0, 27.6, 23.3, 23.0 ppm; MS (ESI) : m/z 319 [$\text{M}+\text{Na}^+$] and 219 [$\text{M}-\text{Boc}+\text{H}+\text{Na}^+$]; HRMS (EI): m/z calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_5$ [M^+]: 296.1367 Found: 296.1370; $[\alpha]_{\text{D}}^{26} +209.4$ (c = 0.86, MeOH, 99 %ee).

***tert*-Butyl [(1*S*,2*S*,5*R*)-2-(Acetylamino)-5-hydroxycyclohex-3-en-1-yl]carbamate (**39**)**

To a solution of **21** (933 mg, 3.15 mmol) in *n*-butanol (79 ml), cesium carbonate (308 mg, 0.95 mmol) was added at 4 °C and the reaction mixture was warmed to room temperature. After stirring for 16 h, the reaction mixture was concentrated in vacuo directly. The residue was purified by flash column chromatography (EtOAc → EtOAc:MeOH 10:1 → 5:1) to afford **39** (733 mg, 2.71 mmol) as a white solid in 86% yield. IR (KBr) ν_{max} = 3303, 2973, 2451, 1685, 1646, 1560 cm^{-1} ; ^1H NMR (d_4 -MeOH): δ = 5.60 (brd, J = 10.1 Hz, 1 H), 5.47 (brd, J = 10.1 Hz, 1 H), 4.40-4.31 (m, 2 H), 3.58-3.50 (m, 1 H), 2.23-2.19 (m, 1 H), 1.92 (s, 3 H), 1.61-1.53 (m, 1 H), 1.42 (s, 9 H) ppm; ^{13}C NMR (d_4 -MeOH): δ = 173.4, 158.1, 134.4, 129.4, 80.2, 67.5, 52.5, 52.1, 39.7, 28.7, 22.7 ppm; MS (ESI) : m/z 293 [$\text{M}+\text{Na}^+$]; HRMS (FAB): m/z calcd for $\text{C}_{13}\text{H}_{23}\text{N}_2\text{O}_4$ [$\text{M}+\text{H}^+$]: 271.1652. Found: 271.1652; $[\alpha]_{\text{D}}^{26} +88.0$ (c = 0.46, MeOH, 99% ee).

***tert*-Butyl [(1*S*,2*S*)-2-(Acetylamino)-5-oxocyclohex-3-en-1-yl]carbamate (**22**)**

To a slurry of **39** (797 mg, 2.95 mmol) in dichloromethane (59 ml), Dess-Martin periodinane (1.5 g, 3.54 mmol) was added at 4 °C. After stirring for 10 min, the reaction mixture was warmed to room temperature. The reaction mixture was stirred for 15 min, and saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (30 ml) was poured into the reaction mixture. The product was extracted with CH_2Cl_2 (30 ml) twice. The combined organic layer was washed with saturated aqueous NaHCO_3 (30 ml) and brine (30 ml) sequentially, and dried over Na_2SO_4 . The solvent was concentrated, and the residue was purified by flash column chromatography (EtOAc:hexane 4:1 → EtOAc → EtOAc:MeOH 10:1) to afford **22** including a small amount of a reagent residue. The crude **22** was washed with EtOAc (20 ml) in order to remove the reagent residue to afford pure **22** (506 mg, 1.89 mmol, 99% ee) in 64% yield. The filtrate was concentrated in vacuo and purified by flash column chromatography (EtOAc:hexane 4:1 → EtOAc → EtOAc:MeOH 10:1) to afford **22** (281 mg). The obtained **22** (281 mg) was recrystallized with EtOAc (3 ml) to afford pure **22** (209 mg, 0.78 mmol, 99% ee) in 26% yield. Enone **22** was obtained in total 90% yield. The optical purity of **22** was determined by HPLC analysis (Chiralpak OD-H, 2-propanol/hexane 1/20, flow 1.0 ml/min, detection at 254 nm; t_{R} 10.4 min (minor) and 15.1 min (major). IR (KBr) ν_{max} = 3350, 3288, 2973, 1704, 1659, 1551 cm^{-1} ; ^1H NMR (CDCl_3): δ = 6.80 (dd, J = 10.1, 2.0 Hz, 1 H), 6.51 (brd, J = 6.7 Hz, 1 H), 6.07 (dd, J = 10.1, 2.0 Hz, 1 H), 4.86 (brd, J = 8.9 Hz, 1 H), 4.71-4.66 (m, 1 H), 4.12-4.02 (m, 1 H), 2.78 (dd, J = 16.0, 4.0 Hz, 1 H), 2.41 (dd, J = 16.0, 13.8 Hz, 1 H), 2.01 (s, 3 H), 1.44 (s, 9 H) ppm; ^{13}C NMR (CDCl_3): δ = 195.9, 170.8, 156.4, 150.4, 129.8, 80.6, 53.8, 51.0, 43.4, 28.2, 23.1

ppm; MS (ESI): m/z 291 $[M+Na]^+$; HRMS (FAB): m/z calcd for $C_{13}H_{21}N_2O_4$ $[M+H]^+$: 269.1496. Found: 269.1495; $[\alpha]_D^{24} +122.1$ ($c = 0.78$, MeOH, 99% ee).

