Supporting Information

De Novo Synthesis of Tamiflu® via a Catalytic Enantioselective Ring-Opening Reaction of *meso*-Aziridines with $TMSN_3$

Yuhei Fukuta, Tsuyoshi Mita, Nobuhisa Fukuda, Motomu Kanai, and Masakatsu Shibasaki

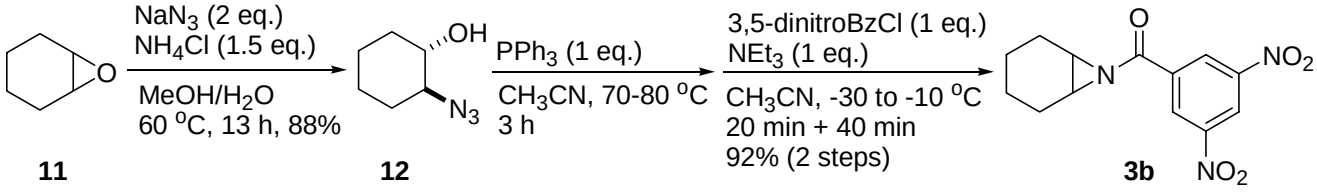
General: Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR, 126.65 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported in the scale relative to $CHCl_3$ (7.26 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.0 ppm) as an internal reference. Chemical shifts in *d*-acetone were reported in the scale relative to *d*-acetone (2.05 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to *d*-acetone (206.26 ppm) as an internal reference. Optical rotations were measured on a JASCO P-1010 polarimeter. ESI mass spectra were measured on Water-ZQ4000. 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, AS-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. $Y(O^iPr)_3$ 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)) **Causion!** Azide compounds are potentially explosive, especially when concentrated to dryness.

(A) Data of Substrates

7-(4-Nitrobenzoyl)-7-azabicyclo[4.1.0]heptane (**3a**): known compound.[2]

***cis*-1-(3,5-Dinitrobenzoyl)-2,3-dimethylaziridine** (**3i**): known compound.[3]

7-(3,5-Dinitrobenzoyl)-7-azabicyclo[4.1.0]heptane (**3b**) was prepared by the following modified method of the reported one.[4]



[1] Kato, N.; Tomita, D.; Maki, K.; Kanai, M.; Shibasaki, M. *J. Org. Chem.* **2004**, *69*, 6128.
[2] Hayashi, M.; Ono, K.; Hoshimi, H.; Oguni, N. *Tetrahedron* **1996**, *52*, 7817.
[3] Szeimies, G.; MannHardt, K.; Junius, M. *Chem. Ber.* **1977**, *110*, 1792.
[4] Zhang, Z.; Scheffold, R. *Helv. Chim. Acta* **1993**, *76*, 2602.

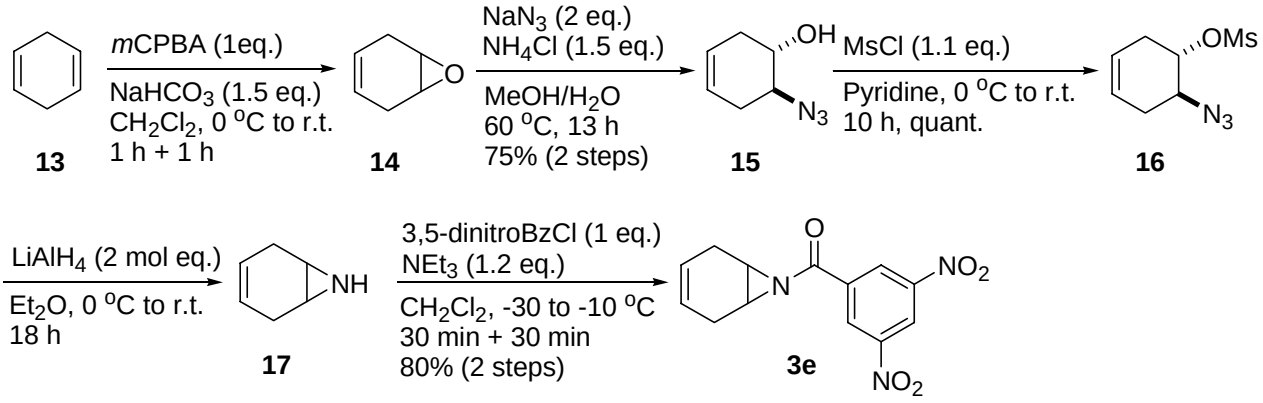
To a solution of cyclohexene oxide (**11**) (2 g, 20.4 mmol) in MeOH/H_2O (30 mL/10 mL), NaN_3 (2.65 g, 40.8 mmol, 2 equiv) and NH_4Cl (1.64 g, 30.6 mmol, 1.5 equiv) were added and the mixture was stirred at 60 ^oC for 13 h. After most of MeOH was removed under reduced pressure, the solution was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford **12** (2.58 g) as a pale yellow oil in 88% yield.

To a solution of **12** (2.58 g, 18.3 mmol) in CH_3CN (30 mL), PPh_3 (4.79 g, 18.3 mmol, 1 equiv) was added and the mixture was stirred at 70-80 ^oC for 3 h. Et_3N (2.6 mL, 18.3 mmol, 1 equiv) was added to the mixture and the mixture was cooled to -30 ^oC. 3,5-Dinitrobenzoyl chloride (4.21 g, 18.3 mmol, 1 equiv) in CH_3CN was added dropwise at -30 ^oC, and the mixture was stirred for 20 min at -30 ^oC and for 40 min at -10 ^oC. Water was added dropwise and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 twice and the combined organic layer was washed with brine before dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexane-AcOEt, 6:1 to 2:1) to afford **3b** (4.87 g, 16.7 mmol) as a colorless solid in 92% yield (2 steps).

8-(3,5-Dinitrobenzoyl)-8-azabicyclo[5.1.0]octane (**3d**), ***N*-(3,5-dinitrobenzoyl)-2,3-iminotetralin** (**3f**), ***cis*-1-(3,5-dinitrobenzoyl)-2,3-dipropylaziridine** (**3j**), ***cis*-1-(3,5-dinitrobenzoyl)-2,3-diphenylaziridine** (**3k**) were prepared by the method similar to the method for **3b**.

7-(3,5-Dinitrobenzoyl)-7-azabicyclo[4.1.0]hept-3-ene (**3e**) could be prepared by the following two methods.

Method 1 (modification of the reported method[5])



To a suspension of *m*CPBA (16.8 g, 63.4 mmol, 1 equiv) and $NaHCO_3$ (7.99 g, 95.1 mmol, 1.5 equiv) in CH_2Cl_2 (200 mL), 1,4-cyclohexadiene (**13**) (6 mL, 63.4 mmol) was added dropwise with cooling in an ice bath. After stirring for 1 h at 0 ^oC, the reaction mixture was allowed to stir at room temperature. After stirring for 1 h, saturated aqueous $Na_2S_2O_3$ was added and the mixture was stirred for 1 h at room temperature. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford crude epoxide **14**.

To a solution of epoxide **14** in MeOH/H_2O (60mL/20mL), NaN_3 (8.25 g, 126.8 mmol, 2 equiv) and

[5] Zipperer, B.; Muller, K. H.; Gallenkamp, B.; Hildebrand, R.; Fletschinger, M.; Burger, D.; Pillat, M.; Hunkler, D.; Knothe, L.; Fritz, H.; Prinzbach, H. *Chem. Ber.* **1988**, *121*, 757.

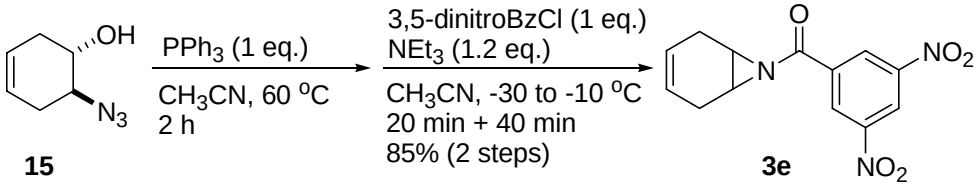
NH_4Cl (5.09 g, 95.1 mmol, 1.5 equiv) were added and the mixture was stirred at 60 ^oC for 13 h. After most of MeOH was removed under reduced pressure, the solution was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane-AcOEt, 3:1) to afford **15** (6.61 g, 47.5 mmol) as pale yellow oil in 75% yield (2 steps).

To a solution of **15** (6.61 g, 47.5 mmol) in pyridine (30 mL) was added methanesulfonyl chloride (4.04 mL, 52.2 mmol, 1.1 equiv) dropwise over 15 min at 0 ^oC. The reaction temperature was allowed to increase to room temperature, and after stirring for 10 h, water was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layer was washed with 1 M HCl and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane-AcOEt, 3:1) to afford **16** (10.3 g, 47.5 mmol) in quantitative yield.

To a suspension of $LiAlH_4$ (3.61 g, 95.0 mmol, 2 mol equiv) in Et_2O (100 mL) was added **16** (10.3 g, 47.5 mmol) dropwise over 30 minutes at 0 ^oC. The reaction mixture was allowed to rise to room temperature and after stirring for 18 h, quenched with H_2O (4 mL), 4 M NaOH (4 mL) and H_2O (12 mL) with cooling in an ice bath. After stirring for 1 h at room temperature, the mixture was filtered and the filtrate was extracted with Et_2O three times. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated carefully under reduced pressure to afford crude aziridine **17** as pale yellow oil.

