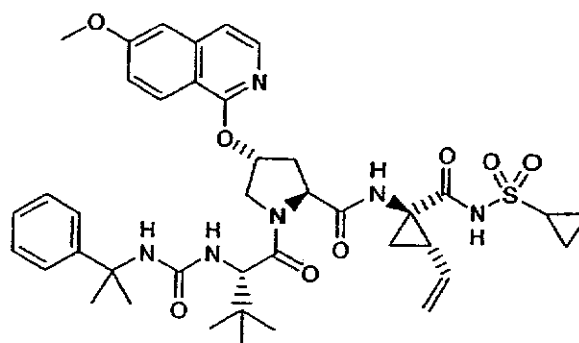


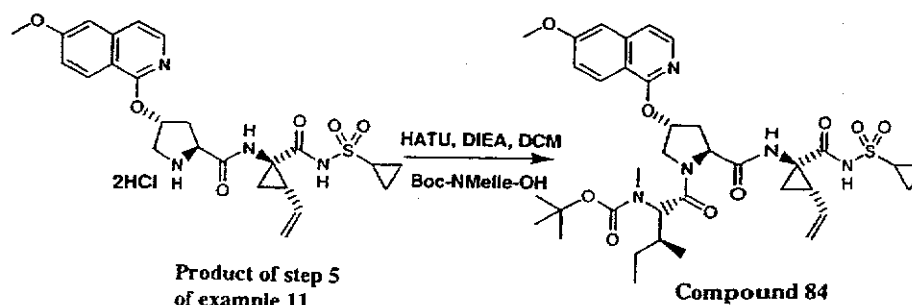
**Compound 83**

Compound 83 was prepared by the same method as **Compound 76** with the following modifications:

5

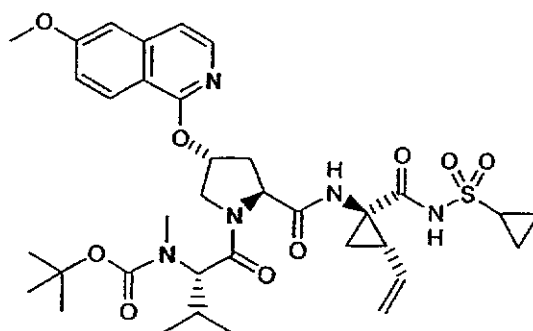
Modifications: Cumylamine was used as a starting material to give **Compound 83** (64.6 mg, 57% yield): $^1\text{H NMR}$ (CD_3OD , 500 MHz) δ 0.87-0.91 (m, 1 H), 0.98 (d, $J=9.46$ Hz, 2 H), 1.01 (s, 9 H), 1.02-1.05 (m, 1 H), 1.17-1.21 (m, 3 H), 1.29 (s, 2 H), 1.40 (dd, $J=9.46$, 5.19 Hz, 1 H), 1.51 (d, $J=3.05$ Hz, 5 H), 1.85 (dd, $J=8.09$, 5.34 Hz, 1 H), 2.17 (q, $J=8.85$ Hz, 1 H), 2.30-2.33 (m, 1 H), 2.58 (dd, $J=13.58$, 7.48 Hz, 1 H), 2.91-2.94 (m, 1 H), 3.92 (d, $J=2.14$ Hz, 1 H), 3.93 (s, 3 H), 4.05 (dd, $J=11.60$, 3.66 Hz, 1 H), 4.32 (d, $J=9.77$ Hz, 1 H), 4.51 (dd, $J=9.92$, 7.17 Hz, 1 H), 5.09 (dd, $J=11.59$, 1.52 Hz, 1 H), 5.27 (dd, $J=16.71$, 1.22 Hz, 1 H), 5.74-5.78 (m, 1 H), 5.82 (s, 1 H), 7.05-7.09 (m, 1 H), 7.18 (d, $J=2.44$ Hz, 1H), 7.19 (d, $J=7.33$ Hz, 1H), 7.22 (d, 15 $J=5.80$ Hz, 1 H), 7.33 (d, $J=7.63$ Hz, 1 H), 7.84 (d, $J=5.80$ Hz, 1 H); LC-MS (retention time: 1.76 min.), MS m/z 775 (MH^+).

Example 84: Preparation of Compound 84



To a solution of the product of step 5 of example 11 (77.0 mg, 0.136 mmol), DIEA (70.4 mg, 0.544 mmol) and HATU (77.5 mg, 0.204 mmol) was added Boc-Melle-OH (43.4 mg, 0.177 mmol). After stirring at rt for 14 hr, the reaction mixture was washed with 5% aqueous NaHCO₃ (1 mL). The aqueous layer was extracted with 2x2 mL DCM. The combined organic layer was washed with 5% aqueous citric acid (2 mL), brine, dried over MgO₄, concentrated and purified by flash column chromatography (SiO₂, 97:3 DCM:MeOH) to give Compound 84 (68.4 mg, 69% yield): ¹H NMR(CD₃OD, 500 MHz) δ 0.89 (t, *J*=7.32 Hz, 3 H) 0.94 (dd, *J*=5.95, 4.43 Hz, 3 H) 1.07 (d, *J*=7.63 Hz, 3 H) 1.13 (s, 5 H) 1.16-1.20 (m, *J*=4.88 Hz, 2 H) 1.23 (s, 3 H) 1.28 (m, 1 H) 1.34-1.38 (m, 1 H) 1.41-1.47 (m, 1 H) 1.55-1.60 (m, *J*=7.63 Hz, 1 H) 1.87-1.91 (m, 1 H) 2.22-2.26 (m, 2 H) 2.36-2.38 (m, 1 H) 2.56-2.62 (m, 1 H) 2.81 (d, *J*=11.30 Hz, 2 H) 2.94-2.99 (m, 1 H) 3.92 (s, 3 H) 4.05-4.12 (m, 2 H) 4.48-4.57 (m, 2 H) 5.12 (d, *J*=10.07 Hz, 1 H) 5.32 (m, 1 H) 5.75-5.82 (m, 1 H) 5.84-5.88 (m, 1 H) 7.09-7.13 (m, 1 H) 7.16-7.20 (m, 1 H) 7.23-7.27 (m, 1 H) 7.88 (dd, *J*=5.95, 2.29 Hz, 1 H) 8.04 (d, *J*=9.16 Hz, 0.6 H) 8.09 (d, *J*=9.46 Hz, 0.4 H); LC-MS (retention time: 1.83 min.), MS *m/z* 728 (MH⁺).

Example 85: Preparation of Example 85

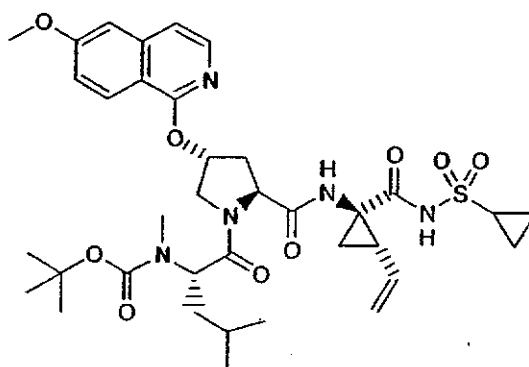


Compound 85

Compound 85 was prepared by the same method as **Compound 84** with the following modifications:

- 5 **Modifications:** Boc-MeVal-OH was used as a starting material to give **Compound 84** (72.1 mg, 74% yield): ^1H NMR(CD_3OD , 500 MHz) δ 0.84 (t, $J=5.80$ Hz, 3 H), 0.96 (d, $J=6.41$ Hz, 3 H), 1.08 (d, $J=7.32$ Hz, 2 H), 1.13 (s, 6 H), 1.16 (s, 4 H), 1.18-1.21 (m, 1 H), 1.23-1.29 (m, 1 H), 1.44 (dd, $J=9.61, 5.34$ Hz, 1 H), 1.88-1.92 (m, 1 H), 2.24 (d, $J=10.07$ Hz, 1 H), 2.32-2.39 (m, 2 H), 2.58 (dd, $J=13.89, 6.26$ Hz, 1 H),
10 2.80 (s, 3 H), 2.93-2.98 (m, 1 H), 3.93 (s, 3 H), 4.01 (dd, $J=11.90, 3.36$ Hz, 0.6 H), 4.12 (dd, $J=11.90, 3.66$ Hz, 0.4 H), 4.16 (d, $J=11.29$ Hz, 0.6 H), 4.38 (d, $J=10.99$ Hz, 0.4 H), 4.45 (d, $J=10.68$ Hz, 1 H), 4.47 (d, $J=10.69$ Hz, 0.6 H), 4.53 (dd, $J=10.38, 7.02$ Hz, 0.4 H), 4.58 (dd, $J=10.07, 7.02$ Hz, 1 H), 5.12 (d, $J=4.28, 0.6$ H), 5.14 (d, $J=4.27$ Hz, 0.4 H), 5.30 (d, $J=7.32$ Hz, 0.6 H), 5.34 (d, $J=7.32$ Hz, 0.4 H), 5.78-5.85
15 (m, 1 H), 5.88 (t, $J=3.05$ Hz, 0.6 H), 5.96 (t, $J=3.97$ Hz, 0.4 H), 7.13 (dd, $J=9.00, 2.29$ Hz, 0.6 H), 7.16 (dd, $J=9.46, 2.44$ Hz, 0.4 H), 7.19 (m, 1 H), 7.24 (d, $J=6.10$ Hz, 0.6 H), 7.26 (d, $J=6.10$ Hz, 0.4 H), 7.88 (d, $J=5.80$ Hz, 1 H), 8.02 (d, $J=9.16$ Hz, 0.6 H) 8.05 (d, $J=9.16$ Hz, 0.4 H).

20 **Example 86: Preparation of Compound 86**

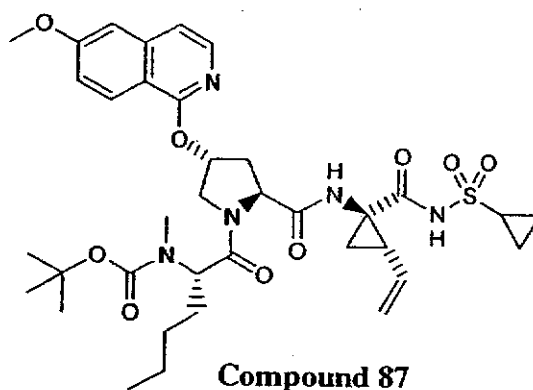


Compound 86

Compound 86 was prepared by the same method as **Compound 84** with the following modifications:

- 5 Modifications: Boc-MeLeu-OH was used as a starting material to give **Compound 85** (56.5 mg, 57% yield): ^1H NMR (CD_3OD , 500 MHz) δ 0.94-0.96 (m, 6 H), 1.04-1.13 (m, 2 H), 1.17 (s, 4.5 H), 1.18 (s, 4.5 H), 1.26-1.31 (m, 1 H), 1.42 (dd, $J=9.46$, 5.49 Hz, 1 H), 1.46-1.51 (m, 2 H), 1.56-1.60 (m, 0.5 H), 1.69-1.72 (m, 0.5 H), 1.75-1.81 (m, 0.5 H), 1.90 (q, $J=7.50$ Hz, 1 H), 2.27 (dd, $J=13.89$, 7.78 Hz, 1 H), 2.32-2.38
- 10 (m, 1 H), 2.58 (dd, $J=14.80$, 7.48 Hz, 1 H), 2.75 (s, 3 H), 2.95-2.99 (m, 1 H), 3.93 (s, 3 H), 4.03 (d, $J=12.21$ Hz, 1 H), 4.11-15 (m, 0.5 H), 4.28 (d, $J=12.21$ Hz, 1 H), 4.53 (t, $J=8.50$ Hz, 0.5 H), 4.59 (t, $J=8.55$ Hz, 0.5 H), 4.83-4.87 (m, $J=6.41$ Hz, 0.5 H), 4.96 (m, 0.5 H), 5.14 (dd, $J=11.14$, 4.73 Hz, 1 H), 5.32 (dd, $J=17.70$, 6.41 Hz, 1 H), 5.75-5.82 (m, 1 H), 5.90 (s, 0.5 H), 5.92 (s, 0.5 H), 7.13-7.18 m, 1 H), 7.20 (s, 1 H),
- 15 7.25-7.27 (m, 1 H), 7.87 (t, $J=4.40$ Hz, 1 H) 8.05 (d, $J=8.85$ Hz, 1 H).

Example 87: Preparation of Compound 87



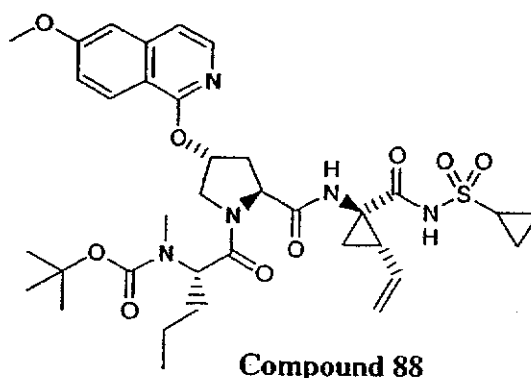
20

Compound 87 was prepared by the same method as **Compound 84** with the following modifications:

- Modifications: Boc-MeNle-OH was used as a starting material to give **Compound**
- 25 **87** (82.3 mg, 83% yield): ^1H NMR(CD_3OD , 500 MHz) δ 0.90-0.96 (q, $J=7.63$ Hz, 3

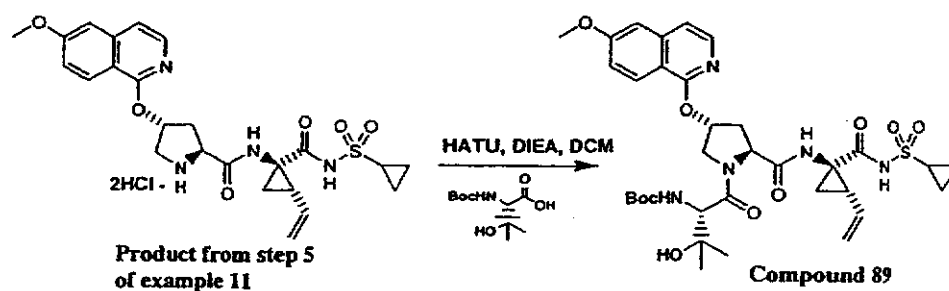
H) 1.05-1.10 (m, 2 H) 1.18 (s, 4.5 H) 1.20 (s, 4.5 H) 1.24-1.30 (m, 3 H) 1.31-1.38 (m, 1 H) 1.42 (dd, $J=9.46, 5.19$ Hz, 2 H) 1.72-1.81 (m, 2 H) 1.88-1.92 (m, 1 H) 2.22-2.29 (m, 1 H) 2.32-2.38 (m, 1 H) 2.58 (dd, $J=13.89, 7.17$ Hz, 1 H) 2.72 (s, 3 H) 2.94-2.99 (m, 1 H) 3.93 (s, 3 H) 4.02 (dd, $J=9.77, 4.27$ Hz, 1 H) 4.12 (dd, $J=11.90, 3.35$ Hz, 0.5 H) 4.24 (dd, $J=11.90, 0.6$ Hz, 0.5 H) 4.51-4.60 (m, 1 H) 5.14 (d, $J=10.38$ Hz, 1 H) 5.33 (dd, $J=17.24, 4.73$ Hz, 1 H) 5.75-5.82 (m, 1 H) 5.91 (s, 1 H) 7.15 (dd, $J=14.34, 7.63$ Hz, 1 H) 7.20 (d, $J=2.44$ Hz, 1 H) 7.25 (d, $J=5.80$ Hz, 1 H) 7.87 (t, $J=4.37$ Hz, 1 H) 8.05 (d, $J=8.85$ Hz, 1 H).

10 **Example 88: Preparative of Compound 88**



Compound 88 was prepared by the same method as **Compound 84** with the following modifications:

Modifications: Boc-N-Me-NVa-OH was used as a starting material to give **Compound 88** (70.5 mg, 73% yield): ^1H NMR(CD_3OD , 500 MHz) δ 0.96 (d, $J=6.41$ Hz, 3 H) 1.06-1.10 (m, 2 H) 1.18 (s, 9 H) 1.27-1.30 (m, 4 H) 1.42 (dd, $J=9.46, 5.49$ Hz, 1 H) 1.66-1.80 (m, 2 H) 1.88-1.92 (m, 1 H) 2.23-2.29 (m, 1 H) 2.30-2.37 (m, 1 H) 2.58 (dd, $J=13.58, 7.17$ Hz, 1 H) 2.73 (s, 3 H) 2.94-2.98 (m, 1 H) 3.93 (s, 3 H) 4.00-4.04 (m, 1 H) 4.12 (d, $J=12.82$ Hz, 0.5 H) 4.25 (d, $J=12.21$ Hz, 0.5 H) 4.51-4.60 (m, 1 H) 5.13 (d, $J=10.68$ Hz, 1 H) 5.32 (d, $J=17.09$ Hz, 1 H) 5.75-5.81 (m, 1 H) 5.90 (s, 1 H) 7.13-7.18 (m, 1 H) 7.20 (d, $J=2.14$ Hz, 1 H) 7.25 (d, $J=5.80$ Hz, 1 H) 7.87 (s, 1 H) 8.05 (d, $J=9.16$ Hz, 1 H).

Example 89: Preparation of Compound 89

5 To a solution of the product from step 5 of example 11 (66.0 mg, 0.123 mmol), DIEA (63.7 mg, 0.492 mmol) and HATU (70.0, 0.184 mmol) was added 2S-tert-butoxycarbonylamino-3-hydroxy-3-methyl-butyl alcohol (34.0 mg, 0.147 mmol). After stirring at rt for 14 hr, the reaction mixture was washed with 5% aqueous

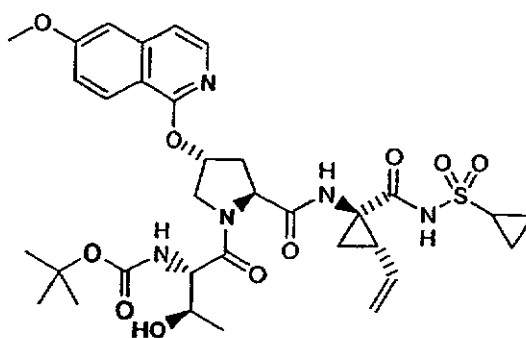
10 NaHCO₃ (1 mL). The aqueous layer was extracted with 2x2 mL DCM. The combined organic layer was washed with 5% aqueous citric acid (2 mL), brine, dried over MgO₄, concentrated and purified by reversed phase prep-HPLC to give

Compound 89 (36.1 mg, 41% yield). ¹H NMR(CD₃OD, 500 MHz) δ 1.07 (d, J=7.93 Hz, 2 H), 1.18 (s, 1 H), 1.20 (s, 9 H), 1.24-1.27 (m, J=11.60 Hz, 3 H), 1.30

15 (s, 3 H), 1.43-1.48 (m, 10 H), 1.59 (s, 1 H), 1.65 (s, 1 H), 1.87 (dd, J=8.24, 5.19 Hz, 1 H), 2.24 (q, J=9.16 Hz, 1 H), 2.33-2.36 (m, 1 H), 2.63 (dd, J=12.97, 6.56 Hz, 1 H), 2.94-2.99 (m, 1 H), 3.92 (s, 3 H), 3.93 (s, 1 H), 4.12 (dd, J=11.60, 3.05 Hz, 1 H), 4.27-4.31 (m, 1 H), 4.54 (t, J=9.77 Hz, 1 H), 5.12 (dd, J=10.53, 1.37 Hz, 1 H), 5.30

20 (d, J=17.09 Hz, 1 H), 5.79-5.83 (m, 1 H), 5.85 (s, 1 H), 7.11 (dd, J=8.55, 1.83 Hz, 1 H), 7.18 (d, J=2.24 Hz, 1 H), 7.24 (d, J=5.49 Hz, 1 H), 7.88 (m, 1 H), 8.10 (d, J=8.85 Hz, 1 H); LC-MS (retention time: 1.637 min.), MS m/z 716 (MH⁺).

Example 91: Preparation of Compound 91

**Compound 91**

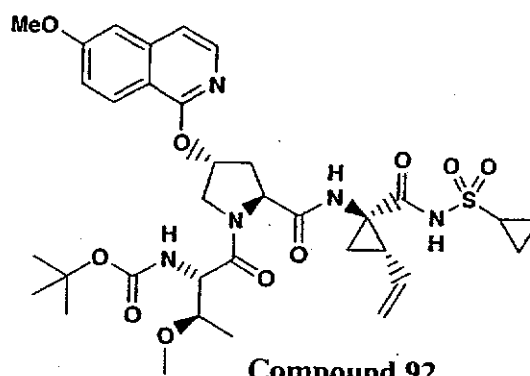
Compound 91 was prepared by the same method as **Compound 89** with the following modifications:

5

Modifications: Boc-L-Thr-OH was used as a starting material to give **Compound 91** (80.5 mg, 66% yield): $^1\text{H NMR}(\text{CD}_3\text{OD}, 500 \text{ MHz}) \delta$ 0.93 (dd, $J=8.24, 2.14 \text{ Hz}$, 2 H), 1.08-1.18 (m, 4 H), 1.20 (d, $J=6.10 \text{ Hz}$, 3 H), 1.29 (s, 9 H), 1.32 (dd, $J=9.61, 5.04 \text{ Hz}$, 1 H), 1.45 (d, $J=4.27 \text{ Hz}$, 1 H), 1.84 (dd, $J=7.63, 5.19 \text{ Hz}$, 1 H), 2.15 (q, $J=8.85 \text{ Hz}$, 1 H), 2.42-2.48 (m, 1 H), 2.64 (dd, $J=14.04, 7.63 \text{ Hz}$, 1 H), 2.85-2.89 (m, 1 H), 3.92 (s, 3 H), 4.1-4.14 (m, 2 H), 4.30 (d, $J=4.88 \text{ Hz}$, 1 H), 4.38 (d, $J=11.60 \text{ Hz}$, 1 H), 4.60 (t, $J=8.55 \text{ Hz}$, 1 H), 5.04 (dd, $J=10.22, 1.68 \text{ Hz}$, 1 H), 5.80-5.84 (m, 2 H), 7.11 (d, $J=9.16 \text{ Hz}$, 1 H), 7.17 (d, $J=1.83 \text{ Hz}$, 1 H), 7.23 (d, $J=5.80 \text{ Hz}$, 1 H), 7.87 (d, $J=5.80 \text{ Hz}$, 1 H), 8.10 (d, $J=8.85 \text{ Hz}$, 1 H); LC-MS (retention time: 1.560 min.), MS m/z 702 (MH^+).

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Example 92: Preparation of Compound 92

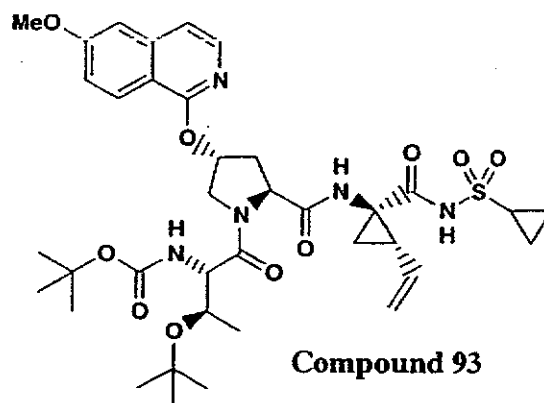
**Compound 92**

Compound 92 was prepared by the same method as **Compound 89** with the following modifications:

- 5 Modifications: Boc-L-Thr(Me)-OH was used as a starting material to give **Compound 92** (47.1 mg, 69% yield): ^1H NMR(CD_3OD , 500 MHz) δ 0.95 (d, $J=4.27$ Hz, 2 H), 1.11-1.16 (m, 3 H), 1.18 (d, $J=6.10$ Hz, 6 H), 1.32 (s, 9 H), 1.38 (dd, $J=9.31$, 5.04 Hz, 1 H), 1.45 (s, 1 H), 1.85 (dd, $J=7.78$, 5.04 Hz, 1 H), 2.13 (d, $J=9.15$ Hz, 1 H), 2.46-2.51 (m, 1 H), 2.63 (dd, $J=14.19$, 7.78 Hz, 1 H), 2.81-2.91 (m, 1 H), 3.68-3.73 (m, 1 H), 3.92 (s, 4 H), 4.14 (d, $J=12.21$ Hz, 1 H), 4.35 (d, $J=5.80$ Hz, 1 H), 4.42 (d, $J=11.29$ Hz, 1 H), 4.60 (t, $J=8.70$ Hz, 1 H), 5.05 (d, $J=10.68$ Hz, 1 H), 5.24 (dd, $J=16.79$, 0.92 Hz, 1 H), 5.81-5.85 (m, 2 H), 7.11 (dd, $J=9.16$, 0.92 Hz, 1 H), 7.17 (s, 1 H), 7.24 (d, $J=5.80$ Hz, 1 H), 7.88 (d, $J=5.80$ Hz, 1 H), 8.11 (d, $J=8.55$ Hz, 1 H); LC-MS (retention time: 1.660 min.), MS m/z 716 (MH^+).

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Example 93: Preparation of Compound 93



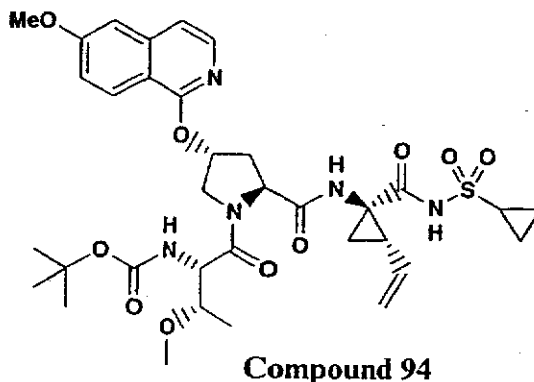
- 20 **Compound 93** was prepared by the same method as **Compound 89** with the following modifications:

Modifications: Boc-L-Thr(tBu)-OH was used as a starting material to give **Compound 93** (52.7 mg, 53% yield): ^1H NMR(CD_3OD , 500 MHz) δ 1.09 (dd, $J=8.24$, 2.44 Hz, 2 H), 1.20-1.24 (m, 3 H), 1.28 (s, 9 H), 1.45 (s, 9 H), 1.89 (dd,

25

$J=7.93$, 5.19 Hz, 1 H), 2.25 (q, $J=8.34$ Hz, 1 H), 2.32-2.36 (m, 1 H), 2.59 (dd, $J=12.82$, 6.41 Hz, 1 H), 2.95-3.00 (m, 1 H), 3.71 (s, 2 H), 3.92 (s, 3 H), 3.93-3.99 (m, 1 H), 4.10 (d, $J=7.02$ Hz, 1 H), 4.15 (d, $J=11.90$ Hz, 1 H), 4.22 (dd, $J=6.10$, 2.44 Hz, 2 H), 4.40 (d, $J=11.60$ Hz, 1 H), 4.54 (dd, $J=10.01$, 6.71 Hz, 1 H), 5.13 (d, $J=10.38$ Hz, 1 H), 5.31 (d, $J=17.09$ Hz, 1 H), 5.76-5.83 (m, 1 H), 5.87 (s, 1 H), 6.06 (d, $J=9.46$ Hz, 1 H), 6.36 (d, $J=7.02$ Hz, 1 H), 7.11 (d, $J=8.85$ Hz, 1 H), 7.18 (s, 1 H), 7.24 (d, $J=5.49$ Hz, 1 H), 7.88 (m, 1 H), 8.08 (d, $J=9.16$ Hz, 1 H).

Example 94: Preparation of Compound 94

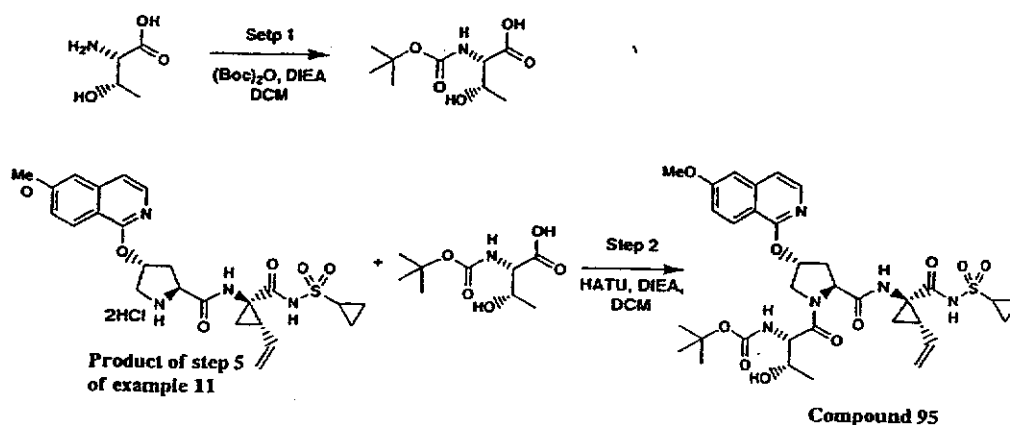


Compound 94 was prepared by the same method as **Compound 89** with the following modifications:

Modifications: Boc-(2*S*,3*S*)-2-amino-3-methoxybutanoic acid was used as a starting material to give **Compound 94** (150.2 mg, 80% yield): $^1\text{H NMR}(\text{CD}_3\text{OD}, 500 \text{ MHz})$ δ 1.04-1.13 (m, 3 H), 1.17 (d, $J=6.10$ Hz, 3 H), 1.20-1.24 (m, 2 H), 1.27 (s, 9 H), 1.44-1.48 (m, 2 H), 1.86 (dd, $J=7.93$, 5.49 Hz, 1 H), 2.24 (q, $J=8.65$ Hz, 1 H), 2.34-2.37 (m, 1 H), 2.61 (dd, $J=14.19$, 7.17 Hz, 1 H), 2.94-2.99 (m, 1 H), 3.66 (m, 1 H), 3.92 (s, 3 H), 4.13 (dd, $J=12.36$, 3.81 Hz, 1 H), 4.37 (dd, $J=22.58$, 10.99 Hz, 2 H), 4.54 (dd, $J=10.38$, 7.63 Hz, 1 H), 5.12 (d, $J=10.68$ Hz, 1 H), 5.31 (d, $J=17.40$ Hz, 1 H), 5.77-5.82 (m, 1 H), 5.85 (s, 1 H), 7.12 (d, $J=9.16$ Hz, 1 H), 7.18 (s, 1 H), 7.25 (d, $J=6.10$ Hz, 1 H), 7.89 (d, $J=5.80$ Hz, 1 H), 8.10 (d, $J=8.85$ Hz, 1 H); LC-MS (retention time: 1.673 min.), MS m/z 716 (MH^+).

Example 95: Preparation of Compound 95

Scheme 1.



5

Step 1

To a mixture of H-allo-THr-OH (5.0 g, 41.98 mmol) and DIEA (10.9 g, 83.96 mmol) in DCM (150 mL) was added di-tert-butyl dicarbonate (13.7 g, 62.97 mmol). After stirring at rt for 14h, the reaction mixture was washed with 3x100 mL DCM. The combined organic layer was dried over MgSO₄ and concentrated. LC/MS indicated most product stayed in the H₂O layer. Thus the water layer was concentrated. The product was purified by a flash column chromatography (SiO₂, 90:10 DCM:MeOH) to give Boc-allo-THr-OH; LC-MS (retention time: 0.727 min.), MS m/z 242 (MNa⁺).

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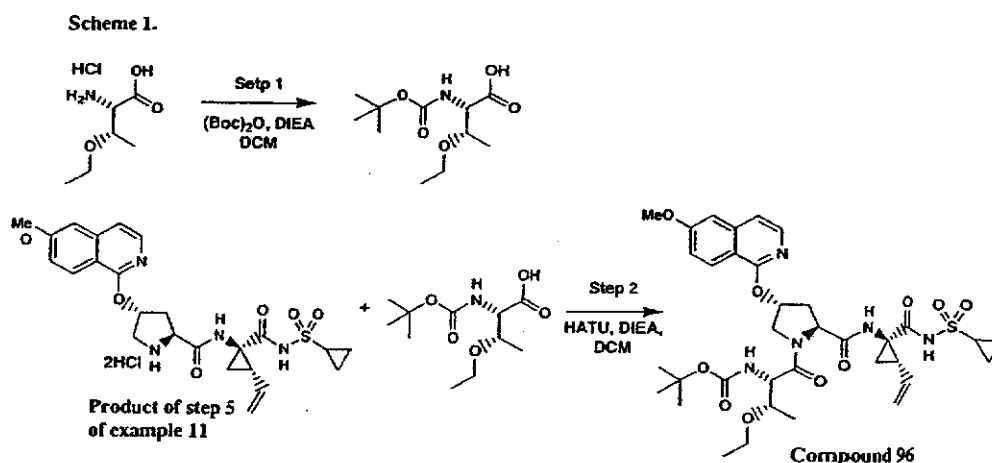
Step 2

To a solution of the product from step 5 of example 11 (100.0 mg, 0.174 mmol), DIEA (67.6 mg, 0.522 mmol) and HATU (106.0 mg, 0.278 mmol) was added the product from step 1 above (57.3 mg, 0.262 mmol). After stirring at rt for 3 hr, the reaction mixture was washed with 5% aqueous NaHCO₃ (1 mL). The aqueous layer was extracted with 2x2 mL DCM. The combined organic layer was washed with 5% aqueous citric acid (2 mL), brine, dried over MgO₄, concentrated and purified by reversed phase prep-HPLC to give Compound 95 (39.1 mg, 32% yield): ¹H NMR(CD₃OD, 500 MHz) δ 1.02 (d, J=8.55 Hz, 1 H), 1.18-1.23 (m, 3 H), 1.25 (s, 9

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H), 1.38 (dd, $J=9.15, 6.30$ Hz, 1 H), 1.84 (dd, $J=7.93, 5.19$ Hz, 1 H), 2.19-2.24 (m, 1 H), 2.38-2.43 (m, 1 H), 2.65 (dd, $J=14.19, 6.87$ Hz, 1 H), 2.92-2.96 (m, 1 H), 3.92 (s, 3 H), 3.93 (s, 2 H), 4.16-4.19 (m, 1 H), 4.23 (d, $J=8.24$ Hz, 1 H), 4.44 (d, $J=12.21$ Hz, 1 H), 4.57-5.81 (m, 1 H), 5.09 (d, $J=10.68$ Hz, 1 H), 5.29 (d, $J=17.09$ Hz, 1 H), 5.75-5.81 (m, 1 H), 5.83-5.85 (m, 1 H), 7.11 (d, $J=10.38$ Hz, 1 H), 7.18 (d, $J=1.83$ Hz, 1 H), 7.24 (d, $J=6.41$ Hz, 1 H), 7.88 (d, $J=5.80$ Hz, 1 H), 8.11 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.583 min.), MS m/z 702 (MH^+).

Example 96: Preparation of Compound 96



Compound 96 was prepared by the same method as Compound 95 with the following modifications:

Modifications:

Step 1

(2*S*,3*S*)-2-Amino-3-ethoxybutanoic acid hydrochloride was used as a starting material in step 1 to give Boc-(2*S*,3*S*)-2-Amino-3-ethoxybutanoic acid; LC-MS (retention time: 1.067 min.), MS m/z 270 ($M+Na^+$).

5

Step 2

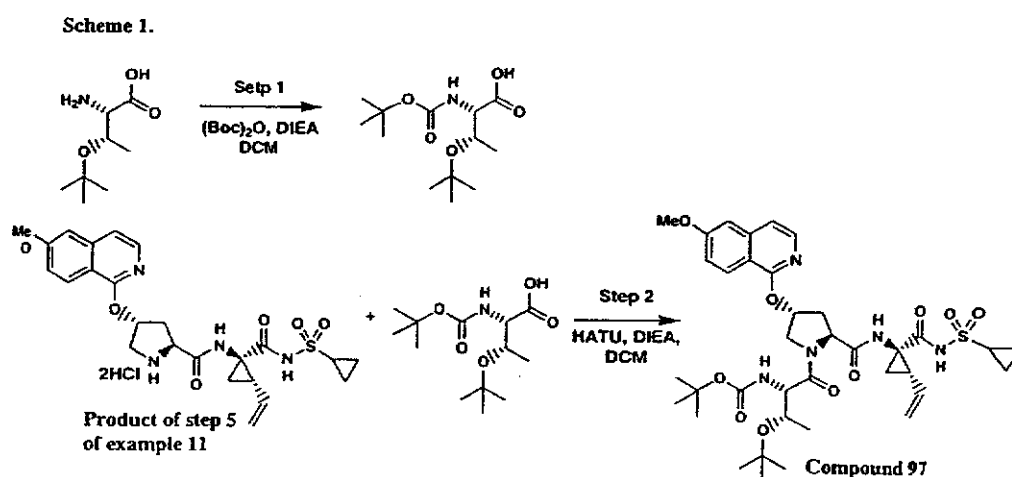
The product from step 1 was then coupled the same way with the product from step 5 of example 11 to give **Compound 96** (55.3 mg, 44% yield): ^1H NMR(CD_3OD , 500 MHz) δ 0.94 (t, $J=6.87$ Hz, 1 H), 0.97-1.03 (m, 2 H), 1.08-1.11 (m, 2 H), 1.13-1.15 (m, 2 H), 1.17 (d, $J=6.10$ Hz, 6 H), 1.29 (s, 9 H), 1.41-1.45 (m, 3 H), 1.85 (dd, $J=7.48, 5.34$ Hz, 1 H), 2.12-2.19 (m, 1 H), 2.43-2.49 (m, 1 H), 2.60 (dd, $J=13.73, 6.80$ Hz, 1 H), 2.89-2.93 (m, 1 H), 3.50-3.57 (m, 2 H), 3.73-3.78 (m, 1 H), 3.92 (s, 3 H), 4.18 (d, $J=8.85$ Hz, 1 H), 4.35 (d, $J=12.21$ Hz, 1 H), 4.39 (d, $J=8.55$ Hz, 1 H), 4.53 (t, $J=7.78$ Hz, 1 H), 5.07 (d, $J=9.16$ Hz, 1 H), 5.25 (d, $J=18.01$ Hz, 1 H), 5.82 (t, $J=9.85$ Hz, 1 H), 5.88 (t, $J=9.80$ Hz, 1H), 7.11 (d, $J=5.19$ Hz, 1 H), 7.18 (d, $J=2.14$ Hz, 1 H), 7.24 (d, $J=5.49$ Hz, 1 H), 7.88 (d, $J=6.10$ Hz, 1 H), 8.10 (d, $J=8.85$ Hz, 1 H); LC-MS (retention time: 1.743 min.), MS m/z 730 (MH^+).

10

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Example 97: Preparation of Compound 97

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Compound 97 was prepared by the same method as **Compound 95** with the following modifications:

Modifications:

Step 1

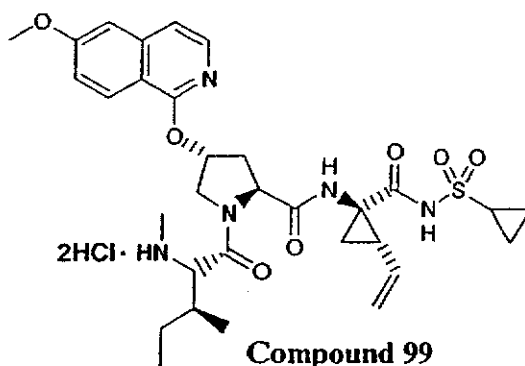
- 5 H-allo-Thr(t-Bu)-OH was used as a starting material in step 1 to give Boc-(2*S*,3*S*)-2-Amino-3-ethoxybutanoic acid; LC-MS (retention time: 1.363 min.), MS m/z 298 ($M+Na^+$).

Step 2

- 10 The product from step 1 was then coupled the same way with the product from step 5 of example 11 to give **Compound 97** (48.2 mg, 37% yield): LC-MS (retention time: 1.820 min.), MS m/z 758 (MH^+).

Example 99: Preparation of Compound 99

15



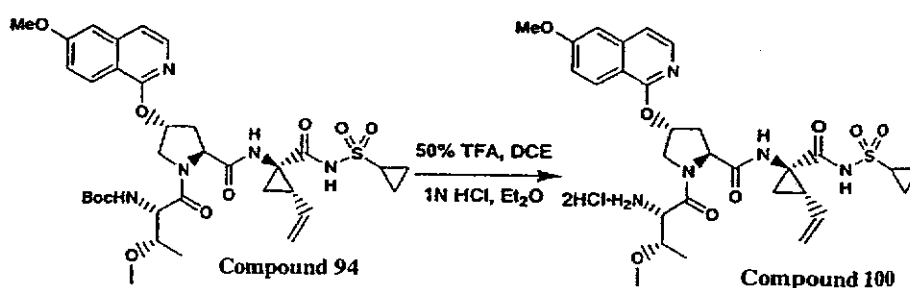
Compound 99 was prepared by the same method as step 1 of **Example 55** with the following modifications:

20

- Modifications: **Compound 84** was used as a starting material to give **Compound 99** (60.3 mg, 98% yield): ^1H NMR(CD_3OD , 500 MHz) δ 1.00 (q, $J=7.12$ Hz, 3 H) 1.10-1.13 (m, 5 H) 1.20-1.31 (m, 3 H) 1.41 (dd, $J=9.46, 5.49$ Hz, 1 H) 1.61-1.68 (m, 1 H) 1.92 (dd, $J=8.24, 5.49$ Hz, 1 H) 2.04-2.09 (m, 1 H) 2.28 (q, $J=8.55$ Hz, 1 H) 2.34-2.39 (m, 1 H) 2.57 (s, 3 H) 2.64-2.70 (m, 1 H) 2.94-2.97 (m, 1 H) 3.93 (s, 3 H) 4.07-4.14 (dd, $J=12.05, 3.81$ Hz, 1 H) 4.13 (d, $J=6.10$ Hz, 1 H) 4.18 (d, $J=5.80$ Hz, 1 H)

4.25 (d, $J=12.21$ Hz, 1 H) 4.66-4.73 (m, 1 H) 5.15 (d, $J=10.68$ Hz, 1 H) 5.32 (d, $J=17.09$ Hz, 1 H) 5.70-5.79 (m, 1 H) 5.92 (t, $J=3.66$ Hz, 0.4 H) 5.95 (t, $J=3.66$ Hz, 0.6 H) 7.17 (dd, $J=9.16$, 2.44 Hz, 1 H) 7.22 (d, $J=2.14$ Hz, 1 H) 7.28 (dd, $J=5.80$, 3.36 Hz, 1 H) 7.91 (dd, $J=5.80$, 4.27 Hz, 1 H) 8.03 (d, $J=8.85$ Hz, 0.6 H) 8.07 (d, $J=9.16$ Hz, 0.4 H); LC-MS (retention time: 1.33 min.), MS m/z 6.28 (MH^+).

Example 100: Preparation of Compound 100



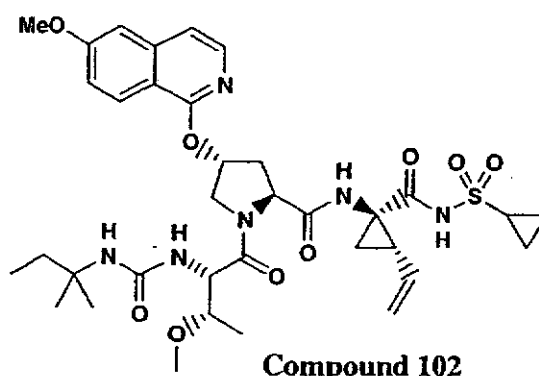
10

To a solution of **Compound 94** (0.600 g, 0.838 mmol) in DCE (3 mL) was added TFA (3 mL). After stirring at rt for 15 min, the reaction mixture was concentrated. The resulting viscous oil was re-dissolved in DCE (5 mL) and reconcentrated. It was then redissolved in DCM (2 mL) and treated with a solution of 1N HCl in Et₂O (10 mL). The resulting suspension was chilled at 0 °C, vacuum filtrated, washed with Et₂O and dried in vacuum oven to give the product as a bis-hydrochloride salt as a white solid (527.1 g, 91% yield): ¹H NMR(CD₃OD, 500 MHz) δ 1.08-1.15 (m, 2 H), 1.21 (d, $J=6.71$ Hz, 4 H), 1.28-1.33 (m, 1 H), 1.41 (dd, $J=9.46$, 5.49 Hz, 1 H), 1.91 (dd, $J=8.24$, 5.49 Hz, 1 H), 2.28 (q, $J=8.65$ Hz, 1 H), 2.34-2.37 (m, 1 H), 2.68 (dd, $J=13.12$, 7.02 Hz, 1 H), 2.81 (s, 3 H), 2.93-2.98 (m, 1 H), 3.45 (s, 3 H), 3.94 (s, 3 H), 3.96-4.00 (m, 1 H), 4.16 (dd, $J=11.90$, 3.66 Hz, 1 H), 4.27 (d, $J=11.60$ Hz, 1 H), 4.59 (d, $J=4.58$ Hz, 1 H), 4.69 (dd, $J=10.07$, 7.02 Hz, 1 H), 5.14 (dd, $J=10.53$, 1.37 Hz, 1 H), 5.32 (d, $J=17.09$ Hz, 1 H), 5.70-5.77 (m, 1 H), 5.94 (t, $J=3.66$ Hz, 1 H), 7.19 (d, $J=9.16$ Hz, 1 H), 7.24 (s, 1 H), 7.32 (s, 1 H), 7.91 (d, $J=5.80$ Hz, 1 H), 8.09 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.213 min.), MS m/z 616 (MH^+).

25

Compound 100
DSC, THF, MW
then tBuNH₂
Compound 101

20 Example 102: Preparation of Compound 102



Compound 102 was prepared by the same method as **Compound 101** with the following modifications:

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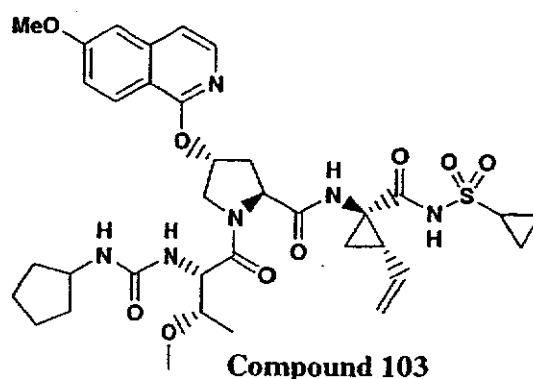
Modifications: tert-amylamine was used as a starting material to give **Compound 102** (62.5 mg, 74% yield): ^1H NMR(CD_3OD , 500 MHz) δ 0.77 (t, $J=7.48$ Hz, 2 H), 0.84 (t, $J=7.48$ Hz, 1 H), 1.04-1.08 (m, 2 H), 1.13 (d, $J=1.22$ Hz, 9 H), 1.16 (d, $J=6.41$ Hz, 3 H), 1.21 (s, 1 H), 1.22-1.28 (m, 2 H), 1.44 (dd, $J=9.46, 5.19$ Hz, 1 H), 1.52-1.57 (m, 1 H), 1.58-1.62 (m, 1 H), 1.85 (dd, $J=7.93, 5.19$ Hz, 1 H), 2.21-2.25 (m, 1 H), 2.34-2.39 (m, 1 H), 2.61 (dd, $J=13.53, 7.17$ Hz, 1 H), 2.93-2.98 (m, 1 H), 3.59-3.64 (m, 1 H), 4.15 (dd, $J=11.75, 3.81$ Hz, 1 H), 4.38 (d, $J=12.51$ Hz, 1 H), 4.50 (d, $J=7.63$ Hz, 1 H), 4.55 (dd, $J=9.92, 7.78$ Hz, 1 H), 5.11 (d, $J=9.77$ Hz, 1 H), 5.29 (d, $J=16.79$ Hz, 1 H), 5.77-5.83 (m, 1 H), 5.86 (t, $J=4.73$ Hz, 1 H), 7.12 (dd, $J=8.85, 2.44$ Hz, 1 H), 7.18 (d, $J=2.44$ Hz, 1 H), 7.24 (d, $J=6.10$ Hz, 1 H), 7.88 (d, $J=5.80$ Hz, 1 H), 8.10 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.690 min.), MS m/z 729 (MH^+).