***tert*-Butyl [(1*S*,5*S*,6*R*)-6-(Acetylamino)-3-cyano-5-hydroxycyclohex-3-en-1-yl]carbamate (**24**)**

To a solution of **22** (206 mg, 0.768 mmol) in tetrahydrofuran (15 ml), diethylphosphoryl cyanide (116 μl , 0.768 mmol) was added at room temperature. The reaction mixture was cooled to -20 $^\circ\text{C}$. Every 1 hour, lithium cyanide (total 31.7 mg, 0.96 mmol)³ was added in 3 divided doses. After stirred for 4 h, saturated aqueous ammonium chloride (10 ml) and water (10 ml) was poured into the reaction mixture at -20 $^\circ\text{C}$. The product was extracted with EtOAc (20 ml) twice. The combined organic layer was washed with brine (30 ml) and dried over Na_2SO_4 . The solvent was concentrated in vacuo.

Toluene (19 ml) was added to **23**, and the reaction mixture was heated at 140 $^\circ\text{C}$ in a sealed tube. After 40 min, the reaction mixture was cooled to room temperature. Subsequently, saturated aqueous ammonium chloride (10 ml) and tetrahydrofuran (10 ml) were added to the reaction mixture, and the heterogeneous mixture was stirred for 3 h vigorously. Finally, aqueous 1 M NaOH (10 ml) was added and the product was extracted with EtOAc (20 ml) twice. The combined organic layer was washed with brine (30 ml) and dried over Na_2SO_4 . The solvent was concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc:hexane 2:1 $\rightarrow$ 4:1 $\rightarrow$ EtOAc $\rightarrow$ EtOAc:MeOH 40:1) to afford **24** (177 mg, 0.596 mmol) as amorphous in 78% yield.

***tert*-Butyl {(1*S*, 2*S*, 5*R*)-2-(Acetylamino)-5-cyano-5-[(diethoxyphosphoryl)oxy]cyclohex-3-en-1-yl} carbamate (**23**)** ^1H NMR (CDCl_3): δ = 6.64 (d, J = 8.0 Hz, 1 H), 6.01 (d, J = 10.3 Hz, 1 H), 5.91 (d, J = 10.3 Hz, 1 H), 5.28 (d, J = 8.0 Hz, 1 H), 4.52 (brd, J = 8.6, 9.0 Hz, 1 H), 4.19-4.10 (m, 4 H), 3.87 (brd, J = 18.9, 9.0 Hz, 1 H), 2.84 (d, J = 12.6 Hz, 1 H), 2.21 (dd, J = 12.6, 12.6 Hz, 1 H), 1.96 (s, 3 H), 1.40 (s, 9 H), 1.33 (t, J = 7.0 Hz, 6 H) ppm.

24: IR (neat) ν_{max} = 3338, 2979, 2224, 1685, 1654, 1534 cm^{-1} ; ^1H NMR (CDCl_3): δ = 6.75 (d, J = 9.2 Hz, 1 H), 6.61 (dd, J = 5.2, 2.3 Hz, 1 H), 5.42 (d, J = 9.2 Hz, 1 H), 4.68 (brd, J = 8.5 Hz, 1 H), 4.20 (brs, 1 H), 4.18-4.07 (m, 1 H), 4.01-3.93 (m, 1 H), 2.69 (dd, J = 17.8, 5.5 Hz, 1 H), 2.34-2.25 (m, 1 H), 2.00 (s, 3 H), 1.39 (s, 9 H) ppm; ^{13}C NMR (CDCl_3): δ = 171.4, 157.1, 141.6, 117.4, 114.5, 80.6, 65.9, 52.8, 45.3, 34.0, 28.3, 23.0 ppm; MS (ESI): m/z 318 $[M+Na]^+$; HRMS (FAB): m/z calcd for $C_{14}H_{22}N_3O_4$ $[M+H]^+$: 296.1605. Found: 296.1640; $[\alpha]_D^{25} +37.6$ ($c = 0.76$, CHCl_3 , 99% ee).

***tert*-Butyl [(1*S*,5*R*,6*R*)-6-(Acetylamino)-3-cyano-5-hydroxycyclohex-3-en-1-yl]carbamate (**25**)**

To a solution of **24** (282 mg, 0.956 mmol), triphenylphosphine (501 mg, 1.91 mmol), and *p*-nitrobenzoic acid (320 mg, 1.91 mmol) in tetrahydrofuran (19 ml), DEAD (40% in toluene, 0.87 ml, 1.91 mmol) was added at 4 °C. After stirring for 15 min, the reaction mixture was cooled to -20 °C. To the reaction mixture, aqueous 1 M lithium hydroxide (3.8 ml, 3.82 mmol) was added. After stirring at the same temperature for 2.5 h, the product was extracted with EtOAc (20 ml) twice. The combined organic layer was washed with brine (30 ml) and dried over Na₂SO₄. The solvent was concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc:hexane 4:1 → EtOAc → EtOAc:MeOH 20:1) to afford **25** (227 mg, 0.769 mmol) as a white solid in 80% yield. IR (KBr) $\nu_{\max}$ = 3322, 2979, 2225, 1683, 1625, 1571 cm⁻¹; ¹H NMR (CDCl₃): δ = 7.12 (d, *J* = 5.2 Hz, 1 H), 6.49 (s, 1 H), 5.01 (d, *J* = 2.3 Hz, 1 H), 4.82 (d, *J* = 8.0 Hz, 1 H), 4.28-4.21 (m, 1 H), 3.92-3.81 (m, 1 H), 3.78-3.70 (m, 1 H), 2.63 (dd, *J* = 16.9, 5.0 Hz, 1 H), 2.32-2.22 (m, 1 H), 2.00 (s, 3 H), 1.44 (s, 9 H) ppm; ¹³C NMR (CDCl₃): δ = 173.6, 157.3, 145.3, 117.2, 109.8, 81.3, 73.1, 59.5, 47.3, 32.7, 28.2, 23.0 ppm; MS (ESI): *m/z* 318 [M+Na⁺]; HRMS (FAB): *m/z* calcd for C₁₄H₂₂N₃O₄ [M+H⁺]: 296.1605. Found: 296.1602; [α]_D²⁷ -89.1 (*c* = 0.69, MeOH, 99% ee).