To a solution of crude aziridine **17** and Et_3N (7.9 mL, 57.0 mmol. 1.2 equiv) in CH_2Cl_2 (100 mL), 3,5-dinitrobenzoyl chloride (11.0 g, 47.5 mmol, 1 equiv) in CH_2Cl_2 was added dropwise at -30 ^oC, and the mixture was stirred for 30 min at -30 ^oC and for 30 min at -10 ^oC. Water was added dropwise and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 twice and the combined organic layer was washed with brine before dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, hexane-AcOEt, 6:1 to 2:1) to afford **3e** (10.96 g, 37.9 mmol) as a colorless solid in 80% yield (2 steps).

Method 2



15 **3e**

Azido alcohol **15** was prepared according to the synthetic scheme of **method 1**. To a solution of **15** (6.89 g, 49.5 mmol) in CH_3CN (50 mL), PPh_3 (13.0 g, 49.6 mmol, 1 equiv) was added and the mixture was stirred at 60 ^oC for 2 h. Et_3N (8.3 mL, 59.1 mmol, 1.2 equiv) was added to the mixture and the mixture was cooled to -30 ^oC. 3,5-Dinitrobenzoyl chloride (11.4 g, 49.4 mmol, 1 equiv) in CH_3CN was added dropwise at -30 ^oC, and the mixture was stirred for 20 min at -30 ^oC and for 40 min at -10 ^oC. Water was added dropwise and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 twice 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, 6:1 to 2:1) to

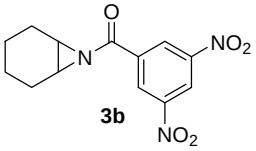
afford **3e** (12.2 g, 42.2 mmol) as a colorless solid in 85% yield (2 steps).

6-(3,5-Dinitrobenzoyl)-6-azabicyclo[3.1.0]hexane (**3c**) was prepared via acylation of 6-azabicyclo[3.1.0]hexane.[4]

3-Oxa-6-(3,5-dinitrobenzoyl)-6-azabicyclo[3.1.0]hexane (**3g**) was prepared via acylation of 3-oxa-6-azabicyclo[3.1.0]hexane.[6]

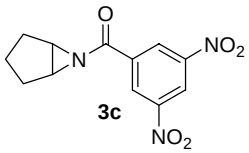
3-Carbobenzyloxy-6-(3,5-dinitrobenzoyl)-3,6-diazabicyclo[3.1.0]hexane (**3h**) was prepared via acylation of 3-carbobenzyloxy-3,6-diazabicyclo[3.1.0]hexane.[7]

7-(3,5-Dinitrobenzoyl)-7-azabicyclo[4.1.0]heptane (**3b**): colorless solid; IR (KBr): 3110, 3061, 2940, 2861, 1673, 1627, 1540, 1348, 1309, 919, 722 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.21 (t, J = 2.2 Hz, 1H), 9.12 (d, J = 2.2 Hz, 2H), 2.93-2.89 (m, 2H), 2.17-2.10 (m, 2H), 2.04-1.97 (m, 2H), 1.66-1.57 (m, 2H), 1.48-1.39 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 175.1, 148.6, 137.0, 128.7, 121.8, 38.4, 23.7, 19.8; MS (ESI): *m/z* 314 [M+Na^+]; Anal. calcd for $C_{13}H_{13}N_3O_5$: C, 53.61; H, 4.50; N, 14.43%. Found: C, 53.68; H, 4.58; N, 14.40%.



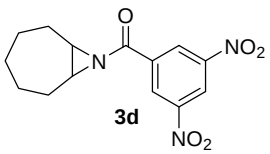
3b

6-(3,5-Dinitrobenzoyl)-6-azabicyclo[3.1.0]hexane (**3c**): colorless solid; IR (KBr): 3114, 3085, 2932, 2858, 1672, 1540, 1382, 1344, 1315, 1281, 1160, 1072, 730, 719 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.20 (t, J = 2.2 Hz, 1H), 9.10 (d, J = 2.2 Hz, 2H), 3.34 (s, 2H), 2.26-2.19 (m, 2H), 1.84-1.75 (m, 3H), 1.50-1.40 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 173.0, 148.6, 137.1, 128.4, 121.7, 44.9, 26.9, 19.4; MS (ESI): *m/z* 300 [M+Na^+]; Anal. calcd for $C_{12}H_{11}N_3O_5$: C, 51.99; H, 4.00; N, 15.16%. Found: C, 51.90; H, 4.17; N, 14.95%.



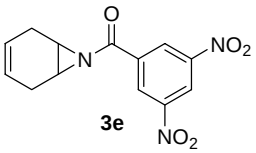
3c

8-(3,5-Dinitrobenzoyl)-8-azabicyclo[5.1.0]octane (**3d**): colorless solid; IR (KBr): 3104, 2925, 2855, 1672, 1542, 1455, 1346, 1309, 1173, 729 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.19 (t, J = 2.2 Hz, 1H), 9.10 (d, J = 2.2 Hz, 2H), 2.87 (t, J = 2.8 Hz, 2H), 2.20-2.01 (m, 4H), 1.77-1.58 (m, 5H), 1.38-1.27 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 174.9, 148.7, 137.0, 128.6, 121.7, 43.1, 31.2, 28.7, 25.3; MS (ESI): *m/z* 328 [M+Na^+]; Anal. calcd for $C_{14}H_{15}N_3O_5$: C, 55.08; H, 4.95; N, 13.76%. Found: C, 55.12; H, 5.04; N, 13.71%.



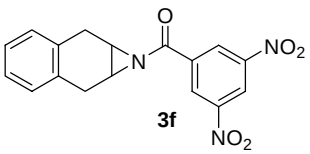
3d

7-(3,5-Dinitrobenzoyl)-7-azabicyclo[4.1.0]hept-3-ene (**3e**): colorless solid; IR (KBr): 3112, 3085, 2908, 2896, 1677, 1537, 1341, 1293, 729, 720, 674 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.19 (t, J = 2.2 Hz, 1H), 9.10 (d, J = 2.2 Hz, 2H), 5.60 (s, 2H), 3.07 (s, 2H), 2.77-2.66 (m, 2H), 2.63-2.52 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 174.5, 148.6, 137.1, 128.7, 122.1, 121.8, 37.5, 23.8; MS (ESI): *m/z* 312 [M+Na^+]; Anal. calcd for $C_{13}H_{11}N_3O_5$: C, 53.98; H, 3.83; N, 14.53%. Found: C, 54.01; H, 3.98; N, 14.47%.



3e

***N*-(3,5-Dinitrobenzoyl)-2,3-iminotetralin** (**3f**): colorless solid; IR (KBr): 3100, 2923, 2834, 1681, 1543, 1419, 1343, 1302, 1284, 729, 719 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.17 (t, J = 2.2 Hz, 1H), 8.96 (d, J = 2.2 Hz, 2H), 7.24 (dd, J = 5.5, 3.4 Hz, 2H), 7.15 (dd, J = 5.5, 3.4 Hz, 2H), 3.44 (d, J = 16.1 Hz, 2H), 3.33-3.25 (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 173.7, 148.3, 136.7, 131.4, 129.0, 128.3, 127.1, 121.5, 38.0, 29.2; MS (ESI): *m/z* 362 [M+Na^+]; Anal. calcd for $C_{17}H_{13}N_3O_5$: C, 60.18; H, 3.86; N, 12.38%. Found: C,

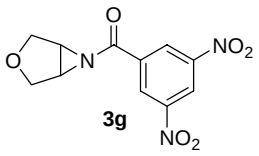


3f

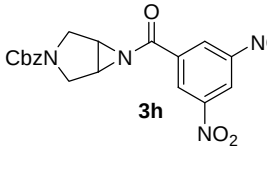
[6] Fanta, P. E.; Walsh, E. N. *J. Org. Chem.* **1966**, *31*, 59.
[7] Oida, S.; Kuwano, H.; Ohashi, Y.; Ohki, E. *Chem. Pharm. Bull.* **1970**, *18*, 2478

59.91; H, 4.13; N, 12.44%.

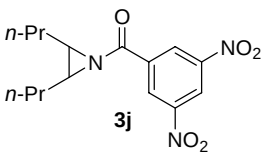
3-Oxa-6-(3,5-dinitrobenzoyl)-6-azabicyclo[3.1.0]hexane (**3g**): colorless solid; IR (KBr): 3110, 2912, 2881, 1669, 1543, 1384, 1347, 1313, 1075, 714 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.20 (t, *J* = 2.3 Hz, 1H), 9.07 (d, *J* = 2.3 Hz, 2H), 4.00 (d, *J* = 10.6 Hz, 2H), 3.65 (d, *J* = 10.6 Hz, 2H), 3.62 (s, 2H); ^{13}C NMR ($CDCl_3$): δ = 171.4, 148.6, 137.1, 128.1, 121.8, 65.9, 41.8; MS (ESI): *m/z* 302 [M+Na^+]; Anal. calcd for $C_{11}H_9N_3O_6$: C, 47.32; H, 3.25; N, 15.05%. Found: C, 47.41; H, 3.39; N, 14.83%.