10

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Example 103: Preparation of Compound 103

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Compound 103 was prepared by the same method as **Compound 101** with the following modifications:

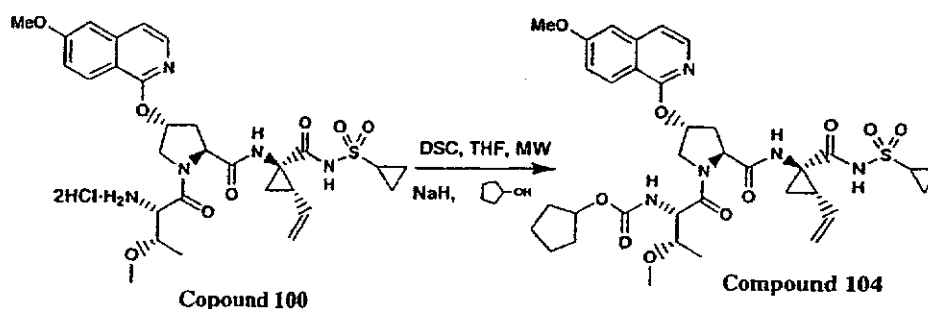
5

Modifications: cyclopentylamine was used as a starting material to give **Compound 103** (56.4 mg, 67% yield): ^1H NMR(CD_3OD , 500 MHz) δ 1.01-1.08 (m, 2 H), 1.07 (d, $J=6.10$ Hz, 1 H), 1.16 (d, $J=6.10$ Hz, 3 H), 1.21-1.25 (m, 3 H), 1.30-1.33 (m, 1 H), 1.44 (dd, $J=9.77$, 5.19 Hz, 1 H), 1.51-1.56 (m, 2 H), 1.60-1.65 (m, 2 H), 1.71-1.75 (m, 1 H), 1.80-1.84 (m, 1 H), 1.86 (dd, $J=8.09$, 5.34 Hz, 1 H), 2.20-2.25 (m, 1 H), 2.37-2.41 (m, 1 H), 2.61 (dd, $J=14.04$, 7.32 Hz, 1 H), 2.93-2.98 (m, 1 H), 3.60-3.65 (m, 1 H), 3.75-3.80 (m, 1 H), 3.92 (s, 3 H), 4.17 (dd, $J=12.05$, 3.81 Hz, 1 H), 4.37 (d, $J=11.90$ Hz, 1 H), 4.55-4.59 (m, 2 H), 5.10 (d, $J=11.60$ Hz, 1 H), 5.29 (d, $J=16.48$ Hz, 1 H), 5.78-5.83 (m, 1 H), 5.85 (d, $J=2.44$ Hz, 1 H), 7.13 (dd, $J=9.16$, 2.44 Hz, 1 H), 7.18 (d, $J=2.44$ Hz, 1 H), 7.24 (d, $J=5.80$ Hz, 1 H), 7.88 (d, $J=5.80$ Hz, 1 H), 8.09 (d, $J=9.16$ Hz, 1 H); LC-MS (retention time: 1.607 min.), MS m/z 727 (MH^+).

10

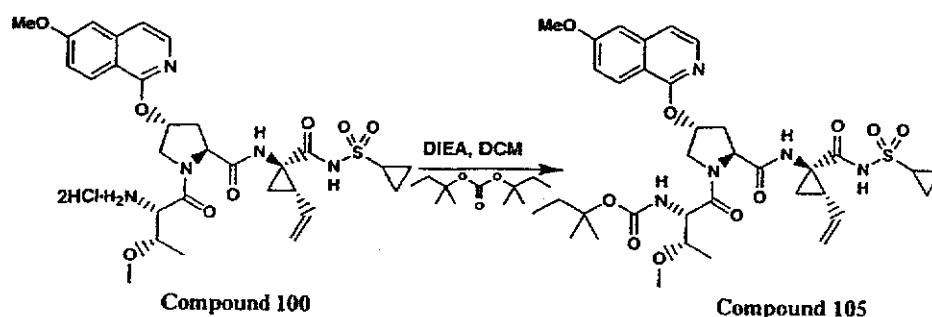
15

Example 104: Preparation of Compound 104



To a solution mixture of Compound 100 (80 mg, 0.116 mmol) and DIEA (31.5 mg, 0.244 mmol) in THF (2 mL) was added N,N'-dissuccinimidyl carbonate (44.6 mg, 0.174 mmol). The resulting suspension was irradiated in a microwave to 80 °C for 15 min. Then was added a slurry solution of sodium cyclopentoxide which was prepared by treating a 0 °C solution of cyclopentanol (110 mg, 1.28 mmol) in THF (1 mL) with NaH (60% in oil, 46.4 mg, 1.16 mmol) for 15 min at rt. After stirring at rt 15 min, the reaction was quenched with saturated aqueous ammonium chloride (1 mL) and extracted with EtOAc (5 mL). The organic layer was then passed through a celite hydromatrix column, concentrated and purified by reversed phase prep-HPLC to give **Compound 104** (38.2 mg, 45%): ¹H NMR(CD₃OD, 500 MHz) δ 1.03-1.09 (m, 3 H), 1.16 (d, *J*=6.10 Hz, 3 H), 1.201.25 (m, 1 H), 1.25-1.30 (m, *J*=10.22, 5.34 Hz, 1 H), 1.40-1.45 (m, *J*=10.83, 3.81 Hz, 1 H), 1.46 (dd, *J*=9.61, 5.34 Hz, 1 H), 1.58-1.63 (m, 3 H), 1.70-1.75 (m, 2 H), 1.86 (dd, *J*=7.63, 5.49 Hz, 1 H), 2.22-2.26 (m, 1 H), 2.34-2.39 (m, 1 H), 2.59-2.64 (m, 1 H), 2.94-2.98 (m, 1 H), 3.67 (dd, *J*=7.78, 6.56 Hz, 1 H), 3.92 (s, 3 H), 4.13 (dd, *J*=10.83, 4.12 Hz, 1 H), 4.37-4.42 (m, 1 H), 4.56 (dd, *J*=10.07, 7.32 Hz, 1 H), 4.71-4.76 (m, 1 H), 5.12 (d, *J*=10.68 Hz, 1 H), 5.31 (d, *J*=16.79 Hz, 1 H), 5.80 (m, 1 H), 5.85 (s, 1 H), 7.13 (d, *J*=10.68 Hz, 1 H), 7.19 (d, *J*=1.83 Hz, 1 H), 7.25 (d, *J*=6.10 Hz, 1 H), 7.89 (d, *J*=5.80 Hz, 1 H), 8.09 (d, *J*=9.16 Hz, 1 H); LC-MS (retention time: 1.697 min.), MS *m/z* 728 (MH⁺).

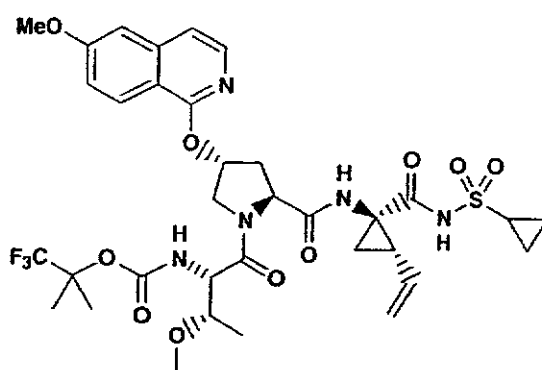
Example 105: Preparation of Compound 105



To a solution mixture of **Compound 100** (80.0 mg, 0.116 mmol) and DIEA (31.5 mg, 0.244 mmol) in DCM (2 mL) was added di-tert-amyl dicarbonate (57.1mg,

0.232 mmol). After stirring at rt for 14 h, solvent was removed and product was purified by reversed phase prep-HPLC to give **Compound 105** (62.5 mg, 74% yield):
¹H NMR(CD₃OD, 500 MHz) δ 0.79 (t, *J*=7.48 Hz, 3 H), 1.04-1.08 (m, 3 H), 1.17 (d, *J*=6.10 Hz, 3 H), 1.19-1.23 (s, 3 H), 1.24 (s, 3 H), 1.39-1.43 (m, 1 H), 1.46 (dd, *J*=9.61, 5.34 Hz, 1 H), 1.60-1.65 (m, 2 H), 1.86 (dd, *J*=7.93, 5.49 Hz, 1 H), 2.22 (q, *J*=8.85 Hz, 1 H), 2.35-2.40 (m, 1 H), 2.61 (dd, *J*=14.04, 7.15 Hz, 1 H), 2.94-3.00 (m, 1 H), 3.64-4.00 (m, 1 H), 3.92 (s, 4 H), 4.14 (dd, *J*=11.90, 3.05 Hz, 1 H), 4.35 (d, *J*=7.93 Hz, 1 H), 4.40 (d, *J*=11.90 Hz, 1 H), 4.55 (dd, *J*=9.31, 7.78 Hz, 1 H), 5.11 (d, *J*=10.68 Hz, 1 H), 5.30 (d, *J*=16.79 Hz, 1 H), 5.79-5.83 (m, 1 H), 5.85 (s, 1 H), 7.12 (d, *J*=9.16 Hz, 1 H), 7.18 (s, 1 H), 7.25 (d, *J*=5.80 Hz, 1 H), 7.86-7.90 (m, 1 H), 8.09 (d, *J*=9.16 Hz, 1 H); LC-MS (retention time: 1.740 min.), MS *m/z* 730 (MH⁺).

Example 106: Preparation of Compound 106



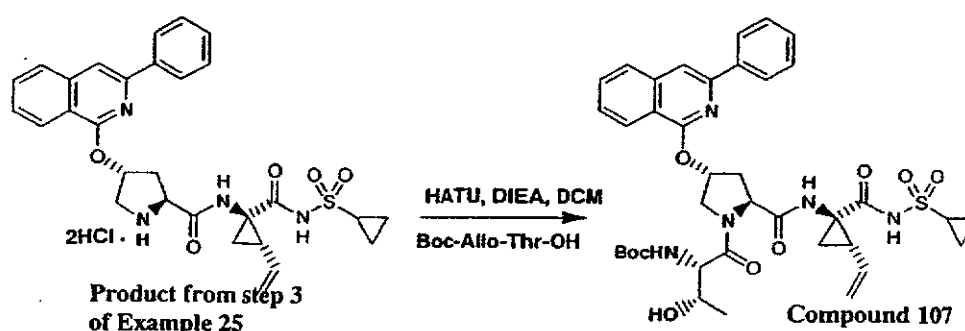
Compound 106

Compound 106 was prepared by the same method as **Compound 105** with the following modifications:

- Modifications: Carboxylic acid pyridin-2-yl ester 2,2,2-trifluoro-1,1-dimethyl-ethyl ester was used as a starting material to give **Compound 106** (58.1 mg, 65% yield): ¹H NMR(CD₃OD, 500 MHz) δ 1.04-1.08 (m, 3 H), 1.17 (d, *J*=6.10 Hz, 3 H), 1.19-1.23 (m, 1 H), 1.23-1.27 (m, 1 H), 1.28 (s, 3 H), 1.46 (dd, *J*=9.46, 5.19 Hz, 2 H), 1.49 (s, 2 H), 1.86 (dd, *J*=8.09, 5.34 Hz, 1 H), 2.21 (q, *J*=8.85 Hz, 1 H), 2.36-2.40 (m, 1 H), 2.62 (dd, *J*=13.74, 7.32 Hz, 1 H), 2.93-2.98 (m, 1 H), 3.65-3.70 (m, 1 H), 3.92 (s, 3

H), 4.12 (dd, $J=11.90, 3.66$ Hz, 1 H), 4.31 (d, $J=8.24$ Hz, 1 H), 4.42 (d, $J=11.90$ Hz, 1 H), 4.57 (dd, $J=10.07, 7.32$ Hz, 1 H), 5.11 (d, $J=10.38$ Hz, 1 H), 5.30 (d, $J=16.79$ Hz, 1 H), 5.78-5.83 (m, 1 H), 5.84 (s, 1 H), 7.12 (dd, $J=9.00, 2.29$ Hz, 1 H), 7.19 (d, $J=2.14$ Hz, 1 H), 7.25 (d, $J=5.80$ Hz, 1 H), 7.89 (d, $J=6.10$ Hz, 1 H), 8.09 (d, $J=8.85$ Hz, 1 H); LC-MS (retention time: 1.770 min.), MS m/z 770 (MH^+).

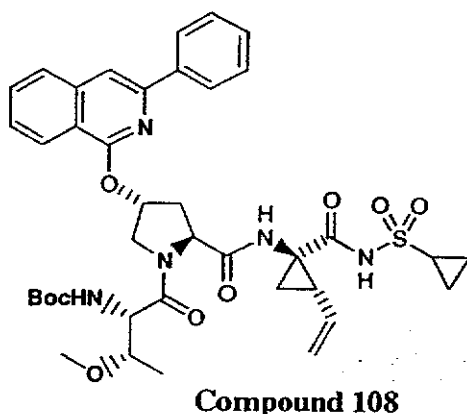
Example 107: Preparation of Compound 107



10

To a solution of the product from step 3 of Example 25 (100.0 mg, 0.116 mmol), DIEA (62.5 mg, 0.463 mmol) and HATU (92.0 mg, 0.242 mmol) was added Boc-allo-Thr-OH (43.5 mg, 0.177 mmol). After stirring at rt for 3 hr, the reaction mixture was washed with 5% aqueous $NaHCO_3$ (1 mL). The aqueous layer was extracted with 2x2 mL DCM. The combined organic layer was washed with 5% aqueous citric acid (1 mL), brine, dried over MgO_4 , concentrated and purified by reversed phase prep-HPLC to give Compound 107 (62.5 mg, 52% yield): ^1H NMR(CD_3OD , 500 MHz) δ 0.8-1.02 (m, 1 H), 1.04-1.08 (m, 2 H), 1.23-1.27 (m, 12 H), 1.42 (dd, $J=9.46, 5.19$ Hz, 1 H), 1.86 (t, $J=6.26$ Hz, 1 H), 2.23-2.27 (m, 1 H), 2.46-2.50 (m, 1 H), 2.76 (dd, $J=14.04, 6.71$ Hz, 1 H), 2.95-2.99 (m, 1 H), 3.94-3.98 (m, 1 H), 4.28 (d, $J=7.32$ Hz, 2 H), 4.52 (d, $J=12.51$ Hz, 1 H), 4.63 (t, $J=9.00$ Hz, 1 H), 5.12 (d, $J=10.07$ Hz, 1 H), 5.31 (d, $J=16.79$ Hz, 1 H), 5.77-5.83 (m, 1 H), 6.09 (s, 1 H), 7.36-7.41 (m, 1 H), 7.47 (t, $J=7.17$ Hz, 3 H), 7.52 (d, $J=7.63$ Hz, 1 H), 7.70 (t, $J=7.17$ Hz, 1 H), 7.85 (s, 1 H), 7.88 (d, $J=8.24$ Hz, 1 H), 8.17 (d, $J=7.93$ Hz, 2 H), 8.22 (d, $J=7.63$ Hz, 1 H); LC-MS (retention time: 1.937 min.), MS m/z 748 (MH^+).

25

Example 108: Preparation of Compound 108

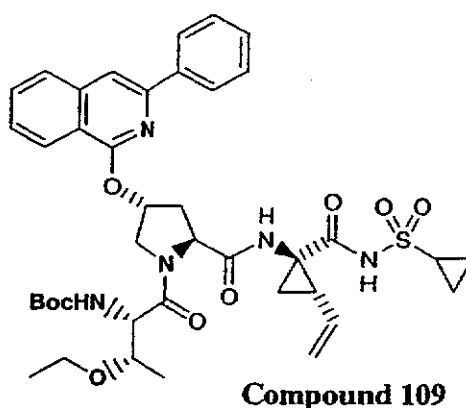
- 5 **Compound 108** was prepared by the same method as Compound 107 with the following modifications:

Modifications: Boc-(2*S*, 3*S*)-Amino-3-methoxybutanoic acid was used as a starting material to give **Compound 108** (75.1 mg, 51% yield): ¹H NMR(CD₃OD, 500 MHz)

10 δ 0.80-1.02 (m, 4 H), 1.18 (d, *J*=6.10 Hz, 3 H), 1.28 (s, 9 H), 1.44 (dd, *J*=9.77, 1.30 Hz, 1 H), 1.45-1.50 (m, 1 H), 1.85-1.90 (m, 1 H), 2.14-2.18 (m, 1 H), 2.55-2.59 (m, 1 H), 2.72-2.76 (m, 1 H), 2.91-2.95 (m, 1 H), 3.34 (s, 3 H), 3.65-3.69 (m, 1 H), 4.32 (d, *J*=10.68 Hz, 1 H), 4.40 (d, *J*=7.93 Hz, 1 H), 4.46 (d, *J*=13.12 Hz, 1 H), 4.60 (t, *J*=8.24 Hz, 1 H), 5.07 (d, *J*=9.46 Hz, 1 H), 5.26 (d, *J*=17.40 Hz, 1 H), 5.82-5.86 (m, 1

15 H), 6.08 (s, 1 H), 7.38 (dd, *J*=7.32, 6.10 Hz, 1 H), 7.47 (t, *J*=7.02 Hz, 3 H), 7.51 (d, *J*=5.80 Hz, 1 H), 7.69 (t, *J*=6.56 Hz, 1 H), 7.69 (t, *J*=6.56 Hz, 1 H), 7.85 (s, 1 H), 7.88 (d, *J*=7.63 Hz, 1 H), 8.18 (d, *J*=8.24 Hz, 3 H), 8.21 (d, *J*=9.16 Hz, 1 H); LC-MS (retention time: 1.973 min.), MS *m/z* 762 (MH⁺).

20 **Example 109: Preparation of Compound 109**



Compound 109 was prepared by the same method as **Compound 107** with the following modifications:

5

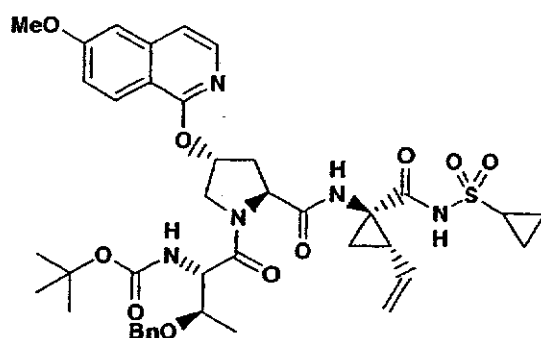
Modifications: Boc-(2*S*, 3*S*)-Amino-3-ethoxybutanoic acid was used as a starting material to give **Compound 109** (57.2 mg, 47% yield): ¹H NMR(CD₃OD, 500 MHz) δ 1.02-1.08 (m, 4 H), 1.17 (d, *J*=6.10 Hz, 6 H), 1.19 (s, 1 H), 1.19-1.24 (m, 1 H), 1.23-1.27 (m, *J*=3.97 Hz, 1 H), 1.30 (s, 9 H), 1.44 (dd, *J*=9.77, 5.50 Hz, 1 H), 1.46 (s, 1 H), 1.88 (dd, *J*=7.78, 5.95 Hz, 1 H), 2.20-1.25 (m, 1 H), 2.49-2.54 (m, 1 H), 2.69-2.73 (m, 1 H), 2.93-2.97 (m, 1 H), 3.53-3.57 (m, 2 H), 3.75-3.80 (m, 1 H), 4.34 (dd, *J*=11.75, 3.20 Hz, 1 H), 4.42 (t, *J*=8.30 Hz, 2 H), 4.57 (t, *J*=8.09 Hz, 1 H), 5.11 (d, *J*=10.38 Hz, 1 H), 5.29 (d, *J*=17.40 Hz, 1 H), 5.78-5.83 (m, 1 H), 6.09 (s, 1 H), 7.38 (t, *J*=7.32 Hz, 1 H), 7.47 (t, *J*=7.63 Hz, 2 H), 7.52 (d, *J*=7.02 Hz, 1 H), 7.70 (t, *J*=7.93 Hz, 1 H), 7.86 (s, 1 H), 7.88 (d, *J*=7.93 Hz, 1 H), 8.18 (d, *J*=7.32 Hz, 2 H), 8.22 (d, *J*=8.24 Hz, 1 H); LC-MS (retention time: 2.030 min.), MS *m/z* 776 (MH⁺).

10

15

Example 110: Preparation of Compound 110

223

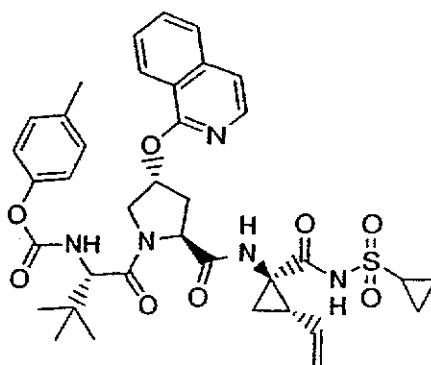
**Compound 110**

Compound 110 was prepared by the same method as **Compound 89** with the following modifications:

5

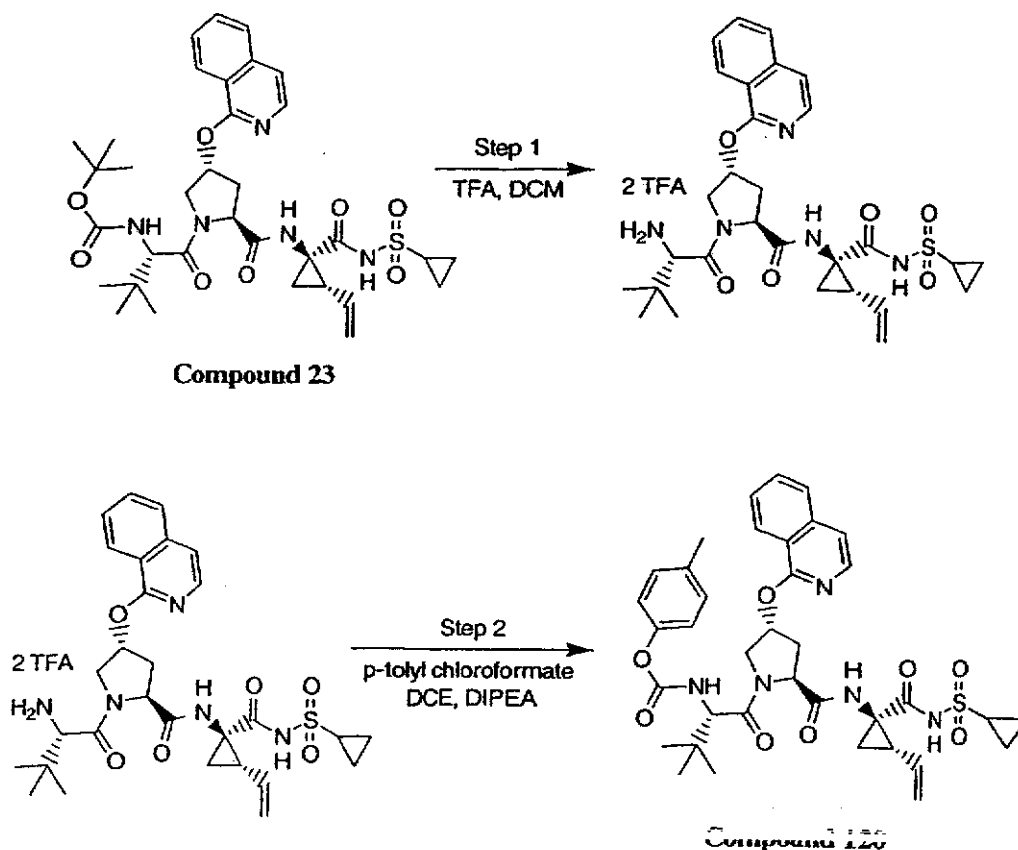
Modifications: Boc-L-Thr(Bn)-OH was used as a starting material to give **Compound 110** (49.8 mg, 48% yield); LC-MS (retention time: 1.857 min.), MS m/z 792 (MH^+).

10

Section D:**Example 120: Preparation of Compound 120****Compound 120**

15

Scheme 1



Step 1:

A solution of Compound 23 (see Example 23) (1.50g, 2.19 mmol) in DCM (50 mL) and trifluoroacetic acid (50 mL) was stirred for 3 h at rt. The mixture was concentrated *in vacuo* to a viscous residue, and was then dissolved in 1,2-dichloroethane and again concentrated *in vacuo* to give the desired bis-trifluoroacetic acid salt product as an off-white glassy solid (quantitative). The material was used directly in the next step without purification.

10

Step 2:

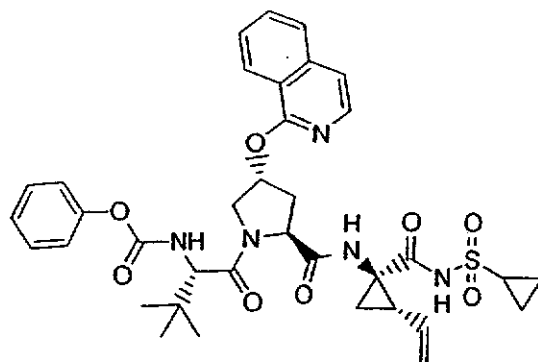
To a solution of the product from Example 120, Step 1 (118 mg, 0.146 mmol) in 1,2-dichloroethane (3 mL) was added *p*-tolyl chloroformate (32.4 mg, 0.190 mmol) and *N,N*-diisopropylethylamine (94.5 mg, 0.731 mmol). The mixture was agitated at rt for 72 h. The reaction mixture was washed with pH = 4 buffer solution

15

(3 x 3 mL), and the washes were back-extracted with 1,2-dichloroethane (3 mL). The organic phases were combined and concentrated *in vacuo*. The crude product was then dissolved in MeOH and purified by reverse phase preparative HPLC to give the title compound (**Compound 120**) as a yellow glassy solid (64.2 mg, 61.1% yield):

5 ^1H NMR (CD_3OD) δ 1.06-1.10 (m, 3 H), 1.12 (s, 9 H), 1.24-1.28 (m, 2 H), 1.44 (dd, $J=9.31, 5.34$ Hz, 1 H), 1.89 (dd, $J=7.93, 5.49$ Hz, 1 H), 2.21-2.28 (m, 2 H), 2.31 (s, 3 H), 2.62-2.66 (m, 1 H), 2.93-2.99 (m, 1 H), 4.12 (dd, $J=11.90, 3.66$ Hz, 1 H), 4.42 (d, $J=11.60$ Hz, 1 H), 4.57 (dd, $J=10.22, 7.17$ Hz, 1 H), 5.13 (d, $J=10.38$ Hz, 1 H), 5.30 (d, $J=17.09$ Hz, 1 H), 5.76 (ddd, $J=17.09, 9.77, 9.46$ Hz, 1 H), 5.87 (s, 1 H), 6.79 (d, $J=8.24$ Hz, 2 H), 7.07 (d, $J=8.24$ Hz, 2 H), 7.30 (d, $J=6.10$ Hz, 1 H), 7.40 (t, $J=7.63$ Hz, 1 H), 7.68 (t, $J=7.63$ Hz, 1 H), 7.79 (d, $J=8.24$ Hz, 1 H), 7.93 (d, $J=5.80$ Hz, 1 H), 8.17 (d, $J=8.24$ Hz, 1 H); MS m/z 718 (MH^+).

Example 121: Preparation of Compound 121



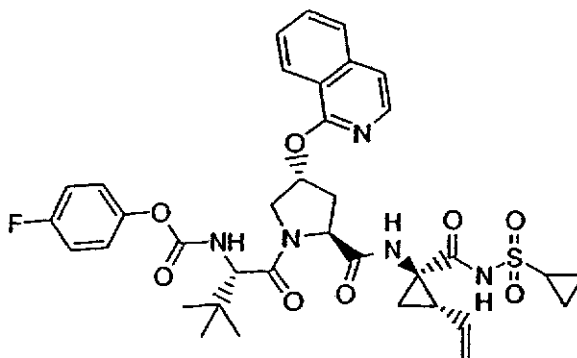
Compound 121

Compound 121 was prepared by following Scheme 1 of Example 120 except that phenyl chloroformate was used in place of *p*-tolyl chloroformate in step 2.

Step 2:

Modifications: 30 mg (0.19 mmol) phenyl chloroformate used, 89.0 mg product obtained as a yellow glassy solid (50% yield): MS m/z 704 (MH^+).

Example 122: Preparation of Compound 122

**Compound 122**

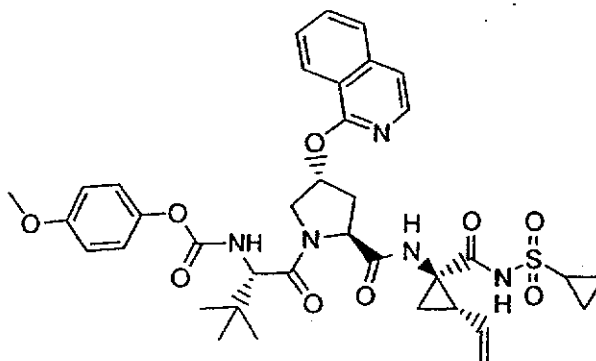
Compound 122 was prepared by following Scheme 1 of Example 120 except that 4-fluorophenyl chloroformate was used in place of *p*-tolyl chloroformate in step 2.

Step 2:

Modifications: 33 mg (0.19 mmol) 4-fluorophenyl chloroformate used, 83.1 mg product obtained as a sticky yellow oil (78.8% yield): MS m/z 722 (MH^+).

10

Example 123: Preparation of Compound 123

**Compound 123**

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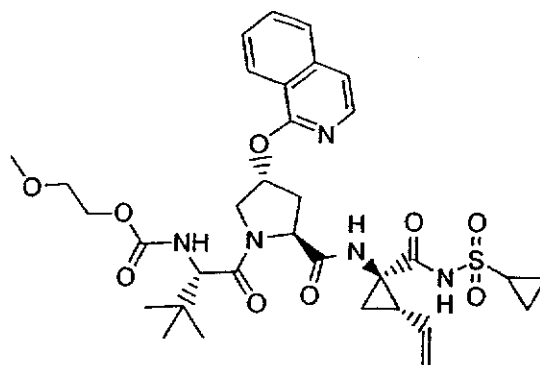
Compound 123 was prepared by following Scheme 1 of Example 120 except that 4-methoxyphenyl chloroformate was used in place of *p*-tolyl chloroformate in step 2.

Step 2:

- 5 Modifications: 35 mg (0.19 mmol) 4-methoxyphenyl chloroformate used, 70.2 mg product obtained as a yellow glassy solid (65.4% yield): ^1H NMR (CD_3OD) δ 1.06-1.10 (m, 3 H), 1.11 (s, 9 H), 1.24-1.28 (m, 2 H), 1.44 (dd, $J=9.46, 5.49$ Hz, 1 H), 1.89 (dd, $J=7.93, 5.49$ Hz, 1 H), 2.24 (q, $J=8.85$ Hz, 1 H), 2.31 (ddd, $J=13.81, 10.30, 3.97$ Hz, 1 H), 2.62-2.66 (m, 1 H), 2.94-2.98 (m, 1 H), 3.77 (s, 3 H), 4.12 (dd, $J=11.60, 3.66$ Hz, 1 H), 4.42 (d, $J=11.60$ Hz, 1 H), 4.57 (dd, $J=10.07, 7.32$ Hz, 1 H), 5.13 (d, $J=10.68$ Hz, 1 H), 5.30 (d, $J=16.79$ Hz, 1 H), 5.72-5.80 (m, 1 H), 5.87 (s, 1 H), 6.80 (d, $J=2.44$ Hz, 4 H), 7.30 (d, $J=5.80$ Hz, 1 H), 7.42 (t, $J=7.48$ Hz, 1 H), 7.69 (t, $J=7.63$ Hz, 1 H), 7.80 (d, $J=7.93$ Hz, 1 H), 7.93 (d, $J=5.80$ Hz, 1 H), 8.18 (d, $J=8.24$ Hz, 1 H); MS m/z 734 (MH^+).

15

Example 124: Preparation of Compound 124



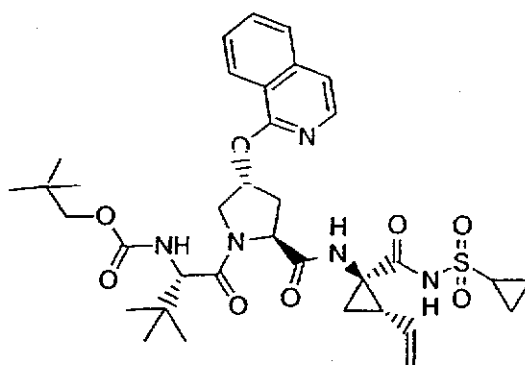
Compound 124

- 20 **Compound 124** was prepared by following Scheme 1 of Example 120 except that chloroformic acid 2-methoxyethyl ester was used in place of *p*-tolyl chloroformate in step 2.

Step 2:

Modifications: 26 mg (0.19 mmol) chloroformic acid 2-methoxyethyl ester used, 87.4 mg product obtained as a sticky yellow oil (87.2% yield): $^1\text{H NMR}$ (CD_3OD) δ 0.96-1.02 (m, 3 H), 1.05 (s, 9 H), 1.16-1.18 (m, 2 H), 1.40 (dd, $J=9.46$, 5.19 Hz, 1 H), 1.85 (dd, $J=7.93$, 5.19 Hz, 1 H), 2.15 (q, $J=8.75$ Hz, 1 H), 2.40 (ddd, $J=13.89$, 10.07, 4.12 Hz, 1 H), 2.65 (dd, $J=13.58$, 7.17 Hz, 1 H), 2.90 (ddd, $J=12.89$, 8.16, 4.88 Hz, 1 H), 3.27 (s, 3 H), 3.36-3.44 (m, 2 H), 3.81-3.84 (m, 1 H), 3.92-3.96 (m, 1 H), 4.12 (dd, $J=11.60$, 3.36 Hz, 1 H), 4.44 (d, $J=11.60$ Hz, 1 H), 4.57 (dd, $J=9.46$, 7.93 Hz, 1 H), 5.07 (d, $J=10.38$ Hz, 1 H), 5.25 (d, $J=17.09$ Hz, 1 H), 5.80 (ddd, $J=17.32$, 9.77, 9.54 Hz, 1 H), 5.87 (s, 1 H), 7.32 (d, $J=5.80$ Hz, 1 H), 7.55 (t, $J=7.32$ Hz, 1 H), 7.70 (t, $J=7.48$ Hz, 1 H), 7.80 (d, $J=7.93$ Hz, 1 H), 7.96 (d, $J=5.80$ Hz, 1 H), 8.19 (d, $J=8.24$ Hz, 1 H); MS m/z 686 (MH^+).

Example 125: Preparation of Compound 125



Compound 125

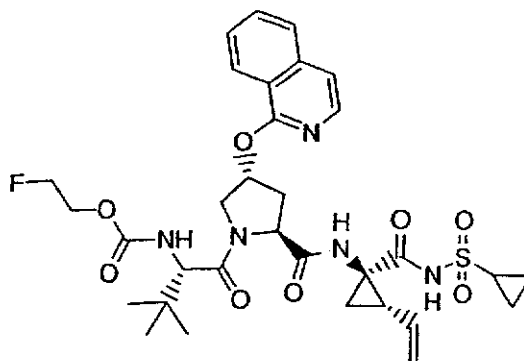
Compound 125 was prepared by following Scheme 1 of Example 120 except that neopentyl chloroformate was used in place of *p*-tolyl chloroformate in step 2.

20 Step 2:

Modifications: 29 mg (0.19 mmol) neopentyl chloroformate used, 57.4 mg product obtained as a yellow glassy solid (56.2% yield): $^1\text{H NMR}$ (CD_3OD) δ 0.83 (s, 9 H), 1.05 (d, $J=2.44$ Hz, 9 H), 1.07-1.09 (m, 2 H), 1.23-1.27 (m, 2 H), 1.43-1.46 (m, 1 H), 1.87-1.90 (m, 1 H), 2.21-2.25 (m, 1 H), 2.29-2.33 (m, 1 H), 2.61-2.65 (m, 1 H), 2.92-

2.96 (m, 1 H), 3.42 (d, $J=10.07$ Hz, 1 H), 3.56 (d, $J=10.07$ Hz, 1 H), 4.09-4.11 (m, 1 H), 4.33 (d, $J=9.16$ Hz, 1 H), 4.43 (d, $J=11.29$ Hz, 1 H), 4.54-4.57 (m, 1 H), 5.12 (d, $J=10.07$ Hz, 1 H), 5.30 (d, $J=17.40$ Hz, 1 H), 5.73-5.80 (m, 1 H), 5.88 (s, 1 H), 7.33 (d, $J=5.49$ Hz, 1 H), 7.53 (m, 1 H), 7.71 (t, $J=6.87$ Hz, 1 H), 7.81 (d, $J=7.93$ Hz, 1 H), 7.97 (d, $J=5.80$ Hz, 1 H), 8.19 (d, $J=7.63$ Hz, 1 H); MS m/z 698 (MH^+).

Example 126: Preparation of Compound 126



Compound 126

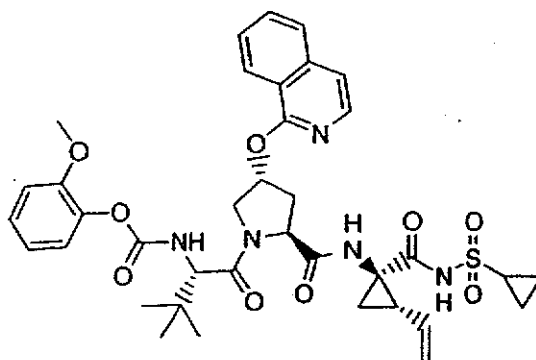
10

Compound 126 was prepared by following Scheme 1 of Example 120 except that 2-fluoroethyl chloroformate was used in place of *p*-tolyl chloroformate in step 2.

Step 2:

15 **Modifications:** 24 mg (0.19 mmol) 2-fluoroethyl chloroformate used, 58.9 mg product obtained as a yellow glassy solid (59.8% yield): ^1H NMR (CD_3OD) δ 1.05 (d, $J=2.14$ Hz, 9 H), 1.07-1.09 (m, 2 H), 1.22-1.27 (m, 2 H), 1.42-1.45 (m, 1 H), 1.87-1.90 (m, 1 H), 2.24 (q, $J=8.75$ Hz, 1 H), 2.28-2.33 (m, 1 H), 2.63 (dd, $J=13.43$, 6.41 Hz, 1 H), 2.92-2.96 (m, 1 H), 3.92-4.10 (m, 3 H), 4.31-4.37 (m, 2 H), 4.42-4.46 (m, 2 H), 4.54-4.57 (m, 1 H), 5.12 (d, $J=10.38$ Hz, 1 H), 5.29 (d, $J=17.09$ Hz, 1 H), 5.71-5.79 (m, 1 H), 5.88 (s, 1 H), 7.33 (d, $J=5.80$ Hz, 1 H), 7.55 (t, $J=7.17$ Hz, 1 H), 7.71 (m, 1 H), 7.81 (d, $J=7.93$ Hz, 1 H), 7.96 (d, $J=5.80$ Hz, 1 H), 8.19 (d, $J=7.63$ Hz, 1 H); MS m/z 674 (MH^+).

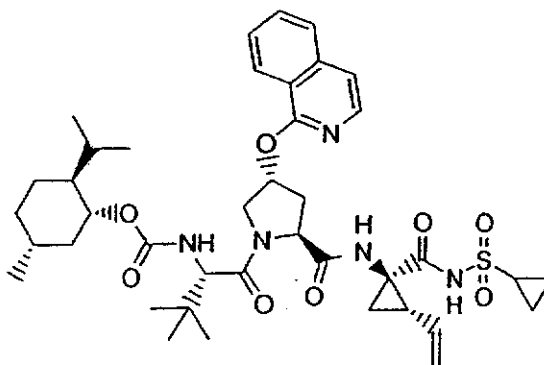
20

Example 127: Preparation of Compound 127**Compound 127**

- 5 **Compound 127** was prepared by following Scheme 1 of Example 120 except that 2-methoxyphenyl chloroformate was used in place of *p*-tolyl chloroformate in step 2.

Step 2:

- Modifications: 35 mg (0.19 mmol) 2-methoxyphenyl chloroformate used, 97.6 mg
10 product obtained as a sticky yellow oil (91.0 % yield): MS *m/z* 734 (MH⁺).

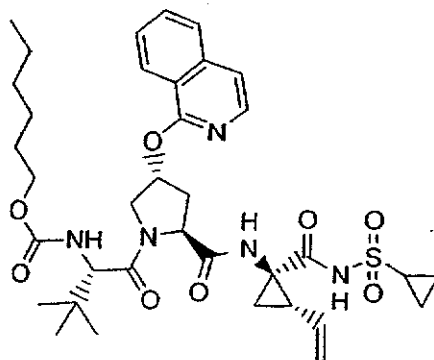
Example 128: Preparation of Compound 128**Compound 128**

Compound 128 was prepared by following Scheme 1 of Example 120 except that 2-(-)-(1*R*)-menthyl chloroformate was used in place of *p*-tolyl chloroformate in step 2.

Step 2:

- 5 Modifications: 42 mg (0.19 mmol) (-)-(1*R*)-menthyl chloroformate used, 69.1 mg product obtained as a white glassy solid (61.7 % yield): MS m/z 766 (MH^+).

Example 129: Preparation of Compound 129



Compound 129

Compound 129 was prepared by following Scheme 1 of Example 120 except that hexyl chloroformate was used in place of *p*-tolyl chloroformate in step 2.

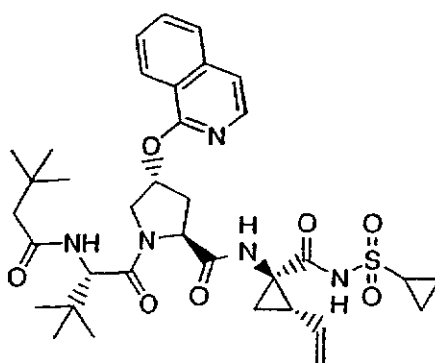
15 Step 2:

Modifications: 31 mg (0.19 mmol) hexyl chloroformate used, 66.7 mg product obtained as a yellow glassy solid (64.1 % yield): ^1H NMR (CD_3OD) δ 0.87-0.99 (m, 5 H), 1.05 (s, 9 H), 1.07-1.09 (m, 2 H), 1.22-1.28 (m, 6 H), 1.43-1.48 (m, 3 H), 1.88 (dd, $J=8.24, 5.49$ Hz, 1 H), 2.24 (q, $J=8.85$ Hz, 1 H), 2.28-2.33 (m, 1 H), 2.63 (dd, $J=14.34, 7.63$ Hz, 1 H), 2.92-2.97 (m, 1 H), 3.72 (dt, $J=10.61, 6.60$ Hz, 1 H), 3.81-3.86 (m, 1 H), 4.10 (dd, $J=11.60, 3.36$ Hz, 1 H), 4.32 (d, $J=8.85$ Hz, 1 H), 4.43 (d, $J=11.90$ Hz, 1 H), 4.55 (dd, $J=9.77, 7.32$ Hz, 1 H), 5.13 (d, $J=10.38$ Hz, 1 H), 5.30 (d, $J=17.09$ Hz, 1 H), 5.76 (ddd, $J=17.09, 10.07, 9.16$ Hz, 1 H), 5.89 (s, 1 H), 7.33 (d,

$J=5.80$ Hz, 1 H), 7.54 (t, $J=7.48$ Hz, 1 H), 7.69-7.72 (m, 1 H), 7.81 (d, $J=8.24$ Hz, 1 H), 7.97 (d, $J=6.10$ Hz, 1 H), 8.20 (d, $J=8.24$ Hz, 1 H); MS m/z 712 (MH^+).

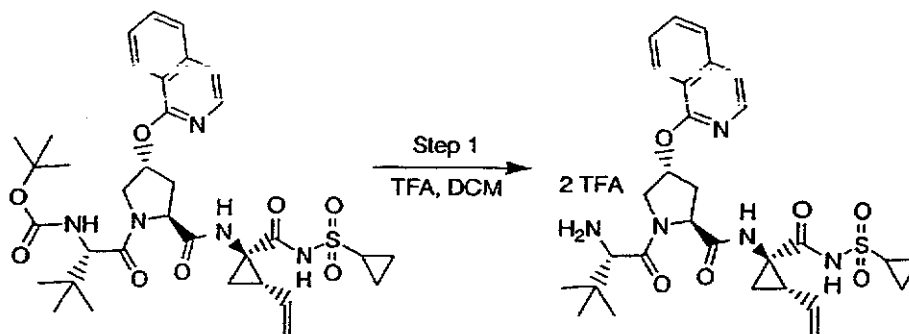
Example 130: Preparation of Compound 130

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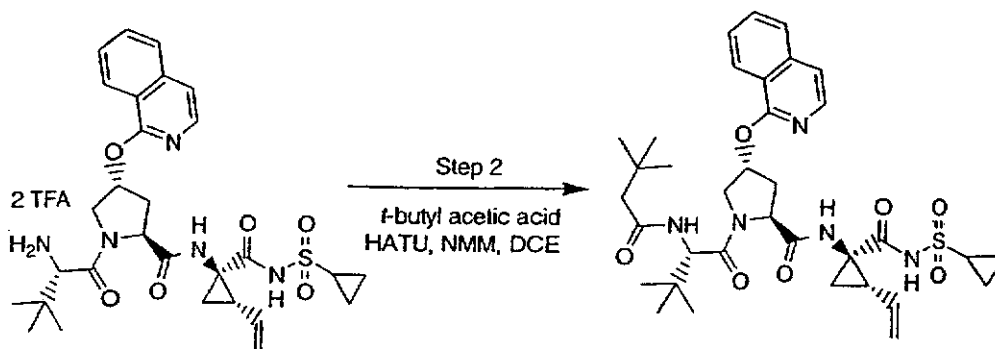


Compound 130

Scheme 1



Compound 23



Compound 130

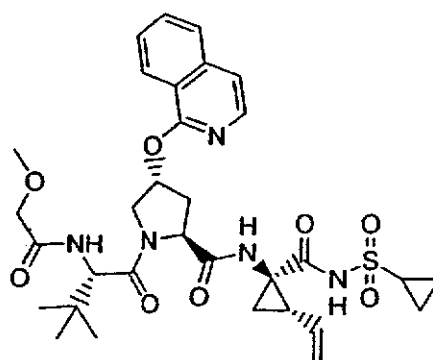
Step 1:

A solution of Compound 23 (see Example 23) (1.50g, 2.19 mmol) in DCM (50 mL) and trifluoroacetic acid (50 mL) was stirred for 3 h at rt. The mixture was concentrated *in vacuo* to a viscous residue, and was then dissolved in 1,2-dichloroethane and again concentrated *in vacuo* to give the desired bis-trifluoroacetic acid salt product as an off-white glassy solid (quantitative). The material was used directly in the next step without purification.