***tert*-Butyl [(1*R*,2*S*,6*S*)-7-Acetyl-4-cyano-7-azabicyclo[4.1.0]hept-4-en-2-yl]carbamate (**26**)**

To a solution of triphenylphosphine (414 mg, 1.58 mmol) in tetrahydrofuran (7.9 mL), DEAD (40% in toluene, 0.72 mL, 1.58 mmol) was added at -20 °C. Then, **25** (234 mg, 0.79 mmol) in THF (2.5 mL) was added to the reaction mixture dropwise for 15 min at the same temperature. After stirring for 1 h, the reaction mixture was concentrated in vacuo. The residue was purified by flash column chromatography twice [first (removal of triphenylphosphine oxide); EtOAc:hexane 4:1 → EtOAc → EtOAc:MeOH 20:1, second (removal of the residue derived from DEAD); Et₂O:hexane 3:1 → 5:1] to afford **26** (144 mg, 0.521 mmol) as an amorphous in 66% yield. IR (neat) $\nu_{\max}$ = 3322, 2978, 2218, 1703, 1525 cm⁻¹; ¹H NMR (CDCl₃): δ = 6.88 (dd, *J* = 3.5, 3.7 Hz, 1 H), 4.54 (brs, 2 H), 3.12-3.04 (m, 2 H), 2.53 (brd, *J* = 17.0 Hz, 1 H), 2.35 (brd, *J* = 17.0, 1 H), 2.13 (s, 3 H), 1.43 (s, 9 H) ppm; ¹³C NMR (CDCl₃): δ = 180.8, 154.8, 140.0, 118.1, 112.3, 80.5, 41.3, 40.5, 31.4, 30.0, 28.3, 23.1 ppm; MS (ESI): *m/z* 300 [M+Na⁺]; HRMS (FAB): *m/z* calcd for C₁₄H₂₀N₃O₃ [M+H⁺]: 278.1499. Found: 278.1500; [α]_D²³ -104.0 (*c* = 0.69, CHCl₃, 99% ee).

***tert*-Butyl [(1*S*,5*R*,6*R*)-6-(Acetylamino)-3-cyano-5-(1-ethylpropoxy)cyclohex-3-en-1-yl]carbamate (27)²**

To a slurry of **26** (119.3 mg, 0.430 mmol) and activated molecular sieves 5A (430 mg) in 3-pentanol (4.3 mL), $\text{BF}_3 \cdot \text{OEt}_2$ (1 M in 3-pentanol, 0.65 mL, 0.645 mmol) was added dropwise for 15 min at -20°C . After stirred for 1 h, water (10 mL) was poured into the reaction mixture at -20°C . The product was extracted with EtOAc (15 mL) twice. The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4 . The solvent was concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc:hexane 1:2 $\rightarrow$ 2:3 $\rightarrow$ 1:1) to afford **27** (88.1 mg, 0.241 mmol)² as a white solid in 56% yield. $[\alpha]_D^{26} -99.6$ ($c = 0.58$, CHCl_3 , 99% ee). [lit. $[\alpha]_D^{21} -108.1$ ($c = 0.660$, CHCl_3)]².

***tert*-Butyl [(3*aR*,4*S*,7*aS*)-6-Cyano-2-methyl-3*a*,4,5,7*a*-tetrahydro-1,3-benzoxazol-4-yl]carbamate (29):** IR (neat) $\nu_{\text{max}} = 3326, 2977, 2221, 1705, 1671, 1524 \text{ cm}^{-1}$; ^1H NMR (CDCl_3): $\delta = 6.64$ (brs, 1 H), 4.92 (brd, $J = 8.6$ Hz, 1 H), 4.82 (d, $J = 6.9$ Hz, 1 H), 4.12 (dd, $J = 8.6, 8.6$ Hz, 1 H), 3.61 (brs, 1 H), 2.79 (brd, $J = 16.6$ Hz, 1 H), 2.24-2.17 (m, 1 H), 1.98 (d, $J = 1.2$ Hz, 3 H), 1.43 (s, 9 H) ppm; ^{13}C NMR (CDCl_3): $\delta = 166.2, 155.3, 138.4, 117.4, 115.4, 80.2, 74.1, 66.4, 49.5, 30.0, 28.3, 14.1$ ppm; MS (ESI): m/z 300 $[\text{M}+\text{Na}^+]$; HRMS (FAB): m/z calcd for $\text{C}_{14}\text{H}_{20}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}^+]$: 278.1499. Found: 278.1500.