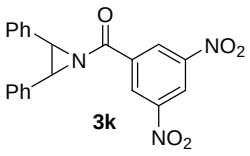
3-Carbobenzyloxy-6-(3,5-dinitrobenzoyl)-3,6-diazabicyclo[3.1.0]hexane (**3h**): colorless solid; IR (KBr): 3095, 2957, 2890, 1697, 1549, 1429, 1364, 1342, 1290, 742, 728, 720 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.17 (t, *J* = 2.2 Hz, 1H), 8.99 (d, *J* = 2.2 Hz, 2H), 7.38-7.28 (m, 5H), 5.09 (s, 2H), 4.12 (d, *J* = 12.5 Hz, 1H), 4.00 (d, *J* = 12.5 Hz, 1H), 3.60-3.50 (m, 2H), 3.49-3.40 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 171.6, 154.7, 148.6, 136.3, 136.0, 128.5, 128.2, 127.8, 122.1, 67.3, 46.1, 45.6, 41.7, 41.6; MS (ESI): *m/z* 435 [M+Na^+]; Anal. calcd for $C_{19}H_{16}N_4O_7$: C, 55.34; H, 3.91; N, 13.59%. Found: C, 55.32; H, 4.03; N, 13.49%.



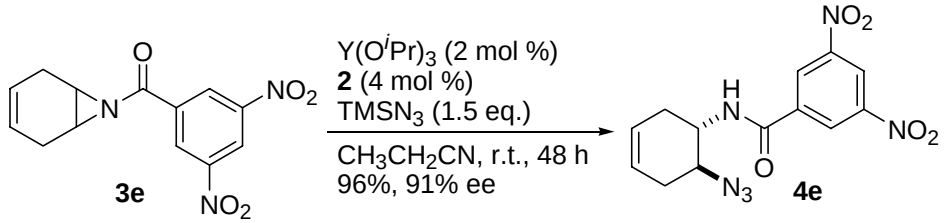
***cis*-1-(3,5-Dinitrobenzoyl)-2,3-dipropylaziridine** (**3j**): colorless solid; IR (KBr): 3082, 2956, 2871, 1679, 1630, 1552, 1343, 1313, 721 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.20 (t, *J* = 2.2 Hz, 1H), 9.12 (d, *J* = 2.2 Hz, 2 H), 2.72-2.66 (m, 2H), 1.82-1.74 (m, 2H), 1.73-1.64 (m, 2H), 1.60-1.48 (m, 4H), 1.02 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ =175.4, 148.6, 137.2, 128.8, 121.8, 43.5, 29.7, 20.5, 13.9; MS (ESI): *m/z* 344 [M+Na^+]; Anal. calcd for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08%. Found: C, 56.25; H, 5.94; N, 13.22%.



***cis*-1-(3,5-Dinitrobenzoyl)-2,3-diphenylaziridine** (**3k**): colorless solid; IR (KBr): 3081, 1684, 1548, 1357, 1342, 1322, 1292, 754, 722, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.20-9.15 (m, 3H), 7.30-7.21 (m, 10H), 4.22 (s, 2H); ^{13}C NMR ($CDCl_3$): δ =174.9, 148.7, 136.0, 132.2, 128.9, 128.4, 128.2, 127.8, 122.2, 47.7; MS (ESI): *m/z* 412 [M+Na^+]; Anal. calcd for $C_{21}H_{15}N_3O_5$: C, 64.78; H, 3.88; N, 10.79%. Found: C, 64.89; H, 4.11; N, 10.89%.



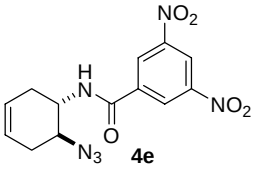
(B) General Procedure for Enantioselective Ring-Opening Reaction of Aziridine with $TMSN_3$



To a solution of ligand **2** (4.6 mg, 0.01 mmol, 4 mol %) in THF (0.15 mL), $Y(O^iPr)_3$ (0.2 M in THF, 25 μL, 0.005 mmol, 2 mol %) was added at room temperature. The mixture was stirred at 45-60 ^oC for 1 h, and then the solvent was evaporated. After drying the resulting pre-catalyst under reduced pressure (<5 mmHg) for 2 h, **3e** (72.3 mg, 0.25 mmol) and propionitrile (1.25 mL) was added at room temperature. After 10 min, $TMSN_3$ (49.1 μL, 0.38 mmol, 1.5 equiv) was added to start the reaction. After 48 h, water was added followed by the addition of AcOEt. The organic layer was separated and the aqueous layer was

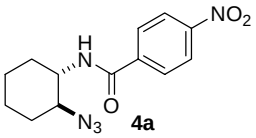
extracted with AcOEt twice and the combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, hexane-AcOEt, 4:1 to 3:2) to afford the **4e** (79.6 mg, 0.24 mmol) in 96% yield as colorless solid. The enantiomeric excess of the product was determined by HPLC analysis to be 91% ee. This reaction was applicable on a 1.45 g scale. (92% ee, 87% yield). 99% ee of **4e** was obtained after recrystallization from 2-propanol (recrystallization yield; 72%).

(4*S*,5*S*)-4-Azido-5-[*N*-(3,5-dinitrobenzoyl)amino]cyclohexene (**4e**): colorless solid; IR (KBr): 3249, 3094, 2093, 1640, 1542, 1342, 1244, 1078, 919, 729, 719, 697cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 9.19 (t, *J* = 2.0 Hz, 1H), 8.96 (d, *J* = 2.0 Hz, 2H), 6.41 (d, *J* = 7.5 Hz, 1H), 5.76-5.68 (m, 2H), 4.35-4.29 (m, 1H), 3.84-3.80 (m, 1H), 2.81-2.70 (m, 1H), 2.66-2.55 (m, 1H), 2.43-2.31 (m, 1H), 2.27-2.16 (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 162.9, 148.7, 137.7, 127.3, 124.5, 124.0, 121.2, 59.0, 50.0, 30.7, 29.7; MS (ESI): *m/z* 355 [M+Na$^+$]; HRMS (FAB): *m/z* calcd for $C_{13}H_{13}N_6O_5$ [M+H$^+$]: 333.0947. Found: 333.0941; $[\alpha]^{22}_D$ +91.1 (*c* = 1.052, $CHCl_3$) (91% ee) $[\alpha]^{25}_D$ +103.2 (*c* = 1.015, $CHCl_3$) (99% ee); HPLC (Chiralpak AS-H, 2-propanol/hexane 1/4, flow 1.0 mL/min, detection at 254 nm.): t_R 23.5 min (minor) and 35.0 min (major).



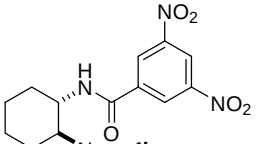
4e

***trans*-1-Azido-2-[*N*-(4-nitrobenzoyl)amino]cyclohexane** (**4a**): colorless solid; IR (KBr): 3276, 2926, 2860, 2096, 1639, 1601, 1523, 1349, 1257, 869, 833, 707 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.27 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 8.5 Hz, 2H), 6.24 (d, *J* = 8.0 Hz, 1H), 4.02-3.90 (m, 1H), 3.35-3.21 (m, 1H), 2.26-2.11 (m, 2H), 1.92-1.823 (m, 1H), 1.817-1.71 (m, 1H), 1.58-1.47 (m, 1H), 1.46-1.28 (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 165.4, 149.5, 140.2, 128.2, 123.8, 63.8, 53.6, 32.0, 30.7, 24.3, 24.2; MS (ESI): *m/z* 312 [M+Na$^+$]; HRMS (FAB): *m/z* calcd for $C_{13}H_{16}N_5O_3$ [M+H$^+$]: 290.1253. Found: 290.1264; $[\alpha]^{21}_D$ +50.9 (*c* = 0.598, $CHCl_3$) (68% ee); HPLC (Chiralpak AD-H, 2-propanol/hexane 1/9, flow 1.0 mL/min, detection at 254 nm.): t_R 27.8 min (minor) and 31.5 min (major).



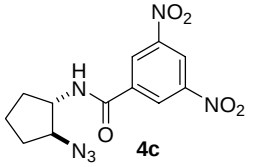
4a

(1*S*,2*S*)-1-Azido-2-[*N*-(3,5-dinitrobenzoyl)amino]cyclohexane (**4b**): colorless solid; IR (KBr): 3268, 3108, 3090, 2944, 2861, 2093, 1646, 1547, 1338, 1259, 1078, 918, 730, 711 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 9.17 (t, *J* = 2.2 Hz, 1H), 8.96 (d, *J* = 2.2 Hz, 2H), 6.34 (d, *J* = 7.7 Hz, 1H), 4.04-3.94 (m, 1H), 3.38-3.27 (m, 1H), 2.29-2.15 (m, 2H), 1.98-1.76 (m, 2H), 1.66-1.50 (m, 1H), 1.50-1.32 (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 162.6, 148.6, 137.9, 127.3, 121.1, 63.6, 54.0, 32.0, 30.7, 24.3, 24.2; MS (ESI): *m/z* 357 [M+Na$^+$]; HRMS (FAB): *m/z* calcd for $C_{13}H_{15}N_6O_5$ [M+H$^+$]: 335.1104. Found: 335.1089; $[\alpha]^{23}_D$ +76.8 (*c* = 0.654, $CHCl_3$) (93% ee); HPLC (Chiralpak AD-H, 2-propanol/hexane 1/9, flow 1.0 mL/min, detection at 254 nm.): t_R 16.8 min (minor) and 22.7 min (major).