Step 2:

A mixture of the product from step 1 (118 mg, 0.146 mmol), *tert*-butyl acetic acid (22 mg, 0.19 mmol), HATU (72 mg, 0.19 mmol) and *N*-methymorpholine (59 mg, 0.58 mmol) in 1,2-dichloroethane was stirred for 24 h at rt. The reaction mixture was washed with pH = 4 buffer solution (3 x 3 mL), and the washes were back-extracted with 1,2-dichloroethane (3 mL). The organic phases were combined and concentrated *in vacuo*. The crude product was then dissolved in MeOH and purified by reverse phase preparative HPLC to give the title compound (**Compound 130**) as a slightly yellow glassy solid (43.4 mg, 43.5% yield): $^1\text{H NMR}$ (CD_3OD) δ 0.82 (d, $J=1.83$ Hz, 9 H), 1.06 (d, $J=2.14$ Hz, 9 H), 1.07-1.10 (m, 2 H), 1.22-1.28 (m, 2 H), 1.43-1.46 (m, 1 H), 1.87-1.90 (m, 1 H), 1.99 (d, $J=1.83$ Hz, 2 H), 2.20-2.26 (m, 1 H), 2.27-2.33 (m, 1 H), 2.59-2.64 (m, 1 H), 2.93-2.97 (m, 1 H), 4.12-4.14 (m, 1 H), 4.42 (d, $J=11.60$ Hz, 1 H), 4.51-4.55 (m, 1 H), 4.67 (dd, $J=9.31, 1.98$ Hz, 1 H), 5.11-5.14 (m, 1 H), 5.29 (d, $J=17.40$ Hz, 1 H), 5.72-5.80 (m, 1 H), 5.89 (d, $J=1.83$ Hz, 1 H), 7.32 (dd, $J=5.80, 2.14$ Hz, 1 H), 7.52-7.55 (m, 1 H), 7.69-7.72 (m, 1 H), 7.81 (d, $J=8.24$ Hz, 1 H), 7.96 (dd, $J=5.80, 1.83$ Hz, 1 H), 8.17 (d, $J=8.24$ Hz, 1 H); MS m/z 682 (MH^+).

Example 131: Preparation of Compound 131

**Compound 131**

Compound 131 was prepared by following Scheme 1 of Example 130 except that methoxyacetic acid was used in place of *tert*-butyl acetic acid in step 2.

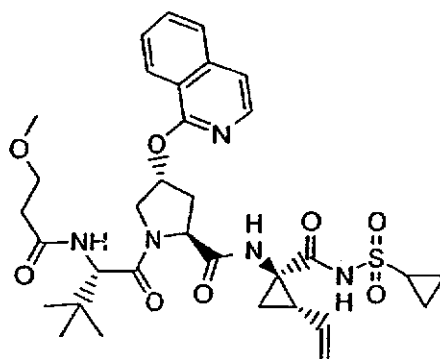
5

Step 2:

Modifications: 17 mg (0.19 mmol) methoxyacetic acid used, 49.9 mg product obtained as a slightly yellow glassy solid (52.0 % yield): ^1H NMR (CD_3OD) δ 1.05-1.08 (m, 11 H), 1.24-1.26 (m, 2 H), 1.45 (ddd, $J=9.31, 5.34, 3.66$ Hz, 1 H), 1.88 (ddd, $J=8.39, 5.19, 3.81$ Hz, 1 H), 2.21-2.27 (m, 1 H), 2.29-2.35 (m, 1 H), 2.60-2.64 (m, 1 H), 2.91-2.97 (m, 1 H), 3.34 (d, $J=3.66$ Hz, 3 H), 3.69 (dd, $J=15.26, 3.66$ Hz, 1 H), 3.81-3.85 (m, 1 H), 4.15 (dt, $J=11.67, 3.62$ Hz, 1 H), 4.35 (d, $J=11.90$ Hz, 1 H), 4.55 (ddd, $J=10.30, 6.94, 3.20$ Hz, 1 H), 4.66 (dd, $J=9.61, 3.51$ Hz, 1 H), 5.11-5.14 (m, 1 H), 5.28-5.32 (m, 1 H), 5.73-5.81 (m, 1 H), 5.90 (d, $J=3.36$ Hz, 1 H), 7.33 (dd, $J=5.65, 3.20$ Hz, 1 H), 7.54-7.58 (m, 1 H), 7.69-7.73 (m, 1 H), 7.80-7.82 (m, 1 H), 7.95-7.97 (m, 1 H), 8.15 (dd, $J=8.39, 2.59$ Hz, 1 H); MS m/z 656 (MH^+).

15

Example 132: Preparation of Compound 132

**Compound 132**

Compound 132 was prepared by following Scheme 1 of Example 130 except that methoxypropionic acid was used in place of *tert*-butyl acetic acid in step 2.

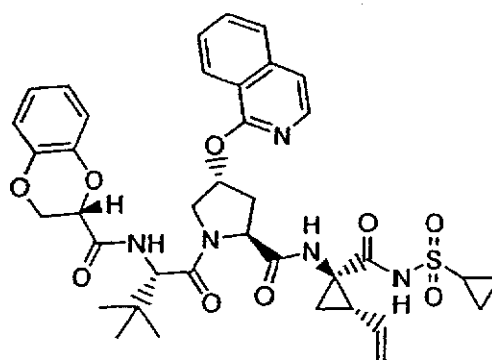
5

Step 2:

Modifications: 20 mg (0.19 mmol) methoxypropionic acid used, 50.0 mg product obtained as a yellow glassy solid (51.1 % yield): ^1H NMR (CD_3OD) δ 1.06 (d,

10 $J=1.83$ Hz, 9 H), 1.07-1.09 (m, 2 H), 1.23-1.27 (m, 2 H), 1.44 (ddd, $J=9.38$, 5.26, 1.83 Hz, 1 H), 1.87-1.90 (m, 1 H), 2.21-2.27 (m, 1 H), 2.29-2.33 (m, 2 H), 2.40-2.46 (m, 1 H), 2.59-2.64 (m, 1 H), 2.92-2.97 (m, 1 H), 3.25 (d, $J=1.83$ Hz, 3 H), 3.45-3.54 (m, 2 H), 4.12-4.16 (m, 1 H), 4.37 (d, $J=11.60$ Hz, 1 H), 4.52-4.55 (m, 1 H), 4.65 (dd, $J=9.16$, 1.83 Hz, 1 H), 5.12 (d, $J=10.38$ Hz, 1 H), 5.30 (d, $J=17.40$ Hz, 1 H), 5.72-5.80 (m, 1 H), 5.89 (s, 1 H), 7.33 (dd, $J=5.65$, 1.98 Hz, 1 H), 7.54-7.58 (m, 1 H), 15 7.69-7.73 (m, 1 H), 7.81 (d, $J=8.24$ Hz, 1 H), 7.96 (dd, $J=6.10$, 1.83 Hz, 1 H), 8.18 (d, $J=8.24$ Hz, 1 H); MS m/z 670 (MH^+).

Example 133: Preparation of Compound 133

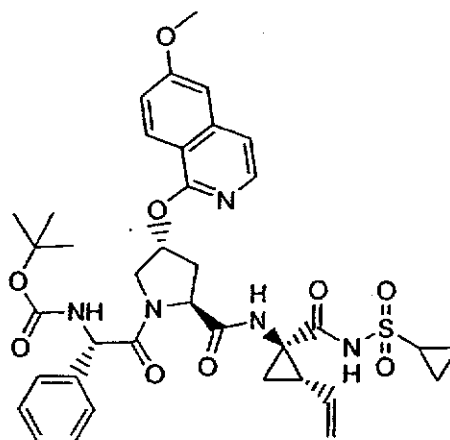
**Compound 133**

Compound 133 was prepared by following Scheme 1 of Example 130 except that
 (S)-1,4-benzodioxane-2-carboxylic acid was used in place of *tert*-butyl acetic acid in
 5 step 2.

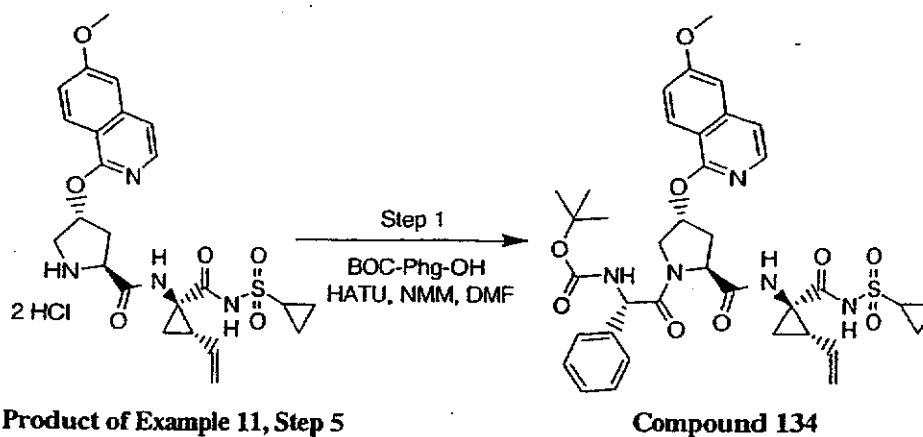
Step 2:

Modifications: 35 mg (0.19 mmol) (S)-1,4-benzodioxane-2-carboxylic acid used,
 54.0 mg product obtained as a slightly yellow glassy solid (49.5 % yield): ¹H NMR
 10 (CD₃OD) δ 0.83 (d, *J*=3.36 Hz, 9 H), 1.05-1.08 (m, 2 H), 1.20-1.25 (m, 1 H), 1.26-
 1.31 (m, 1 H), 1.45-1.49 (m, 1 H), 1.86-1.90 (m, 1 H), 2.21-2.25 (m, 1 H), 2.28-2.34
 (m, 1 H), 2.59-2.65 (m, 1 H), 2.90-2.94 (m, 1 H), 4.12-4.17 (m, 2 H), 4.32 (d,
J=11.90 Hz, 1 H), 4.35-4.39 (m, 1 H), 4.55-4.61 (m, 3 H), 5.11-5.14 (m, 1 H), 5.28-
 5.32 (m, 1 H), 5.75-5.83 (m, 1 H), 5.90 (d, *J*=3.66 Hz, 1 H), 6.80-6.89 (m, 3 H), 7.03-
 15 7.07 (m, 1 H), 7.32-7.34 (m, 1 H), 7.55-7.58 (m, 1 H), 7.68-7.72 (m, 1 H), 7.80-7.82
 (m, 1 H), 7.96-7.98 (m, 1 H), 8.15-8.18 (m, 1 H); MS *m/z* 746 (MH⁺).

Example 134: Preparation of Compound 134

**Compound 134**

Scheme 1

**Product of Example 11, Step 5****Compound 134**

5

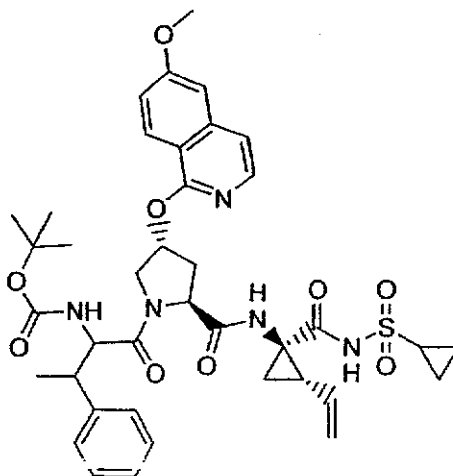
Step 1:

A mixture of the product from Example 11, Step 5 (100 mg, 0.172 mmol), *N*- α -*tert*-butoxycarbonyl-L-phenylglycine (45.3 mg, 0.180 mmol), HATU (84.9 mg, 0.223 mmol), and *N*-methylmorpholine (87.0 mg, 0.859 mmol) in DMF (1.0 mL) was stirred at rt for 18 h. The mixture was purified directly by reverse phase preparative HPLC to give 29.7 mg (23.6% yield) of **Compound 134** as a white powder: ^1H NMR (CD_3OD) δ 0.97-1.07 (m, 2 H), 1.12-1.17 (m, 1 H), 1.22-1.32 (m, 2 H), 1.38 (s, 9 H), 1.90 (dd, $J=8.09, 5.34$ Hz, 1 H), 2.20-2.28 (m, 2 H), 2.54 (dd, $J=13.58, 6.56$ Hz, 1 H), 2.85-2.89 (m, $J=8.24$ Hz, 1 H), 3.50 (d, $J=10.99$ Hz, 1 H), 3.93 (s, 3 H), 4.11

(d, $J=11.60$ Hz, 1 H), 4.63 (dd, $J=9.46, 7.32$ Hz, 1 H), 5.13 (dd, $J=10.38, 1.53$ Hz, 1 H), 5.32 (d, $J=17.09$ Hz, 1 H), 5.47 (s, 1 H), 5.74-5.84 (m, 2 H), 7.16-7.19 (m, 1 H), 7.25 (d, $J=5.80$ Hz, 1 H), 7.32-7.43 (m, 6 H), 7.86 (d, $J=5.80$ Hz, 1 H), 8.13 (d, $J=9.16$ Hz, 1 H); MS m/z 734 (MH^+).

5

Example 135: Preparation of Compound 135



Compound 135

10

Compound 135 was prepared by following Scheme 1 of Example 134 except that *N*- α -*tert*-butoxycarbonyl-erythro-DL- β -methylphenylalanine was used in place of *N*- α -*tert*-butoxycarbonyl-L-phenylglycine in step 1. Compound 135 was prepared from a mixture of *N*- α -*tert*-butoxycarbonyl-erythro DL β -methylphenylalanine and the resulting two diastereomers were separated by reverse phase preparative HPLC. This compound is the single isomer which eluted first from the preparative HPLC column. The exact stereochemistry at the β -methyl phenylalanine portion of the molecule is unknown.

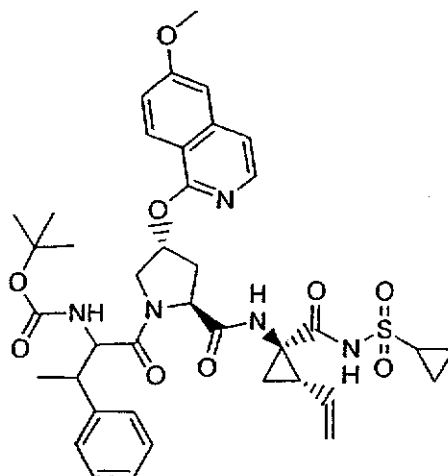
15

20 Step 1:

Modifications: 50.4 mg (0.180 mmol) *N*- α -*tert*-butoxycarbonyl-erythro-DL- β -methylphenylalanine used, 29.7 mg product obtained as a white powder (22.7 %

yield): $^1\text{H NMR}$ (CD_3OD) δ 1.11 (d, $J=7.93$ Hz, 2 H), 1.15 (d, $J=6.10$ Hz, 3 H), 1.24-1.32 (m, 11 H), 1.44 (dd, $J=9.16, 5.19$ Hz, 1 H), 1.90-1.94 (m, 1 H), 2.25-2.29 (m, 1 H), 2.36 (t, $J=13.28$ Hz, 1 H), 2.62 (dd, $J=13.58, 7.17$ Hz, 1 H), 2.98-3.02 (m, 1 H), 3.20-3.24 (m, 1 H), 3.91 (s, 3 H), 4.11 (dd, $J=11.60, 3.05$ Hz, 1 H), 4.51 (d, $J=10.68$ Hz, 1 H), 4.57 (dd, $J=10.07, 7.32$ Hz, 1 H), 4.63 (d, $J=12.21$ Hz, 1 H), 5.14 (d, $J=10.07$ Hz, 1 H), 5.32 (d, $J=16.79$ Hz, 1 H), 5.76-5.84 (m, 1 H), 5.88 (s, 1 H), 7.08 (dd, $J=8.70, 1.68$ Hz, 1 H), 7.16-7.18 (m, 2 H), 7.23-7.27 (m, 5 H), 7.89 (d, $J=5.80$ Hz, 1 H), 8.09 (d, $J=9.46$ Hz, 1 H); MS m/z 762 (MH^+).

10 Example 136: Preparation of Compound 136



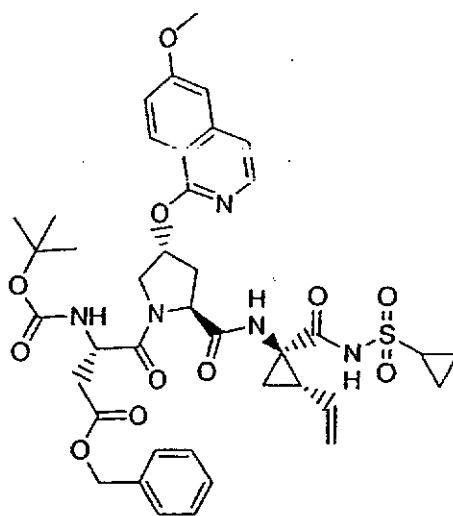
Compound 136

Compound 136 was prepared by following Scheme 1 of Example 134 except that *N*- α -*tert*-butoxycarbonyl-erythro-DL- β -methylphenylalanine was used in place of *N*- α -*tert*-butoxycarbonyl-L-phenylglycine in step 1. **Compound 136** was prepared from a mixture of *N*-*tert*-butoxycarbonyl-erythro DL β -methylphenylalanine and the resulting two diastereomers were separated by reverse phase preparative HPLC. This compound is the single isomer which eluted second from the preparative HPLC column. The exact stereochemistry at the β -methyl phenylalanine portion of the molecule is unknown.

Step 1:

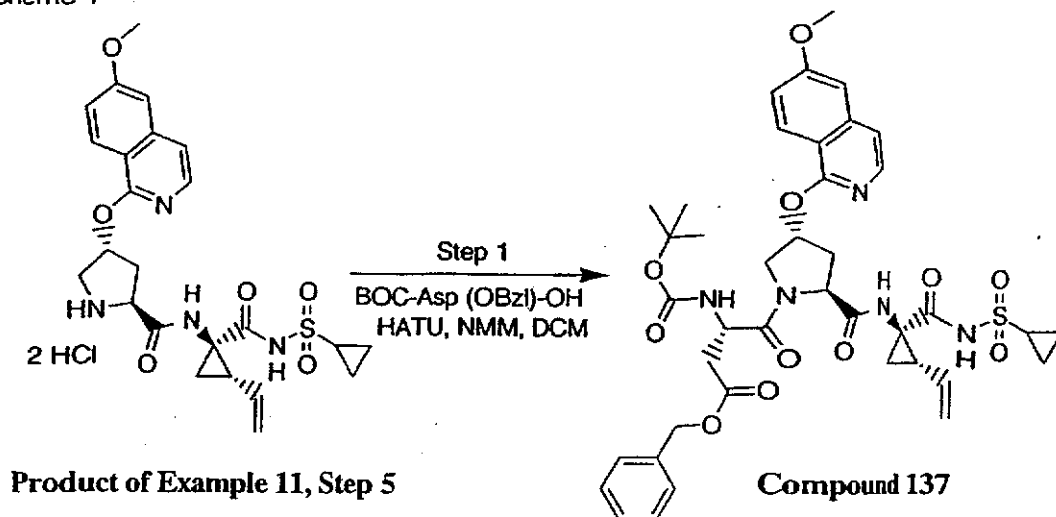
Modifications: 50.4 mg (0.180 mmol) *N*- α -*tert*-butoxycarbonyl-erythro-DL- β -methylphenylalanine used, 26.3 mg product obtained as a white powder (20.1 % yield): ^1H NMR (CD_3OD) δ 1.04 (s, 1 H), 1.13 (d, $J=6.71$ Hz, 3 H), 1.12-1.17 (m, 2 H), 1.30 (s, 9 H), 1.33-1.36 (m, 1 H), 1.41 (dd, $J=9.46, 5.19$ Hz, 1 H), 1.87 (dd, $J=7.78, 5.34$ Hz, 1 H), 2.29 (q, $J=8.85$ Hz, 1 H), 2.36 (ddd, $J=13.81, 9.99, 4.27$ Hz, 1 H), 2.54 (dd, $J=13.58, 7.17$ Hz, 1 H), 3.00-3.04 (m, 1 H), 3.05-3.08 (m, 1 H), 3.80 (d, $J=11.90$ Hz, 1 H), 3.94 (s, 3 H), 4.10 (dd, $J=12.05, 3.81$ Hz, 1 H), 4.53-4.57 (m, 1 H), 4.59 (d, $J=8.24$ Hz, 1 H), 5.14 (d, $J=10.38$ Hz, 1 H), 5.34 (d, $J=17.09$ Hz, 1 H), 5.78-5.85 (m, 2 H), 6.75 (t, $J=7.32$ Hz, 1 H), 7.03 (t, $J=7.48$ Hz, 2 H), 7.12 (s, 1 H), 7.14 (s, 1 H), 7.19 (dd, $J=9.31, 1.68$ Hz, 1 H), 7.22 (s, 1 H), 7.28 (d, $J=6.10$ Hz, 1 H), 7.89 (d, $J=5.80$ Hz, 1 H), 8.03 (d, $J=8.85$ Hz, 1 H); MS m/z 762 (MH^+).

Example 137: Preparation of Compound 137



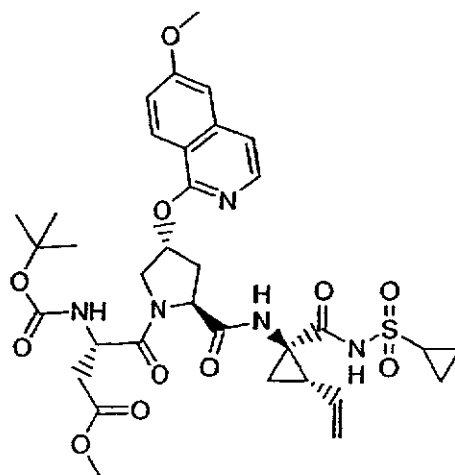
Compound 137

Scheme 1



Step 1:

- 5 A mixture of the product from Example 11, Step 5 (100 mg, 0.172 mmol), *N*- α -*tert*-butoxycarbonyl-L-aspartic acid 4-benzyl ester (59.5 mg, 0.180 mmol), HATU (84.9 mg, 0.223 mmol), and *N*-methylmorpholine (87.0 mg, 0.859 mmol) in DCM (3.0 mL) was stirred at rt for 18 h. The reaction mixture was washed with pH = 4 buffer solution (3 x 3 mL), and the washes were back-extracted with DCM (3 mL).
- 10 The organic phases were combined and concentrated *in vacuo*. The crude product was then dissolved in MeOH and purified by reverse phase preparative HPLC to give **Compound 137** as a slightly off-white glassy solid (26.0 mg, 18.8% yield): ^1H NMR (CD_3OD) δ 0.95-1.01 (m, 2 H), 1.16 (s, 9 H), 1.22-1.29 (m, 2 H), 1.44 (dd, $J=9.46$, 5.19 Hz, 1 H), 1.86 (dd, $J=7.93$, 5.19 Hz, 1 H), 2.26 (q, $J=8.85$ Hz, 1 H), 2.32-2.37
- 15 (m, 1 H), 2.61 (dd, $J=13.73$, 7.32 Hz, 1 H), 2.66 (dd, $J=16.48$, 6.10 Hz, 1 H), 2.89 (ddd, $J=12.67$, 8.09, 4.88 Hz, 1 H), 3.05 (dd, $J=16.63$, 8.39 Hz, 1 H), 3.92 (s, 3 H), 4.04-4.07 (m, 1 H), 4.47 (d, $J=11.90$ Hz, 1 H), 4.52-4.56 (m, 1 H), 4.75 (dd, $J=8.24$, 6.41 Hz, 1 H), 5.12-5.14 (m, 1 H), 5.14 (s, 2 H), 5.31 (d, $J=17.09$ Hz, 1 H), 5.75-5.82
- 20 (m, 2 H), 7.12 (d, $J=9.16$ Hz, 1 H), 7.18 (d, $J=2.14$ Hz, 1 H), 7.24 (d, $J=5.80$ Hz, 1 H), 7.31-7.33 (m, 1 H), 7.36 (t, $J=7.32$ Hz, 2 H), 7.39 (s, 1 H), 7.41 (s, 1 H), 7.88 (d, $J=6.10$ Hz, 1 H), 8.10 (d, $J=9.16$ Hz, 1 H); MS m/z 806 (MH^+).

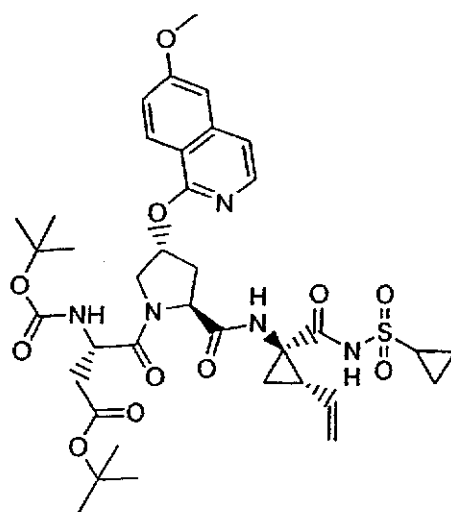
Example 138: Preparation of Compound 138**Compound 138**

- 5 **Compound 138** was prepared by following Scheme 1 of Example 137 except that *N*-tert-butoxycarbonyl-L-aspartic acid 4-methyl ester was used in place of *N*- α -tert-butoxycarbonyl-L-aspartic acid 4-benzyl ester in step 1.

Step 1:

- 10 Modifications: 45.5 mg (0.180 mmol) *N*-tert-butoxycarbonyl-L-aspartic acid 4-methyl ester used, 93.5 mg product obtained as an off-white glassy solid (74.6 % yield): ^1H NMR (CD_3OD) δ 1.07-1.09 (m, 2 H), 1.17 (s, 9 H), 1.20-1.29 (m, 2 H), 1.41-1.44 (m, 1 H), 1.84-1.86 (m, 1 H), 2.26 (q, $J=8.85$ Hz, 1 H), 2.33-2.38 (m, 1 H), 2.58-2.64 (m, 2 H), 2.92-3.02 (m, 2 H), 3.69 (s, 3 H), 3.92 (s, 3 H), 4.15 (dd, $J=11.44, 2.29$ Hz, 1 H), 4.49-4.56 (m, 2 H), 4.72-4.76 (m, 1 H), 5.13 (d, $J=10.38$ Hz, 1 H), 5.32 (d, $J=17.09$ Hz, 1 H), 5.74-5.82 (m, 1 H), 5.87 (s, 1 H), 7.12 (d, $J=9.16$ Hz, 1 H), 7.18 (s, 1 H), 7.24 (d, $J=5.80$ Hz, 1 H), 7.88 (dd, $J=5.80, 0.92$ Hz, 1 H), 8.10 (d, $J=8.85$ Hz, 1 H); MS m/z 730 (MH^+).

- 20 **Example 139: Preparation of Compound 139**

**Compound 139**

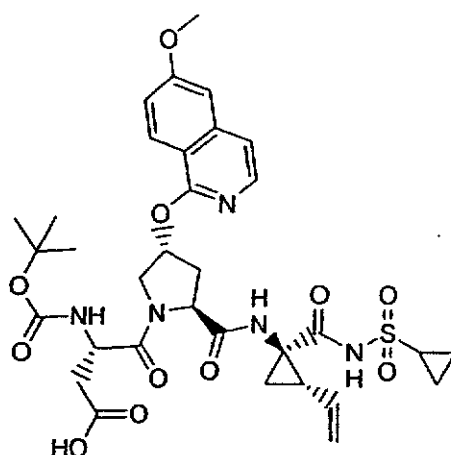
Compound 139 was prepared by following Scheme 1 of Example 137 except that *N*-tert-butoxycarbonyl-L-aspartic acid 4-*tert*-butyl ester was used in place of *N*- α -*tert*-butoxycarbonyl-L-aspartic acid 4-benzyl ester in step 1.

Step 1:

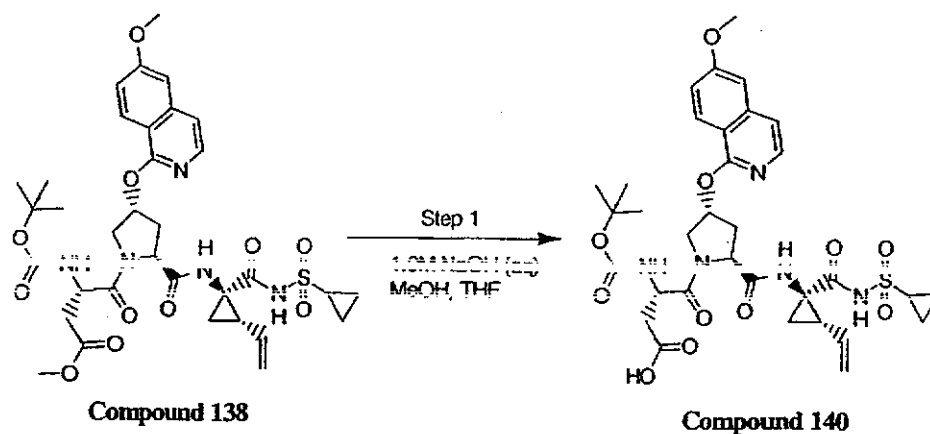
Modifications: 52.2 mg (0.180 mmol) *N*-tert-butoxycarbonyl-L-aspartic acid 4-*tert*-butyl ester used, 125 mg product obtained as an off-white glassy solid (99.8 % yield):

¹H NMR (CD₃OD) δ 1.08-1.10 (m, 2 H), 1.17 (s, 9 H), 1.21-1.29 (m, 2 H), 1.46 (s, 10 H), 1.82 (dd, *J*=7.78, 5.34 Hz, 1 H), 2.26 (q, *J*=8.75 Hz, 1 H), 2.32-2.38 (m, 1 H), 2.51 (dd, *J*=16.33, 7.17 Hz, 1 H), 2.63 (dd, *J*=14.04, 7.02 Hz, 1 H), 2.89 (dd, *J*=16.48, 7.63 Hz, 1 H), 2.92-2.98 (m, 1 H), 3.92 (s, 3 H), 4.15 (dd, *J*=11.60, 3.05 Hz, 1 H), 4.50-4.57 (m, 2 H), 4.70-4.75 (m, 1 H), 5.13 (dd, *J*=10.38, 1.53 Hz, 1 H), 5.32 (d, *J*=17.40 Hz, 1 H), 5.76-5.83 (m, 1 H), 5.87 (s, 1 H), 7.13 (dd, *J*=8.85, 1.53 Hz, 1 H), 7.18 (d, *J*=2.14 Hz, 1 H), 7.25 (d, *J*=5.80 Hz, 1 H), 7.88 (d, *J*=5.80 Hz, 1 H), 8.10 (d, *J*=9.16 Hz, 1 H); MS *m/z* 772 (MH⁺).

Example 140: Preparation of Compound 140

**Compound 140**

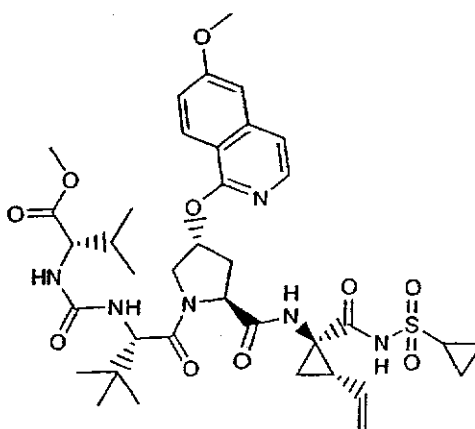
Scheme 1



- 5 **Compound 138** (50.0 mg, 0.0685 mmol) was dissolved in a mixture of THF (1 mL), MeOH (1 mL), and 1.0M aqueous NaOH (0.137 mL, 0.137 mmol). After 3 h, the reaction mixture was neutralized by the addition of 1.0M aqueous HCl (0.137 mL, 0.137 mmol). The crude mixture was concentrated *in vacuo*, then pH = 4 buffer solution (3 mL) and DCM (3 mL) were added and the mixture was shaken. The
- 10 layers were separated and the aqueous layer was further extracted with DCM (2 x 1 mL). The organic phases were combined, dried over anhydrous MgSO₄, filtered and concentrated *in vacuo* to give 48.0 mg (97.9% yield) of **Compound 140** as an off white glassy solid: ¹H NMR (CD₃OD) δ 1.04-1.07 (m, 2 H), 1.17 (s, 9 H), 1.22-1.25 (m, 2 H), 1.38 (dd, *J*=9.31, 5.34 Hz, 1 H), 1.78 (dd, *J*=7.78, 5.34 Hz, 1 H), 2.30 (q,

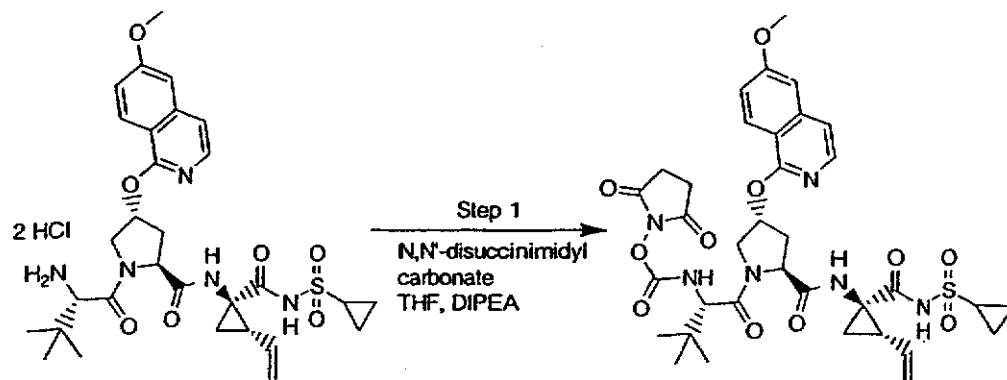
$J=8.75$ Hz, 1 H), 2.37-2.42 (m, 1 H), 2.48 (dd, $J=15.87$, 4.58 Hz, 1 H), 2.72 (dd, $J=13.12$, 7.63 Hz, 1 H), 2.88 (dd, $J=15.72$, 10.53 Hz, 1 H), 2.90-2.95 (m, 1 H), 3.92 (s, 3 H), 4.21 (dd, $J=11.44$, 2.90 Hz, 1 H), 4.57 (t, $J=8.70$ Hz, 1 H), 4.62-4.65 (m, 2 H), 5.10 (d, $J=10.68$ Hz, 1 H), 5.34 (d, $J=17.09$ Hz, 1 H), 5.69-5.76 (m, 1 H), 5.83 (s, 1 H), 7.10 (d, $J=9.16$ Hz, 1 H), 7.17 (s, 1 H), 7.23 (d, $J=6.10$ Hz, 1 H), 7.88 (d, $J=6.10$ Hz, 1 H), 8.12 (d, $J=8.85$ Hz, 1 H); MS m/z 716 (MH^+).

Example 141: Preparation of Compound 141

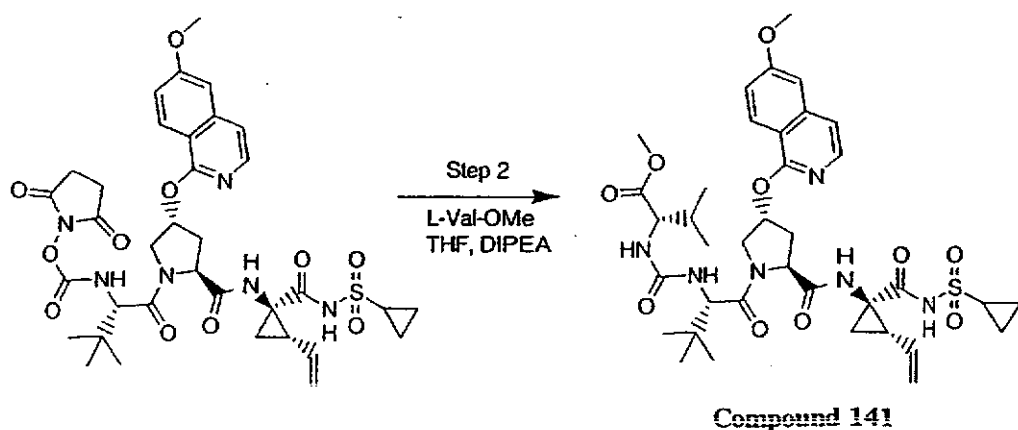


Compound 141

Scheme 1



Product of Example 55, Step 1



Step 1:

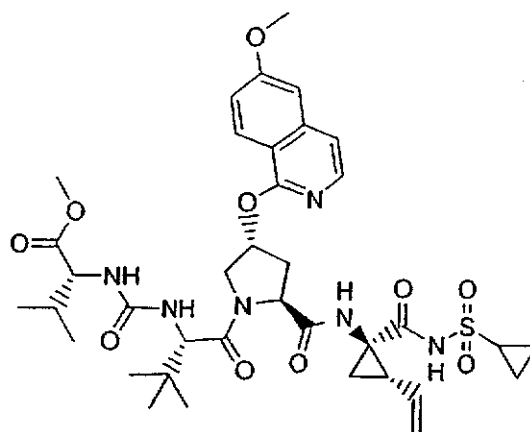
The product of Example 55, Step 1 (65 mg, 0.0947 mmol), N,N' -disuccinimidyl carbonate (41.0 mg, 0.142 mmol) and N,N -diisopropylethylamine (30.6 mg, 0.237 mmol) were combined with anhydrous THF (1 mL) and the resulting suspension was heated to 80 °C in a microwave reactor for 15 min. Upon cooling to rt, this crude mixture was used directly in the next step.

Step 2:

The crude reaction mixture from step 1 was treated with a mixture of L-valine methyl ester hydrochloride (159 mg, 0.947 mmol) and N,N -diisopropylethylamine (122 mg, 0.947 mmol) in anhydrous THF (2 mL). The resulting mixture was stirred for 18 h at rt. Solvent was removed *in vacuo*, and the residue was taken up in DCM (2 mL) and washed with pH = 4 buffer solution (3 x 2 mL). The buffer washes were

combined and back-extracted with DCM (2 mL). The combined DCM phases were concentrated *in vacuo*, and the resulting residue was dissolved in MeOH and purified by reverse phase preparative HPLC to give 38.1 mg (52.2% yield) of **Compound 141** as a white powder: ^1H NMR (CD_3OD) δ 0.83 (dd, $J=6.87, 3.81$ Hz, 6 H), 1.06 (s, 11 H), 1.21-1.26 (m, 2 H), 1.41 (dd, $J=9.46, 5.49$ Hz, 1 H), 1.87 (dd, $J=8.09, 5.34$ Hz, 1 H), 1.95-2.02 (m, 1 H), 2.21 (q, $J=8.85$ Hz, 1 H), 2.29 (ddd, $J=13.89, 9.92, 4.27$ Hz, 1 H), 2.60 (dd, $J=13.73, 7.02$ Hz, 1 H), 2.91-2.97 (m, 1 H), 3.67 (s, 3 H), 3.93 (s, 3 H), 4.00 (d, $J=5.49$ Hz, 1 H), 4.09 (dd, $J=11.90, 3.97$ Hz, 1 H), 4.40-4.43 (m, 2 H), 4.52 (dd, $J=10.07, 7.02$ Hz, 1 H), 5.11 (dd, $J=10.38, 1.53$ Hz, 1 H), 5.28 (dd, $J=17.09, 1.22$ Hz, 1 H), 5.75 (ddd, $J=17.17, 10.15, 9.00$ Hz, 1 H), 5.83 (s, 1 H), 7.11 (dd, $J=9.16, 2.44$ Hz, 1 H), 7.18 (d, $J=2.44$ Hz, 1 H), 7.24 (d, $J=5.80$ Hz, 1 H), 7.87 (d, $J=6.10$ Hz, 1 H), 8.10 (d, $J=8.85$ Hz, 1 H); MS m/z 771 (MH^+).

Example 142: Preparation of Compound 142



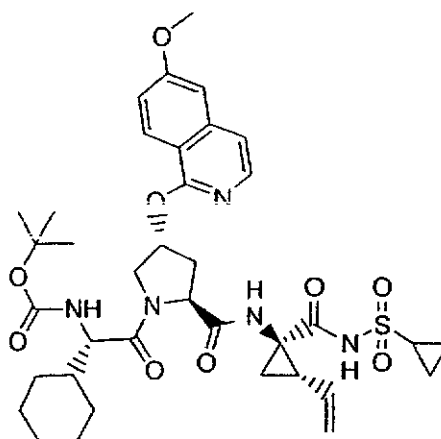
Compound 142

Compound 142 was prepared by following Scheme 1 of Example 141 except that D-valine methyl ester hydrochloride was used in place of L-valine methyl ester hydrochloride in step 2.

Step 2:

Modifications: 159 mg (0.947 mmol) D-valine methyl ester hydrochloride used, 23.0 mg product obtained as a white powder (31.5 % yield): ^1H NMR (CD_3OD) δ 0.88 (dd, $J=13.89, 6.87$ Hz, 6 H), 1.06 (s, 9 H), 1.07-1.09 (m, 2 H), 1.23-1.27 (m, 2 H), 1.41 (dd, $J=9.46, 5.49$ Hz, 1 H), 1.88 (dd, $J=7.93, 5.49$ Hz, 1 H), 2.01-2.07 (m, 1 H),
5 2.23 (q, $J=9.05$ Hz, 1 H), 2.31 (ddd, $J=14.11, 9.99, 4.27$ Hz, 1 H), 2.63 (dd, $J=13.89, 7.17$ Hz, 1 H), 2.93-2.98 (m, 1 H), 3.62 (s, 3 H), 3.96 (s, 3 H), 4.03 (d, $J=5.19$ Hz, 1 H), 4.09 (dd, $J=11.75, 3.81$ Hz, 1 H), 4.38 (s, 1 H), 4.48-4.54 (m, 2 H), 5.12 (dd, $J=10.38, 1.22$ Hz, 1 H), 5.29 (dd, $J=17.24, 1.07$ Hz, 1 H), 5.70-5.77 (m, 1 H), 5.83 (s, 1 H), 7.22 (dd, $J=9.00, 2.59$ Hz, 1 H), 7.25 (d, $J=2.44$ Hz, 1 H), 7.35 (d, $J=6.10$ Hz, 1 H),
10 7.87 (d, $J=6.10$ Hz, 1 H), 8.16 (d, $J=9.16$ Hz, 1 H); MS m/z 771 (MH^+).

Example 143: Preparation of Compound 143



Compound 143

15

Compound 143 was prepared by following Scheme 1 of Example 137 except that *N*-*tert*-butoxycarbonyl-L-cyclohexylglycine was used in place of *N*- α -*tert*-butoxycarbonyl-L-aspartic acid 4-benzyl ester in step 1.

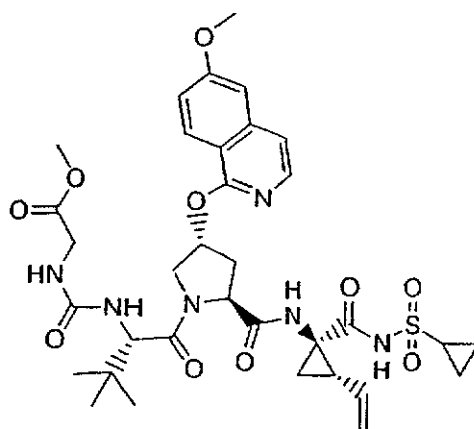
20 Step 1:

Modifications: 46.2 mg (0.180 mmol) *N*-*tert*-butoxycarbonyl-L-cyclohexylglycine used, 93.9 mg product obtained as a white powder (73.8 % yield): ^1H NMR (CD_3OD) δ 1.04-1.08 (dd, $J=7.78, 2.29$ Hz, 4 H), 1.19-1.26 (m, 4 H), 1.25 (s, 9 H),

1.41 (dd, $J=9.46, 5.19$ Hz, 1 H), 1.63-1.82 (m, 7 H), 1.88 (dd, $J=7.93, 5.49$ Hz, 1 H),
2.22 (q, $J=9.05$ Hz, 1 H), 2.32-2.37 (m, 1 H), 2.59 (dd, $J=13.58, 6.87$ Hz, 1 H), 2.91-
2.96 (m, 1 H), 3.92 (s, 3 H), 4.05 (dd, $J=11.75, 3.20$ Hz, 1 H), 4.09 (d, $J=8.85$ Hz, 1
H), 4.47 (d, $J=11.90$ Hz, 1 H), 4.53 (dd, $J=10.22, 7.17$ Hz, 1 H), 5.11 (d, $J=10.38$ Hz,
5 1 H), 5.29 (d, $J=16.79$ Hz, 1 H), 5.79 (ddd, $J=16.86, 9.92, 9.54$ Hz, 1 H), 5.84 (s, 1
H), 7.10 (d, $J=8.85$ Hz, 1 H), 7.17 (d, $J=1.53$ Hz, 1 H), 7.24 (d, $J=5.80$ Hz, 1 H), 7.88
(d, $J=6.10$ Hz, 1 H), 8.09 (d, $J=8.85$ Hz, 1 H); MS m/z 740 (MH^+).

Example 144: Preparation of Compound 144

10



Compound 144

Compound 144 was prepared by following Scheme 1 of Example 141 except that the
15 scale was increased and that glycine methyl ester hydrochloride was used in place of
L-valine methyl ester hydrochloride in step 2.

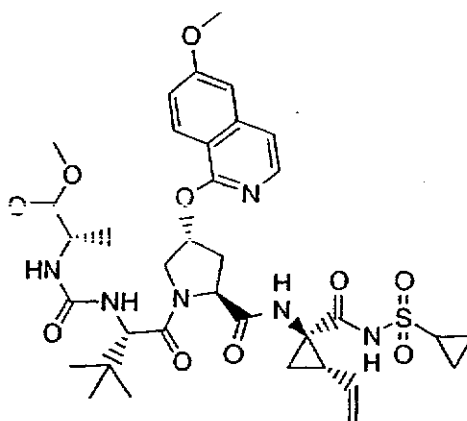
Step 1:

Modifications: 100 mg (0.146 mmol) of the product of Example 55, Step 1; 62.2 mg
20 (0.219 mmol) *N,N'*-disuccinimidyl carbonate, 47.0 mg (0.364 mmol) *N,N*-
diisopropylethylamine used.

