Development of A Concise Synthesis of (-)-Oseltamivir (Tamiflu®)

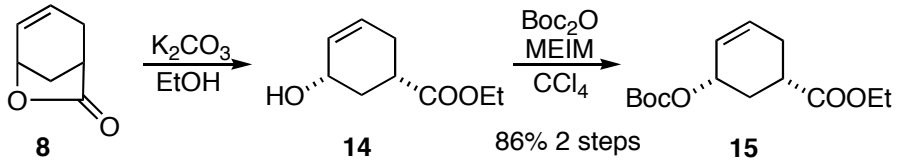
Barry M. Trost* and Ting Zhang

Department of Chemistry, Stanford University, Stanford, CA 94305-5080 (USA)

General:

All reactions were carried out in oven- or flame-dried glassware under a positive pressure of N_2 or Ar. All anhydrous solvents were obtained from elution through alumina column. All reagents were purchased commercially and used without further purification unless stated otherwise. TLC was performed on precoated glass plates (Merck). Flash chromatography was performed with silica gel 60, 230-400 mesh. Enantiomeric excesses were determined by HPLC on Tsp Spectra series P100/UV100 apparatus with a chiral stationary phase (see details where applies). ^{1}H-NMR (7.24ppm for $CDCl_3$ as internal standard) and ^{13}C- NMR (77.1ppm for $CDCl_3$ as internal standard) spectra were recorded on Unity Inova 500 (500 MHz for ^{1}H-NMR). IR spectra (cm^{-1}) were obtained with a Perkin-Elmer FT-IR Paragon 500 spectrometer using neat sample on NaCl plate.

***cis*-ethyl 5-(*tert*-butoxycarbonyloxy)cyclohex-3-enecarboxylate (15)**

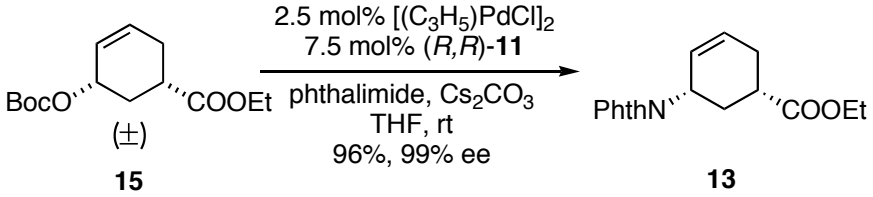


Lactone **8** 5.0g (40 mmol) and K_2CO_3 9.7g (70 mmol) were stirred in 80 ml EtOH at room temperature for 1 h. The reaction mixture was then quenched with 200 ml 1 N $NaHSO_4$ (aq) and extracted with 200 ml ethyl acetate three times. The combined organic phases were washed with brine and dried with $MgSO_4$. Evaporation of solvent yielded 6.2g of crude **14** as a colorless oil. The crude alcohol **14** (6.2 g, 36.5 mmol) was dissolved

in 200 ml CCl_4 and *N*-methylimidazole (MEIM, 506 μl, 6.3 mmol) was added. Boc_2O (22.6 g, 104 mmol) in 20 ml CCl_4 was added and the solution was stirred under N_2 at rt for 8 h. Another 352 μl (4.4 mmol) MEIM was then added and the reaction mixture was stirred for another 10 h. The completion of the reaction was determined by TLC. After concentration of the reaction solution, flash chromatography on silica gel (100:1-10:1 petroleum ether : ethyl acetate) delivered 9.3 g **15** (86% yield from **8**) as a colorless oil. R_f = 0.7 (3:1 petroleum ether : ethyl acetate). IR (neat): 2981, 2936, 1736, 1370, 1278, 1255, 1164 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 5.71 (m, 1H), 5.55 (d, 10.2, 1H), 5.06 (m, 1H), 4.01 (q, 7.2, 2H), 2.54 (m, 1H), 2.28 (m, 1H), 2.15 (m, 2H), 1.63 (dt, 12.9, 10.0 1H), 1.34 (s, 9H), 1.12 (t, 7.3, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.7, 152.9, 129.0, 126.5, 81.7, 71. 8, 60.4, 37.7, 30.4, 27.6, 27.1, 14.0. Anal. Calc'd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 61.97; H, 8.22.

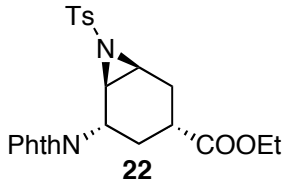
(1*S*,5*S*)-ethyl 5-(1,3-dioxoisoindolin-2-yl)cyclohex-3-enecarboxylate (13)

Starting from **15**:



To a flame-dried round bottom flask was added 18 mg (0.05 mmol) $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 104 mg (0.15 mmol) (*R,R*)-**11**, 788 mg (5.25 mmol) phthalimide and 80 mg (0.25 mmol) Cs_2CO_3. The flask was then flushed with Ar for 5 times. Freeze-thaw degassed THF 40 ml was added to the mixture under Ar and the solution was stirred for 10 min at rt and then 5 min at 40 ^oC. Compound **15** (1.48 g, 5 mmol) in 5 ml degassed THF was cannulated into the reaction mixture and another 5 ml THF was used to rinse the flask containing **15** and was then cannulated to the reaction mixture. The reaction was stirred at 40 ^oC for 20 h until the TLC showed disappearance of **15**. After concentration, the crude mixture was loaded onto alumina (activity III) column and compound **13** was eluted with 10:1-5:1 petroleum ether : ethyl acetate as a white solid (1.48 g, 96% yield).

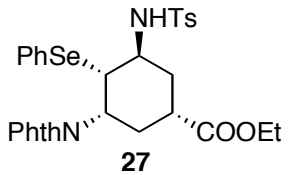
(1*S*,3*R*,5*S*,6*R*)-ethyl 5-(1,3-dioxoisoindolin-2-yl)-7-tosyl-7-aza-bicyclo[4.1.0]heptane-3-carboxylate (22)



22

Under Ar atmosphere, compound **13** (150 mg, 0.5 mmol) was dissolved in 5 ml degassed CH_3CN containing 93 mg (0.25 mmol) $Cu(CH_3CN)_4PF_6$ and 4Å MS. PhI=NTs (373 mg, 1 mmol) was added to the reaction mixture under vigorous stirring. The reaction was soon turn green and the stirring was continued until the PhI=NTs was fully drawn into the solution. Another portion of PhI=NTs (373 mg) was added and the same action was taken. Finally, a third portion of PhI=NTs (373 mg) was added and the reaction turned into a dark brownish green suspension. An hour later, the reaction mixture was filtered through a silica gel cake, which was then washed thoroughly with ethyl acetate. The filtrate was concentrated and loaded onto an alumina column (activity III), to yield 174 mg (74%) yellow solid upon eluting with petroleum ether: ethyl acetate (10:1-2:1). R_f = 0.57 (2:1 petroleum ether : ethyl acetate). $[\alpha]_D$ = 28.9 ^{o}($CHCl_3$, c = 0.45) MP = 172-173 ^{o}C. IR (neat): 2924, 2855, 1772, 1714, 1459, 1386, 1326, 1191, 1159, 1091 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78 (dd, 5.3, 3.2, 2H), 7.72 (d, 8.2, 2H), 7.69 (dd, 5.7, 3.2, 2H), 7.28 (d, 7.9, 2H), 4.43 (dd, 11.9, 7.1, 1H), 4.02 (q, 7.2, 2H), 3.32 (d, 6.6, 1H), 3.13 (d, 7.0), 2.48 (tt, 12.3, 3.0, 1H), 2.39 (s, 3H), 2.25 (d, 14.6, 1H), 1.93 (m, 2H), 1.75 (q, 12.6, 1H), 1.14 (t, 7.0, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6, 167.2, 144.6, 135.1, 134.3, 131.6, 129.8, 127.5, 123.4, 77.3, 60.8, 44.7, 42.1, 41.3, 34.6, 28.3, 25.6, 21.6, 14.1. Anal. Calc'd for $C_{24}H_{24}N_2O_6S$: C, 61.52; H, 5.16. Found: C, 61.41; H, 5.30. HRMS Calc'd for $C_{24}H_{24}N_2O_6S(M^+)$: 468.1355. Found: 468.1362.