Ethyl (3*R*,4*R*,5*S*)-4-Acetylamino-5-amino-3-(1-ethylpropoxy)cyclohexene-1-carboxylate (37: Tamiflu-Free)

The solution of **27** (22.6 mg, 0.062 mmol) in conc. HCl/EtOH (2.5 mL) was stirred at room temperature for 24 h. After cooling to 4°C , water was added to decompose the imino ester. The reaction mixture was warmed to room temperature and stirred for 7.5 h. The reaction mixture was washed with CH_2Cl_2 (10 mL). To the water layer, aqueous 2 M NaOH was added slowly with stirring till $\text{pH} = 10$. The product was extracted with CH_2Cl_2 (15 mL) four times, and the combined organic layer was dried over Na_2SO_4 . The solvent was concentrated in vacuo to afford **37** (11.5 mg, 0.037 mmol) as a colorless oil in 60% yield. $[\alpha]_D^{25} -56.6$ ($c = 0.995$, CHCl_3). [lit. $[\alpha]_D^{24} -56.2$ ($c = 0.566$, CHCl_3)]⁴

(D) Estimation of the Allylic Phosphate (28) Structure

As mentioned in the manuscript, this reaction (**23** $\rightarrow$ **24**) was considered to proceed via the allylic phosphonate **28**. At first, this thermal reaction was studied in order to synthesize oxazoline **29**. A solution of **23** in toluene was heated at $140\text{ }^\circ\text{C}$ in a sealed tube for 1 h. After **23** was consumed completely on TLC analysis, the product was extracted and purified by flash column chromatography. Surprisingly, the α -allylic alcohol **24**, not the desired oxazoline **29**, was isolated as a major product. From this preliminary result, it was expected that this reaction mechanism might be different from the case of **15**.

According to the literature⁸, it is known that β -allyl- α -cyano phosphate rearranges to afford β -allyl- γ -cyano phosphate in a supra-facial fashion under thermal conditions. Based on the precedent, we estimated that this reaction proceeded via β -allyl phosphonate **28** as an intermediate. Although the isolation of **28** was tried, the trials were failed due to its lability. Thus, the reaction mixture was directly analyzed by ESI-MS. The peak of 454 [**28**+ Na^+] was cleanly found even after **23** was consumed completely (The consumption of **23** was confirmed by TLC and ^1H NMR analysis). Therefore, this peak was estimated to be derived from β -allyl phosphonate **28**.

When quenching the thermal rearrangement under basic conditions (for example, aqueous 1 M NaOH), the acetamide group was activated, and the oxazoline **29** was produced as a major product through an $\text{S}_{\text{N}}2$ fashion, along with α -allylic alcohol **24** (the downward arrow from **28** in the above scheme). The oxazoline **29** was stable, and was not converted to α -allylic alcohol **24** at room temperature under basic conditions. Therefore, the α -allylic alcohol **24** can be considered to generate through a substitution reaction of **28** by a hydroxy anion. On the other hand, the α -allylic alcohol **24** was produced as the major product from **28** through an $\text{S}_{\text{N}}2$ fashion by the activation of phosphate group under weakly acidic conditions (for example, saturated aqueous NH_4Cl) in good yield (the rightward arrow from **28**).

⁸ Kurihara, T.; Miki, M.; Yoneda, R.; Harusawa, S. *Chem. Pharm. Bull.* **1986**, *34*, 2747.

It is considered that the cyanide anion attacks enone **22** from the axial direction due to the small size of cyanide and the bulkiness of diethyl phosphate. Therefore, the structure of **23** was considered as the above figure. It was difficult to determine the stereochemistry of **23** by NOE experiments.

(E) Comparison of ^1H NMR Spectra of Tamiflu-Free (**37**)

F:\1. Boc Ac alkene\Boc Ac alkene 1H.als
Boc Ac alkene 1H

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

F:\1. Boc Ac alkene\Boc Ac a
Boc Ac alkene 1H
15-09-2006 18:56:40
1H
single_pulse.ex2
495.13 MHz
4.38 KHz
9.6 Hz
13107
7429.3 Hz
16
1.764 sec
5.000 sec
6.2 us
1H
22.7 c
CDCL3
7.26 ppm
0.12 Hz
38

F:\3. After E2 elimination\After E2 Elimination Ac Boc.als
After E2 Elimination Ac Boc

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

F:\3. After E2 elimination\A
After E2 Elimination Ac Boc
21-09-2006 20:00:38

1H
single pulse.ex2

495.13 MHz

4.38 KHz

9.6 Hz

13107

7429.3 Hz

16

1.764 sec

5.000 sec

6.2 us

1H

22.5 c

CDCL3

7.26 ppm

0.12 Hz

44

NHBoc

F:\4. After hydrolysis OAc Z\Ac, Z.als
1H Line

DFILE
COMNT 1H Line
DATIM Mon Sep 25 19:00:26 2006
OBNUC 1H
EXMOD non
OBFRQ 500.00 MHz
OBSET 160.00 KHz
OBFIN 2160.0 Hz
POINT 32768
FREQU 10000.0 Hz
SCANS 16
ACQTM 3.277 sec
PD 3.723 sec
PW1 5.7 us
IRNUC 1H
CTEMP 27.7 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.12 Hz
RGAIN 20

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SIVNT
EXREF
BF
RGAIN

F:\5. deacetylation allylic
Boc Z allyl Al d-MeOH-1H
28-09-2006 20:21:46
1H
single pulse.ex2
495.13 MHz
4.38 KHz
9.6 Hz
13107
7429.3 Hz
16
1.764 sec
5.000 sec
6.2 us
1H
23.1 C
CD3OD
3.30 ppm
0.12 Hz
44

DFILE F:\6. enone Boc Z\Boc Z enone
COMNT Boc Z enone
DATIM 29-09-2006 22:45:12
OBNUC 1H
EXMOD single pulse.ex2
OBFRQ 495.13 MHz
OBSET 4.38 KHz
OBFIN 9.6 Hz
POINT 13107
FREQU 7429.3 Hz
SCANS 16
ACQTM 1.764 sec
PD 5.000 sec
PW1 6.2 us
IRNUC 1H
CTEMP 22.5 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.12 Hz
RGAIN 40