4b

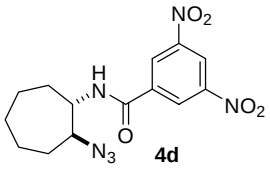
***trans*-1-Azido-2-[*N*-(3,5-dinitrobenzoyl)amino]cyclopentane** (**4c**): colorless solid; IR (KBr): 3303, 3106, 2959, 2874, 2104, 1648, 1544, 1342, 1266, 1077, 917, 729, 695 cm^{-1}; ^{1}H NMR (*d*-acetone): δ = 9.06 (s, 3H), 8.56 (d, *J* = 5.2 Hz, 1H), 4.43-4.35 (m, 1H), 4.09-4.02 (m, 1H), 2.25-2.151 (m, 1H), 2.149-2.06 (m, 1H), 1.88-1.65 (m, 4H); ^{13}C NMR (*d*-acetone): δ = 163.3, 149.6, 138.6, 128.3, 121.7, 67.6, 58.0, 30.43, 30.41, 21.9; MS (ESI): *m/z* 343 [M+Na$^+$]; HRMS (FAB): *m/z* calcd for $C_{12}H_{13}N_6O_5$ [M+H$^+$]: 321.0947. Found: 321.0937;



4c

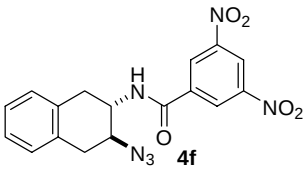
$[\alpha]^{21}_{D}$ +53.9 (*c* = 1.415, Acetone) (94% ee); HPLC (Chiralpak AD-H, 2-propanol/hexane 1/9, flow 1.0 mL/min, detection at 254 nm.): t_R 15.7 min (minor) and 20.0 min (major).

***trans*-1-Azido-2-[*N*-(3,5-dinitrobenzoyl)amino]cycloheptane** (**4d**): colorless solid; IR (KBr): 3296, 3107, 3089, 2934, 2863, 2096, 1650, 1545, 1344, 1259, 1079, 916, 729 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.14 (t, *J* = 2.0 Hz, 1H), 8.98 (d, *J* = 2.0 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 1H), 4.13-4.03 (m, 1H), 3.61-3.54 (m, 1H), 2.09-1.96 (m, 2H), 1.89-1.52 (m, 8H); ^{13}C NMR ($CDCl_3$): δ = 162.4, 148.6, 138.0, 127.3, 121.1, 66.5, 56.8, 31.8, 30.6, 27.2, 24.0, 23.0; MS (ESI): *m/z* 371 [M+Na^+]; HRMS (FAB): *m/z* calcd for $C_{14}H_{17}N_6O_5$ [M+H^+]: 349.1260. Found: 349.1255; $[\alpha]^{23}_{D}$ +55.0 (*c* = 0.606, $CHCl_3$) (86% ee); HPLC (Chiralpak AD-H, 2-propanol/hexane 1/9, flow 1.0 mL/min, detection at 254 nm.): t_R 15.2 min (minor) and 23.1 min (major).



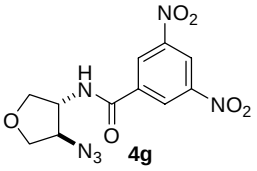
4d

***trans*-2-Azido-3-[*N*-(3,5-dinitrobenzoyl)amino]tetralin** (**4f**): colorless solid; IR (KBr): 3257, 3102, 2101, 1642, 1537, 1348, 1298, 1078, 916, 749, 729 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.18 (t, *J* = 2.2 Hz, 1H), 8.96 (d, *J* = 2.2 Hz, 2H), 7.25-7.11 (m, 4H), 6.47 (d, *J* = 7.7 Hz, 1H), 4.52-4.44 (m, 1H), 4.08-4.00 (m, 1H), 3.48 (dd, *J* = 16.8, 5.5 Hz, 1H), 3.31 (dd, *J* = 16.8, 5.2 Hz, 1H), 3.09 (dd, *J* = 16.8, 8.9 Hz, 1H), 2.95 (dd, *J* = 16.8, 8.9 Hz, 1H); ^{13}C NMR (*d*-acetone): δ = 163.6, 149.7, 138.7, 134.5, 133.9, 129.7, 129.6, 128.4, 127.4, 127.3, 121.9, 60.9, 51.4, 34.8, 34.5; MS (ESI): *m/z* 405 [M+Na^+]; HRMS (FAB): *m/z* calcd for $C_{17}H_{15}N_6O_5$ [M+H^+]: 383.1104. Found: 383.1102; $[\alpha]^{23}_{D}$ +85.6 (*c* = 0.584, $CHCl_3$) (91% ee); HPLC (Chiralpak AS-H, 2-propanol/hexane 1/1, flow 1.0 mL/min, detection at 254 nm.): t_R 9.0 min (minor) and 27.0 min (major).



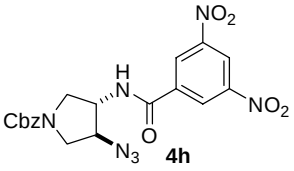
4f

***trans*-3-Azido-4-[*N*-(3,5-dinitrobenzoyl)amino]tetrahydrofuran** (**4g**): colorless solid; IR (KBr): 3309, 2104, 1674, 1654, 1538, 1349, 1283, 1245, 1058, 918, 730 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.19 (t, *J* = 2.3 Hz, 1H), 9.01 (d, *J* = 2.3 Hz, 2H), 6.68 (d, *J* = 6.9 Hz, 1H), 4.67-4.59 (m, 1H), 4.28-4.23 (m, 1H), 4.21 (dd, *J* = 10.0, 6.0 Hz, 1H), 4.10 (dd, *J* = 10.3, 5.2 Hz, 1H), 3.97 (d, *J* = 10.3, 1.8 Hz, 1H), 3.73 (dd, *J* = 10.0, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 162.7, 148.8, 136.8, 127.3, 121.5, 71.6, 71.0, 66.2, 57.7; MS (ESI): *m/z* 345 [M+Na^+]; Anal. calcd for $C_{11}H_{10}N_6O_6$: C, 41.00; H, 3.13; N, 26.08%. Found: C, 41.23; H, 3.32; N, 25.68%; $[\alpha]^{21}_{D}$ +85.3 (*c* = 1.420, Acetone) (96% ee); HPLC (Chiralpak AD-H, 2-propanol/hexane 1/4, flow 1.0 mL/min, detection at 254 nm.): t_R 10.8 min (major) and 16.9 min (minor).



4g

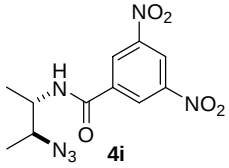
***trans*-1-Carbobenzyloxy-3-azido-4-[*N*-(3,5-dinitrobenzoyl)amino]pyrrolidine** (**4h**): colorless solid; IR (KBr): 3330, 3094, 2125, 1698, 1662, 1541, 1451, 1425, 1345, 1213, 1097, 921, 731, 720 cm^{-1}; ^1H NMR (*d*-acetone): δ = 9.11-9.02 (m, 3H), 8.90-8.77 (m, 1H), 7.44-7.27 (m, 5H), 5.18-5.06 (m, 2H), 4.72-4.60 (m, 1H), 4.49-4.39 (m, 1H), 3.96-3.76 (m, 2H), 3.69-3.57 (m, 1H), 3.56-3.44 (m, 1H); ^{13}C NMR (*d*-acetone): δ = 163.9, 155.0, 149.6, 138.2, 138.1, 129.4, 128.8, 128.7, 128.5, 122.0, 67.4, 64.9, 64.0, 56.2, 55.4, 50.0, 49.7, 49.6, 49.4; MS (ESI): *m/z* 478 [M+Na^+]; HRMS (FAB): *m/z* calcd for $C_{19}H_{18}N_7O_7$ [M+H^+]: 456.1268. Found: 456.1252; $[\alpha]^{21}_{D}$ +6.2 (*c* = 0.910, Acetone) (94% ee); HPLC (Chiralpak AD-H, 2-propanol/hexane 1/9, flow 1.0 mL/min, detection at 254 nm.): t_R 45.7 min (major) and 55.2 min



4h

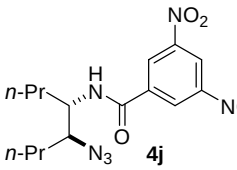
(minor).

(1*S*,2*S*)-2-Azido-3-[*N*-(3,5-dinitrobenzoyl)amino]butane (**4i**): colorless solid; IR (KBr): 3284, 3087, 2985, 2111, 1643, 1548, 1342, 1309, 1261, 1076, 917, 731, 722, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.18 (t, *J* = 2.2 Hz, 1H), 8.95 (d, *J* = 2.2 Hz, 2H), 6.43 (d, *J* = 8.6 Hz, 1H), 4.38-4.30 (m, 1H), 3.81-3.75 (m, 1H), 1.37 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 162.4, 148.6, 137.7, 127.2, 121.2, 61.6, 49.9, 18.9, 17.0; MS (ESI): *m/z* 331 [M+Na^+]; HRMS (FAB): *m/z* calcd for $C_{11}H_{13}N_6O_5$ [M+H^+]: 309.0947. Found: 309.0955; $[\alpha]^{23}_D$ +46.4 (*c* = 0.690, $CHCl_3$) (95% ee); HPLC (Chiralpak AD-H, 2-propanol/hexane 1/9, flow 1.0 mL/min, detection at 254 nm.): t_R 13.9 min (minor) and 15.3 min (major).