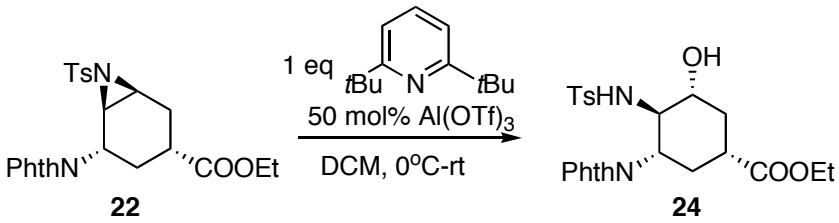
(1*R*,3*S*,4*S*,5*S*)-ethyl 3-(1,3-dioxoisoindolin-2-yl)-5-(4-methylphenylsulfonamido)-4-(phenylselanyl)cyclohexanecarboxylate (27)



27

To PhSeSePh (98 mg 0.31 mmol) in 0.5 ml EtOH was added $NaBH_4$ until the solution turned colorless. Compound **22** (98 mg, 0.21 mmol) in 1.5 ml THF was added to the reaction. Five minutes later, TFA (26 μl, 0.36 mmol) was added. The reaction was stirred at rt for 28 h and then diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$. The aqueous layer was back extracted with ethyl acetate, and the combined organic phase was washed with brine and dried over $MgSO_4$. Silica gel chromatography (3:1-2:1 petroleum ether: ethyl acetate) yielded 118 mg (90%) **27** as yellow solid. R_f = 0.40 (1.5:1 petroleum ether : ethyl acetate). $[\alpha]_D$ = -1.95 ^{o}($CHCl_3$, c = 1.05) MP = 85-87 ^{o}C. IR (neat): 3271, 2925, 1771, 1712, 1440, 1371, 1331, 1194, 1159, 1088 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68 (dd, 5.5, 3.1, 2H), 7.60 (dd, 5.5, 3.0, 2H), 7.55 (d, 8.2, 2H), 7.19 (d, 8.1, 3H), 7.06 (tm, 7.4, 1H), 6.99 (tm, 7.4, 2H), 5.26 (d, 5.7, 1H), 4.73 (dt, 13.1, 3.5, 1H), 4.13 (q, 7.1, 2H), 3.84 (brs, 1H), 3.67 (m, 1H), 3.03 (q, 12.8, 1H), 2.68 (tt, 12.8, 3.4, 1H), 2.39 (s, 3H), 2.30-2.17 (m, 2H), 1.88 (d, 14.6, 1H), 1.23 (t, 7.1, 3H). δ 173.6, 168.3, 143.3, 136.3, 133.7, 133.66, 131.3, 129.7, 129.0, 128.2, 127.3, 127.2, 122.9, 60.8, 53.4, 50.2, 49.9, 38.1, 28.1, 27.6, 21.5, 14.2. HRMS Calc'd for $C_{30}H_{30}N_2O_6SSe(M^+)$: 626.0990. Found: 626.0980.

Opening of aziridine

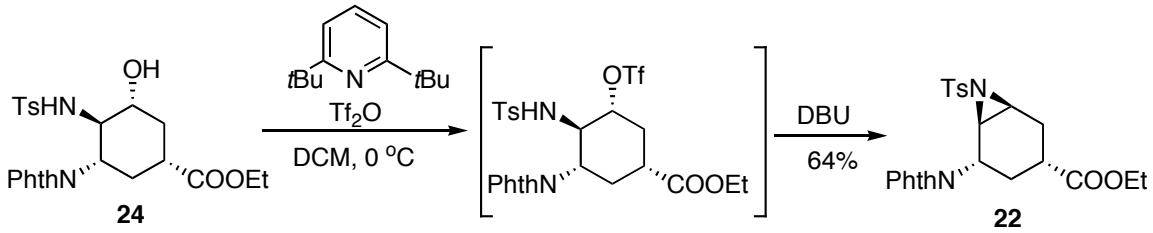


22 **24**

Aziridine **22** (23.4 mg, 0.05 mmol) and $Al(OTf)_3$ (118.5 mg, 0.25 mmol) in DCM was stirred at 0 ^{o}C under N_2. 2,6-Di-*tert*-butylpydridine was added. The reaction was stirred at 0 ^{o}C for 1 h before quenched with pH 7 buffer and back extracted with ethyl acetate (3 x).

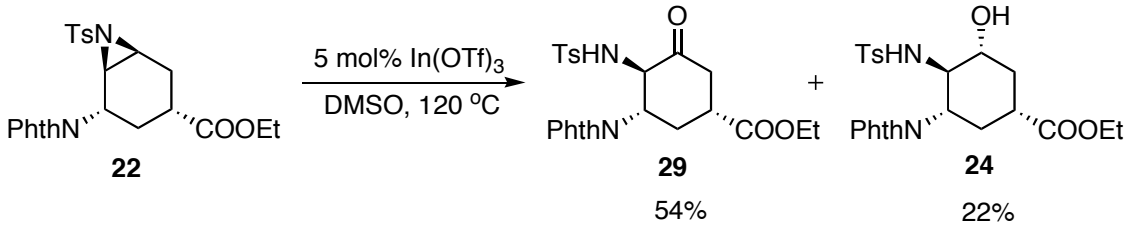
The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Crude NMR with trimethoxybenzene as internal standard indicated around quantitative yield of **24**.

Triflation of 24



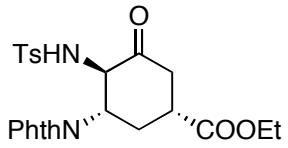
To alcohol **24** (4.9 mg, 0.01 mmol) in DCM (0.1 ml) containing 2,6-di-*tert*-butylpydridine (11.2 μl, 0.05 mmol) was added triflic anhydride (2.5 μl, 0.025 mmol). The reaction was stirred at 4 ^oC overnight. DBU (15 μl, 0.10 mmol) was added and the reaction was loaded on silica gel column. Chromatography (2:1 petroleum ether: ethyl acetate) yielded 3 mg (64%) **22** as yellow solid.