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

C:\My Documents\PGousei\MIT
After cyanation-1
16-11-2006 23:26:18
1H
single_pulse.ex2
495.13 MHz
4.38 KHz
9.64 Hz
16384
9286.78 Hz
16
1.7642 sec
5.0000 sec
6.20 usec
1H
23.8 c
CDCL3
7.26 ppm
0.12 Hz
54

DFILE COMNT DATIM OBNUC EXMOD OBFRQ OBSET OBFIN POINT FREQU SCANS ACQTM PD PW1 IRNUC CTEMP SLVNT EXREF BF RGAIN

```
single_pulse.ex2
495.13 MHz
  4.38 KHz
    9.64 Hz
      16384
        9286.78 Hz
          16
            1.7642 sec
              5.0000 sec
                6.20 usec
```

¹H
 23.9 c
 CDCl₃
 7.26 ppm
 0.12 Hz
 56

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

F:\9. N-Boc oxazolidinone\N-
1H Line
Fri Oct 13 15:49:19 2006
1H
non
500.00 MHz
160.00 KHz
2160.0 Hz
32768
10000.0 Hz
16
3.277 sec
3.723 sec
5.7 us
1H
27.7 c
CDCL3
7.26 ppm
0.12 Hz
21

F:\10. a-alcohol\ a-alcohol-1H-2.als
alcohol-2 1H

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

F:\10. a-alcohol\ a-alcohol-1
alcohol-2 1H
04-02-2006 11:46:40
1H
single pulse.ex2
495.13 MHz
4.38 KHz
9.6 Hz
13107
7429.3 Hz
16
1.764 sec
5.000 sec
6.2 us
1H
18.8 c
CDCL3
7.26 ppm
0.12 Hz
52

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

F:\11. b-cycno enone\b-cycno
b-cycno-enone 1H
21-10-2006 20:29:09
1H
single pulse.ex2
495.13 MHz
4.38 KHz
9.6 Hz
13107
7429.3 Hz
16
1.764 sec
5.000 sec
6.2 us
1H
21.2 c
CDCL3
7.26 ppm
0.12 Hz
40

35

DFILE
COMNT 1H Line
DATIM Fri Oct 13 10:53:35 2006
OBNUC 1H
EXMOD non
OBFRQ 500.00 MHz
OBSET 160.00 KHz
OBFIN 2160.0 Hz
POINT 32768
FREQU 10000.0 Hz
SCANS 16
ACQTM 3.277 sec
PD 3.723 sec
PW1 5.7 us
IRNUC 1H
CTEMP 27.5 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.12 Hz
RGAIN 22

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

F:\13. aziridine\aziridine.a
aziridine
14-10-2006 11:20:55
1H
single pulse.ex2

495.13 MHz
4.38 KHz
9.6 Hz
13107
7429.3 Hz
16
1.764 sec
5.000 sec
6.2 us
1H
20.9 c
CDCL3
7.26 ppm
0.12 Hz
44
RGAIN

18

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

F:\14. After 3-pentanol addi
After 3
20-10-2006 15:16:08
1H
single pulse.ex2
495.13 MHz
4.38 KHz
9.6 Hz
13107
7429.3 Hz
16
1.764 sec
5.000 sec
6.2 us
1H
21.7 c
CDCL3
7.26 ppm
0.12 Hz
44

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

F:\15. Ac Z 3-pentanol\3-pen
3-pentanol AcZ
21-10-2006 21:02:20
1H
single pulse.ex2
495.13 MHz
4.38 KHz
9.6 Hz
13107
7429.3 Hz
16
1.764 sec
5.000 sec
6.2 us
1H
21.6 c
CDCL3
7.26 ppm
0.12 Hz
54

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

F:\16. Tamiflu-Free\Free-Tam
free-Tamiflu
26-10-2006 22:13:46
1H
single_pulse.ex2
495.13 MHz
4.38 KHz
9.6 Hz
13107
7429.3 Hz
16
1.764 sec
5.000 sec
6.2 us
1H
21.3 c
CDCL3
7.26 ppm
0.12 Hz
50

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

C:\My Documents\PGousei\kuk
N3-oxazolizone-H
06-09-2006 16:57:01
1H
single_pulse.ex2
495.13 MHz
4.38 KHz
9.64 Hz
13107
7429.31 Hz
32
1.7642 sec
5.0000 sec
6.20 usec
1H
23.2 c
DMSO
2.49 ppm
0.12 Hz
44

DFILE
COMNT 1H Line
DATIM Mon Jun 12 06:11:25 2006
OBNUC 1H
EXMOD non
OBFRQ 499.10 MHz
OBSET 120.00 KHz
OBFIN 8250.0 Hz
POINT 32768
FREQU 9980.0 Hz
SCANS 16
ACQTM 3.283 sec
PD 3.717 sec
PW1 6.2 us
IRNUC 1H
CTEMP 23.3 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.12 Hz
RGAIN 22

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

F:\Modified 2nd\4. After ACS
cycliccarbamateBoc Ac 1H
02-08-2006 13:39:34
1H
single pulse.ex2
495.13 MHz
4.38 KHz
9.6 Hz
13107
7429.3 Hz
16
1.764 sec
5.000 sec
6.2 us
1H
22.3 c
CDCL3
7.26 ppm
0.12 Hz
42