Step 2:

Modifications: 183 mg (1.46 mmol) glycine methyl ester hydrochloride, 188 mg (1.46 mmol) *N,N*-diisopropylethylamine used, 56.3 mg product obtained as a white powder (52.9 % yield): ^1H NMR (CD_3OD) δ 1.01-1.04 (m, 2 H), 1.05 (s, 9 H), 1.17-1.21 (m, 2 H), 1.40 (dd, $J=9.46, 5.49$ Hz, 1 H), 1.85 (dd, $J=7.78, 5.34$ Hz, 1 H), 2.18 (q, $J=8.55$ Hz, 1 H), 2.33 (ddd, $J=13.89, 9.92, 4.27$ Hz, 1 H), 2.61 (dd, $J=13.73, 7.32$ Hz, 1 H), 2.89-2.94 (m, 1 H), 3.65 (s, 3 H), 3.69-3.77 (m, 2 H), 3.92 (s, 3 H), 4.10 (dd, $J=11.75, 3.81$ Hz, 1 H), 4.40-4.42 (m, 2 H), 4.53 (dd, $J=9.92, 7.17$ Hz, 1 H), 5.08 (d, $J=10.38$ Hz, 1 H), 5.26 (d, $J=17.09$ Hz, 1 H), 5.77 (ddd, $J=17.09, 10.22, 9.00$ Hz, 1 H), 5.83 (s, 1 H), 7.13 (dd, $J=8.85, 2.44$ Hz, 1 H), 7.17 (s, 1 H), 7.23 (d, $J=5.80$ Hz, 1 H), 7.87 (d, $J=5.80$ Hz, 1 H), 8.09 (d, $J=8.85$ Hz, 1 H); MS m/z 729 (MH^+).

Example 145: Preparation of Compound 145



Compound 145

Compound 145 was prepared by following Scheme 1 of Example 141 except that the scale was increased and that L-alanine methyl ester hydrochloride was used in place of L-valine methyl ester hydrochloride in step 2.

Step 1:

Modifications: 100 mg (0.146 mmol) of the product of Example 55, Step 1; 62.2 mg (0.219 mmol) *N,N'*-disuccinimidyl carbonate, 47.0 mg (0.364 mmol) *N,N*-diisopropylethylamine used.

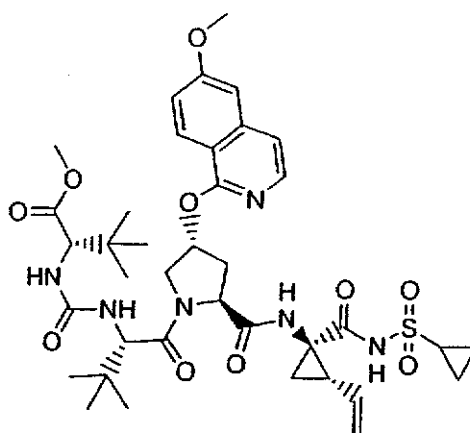
Step 2:

Modifications: 203 mg (1.46 mmol) L-alanine methyl ester hydrochloride, 188 mg (1.46 mmol) *N,N*-diisopropylethylamine used, 64.3 mg product obtained as a white

5 powder (59.3 % yield): ^1H NMR (CD_3OD) δ 0.97-1.02 (m, 2 H), 1.05 (s, 9 H), 1.19 (d, $J=7.02$ Hz, 3 H), 1.18-1.22 (m, 2 H), 1.41 (dd, $J=9.46, 5.19$ Hz, 1 H), 1.86 (dd, $J=8.09, 5.34$ Hz, 1 H), 2.19 (q, $J=8.85$ Hz, 1 H), 2.32 (ddd, $J=13.81, 9.84, 4.43$ Hz, 1 H), 2.61 (dd, $J=13.73, 7.02$ Hz, 1 H), 2.93 (ddd, $J=12.82, 8.09, 4.73$ Hz, 1 H), 3.65 (s, 3 H), 3.93 (s, 3 H), 3.99 (q, $J=7.22$ Hz, 1 H), 4.08 (dd, $J=11.75, 3.81$ Hz, 1 H),
10 4.38 (s, 1 H), 4.42 (d, $J=11.60$ Hz, 1 H), 4.53 (dd, $J=10.07, 7.32$ Hz, 1 H), 5.09 (dd, $J=10.38, 1.53$ Hz, 1 H), 5.27 (dd, $J=17.09, 1.22$ Hz, 1 H), 5.77 (ddd, $J=17.09, 10.07, 9.16$ Hz, 1 H), 5.82 (s, 1 H), 7.13 (dd, $J=9.16, 2.44$ Hz, 1 H), 7.18 (d, $J=2.44$ Hz, 1 H), 7.24 (d, $J=5.80$ Hz, 1 H), 7.87 (d, $J=5.80$ Hz, 1 H), 8.10 (d, $J=9.16$ Hz, 1 H); MS m/z 743 (MH^+).

15

Example 146: Preparation of Compound 146



Compound 146

20 **Compound 147** was prepared by following Scheme 1 of Example 141 except that the scale was increased and that *L-tert*-leucine methyl ester hydrochloride was used in place of *L*-valine methyl ester hydrochloride in step 2.

Step 1:

Modifications: 100 mg (0.146 mmol) of the product of Example 55, Step 1; 62.2 mg (0.219 mmol) *N,N'*-disuccinimidyl carbonate, 47.0 mg (0.364 mmol) *N,N*-diisopropylethylamine used.

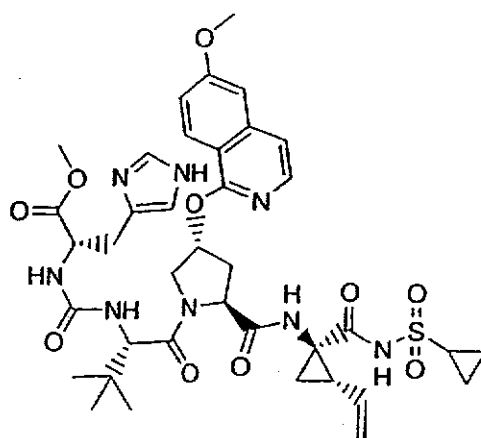
5

Step 2:

Modifications: 265 mg (1.46 mmol) *L*-*tert*-leucine methyl ester hydrochloride, 188 mg (1.46 mmol) *N,N*-diisopropylethylamine used, 68.3 mg product obtained as a white powder (59.6 % yield): ^1H NMR (CD_3OD) δ 0.88 (s, 9 H), 0.97-1.03 (m, 2 H), 1.06 (s, 9 H), 1.18-1.24 (m, 2 H), 1.41 (dd, $J=9.46, 5.49$ Hz, 1 H), 1.86 (dd, $J=7.93, 5.49$ Hz, 1 H), 2.19 (q, $J=8.75$ Hz, 1 H), 2.30 (ddd, $J=13.89, 10.07, 4.43$ Hz, 1 H), 2.60 (dd, $J=13.73, 7.32$ Hz, 1 H), 2.91-2.96 (m, 1 H), 3.65 (s, 3 H), 3.91 (s, 1 H), 3.93 (s, 3 H), 4.09 (dd, $J=11.60, 3.97$ Hz, 1 H), 4.38 (s, 1 H), 4.43 (d, $J=11.60$ Hz, 1 H), 4.51 (dd, $J=10.07, 7.32$ Hz, 1 H), 5.10 (dd, $J=10.38, 1.53$ Hz, 1 H), 5.27 (dd, $J=17.24, 1.37$ Hz, 1 H), 5.76 (ddd, $J=17.09, 10.07, 9.16$ Hz, 1 H), 5.82 (s, 1 H), 7.12 (dd, $J=9.16, 2.44$ Hz, 1 H), 7.18 (d, $J=2.14$ Hz, 1 H), 7.24 (d, $J=6.10$ Hz, 1 H), 7.87 (d, $J=5.80$ Hz, 1 H), 8.11 (d, $J=9.16$ Hz, 1 H); MS m/z 785 (MH^+).

20

Example 147: Preparation of Compound 147



Compound 147

Compound 147 was prepared by following Scheme 1 of Example 141 except that the scale was increased and that L-histidine methyl ester hydrochloride was used in place of L-valine methyl ester hydrochloride in step 2, and the amount of *N,N*-diisopropylethylamine used in step 2 was doubled.

5

Step 1:

Modifications: 100 mg (0.146 mmol) of the product of Example 55, Step 1; 62.2 mg (0.219 mmol) *N,N'*-disuccinimidyl carbonate, 47.0 mg (0.364 mmol) *N,N*-diisopropylethylamine used.

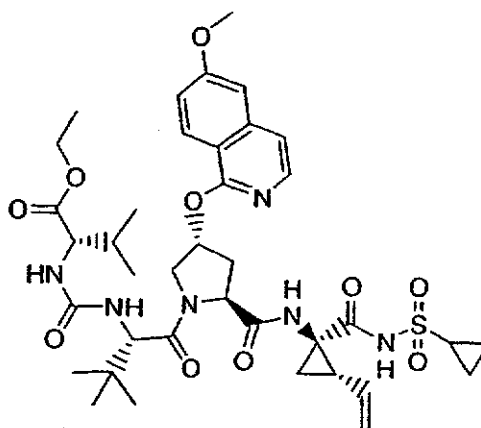
10

Step 2:

Modifications: 352 mg (1.46 mmol) L-histidine methyl ester hydrochloride, 377 mg (2.91 mmol) *N,N*-diisopropylethylamine used, 51.0 mg product obtained as a white powder (43.2 % yield): ¹H NMR (CD₃OD) δ 1.04 (s, 11 H), 1.20-1.22 (m, 2 H), 1.41 (ddd, *J*=9.46, 5.34, 1.07 Hz, 1 H), 1.86-1.88 (m, 1 H), 2.23 (q, *J*=8.75 Hz, 1 H), 2.28-2.33 (m, 1 H), 2.60 (dd, *J*=13.73, 7.02 Hz, 1 H), 2.92 (d, *J*=6.41 Hz, 2 H), 2.92-2.96 (m, 1 H), 3.64 (s, 3 H), 3.91 (d, *J*=1.53 Hz, 3 H), 4.04 (dd, *J*=11.90, 3.66 Hz, 1 H), 4.35 (s, 1 H), 4.36-4.41 (m, 2 H), 4.53 (dd, *J*=9.77, 7.63 Hz, 1 H), 5.10 (d, *J*=10.38 Hz, 1 H), 5.28 (d, *J*=17.40 Hz, 1 H), 5.73-5.78 (m, 1 H), 5.81 (s, 1 H), 6.82 (s, 1 H), 7.06-7.09 (m, 1 H), 7.15 (s, 1 H), 7.23 (d, *J*=5.80 Hz, 1 H), 7.63 (s, 1 H), 7.87 (dd, *J*=5.80, 1.22 Hz, 1 H), 8.08 (d, *J*=9.16 Hz, 1 H); MS *m/z* 809 (MH⁺).

20

Example 148: Preparation of Compound 148



Compound 148

Compound 148 was prepared by following Scheme 1 of Example 141 except that the scale was increased and that L-valine ethyl ester hydrochloride was used in place of
 5 L-valine methyl ester hydrochloride in step 2.

Step 1:

Modifications: 100 mg (0.146 mmol) of the product of Example 55, Step 1; 62.2 mg (0.219 mmol) *N,N*-disuccinimidyl carbonate, 47.0 mg (0.364 mmol) *N,N*-diisopropylethylamine used.
 10

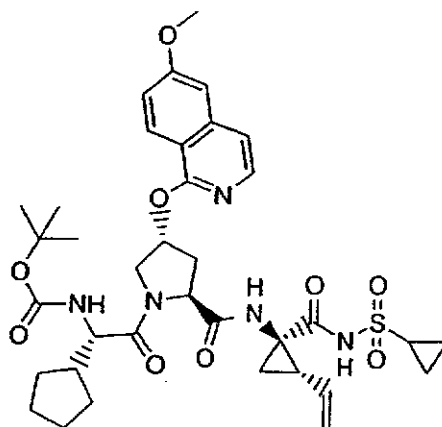
Step 2:

Modifications: 265 mg (1.46 mmol) L-valine ethyl ester hydrochloride, 188 mg (1.46 mmol) *N,N*-diisopropylethylamine used, 69.2 mg product obtained as a white
 15 powder (60.4 % yield): ^1H NMR (CD_3OD) δ 0.83 (dd, $J=6.71, 5.19$ Hz, 6 H), 1.01-1.03 (m, 2 H), 1.06 (s, 9 H), 1.17-1.22 (m, 2 H), 1.23 (t, $J=7.17$ Hz, 3 H), 1.40 (dd, $J=9.46, 5.19$ Hz, 1 H), 1.86 (dd, $J=8.09, 5.34$ Hz, 1 H), 1.95-2.02 (m, 1 H), 2.18 (q, $J=9.05$ Hz, 1 H), 2.33 (ddd, $J=13.89, 9.92, 4.27$ Hz, 1 H), 2.60 (dd, $J=13.89, 7.17$ Hz, 1 H), 2.92 (ddd, $J=12.82, 8.09, 4.73$ Hz, 1 H), 3.93 (s, 3 H), 3.98 (d, $J=5.19$ Hz, 1 H),
 20 4.08-4.17 (m, 3 H), 4.41 (s, 1 H), 4.41-4.43 (m, 1 H), 4.52 (dd, $J=10.07, 7.32$ Hz, 1 H), 5.09 (dd, $J=10.38, 1.53$ Hz, 1 H), 5.26 (dd, $J=17.09, 1.22$ Hz, 1 H), 5.77 (ddd, $J=17.09, 10.07, 9.16$ Hz, 1 H), 5.82 (s, 1 H), 7.12 (dd, $J=9.16, 2.44$ Hz, 1 H), 7.18 (d,

$J=2.44$ Hz, 1 H), 7.23 (d, $J=6.10$ Hz, 1 H), 7.87 (d, $J=6.10$ Hz, 1 H), 8.10 (d, $J=9.16$ Hz, 1 H); MS m/z 785 (MH^+).

Example 149: Preparation of Compound 149

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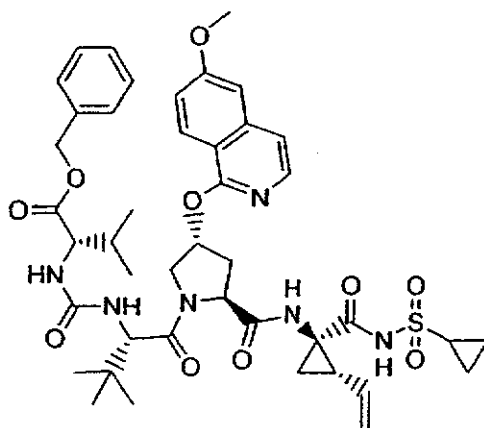


Compound 149

Compound 149 was prepared by following Scheme 1 of Example 137 except that *N*-tert-butoxycarbonyl-L-cyclopentylglycine dicyclohexylamine salt was used in place
10 of *N*- α -tert-butoxycarbonyl-L-aspartic acid 4-benzyl ester in step 1.

Step 1:

Modifications: 76.2 mg (0.180 mmol) *N*-tert-butoxycarbonyl-L-cyclopentylglycine dicyclohexylamine salt used, 111 mg product obtained as a white powder (89.3 %
15 yield): ^1H NMR (CD_3OD) δ 0.98 (d, $J=8.24$ Hz, 2 H), 1.15-1.18 (m, 2 H), 1.24 (s, 9 H), 1.29-1.32 (m, $J=18.01$ Hz, 2 H), 1.38-1.40 (m, 1 H), 1.44 (dd, $J=4.88, 1.53$ Hz, 1 H), 1.49-1.55 (m, 2 H), 1.62-1.67 (m, 2 H), 1.74-1.80 (m, 1 H), 1.85-1.88 (m, 1 H), 2.16 (q, $J=8.75$ Hz, 1 H), 2.21-2.26 (m, 1 H), 2.42 (t, $J=11.90$ Hz, 1 H), 2.60-2.64 (m, 1 H), 2.89-2.93 (m, 1 H), 3.92 (d, $J=1.53$ Hz, 3 H), 4.06-4.11 (m, 2 H), 4.51-4.57 (m,
20 2 H), 5.07 (d, $J=10.38$ Hz, 1 H), 5.25 (d, $J=17.09$ Hz, 1 H), 5.78-5.85 (m, 2 H), 7.10 (d, $J=8.85$ Hz, 1 H), 7.17 (s, 1 H), 7.23 (d, $J=4.27$ Hz, 1 H), 7.88 (dd, $J=5.95, 1.68$ Hz, 1 H), 8.10 (d, $J=9.16$ Hz, 1 H); MS m/z 726 (MH^+).

Example 150: Preparation of Compound 150**Compound 150**

- 5 **Compound 150** was prepared by following Scheme 1 of Example 141 except that the scale was increased and that L-valine benzyl ester hydrochloride was used in place of L-valine methyl ester hydrochloride in step 2.

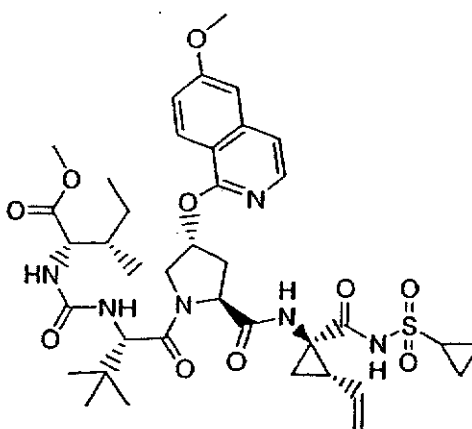
Step 1:

- 10 **Modifications:** 100 mg (0.146 mmol) of the product of Example 55, Step 1; 62.2 mg (0.219 mmol) *N,N'*-disuccinimidyl carbonate, 47.0 mg (0.364 mmol) *N,N*-diisopropylethylamine used.

Step 2:

- 15 **Modifications:** 356 mg (1.46 mmol) L-valine benzyl ester hydrochloride, 188 mg (1.46 mmol) *N,N*-diisopropylethylamine used, 41.0 mg product obtained as a white powder (33.2 % yield): MS *m/z* 848 (MH⁺).

Example 151: Preparation of Compound 151

**Compound 151**

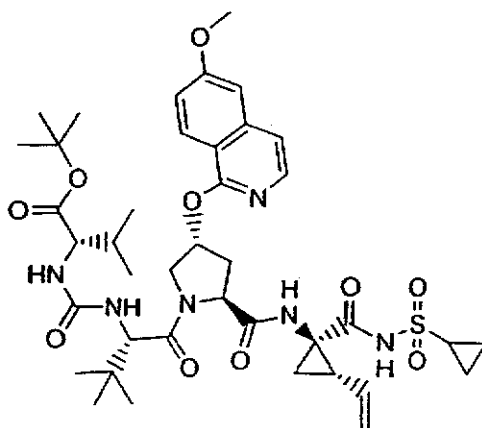
Compound 151 was prepared by following Scheme 1 of Example 141 except that the scale was increased and that L-isoleucine methyl ester hydrochloride was used in place of L-valine methyl ester hydrochloride in step 2.

Step 1:

Modifications: 100 mg (0.146 mmol) of the product of Example 55, Step 1; 62.2 mg (0.219 mmol) *N,N'*-disuccinimidyl carbonate, 47.0 mg (0.364 mmol) *N,N*-diisopropylethylamine used.

Step 2:

Modifications: 265 mg (1.46 mmol) L-isoleucine methyl ester hydrochloride, 188 mg (1.46 mmol) *N,N*-diisopropylethylamine used, 75.5 mg product obtained as a white powder (65.9 % yield): ^1H NMR (CD_3OD) δ 0.78-0.80 (m, 3 H), 0.83-0.84 (m, 3 H), 0.90-0.95 (m, 1 H), 1.01-1.03 (m, 2 H), 1.06 (d, $J=3.05$ Hz, 9 H), 1.17-1.21 (m, 2 H), 1.32-1.42 (m, 2 H), 1.68-1.72 (m, 1 H), 1.84-1.87 (m, 1 H), 2.14-2.20 (m, 1 H), 2.30-2.36 (m, 1 H), 2.57-2.62 (m, 1 H), 2.90-2.95 (m, 1 H), 3.66 (d, $J=2.75$ Hz, 3 H), 3.92 (d, $J=2.75$ Hz, 3 H), 4.05-4.12 (m, 2 H), 4.39-4.42 (m, 2 H), 4.50-4.53 (m, 1 H), 5.07-5.10 (m, 1 H), 5.23-5.28 (m, 1 H), 5.73-5.79 (m, 1 H), 5.81-5.83 (m, 1 H), 7.10-7.13 (m, 1 H), 7.17 (t, $J=2.44$ Hz, 1 H), 7.22-7.24 (m, 1 H), 7.85-7.87 (m, 1 H), 8.10 (dd, $J=9.16, 2.75$ Hz, 1 H); MS m/z 785 (MH^+).

Example 152: Preparation of Compound 152**Compound 152**

- 5 **Compound 152** was prepared by following Scheme 1 of Example 141 except that the scale was increased and that L-valine *tert*-butyl ester hydrochloride was used in place of L-valine methyl ester hydrochloride in step 2.

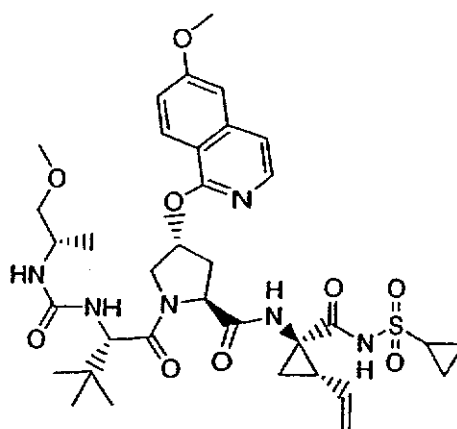
Step 1:

- 10 Modifications: 100 mg (0.146 mmol) of the product of Example 55, Step 1; 62.2 mg (0.219 mmol) *N,N'*-disuccinimidyl carbonate, 47.0 mg (0.364 mmol) *N,N*-diisopropylethylamine used.

Step 2:

- 15 Modifications: 306 mg (1.46 mmol) L-valine *tert*-butyl ester hydrochloride, 188 mg (1.46 mmol) *N,N*-diisopropylethylamine used, 93.5 mg product obtained as a white powder (78.8 % yield): MS *m/z* 814 (MH^+).

Example 153: Preparation of Compound 153

**Compound 153**

Compound 153 was prepared by following Scheme 1 of Example 141 except that the scale was increased and that (*S*)-(+)-1-methoxy-2-propylamine was used in place of
 5 L-valine methyl ester hydrochloride in step 2.

Step 1:

Modifications: 100 mg (0.146 mmol) of the product of Example 55, Step 1; 62.2 mg (0.219 mmol) *N,N'*-disuccinimidyl carbonate, 47.0 mg (0.364 mmol) *N,N*-
 10 diisopropylethylamine used.

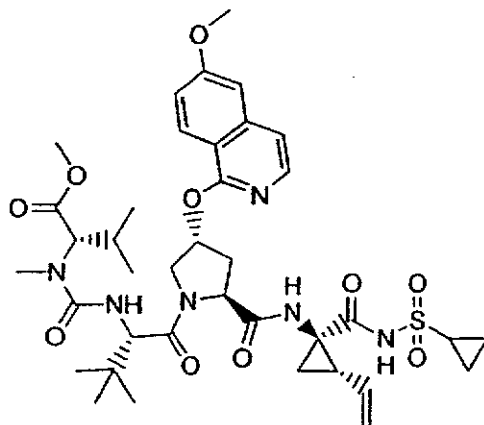
Step 2:

Modifications: 130 mg (1.46 mmol) (*S*)-(+)-1-methoxy-2-propylamine, 188 mg (1.46 mmol) *N,N*-diisopropylethylamine used, 50.3 mg product obtained as a white
 15 powder (47.3 % yield): ¹H NMR (CD₃OD) δ 0.96 (d, *J*=7.02 Hz, 3 H), 0.99-1.01 (m, 2 H), 1.04 (s, 9 H), 1.15-1.18 (m, 2 H), 1.39 (dd, *J*=9.61, 5.34 Hz, 1 H), 1.84 (dd, *J*=7.93, 5.19 Hz, 1 H), 1.93 (s, 3 H), 2.15 (q, *J*=9.05 Hz, 1 H), 2.37 (ddd, *J*=13.96, 9.84, 4.58 Hz, 1 H), 2.61 (dd, *J*=14.04, 7.32 Hz, 1 H), 2.90 (ddd, *J*=12.89, 8.16, 4.88 Hz, 1 H), 3.19-3.28 (m, 2 H), 3.64-3.67 (m, 1 H), 3.92 (s, 3 H), 4.12 (dd, *J*=11.60, 3.97 Hz, 1 H), 4.40 (s, 1 H), 4.44 (d, *J*=11.90 Hz, 1 H), 4.53 (dd, *J*=9.77, 7.32 Hz, 1
 20 H), 5.07 (dd, *J*=10.22, 1.68 Hz, 1 H), 5.24 (dd, *J*=17.24, 1.37 Hz, 1 H), 5.76-5.81 (m, 1 H), 5.83 (s, 1 H), 7.10 (dd, *J*=9.16, 2.44 Hz, 1 H), 7.17 (d, *J*=2.44 Hz, 1 H), 7.23 (d,

$J=5.80$ Hz, 1 H), 7.87 (d, $J=5.80$ Hz, 1 H), 8.10 (d, $J=9.16$ Hz, 1 H); MS m/z 729 (MH^+).

Example 154: Preparation of Compound 154

5



Compound 154

Compound 154 was prepared by following Scheme 1 of Example 141 except that the scale was increased and that *N*-methyl *L*-valine methyl ester hydrochloride was used in place of *L*-valine methyl ester hydrochloride in step 2.

10

Step 1:

Modifications: 100 mg (0.146 mmol) of the product of Example 55, Step 1; 62.2 mg (0.219 mmol) *N,N'*-disuccinimidyl carbonate, 47.0 mg (0.364 mmol) *N,N*-diisopropylethylamine used.

15

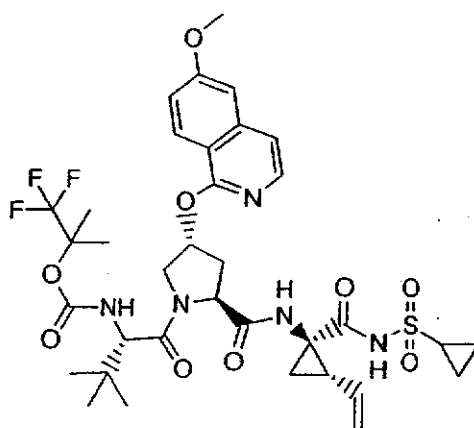
Step 2:

Modifications: 265 mg (1.46 mmol) *N*-methyl *L*-valine methyl ester hydrochloride, 188 mg (1.46 mmol) *N,N*-diisopropylethylamine used, 68.2 mg product obtained as a white powder (59.5 % yield): ^1H NMR (CD_3OD) δ 0.70 (dd, $J=6.71$, 2.14 Hz, 3 H), 0.89 (dd, $J=6.41$, 2.44 Hz, 3 H), 0.96-0.98 (m, 1 H), 1.02-1.04 (m, 2 H), 1.07 (d, $J=2.14$ Hz, 9 H), 1.18-1.22 (m, 2 H), 1.43-1.47 (m, 1 H), 1.84-1.87 (m, 1 H), 2.11-2.19 (m, 2 H), 2.31-2.37 (m, 1 H), 2.58-2.63 (m, 1 H), 2.87 (d, $J=2.44$ Hz, 3 H), 2.90-

20

2.94 (m, 1 H), 3.65 (d, $J=2.14$ Hz, 3 H), 3.92 (d, $J=2.14$ Hz, 3 H), 4.10-4.14 (m, 1 H),
 4.25 (dd, $J=10.07, 1.22$ Hz, 1 H), 4.48 (d, $J=2.44$ Hz, 1 H), 4.50-4.54 (m, 1 H), 5.08-
 5.10 (m, 1 H), 5.25-5.28 (dd, $J=17.09, 1.53$ Hz, 1 H), 5.78-5.85 (m, 2 H), 7.10-7.13
 (m, 1 H), 7.18-7.19 (m, 1 H), 7.24 (dd, $J=5.95, 2.59$ Hz, 1 H), 7.87-7.89 (m, 1 H),
 5 8.10 (dd, $J=9.00, 2.59$ Hz, 1 H); MS m/z 785 (MH^+).

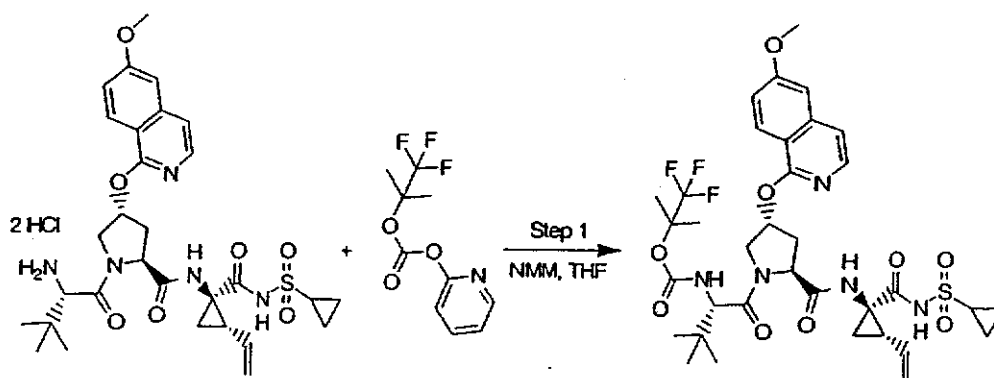
Example 155: Preparation of Compound 155



Compound 155

10

Scheme 1



Product of Example 55, Step 1

Compound 155

Step 1:

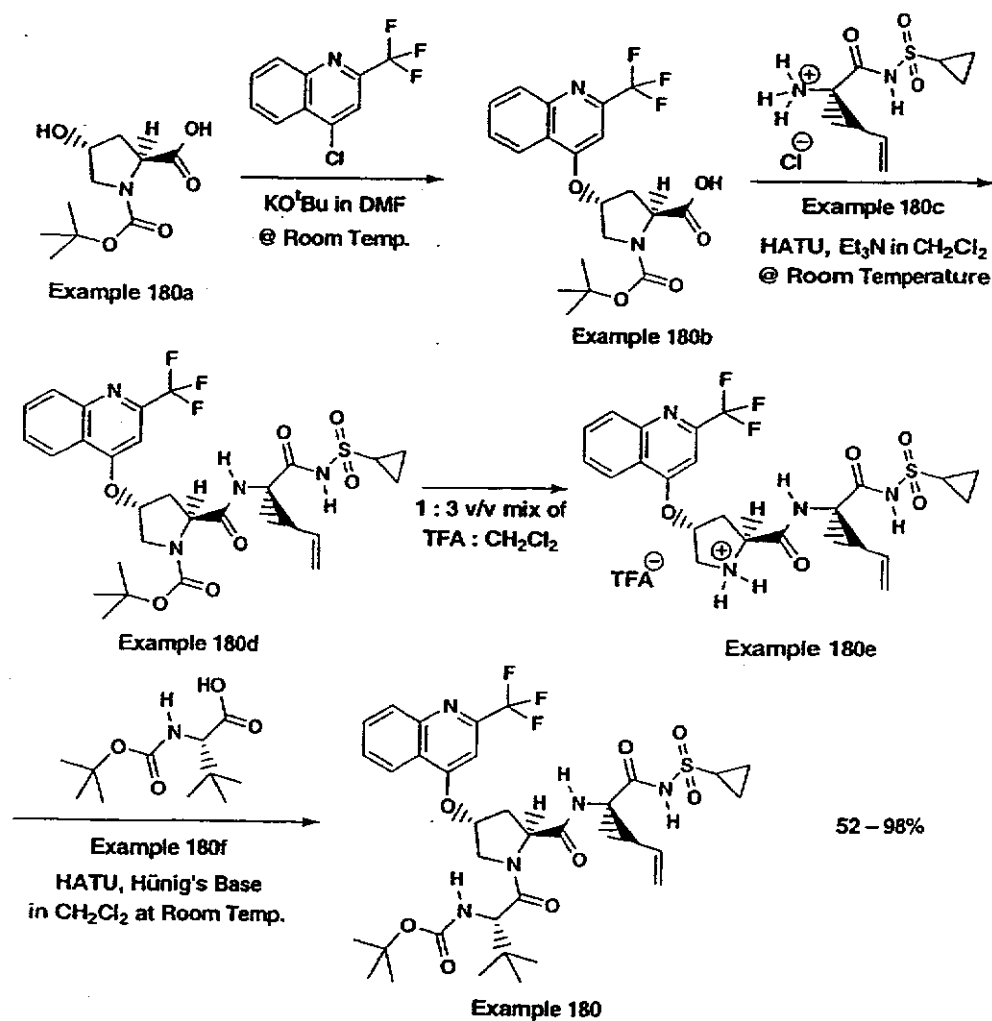
To a solution of the product of Example 55, Step 1 (100 mg, 0.146 mmol) in
 15 anhydrous THF (2 mL) was added carbonic acid pyridin-2-yl ester 2,2,2-trifluoro-

1,1-dimethyl-ethyl ester (44.0 mg, 0.175 mmol) and *N*-methylmorpholine (59 mg, 0.58 mmol). The mixture was agitated at rt for 24 h. The reaction mixture was washed concentrated *in vacuo* and the residue was dissolved in DCM (2 mL). The solution was washed with pH = 4 buffer solution (3 x 3 mL), and the washes were
5 back-extracted with DCM (3 mL). The organic phases were combined and concentrated *in vacuo*. The crude product was then dissolved in MeOH and purified by reverse phase preparative HPLC to give **Compound 155** as a white powder (38.5 mg, 34.3% yield): ¹H NMR (CD₃OD) δ 1.04 (s, 11 H), 1.19-1.22 (m, 2 H), 1.23 (s, 3 H), 1.43 (dd, *J*=9.31, 5.34 Hz, 1 H), 1.46 (s, 3 H), 1.87 (dd, *J*=7.93, 5.49 Hz, 1 H),
10 2.19 (q, *J*=8.85 Hz, 1 H), 2.34 (m, 1 H), 2.62 (dd, *J*=13.73, 7.02 Hz, 1 H), 2.92 (ddd, *J*=12.67, 8.09, 4.88 Hz, 1 H), 3.92 (s, 3 H), 4.06 (dd, *J*=11.90, 3.36 Hz, 1 H), 4.23 (s, 1 H), 4.43 (d, *J*=11.60 Hz, 1 H), 4.56 (dd, *J*=10.38, 7.32 Hz, 1 H), 5.10 (d, *J*=10.38 Hz, 1 H), 5.27 (d, *J*=17.09 Hz, 1 H), 5.75-5.80 (m, 1 H), 5.82 (s, 1 H), 7.10 (dd, *J*=9.16, 2.44 Hz, 1 H), 7.18 (d, *J*=2.44 Hz, 1 H), 7.25 (d, *J*=6.10 Hz, 1 H), 7.89 (d,
15 *J*=5.80 Hz, 1 H), 8.07 (d, *J*=9.16 Hz, 1 H); MS *m/z* 768 (MH⁺).

Section E:

LC-MS conditions for section E

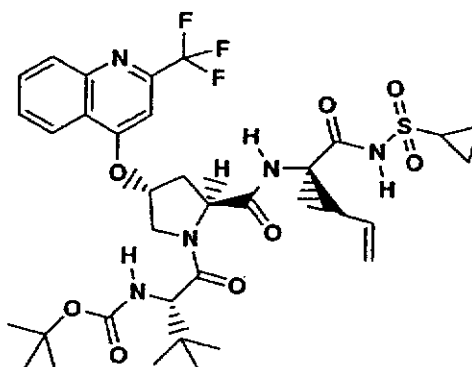
- 20 "method A" is 3.0X50mm Xterra @4min gradient and 4 mL/min flow
"method B" is 3.0X50mm Xterra @3min gradient and 4 mL/min flow
"method C" is 4.6X50mm Xterra @4min gradient and 4 mL/min flow
"method D" is 4.6X50mm Xterra @3min gradient and 4 mL/min flow

Example 180: Preparation of Compound 180**General Synthetic Scheme**

5

Compound 180 to 183 were prepared by the general synthetic scheme as depicted above. These individual reactions were described in detail elsewhere. With the exception of the first alkylation step for which potassium *tert*-butoxide in THF (as supplied by Aldrich Chemicals) in DMF offered a more convenient work up procedure: most of the DMF solvent was washed away with water once the alkylation was complete.

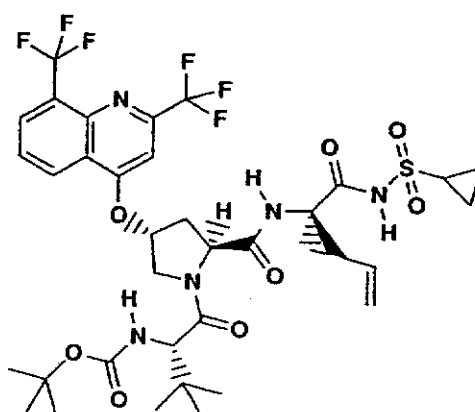
10



Thus **Compound 180**: BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(2-trifluoromethyl
 quinolin-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the
 5 material was obtained as a white foam in 61% yield. LC/MS *R*_t-min (MNa⁺) [method
 A]: 3.35 (774). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.05 (m, 13 H) 1.21 (s, 9 H)
 1.42 (dd, *J*=9.17, 5.26 Hz, 1 H) 1.86 (dd, *J*=8.07, 5.38 Hz, 1 H) 2.21 (m, 1 H) 2.33
 (m, 1 H) 2.64 (dd, *J*=13.94, 6.60 Hz, 1 H) 2.93 (m, 1 H) 4.09 (dd, *J*=11.49, 2.69 Hz, 1
 H) 4.21 (s, 1 H) 4.52 (m, 1 H) 4.56 (d, *J*=12.23 Hz, 1 H) 5.10 (dd, *J*=10.39, 1.59 Hz,
 10 1 H) 5.27 (d, *J*=16.87 Hz, 1 H) 5.58 (s, 1 H) 5.72 (m, 1 H) 7.36 (s, 1 H) 7.61 (t,
J=7.70 Hz, 1 H) 7.83 (t, *J*=7.34 Hz, 1 H) 8.07 (d, *J*=8.56 Hz, 1 H) 8.26 (d, *J*=8.56 Hz,
 1 H).

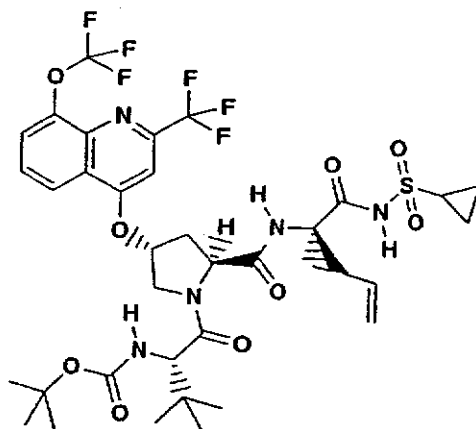
Example 181: Preparation of Compound 181

15

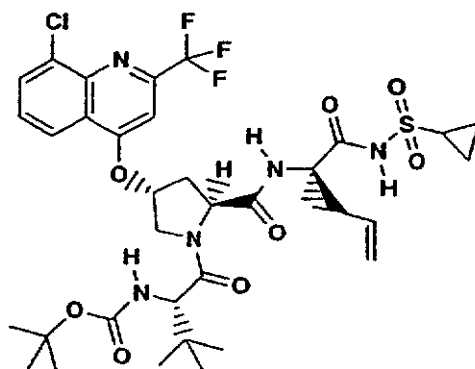


BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(2,8-bistrifluoromethyl quinolin-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a white foam in 52% yield. LC/MS *R*_t-min (MNa⁺) [method A]: 3.60 (843). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.05 (m, 11 H) 1.16 (s, 9 H) 1.22 (m, 2 H) 1.42 (dd, *J*=9.29, 5.38 Hz, 1 H) 1.86 (dd, *J*=8.07, 5.38 Hz, 1 H) 2.21 (q, *J*=8.97 Hz, 1 H) 2.33 (m, 1 H) 2.65 (dd, *J*=13.94, 6.85 Hz, 1 H) 2.93 (m, 1 H) 4.07 (dd, *J*=11.98, 2.69 Hz, 1 H) 4.17 (s, 1 H) 4.52 (dd, *J*=10.52, 6.85 Hz, 1 H) 4.58 (d, *J*=11.98 Hz, 1 H) 5.10 (d, *J*=10.27 Hz, 1 H) 5.27 (d, *J*=17.12 Hz, 1 H) 5.60 (s, 1 H) 5.72 (m, 1 H) 7.46 (s, 1 H) 7.69 (t, *J*=7.83 Hz, 1 H) 8.18 (d, *J*=7.34 Hz, 1 H) 8.50 (d, *J*=8.31 Hz, 1 H).

Example 182: Preparation of Compound 182



BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(2-trifluoromethyl, 8-trifluoromethoxy quinolin-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a white foam in 99% yield. LC/MS *R*_t-min (MNa⁺) [method A]: 3.62 (858). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.05 (m, 11 H) 1.21 (m, 11 H) 1.42 (dd, *J*=9.05, 5.14 Hz, 1 H) 1.86 (dd, *J*=8.07, 5.38 Hz, 1 H) 2.21 (q, *J*=8.64 Hz, 1 H) 2.33 (m, 1 H) 2.64 (dd, *J*=13.94, 6.60 Hz, 1 H) 2.93 (m, 1 H) 4.08 (dd, *J*=11.98, 2.69 Hz, 1 H) 4.18 (s, 1 H) 4.51 (dd, *J*=10.52, 6.85 Hz, 1 H) 4.57 (d, *J*=12.23 Hz, 1 H) 5.10 (dd, *J*=10.52, 1.22 Hz, 1 H) 5.27 (d, *J*=17.12 Hz, 1 H) 5.59 (s, 1 H) 5.72 (m, 1 H) 7.44 (s, 1 H) 7.63 (t, *J*=8.07 Hz, 1 H) 7.78 (d, *J*=7.58 Hz, 1 H) 8.24 (d, *J*=8.56 Hz, 1 H).

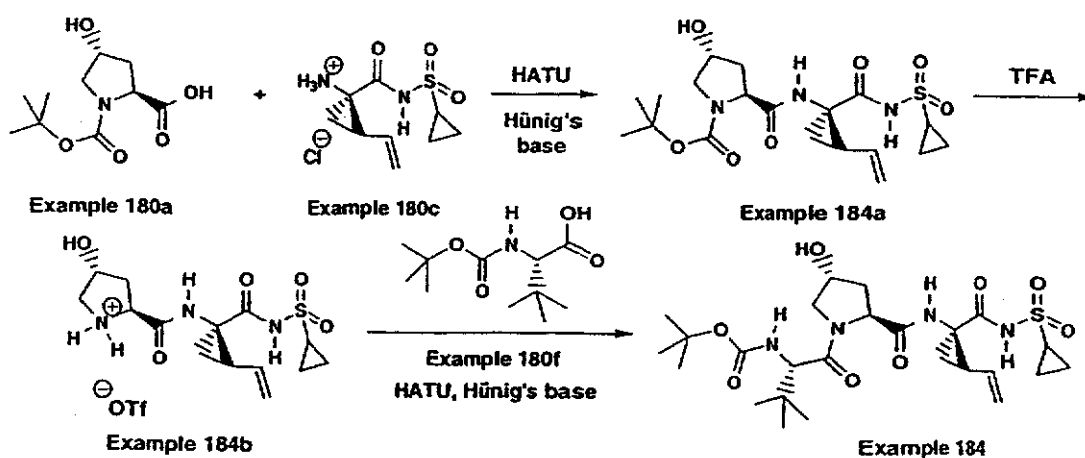
Example 183: Preparation of Compound 183

- 5 BOCNH-P3(*L-tert*-BuGly)-P2[(4*R*)-(2-trifluoromethyl, 8-chloro quinolin-4-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a white foam in 64% yield. LC/MS *R*_t-min (MNa⁺) [method A]: 3.52 (808). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.04 (m, 11 H) 1.21 (m, 11 H) 1.41 (dd, *J*=9.41, 5.50 Hz, 1 H) 1.86 (dd, *J*=8.07, 5.62 Hz, 1 H) 2.20 (q, *J*=8.80 Hz, 1 H) 2.32 (m, 1 H)
- 10 2.63 (dd, *J*=13.82, 6.72 Hz, 1 H) 2.92 (m, 1 H) 4.07 (dd, *J*=12.10, 2.81 Hz, 1 H) 4.19 (s, 1 H) 4.50 (dd, *J*=10.52, 6.85 Hz, 1 H) 4.56 (d, *J*=11.98 Hz, 1 H) 5.10 (dd, *J*=10.27, 1.47 Hz, 1 H) 5.26 (d, *J*=17.12 Hz, 1 H) 5.57 (s, 1 H) 5.72 (m, 1 H) 7.41 (s, 1 H) 7.52 (t, *J*=8.07 Hz, 1 H) 7.93 (d, *J*=7.58 Hz, 1 H) 8.19 (d, *J*=8.56 Hz, 1 H).

- 15 **Example 184: General procedure for alkylation with the tripeptide (Compound 184) and P2***

General Scheme – Preparation of Example 184 (Compound 184)

- 20 The preparation of the tripeptide component, **Example 184** was achieved by a sequential amide coupling using HATU as the coupling agent. It is understood that many standard coupling agents could be employed for the following scheme.



Preparation of intermediate **Example 184a**:

To a mixture of HATU (820 mg, 2.2 mmol), **Example 180a** (Boc-4R-hydroxyproline, 417 mg, 1.8 mmol) and **Example 180c** (cyclopropanesulfonic acid (1*R*)-amino-2(*S*)-vinyl-cyclopropanecarbonyl)-amide hydrochloride salt, 490 mg, 1.8 mmol) in a flame dried flask at room temperature was added dry CH₂Cl₂ (8 mL). The mixture was kept under dry N₂ before it was chilled to -78 °C. Hunig's base (diisopropylethylamine, 625 µL, 3.6 mmol) was added slowly over a period 5 min and the mixture turned into a pale orange suspension. Stirring was continued for an hour while temperature was allow to raise to ambient. LC/MS showed complete conversion into the desired product **184a**. The crude reaction was worked up as usual, washed with three portions (5 mL) of water, organic residues were extracted into ethyl acetate (3 X 5 mL). The crude product was obtained by removal of organic solvents in vacuo. The material was used in the next step without further purification.

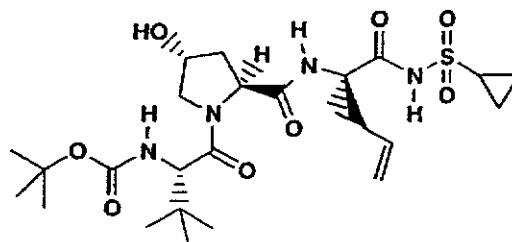
Preparation of intermediate **Example 184b**:

The dried solid from the previous step was taken into 9 mL of CH₂Cl₂ at room temperature. To this solution was added 3 mL of trifluoroacetic acid forming a pale yellowish solution. Stirring was continued for 2 hours at room temperature. LC/MS showed no starting material **184a** while the desired product **184b** was the major signal along with a signal corresponding to a side product carried over from HATU in

the step earlier. The solvents were evaporated and the solid residue was used in the next step immediately without further purification.