Oxidative opening of aziridine



To a mixture of compound **22** (800 mg, 1.71 mmol) and dry $In(OTf)_3$ (48 mg, 0.0854 mmol) was added DMSO (1.7 ml, distilled over CaH_2) under nitrogen. The resulting solution was put into a 120 ^oC oil bath and stirred until the disappearance of **22** by TLC. The reaction mixture was then cooled to room temperature, diluted with 100 ml DCM, and washed with 20 ml brine. The aqueous phase was back extracted with 2 × 20ml DCM. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography with 3:1-1:2 petroleum ether: ethyl acetate yielded 450 mg (58%) **29** and 180 mg (34%) **24**.

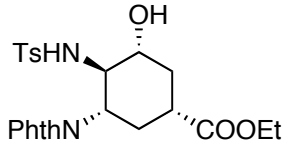
(1*R*,3*S*,4*R*)-ethyl 3-(1,3-dioxoisoindolin-2-yl)-4-(4-methylphenylsulfonamido)-5-oxocyclohexanecarboxylate (29)



29

R_f = 0.44 (1:1 petroleum ether : ethyl acetate). $[\alpha]_D$ = -47.6 ^{o}($CHCl_3$, c = 0.10) MP = 74-76 ^{o}C. IR (neat): 3284, 2924, 2855, 1773, 1711, 1599, 1464, 1377, 1336, 1294, 1259, 1189, 1161, 1093, 1028 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500MHz) δ 7.82 (dd, 5.4, 3.1, 2H), 7.71 (dd. 5.5, 3.0, 2H), 7.56 (dt, 8.4, 1.8, 2H), 7.11 (d, 8.0, 2H), 5.63 (d, 7.1, 1H), 4.60 (dd, 11.2, 7.3, 1H), 4.22 (ddd, 12.6, 11.2, 4.2, 1H), 4.12 (q, 7.1, 2H), 2.94 (q, 12.6, 1H), 2.76 (m, 1H), 2.62 (m, 2H), 2.39 (m, 1H), 2.29 (s, 3H), 1.22 (t, 7.1, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz, data of major isomer) δ 201.2, 171.5, 143.8, 135.6, 134.0, 129.7, 127.3, 123.8, 123.3, 61.7, 61.3, 53.6, 42.0, 39.6, 30.8, 21.6, 14.2. HRMS Calc'd for $C_{24}H_{24}N_2O_7SNa$($M+Na^+$): 507.1202. Found: 507.1199.

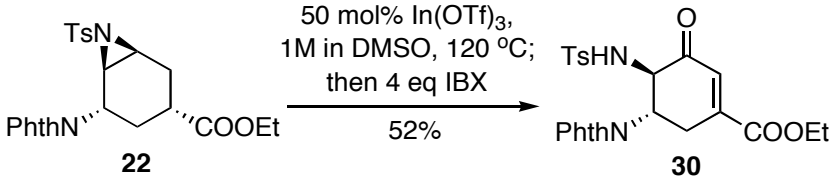
(1*R*,3*S*,4*R*,5*R*)-ethyl 3-(1,3-dioxoisoindolin-2-yl)-5-hydroxy-4-(4-methylphenylsulfonamido)cyclohexanecarboxylate (24)



24

R_f = 0.12 (1:1 petroleum ether : ethyl acetate). $[\alpha]_D$ = 34.1 ^{o}($CHCl_3$, c = 0.13) MP = 138-140 ^{o}C. IR(film): 3494, 3268, 2926, 1771, 1712, 1372, 1158, 1094 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500MHz) δ 7.75 (d, 6.4, 1H), 7.71-7.65 (m, 2H), 7.53 (d, 6.5, 1H), 7.47 (d, 8.3, 2H), 6.8 (d, 8.2, 2H), 5.16 (d, 9.0, 1H), 4.10 (qd, 7.2, 1.2, 2H), 4.03 (ddd, 12.4, 11.2, 4.2, 1H), 3.77 (dt, 10.9, 9.3, 1H), 3.55 (m, 1H), 3.24 (d, 3.3, 1H), 2.57 (q, 12.8, 1H), 2.48-2.37 (m, 2H), 2.11 (s, 3H), 1.96 (d, 12.8, 1H), 1.67 (dd, 24.4, 12.7, 1H), 1.20 (t, 7.2, 3H). δ 173.0, 168.5, 167.7, 143.0, 137.3, 133.9, 131.8, 131.0, 129.5, 126.7, 123.5, 123.2, 72.7, 61.0, 60.0, 51.3, 38.9, 35.3, 30.5, 21.6, 14.2. HRMS Calc'd for $C_{24}H_{26}N_2O_7S$(M^+): 486.1461. Found: 486.1454

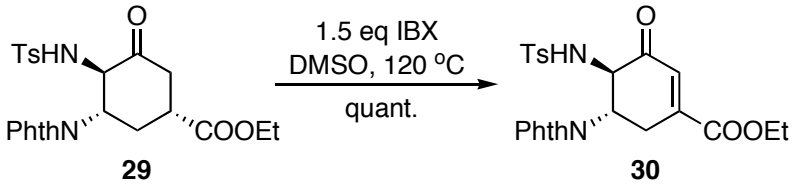
(4*R*,5*S*)-ethyl 5-(1,3-dioxoisoindolin-2-yl)-4-(4-methylphenylsulfonamido)-3-oxocyclohex-1-enecarboxylate (30)



From aziridine **22**:

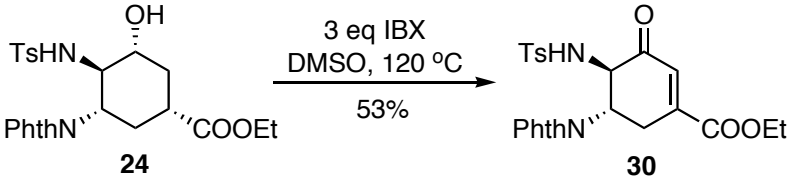
Aziridine **22** (9.4 mg, 0.02 mmol) and dry $In(OTf)_3$ (2.6 mg, 0.01 mmol) in 200 µl DMSO was stirred at 120 °C for 14 h until full conversion. The reaction was cooled and IBX (22.4 mg, 0.08 mmol) was added in one portion. The reaction was then put into a 120 °C oil bath and stirred overnight. The reaction mixture was then cooled to room temperature and diluted with 10 ml ethyl acetate and 5 ml brine. Layers were separated and the organic layer was extracted with 2 × 5 ml ethyl acetate. The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Silica gel chromatography with 3:1-1:1 petroleum ether: ethyl acetate yielded 5.0 mg (52%) **30**.

From ketone **29**:



To ketone **29** (2.4 mg, 0.005 mmol) in 25 µl DMSO was added IBX (2.1 mg, 0.0075 mmol) and the reaction was stirred at 120 °C for 4 h until full conversion. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate and brine. Layers were separated and the organic layer was extracted with 2 × ethyl acetate. The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Silica gel chromatography with 1:1 petroleum ether: ethyl acetate yielded 2.4 mg (quant.) **30**.

From alcohol **24**:

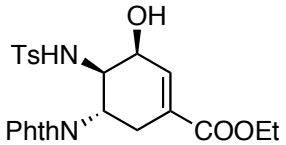


24 **30**

To alcohol **24** (11.5 mg, 0.024 mmol) in 200 µl DMSO was added IBX (19.9 mg, 0.071 mmol) and the reaction was stirred at 120 °C for 3 h. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate and brine. Layers were separated and the organic layer was extracted with 2 × ethyl acetate. The combined organic phase was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Silica gel chromatography with 1:1 petroleum ether: ethyl acetate yielded 6.0 mg (53%) **30**.