DFILE
COMNT 1H Line
DATIM Wed Jul 19 14:43:21 2006
OBNUC 1H
EXMOD non
OBFRQ 499.10 MHz
OBSET 120.00 KHz
OBFIN 8108.5 Hz
POINT 32768
FREQU 10000.0 Hz
SCANS 32
ACQTM 3.277 sec
PD 3.723 sec
PW1 6.2 us
IRNUC 1H
CTEMP 23.4 C
SLVNT CD3OD
EXREF 3.30 ppm
BF 0.12 Hz
RGAIN 19

1.4178
1.5315
1.5560
1.5761
1.6000
1.9191
2.1862
2.1948
2.2052
2.2107
3.2933
3.2969
3.3000
3.3037
3.3067
3.4803
3.5720
4.2665
4.4321
5.4560
5.4762
5.7397
5.7599

1.177

1.088

0.987

2.107

1.005

1.000

10.127

DFILE
COMNT 1H Line
DATIM Sun Jul 30 03:07:21 2006
OBNUC 1H
EXMOD non
OBFRQ 500.00 MHz
OBSET 160.00 KHz
OBFIN 2160.0 Hz
POINT 32768
FREQU 10000.0 Hz
SCANS 16
ACQTM 3.277 sec
PD 3.723 sec
PW1 5.7 us
IRNUC 1H
CTEMP 27.2 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.12 Hz
RGAIN 23

```
DFILE C:\My Documents\PGousei\ufukuda\Shioiri-adduct.als
COMMENT CN-OP(0)(OEt)2
DATIM 02-09-2006 17:48:17
```

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

C:\My Documents\PGousei\kuk
a-alcohol-H
06-10-2006 16:33:34
1H
single_pulse.ex2
495.13 MHz
4.38 KHz
9.64 Hz
13107
7429.31 Hz
16
1.7642 sec
5.0000 sec
6.20 usec
1H
22.1 c
CDCL3
7.24 ppm
0.12 Hz
46

```

F:\Tamilflu\Wita-route\NHAc-NHBoc\up-O-
CDCL3
up-OH-H
COMT 1H
11-09-2006 10:33:12
OENUC 1H
single pulse.ex2
495.13 MHz
OBFRO 4.38 KHz
OBSER 9.6 Hz
OBFIN 13107
POINT 7429.3 Hz
16
SCANS 1.764 sec
ACOTM 5.000 sec
PPD 6.2 us
PW1
1H
IRNUC 19.6 c
CTEMP
SLVNT CDCL3
EXREF 7.24 ppm
BF 0.12 Hz
RGAIN 52

```

DFILE C:\My Documents\PGousei\Fukuda\NHAc-NHBoc\aziridine\Fuku061013-1.1
COMET aziridine
DATIM 13-10-2006 16:09:35
ORNUC 1H
EXMOD single_pulse.ex2
OBFRQ 496.13 MHz
OBSET 4.38 KHz
OBFIN 9.64 Hz
POINT 16384
FREQU 9286.78 Hz
SCANS 16
AQTM 1.7642 sec
PD 5.0000 sec
PWI 6.20 usec
IRNUC 1H
CTEMP 22.0 c
SLVNT CDCl3
EXREF 7.24 ppm
BF 1.20 Hz
RGAIN 44

C:\Documents and Settings\NMRmanager\My Documents\ukuda\savedata25\savedata25.mmdata3-pentyl

```

C:\Documents and Settings\NMRmanager\
3-pentyl
Tue Oct 17 18:07:18 2006
1H
non
500.00 MHz
160.00 KHz
2160.0 Hz
32768
10000.0 Hz
16
3.277 sec
3.723 sec
5.7 us
1H
CDCL3
7.24 ppm
0.12 Hz
BF
RGAIN
23

```

DFILE C:\My Documents\PGousei\Fukuda\NHAc-NHBoc\oxazoline-pure-1.1
 COMNT oxazoline-1H
 DATIM 26-10-2006 19:00:17
 OBNUC 1H
 EXMOD single_pulse_ex2
 OBRQ 495.13 MHz
 OBSEI 4.38 kHz
 OBFIN 9.64 Hz
 POINT 16384
 FREQU 9286.78 Hz
 SCANS 16
 ACQTM 1.7642 sec
 PD 5.0000 sec
 PW1 6.20 usec
 IRNUC 1H
 CTEMP 21.0 c
 SLVNT CDCl3
 EXREF 7.24 ppm
 BF 0.12 Hz
 RGAIN 52

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

C:\My Documents\PGousei\MIT
Boc Ac alkene 13 C
15-09-2006 19:05:21
13C
single_pulse_dec
124.51 MHz
3.45 KHz
6.0 Hz
26214
31249.5 Hz
130
0.839 sec
2.000 sec
3.6 us
1H
23.3 C
CDCL3
77.00 ppm
0.10 Hz
60

DFILE C:\My Documents\PGousei\MIT
 COMNT oxazine 13
 DATIM 04-11-2006 10:16:38
 OBNUC 13C
 EXMOD single_pulse_dec
 OBFRQ 124.51 MHz
 OBSET 3.45 KHz
 OBFIN 6.00 Hz
 POINT 32768
 FREQU 39062.50 Hz
 SCANS 14714
 ACQTM 0.8389 sec
 PD 2.0000 sec
 PW1 3.57 usec
 IRNUC 1H
 CTEMP 21.9 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.12 Hz
 RGAIN 56