Preparation of the tripeptide, Compound 184:

5



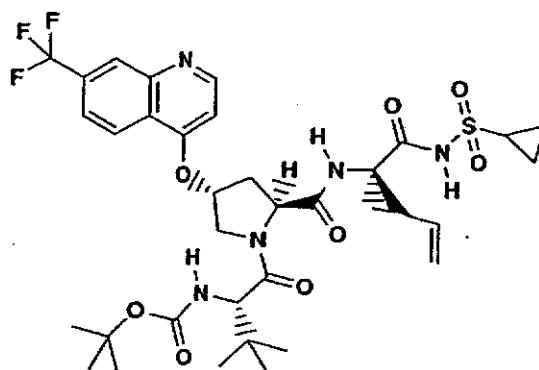
BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-hydroxy-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane [Notebook 46877-128]

10 The crude product from the previous step (**Example 184b**, 1.8 mmol) was mixed with HATU (700 mg, 1.8 mmol) and BOC-*L*-*tert*-leucine (**Example 180f**, Fluka Chemicals, 420 mg, 1.8 mmol) in CH₂Cl₂ (10 mL) at room temperature. To this suspension was treated Hünig's base (1 mL, excess) forming a somewhat thinner, orange suspension. LC/MS showed some conversion into **compound 184**. Complete
15 conversion into the desired product **184** was observed after stirring was continued for two days at room temperature. Crude reaction mixture was evaporated to dryness. The residue was taken into ethyl acetate. Most of HATU residue was removed by extractions with half saturated, freshly prepared sodium bicarbonate solution. The last
20 traces of HATU residue (1-hydroxy 7-azabenzotriazole) was removed by washing with deionized water. Evaporation of solvents gave 990 mg (98%) of the desired product as white foam. This material is suitable for the subsequent alkylation with electrophiles such as quinolines and isoquinolines directly without further purification. LC/MS *R*_f-min (MNa⁺) [method A]: 2.65 (579). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.95 (s, 2 H) 0.99 (s, 9 H) 1.05 (m, 2 H) 1.21 (m, 1 H) 1.39 (m, 9 H)
25 1.84 (dd, *J*=8.31, 5.38 Hz, 1 H) 1.96 (m, 1 H) 2.11 (m, 1 H) 2.20 (m, 1 H) 2.91 (m, 1 H) 3.80 (m, 2 H) 4.28 (d, *J*=9.78 Hz, 1 H) 4.35 (dd, *J*=9.90, 6.97 Hz, 1 H) 4.47 (s, 1 H) 5.11 (m, 1 H) 5.29 (d, *J*=17.12 Hz, 1 H) 5.75 (m, 1 H).

Alkylation of the tripeptide (compound 184) with electrophiles:

To a flame-dried 25 mL round bottom flask was charged with **Compound 184**, (0.5 - 1.0 mmol), substituted 4-chloroquinoline (1.0 equivalent) and lanthanum chloride (LaCl_3 anhydrous beads, used as supplied by Aldrich, M.W. 245 g/mol; 1.0 equivalent. Note: the inclusion of such additive was found to be helpful in some cases especially with those less reactive electrophiles. This reagent can, at times, be omitted if the electrophiles are sufficiently reactive towards anionic alkylation) in 2 mL dry DMF. The inorganic salt was only sparingly soluble in DMF at room temperature. The mixture was chilled to $-78\text{ }^\circ\text{C}$ (dry-ice/acetone bath) with stirring under nitrogen. To this chilled mixture was added a THF solution of potassium *tert*-butoxide (1.0 M, used as supplied by Aldrich, 5.5 equivalents) and the color of mixture changed from colorless to pale yellowish or greenish. It was stirred at $-78\text{ }^\circ\text{C}$ for a period dependent upon the 4-chloroquinoline reactivity (a few hrs. at $-78\text{ }^\circ\text{C}$ to overnight at room temperature). The inorganic salt was also found to change into a fine emulsion at the end. It was quenched with a half saturated NH_4Cl aqueous solution (2 mL). Organic materials were extracted into ethyl acetate (10 mL X 3). Organic layers were combined, back washed with deionized water (10 mL X 2). Evaporation of the organic fraction gave a crude mixture rich in the desired product as determined by LC/MS. The desired product was isolated by preparative HPLC using standard separation parameters (typically: 3.0X50mm Xterra column @4min gradient and 4 mL/min flow rate) to give the analytically pure desired product. The alkylation of 1-halo isoquinoline series was carried out in exactly the same way.

Example 185: Preparation of Compound 185

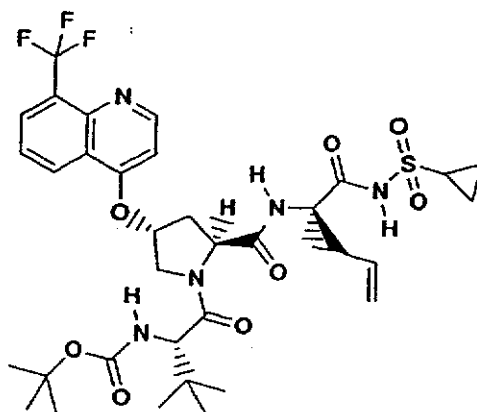


Following the general tripeptide alkylation procedure as described in **Example 184**, BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(7-trifluoromethyl quinolin-4-oxo)-*S*-proline]-

5 P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane was obtained as a white foam in 50% yield. LC/MS *R*_t-min (MH⁺) [method B]: 2.32 (752). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.02 (s, 9 H) 1.06 (m, 11 H) 1.22 (m, 2 H) 1.43 (dd, *J*=9.41, 5.26 Hz, 1 H) 1.88 (dd, *J*=8.19, 5.50 Hz, 1 H) 2.23 (q, *J*=8.80 Hz, 1 H) 2.42 (m, 1 H) 2.75 (dd, *J*=14.06, 6.48 Hz, 1 H) 2.93 (m, 1 H) 4.10 (m, 2 H) 4.61 (m, 2 H) 5.12 (dd, *J*=10.39, 1.59 Hz, 1 H) 5.29 (d, *J*=17.12 Hz, 1 H) 5.72 (m, 2 H) 7.61 (d, *J*=6.36 Hz, 1 H) 7.96 (d, *J*=8.80 Hz, 1 H) 8.38 (s, 1 H) 8.59 (d, *J*=8.56 Hz, 1 H) 9.14 (d, *J*=6.36 Hz, 1 H).

10

Example 186: Preparation of Compound 186



15

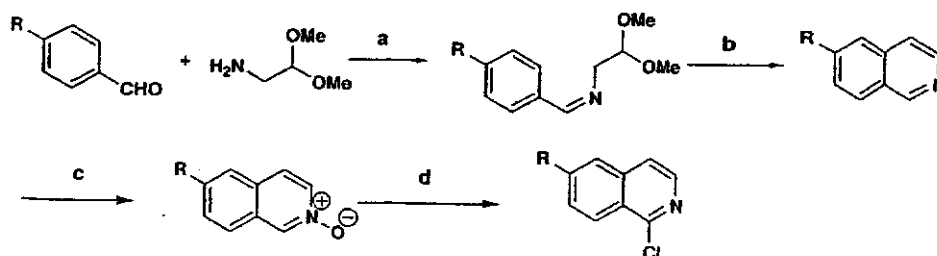
Following the general tripeptide alkylation procedure as described in **Example 184**, BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(8-trifluoromethyl quinolin-4-

oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the desired product was obtained as a white foam in 50% yield. LC/MS *R*_t-min (MH⁺) [method B]: 2.48 (752). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.02 (s, 9 H) 1.05 (m, 2 H) 1.13 (s, 9 H) 1.23 (m, 2 H) 1.42 (dd, *J*=8.68, 5.50 Hz, 1 H) 1.87 (dd, *J*=8.07, 5.38 Hz, 1 H) 2.21 (q, *J*=8.80 Hz, 1 H) 2.36 (m, 1 H) 2.69 (dd, *J*=14.06, 6.97 Hz, 1 H) 2.93 (m, 1 H) 4.08 (dd, *J*=11.98, 2.93 Hz, 1 H) 4.15 (s, 1 H) 4.54 (dd, *J*=10.52, 7.09 Hz, 1 H) 4.60 (d, *J*=12.47 Hz, 1 H) 5.11 (dd, *J*=10.52, 1.71 Hz, 1 H) 5.28 (d, *J*=15.90 Hz, 1 H) 5.58 (s, 1 H) 5.72 (m, 1 H) 7.32 (d, *J*=5.87 Hz, 1 H) 7.69 (t, *J*=7.95 Hz, 1 H) 8.22 (d, *J*=7.09 Hz, 1 H) 8.55 (d, *J*=8.07 Hz, 1 H) 8.88 (d, *J*=5.62 Hz, 1 H).

Preparation of isoquinoline intermediates for 6-F, 6-Ethyl, 6-isopropyl and 6-*tert*-butyl isoquinoline P2* building blocks.

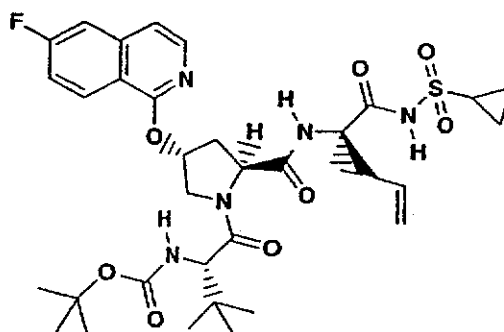
In general, the 6-fluoro and 6-alkyl isoquinolines used in the following experiments were prepared via a Pomeranz-Fritsch synthesis (Typical procedure: Preparation of optically active 8,8-disubstituted 1,1-biisoquinoline, K. Hirao, R. Tsuchiya, Y. Yano, H. Tsue, *Heterocycles* 42(1) 1996, 415-422) as outlined below. The products were converted into the 1-chloro derivatives via *N*-oxide intermediates as described elsewhere.

General Synthetic Scheme



Reagents and reaction conditions: (a) reflux in benzene, azeotropic removal of water; (b) first step: ethyl chloroformate, trimethyl phosphite in THF, second step: titanium tetrachloride in chloroform; (c) MCPBA in CH₂Cl₂; (d) POCl₃ in benzene

R	Isoquinoline, Yield	1-Chloride, combined yield
F	20	43
Et	76	65
i-Pr	14	18
t-Bu	47	55

Example 187: Preparation of Compound 187

5

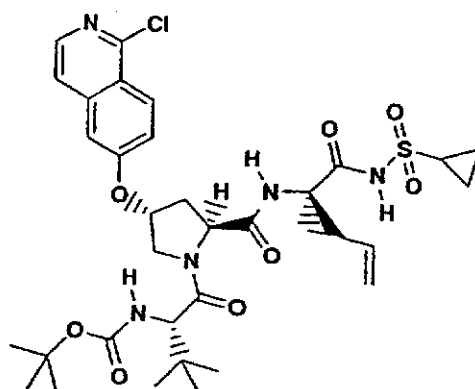
BOC-NH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(6-fluoro isoquinolin-1-oxo)-*S*-proline]-

F1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane. the material was obtained as a

white foam in 12% yield. LC/MS R_f-min (MNa⁺) [method C]: 3.81 (724). ¹H NMR

(400 MHz, CD₃OD) δ ppm 1.05 (m, 13 H) 1.22 (s, 9 H) 1.42 (m, 1 H) 1.86 (m, 1 H)
 10 2.21 (m, 2 H) 2.61 (dd, *J*=13.69, 6.60 Hz, 1 H) 2.93 (m, 1 H) 4.05 (d, *J*=13.69 Hz, 1
 H) 4.21 (s, 1 H) 4.49 (m, 2 H) 5.11 (d, *J*=10.03 Hz, 1 H) 5.28 (d, *J*=17.61 Hz, 1 H)
 5.72 (m, 1 H) 5.86 (d, *J*=4.40 Hz, 1 H) 7.31 (m, 2 H) 7.48 (d, *J*=8.31 Hz, 1 H) 7.97
 (d, *J*=6.36 Hz, 1 H) 8.26 (d, *J*=6.11 Hz, 1 H).

15 **Example 188: Preparation of Compound 188**



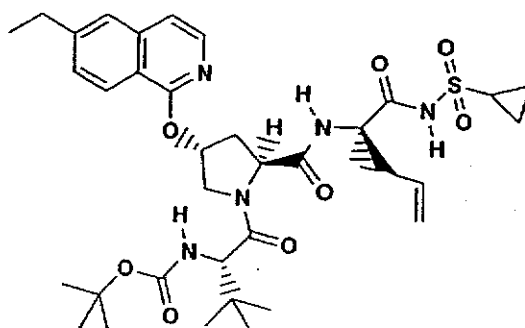
The alkylation described above gave the 1-chloroisoquinoline as the major product:

BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(1-chloro isoquinolin-6-oxo)-*S*-proline]-

- 5 P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a white foam in 40.2% yield. LC/MS *R*_t-min (MH⁺) [method C]: 3.81 (718). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.00 (s, 9 H) 1.06 (m, 2 H) 1.25 (s, 11 H) 1.41 (m, 1 H) 1.86 (dd, *J*=8.07, 5.38 Hz, 1 H) 2.25 (m, 2 H) 2.54 (dd, *J*=12.96, 6.60 Hz, 1 H) 2.92 (m, 1 H) 4.06 (dd, *J*=11.98, 2.69 Hz, 1 H) 4.20 (s, 1 H) 4.31 (d, *J*=11.74 Hz, 1 H)
- 10 4.45 (dd, *J*=9.78, 7.58 Hz, 1 H) 5.11 (dd, *J*=10.27, 1.71 Hz, 1 H) 5.28 (dd, *J*=17.36, 1.47 Hz, 1 H) 5.36 (s, 1 H) 5.74 (m, 1 H) 7.35 (d, *J*=9.29 Hz, 1 H) 7.40 (s, 1 H) 7.70 (d, *J*=5.87 Hz, 1 H) 8.13 (d, *J*=5.87 Hz, 1 H) 8.25 (d, *J*=9.29 Hz, 1 H).

Example 189: Preparation of Compound 189

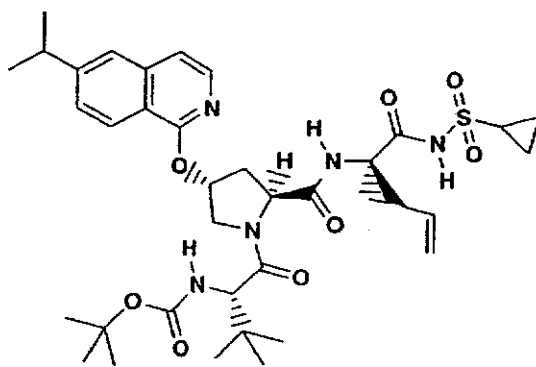
15



- BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(6-ethyl isoquinolin-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a white foam in
- 20 4.6 mg of yellow solid was obtained (4.2%). LC/MS *rt*-min (MH⁺) [method B]: 2.70

(712). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.01 (s, 9 H) 1.07 (m, 2 H) 1.22 (m, 1 H) 1.28 (t, *J*=7.91 Hz, 3 H) 1.41 (m, 1 H) 1.85 (m, 1 H) 2.25 (m, 2 H) 2.60 (dd, *J*=13.69, 6.85 Hz, 1 H) 2.80 (q, *J*=7.66 Hz, 2 H) 2.93 (m, 1 H) 4.02 (d, *J*=31.06 Hz, 1 H) 4.23 (s, 1 H) 4.42 (m, 1 H) 4.54 (m, 1 H) 5.10 (d, *J*=10.27 Hz, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.74 (m, 1 H) 5.84 (s, 1 H) 7.25 (d, *J*=5.87 Hz, 1 H) 7.38 (d, *J*=8.56 Hz, 1 H) 7.59 (s, 1 H) 7.90 (d, *J*=6.24 Hz, 1 H) 8.09 (d, *J*=8.56 Hz, 1 H).

Example 190: Preparation of Compound 190

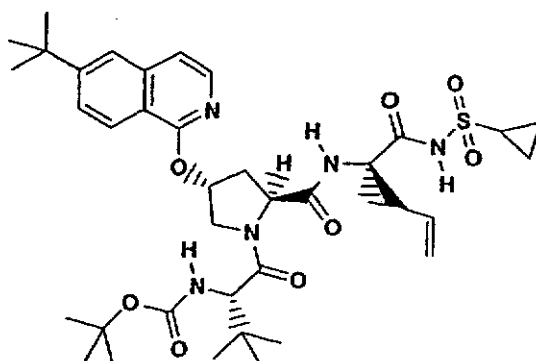


10

BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(6-isopropyl isoquinolin-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a white foam in 69% yield. LC/MS *R*_t-min (MNa⁺) [method B]: 2.76 (749). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.05 (m, 13 H) 1.20 (m, 9 H) 1.31 (d, *J*=6.85 Hz, 6 H) 1.42 (m, 1 H) 1.86 (dd, *J*=8.07, 5.62 Hz, 1 H) 2.26 (m, 2 H) 2.62 (dd, *J*=13.69, 6.85 Hz, 1 H) 2.93 (m, 1 H) 3.07 (m, 1 H) 4.06 (m, 1 H) 4.21 (s, 1 H) 4.52 (m, 2 H) 5.11 (d, *J*=10.27 Hz, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.74 (m, 1 H) 5.84 (s, 1 H) 7.32 (d, *J*=6.11 Hz, 1 H) 7.46 (d, *J*=8.56 Hz, 1 H) 7.64 (s, 1 H) 7.90 (d, *J*=6.11 Hz, 1 H) 8.13 (d, *J*=8.56 Hz, 1 H).

20

Example 191: Preparation of Compound 191



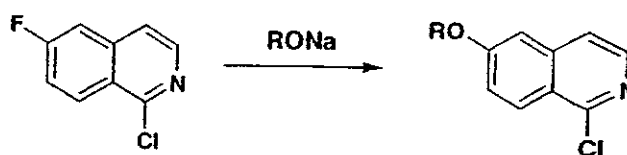
BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(6-*tert*-butyl isoquinolin-1-oxo)-*S*-proline]-
 P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a
 5 white foam in 81% yield. LC/MS *R*_t-min (MH⁺) [method B]: 2.84 (740). ¹H NMR
 (400 MHz, CD₃OD) δ ppm 1.01 (s, 9 H) 1.06 (m, 2 H) 1.18 (s, 9 H) 1.22 (m, 2 H)
 1.39 (s, 9 H) 1.43 (m, 1 H) 1.87 (dd, *J*=8.19, 5.50 Hz, 1 H) 2.27 (m, 2 H) 2.63 (dd,
J=13.57, 6.97 Hz, 1 H) 2.93 (m, 1 H) 4.06 (m, 1 H) 4.20 (s, 1 H) 4.52 (m, 2 H) 5.10
 (d, *J*=11.49 Hz, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.73 (m, 1 H) 5.84 (s, 1 H) 7.36 (d,
 10 *J*=6.11 Hz, 1 H) 7.66 (dd, *J*=8.80, 1.22 Hz, 1 H) 7.78 (s, 1 H) 7.91 (d, *J*=5.87 Hz, 1
 H) 8.15 (d, *J*=8.80 Hz, 1 H).

Preparation of 6-isopropoxyl and 6-*tert*-butoxyl isoquinoline intermediates:

15 Some 6-alkoxy-1-chloro isoquinolines were prepared by a direct, ipso
 displacement of the 6-fluoro-1-chloroisoquinoline with the corresponding alkoxide
 metal ions such as potassium *tert*-butoxide (53%) and sodium isopropoxide (54%).

General Synthetic Scheme

20

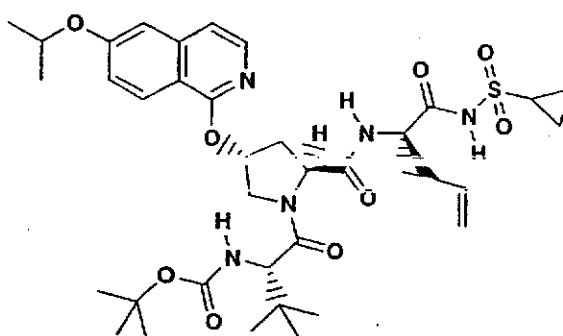


R = alkoxide anions such as *tert*-Bu, iso-Pr

The 6-fluoro-1-chloroisoquinoline was subjected to an aromatic nucleophilic displacement with sodium isopropoxide and potassium *tert*-butoxide in DMF to give the corresponding

- 6-isopropoxyl (54%): ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.43 (d, *J*=6.11 Hz, 6 H) 4.76 (m, *J*=6.11 Hz, 1 H) 7.08 (d, *J*=2.45 Hz, 1 H) 7.29 (dd, *J*=9.29, 2.45 Hz, 1 H) 7.50 (d, *J*=5.62 Hz, 1 H) 8.18 (d, *J*=5.87 Hz, 1 H) 8.24 (d, *J*=9.29 Hz, 1 H) and 6-*tert*-butoxyl-1-chloro isoquinolines (55%): ¹H NMR (400 MHz, CHLOROFORM-d) δ ppm 1.48 (s, 9 H) 7.31 (m, 2 H) 7.47 (d, *J*=5.62 Hz, 1 H) 8.18 (d, *J*=5.62 Hz, 1 H) 8.21 (d, *J*=9.78 Hz, 1 H) as the major product respectively. These 6-alkoxyl-1-chloro isoquinolines were alkylated with the tripeptide as described in Example 184 to give the desired products shown below.

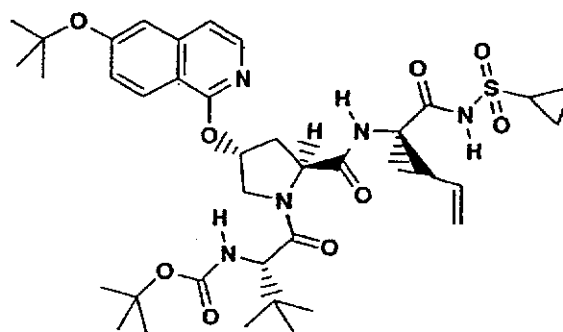
Example 192: Preparation of Compound 192



15

- BOCNH-P3(*L-tert*-BuGly)-P2[(4*R*)-(6-isopropoxy isoquinolin-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a white foam in 59% yield. LC/MS *R*_t-min (MH⁺) [method C]: 3.87 (742). ¹H NMR (400 MHz, CD₃OD) δ ppm 0.99 (s, 11 H) 1.06 (m, 2 H) 1.21 (s, 9 H) 1.37 (d, *J*=5.87 Hz, 6 H) 1.42 (m, 1 H) 1.86 (dd, *J*=8.07, 5.38 Hz, 1 H) 2.25 (m, 2 H) 2.61 (dd, *J*=13.69, 6.85 Hz, 1 H) 2.92 (m, 1 H) 4.04 (dd, *J*=11.86, 3.30 Hz, 1 H) 4.21 (br. s, 1H) 4.49 (m, 2 H) 4.78 (h, *J*=5.87 Hz, 1 H) 5.10 (dd, *J*=10.39, 1.35 Hz, 1 H) 5.28 (d, *J*=16.87 Hz, 1 H) 5.73 (m, 1 H) 5.79 (d, *J*=11.25 Hz, 1 H) 7.07 (dd, *J*=9.05, 1.96 Hz, 1 H) 7.18 (d, *J*=2.20 Hz, 1 H) 7.26 (d, *J*=6.11 Hz, 1 H) 7.85 (d, *J*=6.11 Hz, 1 H) 8.10 (d, *J*=9.05 Hz, 1 H).

25

Example 193: Preparation of Compound 193

5

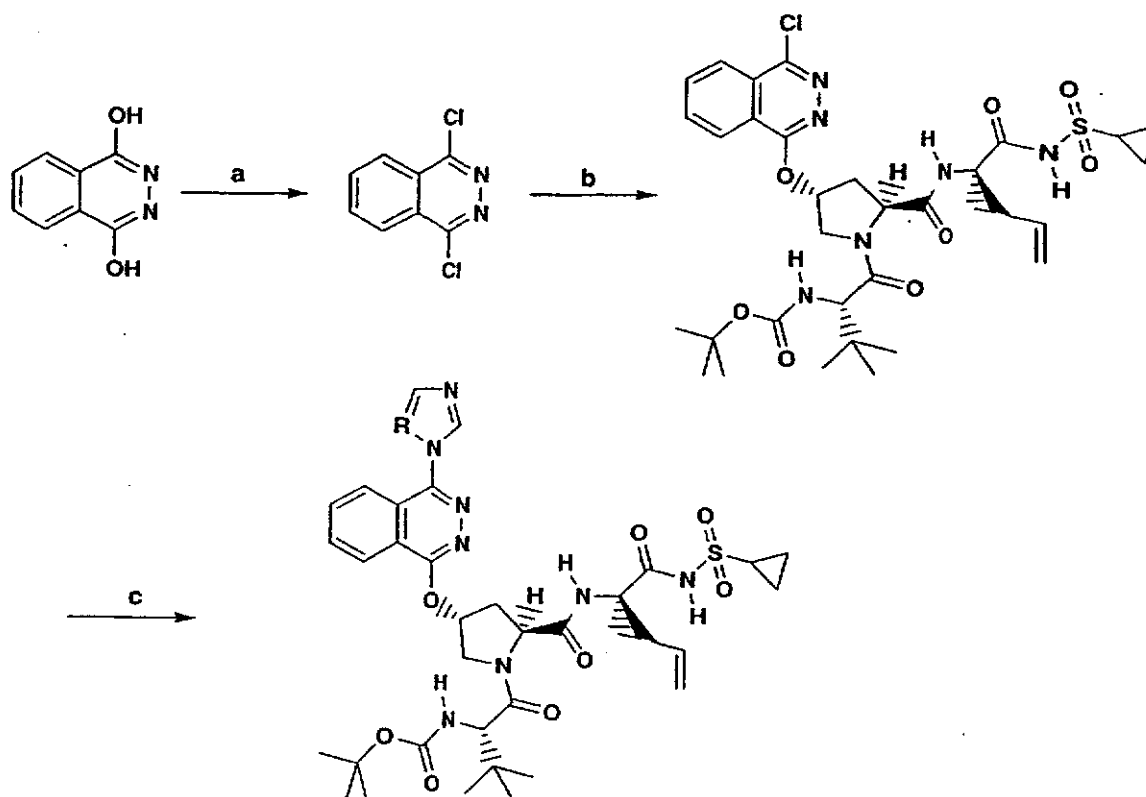
BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(6-*tert*-butoxy isoquinolin-1-oxo)-*S*-proline]-
 P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a
 white foam in 39% yield. LC/MS *R*_f-min (MH⁺) [method C]: 3.99 (756). ¹H NMR
 (400 MHz, CD₃OD) δ ppm 1.03 (br s, 13 H) 1.19 (s, 9 H) 1.42 (m, 10 H) 1.86 (dd,
 10 *J*=7.83, 5.62 Hz, 1 H) 2.24 (m, 2 H) 2.60 (dd, *J*=13.69, 6.85 Hz, 1 H) 2.93 (m, 1 H)
 4.04 (dd, *J*=11.49, 2.93 Hz, 1 H) 4.23 (s, 1 H) 4.49 (m, 2 H) 5.10 (d, *J*=11.25 Hz, 1
 H) 5.27 (d, *J*=16.87 Hz, 1 H) 5.73 (m, 1 H) 5.81 (s, 1 H) 7.13 (dd, *J*=8.80, 1.47 Hz, 1
 H) 7.25 (d, *J*=5.87 Hz, 1 H) 7.33 (d, *J*=2.20 Hz, 1 H) 7.87 (d, *J*=6.11 Hz, 1 H) 8.10
 (d, *J*=9.05 Hz, 1 H).

15

Preparation of phthalazine P2* derivatives:

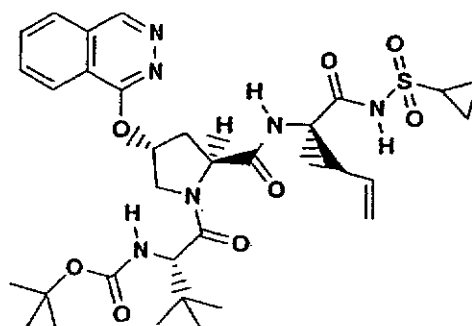
In general, both 1-chlorophthalazine and 1,4-dichlorophthalazine undergo alkylation
 smoothly to give the desired products. However, the commercially available 1-
 20 chlorophthalazine and 1,4-dichlorophthalazine are often contaminated with some
 hydrolyzed materials. A pre-treatment with POCl₃ followed by alkylation
 immediately afterward furnished more consistent results.

General Synthetic Scheme



Reaction Conditions: (a) POCl_3 in DCE; (b) Alkylation with tripeptide; (c) sodium derivatives of imidazole ($\text{R} = \text{CH}$), triazole ($\text{R} = \text{N}$)

Example 194: Preparation Compound 194

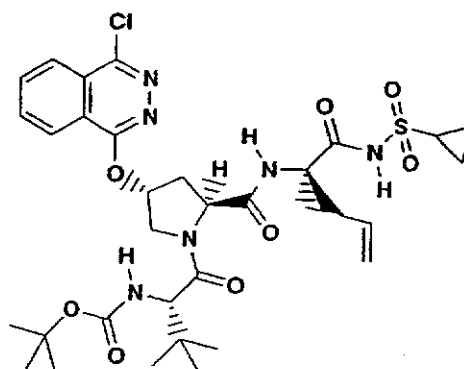


10

BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(phthalazine-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a white foam in 41%

yield. LC/MS R_f -min (MNa^+) [method B]: 2.07 (707). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.03 (m, 9 H) 1.06 (m, 4 H) 1.14 (s, 9 H) 1.20 (m, 1 H) 1.43 (m, 1 H) 1.87 (dd, $J=8.07, 5.62$ Hz, 1 H) 2.24 (q, $J=8.80$ Hz, 1 H) 2.38 (m, 1 H) 2.76 (dd, $J=14.18, 7.09$ Hz, 1 H) 2.92 (m, 1 H) 4.11 (m, 2 H) 4.62 (m, 1 H) 5.11 (dd, $J=10.27, 1.71$ Hz, 1 H) 5.29 (dd, $J=17.12, 1.22$ Hz, 1 H) 5.72 (m, 1 H) 5.96 (s, 1 H) 8.26 (m, 2 H) 8.46 (m, 2 H) 9.84 (s, 1 H).

Example 195: Preparation of Compound 195



10

BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(4-chloro phthalazine-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a white foam in 23% yield. LC/MS R_f -min (MNa^+) [method C]: 3.52 (742). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.01 (s, 11 H) 1.06 (m, 2 H) 1.14 (s, 9 H) 1.22 (m, 1 H) 1.43 (m, 1 H) 1.87 (m, 1 H) 2.21 (m, 1 H) 2.35 (m, $J=10.27$ Hz, 1 H) 2.70 (m, 1 H) 2.93 (m, 1 H) 4.05 (d, $J=3.42$ Hz, 1 H) 4.58 (m, 2 H) 5.11 (dd, $J=10.39, 1.10$ Hz, 1 H) 5.28 (d, $J=17.36$ Hz, 1 H) 5.73 (m, 1 H) 5.93 (s, 1 H) 7.99 (m, 1 H) 8.07 (t, $J=7.70$ Hz, 1 H) 8.26 (dd, $J=8.19, 2.32$ Hz, 2 H).

20

Preparation of 4-(imidazo-1-yl)phthalazine and 4-(1,2,4-triazo-1-yl)phthalazine P2* derivatives:

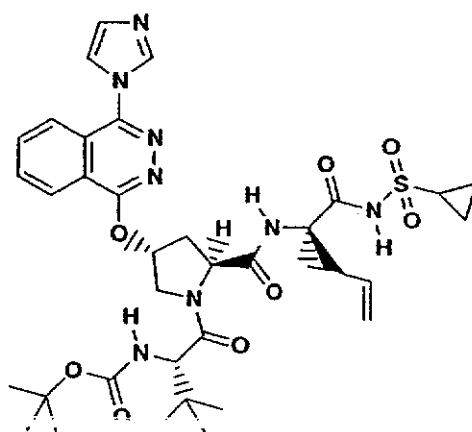
The product, **compound 195** from above, BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(4-chloro phthalazine-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-

25

Cyclopropane, was subjected to displacement by the anions of typical azoles such as imidazole and triazole to give 4-azole substituted phthalazine derivatives shown below:

5 Example 196: Preparation of Compound 196

This was made by displacing the 4-chloro phthalazine (Compound 195) with the sodium salt of imidazole in DMF at 55-65 °C.

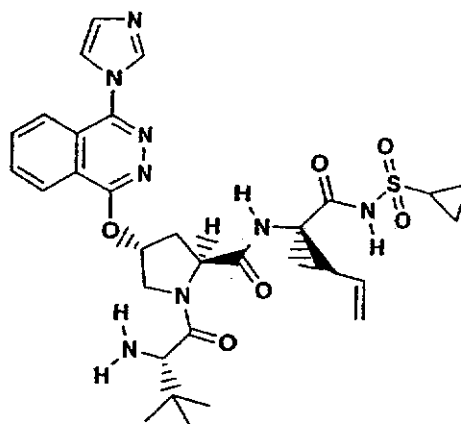


10

BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(4-(imidazo-1-yl)phthalazine-1-oxo)-*S*-proline]-
 P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a
 white foam in 23% yield. LC/MS *R*_f-min (MNa⁺) [method B]: 1.94 (773). ¹H NMR
 15 (400 MHz, CD₃OD) δ ppm 1.03 (s, 9 H) 1.07 (m, 2 H) 1.20 (m, 9 H) 1.24 (m, 1 H)
 1.41 (m, 2 H) 1.88 (dd, *J*=8.19, 5.50 Hz, 1 H) 2.23 (m, 1 H) 2.41 (m, 1 H) 2.75 (m,
J=14.92 Hz, 1 H) 2.93 (m, 1 H) 4.14 (m, 2 H) 4.60 (dd, *J*=10.15, 6.97 Hz, 2 H) 5.12
 (dd, *J*=10.27, 1.47 Hz, 1 H) 5.29 (dd, *J*=17.24, 1.35 Hz, 1 H) 5.74 (m, 1 H) 6.09 (s, 1
 H) 7.85 (s, 1 H) 7.94 (m, 1 H) 8.10 (m, 2 H) 8.43 (m, 1 H) 9.17 (s, 1 H) 9.46 (s, 1 H).

20

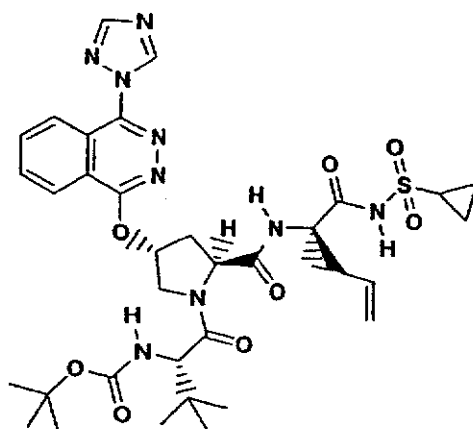
During the displacement reaction, small amount of de-BOC by-product
 (Compound 197) was also isolated:



- NH₂-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(4-(imidazo-1-yl)phthalazine-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a white foam in 17% yield. LC/MS R_t-min (MH⁺) [method B]: 1.22 (651). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.16 (s, 9 H) 1.23 (m, 2 H) 1.42 (dd, *J*=9.41, 5.50 Hz, 1 H) 1.89 (m, 1 H) 2.26 (q, *J*=8.97 Hz, 1 H) 2.43 (m, 1 H) 2.78 (dd, *J*=14.06, 7.21 Hz, 1 H) 2.93 (m, 1 H) 3.74 (m, 1 H) 4.11 (s, 1 H) 4.22 (dd, *J*=12.23, 3.91 Hz, 1 H) 4.47 (m, 2 H) 4.71 (dd, *J*=10.27, 7.09 Hz, 1 H) 5.12 (m, 1 H) 5.29 (d, *J*=17.36 Hz, 1 H) 5.71 (m, 1 H) 6.13 (t, *J*=3.67 Hz, 1 H) 7.87 (s, 1 H) 7.97 (m, 1 H) 8.14 (m, 3 H) 8.41 (m, 1 H) 9.47 (s, 1 H).

Example 198: Preparation Compound 198

- This was made by displacing the 4-chloro phthalazine (**Compound 195**) with the sodium salt of 1,2,4-triazole in DMF at 55-65 °C.



10

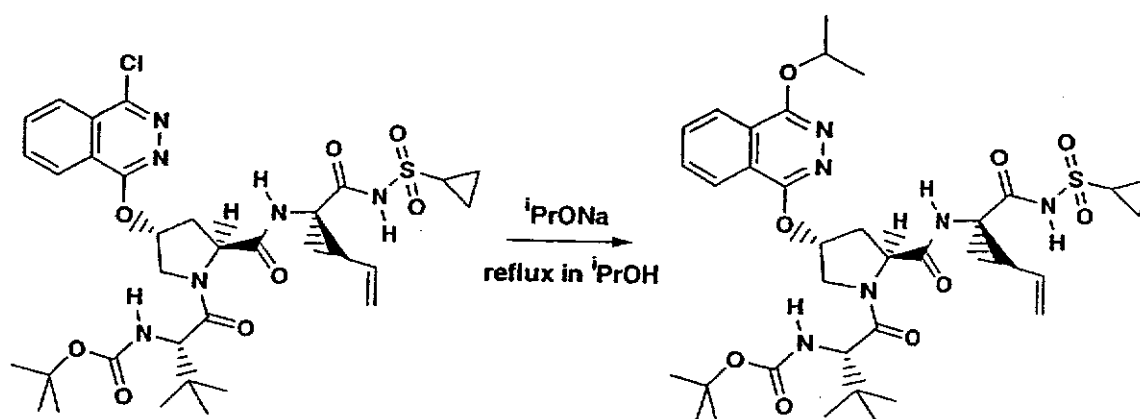
Preparation of 4-hydroxy and 4-alkoxy phthalazine P2* derivatives



Reaction Conditions: (a) sodium alkoxides such as methoxide, ethoxide and isopropoxide

Example 199: Preparation of Compound 199

5

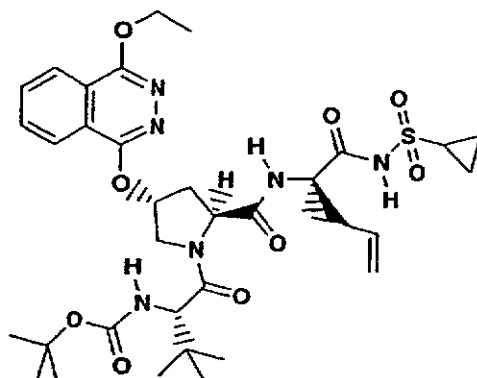


The 4-chloro phthalazine (**Example 195**) was dissolved in dry isopropyl alcohol at room temperature and 1.0 eq of sodium isopropoxide was added, the resulted suspension was brought to reflux. The desired product, 4.5 mg of yellow solid was obtained (20.0%). LC/MS rt-min (MH^+): 2.68 (743) [method B]. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.02 (m, 11 H) 1.20 (m, 11 H) 1.42 (m, 1 H) 1.49 (d, $J=6$ Hz, 6 H) 1.87 (dd, $J=7.95, 5.50$ Hz, 1 H) 2.21 (m, 1 H) 2.23 (m, 1 H) 2.66 (m, 1 H) 2.93 (m, 1 H) 4.08 (q, $J=7.09$ Hz, 1 H) 4.19 (s, 1 H) 4.55 (m, 2 H) 5.11 (d, $J=10.27$ Hz, 1 H) 5.28 (d, $J=17.61$ Hz, 1 H) 5.48 (m, 1 H) 5.70 (d, $J=10.03$ Hz, 1 H) 5.81 (m, 1 H) 7.90 (m, 2 H) 8.16 (m, 2 H).

Example 200: Preparation of Compound 200

20

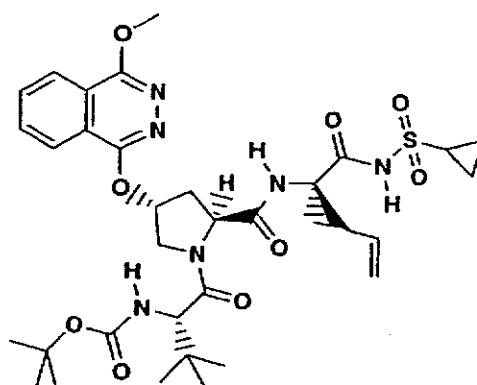
Likewise, the 4-ethoxy derivative was prepared: BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(4-ethoxyphthalazine-1-oxo)-*S*-proline]-P1(1*R*,2*S* VinylAcce)-CONHSO₂Cyclopropane.



4.0 mg of yellow solid was obtained (16.0%).LC/MS rt-min (MH^+): 2.52 (729)

[method B]. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.01 (s, 9 H) 1.06 (m, 2 H) 1.16 (s, 9 H) 1.24 (m, 2 H) 1.43 (dd, $J=9.78, 5.14$ Hz, 1 H) 1.53 (t, $J=6.97$ Hz, 3 H) 1.87 (dd, $J=8.19, 5.50$ Hz, 1 H) 2.22 (q, $J=8.97$ Hz, 1 H) 2.32 (m, 1 H) 2.67 (m, 1 H) 2.93 (m, 1 H) 4.06 (d, $J=8.56$ Hz, 1 H) 4.19 (s, 1 H) 4.56 (m, 4 H) 5.10 (m, 1 H) 5.30 (m, 1 H) 5.74 (m, 1 H) 5.82 (s, 1 H) 7.94 (m, 2 H) 8.16 (d, $J=7.83$ Hz, 1 H) 8.21 (m, 1 H).

10 Example 201: Preparation of Compound 201

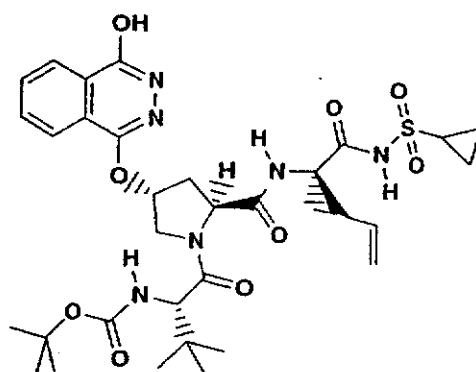


BOCNH-P3(*L*-*t*-BuGly)-P2[(4R)-(4-methoxyphthalazine-1-oxo)-S-proline]-P1(1R,2S VinylAcce)-CONHSO₂Cyclopropane was prepared in 30.2% yield. LC/MS rt-min (MH^+): 2.42 (715) [method B] ^1H NMR (400 MHz, CD_3OD) δ ppm 0.96 (s, 9 H) 1.07 (m, 2 H) 1.20 (m, 11 H) 1.43 (dd, $J=9.29, 5.38$ Hz, 1 H) 1.87 (dd, $J=8.07, 5.62$ Hz, 1 H) 2.22 (q, $J=8.80$ Hz, 1 H) 2.31 (m, 1 H) 2.66 (d, $J=8.07$ Hz, 1 H) 2.93 (m, 1

H) 4.06 (dd, $J=11.98, 3.18$ Hz, 1 H) 4.19 (d, $J=3.42$ Hz, 4 H) 4.54 (m, 2 H) 5.11 (m, 1 H) 5.28 (d, $J=17.36$ Hz, 1 H) 5.73 (m, 1 H) 5.83 (s, 1 H) 7.95 (m, 2 H) 8.19 (m, 2 H).

5 Example 202: Preparation of Compound 202

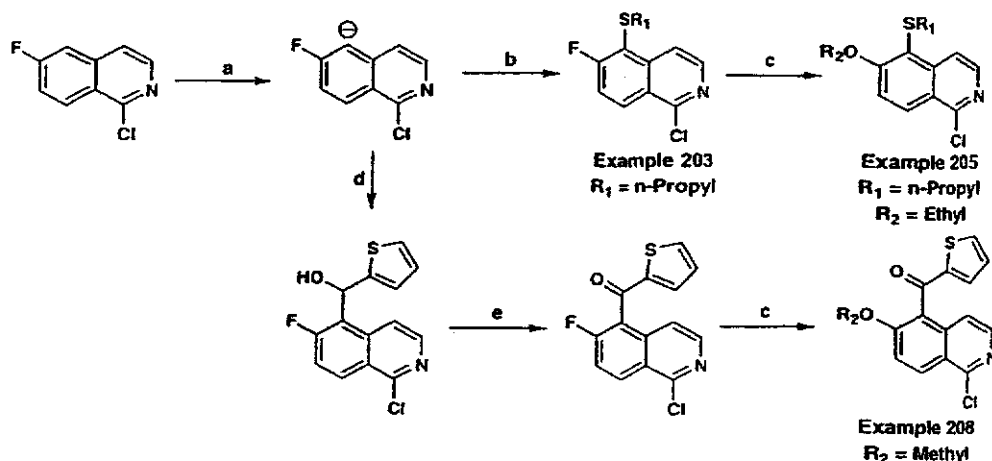
An attempt was made to displace BOCNH-P3(*L-tert*-BuGly)-P2[(4*R*)-(4-chloro phthalazine-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane (Example 195) with the sodium salt of tetrazole gave mostly the 4-hydroxy, hydrolyzed material.



BOCNH-P3(*L-tert*-BuGly)-P2[(4*R*)-(4-hydroxyphthalazine-1-oxo)-*S*-proline]
 15 P1(1*R*,2*S* VinylAcca)-CONHSO₂Cyclopropane was obtained (44.2%) as a pale
 creamy solid. LC/MS rt-min (MH⁺): 2.18 (701) [method B]. ¹H NMR (400 MHz,
 CD₃OD) δ ppm 1.01 (s, 9 H) 1.05 (m, 2 H) 1.23 (m, 11 H) 1.42 (dd, $J=9.29, 5.38$ Hz,
 1 H) 1.87 (dd, $J=8.07, 5.38$ Hz, 1 H) 2.21 (m, 2 H) 2.63 (m, 1 H) 2.93 (m, 1 H) 4.00
 (s, 1 H) 4.20 (s, 1 H) 4.50 (m, 2 H) 5.11 (dd, $J=10.27, 1.47$ Hz, 1 H) 5.29 (d, $J=16.87$
 20 Hz, 1 H) 5.59 (s, 1 H) 5.73 (m, 1 H) 7.86 (dd, $J=5.75, 3.30$ Hz, 2 H) 8.01 (dd, $J=5.87,$
 3.42 Hz, 1 H) 8.29 (dd, $J=5.87, 3.42$ Hz, 1 H).

Preparation of 5,6-disubstituted isoquinoline P2* derivatives via an alkylation
 protocol.

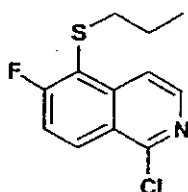
General Synthetic Scheme



- 5 Reaction Conditions: (a) LDA in THF; (b) Alkyl disulfide such as (n-PrS)₂; (c) Sodium alkoxide such as MeONa; (d) Thiophene 2-carboxaldehyde; (e) MnO₂ in benzene

Example 203: Preparation of 1-chloro-5-propylthio-6-fluoro isoquinoline:

10



- 15 To a chilled (-78 °C) solution of 1-chloro-6-fluoro isoquinoline (59mg, 0.32 mmol) in 2 mL of THF was added LDA solution in cyclohexane (1.5 Molar, 0.23 mL, 0.35 mmol). The orange solution was stirred for 2 hrs before it was treated with n-propyl disulfide (60 µL, neat material, excess). The reaction was allowed to warm to room temperature over 30 min. It was quenched with a solution of half saturated NH₄Cl, the organic residues were extracted into ethyl acetate. LC-MS analysis indicated

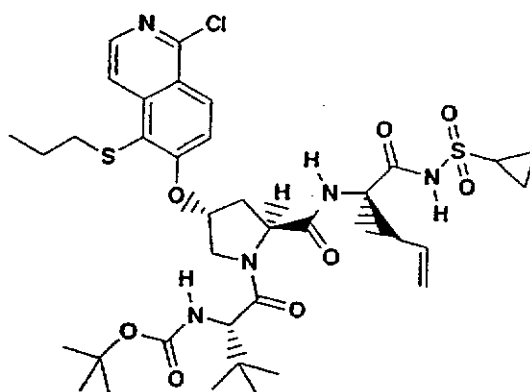
about 50% conversion into the desired product along with mainly starting material.