R_f = 0.48 (1:1 petroleum ether : ethyl acetate). $[\alpha]_D$ = -149.5 °($CHCl_3$, c = 0.58) MP = 92-94 °C. IR (neat): 3279, 2924, 1774, 1710, 1466, 1378, 1337, 1251, 1160. 1093 cm^{-1}.^{1}H NMR ($CDCl_3$, 500MHz): δ 7.80 (dd, 5.2, 3.1, 2H), 7.69 (dd, 5.4, 3.0, 2H), 7.60 (d, 8.2, 2H), 7.09 (d, 8.3, 2H), 6.82 (d, 3.1, 1H), 5.65 (d, 6.3, 1H), 4.65-4.56 (m, 2H), 4.23 (q, 7.0, 2H), 3.74 (ddd, 19.3, 11.6, 3.0, 1H), 2.97 (dd, 19.1, 4.8, 1H), 2.26 (s, 3H), 1.26 (t, 7.1, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 193.7, 164.7, 147.9, 143.7, 135.4, 134.1, 130.8, 129.5, 127.5, 123.5, 62.3, 59.6, 50.4, 28.4, 21.6, 14.0. HRMS Calc'd for $C_{24}H_{22}N_2O_7SNa$(M+Na^+): 505.1046. Found: 505.1048.

(3*S*,4*R*,5*S*)-ethyl 5-(1,3-dioxoisoindolin-2-yl)-3-hydroxy-4-(4-methylphenylsulfonamido)cyclohex-1-enecarboxylate (31)

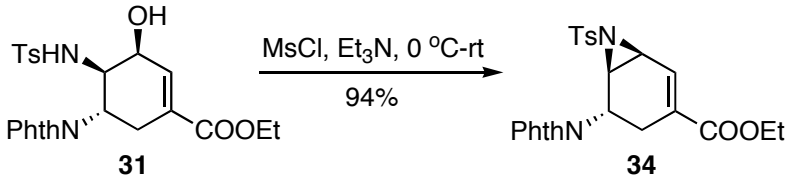


31

Sodium borohydride (5.23 mg, 0.1382 mmol) was added at 0 °C to **30** (266.8 mg, 0.553 mmol) dissolved in 9 ml DCM and 3.6 ml MeOH. The reaction was stirred for 30 min at 0 °C and the solvent was subsequently removed *in vacuo*. The residue was then dissolved in 20 ml DCM and washed with 10 ml 1M $NaHSO_4$ solution. The aqueous phase was

extracted with DCM 2 × 20 ml and the combined organic phase was washed with 5 ml brine, dried with $MgSO_4$, concentrated *in vacuo*. Silica gel chromatography with 2:1-1:1 petroleum ether : ethyl acetate yielded 205.6 mg white foam. R_f = 0.26 (1:1 petroleum ether : ethyl acetate). $[\alpha]_D$ = -30.1 ^{o}($CHCl_3$, c = 0.30) MP = 95-97 ^{o}C. IR (neat): 3471, 3273, 2924, 1772, 1708, 1465, 1379, 1330, 1259, 1156, 1092 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.65 (2H), 7.47 (2H), 6.83 (2H), 6.81 (1H), 5.87 (1H), 4.45 (d, 2.1, 1H), 4.38 (td, 11.4, 6.3, 1H), 4.14 (qd, 7.1, 3.1, 2H), 4.10-4.01 (m, 1H), 3.71 (d, 3.3, 1H), 3.28 (ddt, 17.7, 11.0, 3.3, 1H), 2.59 (dd, 17.4, 6.0, 1H), 2.14 (s, 3H), 1.22 (t, 7.2, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.7, 143.0, 138.2, 137.3, 133.9, 129.4, 128.6, 126.7, 123.4, 77.4, 72.2, 61.1, 57.6, 48.5, 27.4, 21.6, 14.2. HRMS Calc'd for $C_{24}H_{24}N_2O_7SNa$($M+Na^+$): 507.1202. Found: 507.1197.

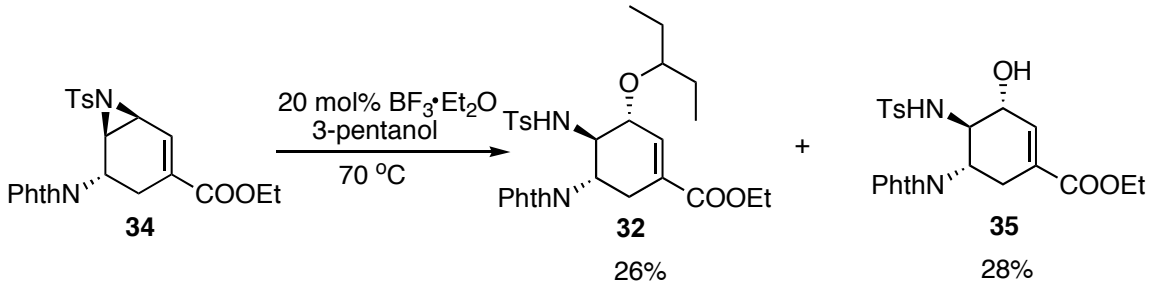
Attempted mesylation of 31



31 **34**

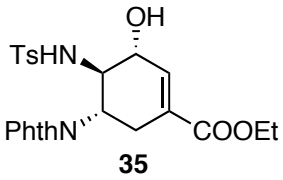
At 0 ^{o}C, to **31** (10.6 mg, 0.022 mmol) in DCM (0.2 ml) containing Et_3N (7.7 μl, 0.055 mmol) was added MsCl (2 μl, 0.026 mmol). The reaction was stirred at 4 ^{o}C for 6 h before quenched with 1M $NaHSO_4$ (0.2 ml). The aqueous layer was extracted with DCM (0.5 ml). The combined organic layer was washed with water followed by brine, dried over $MgSO_4$, and concentrated to give 9.6 mg (94%) **34**. R_f = 0.38 (2:1 petroleum ether : ethyl acetate). $[\alpha]_D$ = 32.6 ^{o}($CHCl_3$, c = 0.31) MP = 70-72 ^{o}C. IR (film): 3354, 3264, 3028, 2962, 2926, 1772, 1715, 1386, 1331, 1263, 1161, 1090, 1006 cm^{-1} . ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.78-7.75 (m, 4H), 7.68 (dd, 5.4, 3.1, 2H), 7.32 (d, 8.2, 2H), 7.12 (dd, 4.5, 2.8, 1H), 4.82 (dt, 7.6, 2.4, 1H), 4.11 (qd, 7.2, 3.4, 2H), 3.58 (dd, 6.6, 4.9, 1H), 3.44 (dt, 6.6, 1.9, 1H), 2.73 (d, 18.2, 1H), 2.48 (ddd, 18.0, 7.7, 2.8, 1H), 2.42 (s, 3H), 1.21 (t, 7.2, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 165.5, 145.1, 134.4, 134.3, 132.2, 131.5, 130.9, 130.0, 127.9, 61.1, 42.5, 41.0, 37.3, 26.2, 21.7,14.1. HRMS Calc'd for $C_{24}H_{22}N_2O_6S$ (M^+): 466.1199 Found: 466.1196.