DFILE
 COMNT
 DATIM
 OBNUC
 EXMOD
 OBFRO
 OBSET
 OBFIN
 POINT
 FREQU
 SCANS
 ACQTM
 PD
 PW1
 IRNUC
 CTEMP
 SLVNT
 EXREF
 BF
 RGAIN

C:\My Documents\PGousei\MIT
 AC, Z-13C
 25-09-2006 17:15:10
 13C
 single_pulse_dec
 124.51 MHz
 3.45 KHz
 6.0 Hz
 32768
 39062.5 Hz
 2048
 0.839 sec
 2.000 sec
 3.6 us
 1H
 23.5 c
 CDCL3
 77.00 ppm
 0.12 Hz
 56

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

C:\My Documents\PGousei\MIT
Boc Z allylic Al 13C d-MeOH
28-09-2006 20:36:16
13C
single_pulse_dec
124.51 MHz
3.45 KHz
6.0 Hz
32768
39062.5 Hz
256
0.839 sec
2.000 sec
3.6 us
1H
24.1 c
CD3OD
49.00 ppm
0.10 Hz
60

158.5473
158.5186
138.3345
133.9779
130.0426
129.4394
128.9415
128.7787
80.2719
67.4797
67.3935
53.4045
53.0789
49.5170
49.3447
49.1723
49.0000
48.8277
48.6553
48.4830
39.8176
28.7298

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
PPM

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

C:\My Documents\PGousei\MTT
Boc Z enone 13C
29-09-2006 23:00:06
13C
single_pulse_dec
124.51 MHz
3.45 KHz
6.0 Hz
32768
39062.5 Hz
256
0.839 sec
2.000 sec
3.6 us
1H
23.3 C
CDCL3
77.00 ppm
0.12 Hz
58

14

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

C:\My Documents\PGousei\MIT
N-Bocoxazoline 13C
04-10-2006 16:35:52
13C
single_pulse_dec
124.51 MHz
3.45 KHz
6.00 Hz
32768
39062.50 Hz
256
0.8389 sec
2.0000 sec
3.57 usec
1H
23.0 C
CDCL3
77.00 ppm
0.12 Hz
60

1H Line

DFILE
COMNT 1H Line
DATIM Thu Oct 5 16:01:28 2006
OBNUC 13C
EXMOD bcm
OBFRQ 125.65 MHz
OBSET 120.00 KHz
OBFIN 7958.0 Hz
POINT 32768
FREQU 33898.3 Hz
SCANS 256
ACQTM 0.967 sec
PD 2.033 sec
PW1 6.2 us
IRNUC 1H
CTEMP 28.9 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 30

DFILE C:\My Documents\PGousei\MIT
 COMNT b-cycno enone 13C
 DATIM 21-10-2006 20:55:23
 OBNUC 13C
 EXMOD single_pulse_dec
 OBFRQ 124.51 MHz
 OBSET 3.45 KHz
 OBFIN 6.00 Hz
 POINT 32768
 FREQU 39062.50 Hz
 SCANS 512
 ACQTM 0.8389 sec
 PD 2.0000 sec
 PW1 3.57 usec
 IRNUC 1H
 CTEMP 22.1 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 1.20 Hz
 RGAIN 60

DFILE
 COMNT After Reduction 13C
 DATIM 03-10-2006 15:49:07
 OBNUC 13C
 EXMOD single_pulse_dec
 OBFRQ 124.51 MHz
 OBSET 3.45 KHz
 OBFIN 6.00 Hz
 POINT 32768
 FREQU 39062.50 Hz
 SCANS 256
 ACQTM 0.8389 sec
 PD 2.0000 sec
 PW1 3.57 usec
 IRNUC 1H
 CTEMP 22.7 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.12 Hz
 RGAIN 60

17

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

C:\My Documents\PGousei\MITA
aziridine 13C
14-10-2006 11:47:04
13C
single pulse dec
124.51 MHz
3.45 KHz
6.00 Hz
32768
39062.50 Hz
512
0.8389 sec
2.0000 sec
3.57 usec
1H
21.9 c
CDCL3
77.00 ppm
1.20 Hz
60

159.9288
155.3711
140.2522
135.8190
128.6186
128.4080
128.2548
118.1053
112.2550
82.8216
77.2585
77.0000
76.7511
67.2623
41.7833
41.2758
31.8732
29.9773
27.7751

18

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

C:\My Documents\PGousei\MIT
After 3 13C
20-10-2006 15:43:27
13C
single_pulse_dec
124.51 MHz
3.45 KHz
6.00 Hz
32768
39062.50 Hz
512
0.8389 sec
2.0000 sec
3.57 usec
1H
22.5 c
CDCL3
77.00 ppm
0.12 Hz
60

83.2333
80.1502
77.2585
77.0000
76.7511
74.9605
66.7835
54.1350
49.2996
32.6392
28.1964
26.0899
25.7835
9.3529
9.2954

PPM

DFILE C:\My Documents\PGousei\MIT
 COMNT 3-pentanol Ac 13C
 DATIM 17-10-2006 16:53:54
 OBNUC 13C
 EXMOD single_pulse_dec
 OBFRQ 124.51 MHz
 OBSET 3.45 KHz
 OBFIN 6.00 Hz
 POINT 32768
 FREQU 39062.50 Hz
 SCANS 1024
 ACQTM 0.8389 sec
 PD 2.0000 sec
 PW1 3.57 usec
 IRNUC 1H
 CTEMP 22.9 C
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.12 Hz
 RGAIN 60