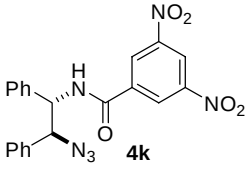
4i

***anti*-4-Azido-5-[*N*-(3,5-dinitrobenzoyl)amino]octane** (**4j**): colorless solid; IR (KBr): 3312, 2960, 2107, 1647, 1542, 1344, 1079, 916, 729, 720 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.16 (t, *J* = 2.1 Hz, 1H), 8.95 (d, *J* = 2.1 Hz, 2H), 6.44 (d, *J* = 9.2 Hz, 1H), 4.39-4.29 (m, 1H), 3.64-3.56 (m, 1H), 1.77-1.33 (m, 8H), 0.99-0.91 (m, 6H); ^{13}C NMR ($CDCl_3$): δ = 162.6, 148.6, 137.7, 127.2, 121.1, 65.8, 52.4, 35.6, 34.4, 19.5, 19.3, 13.79, 13.77; MS (ESI): *m/z* 387 [M+Na^+]; HRMS (FAB): *m/z* calcd for $C_{15}H_{21}N_6O_5$ [M+H^+]: 365.1573. Found: 365.1562; $[\alpha]^{23}_D$ -20.5 (*c* = 1.428, $CHCl_3$) (87% ee); HPLC (Chiralcel OD-H, 2-propanol/hexane 1/9, flow 1.0 mL/min, detection at 254 nm.): t_R 24.4 min (minor) and 31.7 min (major).



4j

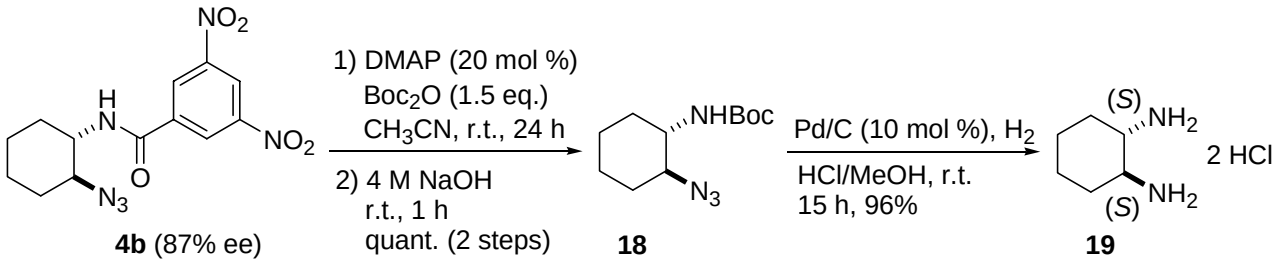
***anti*-1-Azido-2-[*N*-(3,5-dinitrobenzoyl)amino]-1,2-diphenylethane** (**4k**): colorless solid; IR (KBr): 3320, 3092, 2105, 1642, 1541, 1344, 1077, 919, 730, 721, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 9.11 (t, *J* = 2.2 Hz, 1H), 8.98 (d, *J* = 2.2 Hz, 2H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.44-7.21 (m, 10H), 5.53 (dd, *J* = 8.0, 6.7 Hz 1H), 5.06 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 162.8, 148.5, 137.9, 137.4, 135.9, 128.94, 128.92, 128.7, 128.3, 127.3, 127.1, 127.0, 121.2, 69.5, 59.1; MS (ESI): *m/z* 455 [M+Na^+]; HRMS (FAB): *m/z* calcd for $C_{21}H_{17}N_6O_5$ [M+H^+]: 433.1260. Found: 433.1235; $[\alpha]^{23}_D$ +42.8 (*c* = 1.384, $CHCl_3$) (93% ee); HPLC (Chiralpak AD-H, 2-propanol/hexane 1/9, flow 1.0 mL/min, detection at 254 nm.): t_R 26.5 min (minor) and 33.0 min (major).



4k

(C) Transformation into 1,2-Diamine

(1*S*,2*S*)-1,2-Diaminocyclohexane dihydrochloride (**19**):



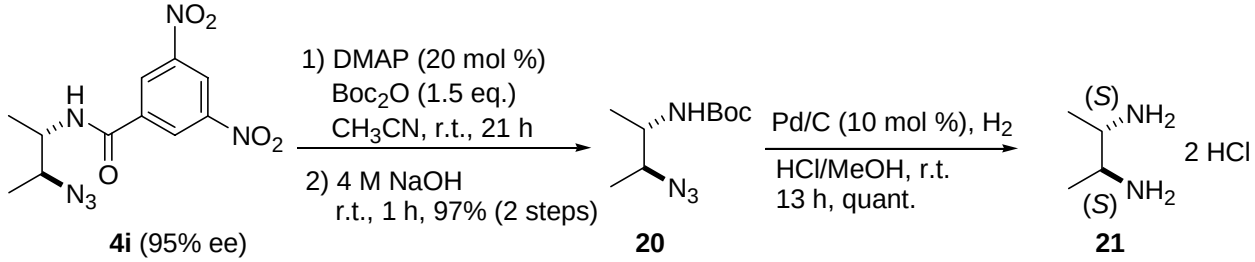
4b (87% ee) **18** **19**

To a solution of **4b** (68.8 mg, 0.21 mmol, 87% ee) in CH_3CN (1 mL), Boc_2O (71 μL, 0.31 mmol, 1.5 equiv) and DMAP (5.0 mg, 0.041 mmol, 20 mol %) were added and the mixture was stirred at room temperature for 24 h. 4 M NaOH (1 mL) was added and the mixture was stirred at room temperature for 1 h. Water was added and the mixture was extracted with CH_2Cl_2 three times. Combined organic layer was

washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (silica gel, hexane-AcOEt, 4:1) to afford **18** (49.5 mg, 0.21 mmol) as a colorless solid in quantitative yield (2 steps). IR (KBr): 3349, 2942, 2859, 2104, 1683, 1531, 1368, 1319, 1266, 1173, 1049, 661 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 4.62-4.45 (m, 1H), 3.46-3.32 (m, 1H), 3.16-3.02 (m, 1H), 2.10-1.98 (m, 2H), 1.80-1.63 (m, 2H), 1.49-1.34 (m, 10H), 1.33-1.16 (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 155.3, 79.6, 64.3, 53.8, 32.2, 30.6, 28.3, 24.3, 24.0; MS (ESI): *m/z* 263 [M+Na^+]; HRMS (FAB): *m/z* calcd for $C_{11}H_{21}N_4O_2$ [M+H^+]: 241.1665. Found: 241.1664.

To a solution of **18** (49.5 mg, 0.21 mmol) in MeOH, 1 M HCl/MeOH (2 mL) was added and the mixture was stirred at r.t. for 1 h. 10% Pd/C (21.9 mg, 10 mol % (based on Pd)) was added and the mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 15 h. The mixture was filtered through celite pad and concentrated under reduced pressure to afford (1*S*,2*S*)-1,2-diaminocyclohexane dihydrochloride[8] (**19**) (36.8 mg, 0.20 mmol) as a colorless solid in 96% yield. The absolute configuration was determined to be 1*S*,2*S* based on the comparison of the optical rotation with the reported value.[8] $[\alpha]^{21}_D$ +13.5 (*c* = 1.840, H_2O). [lit. $[\alpha]_D$ -15.8 (*c* = 2.53, H_2O) for 1*R*,2*R* enantiomer.]

(2*S*,3*S*)-2,3-Diaminobutane dihydrochloride (**21**):



To a solution of **4i** (285.9 mg, 0.93 mmol, 95% ee) in CH_3CN (2 mL), Boc_2O (320 μL, 1.39 mmol, 1.5 equiv) and DMAP (22.7 mg, 0.19 mmol, 20 mol %) were added and the mixture was stirred at room temperature for 21 h. 4 M NaOH (3 mL) was added and the mixture was stirred at room temperature for 1 h. Water was added and the mixture was extracted with CH_2Cl_2 three times. Combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (silica gel, hexane-AcOEt, 4:1) to afford **20** (193.7 mg, 0.91 mmol) as a yellow oil in 97% yield (2 steps). IR (neat): 3341, 2979, 2934, 2108, 1698, 1520, 1366, 1249, 1168, 1073, 1010, 855 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 4.58-4.44 (m, 1H), 3.80-3.66 (m, 1H), 3.64-3.53 (m, 1H), 1.44 (s, 9H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 155.5, 79.5, 61.7, 49.8, 28.3, 18.6, 16.1; MS (ESI): *m/z* 237 [M+Na^+]; HRMS (FAB): *m/z* calcd for $C_9H_{19}N_4O_2$ [M+H^+]: 215.1508. Found: 215.1509.