The desired product was purified by a short column (4 cm X 2 cm, silica gel type-H) eluted with 5% ether in hexanes, 29mg (36% yield) of the desired product was obtained. LC/MS R_t -min (MH^+) [method C]: 3.79 (256). ^1H NMR (400 MHz,

- 5 CHLOROFORM-D) δ ppm 0.96 (t, $J=7.34$ Hz, 3 H) 1.52 (m, 2 H) 2.86 (m, 2 H) 7.45 (dd, $J=9.29, 8.56$ Hz, 1 H) 8.34 (d, $J=0.73$ Hz, 2 H) 8.37 (m, 1 H). This compound was alkylated with the tripeptide by way of the procedure described in **Example 184** to give the following compound:

10 **Example 204: Preparation of Compound 204**

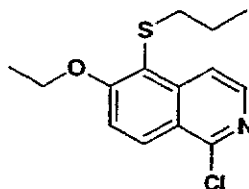
BOCNH-P3(*L*-*t*-BuGly)-P2[(4R)-(1-Chloro-5-propylthio-isoquinolin-6-oxo)-S-proline]-P1(1R,2S VinylAcce)-CONHSO₂Cyclopropane, Shown below



15

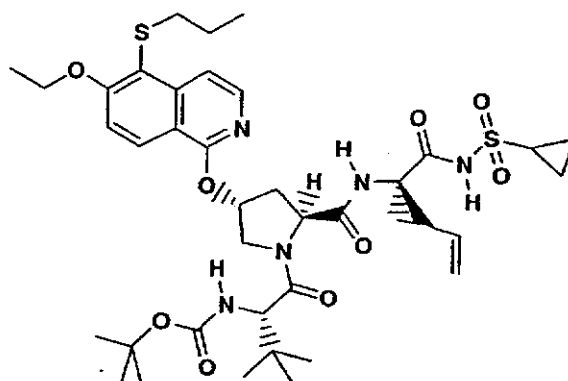
- Following the general procedure, 4.6 mg of yellow solid was obtained (3.2%). LC/MS R_t -min (MH^+): 2.73 (792) (method B). ^1H NMR (400 MHz, CD₃OD) δ ppm 0.93 (t, $J=7.34$ Hz, 3 H) 0.97 (s, 9 H) 1.08 (m, 2 H) 1.24 (m, 11 H) 1.43 (m, 3 H) 1.86 (m, 1 H) 2.24 (m, 2 H) 2.56 (m, 1 H) 2.78 (q, $J=7.09$ Hz, 2 H) 2.92 (m, 1 H) 4.01 (d, $J=9.29$ Hz, 1 H) 4.22 (s, 1 H) 4.29 (s, 1 H) 4.59 (d, $J=6.85$ Hz, 1 H) 5.11 (d, $J=10.76$ Hz, 1 H) 5.28 (d, $J=17.36$ Hz, 1 H) 5.49 (s, 1 H) 5.74 (m, 1 H) 7.66 (d, $J=9.29$ Hz, 1 H) 8.18 (d, $J=6.11$ Hz, 1 H) 8.41 (m, 2 H).
- 20

Example 205: Preparation of 5-propylthio-6-ethoxy isoquinoline P2* derivatives.



- 5 The following procedure is equally applicable to other 5-alkylthio-6-alkoxy isoquinolines by changing the reagents shown here. To a solution of 1-chloro-6-fluoro isoquinoline (88mg, 0.48 mmol) in 2.0 mL THF under nitrogen at -78°C was added LDA (1.5 Molar in cyclohexane, 0.42 mL, 0.63 mmol) forming a dark
- 10 brownish solution. Neat n-propyl disulfide (85 μL , excess) was introduced after it was stirred at -78°C for 30 min. The reaction was allowed to warm to room temperature over a period of 30 min. It was quenched with a solution of half saturated NH_4Cl , the organic residues were extracted into ethyl acetate. The organic layers were combined and dried under vacuum to 50 microns(Hg). The crude product was
- 15 taken into 2 mL of THF, cooled to -78°C , added with excess potassium ethoxide (60mg). The isoquinoline intermediate was finally purified by a silica gel column (type-H, Merck) eluted with ether-hexanes mixture, 32.2mg (24%) of the pure compound was obtained. LC-MS showed 1-chloro-5-propylthio-6-ethoxyl isoquinoline at rt-min (MH^+) [method C]: 3.77 (282). ^1H NMR (400 MHz,
- 20 CHLOROFORM-D) δ ppm 0.94 (t, $J=7.34$ Hz, 3 H) 1.46 (m, 2 H) 1.55 (t, $J=6.97$ Hz, 3 H) 2.83 (t, $J=7.21$ Hz, 2 H) 4.32 (q, $J=6.85$ Hz, 2 H) 7.36 (d, $J=9.29$ Hz, 1 H) 8.22 (d, $J=6.11$ Hz, 1 H) 8.32 (d, $J=9.29$ Hz, 1 H) 8.35 (d, $J=6.11$ Hz, 1 H). Following the general tripeptide alkylation procedure (Example 184), this 1-chloro-5-propylthio-6-ethoxy isoquinoline was alkylated with the tripeptide (compound
- 25 184) to give 40.7 mg (44.8%) of the desired product shown below.

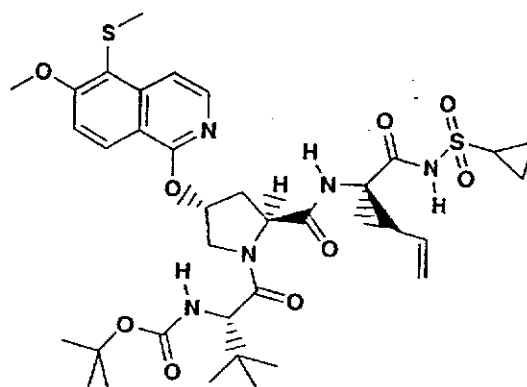
Example 206: Preparation of Compound 206



- BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(6-ethoxy-5-propylthio-isoquinoline-1-oxo)-*S*-proline]-P1(1*R*,2*S* VinylAcca)-CONHSO₂Cyclopropane. LC/MS *rt*-min (*MH*⁺): 2.93
- 5 (803) [method B]. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.93 (t, *J*=7.34 Hz, 3 H) 1.01 (s, 9 H) 1.07 (m, 2 H) 1.21 (m, 11 H) 1.41 (m, 3 H) 1.48 (t, *J*=6.85 Hz, 3 H) 1.86 (dd, *J*=8.07, 5.62 Hz, 1 H) 2.25 (m, 2 H) 2.60 (dd, *J*=13.69, 6.85 Hz, 1 H) 2.81 (q, *J*=6.97 Hz, 2 H) 2.93 (m, 1 H) 4.05 (m, 1 H) 4.21 (s, 1 H) 4.27 (q, *J*=7.09 Hz, 2 H) 4.43 (d, *J*=11.74 Hz, 1 H) 4.52 (m, 1 H) 5.10 (d, *J*=10.76 Hz, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H)
- 10 5.74 (m, 1 H) 5.82 (s, 1 H) 7.30 (d, *J*=9.05 Hz, 1 H) 7.92 (d, *J*=6.36 Hz, 1 H) 7.97 (m, 1 H) 8.22 (d, *J*=9.05 Hz, 1 H).

Example 207: Preparation of Compound 207

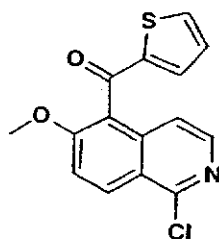
- 15 Likewise the same procedure was applied to the preparation of BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(6-methoxy-5-methylthio-isoquinolin-1-oxo)-*S*-proline]-P1(1*R*,2*S* VinylAcca)-CONHSO₂Cyclopropane.



To the solution of 100 mg 1-Chloro-6-fluoro-isoquinoline (0.55 mmole) in 2 ml dry THF at -78°C was added LDA in THF (1.3 eq). Dark brown solution was formed, then disulfide was added and the color of solution changed to greenish, then light
5 brown. The reaction was quenched with 2 mL of water and 2 mL of NH_4Cl , extracted with ethyl acetate, dried over sodium sulfate. The solvent was evaporated under vacuum and the resulted residue was used as crude. LC/MS rt-min (MH^+): 2.23 (228) [method B]. The crude material was redissolved in 2 ml of dry THF at -78°C and 1.3 eq. of KOMe was added then the reaction mixture was allowed to warmed up to RT,
10 stirred overnight. The reaction mixture was diluted with ethyl acetate and washed with brine, dried over sodium sulfate. 104 mg was obtained (79%). LC/MS rt-min (MH^+): 2.04 (240) [method B]. The intermediate, 1-chloro-5-methylthio-6-methoxy isoquinoline was subjected to the tripeptide alkylation protocol described previously. Following the general procedure, 70.0 mg of yellow solid was obtained (42.7%).
15 LC/MS rt-min (MH^+): 2.65 (760) [method B]. ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.94 (m, 11 H) 1.17 (s, 9 H) 1.26 (m, 2 H) 1.39 (m, 1 H) 1.83 (dd, $J=8.07, 5.62$ Hz, 1 H) 2.01 (m, 2 H) 2.23 (s, 3 H) 2.45 (m, 1 H) 2.79 (m, 1 H) 3.94 (s, 3 H) 3.97 (d, $J=3.91$ Hz, 1 H) 4.15 (s, 1 H) 4.25 (d, $J=11.74$ Hz, 1 H) 4.36 (dd, $J=9.66, 7.21$ Hz, 1 H) 4.99 (d, $J=10.27$ Hz, 1 H) 5.12 (d, $J=16.87$ Hz, 1 H) 5.69
20 (m, 1 H) 5.74 (s, 1 H) 7.08 (d, $J=9.05$ Hz, 1 H) 7.83 (m, 2 H) 8.06 (d, $J=9.05$ Hz, 1 H).

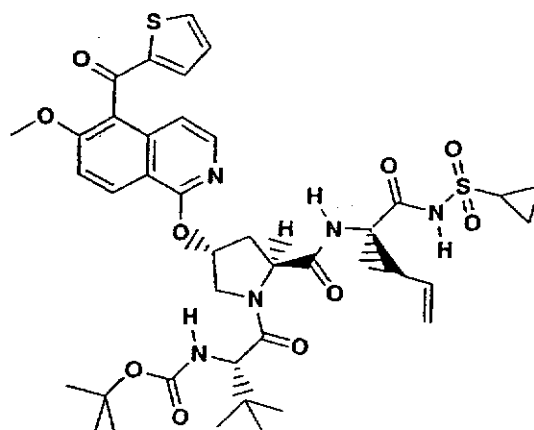
Example 208: Preparation of 1-chloro-6-methoxy-isoquinolin-5-yl-thiophen-2-yl-methanone

25



Following the same LDA deprotonation protocol (preparation of **Example 203**) of 1-chloro-6-fluoro isoquinoline described previously, the initial anion was quenched with 2-thiophenecarboxaldehyde instead, to give 1-chloro-6-fluoro isoquinolin-5-yl-thiophen-2-yl-methanol. The material was oxidized to the 1-chloro-6-fluoro-isoquinolin-5-yl-thiophen-2-yl-methanone using MnO_2 in benzene in 49.6% overall yield after chromatographic purification. LC/MS rt-min (MH^+) [method C]: 2.98 (292). ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 7.12 (dd, $J=4.89, 3.91$ Hz, 1 H) 7.40 (m, 1 H) 7.53 (m, 1 H) 7.56 (dd, $J=5.87, 0.73$ Hz, 1 H) 7.82 (dd, $J=5.01, 1.10$ Hz, 1 H) 8.27 (d, $J=5.87$ Hz, 1 H) 8.54 (ddd, $J=9.29, 5.38, 0.73$ Hz, 1 H). Ipso nucleophilic aromatic displacement of the fluorine atom was accomplished in a solution of excess of potassium methoxide to give, mainly 1-chloro-6-methoxy-isoquinolin-5-yl-thiophen-2-yl-methanone along with 25-33% of 1,6-dimethoxy-isoquinolin-5-yl-thiophen-2-yl-methanone. The crude material (77mg) was used in the alkylation step with the tripeptide without further purification.

Example 209: Preparation of Compound 209



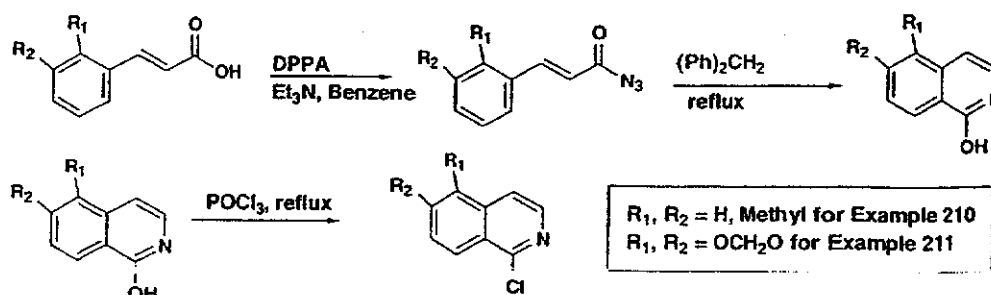
Following the general procedure of tripeptide alkylation (**Example 184**), 35.3 mg of $\text{BOC-NH-P3(L-}t\text{-BuGly)-P2[(4R)-6-methoxy-5-(thiophene-2-carbonyl)-isoquinoline-1-oxo-S-proline]-P1(1R,2S VinylAcce)-CONHSO}_2\text{Cyclopropane}$ was obtained as pale solid (26.5%). LC/MS rt-min (MH^+): 2.54 (825) [method B]. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.02 (s, 9 H) 1.06 (m, 2 H) 1.22 (m, 2 H) 1.26 (s, 9 H) 1.43

(m, 1 H) 1.87 (dd, $J=7.95, 5.50$ Hz, 1 H) 2.28 (m, 2 H) 2.62 (dd, $J=13.82, 6.97$ Hz, 1 H) 2.93 (m, 1 H) 3.90 (s, 3 H) 4.07 (dd, $J=11.62, 3.06$ Hz, 1 H) 4.23 (s, 1 H) 4.43 (m, 1 H) 4.55 (dd, $J=9.78, 7.34$ Hz, 1 H) 5.09 (m, 1 H) 5.29 (d, $J=17.12$ Hz, 1 H) 5.74 (m, 1 H) 5.86 (s, 1 H) 6.93 (d, $J=6.11$ Hz, 1 H) 7.11 (m, 1 H) 7.32 (dd, $J=3.91, 0.98$ Hz, 1 H) 7.46 (d, $J=9.29$ Hz, 1 H) 7.86 (t, $J=6.72$ Hz, 1 H) 7.91 (dd, $J=4.89, 1.22$ Hz, 1 H) 8.39 (d, $J=9.29$ Hz, 1 H).

Preparation of P2* by way of cinnamic acid derivatives. The general procedure depicted below has been described extensively elsewhere.

10

General Synthetic Scheme

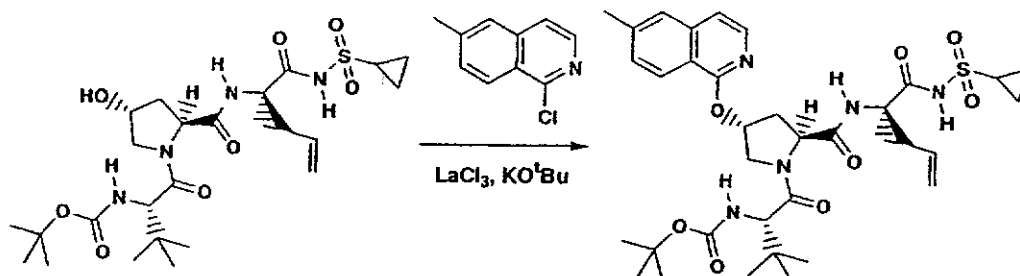


Example 210: Preparation of Compound 210

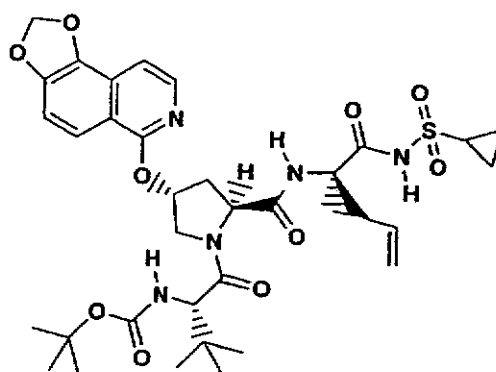
15

10.0 g of meta-tolyl-acrylic acid (61.7 mmole) was suspended in 50 ml of benzene , 12.6 mL of DPPA (0.95 eq) was added followed by 10.3 ml of triethylamine (1.2 eq). The resulted solution was stirred at room temperature for 1 hr. The volatile was removed under vacuum and the meta-tolyl-acryloyl azide was purified by flash chromatograph to yield 11.5 g of pure compound (quantitative). This material, in 100 mL of diphenylmethane, was introduced dropwise into 100 ml of diphenylmethane previously heated up to 200 °C over a period of an hr. The resulted solution was kept at this temperature for another 4 hour then cooled down to room temp.. White precipitate was formed, it was filtered off. The solid was washed with hexanes three times and dried. The filtrate was diluted with 200 ml of hexanes, the solution was left

standing overnight to allow for separation of the second crop. The materials were combined to give 4.2 g of 6-methyl-isoquinolin-1-ol (50%). LC/MS r_t -min (MH^+): 1.31 (160) [method B]. ^1H NMR (400 MHz, CD_3OD) δ ppm 2.49 (s, 3 H) 6.61 (d, $J=7.32$ Hz, 1 H) 7.13 (d, $J=7.02$ Hz, 1 H) 7.36 (d, $J=8.24$ Hz, 1 H) 7.45 (s, 1 H) 8.18 (d, $J=8.24$ Hz, 1 H). The material was suspended in 15 ml of $POCl_3$ and brought to reflux for 3 hours. After removal of the $POCl_3$ in vacuo, the residue was partitioned between EtOAc (1L), and cold aqueous NaOH (generated from 1.0N 200 mL NaOH and 20 mL 10.0 N NaOH) and stirred for 15 min. The organic layer was washed with water (2 x 200 mL), brine (200 mL), dried ($MgSO_4$), and concentrated in vacuo to supply 1-chloro-6-methyl-isoquinoline (67.4%). LC/MS r_t -min (MH^+): 1.92 (178) [method B]. ^1H NMR (400 MHz, $CHLOROFORM-D$) δ ppm 2.53 (s, 3 H) 7.47 (d, $J=6.11$ Hz, 2 H) 7.56 (s, 1 H) 8.18 (m, 2 H). The final alkylation of 1-chloro-6-methyl-isoquinoline with the tripeptide was carried out using the protocol described previously (Example 184).

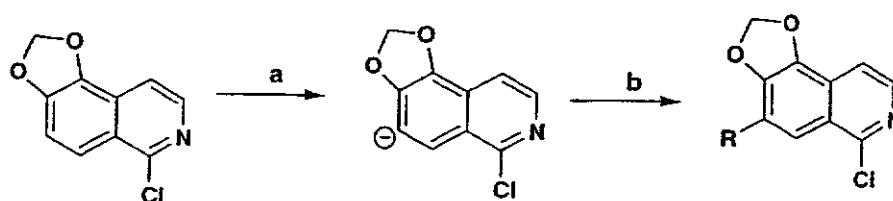


BOCNH-P3(*L*-*tert*-BuGly)-P2[(4*R*)-(6-methyl isoquinolin-1-oxo)-*S*-proline]-P1(1*R*,2*S* Vinyl Acca)-CONHSO₂-Cyclopropane: the material was obtained as a white foam in 18% yield. LC/MS R_t -min (MNa^+) [method B]: 2.64 (720). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.05 (m, 13 H) 1.23 (m, 9 H) 1.42 (m, 1 H) 1.86 (dd, $J=7.95, 5.50$ Hz, 1 H) 2.25 (m, 2 H) 2.49 (s, 3 H) 2.61 (dd, $J=13.82, 6.48$ Hz, 1 H) 2.93 (m, 1 H) 4.05 (dd, $J=11.86, 3.30$ Hz, 1 H) 4.23 (s, 1 H) 4.43 (d, $J=11.49$ Hz, 1 H) 4.52 (m, 1 H) 5.10 (d, $J=11.49$ Hz, 1 H) 5.28 (d, $J=17.12$ Hz, 1 H) 5.74 (m, 1 H) 5.83 (s, 1 H) 7.24 (d, $J=5.87$ Hz, 1 H) 7.35 (d, $J=8.07$ Hz, 1 H) 7.58 (s, 1 H) 7.89 (d, $J=5.87$ Hz, 1 H) 8.07 (d, $J=8.56$ Hz, 1 H).

Example 211: Preparation of Compound 211

- 5 Following the general procedure described previously, BOCNH-P3(*L*-*t*-BuGly)-
 P2[(4R)-(1,3-Dioxo-7-aza-cyclopenta[a]naphthalen-6-yl)-S-proline]-P1(1*R*,2*S*
 VinylAcce)-CONHSO₂Cyclopropane, 51.0 mg was obtained as a pale solid
 (64.9%). LC/MS rt-min (MH⁺): 2.57 (728) [method B]. ¹H NMR (400 MHz, CD₃OD)
 δ ppm 0.99 (s, 9 H) 1.07 (m, 2 H) 1.18 (m, 11 H) 1.42 (m, 1 H) 1.86 (dd, *J*=8.07,
 10 5.62 Hz, 1 H) 2.23 (m, 2 H) 2.59 (dd, *J*=13.69, 6.85 Hz, 1 H) 2.93 (m, 1 H) 4.04 (dd,
J=11.74, 2.20 Hz, 1 H) 4.22 (s, 1 H) 4.43 (d, *J*=11.74 Hz, 1 H) 4.51 (m, 1 H) 5.10 (d,
J=10.27 Hz, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.73 (m, 1 H) 5.82 (s, 1 H) 6.18 (s, 2 H)
 7.13 (d, *J*=8.56 Hz, 1 H) 7.19 (d, *J*=6.11 Hz, 1 H) 7.81 (d, *J*=8.56 Hz, 1 H) 7.85 (d,
J=6.11 Hz, 1 H).

15

Preparation of 5,6,7-trisubstituted isoquinoline P2* derivatives:

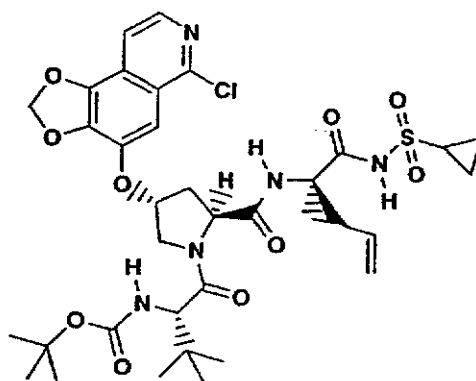
- 20 Reaction Conditions: (a) LDA in THF; (b) N-fluorobenzenesulfonimide (NFSI) for R
 = F, or dimethyl sulfide (MeS)₂, for R = SMe.

The 5,6-methylenedioxy-1-chloroisoquinoline prepared above was deprotonated directly in the presence of strong base such as LDA to provide the corresponding 7-anion without interfering with the 1-chloro functionality. The 7-anion was quenched with electrophiles such as NFSI (N-fluorobenzenesulfonimide) and dimethylsulfide to produce the corresponding 7-substituted isoquinoline ring system.

Example 212: Preparation of Compound 212

Step 1:

- 10 Preparation of 5,6-methylenedioxy-7-fluoro-1-chloro isoquinoline. To a solution of 5,6-methylenedioxy-1-chloro isoquinoline (126mg, 0.61 mmol) in 4 mL of THF under nitrogen at -78°C was added LDA solution in cyclohexane (1.5 Molar, 0.65 mL, 0.98 mmol). The light brownish solution was stirred for 15 min before it was treated with N-fluorobenzenesulfonimide (NFSI, 0.3g, 1.5 equivalents).
- 15 TLC analysis showed the formation of a new spot, in addition of the unchanged starting material. Aqueous work up followed by extractions with ethyl acetate furnished an oily crude product which was purified by preparative HPLC to give 52mg (38%). LC/MS rt-min (MH^+) [method C]: 3.09 (226). ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 6.33 (s, 2 H) 7.52 (d, $J=5.87$ Hz, 1 H) 7.71 (d, $J=10.51$ Hz, 1 H) 8.16 (d, $J=5.87$ Hz, 1 H). Step 2: The alkylation of 5,6-methylenedioxy-7-fluoro-1-chloro isoquinoline with the tripeptide was carried out as described previously (Example 184) to provide the major product as a result of fluorine displacement.
- 25 BOCNH-P3(*L*-*t*-BuGly)-P2[(4R)-(6-Chloro-1,3-dioxo-7-aza-cyclopenta[*a*]naphthalen-4-oxo)-S-proline]-PI(1*R*,2*S* VinylAcce)-CONHSO₂Cyclopropane, Shown below



Following the general procedure, 24.3 mg of yellow solid was obtained (24.3%). LC/MS rt-min (MH^+): 2.54 (763) [method B]. ^1H NMR (400 MHz, CD_3OD)

5 δ ppm 1.00 (s, 9 H) 1.06 (m, 2 H) 1.20 (m, 2 H) 1.29 (s, 9 H) 1.42 (dd, $J=9.41, 5.26$ Hz, 1 H) 1.86 (dd, $J=8.07, 5.38$ Hz, 1 H) 2.24 (m, 2 H) 2.54 (dd, $J=13.57, 6.48$ Hz, 1 H) 2.92 (m, 1 H) 4.04 (dd, $J=12.10, 2.81$ Hz, 1 H) 4.20 (d, $J=7.34$ Hz, 1 H) 4.33 (d, $J=12.23$ Hz, 1 H) 4.47 (dd, $J=10.52, 6.85$ Hz, 1 H) 5.10 (dd, $J=10.39, 1.59$ Hz, 1 H) 5.28 (dd, $J=17.12, 1.22$ Hz, 1 H) 5.46 (d, $J=5.87$ Hz, 1 H) 5.74 (m, 1 H) 6.29 (m, 2

10 H) 7.40 (s, 1 H) 7.56 (m, 1 H) 8.01 (d, $J=5.62$ Hz, 1 H).

Example 213: Preparation of Compound 213

To a solution of 5,6-methylenedioxy-1-chloro isoquinoline (84mg, 0.41 mmol) in 4

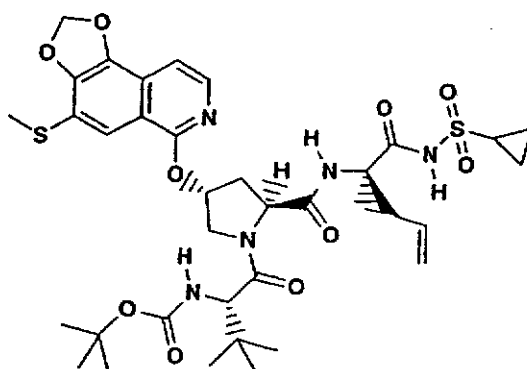
15 mL of THF under nitrogen at $-78^\circ C$ was added LDA solution in cyclohexane (1.5 Molar, 0.60 mL, 0.9 mmol). The light brownish solution was stirred for 15 min at $-78^\circ C$ before it was treated with methyl disulfide (50 μL of neat reagent, 1.4 equivalents). TLC analysis showed the formation of a new spot, in addition of the unchanged starting material. Aqueous work up followed by extractions with ethyl

20 acetate furnished an oily crude product which was purified by preparative HPLC to give 51mg (49%). LC/MS rt-min (MH^+) [method C]: 3.39 (254). ^1H NMR (400 MHz, $CHLOROFORM-D$) δ ppm 2.64 (s, 3 H) 6.29 (s, 2 H) 7.49 (d, $J=4.89$ Hz, 1 H) 7.71 (s, 1 H) 8.11 (d, $J=5.87$ Hz, 1 H). The alkylation of 5,6-methylenedioxy-7-methylthio-1-chloro isoquinoline with the tripeptide was carried out as described

25 previously (Example 184) to provide the desired product shown below:

BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(4-methylthio-1,3-dioxo-7-aza-cyclopenta[*a*]naphthalen-6-yloxy)-*S*-proline]-P1(1*R*,2*S* VinylAcce)-CONHSO₂Cyclopropane

5



Following the general procedure, 59.6 mg of yellow solid was obtained

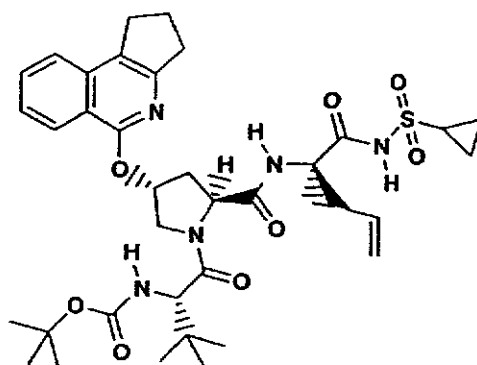
(42.2%).LC/MS rt-min (MH⁺): 2.70 (774) [method B]. ¹H NMR (400 MHz,

10 CHLOROFORM-D) δ ppm 1.02 (m, 11 H) 1.16 (s, 9 H) 1.32 (s, 2 H) 1.45 (m, 1 H) 1.94 (m, 1 H) 2.12 (d, *J*=8.56 Hz, 1 H) 2.56 (s, 3 H) 2.62 (m, 2 H) 2.90 (d, *J*=4.40 Hz, 1 H) 4.15 (d, *J*=7.83 Hz, 2 H) 4.48 (d, *J*=12.47 Hz, 1 H) 4.62 (t, *J*=7.83 Hz, 1 H) 5.13 (d, *J*=10.52 Hz, 1 H) 5.26 (d, *J*=17.12 Hz, 1 H) 5.74 (d, *J*=16.38 Hz, 1 H) 5.95 (s, 1 H) 6.28 (s, 2 H) 7.41 (s, 1 H) 7.59 (s, 1 H) 7.85 (d, *J*=6.11 Hz, 1 H).

15

Preparation of 3,4-disubstituted isoquinoline P2* derivatives

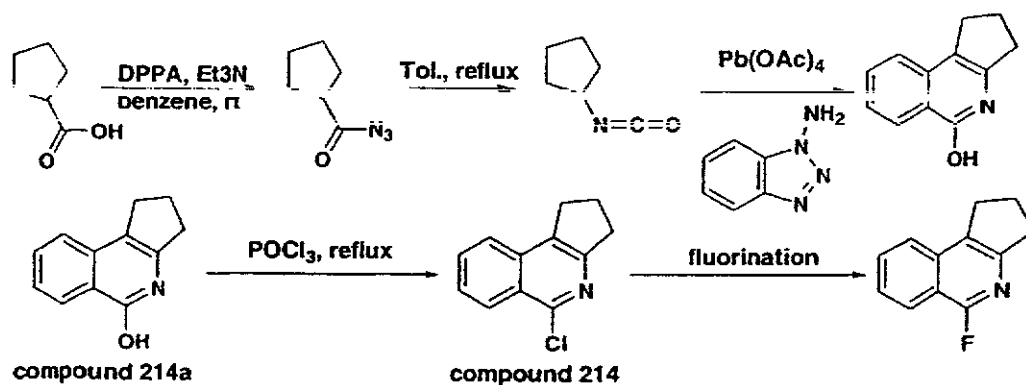
Example 215: Preparation of Compound 215



Example 215

BOCNH-P3(*L*-*t*-BuGly)-P2[(1*R*)-(2,3-dihydro-1*H*-4-aza-cyclopenta[*a*]naphthalen-5-yloxy)-*S*-proline]-P1(1*R*,2*S* VinylAcce)-CONHSO₂Cyclopropane, shown below was prepared as depicted in the following scheme:

General Synthetic Scheme of the isoquinoline component **compound 214**



10

Notes:

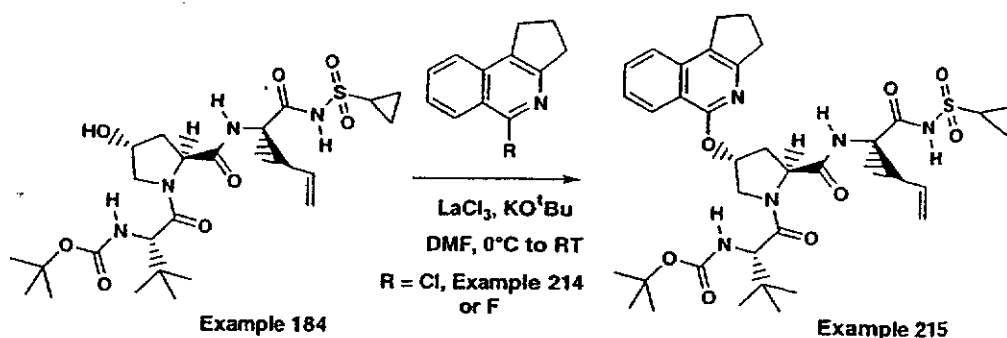
The synthesis of the novel 1-fluoro P2* was made successful by the technologies cited below:

(1) Rigby, James H.; Holsworth, Daniel D.; James, Kelly. Vinyl Isocyanates In Synthesis. [4 + 2] Cycloaddition Reactions With Benzyne Addends.

5 *Journal Of Organic Chemistry* (1989), 54(17), 4019-20

(2) Uchibori, Y.; Umeno, M.; Yoshiokai, H.; *Heterocycles*, 1992, 34 (8), 1507-1510

10 **Example 214: Preparation of Compounds 214, 5-chloro-2,3-dihydro-1H-4-aza-cyclopenta[*a*]naphthalene, and Compound 215 of Example 215**



2,3-Dihydro-1H-4-aza-cyclopenta[*a*]naphthalen-5-ol was prepared in accordance to
 15 the method of Rigby described in (reference 1) cited above. Using POCl₃ as
 described elsewhere, **Compound 214**, was synthesized in 59.8% (430mg). LC/MS rt-
 min (MH⁺): 2.29 (204) [method B]. ¹H NMR (400 MHz, CHLOROFORM-D) □ ppm
 2.28 (m, 2 H) 3.19 (q, *J*=7.74 Hz, 4 H) 7.58 (m, 1 H) 7.71 (m, 2 H) 8.32 (d, *J*=8.56
 Hz, 1 H). The chloride is sufficiently reactive to be alkylated with the tripeptide
 20 according to the procedure of **Example 184**, to give the desired product **Compound**
215. However the overall yield could be doubled if the chloride was exchanged into
 the fluoride by the method of Uchibori described in (reference 2). Thus 17.0 mg of
Compound 215, isolated as a pale yellow solid (23.6%). LC/MS rt-min (MH⁺): 2.80
 (724) [method B]. ¹H NMR (500 MHz, CD₃OD) δ ppm 1.03 (s, 9 H) 1.09 (m, 2 H)
 25 1.24 (m, 11 H) 1.44 (dd, *J*=8.24, 5.49 Hz, 1 H) 1.88 (dd, *J*=7.93, 5.49 Hz, 1 H) 2.25
 (m, 4 H) 2.63 (dd, *J*=13.73, 7.02 Hz, 1 H) 2.94 (m, 1 H) 3.05 (m, 2 H) 3.10 (m, 2 H)

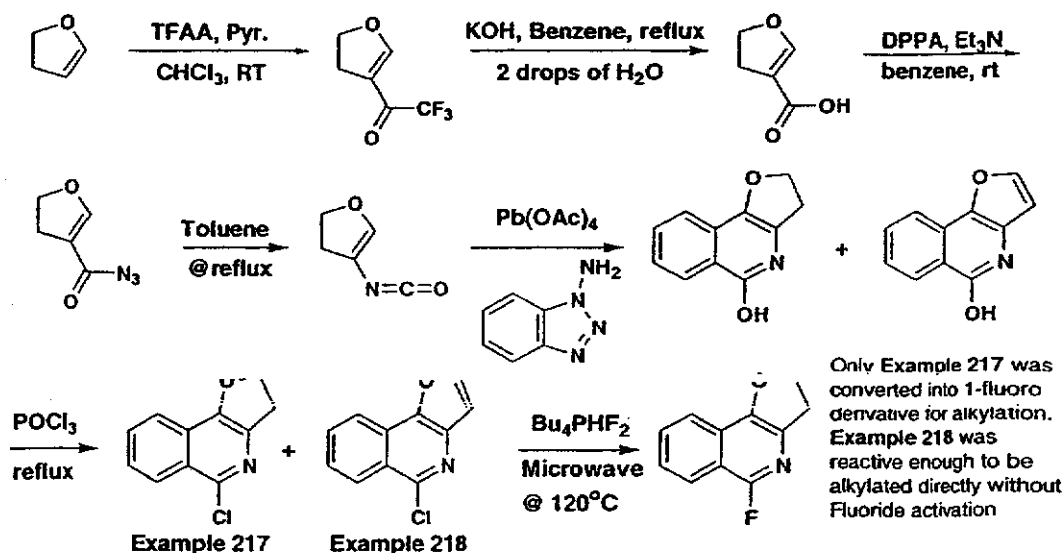
4.08 (dd, $J=11.60, 2.75$ Hz, 1 H) 4.24 (d, $J=20.45$ Hz, 1 H) 4.45 (d, $J=11.90$ Hz, 1 H) 4.54 (dd, $J=9.46, 7.63$ Hz, 1 H) 5.11 (m, 1 H) 5.30 (d, $J=17.09$ Hz, 1 H) 5.75 (m, 1 H) 5.87 (s, 1 H) 7.44 (t, $J=7.02$ Hz, 1 H) 7.69 (m, 2 H) 8.18 (d, $J=8.24$ Hz, 1 H).

5

Preparation of 3,4-dihydrofuranyl and furanyl isoquinoline P2* components, Examples 217 and 218,

General Synthetic Scheme

10



Example 217: Preparation of Compound 217, 5-chloro-2,3-dihydro-1-oxa-4-aza-cyclopenta[a]naphthalene and Compound 218, 5-chloro-1-oxa-4-aza-cyclopenta[a]naphthalene.

15

This synthesis made use of the technologies described, in part, in the following references:

20

(1) Hojo, Masaru; Masuda, Ryoichi; Sakaguchi, Syuhei; Takagawa, Makoto, *Synthesis* (1986), (12), 1016-17

(2) Rigby, James H.; Holsworth, Daniel D.; James, Kelly. Vinyl Isocyanates In Synthesis. [4 + 2] Cycloaddition Reactions With Benzyne Addends. *Journal Of Organic Chemistry* (1989), 54(17), 4019-20

- 5 (3) Uchibori, Y.; Umeno, M.; Yoshiokai, H.; *Heterocycles*, 1992, 34 (8), 1507-1510

Both 2,3-dihydro-1-oxa-4-aza-cyclopenta[*a*]naphthalen-5-ol and 1-oxa-4-aza-cyclopenta[*a*]naphthalen-5-ol were produced together when the procedures
10 (references 1 and 2) cited above were followed. Conversion of the pair into their chloro derivatives was accomplished by POCl₃ as usual: The crude hydroxy products (about 2g, pale yellow oil) was treated with 15 mL of POCl₃ and the mixture was brought to reflux for 3 hours. After removal of the POCl₃ in vacuo, the residue was stirred with EtOAc (1L), and cold aqueous NaOH (220 mL, 1.0 N) for 15 min. The
15 organic layer was separated, washed with water (2 x 200 mL), brine (200 mL), and dried over MgSO₄, and concentrated in vacuo to supply 300 mg of **Example 217**, 5-chloro-2,3-dihydro-1-oxa-4-aza-cyclopenta[*a*]naphthalene (13.2%) and 100 mg of **Example 218**, 5-chloro-1-oxa-4-aza cyclopenta[*a*]naphthalene (4.4%) as light brown solids after silica gel chromatographic separation. **Compound 217**: LC/MS rt-min
20 (MH⁺): 2.05 (206) [method B]. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 3.46 (t, *J*=9.05 Hz, 2 H) 4.82 (t, *J*=9.17 Hz, 2 H) 7.58 (m, 1 H) 7.66 (m, 1 H) 7.85 (d, *J*=8.31 Hz, 1 H) 8.21 (d, *J*=8.56 Hz, 1 H). **Compound 218**: LC/MS rt-min (MH⁺): 2.16 (204) [method B]. ¹H NMR (400 MHz, CHLOROFORM-D) □ ppm 7.15 (d, *J*=2.20 Hz, 1 H) 7.70 (m, 1 H) 7.89 (m, 2 H) 8.27 (d, *J*=8.31 Hz, 1 H) 8.44 (d, *J*=8.80
25 Hz, 1 H).

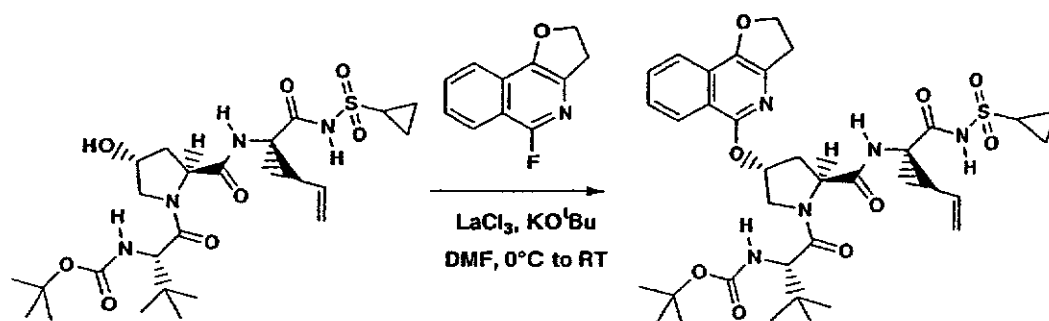
Preparation of 5-fluoro-2,3-dihydro-1-oxa-4-aza-cyclopenta[*a*]naphthalene, and final P2* coupling products.

- 30 The chloride/fluoride exchange was achieved by the method (reference 3) cited above. Thus 90 mg of 5-chloro-2,3-dihydro-1-oxa-4-aza-cyclopenta[*a*]naphthalene (**Example 217**) was suspended in 1.5 mL of Bu₄PHF₂ and was irradiated under

microwave (Smith Reactor) to about 120 °C for 2 hours. After aqueous work up and column purification, 22 mg of fluoride product was obtained (26.9%). LC/MS rt-min (MH⁺): 1.91 (190) [method B]. The furan derivative (Example 218), 5-chloro-1-oxa-4-aza-cyclopenta[*a*]naphthalene was sufficiently reactive to be alkylated with the

5 tripeptide directly without fluoride activation.

Example 219: Preparation of Compound 219



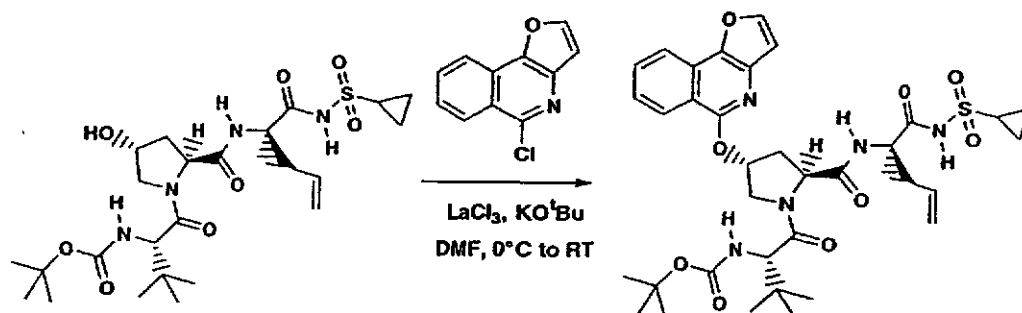
10 BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(2,3-dihydro-1-oxa-4-aza-cyclopenta[*a*]naphthalen-5-yloxy)-*S*-proline]-P1(1*R*,2*S* VinylAcce)-CONHSO₂Cyclopropane. Following the general alkylation procedure, 22.0 mg of yellow solid was obtained (26.3%) LC/MS

rt-min (MH⁺): 2.65 (726) [method B]. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.99 (s, 9 H) 1.07 (m, 2 H) 1.20 (m, 11 H) 1.40 (m, 1 H) 1.86 (dd, *J*=8.07, 5.62 Hz, 1 H) 2.21

15 (dd, *J*=17.48, 8.93 Hz, 2 H) 2.60 (dd, *J*=13.45, 6.85 Hz, 1 H) 2.93 (m, 1 H) 3.34 (m, 2 H) 4.04 (dd, *J*=11.74, 3.18 Hz, 1 H) 4.24 (s, 1 H) 4.41 (d, *J*=11.49 Hz, 1 H) 4.51 (m, 1 H) 4.74 (t, *J*=9.05 Hz, 2 H) 5.11 (d, *J*=10.27 Hz, 1 H) 5.28 (d, *J*=17.36 Hz, 1 H) 5.73 (m, 1 H) 5.78 (s, 1 H) 7.43 (m, 1 H) 7.65 (t, *J*=7.46 Hz, 1 H) 7.74 (d, *J*=8.31 Hz, 1 H) 8.12 (d, *J*=8.56 Hz, 1 H).