Procedure for opening aziridine 34 with 3-pentanol:



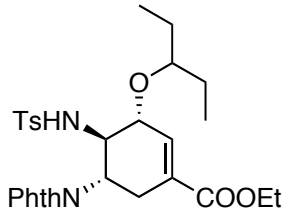
BF_3•Et_2O (3.8 μl, 0.03 mmol) was added to **34** (69.3mg, 0.149mmol) in 150 μl 3-pentanol. The reaction was heated to 70 °C and stirred for 30 min before quenched with saturated sodium bicarbonate. The mixture was extracted with DCM and dried with $MgSO_4$. Silica gel column 4:1-1:2 petroleum ether : ethyl acetate yielded 20 mg **35** (28%) and a mixture containing **32**. The mixture was loaded to preparative alumina TLC, which yielded 26 mg **32** (26%).

(3*R*,4*R*,5*S*)-ethyl 5-(1,3-dioxoisoindolin-2-yl)-3-hydroxy-4-(4-methylphenylsulfonamido)cyclohex-1-enecarboxylate (35)



R_f = 0.26 (1:1 petroleum ether : ethyl acetate). $[\alpha]_D$ = -85.7 °($CHCl_3$, c = 0.15) MP > 200 °C. IR (neat): 3213, 2924, 1770, 1701, 1463, 1384, 1334, 1260, 1158 cm^{-1}. ^1H NMR ($CDCl_3$, 500MHz): δ 7.66 (m, 4H), 7.46(d, 8.4, 2H), 6.84 (brs, 2H), 6.83 (s, 1H), 5.41 (d, 9.2, 1H), 4.43 (m, 1H), 4.35 (m, 1H), 4.17 (m, 2H), 4.01 (m, 1H), 3.59 (brs, 1H), 3.31 (ddt, 17.6, 11.1, 3.2, 1H), 2.60 (dd, 17.7, 6.5, 1H), 2.18 (s, 3H), 1.24 (t, 7.1, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.6, 143.3, 137.8, 137.0, 134.0, 131.3, 129.6, 128.7, 126.8, 123.4, 72.6, 61.2, 57.8, 48.4, 27.3, 21.7, 14.2. 3474, 3272, 3023, 2926, 2856, 1772, 1715, 1456, 1384, 1331, 1260, 1156, 1120, 1093. HRMS Calc'd for $C_{24}H_{24}N_2O_7SNa(M+Na^+)$: 507.1202. Found: 507.1197.

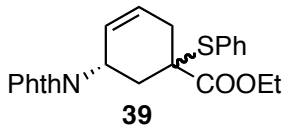
(3*R*,4*R*,5*S*)-ethyl 5-(1,3-dioxoisoindolin-2-yl)-4-(4-methylphenylsulfonamido)-3-(pentan-3-yloxy)cyclohex-1-enecarboxylate (32)



32

R_f = 0.68 (1:1 petroleum ether : ethyl acetate). $[\alpha]_D$ = -18.7 ^{o}($CHCl_3$, c = 0.97) MP = > 200 ^{o}C. IR (neat): 3474, 3272, 2926, 1773, 1709, 1468, 1380, 1330, 1260, 1156, 1118, 1093 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500MHz): δ 7.76 (dd, 5.1, 3.1, 2H), 7.66 (dd, 5.3, 3.0, 2H), 7.76 (d, 8.1, 2H), 7.01 (d, 8.2, 2H), 6.78 (s, 1H), 4.71 (d, 7.9, 1H), 4.40 (td, 11.0, 6.0, 1H), 4.17(q, 7.1, 2H), 4.07 (m, 1H), 4.02 (m, 1H), 3.43 (ddt, 17.9, 11.2, 2.9, 1H), 3.26 (septet, 3.8, 1H), 2.63 (17.7, 5.9, 1H), 2.21 (s, 3H), 1.41 (m, 4H), 1.25 (t, 7.1, 3H), 0.77 (m, 6H). δ 168.6, 165.8, 142.6, 136.3, 133.8, 129.5, 129.3, 129.2, 127.1, 126.7, 123.3, 80.2, 75.6, 61.1, 56.3, 49.6, 27.6, 25.8, 24.9, 21.5, 14.2, 9.6, 9.5. HRMS Calc'd for $C_{29}H_{34}N_2O_7SNa$ ($M+Na^+$): 577.1985. Found: 507.1974.

(5*S*)-ethyl-5-(1,3-dioxoisoindolin-2-yl)-1-(phenylthio)cyclohex-3-enecarboxylate (39)

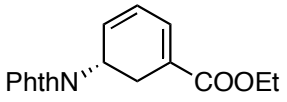


39

Compound **13** (4.88 g, 16.3 mmol) was dried by azeotropic removal of water with toluene for three cycles and then dissolved in 60 ml THF under N_2. Freshly prepared KHMDS (4.88 g, 24.5 mmol) was dissolved in 60 ml THF at -78 ^{o}C under N_2 and warmed up to room temperature. The KHMDS solution was injected into **13** in THF at -78 ^{o}C and the reaction mixture was stirred at the same temperature for 6 h. $PhSSO_2Ph$ (7.33 g, 29.3 mmol) was also dried by azeotropic removal of water with toluene for three cycles and then dissolved in 20 ml THF under N_2. The $PhSSO_2Ph$ solution was cannulated into the previous reaction mixture at -78 ^{o}C and the reaction was slowly warmed up to room temperature and stirred overnight. The reaction was diluted with 1 L

ether and washed with 1 L saturated sodium bicarbonate solution. The aqueous phase was extracted with ether 2 × 500 ml. The combined organic phase was dried with $MgSO_4$, concentrated *in vacuo* and loaded to a silica gel column, eluted with 10:1-5:1-2:1 petroleum ether : ethyl acetate. Product **39** (6.22 g, 94%) was collected as a yellow gum in a roughly 1:1 diastereomeric ratio. R_f = 0.62 (2:1 petroleum ether : ethyl acetate). IR (film): 2978, 1772, 1715, 1383, 1244, 1189,1115 cm^{-1}. $[\alpha]_D$ = -85.5 ^{o} ($CHCl_3$, c=1.03). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.82-7.79 (m, 4H), 7.70-7.68 (m, 4H), 7.60-7.58 (m, 2H), 7.45-7.43 (m, 2H), 7.38-7.33 (m, 4H), 7.32-7.27 (m, 2H), 5.88-5.84 (m, 2H), 5.68 (d, 10.0, 1H), 5.52-5.48 (m, 2H), 4.97-4.92 (m, 1H), 4.22-4.16 (m, 1H), 4.14-4.00 (m, 4H), 2.82 (dm, 17.2, 1H), 2.69 (dm, 19.3, 1H), 2.55 (dd, 11.9, 11.0, 1H), 2.49-2.38 (m, 4H), 2.15 (dd, 13.6, 5.7, 1H), 1.20 (t, 7.3, 3H), 1.14 (t, 7.3, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 171.6, 168.1, 167.8, 137.2, 137.1, 134.1, 132.0, 131.95, 130.3, 129.8, 129.6, 128.9, 128.8, 127.8, 126.4, 126.1, 125.4, 123.3, 61.5, 61.3, 54.0, 53.5, 45.6, 45.5, 34.3, 33.4, 32.1, 30.8, 14.0. Anal. Calc'd for $C_{23}H_{21}NO_4S$: C, 7.79; H, 5.19. Found: C, 67.70; H, 5.25. HRMS Calc'd for $C_{23}H_{21}NO_4S(M^+)$: 407.1191. Found: 407.1186.