DFILE
 COMNT
 DATIM
 OBNUC
 EXMOD
 OBFRQ
 OBSET
 OBFIN
 POINT
 FREQU
 SCANS
 ACQTM
 PD
 PW1
 IRNUC
 CTEMP
 SLVNT
 EXREF
 BF
 RGAIN

C:\My Documents\PGousei\free-Tamiflu-13C
 26-10-2006 23:02:55
 13C
 single_pulse_dec
 124.51 MHz
 3.45 KHz
 6.00 Hz
 32768
 39062.50 Hz
 985
 0.8389 sec
 2.0000 sec
 3.57 usec
 1H
 21.8 c
 CDCL3
 77.00 ppm
 0.12 Hz
 60

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFREQ
OBFSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PWL
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

F:\Tamiflu\Mita-route\NHAc-NHBoc\N3-oxazolizone-13C
06-09-2006 17:05:31
13C
single_pulse_dec
124.51 MHz
3.45 KHz
6.0 Hz
26214
31249.5 Hz
131
0.839 sec
2.000 sec
3.6 us
1H
23.8 c
DMSO
39.50 ppm
0.12 Hz
56

1H Line

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

C:\My Documents\PGousei\MIT
1H Line
Thu Jun 8 08:51:30 2006
13C
bcm
125.40 MHz
140.00 KHz
3041.0 Hz
32768
33898.3 Hz
256
0.967 sec
2.033 sec
5.2 us
1H
23.7 c
CDCL3
77.00 ppm
1.20 Hz
28

151.1441
147.5511
129.0006
126.8909
84.6394
77.2555
77.0000
76.7445
67.0037
56.9332
52.1782
27.8425
23.1122

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

C:\My Documents\PGousei\MITA
cycliccarbamateBoc Ac 13C
02-08-2006 14:30:22
13C
single_pulse_dec
124.51 MHz
3.45 KHz
6.0 Hz
32768
39062.5 Hz
1024
0.839 sec
2.000 sec
3.6 us
1H
23.2 C
CDCL3
77.00 ppm
0.12 Hz
58

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
OBFIN
POINT
FREOU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

C:\My Documents\PGousei\MIT
1H Line
Wed Jul 19 15:35:48 2006
13C
bcm

125.40 MHz
140.00 KHz
3041.0 Hz
32768
33898.3 Hz
1024
0.967 sec
2.033 sec
5.2 us
1H
24.0 C
CD3OD
49.00 ppm
0.12 Hz
29

39

1H Line

DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN

C:\My Documents\PGousei\MIT
1H Line
Sat Jul 22 14:11:46 2006
13C
bcm
125.40 MHz
140.00 KHz
3041.0 Hz
32768
33898.3 Hz
2048
0.967 sec
2.033 sec
5.2 us
1H
25.7 c
CDCL3
77.00 ppm
0.12 Hz
30

195.9421
170.8318
156.4019
150.3777
129.8165
80.6178
77.2555
77.0000
76.7445
53.7851
50.9667
43.4180
28.2051
23.0875

22

DFILE C:\My Documents\PGousei\fuk
COMNT a-alcohol-13C
DATIM 06-10-2006 16:50:41
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 124.51 MHz
OBSET 3.45 KHz
OBFIN 6.00 Hz
POINT 32768
FREQU 39062.50 Hz
SCANS 302
ACQTM 0.8389 sec
PD 2.0000 sec
PW1 3.57 usec
IRNUC 1H
CTEMP 23.0 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 56

F:\Tamiflu\Mita-route\NHAc-NHBoc\up-OH-13C.als
up-OH-13C

DFILE F:\Tamiflu\Mita-route\NHAc-NHBoc\up-O
COMNT up-OH-13C
DATIM 11-09-2006 12:10:11
OBNUC 13C
EXMOD single pulse dec
OBFRQ 124.51 MHz
OBSET 3.45 KHz
OBFIN 6.0 Hz
POINT 26214
FREQU 31249.5 Hz
SCANS 2000
ACQTM 0.839 sec
PD 2.000 sec
PWL 3.6 us
IRNUC 1H
CTEMP 21.5 c
SLVNT CDCl3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 60

DFILE C:\My Documents\PGousei\#fukuda\#NHAc-NHBoc\aziridine\#fuku061013-2.1
COMNT aziridine-13C
DATIM 13-10-2006 16:57:33
ORNUC 13C
EXMOD single_pulse_dec
OBRQ 124.51 MHz
ORSET 3.45 KHz
OBFIN 6.00 Hz
POINT 32768
FREQU 39062.50 Hz
SCANS 963
AQTM 0.8389 sec
PD 2.0000 sec
PWI 3.57 usec
IRNUC 1H
SLVNT CDCl3
EXREF 77.00 ppm
BF 1.20 Hz
RGAIN 56

DFILE C:\My Documents\PGousei\Fukuda\NHAc-NHBoc\oxazoline-pure\ft
 COMNT oxazoline-13C
 DATIM 30-10-2006 22:05:36
 ORNUC 13C
 EXMOD single_pul se dec
 OBFRQ 124.51 MHz
 OBSET 3.45 KHz
 OBFIN 6.00 Hz
 POINT 32768
 FREQU 39062.50 Hz
 SCANS 3256
 ACQTM 0.8389 sec
 PD 2.0000 sec
 PW1 3.57 usec
 1H 21.3 c
 CDCL3
 SLVNT
 EXREF 77.00 ppm
 BF 0.72 Hz
 RGAIN 80