20

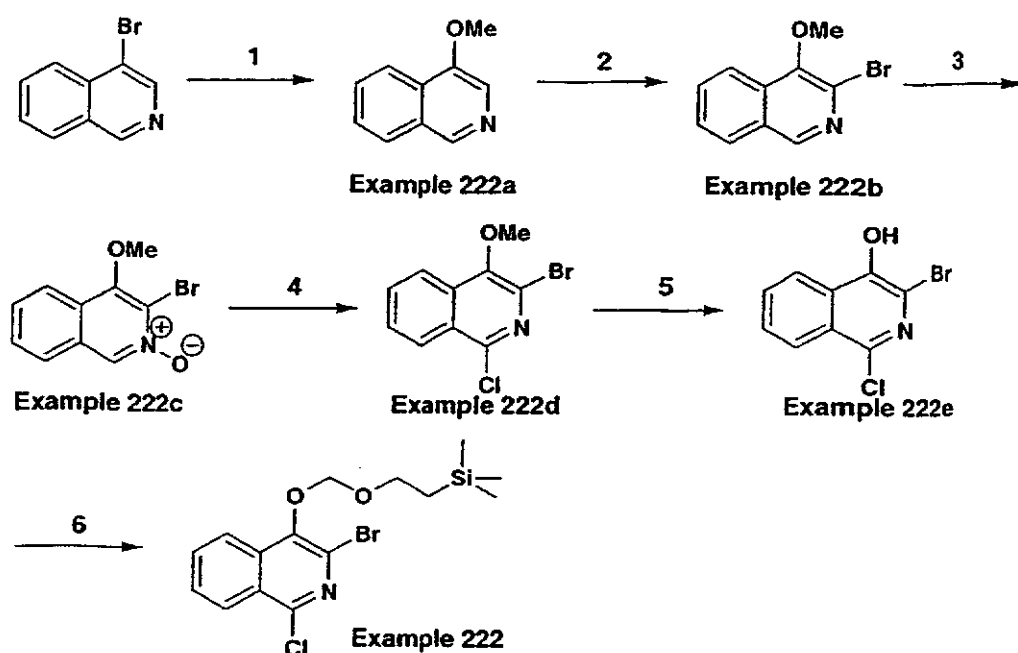
Example 220: Preparation of Compound 220



- BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(1-oxa-4-aza-cyclopenta[*a*]naphthalen-5-yloxy)-S-proline]-P1(1*R*,2*S* VinylAcca)-CONHSO₂Cyclopropane. Following the general alkylation procedure, 13.0 mg of yellow solid was obtained (20%). LC/MS rt-min (MH⁺): 2.70 (724) [method B]. ¹H NMR (500 MHz, CD₃OD) δ ppm 1.01 (s, 9 H) 1.09 (m, 2 H) 1.22 (s, 9 H) 1.27 (m, 2 H) 1.46 (m, 1 H) 1.89 (dd, *J*=7.78, 5.65 Hz, 1 H) 2.24 (d, *J*=8.55 Hz, 1 H) 2.33 (t, *J*=9.92 Hz, 1 H) 2.68 (dd, *J*=13.73, 7.02 Hz, 1 H) 2.95 (m, 1 H) 4.14 (m, 1 H) 4.26 (s, 1 H) 4.50 (d, *J*=11.90 Hz, 1 H) 4.57 (d, *J*=17.09 Hz, 1 H) 5.12 (d, *J*=10.07 Hz, 1 H) 5.30 (d, *J*=17.40 Hz, 1 H) 5.75 (m, 1 H) 5.93 (s, 1 H) 6.97 (d, *J*=2.14 Hz, 1 H) 7.51 (t, *J*=7.32 Hz, 1 H) 7.81 (t, *J*=7.48 Hz, 1 H) 7.92 (s, 1 H) 8.13 (d, *J*=7.94 Hz, 1 H) 8.28 (d, *J*=8.24 Hz, 1 H).

15 **Preparation of 3-halo and 3-heteroaryl 4-alkoxy and 4-hydroxy isoquinoline P2* derivatives**

General Synthetic Scheme



Reaction conditions: (1) MeOK in DMPU; (2) NBS in dichloroethane; (3) MCPBA in CH₂Cl₂; (4) POCl₃ in dichloroethane; (5) BBr₃ in CH₂Cl₂; (6) SEM-Chloride and Hunig's Base in CH₂Cl₂

5

4-Methoxy isoquinoline (Example 222a) was prepared from 1-bromoisoquinoline by a novel and convenient procedure using ordinary laboratory equipments and reagents. A regioselective NBS bromination gave 3-bromo-4-methoxy isoquinoline (Example 222b) in good yields. MCPBA oxidation proceeded uneventfully to furnish the corresponding N-oxide (Example 222c), which was isomerized into 1-chloro-3-bromo-4-methoxy isoquinoline (Example 222d) using the usual POCl₃ procedure. The 4-methoxy isoquinoline was alkylated with the tripeptide to give the corresponding 3-bromo-4-methoxy P2* derivative suitable for Stille and Suzuki coupling. Alternatively the 4-methoxy isoquinoline was de-methylated in BBr₃ to give the 4-hydroxy-3-bromo-1-chloro isoquinoline (Example 222e). The 4-hydroxy group was re-protected with SEM-chloride to give the 4-SEM protected intermediate Example 222. The 4-hydroxy compound was re-generated once the coupling was achieved by either an acid induced, or a fluoride induced deprotection protocol.

10

15

Example 222d: Preparation of 1-chloro-3-bromo-4-methoxy isoquinoline**Step 1:**

A solution of 4-bromo isoquinoline (15g, 73 mmol, commercial material) in
5 200 mL dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU, Aldrich) was
added solid potassium methoxide (5.6gm, 80 mmol). The reaction vessel was
immersed in an oil bath at 105 °C for 20 min. The color of mixture changed rapidly
from its initial very pale to dark greenish brown immediately after warming. The
reaction vessel was removed from the oil bath and was diluted with water, the
10 organic residues were partitioned into ether by multiple extraction with portions of
ether. TLC analysis showed two new, spots (1:1 v/v mixture of hexanes and ethyl
acetate as eluent) of roughly equal size. These were separated on silica-gel (Merck,
type-H) column eluted with straight hexanes, followed by gradual addition of ether
into the mobil phase. The desired product, 4-methoxy isoquinoline (4.1gm, 35.3%)
15 was isolated after evaporation of solvents. The other product was also isolated as the
reduction by-product isoquinoline. The identity of the by-product was confirmed by
NMR comparison with authentic material. **Example 222a:** LC/MS R_t -min (MH^+)
[method C]: 1.16 (160). ^1H NMR (400 MHz, $CHCl_3$ - d_3) δ 4.07 (s, 3 H)
7.61 (m, 1 H) 7.69 (m, 1 H) 7.93 (d, $J=8.07$ Hz, 1 H) 8.08 (s, 1 H) 8.19 (d, $J=8.56$
20 Hz, 1 H) 8.89 (s, 1 H). [Note: this compound was previously prepared in Zoltewicz,
John A.; Oestreich, Terence M.; Sale, Alan A. *Journal of the American Chemical*
Society (1975), 97(20), 5889-96 in a "Monel Bomb", and later by a "focused
microwave" initiated procedure in Cherng, Yie-Jia, *Tetrahedron* (2002), 58(6), 1125-
1129. The present procedure required neither special high pressure apparatus nor
25 preparative scale microwave equipment].

Step 2:

The material (**Example 222a**) was subjected to NBS bromination, thus 4-
methoxy isoquinoline (**Example 222a**, 2.1gm, 13.2 mmol) in 1,2-dichloroethane
30 (DCE, 150 mL) was treated with N-bromosuccinimide (NBS, 1.5gm, 8.4 mmol,
0.6X) at 70°C for an hr followed by addition of second portion of 1.5gm NBS. The
dark brownish mixture was stirred for another hr before the addition of third portion

of 1.0gm NBS. The bromination was monitored by LC-MS until there was no starting material left. The crude mixture was evaporated to dryness and the desired product was filtered over a short bed of silica-gel (Type-H, Merck, 3cm diameter by 1.5cm height) eluted with straight hexanes first followed by gradually increasing the amount of ether. The desired product, (**Example 222b**), was isolated as an oily material (1.7gm, 54%). LC/MS R_f -min (MH^+) [method C]: 2.65 (238). ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 4.04 (s, 3 H) 7.64 (t, $J=7.58$ Hz, 1 H) 7.76 (t, $J=7.09$ Hz, 1 H) 7.99 (d, $J=8.31$ Hz, 1 H) 8.11 (d, $J=8.31$ Hz, 1 H) 8.85 (s, 1 H). [3-Bromo-4-methoxy isoquinoline was previously prepared by a different procedure: Finkentey, Christel; Langhals, Elke; Langhals, Heinz. *Chemische Berichte* (1983), 116(6), 2394-7. NMR of the product was identical to that reported].

Step 3:

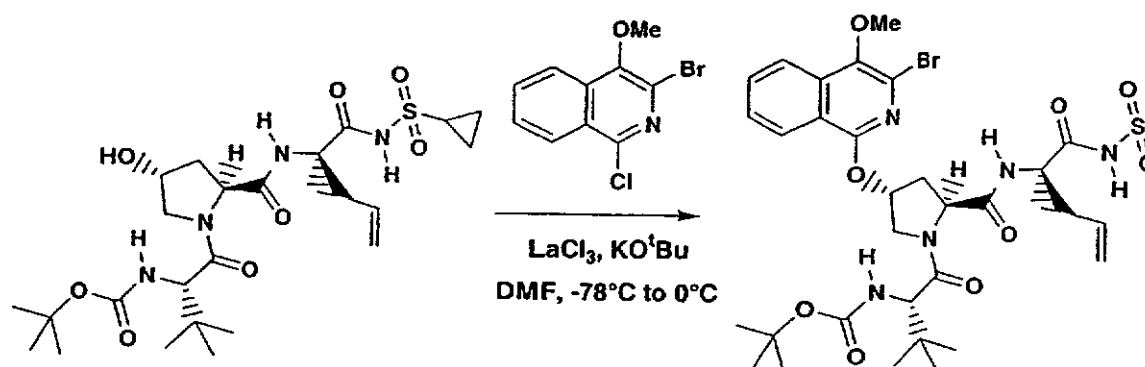
The product from NBS bromination was subjected to MCPBA oxidation in methylene chloride at room temperature. Thus MCPBA (1.80gm, 77% pure, 8.0 mmol) was added into a solution of 3-bromo-4-methoxy isoquinoline (**Example 222b**, 1.65gm, 6.9 mmol) in 35 mL of CH_2Cl_2 . The solution was stirred for 4 hrs forming a white suspension. Sodium bicarbonate solution (5%, freshly prepared, 20 mL) was added into the mixture, organic residues were extracted into CH_2Cl_2 (10 X 25 mL). Multiple extraction in organic solvent was necessary to recover the somewhat water solution N-oxide product. The crude material obtained after evaporation of solvents was further purified by a filtration over silica-gel to give 1.36gm (5.4 mmol, 78%) of the N-oxide (**Example 222c**) as a ceraceous solid. LC/MS R_f -min (MH^+) [method C]: 1.79 (254). ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 4.07 (s, 3 H) 7.63 (m, 2 H) 7.72 (m, 1 H) 8.00 (m, 1 H) 8.86 (s, 1 H).

Step 4:

The final N-oxide rearrangement was done as usual in $POCl_3$ using procedure described elsewhere. Yield of **Example 222d** was essentially quantitative. LC/MS R_f -min (MH^+) [method D]: 2.69 (272). ^1H NMR as HCl salt, (400 MHz, CHLOROFORM-D) δ ppm 4.07 (s, 3 H) 7.81 (m, 1 H) 7.92 (m, 1 H) 8.17 (d, $J=8.31$

Hz, 1 H) 8.34 (d, $J=8.31$ Hz, 1 H). ^1H NMR as free base, (400 MHz, CHLOROFORM-D) δ ppm 4.03 (s, 3 H) 7.72 (m, 1 H) 7.81 (m, 1 H) 8.12 (d, $J=8.56$ Hz, 1 H) 8.28 (d, $J=8.56$ Hz, 1 H).

5 **Example 223: Preparation of Compound 223**

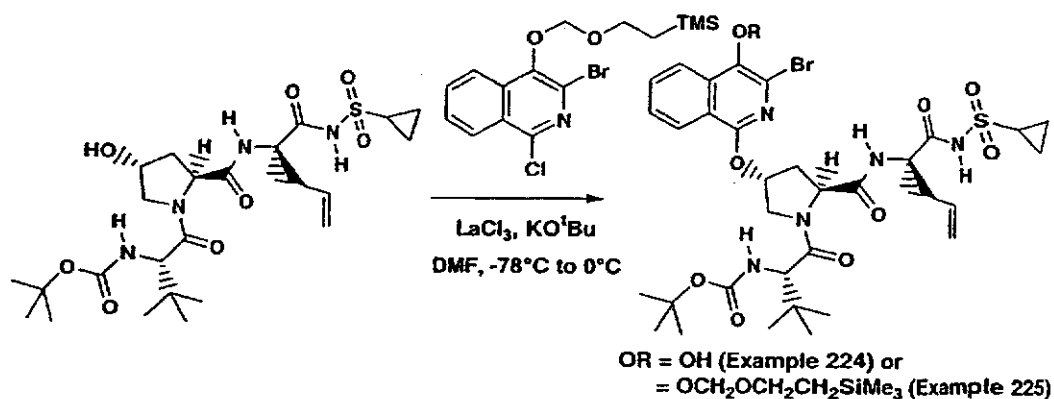


The free base (**Example 222d**) obtained in the previous step was alkylated with the
 10 tripeptide fragment using the alkylation protocol (**Example 184**) described elsewhere
 to give 79% of the desired product as a paper-white solid. LC/MS R_t -min (MNa^+)
 [method C]: 3.91 (814). ^1H NMR (400 MHz, CD_3OD) δ ppm 1.02 (s, 9 H) 1.06 (dd,
 $J=8.07, 1.47$ Hz, 2 H) 1.22 (m, 11 H) 1.42 (dd, $J=9.78, 5.14$ Hz, 1 H) 1.86 (dd,
 $J=8.07, 5.38$ Hz, 1 H) 2.22 (dd, $J=18.10, 9.29$ Hz, 1 H) 2.28 (m, 1 H) 2.61 (dd,
 15 $J=13.57, 6.97$ Hz, 1 H) 2.93 (m, 1 H) 3.92 (s, 3 H) 4.06 (dd, $J=11.86, 2.81$ Hz, 1 H)
 4.22 (s, 1 H) 4.43 (d, $J=11.49$ Hz, 1 H) 4.51 (m, 1 H) 5.10 (d, $J=10.52$ Hz, 1 H) 5.28
 (d, $J=17.12$ Hz, 1 H) 5.74 (m, 1 H) 5.81 (s, 1 H) 7.56 (t, $J=7.58$ Hz, 1 H) 7.78 (t,
 $J=7.58$ Hz, 1 H) 8.00 (d, $J=8.31$ Hz, 1 H) 8.16 (d, $J=8.56$ Hz, 1 H).

20 **Example 224 and 225: Preparation of Compounds 224 and Compound 225**

The 4-methoxy group in 1-chloro-3-bromo-4-methoxy isoquinoline (**Example 222d**)
 described previously was converted into α -trimethylsilyl ethoxy methyl (SEM)
 moiety by the following procedure. 1-Chloro-3-bromo-4-methoxy isoquinoline
 25 (**Example 222d**) was demethylated using BBr_3 (final adjusted reaction concentration
 was 0.2-0.3 Molar BBr_3) at room temperature for 12 hrs. The high BBr_3

concentration for such de-methylation was found to be necessary and efficient. The crude reaction mixture was diluted with 50 volumes of anhydrous methanol prior to evaporation to dryness. The demethylation was essentially quantitative. **Example 222e**: LC/MS R_t -min (MH^+) [method D]: 2.32 (258). ^1H NMR of free HCl salt (400 MHz, CHLOROFORM-D) δ ppm 5.83 (br. s, 1 H) 7.73 (t, $J=7.70$ Hz, 1 H) 7.79 (t, $J=7.58$ Hz, 1 H) 8.22 (m, 2 H). The 4-hydroxy-3-bromo-1-chloro isoquinoline (**Example 222e**) was re-protected with 2-(trimethylsilyl) ethoxy methyl chloride (SEM-Cl). The crude free base from the previous preparation was dried to 40 microns(Hg) at room temperature prior to re-protection with SEM-chloride. To a solution of the 4-hydroxy compound (**Example 222e**, 1.33gm, 5.2 mmol) in methylene chloride (50 ml) at 0°C was added sequentially diisopropylethyl amine (2 mL, 11.5 mmol) and SEM-chloride (1.8 mL, 10 mmol). The mixture was stirred for 10 min before it was washed with a freshly prepared $NaHCO_3$ solution (5%, 100 mL). The organic residues were extracted into several portions of methylene chloride, the combined organic layers were back-washed with 20 mL deionized water before it was concentrated in vacuo. The SEM protection was essentially quantitative. **Example 222**: LC/MS R_t -min (MH^+) [method D]: 3.40 (410). ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 0.03 (s, 9 H) 0.99 (m, 2 H) 3.98 (m, 2 H) 5.33 (s, 2 H) 7.72 (m, 1 H) 7.80 (m, 1 H) 8.17 (d, $J=8.56$ Hz, 1 H) 8.27 (d, $J=8.07$ Hz, 1 H). Alkylation of 4-SEM protected isoquinoline with tripeptide: **Compound 224** and **Compound 225** were generated from the same tripeptide alkylation reaction. The 4-hydroxy compound (**Compound 224**) was produced most probably as a result of the TFA present during the preparative HPLC purification.



Example 224 (15.4%): LC/MS R_f -min (MNa^+) [method D]: 2.87 (800). ^1H NMR

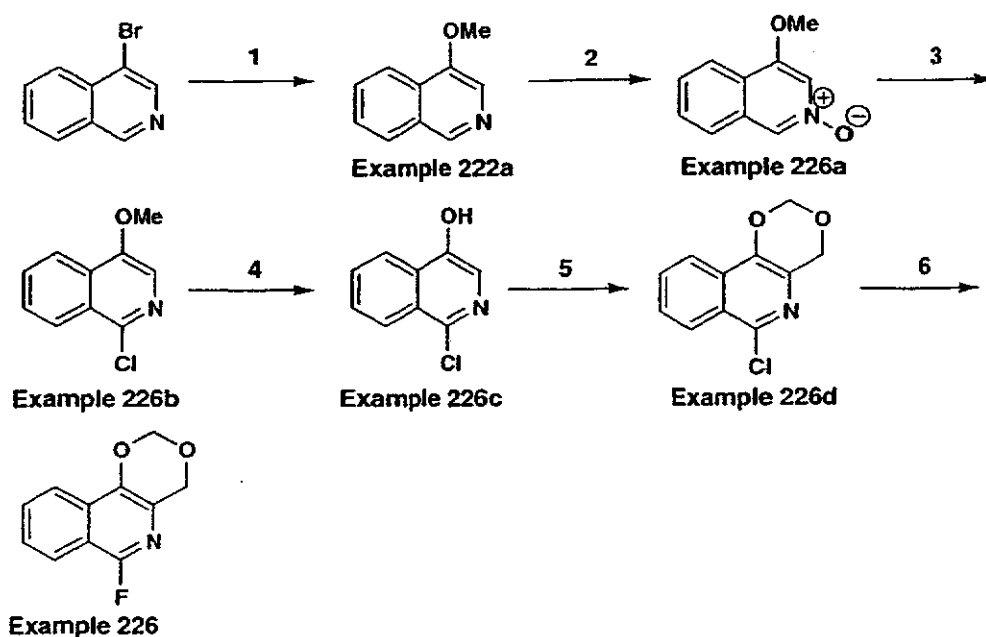
- 5 (400 MHz, CD₃OD) δ ppm 1.02 (s, 9 H) 1.06 (d, $J=8.31$ Hz, 2 H) 1.25 (s, 9 H) 1.42 (s, 2 H) 1.86 (m, 1 H) 2.23 (m, 2 H) 2.60 (dd, $J=13.21, 7.34$ Hz, 1 H) 2.93 (m, 1 H) 4.06 (d, $J=11.00$ Hz, 1 H) 4.24 (m, 2 H) 4.38 (d, $J=11.98$ Hz, 1 H) 4.49 (dd, $J=9.78, 7.09$ Hz, 1 H) 5.10 (d, $J=10.03$ Hz, 1 H) 5.28 (d, $J=17.36$ Hz, 1 H) 5.72 (m, 1 H) 5.76 (s, 1 H) 7.52 (t, $J=7.46$ Hz, 1 H) 7.71 (t, $J=7.09$ Hz, 1 H) 8.09 (d, $J=4.40$ Hz, 1 H)
- 10 8.11 (d, $J=4.16$ Hz, 1 H).

Example 225 (8.0%): LC/MS R_f -min ($[M-BOC]^+$) [method D]: 3.46 (808). ^1H NMR

- (400 MHz, CD₃OD) δ ppm 0.01 (s, 9 H) 0.96 (m, 2 H) 1.02 (s, 11 H) 1.06 (d, $J=6.60$ Hz, 2 H) 1.24 (s, 9 H) 1.42 (m, 1 H) 1.86 (dd, $J=7.83, 5.38$ Hz, 1 H) 2.25 (m, 2 H)
- 15 2.62 (dd, $J=13.69, 7.34$ Hz, 1 H) 2.93 (m, 1 H) 3.97 (m, 2 H) 4.07 (dd, $J=10.88, 3.55$ Hz, 1 H) 4.23 (s, 1 H) 4.43 (d, $J=11.25$ Hz, 1 H) 4.50 (m, 1 H) 5.10 (d, $J=10.76$ Hz, 1 H) 5.25 (m, 3 H) 5.74 (m, 1 H) 5.82 (s, 1 H) 7.57 (m, 1 H) 7.77 (t, $J=7.83$ Hz, 1 H) 8.06 (d, $J=8.56$ Hz, 1 H) 8.16 (d, $J=8.31$ Hz, 1 H).

20 Preparation of 4*H*-[1,3]dioxino[5,4-*c*]isoquinolin P2* derivatives

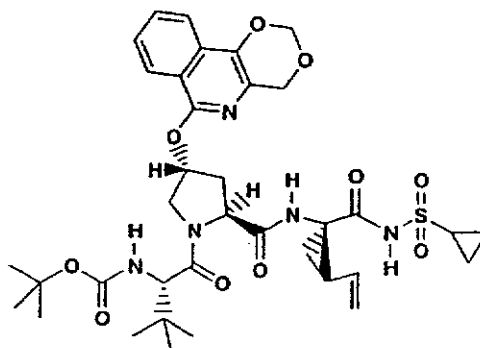
General Synthetic Scheme



Reaction Conditions: (1) MeOK in DMPU; (2) MCPBA in CH_2Cl_2 ; (3) POCl_3 in DCE; (4) BBr_3 in CH_2Cl_2 ; (5) HCHO solution in 40% H_2SO_4 by procedure of

- 5 Synthesis of 1,3-oxazino[5,6-c]isoquinolines and related compounds. Miyoko Toyama and Hirotaka Otomasu, *Chem. Pharm. Bull.* 33(12), 5543-5546, 1985; (6) Fluororination procedure by Uchibori, Y., Umeno, M., Yoshiokai, H., *Heterocycles*, 1992, 34 (8), 1507-1510

10 Example 227: Preparation of Compound 227



- 6-Chloro-1,3-Oxazino[5,6-c]isoquinoline was prepared by the procedure of Miyoko Toyama and Hirotaka Otomasu starting from 1-chloro-4-hydroxy isoquinoline. The
- 15

starting material: 1-chloro-4-hydroxy isoquinoline (**Example 226c**) was prepared by the synthetic sequence shown above. MCPBA oxidation of 4-methoxy isoquinoline (**Example 222a**) was carried as usual to give 79.1% of the corresponding N-oxide (**Example 226a**). The material was converted into the 1-chloro derivative immediately afterward in POCl₃ to give the chloride (**Example 226b**) in essentially quantitative yield. The crude 1-chloro-4-methoxy isoquinoline was de-methylated in BBr₃ at room temperature to give the corresponding 1-chloro-4-hydroxy isoquinoline (**Example 226c**) after treating the crude BBr₃ mixture with anhydrous methanol at room temperature, followed by evaporation to get rid of excess of borate residues.

10 The reaction of Miyoko Toyama and Hirotaka Otomasu gave 266mg of 6-chloro-1,3-oxazino[5,6-*c*]isoquinoline (**Example 226d**, 62.3%) overall yield from 300mg of 4-methoxy isoquinoline in 4 steps. LC/MS R_t-min ([M-HCHO]H⁺) [method D]: 2.45 (192). ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 5.02 (s, 2 H) 5.41 (s, 2 H) 7.68 (m, 1 H) 7.77 (ddd, *J*=8.25, 6.91, 1.22 Hz, 1 H) 8.10 (d, *J*=8.31 Hz, 1 H) 8.26 (d, *J*=8.56 Hz, 1 H).

15

The chloride was found to be unreactive under the alkylation protocol of **Example 184**. The corresponding 6-fluoro-1,3-oxazino[5,6-*c*]isoquinoline (**Example 226**) was prepared by the method of [Uchibori, Y.; Umeno, M.; Yoshiokai, H.; Heterocycles, 1992, 34 (8), 1507-1510] cited earlier. The reaction was not allowed to go to completion, and the crude reaction mixture was recovered as a mixture of ratio of 1:2.4 (Cl : F). Without further purification, the chloride/fluoride mixture was alkylated with the tripeptide using the procedure of **Example 184** to give 66mg (50.0%) of BOCNH-P3(*L*-*t*-BuGly)-P2[(4R)-(1,3-oxazino[5,6-*c*]isoquinoline-6-oxo)-S-proline]-P1(1R,2S VinylAcCa)-CONHSO₂Cyclopropane after preparative HPLC purification. LC/MS R_t-min (MNa⁺) [method D]: 3.03 (764). ¹H NMR (400 MHz, CD₃OD) δ ppm 1.01 (s, 9 H) 1.06 (dd, *J*=8.07, 1.96 Hz, 2 H) 1.22 (s, 10 H) 1.34 (d, *J*=6.11 Hz, 1 H) 1.42 (m, 1 H) 1.86 (dd, *J*=8.07, 5.38 Hz, 1 H) 2.23 (m, 2 H) 2.59 (dd, *J*=13.82, 6.97 Hz, 1 H) 2.93 (m, 1 H) 4.03 (dd, *J*=11.86, 3.06 Hz, 1 H) 4.23 (s, 1 H) 4.41 (d, *J*=11.98 Hz, 1 H) 4.50 (dd, *J*=9.66, 6.97 Hz, 1 H) 4.87 (m, 2 H) 5.11 (d, *J*=10.52 Hz, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.34 (s, 2 H) 5.74 (m, 2 H) 7.51 (t,

20

25

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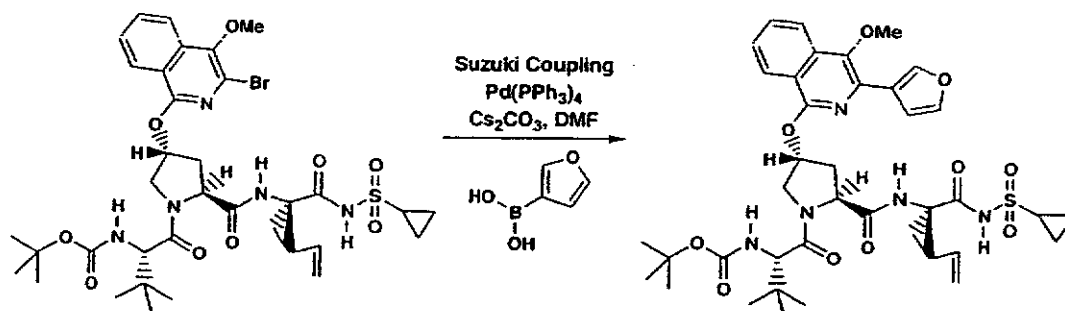
$J=7.46$ Hz, 1 H) 7.70 (t, $J=7.58$ Hz, 1 H) 7.95 (d, $J=8.31$ Hz, 1 H) 8.12 (d, $J=8.31$ Hz, 1 H).

Preparation of 4-methoxy-3-heteroaryl and 3-azoyl isoquinoline P2* derivatives via Suzuki and Stille coupling reactions

The coupling technologies shown below demonstrated the general utility with the bromo derivative of **Example 223**. It is understood that a similar protocol is equally applicable to other combinations coupling reagents and catalysts other than boron and tin.

Example 229: Preparation of Compound 229

BOCNH-P3(*L*-*t*-BuGly)-P2[(4R)-(3-furan-3-yl-4-methoxy-isoquinolin-1-oxo)-*S*-proline]-P1(1*R*,2*S* VinylAcce)-CONHSO₂Cyclopropane via a Suzuki coupling shown below:



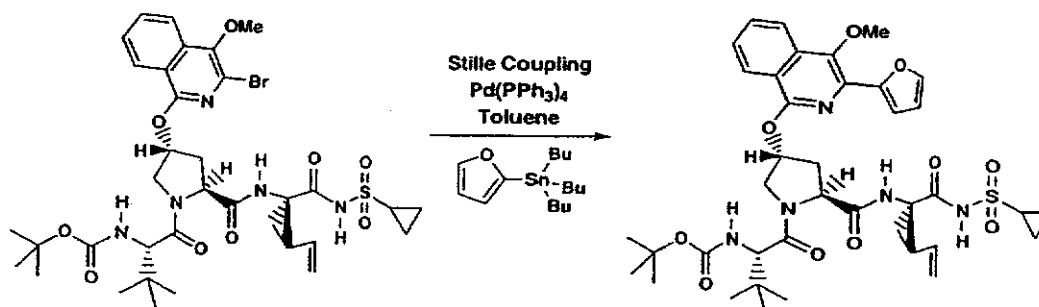
22 mg (0.028 mmole) of **Example 223** was dissolve in 1 ml of DMF, 9.4 mg of the commercial boronic acid (3 eq), 3 mg of catalyst (10% mmole) and 18 mg of cesium carbonate were added. The mixture was degassed twice, and then heated up to 110 °C for 3 hours. The final product was purified by prep-HPLC, 13.6 mg of yellow solid was obtained (64.0%). LC/MS rt-min (MH⁺): 2.85 (780) [method B]. ¹H NMR (500 MHz, CD₃OD) δ ppm 1.09 (m, 11 H) 1.26 (m, 12 H) 1.68 (m, 1 H) 2.27 (s, 1 H) 2.64 (m, 2 H) 2.97 (m, 1 H) 3.86 (s, 3 H) 4.15 (d, $J=10.38$ Hz, 1 H) 4.28 (s, 1 H) 4.43 (d,

$J=10.99$ Hz, 1 H) 4.56 (m, 1 H) 5.11 (m, 2 H) 5.63 (m, 1 H) 5.99 (s, 1 H) 7.20 (s, 1 H) 7.51 (m, 1 H) 7.61 (m, 1 H) 7.75 (t, $J=7.17$ Hz, 1 H) 8.03 (d, $J=8.24$ Hz, 1 H) 8.16 (d, $J=8.24$ Hz, 1 H) 8.27 (s, 1 H).

5 Example 230: Preparation of Compound 230

BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(3-furan-2-yl-4-methoxy-isoquinolin-1-oxo)-S-proline]-P1(1*R*,2*S* VinylAcce)-CONHSO₂Cyclopropane was synthesized via a Stille coupling reaction shown below:

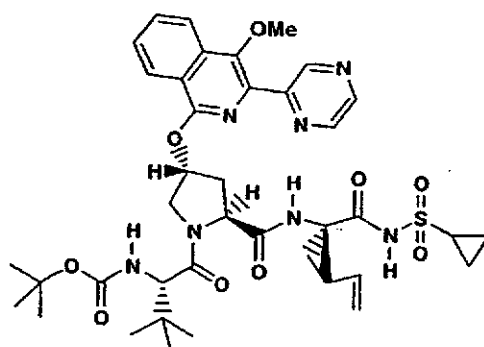
10



40 mg (0.05 mmole) of Example 223, 4 mg of catalyst (5% mmole) and 100 μ l (4 eq) of the commercial tin reagent was dissolved in 1 ml of toluene, the mixture was degassed twice and then heated up to 90 $^{\circ}$ C for overnight. After prep HPLC separation, 19.6 mg of greenish solid was obtained (50.0%). LC/MS rt-min (MH⁺): 2.76 (780) [method B]. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.94 (m, 2 H) 0.98 (s, 9 H) 1.09 (m, 2 H) 1.25 (s, 9 H) 1.39 (m, 1 H) 1.60 (m, 1 H) 2.35 (m, 1 H) 2.48 (m, 1 H) 2.74 (m, 1 H) 2.95 (m, 1 H) 3.87 (s, 3 H) 4.14 (m, 1 H) 4.22 (d, $J=4.16$ Hz, 1 H) 4.41 (s, 1 H) 4.69 (m, 1 H) 5.26 (m, 1 H) 5.35 (m, 1 H) 5.93 (s, 1 H) 6.03 (m, 1 H) 6.61 (m, 1 H) 7.16 (d, $J=3.18$ Hz, 1 H) 7.50 (d, $J=7.58$ Hz, 1 H) 7.67 (s, 1 H) 7.73 (t, $J=7.34$ Hz, 1 H) 8.04 (m, 1 H) 8.17 (d, $J=8.31$ Hz, 1 H).

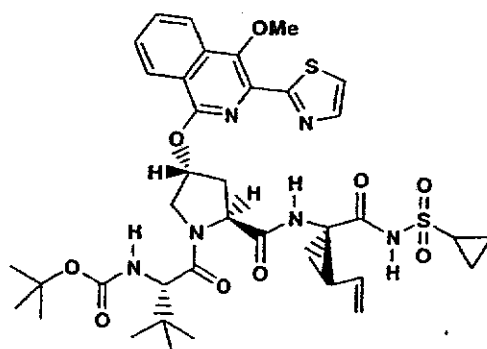
Example 231: Preparation of Compound 231

25



BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(3-pyrazine-2-yl-4-methoxy-isoquinolin-1-oxo)-*S*-proline]-P1(1*R*,2*S* VinylAcca)-CONHSO₂Cyclopropane was similarly prepared by a
 5 Stille coupling reaction in 7.1% yield. LC/MS rt-min (MH⁺): 2.51 (792) [method B].
¹H NMR (400 MHz, CD₃OD) δ ppm 0.98 (m, 9 H) 1.11 (m, 2 H) 1.19 (s, 9 H) 1.27 (m, 2 H) 1.42 (m, 1 H) 2.37 (m, 1 H) 2.48 (m, 2 H) 2.81 (m, 1 H) 2.97 (m, 1 H) 3.83 (s, 3 H) 4.07 (s, 1 H) 4.20 (d, *J*=4.16 Hz, 1 H) 4.54 (d, *J*=11.49 Hz, 1 H) 4.72 (m, 1 H) 5.27 (m, 1 H) 5.39 (m, 1 H) 5.96 (s, 1 H) 6.04 (m, 1 H) 7.63 (s, 1 H) 7.83 (s, 1 H)
 10 8.17 (s, 1 H) 8.26 (s, 1 H) 8.60 (d, *J*=2.20 Hz, 1 H) 8.76 (d, *J*=2.20 Hz, 1 H) 9.33 (s, 1 H).

Example 232: Preparation of Compound 232

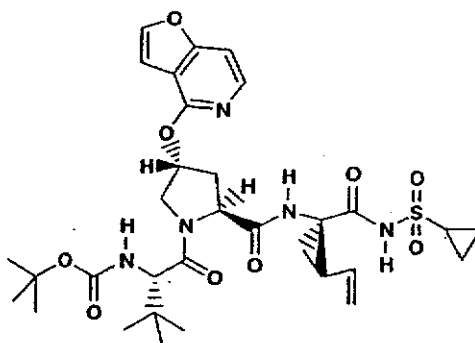


15

BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(4-methoxy-3-thiazol-2-yl-isoquinolin-1-oxo)-*S*-proline]-P1(1*R*,2*S* VinylAcca)-CONHSO₂Cyclopropane was similarly prepared by a
 Stille coupling reaction in 32.2% yield. LC/MS rt-min (MH⁺): 2.42 (797) [method B].
 20 ¹H NMR (400 MHz, CD₃OD) δ ppm 1.03 (s, 9 H) 1.07 (m, 2 H) 1.13 (s, 9 H) 1.22

(m, 2 H) 1.43 (dd, $J=9.78, 5.14$ Hz, 1 H) 1.88 (dd, $J=8.07, 5.38$ Hz, 1 H) 2.23 (q, $J=8.97$ Hz, 1 H) 2.36 (m, 1 H) 2.67 (m, 1 H) 2.94 (m, 1 H) 4.10 (s, 3 H) 4.15 (m, 1 H) 4.18 (s, 1 H) 4.53 (d, $J=25.92$ Hz, 1 H) 4.59 (dd, $J=10.27, 7.09$ Hz, 1 H) 5.12 (m, 1 H) 5.29 (d, $J=17.36$ Hz, 1 H) 5.73 (m, 1 H) 6.09 (s, 1 H) 7.74 (t, $J=7.58$ Hz, 1 H) 7.91 (t, $J=7.70$ Hz, 1 H) 8.00 (d, $J=3.42$ Hz, 1 H) 8.18 (d, $J=3.18$ Hz, 1 H) 8.22 (d, $J=8.31$ Hz, 1 H) 8.29 (d, $J=8.31$ Hz, 1 H).

Example 233: Preparation of Compound 233

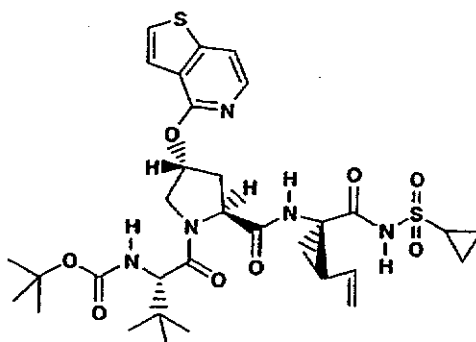


10

Following the general tripeptide alkylation procedure with the commercial 4-chlorofuro[3,2-c]pyridine, 5.7 mg of yellow solid was obtained (8.2%). LC/MS rt-min (MH^+): 2.32 (674) [method B]. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.00 (s, 9 H) 1.07 (m, 2 H) 1.21 (m, 11 H) 1.41 (m, 1 H) 1.86 (dd, $J=8.07, 5.38$ Hz, 1 H) 2.22 (dd, $J=17.61, 9.05$ Hz, 2 H) 2.54 (dd, $J=13.69, 7.09$ Hz, 1 H) 2.92 (m, 1 H) 4.06 (m, 1 H) 4.21 (m, 1 H) 4.32 (s, 1 H) 4.49 (m, 1 H) 5.11 (dd, $J=10.27, 1.47$ Hz, 1 H) 5.29 (dd, $J=17.36, 1.22$ Hz, 1 H) 5.74 (m, 1 H) 5.81 (s, 1 H) 6.83 (d, $J=1.22$ Hz, 1 H) 7.19 (d, $J=5.87$ Hz, 1 H) 7.76 (d, $J=1.22$ Hz, 1 H) 7.97 (d, $J=5.87$ Hz, 1 H).

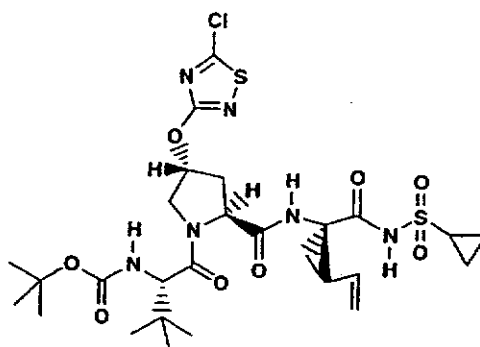
20

Example 235: Preparation of Compound 235



Following the general tripeptide alkylation procedure with the commercial 4-chlorothieno[3,2-*c*]pyridine, 20.0 mg of yellow solid was obtained (28.1%). LC/MS
 5 rt-min (MH^+): 2.50 (690) [method B]. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.01 (s, 9 H) 1.06 (m, 2 H) 1.21 (m, 11 H) 1.42 (m, 1 H) 1.86 (dd, $J=8.19, 5.50$ Hz, 1 H) 2.24 (m, 2 H) 2.57 (dd, $J=13.69, 6.85$ Hz, 1 H) 2.93 (m, 1 H) 4.05 (dd, $J=11.98, 3.18$ Hz, 1 H) 4.22 (s, 1 H) 4.39 (d, $J=11.74$ Hz, 1 H) 4.50 (dd, $J=9.90, 7.21$ Hz, 1 H) 5.10 (dd, $J=10.39, 1.34$ Hz, 1 H) 5.28 (d, $J=17.12$ Hz, 1 H) 5.73 (m, 1 H) 5.81 (s, 1 H) 7.45 (d, $J=5.62$ Hz, 1 H) 7.53 (m, 2 H) 7.94 (d, $J=5.87$ Hz, 1 H).

Example 236: Preparation of Compound 236



15

Following the general tripeptide alkylation procedure with the commercial 3,5-dichloro-1,2,4-thiadiazole, 8.0 mg of yellow solid was obtained (11.9%). LC/MS rt-min (MNa^+): 2.37 (697) [method B]. ^1H NMR (400 MHz, CD_3OD) δ ppm 1.00 (s, 9 H) 1.06 (m, 2 H) 1.22 (m, 2 H) 1.36 (s, 9 H) 1.42 (m, 1 H) 1.86 (dd, $J=8.07, 5.38$ Hz, 1 H) 2.25 (m, 2 H) 2.60 (dd, $J=14.18, 6.85$ Hz, 1 H) 2.92 (m, 1 H) 4.03 (dd, $J=12.47,$

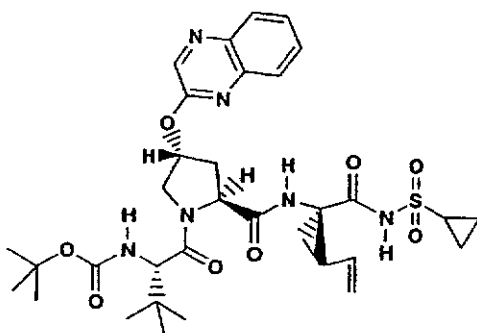
20

3.18 Hz, 1 H) 4.17 (s, 1 H) 4.42 (m, 2 H) 5.11 (dd, $J=10.27, 1.71$ Hz, 1 H) 5.29 (dd, $J=17.12, 1.47$ Hz, 1 H) 5.68 (s, 1 H) 5.74 (m, 1 H).

Example 237: Preparation of Compound 237

5

BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(quinoxaline-2-oxo)-*S*-proline]-P1(1*R*,2*S* VinylAcce)-CONHSO₂Cyclopropane, Shown below



10

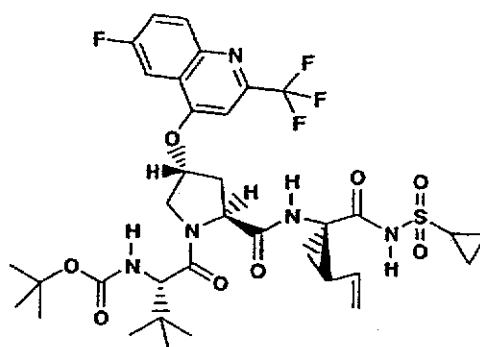
Following the general tripeptide alkylation procedure with commercial 2-chloroquinoxaline, 113.0mg of yellow solid was obtained (19.2%). LC/MS *rt*-min (MNa⁺): 2.48 (707) [method B]. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.01 (s, 9 H) 1.06 (m, 2 H) 1.22 (m, 11 H) 1.42 (m, 1 H) 1.87 (dd, $J=8.19, 5.50$ Hz, 1 H) 2.24 (m, 1 H) 2.31 (m, 1 H) 2.57 (dd, $J=13.57, 6.97$ Hz, 1 H) 2.93 (m, 1 H) 4.09 (dd, $J=11.98, 3.18$ Hz, 1 H) 4.17 (s, 1 H) 4.38 (d, $J=11.74$ Hz, 1 H) 4.50 (dd, $J=10.27, 7.09$ Hz, 1 H) 5.11 (dd, $J=10.27, 1.71$ Hz, 1 H) 5.29 (dd, $J=17.12, 1.47$ Hz, 1 H) 5.74 (m, 1 H) 5.87 (s, 1 H) 7.62 (t, $J=7.46$ Hz, 1 H) 7.73 (t, $J=7.70$ Hz, 1 H) 7.87 (m, 1 H) 7.96 (d, $J=8.31$ Hz, 1 H) 8.42 (s, 1 H).

20

Example 238: Preparation of Compound 238

BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(2-trifluoro-6-fluoroquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S* VinylAcce)-CONHSO₂Cyclopropane, Shown below

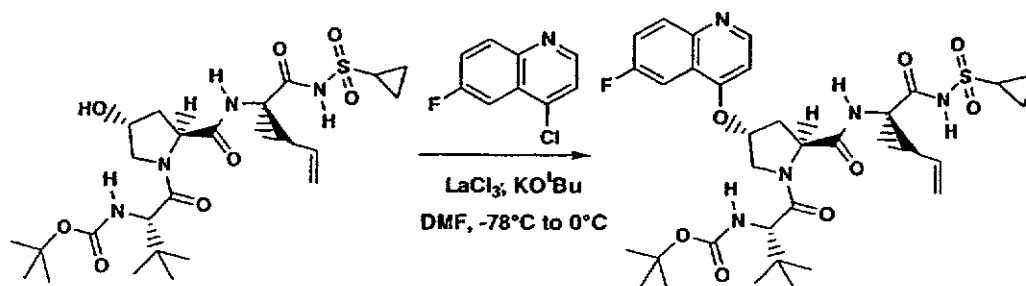
25



Following the general tripeptide alkylation procedure with the commercial 2-trifluoromethyl-4-chloro-6-fluoro quinoline, 17.0 mg of yellow solid was obtained (23.2%). LC/MS rt-min (MNa⁺): 2.66 (792) [method B]. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.02 (s, 9 H) 1.06 (m, 2 H) 1.17 (s, 9 H) 1.23 (m, 2 H) 1.42 (m, 1 H) 1.86 (dd, *J*=8.07, 5.38 Hz, 1 H) 2.21 (q, *J*=8.64 Hz, 1 H) 2.32 (m, 1 H) 2.63 (dd, *J*=13.94, 6.85 Hz, 1 H) 2.93 (m, 1 H) 4.08 (m, 1 H) 4.18 (s, 1 H) 4.53 (m, 2 H) 5.10 (m, 1 H) 5.27 (d, *J*=17.12 Hz, 1 H) 5.58 (s, 1 H) 5.72 (m, 1 H) 7.39 (s, 1 H) 7.65 (m, 1 H) 7.83 (dd, *J*=9.29, 2.69 Hz, 1 H) 8.12 (dd, *J*=9.29, 5.14 Hz, 1 H).

Example 239: Preparation of Compound 239

BOC-NH-P3(*L*-*t*-BuGly)-P2[(4R)-(6-fluoroquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S*-VinylAcce)-CONHSO₂Cyclopropane, Shown below



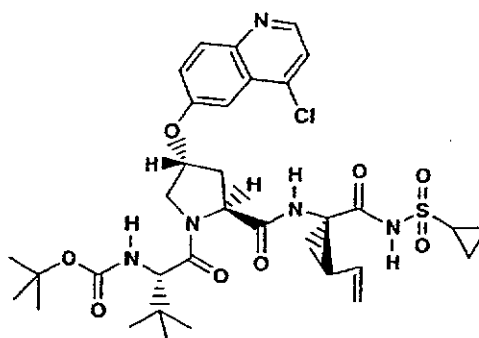
Following the general tripeptide alkylation procedure with the commercial 4-chloro-6-fluoro quinoline, 26.0 mg of yellow solid was obtained (39.0%). LC/MS rt-min (MH⁺): 1.98 (702) [method B]. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.04 (m, 11 H)

1.14 (s, 9 H) 1.23 (m, 2 H) 1.42 (m, 1 H) 1.87 (dd, $J=8.07, 5.38$ Hz, 1 H) 2.23 (q, $J=8.80$ Hz, 1 H) 2.41 (m, 1 H) 2.75 (dd, $J=14.43, 6.85$ Hz, 1 H) 2.93 (m, 1 H) 4.09 (s, 1 H) 4.12 (d, $J=2.69$ Hz, 1 H) 4.61 (m, 2 H) 5.11 (dd, $J=10.39, 1.59$ Hz, 1 H) 5.28 (dd, $J=17.24, 1.34$ Hz, 1 H) 5.70 (m, 1 H) 5.75 (s, 1 H) 7.62 (d, $J=6.60$ Hz, 1 H) 7.93 (m, 1 H) 8.06 (dd, $J=8.68, 2.57$ Hz, 1 H) 8.20 (dd, $J=9.29, 4.40$ Hz, 1 H) 9.06 (d, $J=6.60$ Hz, 1 H). A small amount of the by-product due to F-displacement was also isolated from the same reaction and was separated by preparative HPLC.