(*S*)-ethyl 5-(1,3-dioxoisoindolin-2-yl)cyclohexa-1,3-dienecarboxylate (38)

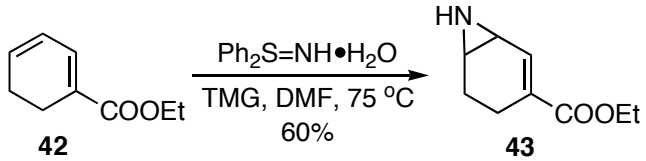


38

The diastereomeric mixuture of **39** (6.10 g, 15.0 mmol) was dissolved in 150 ml toluene and cooled to 0 ^{o}C. $NaHCO_3$ (2.52 g, 30.0 mmol) was added in one portion followed by 70% *m*CPBA (3.70 g, 15.0 mmol) and the reaction was stirred at 0 ^{o}C for 2 h. Freshly distilled DBU (2.24 ml, 15.0 mmol) was added and the reaction was then stirred at 60 ^{o}C for 5 h monitored by TLC. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in 300 ml ethyl acetate and washed with 150 ml saturated sodium bicarbonate solution. The aqueous phase was then extracted with 2 × 100 ml ethyl acetate. The combined organic phase was dried with $MgSO_4$, concentrated and loaded onto a silica gel column. Eluting with 10:1 - 4:1 petroleum ether : ethyl acetate yielded 3.80 g **38** as an approximately 10:1 regioisomeric mixture. R_f = 0.75 (2:1 petroleum ether : ethyl acetate). MP = 124~125 ^{o}C. $[\alpha]_D$ = -168.2

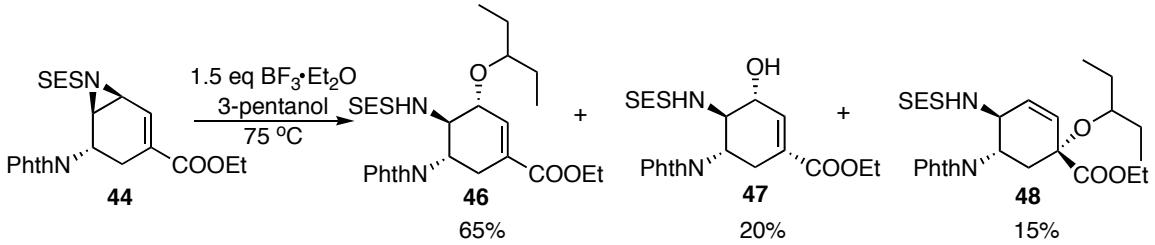
^{o} ($CHCl_3$, c = 2.80). IR (neat): 2983, 1704, 1394, 1255, 1114, 1096 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500MHz, data of major isomer): δ 7.82 (dd, 5.4, 3.2, 2H), 7.70 (dd, 5.4, 3.2, 2H), 7.06 (m, 1H), 6.20 (ddd, 9.2, 5.7, 2.6, 1H), 5.98 (dd, 9.4, 3.1, 1H), 5.20 (ddm, 14.8, 10.2, 1H), 4.19(q, 7.1, 2H), 2.89 (17.4, 14.7, 2.4, 1H), 2.77 (ddd, 17.4, 10.1, 0.7, 1H), 1.27 (t, 7.0, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz, data of major isomer) δ 167.8, 166.7, 134.2, 132.0, 131.9, 131.6, 127.7, 124.9, 123.4. 60.7, 46.0, 26.5, 14.3. EA: Anal. Calc'd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09. Found: C, 68.80; H, 5.15. HRMS Calc'd for $C_{17}H_{15}NO_4$ (M^+): 297.1001. Found: 297.0991.

ethyl 7-aza-bicyclo[4.1.0]hept-2-ene-3-carboxylate (43)



Substrate **42** (13 μl, 0.1 mmol) in DMF (0.1 ml) containing $Ph_2S{=}NH{\bullet}H_2O$ (33 mg, 0.15 mmol) and tetramethylguanidine (13 μl, 0.1 mmol) was heated at 75 ^{o}C for 2.5 h. Column chromatography with 2:1:0.2 petroleum ether : ethyl acetate : triethylamine yielded 10 mg (60%) **43** as tan oil. R_f = 0.29 (ethyl acetate). IR (neat) 3299, 2982, 2933, 2857, 1713, 1643, 1446, 1382, 1269, 1089, 1037 cm^{-1}. 7.21 (dd, 4.6, 2.8, 1H), 4.16 (qd, 7.1, 1.1, 2H), 2.66 (brs, 1H), 2.56 (d, 15.2, 1H), 2.46 (brs, 1H), 2.20 (dd, 13.8, 7.4, 1H), 1.95 (brs, 1H), 1.60 (brs, 1H), 1.26 (t, 7.1, 3H).

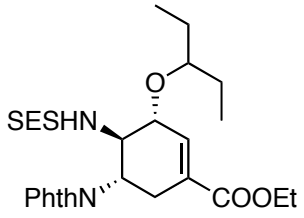
Procedure for opening aziridine 44 with 3-pentanol:



3-Pentanol was distilled over CaO then Mg and stored under inert atmosphere with 4 Å MS beads. Aziridine **44** (100 mg, 0.21 mmol) was thoroughly dried by azeotropically removing water with toluene then chemically removing water with BSA. After all the

volatiles were removed under high vacuum with gentle heating, the compound was placed under dry N_2 with a stirbar in a round bottom flask. Dry 3-pentanol (1.4 ml) was injected into the flask and the solution was heated to 75 ^oC. Redistilled $BF_3 \bullet Et_2O$ (40 μl, 0.32 mmol) was injected quickly into the hot reaction solution. After 1 min, a massive white solid formed. The reaction was stirred for a total of 15 min. After cooling to rt, 10 ml DCM and 5 ml saturated $NaHCO_3$ aqueous solution was added and layers were separated. The aqueous layer was back extracted with 2 × 5 ml DCM. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* (3-pentanol was thoroughly removed under high vacuum with gentle heating). The crude white solid was loaded to silica gel column with 1:1 petroleum ether : DCM. Eluting with 15:15:1 then 6:6:1 petroleum ether : DCM : ethyl acetate yielded 77.4 mg (65%) **46,** 20.7 mg (20%) **47** and 17.5 mg (15%) **48** as white solids.