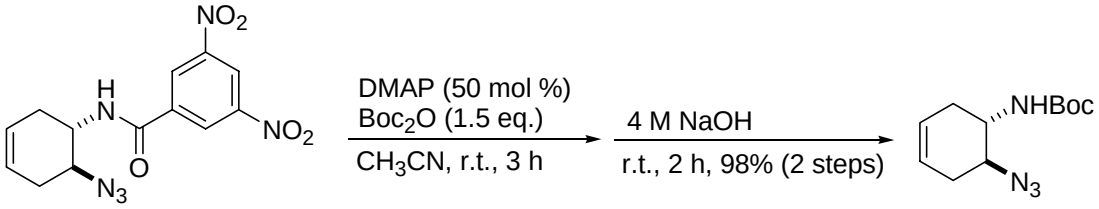
To a solution of **20** (56.9 mg, 0.27 mmol) in MeOH, 1 M HCl/MeOH (2 mL) was added and the mixture was stirred at r.t. for 1 h. 10% Pd/C (28.3 mg, 10 mol % (based on Pd)) was added and the mixture was stirred under hydrogen atmosphere (1 atm) at room temperature for 13 h. The mixture was filtered through celite pad and concentrated under reduced pressure to afford (2*S*,3*S*)-2,3-diaminobutane

[8] Kawai, M.; Iwase, T.; Butsugan, Y.; Nagai, U. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 304.

dihydrochloride[9] (**21**) (42.8 mg, 0.27 mmol) as a colorless solid in quantitative yield. The absolute configuration was determined to be 1*S*,2*S* based on the comparison of the optical rotation with the reported value.[9] $[\alpha]^{23}_{D}$ -10.0 (*c* = 0.858, MeOH). [lit. $[\alpha]_{D}$ -22.9 (*c* = 0.8, MeOH) for 1*S*,2*S* enantiomer.]

(D) Asymmetric Synthesis of Tamiflu®

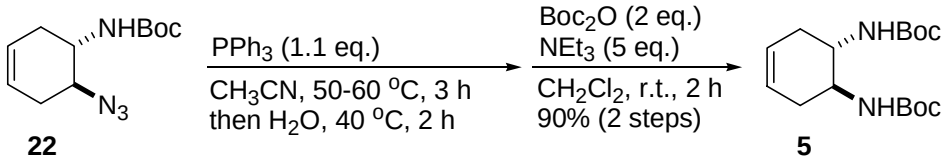
(4*S*,5*S*)-4-Azido-5-(*tert*-butoxycarbonylamino)cyclohexene (**22**):



4e (99% ee) **22**

To a solution of **4e** (1.48 g, 4.45 mmol, 99% ee) in CH_3CN (25 mL), Boc_2O (1.46 g, 6.68 mmol, 1.5 equiv) and DMAP (270 mg, 2.23 mmol, 50 mol %) were added and the mixture was stirred at room temperature for 3 h. 4 M NaOH (20 mL) was added and the mixture was stirred at room temperature for 2 h. Water was added and the product was extracted with CH_2Cl_2 three times. Combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (silica gel, hexane-AcOEt, 5:1) to afford **22** (1.03 g, 4.34 mmol) as a colorless solid in 98% yield (2 steps). IR (KBr): 3330, 2987, 2913, 2490, 2105, 1677, 1534, 1306, 1173, 668 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.59 (s, 2H), 4.66 (brs, 1H), 3.75 (brs, 1H), 3.61 (brs, 1H), 2.62-2.40 (m, 2H), 2.27-2.12 (m, 1H), 2.09-1.94 (m, 1H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$): δ = 155.3, 124.7, 123.6, 79.7, 59.4, 49.2, 30.4, 29.1, 28.3; MS (ESI): *m/z* 261 [M+Na^+]; Anal. calcd for $C_{11}H_{18}N_4O_2$: C, 55.44; H, 7.61; N, 23.51%. Found: C, 55.79; H, 7.53; N, 23.64%. $[\alpha]^{23}_{D}$ +36.2 (*c* = 1.890, $CHCl_3$).

(4*S*,5*S*)-4,5-Bis(*tert*-butoxycarbonylamino)cyclohexene (**5**):



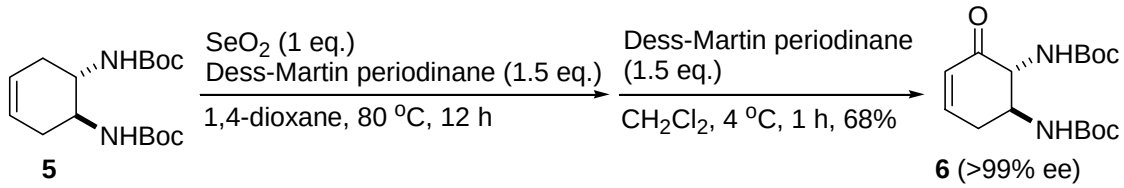
22 **5**

To a solution of **22** (1.03 g, 4.34 mmol) in CH_3CN (30 mL), PPh_3 (1.25 g, 4.78 mmol, 1.1 equiv) was added and the mixture was stirred at 50-60 °C for 3 h. Water (10 mL) was added and the reaction mixture was stirred at 40 °C for 2 h. After most of CH_3CN was removed under reduced pressure, water was removed by azeotropic evaporation with toluene (three times). CH_2Cl_2 (20 mL), Et_3N (3.0 mL, 21.7 mmol, 5 equiv), and Boc_2O (1.9 g, 8.69 mmol, 2 equiv) were added to the residue, and the mixture was stirred at room temperature. After 2 h, 1% H_2O_2 was added dropwise to oxidize the remaining PPh_3 and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 twice 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, 20:1 to 4:1) to afford **5** (1.22 g, 3.90 mmol) as a colorless solid in 90% yield (2 steps). IR (KBr): 3323, 2979, 2908, 1694, 1556, 1363, 1173, 999, 658, 601 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.56 (s, 2H), 4.88 (brs, 2H), 3.65 (brs, 2H), 2.46 (d, *J* = 16.0 Hz, 2H), 1.97

[9] Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *Tetrahedron Asymm.* **1997**, *8*, 2381.

(dd, J = 9.7, 16.0 Hz, 2H), 1.42 (s, 18H); ^{13}C NMR ($CDCl_3$): δ = 156.5, 125.0, 79.3, 51.3, 32.8, 28.4; MS (ESI): *m/z* 335 [M+Na^+]; Anal. calcd for $C_{16}H_{28}N_2O_4$: C, 61.51; H, 9.03; N, 8.97%. Found: C, 61.28; H, 8.89; N, 8.81%. $[\alpha]^{21}_D$ -34.5 (*c* = 1.100, $CHCl_3$).

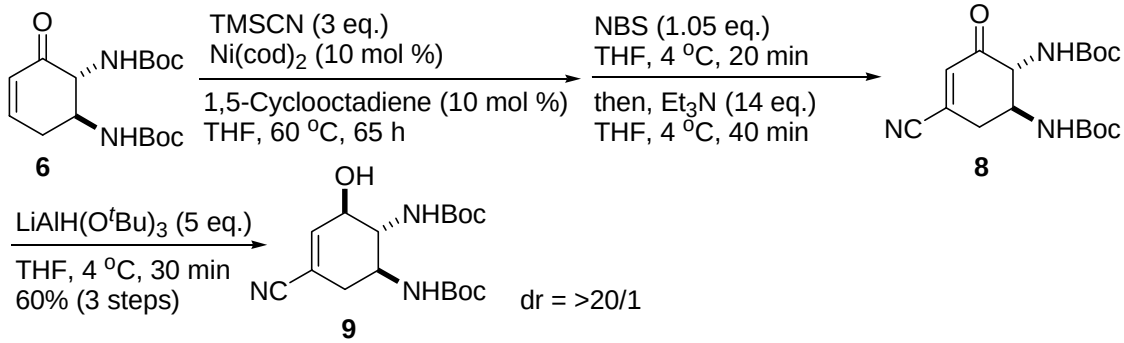
(4*R*,5*S*)-4,5-Bis(*tert*-butoxycarbonylamino)cyclohexen-3-one (**6**):



5 **6** (>99% ee)

To a solution of **5** (462 mg, 1.48 mmol) in 1,4-dioxane (15 mL), SeO_2 (164 mg, 1.48 mmol, 1 equiv) and Dess-Martin periodinane (941 mg, 2.22 mmol, 1.5 equiv) were added and the resulting mixture was stirred at 80 °C. After 12 h, saturated aqueous $NaHCO_3$ was added to quench the reaction. The product was extracted with AcOEt three times and the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and CH_2Cl_2 (15 mL) was added to the residue. After cooling to 4 °C (ice bath), Dess-Martin periodinane (941 mg, 2.22 mmol, 1.5 equiv) was added. After 1 h, saturated aqueous $Na_2S_2O_3$ was added and the organic layer was separated. The aqueous layer was extracted with AcOEt three times and the combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexane-AcOEt, 2:1) to afford **6** (330 mg, 1.01 mmol) as a colorless solid in 68% yield. Recrystallization from diisopropylether-hexane gave enantiomerically pure **6** (>99% ee, recrystallization yield; 62 %). IR (KBr): 3323, 2978, 2931, 2250, 1687, 1540, 1285, 1173, 1058, 728 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 6.99-6.90 (m, 1H), 6.12 (dd, J = 3.1, 10.0 Hz, 1H), 5.89 (d, J = 6.8 Hz, 1H), 5.49 (d, J = 5.5 Hz, 1H), 4.30 (dd, J = 6.8, 13.1 Hz, 1H), 3.95-3.83 (m, 1H), 2.93 (dt, J = 5.4, 18.8 Hz, 1H), 2.39 (dd, J = 10.4, 18.8 Hz, 1H), 1.45 (s, 9H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$): δ = 194.7, 157.6, 155.8, 148.5, 128.5, 80.4, 79.4, 60.6, 54.2, 34,5, 28.3, 28.2; MS (ESI): *m/z* 349 [M+Na^+]; Anal. calcd for $C_{16}H_{26}N_2O_5$: C, 58.88; H, 8.03; N, 8.58%. Found: C, 58.68; H, 7.84; N, 8.35%. $[\alpha]^{20}_D$ -116.3 (*c* = 0.945, $CHCl_3$). HPLC (Chiralpak AD-H, 2-propanol/hexane 1/20, flow 1.0 mL/min, detection at 254 nm.): t_R 15.2 min (minor (no detection)) and 17.0 min (major).