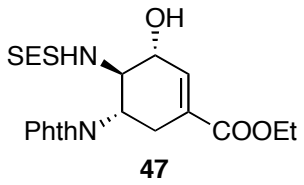
(3*R*,4*R*,5*S*)-ethyl 5-(1,3-dioxoisoindolin-2-yl)-3-(pentan-3-yloxy)-4-(2-(trimethylsilyl) ethylsulfonamido)cyclohex-1-enecarboxylate (46)



46

R_f = 0.39 (5:1:1 DCM : petroleum ether : ethyl acetate). MP > 230 ^oC $[\alpha]_D$ = -129.1^o ($CHCl_3$, c = 1.68), IR (film): 3233, 2962, 1771, 1700, 1401, 1385, 1331, 1255, 1121 cm^{-1}. ^1H NMR ($CDCl_3$, 500MHz): δ 7.82 (brs, 2H), 7.68 (dd, 5.4, 3.0, 2H), 6.91 (s, 1H), 4.73 (d, 9.2, 1H), 4.42 (td, 11.2, 6.4, 1H), 4.21 (q, 7.1, 2H), 4.13 (dm, 8.9, 1H), 3.98 (dt, 11.3, 9.2, 1H), 3.62 (ddt, 17.9, 11.0, 3.1, 1H), 3.40 (septet, 3.9, 1H), 3.03 (td, 14.0, 4.1, 1H), 2.79 (td, 13.9, 4.0, 1H), 2.72 (dd, 17.9, 6.3, 1H), 1.69-1.57 (m, 2H), 1.45-1.32 (m, 2H), 1.27 (t, 7.1, 3H), 1.00-0.89 (m, 2H), 0.94 (t, 7.5, 3H), 0.85 (t, 7.5, 3H). -0.065 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ165.9, 135.5, 130.4, 129.8, 123.4, 79.8, 75.4, 61.1, 56.2, 50.5, 50.0, 27.2, 26.8, 25.7, 14.3, 10.0, 9.93, 9.86, -1.96. EA: Anal. Calc'd for $C_{27}H_{40}N_2O_7SSi$: C, 57.42; H, 7.14. Found: C, 57.60; H, 7.01. HRMS Calc'd for $C_{27}H_{41}N_2O_7SSi$ ($M^+ + H$): 565.2404 Found: 565.2402.

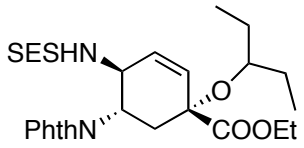
(3*R*,4*R*,5*S*)-ethyl 5-(1,3-dioxoisoindolin-2-yl)-3-hydroxy-4-(2-(trimethylsilyl)ethylsulfonamido)cyclohex-1-enecarboxylate (47)



47

R_f = 0.06 (5:1:1 DCM : petroleum ether : ethyl acetate). MP = 120-122 ^oC $[\alpha]_D$ = -19.2 ^{o} ($CHCl_3$, c = 0.73), IR (film): 3492, 3281, 2954, 1774, 1711, 1381, 1325, 1254, 1145, 1115 cm^{-1}. ^1H NMR ($CDCl_3$, 500MHz): δ 7.85 (dd, 5.5, 3.1, 2H), 7.74 (dd, 5.5, 3.1, 2H), 6.85 (t, 2.2, 1H), 4.84 (d, 9.7, 1H), 4.40-4.34 (m, 2H), 4.23-4.15 (m, 2H), 4.08 (td, 11.5, 9.1, 1H), 3.73 (d, 6.1, 1H), 3.40-3.33 (m, 1H), 3.01 (td, 14.0, 4.3, 1H), 2.87 (td, 13.8, 4.2, 1H), 2.71 (dd, 17.9, 6.0, 1H), 1.26 (t, 7.0, 3H), 0.89(dtd, 33.6, 13.9, 4.2, 2H). -0.082 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ165.6, 138.7, 134.5, 129.0, 123.6, 71.9, 61.2, 57.6, 50.0, 49.4, 27.5, 14.2, 10.2, -2.0. HRMS Calc'd for $C_{22}H_{31}N_2O_7SSi$ (M^+ + H): 495.1626. Found: 495.1616.

(1*R*,4*S*,5*S*)-ethyl 5-(1,3-dioxoisoindolin-2-yl)-1-(pentan-3-yloxy)-4-(2-(trimethylsilyl)ethylsulfonamido)cyclohex-2-enecarboxylate (48)

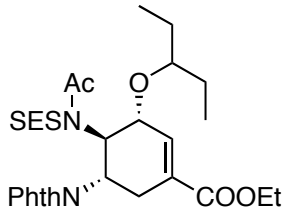


48

R_f = 0.52 (5:1:1 DCM : petroleum ether : ethyl acetate). MP = 115-117 ^oC $[\alpha]_D$ = 50.1 ^{o} ($CHCl_3$, c = 1.07), IR (film): 3269, 2926, 1774, 1712, 1452, 1392, 1328, 1249, 1193, 1171, 1143, 1120, 1047 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.82 (dd, 5.2, 2.9, 2H), 7.69 (dd, 5.2, 2.9, 2H), 6.23(d, 10.4, 1H), 5.99 (dd, 10.2, 1.4, 1H), 4.66-4.58 (m, 2H), 4.44-4.36 (m, 1H), 4.16 (q, 7.2, 2H), 3.48 (quintet, 5.6, 1H), 2.87 (t, 12.8, 1H), 2.73-2.67 (m, 2H), 2.20 (d, 13.4, 1H), 2.13 (s, 3H), 1.55-1.39 (m, 4H), 0.89 (t, 7.5, 3H), 0.80 (t, 7.5, 3H), -0.18 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.3, 134.3, 133.6, 128.8, 123.5,

77.4, 75.9, 61.6, 52.8, 50.0, 48.7, 36.1, 31.0, 29.7, 26.7, 26.4, 14.1, 10.4, 9.4, 9.1, -2.2. HRMS Calc'd for $C_{29}H_{39}N_2O_7SSiNa$ (M^+ + Na): 587.2247 Found: 587.2236.

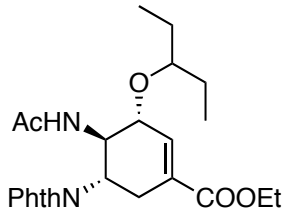
(3*R*,4*R*,5*S*)-ethyl 5-(1,3-dioxoisoindolin-2-yl)-3-(pentan-3-yloxy)-4-(*N*-(2-(trimethylsilyl)ethylsulfonyl)acetamido)cyclohex-1-enecarboxylate (49)



49

To **46** (100 mg, 0.177 mmol) and DMAP (43.2 mg, 0.354 mmol) in a 0.5-2 ml capacity Biotage microwave vial containing a stir bar was added 1.77 ml Ac_2O then 79.1 μl pyridine (3.54 mmol). The mixture was subjected to microwave heating at 150 ^oC for 1 h. After cooling down to rt, the interior pressure was released with a small-gauged needle. The reaction mixture was concentrated *in vacuo* with gentle heating. The crude mixture was loaded onto a silica gel column. Eluting with 10:1 petroleum ether : ethyl acetate yielded 90.0 mg **49** as a pale yellow foam. NMR studies suggested **49** exist as a rotameric mixture at rt (4:1 in $CDCl_3$, 3:1 in C_6D_6). R_f = 0.58 (2:1 petroleum ether : ethyl acetate). MP: broad, 50 ~ 60 ^oC. $[\alpha]_D$ = -39.9 ^{o} ($CHCl_3$, c = 1.47), IR (film): 2964, 1776, 1716, 1359, 1253, 1148 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, data of major rotamer): δ 7.80 (brs, 2H), 7.70 (dd, 5.4, 3.0, 2H), 6.88 (t, 2.2, 1H), 5.30 (td, 11.2, 5.3, 1H), 4.95 (dd, 11.5, 9.3, 1H), 4.84 (dm, 9.3, 1H), 4.17 (qd, 7.0, 1.4, 2H), 3.55 (quintet, 5.5, 1H), 3.30 (td, 13.3, 4.2, 1H), 3.18 (td, 13.3, 4.2, 1H), 2.88 (ddt, 17.0, 10.9, 2.9, 1H), 2.72 (dd, 16.6, 5.1, 1H), 2.49 (s, 3H), 1.63-1.55 (m, 2H), 1.54-1.46 (m, 2H), 1.25 (t, 7.1, 3H), 0.98-0.88 (m, 2H), 0.90 (t, 7.3, 3H), 0.81 (t, 7.3, 3H). -0.18 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz, data of major rotamer) δ 175.2, 165.6, 137.6, 134.5, 131.6, 129.1, 81.2, 75.1, 62.8, 61.2, 54.1, 47.4, 30.7, 25.6, 25.0, 24.3, 14.2, 9.1, 9.0, -2.2. HRMS Calc'd for $C_{29}H_{42}N_2O_8SSiNa$ (M^+ + Na): 629.2329 Found: 629.2308.