(3*R*,4*R*,5*S*)-4,5-Bis(*tert*-butoxycarbonylamino)-1-cyano-3-hydroxycyclohexene (**9**):



6 **8** **9**

A degassed solution of **6** (19.7 mg, 0.060 mmol), $Ni(cod)_2$ (1.7 mg, 0.006 mmol, 10 mol %), and 1,5-cyclooctadiene (0.1 M in THF, 60 μL, 0.006 mmol, 10 mol %) in THF (0.75 mL) was heated at 60 °C for 65 h. After filtration on celite pad to remove $Ni(cod)_2$, the filtrate was dissolved in THF and NBS

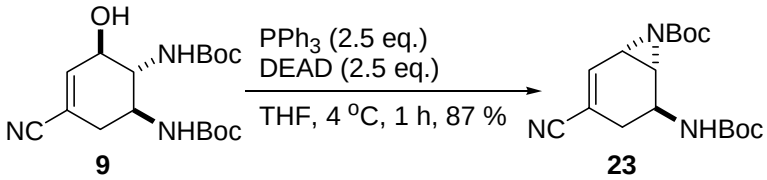
(11.3 mg, 0.063 mmol, 1.05 equiv) was added at 4 °C (ice bath). After 20 min, Et_3N (0.12 mL, 0.85 mmol, 14 equiv) was added dropwise. After 40 min, toluene and 5% NaH_2PO_4 were added and the organic layer was separated. The product was extracted with toluene twice and the combined organic layer was dried over Na_2SO_4. Most of toluene was removed under reduced pressure (volume of mixture: ca. 1 mL). The resulting crude **8** was used in next step without purification. (β-Cyanoenone **8** was relatively unstable on silica gel column chromatography. However, **8** can be isolated in 71% yield.)

To a solution of $LiAlH(O^tBu)_3$ (1 M in THF, 0.30 mL, 0.30 mmol, 5 equiv) in THF (2 mL), crude **8** (toluene solution) was added and the resulting mixture was stirred at 4 °C (ice bath). After 30 min, saturated aqueous NH_4Cl was added to quench the reaction. The product was extracted with AcOEt twice and the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexane-AcOEt, 2:1 to 3:2) to afford **9** (12.9 mg, 0.036 mmol) as a colorless solid in 60% yield (3steps). The diastereoselectivity of the product was determined by ^{1}H NMR analysis to be >20/1. If isolated **8** was used as a starting material, the yield of this reduction to give **9** was 94%.

(4*R*,5*S*)-4,5-Bis(*tert*-butoxycarbonylamino)-1-cyanocyclohexen-3-one (**8**): IR (KBr): 3370, 2979, 2934, 1696, 1523, 1367, 1169, 1019, 877, 557 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 6.61 (d, *J* = 3.4 Hz, 1H), 5.90 (d, *J* = 7.0 Hz, 1H), 5.40 (d, *J* = 6.1 Hz, 1H), 4.38 (dd, *J* = 6.1, 12.8 Hz, 1H), 3.98-3.93 (m, 1H), 3.09 (dd, *J* = 4.6, 18.6 Hz, 1H), 2.64-2.57 (m, 1H), 1.44 (s, 9H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$): δ = 192.4, 157.3, 155.6, 137.2, 129.6, 115.8, 81.1, 80.1, 60.4, 53.3, 35.8, 28.3, 28.1; MS (ESI): *m/z* 374 [M+Na$^+$]; HRMS (FAB): *m/z* calcd for $C_{17}H_{26}N_3O_5$ [M+H$^+$]: 352.1872. Found: 352.1869.

(3*R*,4*R*,5*S*)-4,5-Bis(*tert*-butoxycarbonylamino)-1-cyano-3-hydroxycyclohexene (**9**): IR (KBr): 3343, 2979, 2225, 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 6.48 (t, *J* = 2.2 Hz, 1H), 5.55 (brs, 1H), 4.75 (brd, *J* = 8.2 Hz, 1H), 4.27-4.20 (m, 1H), 4.06 (brs, 1H), 3.87-3.77 (m, 1H), 3.54-3.45 (m, 1H), 2.65 (dd, *J* = 5.2, 17.1 Hz, 1H), 2.28-2.18 (m, 1H), 1.44 (s, 9H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$): δ = 158.1, 156.5, 145.0, 117.3, 110.6, 80.7, 80.6, 72.4, 58.5, 47.9, 33.3, 28.3, 28.2; MS (ESI): *m/z* 376 [M+Na$^+$]; HRMS (FAB): *m/z* calcd for $C_{17}H_{28}N_3O_5$ [M+H$^+$]: 354.2029. Found: 354.2032; $[\alpha]^{22}_D$ -21.6 (*c* = 1.425, $CHCl_3$).

(3*S*,4*R*,5*S*)-5-*tert*-Butoxycarbonylamino-3,4-*tert*-butoxycarbonylimino-1-cyanocyclohexene (**23**):

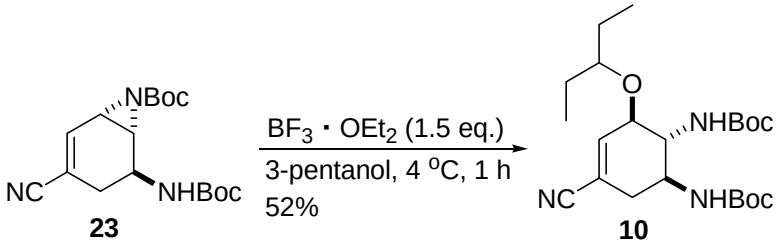


9 **23**

To a solution of PPh_3 (124 mg, 0.47 mmol, 2.5 equiv) in THF (6.3 mL), DEAD (40% in toluene, 0.22 mL, 0.47 mmol, 2.5 equiv) and **9** (66.9 mg, 0.19 mmol) in THF (3.1 mL) were added and the resulting mixture was stirred at 4 °C (ice bath). After 1 h, mixture was concentrated and purified by column chromatography (silica gel, hexane-AcOEt, 3:1 to 2:1) to afford **23** (55.4 mg, 0.17 mmol) as a colorless amorphous in 87% yield. IR (KBr): 3369, 2979, 2220, 1715, 1526 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 6.88 (t, *J* = 3.8 Hz, 1H), 4.54 (brs, 1H), 4.46 (brs, 1H), 3.06 (brs, 1H), 2.95 (t, *J* = 5.3 Hz, 1H), 2.55 (d, *J* = 15.8 Hz, 1H), 2.31 (d, *J* = 15.8 Hz, 1H), 1.43 (s, 18H); ^{13}C NMR ($CDCl_3$): δ = 160.0, 154.7, 140.3, 118.2, 112.3, 82.6, 80.3, 41.4, 41.2, 31.9, 30.1, 28.3, 27.8; MS (ESI): *m/z* 358 [M+Na$^+$]; HRMS (FAB): *m/z* calcd for

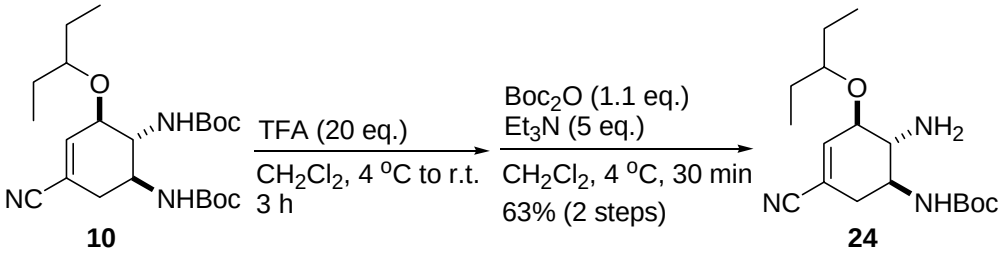
$C_{17}H_{26}N_3O_4$ [M+H$^+$]: 336.1923. Found: 336.1921; $[\alpha]^{20}_D$ -46.6 (*c* = 0.635, $CHCl_3$).

(3*R*,4*R*,5*S*)-4,5-Bis(*tert*-butoxycarbonylamino)-1-cyano-3-(1-ethylpropoxy)cyclohexene (**10**):



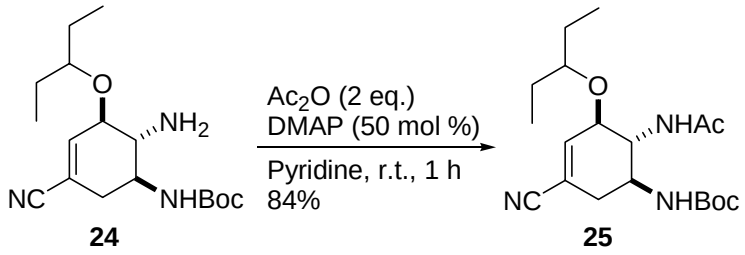
To a solution of **23** (22.6 mg, 0.067 mmol) in 3-pentanol (0.5 mL), $BF_3 \cdot OEt_3$ (0.1 M in 3-pentanol, 1 mL, 0.1 mmol, 1.5 equiv) was added dropwise and the resulting mixture was stirred at 4 ^oC (ice bath). After 1 h, saturated aqueous $NaHCO_3$ was added to quench the reaction. The product was extracted with AcOEt twice and the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, hexane-AcOEt, 4:1) to afford **10** (14.9 mg, 0.035 mmol) as a colorless solid in 52% yield. IR (KBr): 3338, 2977, 2223, 1681, 1538 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 6.45 (s, 1H), 5.24 (brd, *J* = 7.4 Hz, 1H), 4.57 (brd, *J* = 8.2 Hz, 1H), 3.90-3.79 (m, 2H), 3.74-3.64 (m, 1H), 3.33 (br quintet, *J* = 5.5 Hz, 1H), 2.60 (dd, *J* = 4.6, 12.8 Hz, 1H), 2.34-2.26 (m, 1H), 1.55-1.40 (m, 4H), 1.41 (s, 9H), 1.41 (s, 9H), 0.88 (t, *J* = 7.7 Hz, 3H), 0.88 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 156.2, 156.0, 143.6, 117.6, 111.8, 83.1, 79.9, 79.7, 75.4, 54.7, 48.6, 32.9, 28.33, 28.30, 26.0, 25.8, 9.3; MS (ESI): *m/z* 446 [M+Na$^+$]; HRMS (FAB): *m/z* calcd for $C_{22}H_{38}N_3O_5$ [M+H$^+$]: 424.2811. Found: 424.2818; $[\alpha]^{21}_D$ -41.0 (*c* = 0.505, $CHCl_3$).

(3*R*,4*R*,5*S*)-4-Amino-5-*tert*-butoxycarbonylamino-1-cyano-3-(1-ethylpropoxy)cyclohexene (**24**):



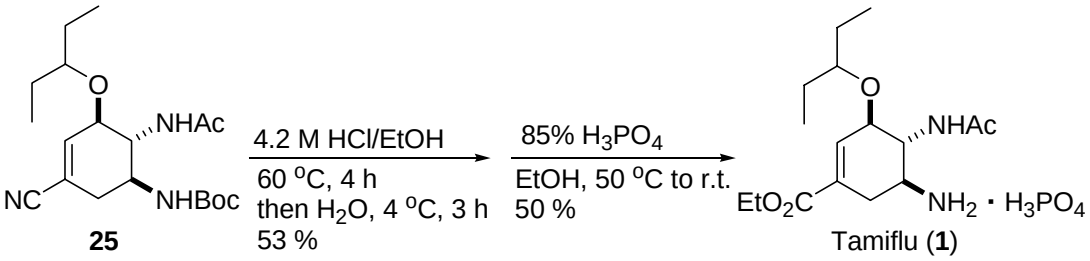
To a solution of **10** (96.3 mg, 0.23 mmol) in CH_2Cl_2 (5 mL), TFA (340 μL, 4.55 mmol, 20 equiv) was added at 4 ^oC (ice bath). After stirring at room temperature for 3 h, the reaction mixture was concentrated in *vacuo* and then, diluted with CH_2Cl_2 (5 mL). After cooling to 4 ^oC, Et_3N (160 μL, 1.14 mmol, 5 equiv) and Boc_2O (55.3 mg, 0.25 mmol, 1.1 equiv) were added dropwise. After 30 min, the mixture was concentrated and purified by column chromatography (silica gel, hexane-AcOEt, 2:1 to 0:1) to afford **24** (46.6 mg, 0.14 mmol) as a colorless oil in 63% yield. IR (KBr): 3373, 2971, 2221, 1705, 1516 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 6.47 (qlike, *J* = 0.9 Hz, 1H), 5.14 (brs, 1H), 3.75 (brs, 1H), 3.72-3.65 (m, 1H), 3.31 (quintet, *J* = 5.8 Hz, 1H), 2.90 (dd, *J* = 6.8, 9.5 Hz, 1H), 2.77-2.68 (m, 1H), 2.27-2.19 (m, 1H), 1.60-1.42 (m, 4H), 1.41 (s, 9H), 0.901 (t, *J* = 7.6 Hz, 3H), 0.896 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 155.5, 142.5, 117.9, 111.7, 81.8, 77.5, 54.1, 29.7, 28.3, 26.1, 25.7, 9.6, 9.4; MS (ESI): *m/z* 346 [M+Na$^+$]; HRMS (FAB): *m/z* calcd for $C_{17}H_{30}N_3O_3$ [M+H$^+$]: 324.2287. Found: 324.2279; $[\alpha]^{21}_D$ -15.4 (*c* = 0.440, $CHCl_3$).

(3*R*,4*R*,5*S*)-4-Acetoamide-5-*tert*-butoxycarbonylamino-1-cyano-3-(1-ethylpropoxy)cyclohexene (**25**):



To a solution of **24** (46.6 mg, 0.14 mmol) in pyridine (2 mL), Ac_2O (27 μL, 0.28 mmol, 2 equiv) was added at room temperature. After 1 h, the reaction mixture was directly concentrated in *vacuo* to remove pyridine. The residue was purified by column chromatography (silica gel, hexane-AcOEt, 4:1 to 1:1) to afford **25** (44.3 mg, 0.12 mmol) as a colorless solid in 84% yield. IR (KBr): 3335, 3287, 2968, 2220, 1686, 1654, 1541 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 6.47 (s, 1H), 5.66 (brd, *J* = 8.6 Hz, 1H), 5.12, (brd, *J* = 8.6 Hz, 1H), 4.09-4.01 (m, 1H), 3.95-3.90 (m, 1H), 3.87-3.78 (m, 1H), 3.29 (quintet, *J* = 5.8 Hz, 1H), 2.60 (dd, *J* = 5.5, 18.1 Hz, 1H), 2.37-2.29 (m, 1H), 1.97 (s, 3H), 1.47 (quintet, *J* = 7.5 Hz, 4H), 1.40 (s, 9H), 0.87 (t, *J* = 7.5 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 170.9, 156.1, 143.7, 117.5, 111.6, 82.6, 80.0, 75.0, 53.6, 48.3, 32.6, 28.3, 26.0, 25.6, 23.2, 9.4, 9.1; MS (ESI): *m/z* 388 [M+Na^+]; HRMS (FAB): *m/z* calcd for $C_{19}H_{32}N_3O_4$ [M+H^+]: 366.2393. Found: 366.2401; $[\alpha]^{21}_D$ -108.1 (*c* = 0.660, $CHCl_3$).

Ethyl (3*R*,4*R*,5*S*)-4-Acetamide-5-amino-3-(1-ethylpropoxy)cyclohexene-1-carboxylate Phosphate[10] (**1**) (**Tamiflu**®):



The solution of **25** (25.9 mg, 0.071 mmol) in 4.2 M HCl/EtOH was heated at 60 °C for 4 h. After cooling to 4 °C (ice bath), water was added to decompose the imino ester and the mixture was stirred for 3 h. CH_2Cl_2 was added followed by the slow addition of 2 M NaOH. The organic layer was separated and the product in water layer was extracted with CH_2Cl_2 twice and AcOEt once. The combined organic layer was washed with brine and dried over Na_2SO_4. A filtration and removal of solvent gave the free base (11.8 mg, 0.037 mmol) in 53% yield. To the solution of free base (10.4 mg, 0.033 mmol) in EtOH (250 μL), H_3PO_4 (1 M in EtOH, 33 μL, 0.033 mmol, 1 equiv) was added slowly and the mixture was warmed to 50 °C. Crystallization commenced immediately. The suspension was cooled to room temperature and stirred for 1 h. The crystal was filtered and washed with acetone twice to afford Tamiflu (**1**) (6.9 mg, 0.017 mmol) as colorless crystal in 50% yield. IR (KBr): 3195, 1718, 1661, 1551, 1246, 1127, 513 cm^{-1}; ^1H NMR (D_2O): δ = 6.91 (s, 1H), 4.39 (brd, *J* = 7.4 Hz, 1H), 4.34-4.26 (m, 2H), 4.11 (dd, *J* = 8.9, 11.6 Hz, 1H), 3.69-3.56 (m, 2H), 3.02 (dd, *J* = 5.1, 17.2 Hz, 1H), 2.62-2.53 (m, 1H), 2.14 (s, 3H), 1.64-1.46 (m,

[10] 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.

4H), 1.35 (t, J = 7.2 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (D_2O): δ = 178.1, 170.3, 140.7, 130.5, 87.2, 77.9, 65.3, 55.5, 52.0, 31.0, 28.3, 27.9, 25.2, 16.1, 11.4, 11.3; ^{31}P NMR (D_2O): δ = 2.85; mp: 184-186 ^{o}C; MS (ESI): *m/z* 313 [M-H_3PO_4+H^+]; HRMS (FAB): *m/z* calcd for $C_{16}H_{29}N_2O_4$ [M-H_3PO_4+H^+]: 313.2127. Found: 313.2124; $[\alpha]^{22}_D$ -30.5 (*c* = 0.480, H_2O). [lit. $[\alpha]_D$ -32.1 (*c* = 1, H_2O) [11]] [lit. $[\alpha]_D$ -39.9 (*c* = 1, H_2O)[10]].

This analytical data completely matched with reported one.[10]

[11] Iding, H.; Wirz, B; Zutter, U. EP Patent 1,146,036, 2001.