(3*R*,4*R*,5*S*)-ethyl 5-(1,3-dioxoisoindolin-2-yl)-3-(pentan-3-yloxy)-4-(2-(trimethylsilyl) ethylsulfonamido)cyclohex-1-enecarboxylate (50)

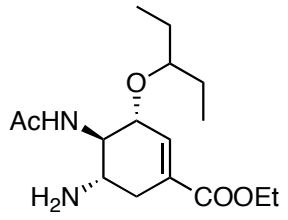


50

To **49** (203 mg, 0.33mmol) in 2.7 ml THF was added 1 M TBAF solution (670 μl, 0.67 mmol) and the reaction was stirred at rt for 30 min. Ethyl acetate (20 ml) and saturated NH_4Cl aqueous solution (10 ml) was added and layers separated. The aqueous layer was back extracted with 2 × 10 ml ethyl acetate. The combined organic layer was washed with brine and dried over $MgSO_4$. Silica gel chromatography with diethyl ether as eluant yielded 140 mg of white foamy solid. NMR studies suggested **50** exist as a rotameric mixture at rt (4:1 in $CDCl_3$, 5:1 in C_6D_6).

R_f = 0.15 (5:1:1 DCM : petroleum ether : ethyl acetate). MP: 215 ~ 216 ^oC. $[\alpha]_D$ = -50.3 ^{o} ($CHCl_3$, c = 1.05), IR (film): 3270, 3082, 2966, 2937, 2877, 1775, 1715, 1658, 1376, 1242 cm^{-1}. ^1H NMR ($CDCl_3$, 500MHz, data of major rotamer): δ 7.77 (dd, 5.5, 3.0, 2H), 7.66 (dd, 5.4, 3.0, 2H), 6.81 (m, 1H), 5.93 (d, 7.9, 1H), 4.73 (td, 11.3, 5.8, 1H), 4.44-4.36 (m, 2H), 4.16 (qd, 7.1, 1.0, 2H), 3.31 (quintet, 5.7, 1H), 3.20 (ddt, 17.3, 11.2, 3.0, 1H), 2.65 (dd, 17.4, 5.6, 1H), 1.70 (s, 3H), 1.49-1.41(m, 4H), 1.24 (t, 7.1, 3H), 0.85 (t, 7.4, 3H), 0.81 (t, 7.4, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz, data of major rotamer) δ 170.4, 168.2, 165.9, 138.3, 134.1, 129.0, 123.3, 81.9, 74.8, 61.0, 53.5, 48.5, 28.1, 26.3, 25.6, 23.2, 14.2, 9.6, 9.3. HRMS Calc'd for $C_{24}H_{31}N_2O_6$ (M^+ + H): 443.2182 Found: 443.2181.

(-)-Oseltamivir (2)



2

To **68** (44 mg, 0.1 mmol) in 2.5 ml absolute ethanol under N_2 was injected 15.7 μl (0.5 mmol) anhydrous hydrazine. The reaction mixture was stirred at 68 ^oC under N_2 for 10 h

before filtered through a pad of glass wool (gravity filtration). The glass wool was rinsed with DCM and the combined filtrate was concentrated *in vacuo*. The crude product was purified by passing through a silica gel column with 20:1:0.1 DCM : MeOH : Et_3N as eluant, yielding 31 mg **2** as a pale yellow oil. $[\alpha]_D$ = -57.5 ^{o} ($CHCl_3$, c = 1.8), IR (film): 3280, 2964, 2927, 2877, 2854, 1715, 1652, 1556, 1241, 1061 cm^{-1}. R_f = 0.11 (10:1 DCM : MeOH). ^1H NMR ($CDCl_3$, 500MHz): δ 6.75 (t, 2.0, 1H), 5.72 (d, 7.8, 1H), 4.19-4.15 (m, 3H), 3.49 (dt, 10.3, 8.2, 1H), 3.31 (quintet, 5.8, 1H), 3.20 (td, 10.3, 5.5, 1H), 2.72 (dd, 17.8, 5.1, 1H), 2.11 (ddt, 17.8, 9.7, 2.9, 1H), 2.01 (s, 3H), 1.61 (brs, 2H), 1.51-1.44 (m, 4H), 1.26 (t, 7.2, 3H), 0.87 (td, 7.4, 4.8, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 166.4, 137.7, 129.6, 81.7, 74.9, 60.9, 59.0, 49.2, 33.6, 26.3, 25.7, 23.8, 14.2, 9.6, 9.4. Data matched reported ones.

Comparison of synthetic data with data obtained from a basic extraction of a Gilead Tamiflu sample:

^1H NMR	Synthesized	Gilead Sample
1	6.75 (t, 2.0, 1H)	6.73 (t, 2.0, 1H)
2	5.72 (d, 7.8, 1H)	5.94 (d, 8.2, 1H)
3	4.19-4.15 (m, 3H)	4.18-4.13 (m, 3H)
4	3.49 (dt, 10.3, 8.2, 1H)	3.47 (dt, 10.2, 8.5, 1H)
5	3.31 (quintet, 5.8, 1H)	3.29 (quintet, 5.6, 1H)
6	3.20 (td, 10.3, 5.5, 1H)	3.14 (td, 10.1, 5.4, 1H)
7	2.72 (dd, 17.8, 5.1, 1H)	2.70 (dd, 17.7, 5.0, 1H)
8	2.11 (ddt, 17.8, 9.7, 2.9, 1H)	2.08 (ddt, 17.7, 9.8, 3.0, 1H)
9	2.01 (s, 3H)	1.99 (s, 3H)
10	1.61 (brs, 2H)	1.53 (brs, 2H)
11	1.51-1.44 (m, 4H)	1.49-1.42 (m, 4H)
12	1.26 (t, 7.2, 3H)	1.24 (t, 7.1, 3H)
13	0.87 (td, 7.4, 4.8, 6H)	0.84 (td, 7.4, 5.9, 6H)

^{13}C NMR	Synthesized	Gilead Sample
1	171.0	171.0
2	166.4	166.4
3	137.7	137.7
4	129.6	129.5
5	81.7	81.7
6	74.9	74.9
7	60.9	60.9
8	59.0	59.0
9	49.2	49.2
10	33.6	33.7
11	26.3	26.2
12	25.7	25.7
13	23.8	23.7
14	14.2	14.2
15	9.6	9.6
16	9.4	9.4