Example 240, Isolation of Compound 240

10

BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(4-chloroquinoline-6-oxo)-*S*-proline]-PI(1*R*,2*S* VinylAcCa)-CONHSO₂Cyclopropane, Shown below



15

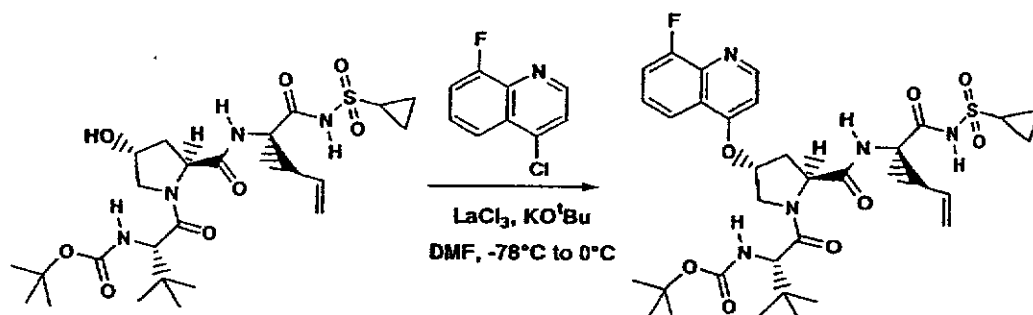
By-product, 8.0 mg of yellow solid was obtained (11.7%). LC/MS rt-min (MNa^+): 2.240 (740) [method B]. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.00 (s, 9 H) 1.06 (m, 2 H) 1.23 (m, 11 H) 1.42 (m, 1 H) 1.86 (dd, $J=8.19, 5.50$ Hz, 1 H) 2.22 (m, 1 H) 2.29 (m, 1 H) 2.55 (m, 1 H) 2.92 (m, 1 H) 4.09 (m, 1 H) 4.21 (s, 1 H) 4.30 (m, 1 H) 4.46 (dd, $J=10.27, 6.85$ Hz, 1 H) 5.11 (dd, $J=10.27, 1.47$ Hz, 1 H) 5.28 (dd, $J=17.36, 1.47$ Hz, 1 H) 5.43 (s, 1 H) 5.74 (m, 1 H) 7.60 (dd, $J=9.29, 2.45$ Hz, 1 H) 7.64 (d, $J=2.45$ Hz, 1 H) 7.81 (d, $J=4.89$ Hz, 1 H) 8.06 (d, $J=9.29$ Hz, 1 H) 8.72 (d, $J=5.14$ Hz, 1 H).

20

Example 241: Preparation of Compound 241

25

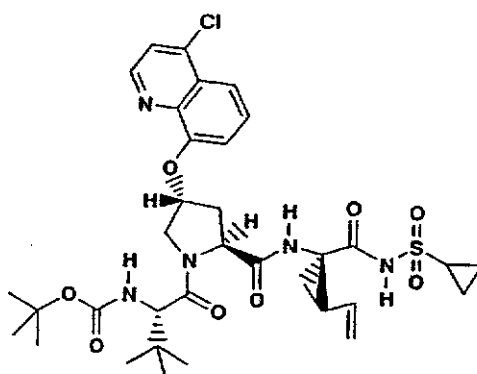
BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(8-fluoroquinoline-4-oxo)-*S*-proline]-P1(1*R*,2*S*
 VinylAcCa)-CONHSO₂Cyclopropane, Shown below



- 5 Following the general tripeptide alkylation procedure with the commercial 4-chloro-8-fluoro quinoline, 10.3 mg of yellow solid was obtained (14.7%). LC/MS rt-min (MH⁺): 1.95 (702) [method B]. ¹H NMR (400 MHz, CD₃OD) δ ppm 0.98 (s, 9 H) 1.06 (m, 2 H) 1.14 (s, 9 H) 1.22 (m, 2 H) 1.42 (m, 1 H) 1.87 (dd, *J*=8.07, 5.62 Hz, 1 H) 2.22 (q, *J*=8.72 Hz, 1 H) 2.41 (m, 1 H) 2.74 (dd, *J*=14.06, 6.97 Hz, 1 H) 2.93 (m, 1 H) 4.11 (m, 2 H) 4.57 (dd, *J*=10.39, 6.97 Hz, 1 H) 4.66 (d, *J*=12.23 Hz, 1 H) 5.11 (dd, *J*=10.27, 1.22 Hz, 1 H) 5.28 (d, *J*=17.12 Hz, 1 H) 5.71 (m, 2 H) 7.59 (d, *J*=6.36 Hz, 1 H) 7.75 (m, 1 H) 7.86 (m, 1 H) 8.23 (d, *J*=8.56 Hz, 1 H) 9.02 (d, *J*=6.36 Hz, 1 H). During the preparative HPLC purification, a by-product was also isolated. The 4-chloroquinoline-8-oxo-quinoline derivative was formed as a result of displacement of the fluorine atom instead of the chlorine leaving group.

Example 242, Isolation of Compound 242

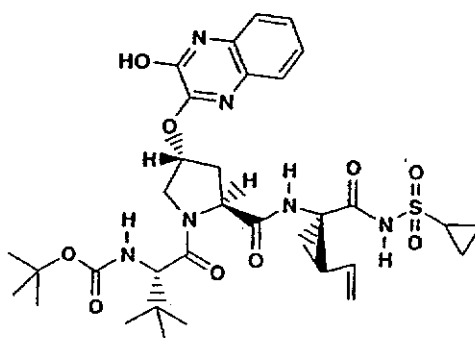
BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(4-chloroquinoline-8-oxo)-*S*-proline]-P1(1*R*,2*S*
 20 VinylAcCa)-CONHSO₂Cyclopropane, Shown below



Thus the by-product, 9.0 mg of yellow solid was obtained (13.2%). LC/MS rt-min
 (MH⁺): 2.37 (718) [method B]. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.00 (s, 9 H)
 5 1.06 (m, 2 H) 1.12 (s, 9 H) 1.23 (m, 2 H) 1.43 (dd, *J*=9.41, 5.50 Hz, 1 H) 1.87 (dd,
J=8.19, 5.50 Hz, 1 H) 2.25 (m, 1 H) 2.35 (m, 1 H) 2.67 (dd, *J*=13.94, 7.09 Hz, 1 H)
 2.93 (m, 1 H) 4.10 (m, 1 H) 4.13 (s, 1 H) 4.43 (d, *J*=11.98 Hz, 1 H) 4.65 (dd,
J=10.03, 7.09 Hz, 1 H) 5.12 (dd, *J*=10.27, 1.47 Hz, 1 H) 5.30 (dd, *J*=17.12, 1.22 Hz,
 1 H) 5.51 (s, 1 H) 5.75 (m, 1 H) 7.61 (d, *J*=7.83 Hz, 1 H) 7.88 (t, *J*=8.19 Hz, 1 H)
 10 8.04 (m, 2 H) 8.91 (d, *J*=5.38 Hz, 1 H).

Example 243: Preparation of Compound 243

BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(3-hydroxyquinoxaline-2-oxo)-*S*-proline]-P1(1*R*,2*S*
 15 VinylAcce)-CONHSO₂Cyclopropane, Shown below

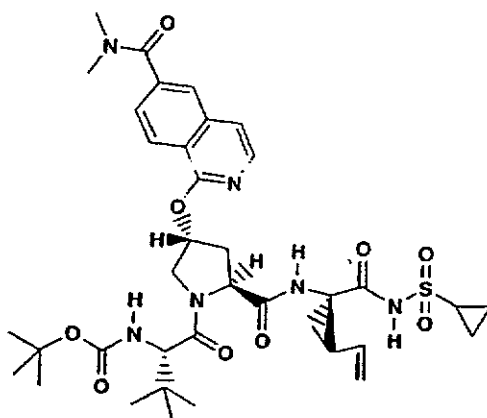


Following the general tripeptide alkylation procedure with commercial 2,3-
 20 dichloroquinoxaline, the mono alkylation product was spontaneously hydrolyzed to

give 8.0 mg of pale yellow solid (11.4%). LC/MS rt-min (MNa^+): 2.42 (723) [method B]. ^1H NMR (400 MHz, CD_3OD) δ ppm 0.99 (s, 9 H) 1.05 (m, 2 H) 1.24 (s, 9 H) 1.40 (m, 3 H) 1.86 (m, 1 H) 2.24 (m, 2 H) 2.53 (m, 1 H) 2.92 (m, 1 H) 4.06 (m, 1 H) 4.16 (s, 1 H) 4.40 (m, 1 H) 4.55 (dd, $J=10.39, 6.97$ Hz, 1 H) 5.11 (m, 1 H) 5.29 (m, 1 H) 5.73 (m, 1 H) 5.78 (s, 1 H) 7.15 (s, 1 H) 7.26 (m, 2 H) 7.36 (t, $J=7.83$ Hz, 1 H) 7.61 (d, $J=8.07$ Hz, 1 H).

Example 244: Preparation of Compound 244

- 10 Using a combination of Pd^0 coupling scheme and a step by step procedure starting from 6-bromo-1-chloro isoquinoline, BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(6-carboxylic acid dimethylamideisoquinoline-1-oxo)-*S*-proline]-P1(1*R*,2*S* VinylAcce)-CONHSO₂Cyclopropane, was prepared.



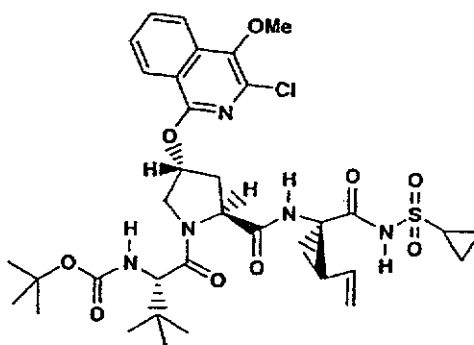
15

LC/MS rt-min (MNa^+): 2.34 (777) [method B]. ^1H NMR (400 MHz, CD_3OD) δ ppm 0.98 (m, 11 H) 1.23 (m, 11 H) 1.35 (m, 1 H) 1.91 (m, 1 H) 2.29 (m, 2 H) 2.47 (m, 1 H) 2.58 (m, 1 H) 2.97 (s, 3 H) 3.11 (s, 3 H) 4.09 (m, 1 H) 4.24 (s, 1 H) 4.44 (m, 1 H) 4.61 (m, 1 H) 5.16 (m, 2 H) 5.57 (m, 1 H) 5.90 (s, 1 H) 7.38 (d, $J=5.87$ Hz, 1 H) 7.50 (d, $J=8.07$ Hz, 1 H) 7.86 (s, 1 H) 8.03 (d, $J=5.87$ Hz, 1 H) 8.27 (d, $J=8.56$ Hz, 1 H),

Example 245: Preparation of Compound 245

During one of the Pd⁰ catalyzed Stille coupling preparations (**Example 230**), a side product was isolated as a minor product which was subsequently identified as: BOCNH-P3(*L*-*t*-BuGly)-P2[(4*R*)-(3-chloro-4-methoxyisoquinoline-1-oxo)-S-proline]-P1(1*R*,2*S* VinylAcce)-CONHSO₂Cyclopropane, shown below

5

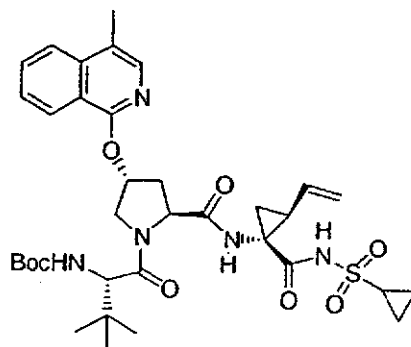


LC/MS rt-min (MNa⁺): 2.62 (770) [method B]. ¹H NMR (400 MHz, CD₃OD) δ ppm
 1.01 (s, 9 H) 1.08 (m, 2 H) 1.18 (s, 9 H) 1.27 (m, 2 H) 1.37 (m, 1 H) 1.62 (m, 1 H)
 10 2.36 (m, 2 H) 2.73 (m, 1 H) 2.97 (m, 1 H) 3.92 (s, 3 H) 4.02 (m, 1 H) 4.18 (s, 1 H)
 4.48 (m, 1 H) 4.66 (m, 1 H) 5.30 (m, 2 H) 5.78 (s, 1 H) 6.04 (m, 1 H) 7.53 (t, *J*=7.70
 Hz, 1 H) 7.77 (t, *J*=7.58 Hz, 1 H) 8.00 (d, *J*=8.56 Hz, 1 H) 8.19 (d, *J*=8.07 Hz, 1 H).

Section F:

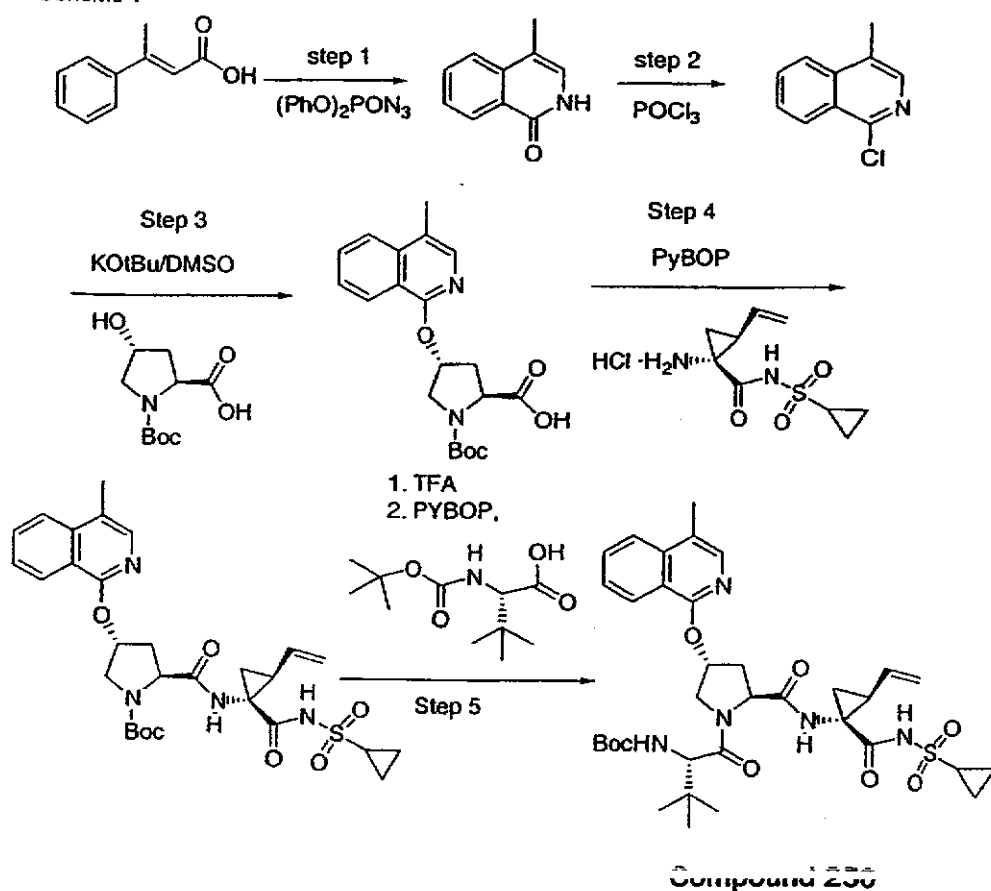
15

Example 250: Preparation of Compound 250



Compound 250

Scheme 1



Step 1:

A solution of 3-phenylbut-2-enoic acid (16.2 g), diphenylphosphoryl azide (27.5 g), and triethylamine (10.1 g) in benzene (100 mL) was stirred for 1 h. After filtration through a silica gel plug washing with benzene and concentration, the residue was dissolved in diphenylmethane (80 mL) and refluxed for 3 h. After cooling to rt, solids were collected through a plug washing with benzene and dried to give 10 g (63%) of the desired product as a solid. ^1H NMR (400 MHz, CD_3OD) δ ppm 2.30 (s, 3 H), 7.00 (s, 1 H), 7.54 (m, 1 H), 7.77 (m, 2 H), 8.33 (d, $J=7.34$ Hz, 1 H).

Step 2

A solution of 4-methyl-2*H*-isoquinolin-1-one (4.8 g) in POCl₃ (50 mL) was refluxed for 3 h. After cooling and concentration, the residue was based with 5 N NaOH and extracted with CH₂Cl₂. The organic layer was washed with brine and dried over MgSO₄. After concentration, purification by flash chromatography of Biotage with 5% ethyl acetate in hexanes gave 4.8 g (90%) of the desired product as a solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.59 (s, 3 H), 7.68 (t, *J*=7.70 Hz, 1 H), 7.78 (m, 1 H), 7.94 (d, *J*=8.31 Hz, 1 H), 8.11 (s, 1 H), 8.35 (d, *J*=8.31 Hz, 1 H).

Step 3:

10 A solution of Boc-Hyp-OH (231 mg) and *tert*-BuOK (336 mg) in DMSO (10 mL) was stirred for 0.5 h. To the solution was added 1-chloro-4-methyl-isoquinoline (178 mg) and the resulting mixture was stirred for 1 day. The reaction was quenched with 5% citric acid and extracted with ethyl acetate. The organic layer was washed with brine and dried over MgSO₄. Concentration gave 350 mg (94%) of the desired product as a solid which was used in the next step without further purification. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.39, 1.43 (2s, 9 H, rotamers), 2.40 (dd, *J*=17.97, 4.52 Hz, 1 H), 2.48 (s, 3 H), 2.68 (m, 1 H), 3.84 (m, 2 H), 4.46 (m, 1 H), 5.71 (s, 1 H), 7.58 (t, *J*=7.70 Hz, 1 H), 7.75 (m, 2 H), 7.91 (d, *J*=8.31 Hz, 1 H), 8.19 (m, 1 H); MS: (M+Na)⁺ 396.

20

Step 4:

A solution of 4-(4-methyl-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (74 mg), cyclopropanesulfonic acid (1(*R*)-amino-2(*S*)-vinyl-cyclopropanecarbonyl)-amide hydrochloride (59 mg), PyBOP (114 mg) and *i*-Pr₂NEt (0.2 mL) in CH₂Cl₂ (2 mL) was stirred for 2 h. Purification by flash chromatograph of Biotage with 5% MeOH in ethyl acetate gave 105 mg (90%) of the desired product. ¹H NMR (400 MHz, Methanol-D₄) δ ppm 1.18 (m, 5 H), 1.39 (s, 9 H), 1.87 (dd, *J*=8.2, 5.3 Hz, 1 H), 2.28 (m, 2 H), 2.54 (m, 4 H), 2.95 (m, 1 H), 3.86 (m, 2 H), 4.40 (dd, *J*=9.8, 6.9 Hz, 1 H), 5.12 (d, *J*=10.5 Hz, 1 H), 5.31 (d, *J*=17.6 Hz, 1 H), 5.79 (m, 2 H), 7.60 (t, *J*=7.5 Hz, 1 H), 7.78 (m, 2 H), 7.93 (d, *J*=8.3 Hz, 1 H), 8.20 (d, *J*=8.1 Hz, 1 H); MS: (M+Na)⁺ 607.

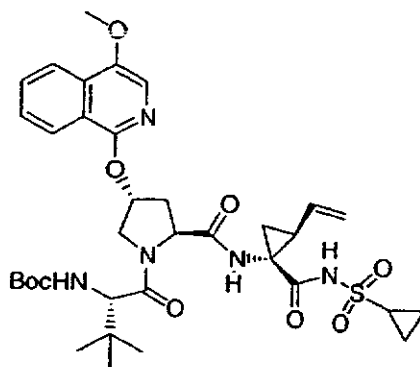
30

Step 5:

A solution of 2-(1-cyclopropanesulfonylamino-2-vinyl-cyclopropylcarbamoyl)-4-(4-methyl-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

- 5 (100 mg) and TFA (3 mL) in CH_2Cl_2 (3 mL) was stirred for 1 h. After concentration, the residue was dissolved in CH_2Cl_2 (2 mL), and Boc-L-*tert*-leucine (40 mg), PyBOP (104 mg) and *i*-Pr₂NEt (0.2 mL) was added. The mixture was stirred for 1 h. After work-up, purification Prep HPLC gave 60 mg (52%) of the desired product
- 10 **compound 250** as a solid. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.04 (m, 12H), 1.26 (m, 10 H), 1.44 (dd, *J*=9.5, 5.1 Hz, 1 H), 1.88 (dd, *J*=8.1, 5.4 Hz, 1 H), 2.26 (m, 2 H), 2.49 (s, 3 H), 2.62 (dd, *J*=13.7, 7.1 Hz, 1 H), 2.94 (m, 1 H), 4.06 (dd, *J*=12.0, 3.4 Hz, 1 H), 4.25 (m, 1 H), 4.45 (d, *J*=11.3 Hz, 1 H), 4.53 (dd, *J*=10.3, 6.6 Hz, 1 H), 5.12 (d, *J*=10.0 Hz, 1 H), 5.29 (d, *J*=17.1 Hz, 1 H), 5.77 (m, 2 H), 6.63 (d, *J*=8.6 Hz, 1 H), 7.53 (t, *J*=7.8 Hz, 1 H), 7.76 (t, *J*=8.1 Hz, 1 H), 7.80 (s, 1 H), 7.91 (d, *J*=8.1 Hz, 1 H),
- 15 8.22 (d, *J*=8.3 Hz, 1 H); MS: (M+Na)⁺ 720.

Example 251: Preparation of Compound 251



Compound 251

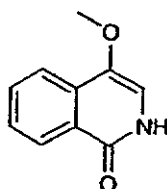
- 20 **Compound 251** was prepared by following Scheme 1 of Example 250 except that 3-methoxy-3-phenyl-acrylic acid was used in place of 3-phenyl-but-2-enoic acid in step 1.

Step 1:

327

Modifications: 15 g 3-methoxy-3-phenyl-acrylic acid used, 250 mg product obtained (2% yield).

Product:

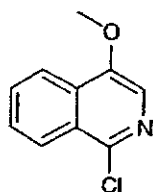


- 5 ^1H NMR (400 MHz, CD_3COCD_3) δ ppm 3.85 (s, 3 H), 6.96 (s, 1 H), 7.54 (m, 1 H), 7.71 (m, 1 H), 7.86 (d, $J=8.07$ Hz, 1 H), 8.31 (d, $J=8.07$ Hz, 1 H).

Step 2:

- 10 Modifications: 200 mg 4-methoxy-2*H*-isoquinolin-1-one used, 150 mg product obtained (68% yield).

Product:

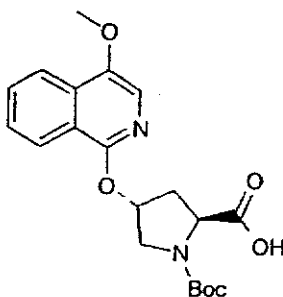


- 15 ^1H NMR (400 MHz, CDCl_3) δ ppm 4.05 (s, 2 H), 7.71 (m, 1 H), 7.72 (m, 2 H), 7.80 (s, 1 H), 8.23 (dd, $J=18.71$, 7.70 Hz, 2 H).

Step 3:

- Modifications: 122 mg 1-chloro-4-methoxy-isoquinoline used, 218 mg product obtained (89% yield).

Product:



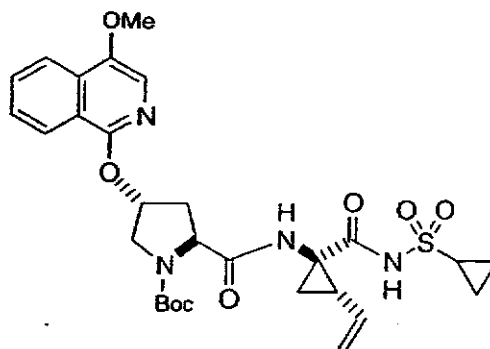
20

MS: $(\text{M}+\text{Na})^+$ 411.

Step 4:

Modifications: 194 mg 4-(4-methoxy-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester used, 298 mg product obtained (99% yield).

5 Product:

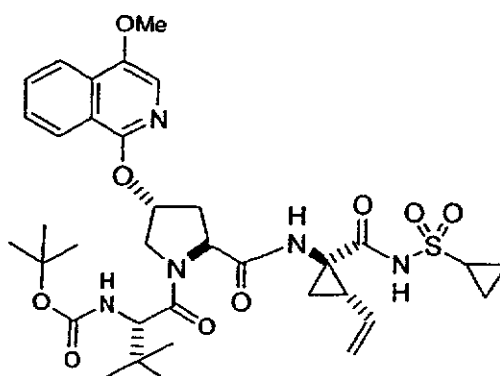


¹H NMR (400 MHz, CD₃OD) δ ppm 1.17 (m, 5 H), 1.42 (s, 9 H), 1.87 (dd, *J*=8.2, 5.5 Hz, 1 H), 2.27 (m, 2 H), 2.54 (dd, *J*=13.3, 6.2 Hz, 1 H), 2.95 (m, 1 H), 3.85 (m, 2 H), 4.00 (s, 3 H), 4.39 (dd, *J*=9.8, 6.9 Hz, 1 H), 5.12 (d, *J*=10.5 Hz, 1 H), 5.31 (d, *J*=17.1 Hz, 1 H), 5.76 (m, 2 H), 7.52 (s, 1 H), 7.62 (t, *J*=7.6 Hz, 1 H), 7.74 (t, *J*=7.2 Hz, 1 H), 8.12 (t, *J*=8.3 Hz, 2 H).

Step 5:

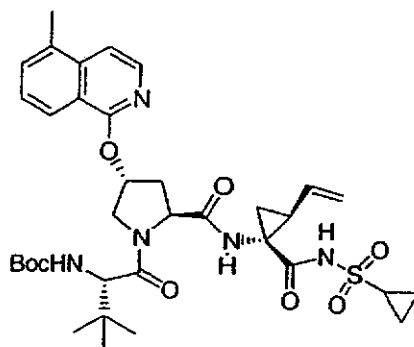
Modifications: 190 mg 2-(1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-(4-methoxy-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester used, 270 mg product obtained (51% yield).

Product:

**Compound 251**

Data: ^1H NMR (500 MHz, CD_3OD) δ ppm 1.06 (m, 12 H), 1.26 (m, 10 H), 1.43 (dd, $J=8.6, 4.6$ Hz, 1 H), 1.88 (dd, $J=7.9, 5.5$ Hz, 1 H), 2.24 (m, 2 H), 2.61 (dd, $J=13.6, 6.9$ Hz, 1 H), 2.94 (m, 1 H), 4.00 (s, 3 H), 4.06 (dd, $J=11.3, 3.1$ Hz, 1 H), 4.25 (d, $J=8.9$ Hz, 1 H), 4.43 (d, $J=11.3$ Hz, 1 H), 4.52 (m, 1 H), 5.12 (d, $J=10.1$ Hz, 1 H), 5.29 (d, $J=17.1$ Hz, 1 H), 5.75 (m, 2 H), 6.60 (d, $J=8.6$ Hz, 1 H), 7.55 (m, 2 H), 7.71 (t, $J=7.3$ Hz, 1 H), 8.09 (d, $J=8.2$ Hz, 1 H), 8.14 (d, $J=8.2$ Hz, 1 H); MS: $(\text{M}+\text{Na})^+$ 736.

10

Example 252: Preparation of Compound 252**Compound 252**

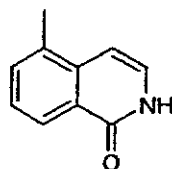
Compound 252 was prepared by following Scheme 1 of Example 250 except 2-methylcinnamic acid was used in place of 3-phenyl-but-2-enoic acid in step 1.

15

Step 1:

Modifications: 20 g 2-methylcinnamic acid used, 14.3 g product obtained (72% yield)

Product:

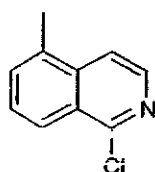


- 5 Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 2.54 (s, 1 H), 6.69 (d, $J=7.3$ Hz, 1 H), 7.23 (d, $J=7.3$ Hz, 1 H), 7.39 (t, $J=7.8$ Hz, 1 H), 7.50 (d, $J=7.1$ Hz, 1 H), 8.30 (d, $J=8.1$ Hz, 1 H), 11.62 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 160.

Step 2:

- 10 Modifications: 14.4 g 5-methyl-2H-isoquinolin-1-one used, 10.6 g product obtained (66% yield).

Product:

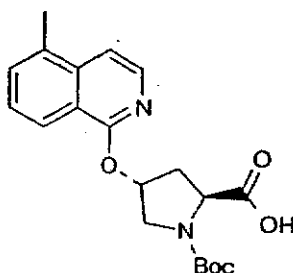


- 15 Data: ^1H NMR (400 MHz, CDCl_3) δ ppm 2.67 (s, 3 H), 7.55 (m, 2 H), 7.70 (dd, $J=5.9, 1.0$ Hz, 1 H), 8.19 (m, 1 H), 8.28 (d, $J=5.9$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 178.

Step 3:

Modifications: 533 mg 1-chloro-5-methyl-isoquinoline used, 1116 mg product obtained (100% yield).

- 20 Product:

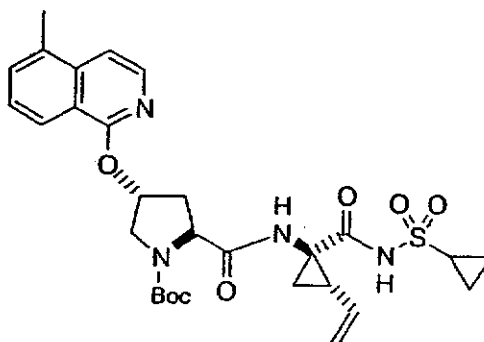


Data: MS: $(\text{M}+\text{H})^+$ 373.

Step 4:

Modifications: 372 mg 4-(5-methyl-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester used, 551 mg product obtained (94% yield).

Product:



5

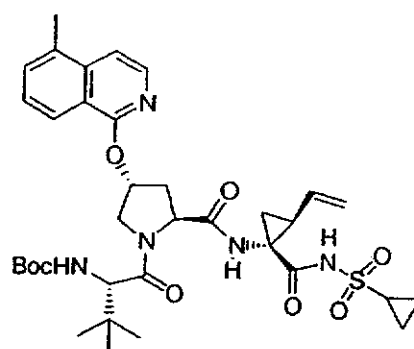
Data: MS: (M+Na)⁺ 607.

Step 5:

Modifications: 551 mg 2-(1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-(5-methyl-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester used, 274 mg product obtained (44% yield).

10

Product:

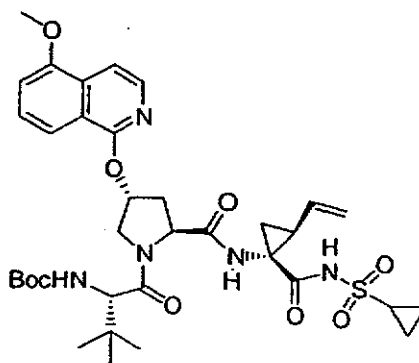


Compound 252

15 Data: ¹H NMR (400 MHz, CD₃OD) δ ppm 1.00 (m, 12 H), 1.23 (m, 10 H), 1.44 (m, 1 H), 1.87 (dd, *J*=8.1, 5.4 Hz, 1 H), 2.26 (m, 2 H), 2.62 (m, 4 H), 2.94 (m, 1 H), 4.07 (dd, *J*=11.9, 3.3 Hz, 1 H), 4.25 (d, *J*=9.5 Hz, 1 H), 4.46 (d, *J*=11.5 Hz, 1 H), 4.53 (dd, *J*=10.3, 7.1 Hz, 1 H), 5.12 (d, *J*=10.5 Hz, 1 H), 5.29 (d, *J*=16.9 Hz, 1 H), 5.75 (m, 1 H), 5.86 (s, 1 H), 6.62 (d, *J*=9.3 Hz, 1 H), 7.39 (t, *J*=7.7 Hz, 1 H), 7.44 (d, *J*=5.9 Hz,

1 H), 7.53 (d, $J=7.1$ Hz, 1 H), 8.00 (d, $J=6.1$ Hz, 1 H), 8.06 (d, $J=8.3$ Hz, 1 H); MS: (M+H)⁺ 698.

Example 253: Preparation of Compound 253



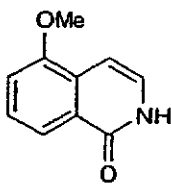
Compound 253

Compound 253 was prepared by following Scheme 1 of Example 250 except 2-methoxy cinnamic acid was used in place of 3-phenyl-but-2-enoic acid in step 1.

Step 1:

Modifications: 10 g 2-methoxy cinnamic acid used, 5.3 g product obtained (53% yield).

Product:

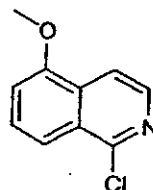


15 Data: ¹H NMR (400 MHz, CD₃OD) δ ppm 3.95 (s, 3 H), 6.94 (d, $J=7.3$ Hz, 1 H), 7.08 (d, $J=8.1$ Hz, 1 H), 7.14 (d, $J=7.3$ Hz, 1 H), 7.43 (t, $J=8.1$ Hz, 1 H), 7.99 (d, $J=8.1$ Hz, 1 H), 10.92 (s, 1 H); MS: (M+H)⁺ 176.

Step 2:

20 Modifications: 5.3 g 5-methoxy-2H-isoquinolin-1-one used, 5.38 g product obtained (92% yield).

Product:

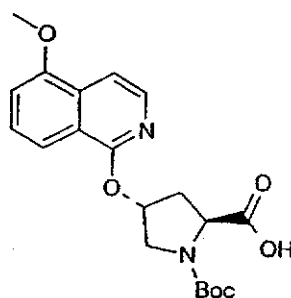


Data: ^1H NMR (400 MHz, CDCl_3) δ ppm 4.01 (s, 3 H), 7.04 (d, $J=7.8$ Hz, 1 H), 7.57 (t, $J=8.1$ Hz, 1 H), 7.88 (d, $J=8.6$ Hz, 1 H), 7.97 (d, $J=5.9$ Hz, 1 H), 8.25 (d, $J=5.9$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 194.

Step 3:

Modifications: 581 mg 1-chloro-5-methoxy-isoquinoline used, 1163 mg product obtained (100% yield).

10 Product:

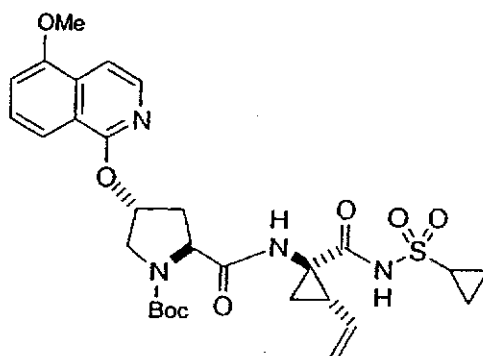


Data: MS: $(\text{M}+\text{H})^+$ 389.

Step 4:

15 Modifications: 117 mg 4-(5-methoxy-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester used, 180 mg product obtained (100% yield).

Product:

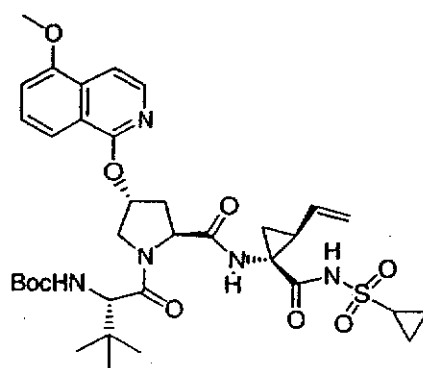


Data: MS: (M+H)⁺ 601.

Step 5:

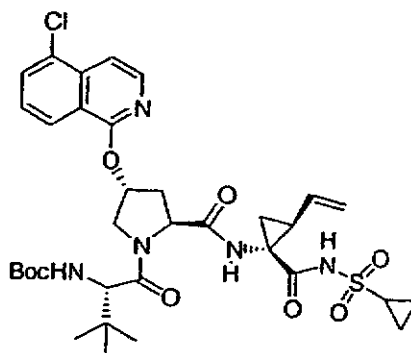
- Modifications: 177 mg 2-(1-cyclopropanesulfonylamino-2-vinyl-
 5 cyclopropylcarbamoyl)-4-(5-methoxy-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic
 acid *tert*-butyl ester used, 63 mg product obtained (44% yield).

Product:



Compound 253

- 10 Data: ¹H NMR (400 MHz, CD₃OD) δ ppm 1.00 (m, 12 H), 1.21 (m, 10 H), 1.38 (m, 1
 H), 1.82 (dd, *J*=8.1, 5.6 Hz, 1 H), 2.20 (m, 2 H), 2.56 (dd, *J*=13.6, 6.7 Hz, 1 H), 2.88
 (m, 1 H), 3.08 (m, 2 H), 3.93 (s, 3 H), 4.01 (dd, *J*=11.9, 3.3 Hz, 1 H), 4.20 (d, *J*=9.1
 Hz, 1 H), 4.39 (d, *J*=12.2 Hz, 1 H), 4.47 (dd, *J*=9.7, 7.0 Hz, 1 H), 5.06 (d, *J*=10.0 Hz,
 1 H), 5.23 (d, *J*=16.9 Hz, 1 H), 5.70 (m, 1 H), 5.79 (s, 1 H), 6.55 (d, *J*=9.5 Hz, 1 H),
 15 7.08 (d, *J*=7.6 Hz, 1 H), 7.37 (t, *J*=8.0 Hz, 1 H), 7.54 (d, *J*=5.9 Hz, 1 H), 7.68 (d,
J=8.3 Hz, 1 H), 7.89 (d, *J*=5.9 Hz, 1 H); MS: (M+H)⁺ 714.

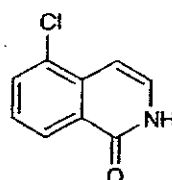
Example 254: Preparation of Compound 254**Compound 254**

Compound 254 was prepared by following Scheme 1 of Example 250 except that 2-chlorocinnamic acid was used in place of 3-phenyl-but-2-enoic acid in step 1.

Step 1:

Modifications: 25 g 2-chlorocinnamic acid used, 14.6 g product obtained (59% yield).

Product:



Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 7.22 (d, $J=7.3$ Hz, 1 H), 7.42 (t, $J=7.8$ Hz, 1 H), 7.73 (d, $J=7.8$ Hz, 1 H), 8.34 (d, $J=8.1$ Hz, 1 H), 10.61 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 180.

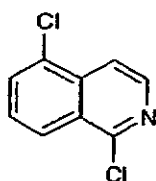
15

Step 2:

Modifications: 14.2 g 5-chloro-2H-isoquinolin-1-one used, 8.28 g product obtained (53% yield).

Product:

336



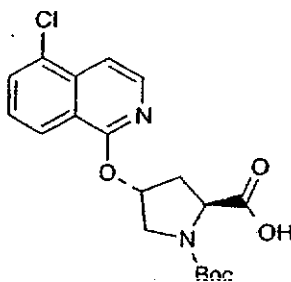
Data: ^1H NMR (400 MHz, CDCl_3) δ ppm 7.60 (dd, $J=8.6, 7.6$ Hz, 1 H), 7.83 (m, 1 H), 8.00 (d, $J=5.9$ Hz, 1 H), 8.29 (dt, $J=8.9, 1.0$ Hz, 1 H), 8.38 (d, $J=5.9$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 198.

5

Step 3:

Modifications: 594 mg 1,5-dichloro-isoquinoline used, 1174 mg product obtained (100% yield).

Product:



10

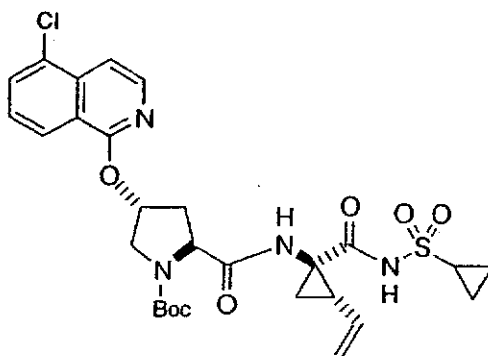
Data: MS: $(\text{M}+\text{H})^+$ 393.

Step 4:

Modifications: 118 mg 4-(5-chloro-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester used, 154 mg product obtained (85% yield).

15

Product:

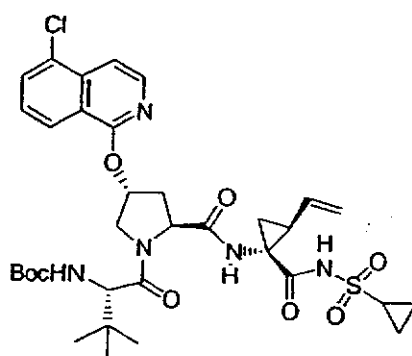


Data: MS: $(\text{M}+\text{H})^+$ 605.

Step 5:

Modifications: 150 mg 2-(1-cyclopropanesulfonylamino-2-vinyl-cyclopropylcarbamoyl)-4-(5-chloro-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester used, 91 mg product obtained (51% yield).

5 Product:

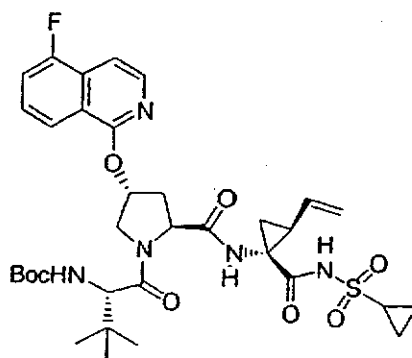


Compound 254

Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 0.97 (m, 12 H), 1.17 (m, 10 H), 1.38 (dd, $J=9.4, 5.3$ Hz, 1 H), 1.82 (dd, $J=8.0, 5.5$ Hz, 1 H), 2.21 (m, 2 H), 2.58 (dd, $J=13.8, 7.0$ Hz, 1 H), 2.88 (m, 1 H), 4.01 (dd, $J=11.9, 2.8$ Hz, 1 H), 4.16 (d, $J=9.3$ Hz, 1 H), 4.47 (m, 2 H), 5.06 (d, $J=10.3$ Hz, 1 H), 5.24 (d, $J=16.9$ Hz, 1 H), 5.70 (m, 1 H), 5.82 (s, 1 H), 6.52 (d, $J=9.3$ Hz, 1 H), 7.42 (t, $J=8.0$ Hz, 1 H), 7.57 (d, $J=6.1$ Hz, 1 H), 7.76 (d, $J=7.6$ Hz, 1 H), 8.05 (d, $J=6.1$ Hz, 1 H), 8.13 (d, $J=8.3$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 718.

15

Example 255: Preparation of Compound 255



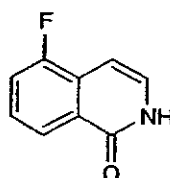
Compound 255

Compound 255 was prepared by following Scheme 1 of Example 250 except that 2-fluorocinnamic acid was used in place of 3-phenyl-but-2-enoic acid in step 1.

5 Step 1:

Modifications: 16.6 g 2-fluorocinnamic acid used, 8.55 g product obtained (51% yield).

Product:

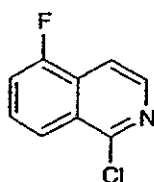


- 10 Data: ^1H NMR (400 MHz, CD_3COCD_3) δ ppm 6.62 (d, $J=7.3$ Hz, 1 H), 7.32 (d, $J=7.3$ Hz, 1 H), 7.47 (m, 2 H), 8.09 (m, 1 H).

Step 2:

- 15 Modifications: 8.4 g 5-fluoro-1H-isoquinolin-1-one used, 1.5 g product obtained (80% yield).

Product:

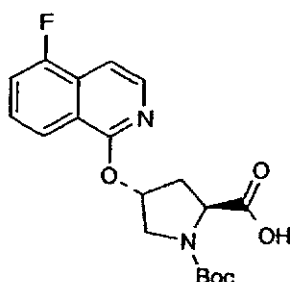


- 20 Data: ^1H NMR (400 MHz, CDCl_3) δ ppm 7.43 (ddd, $J=9.7, 7.8, 0.9$ Hz, 1 H), 7.62 (td, $J=8.2, 5.4$ Hz, 1 H), 7.84 (d, $J=5.6$ Hz, 1 H), 8.14 (d, $J=8.6$ Hz, 1 H), 8.33 (d, $J=5.9$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 182.

Step 3:

- 25 Modifications: 203 mg 1-chloro-5-fluoro-isoquinoline used, 384 mg product obtained (90% yield).

Product:

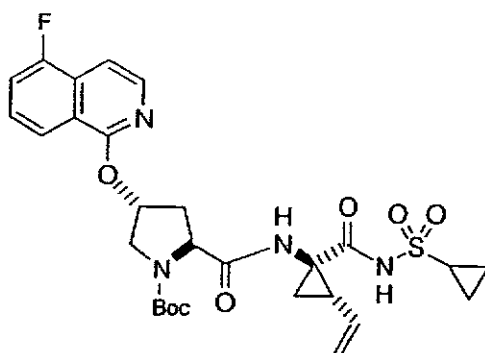


Data: ^1H NMR (400 MHz, CD_3SOCD_3) δ ppm 1.34, 1.36 (2s, 9 H, rotamers), 2.35 (m, 1 H), 2.61 (m, 1 H), 3.65 (d, $J=12.23$ Hz, 1 H), 3.80 (m, 1 H), 4.35 (m, 1 H), 5.70 (s, 1 H), 7.48 (d, $J=6.11$ Hz, 1 H), 7.63 (m, 2 H), 7.99 (m, 1 H), 8.10 (d, $J=5.87$ Hz, 1 H); MS: $(\text{M}+\text{Na})^+$ 399.

Step 4:

Modifications: 76 mg 4-(5-fluoro-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester used, 116 mg product obtained (99% yield).

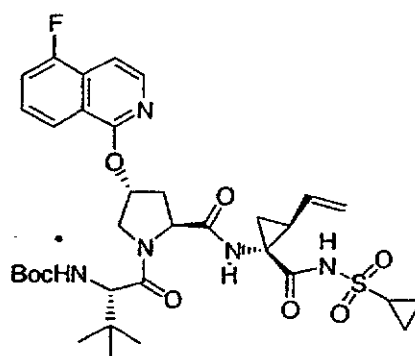
10 Product:



Step 5:

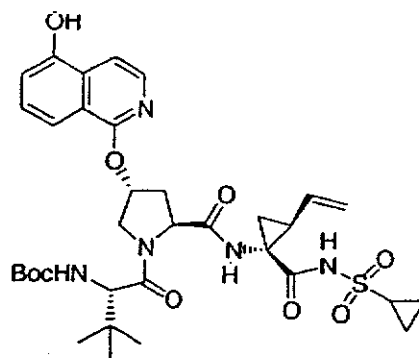
Modifications: 110 mg 2-(1-cyclopropanesulfonylamino-2-vinylcyclopropylcarbamoyl)-4-(5-fluoro-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester used, 39 mg product obtained (30% yield).

Product:

**Compound 255**

Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.05 (m, 12 H), 1.25 (m, 10 H), 1.44 (dd, $J=9.5, 5.4$ Hz, 1 H), 1.88 (dd, $J=8.1, 5.4$ Hz, 1 H), 2.28 (m, 2 H), 2.63 (dd, $J=13.8, 7.0$ Hz, 1 H), 2.94 (m, 1 H), 4.07 (dd, $J=11.9, 3.1$ Hz, 1 H), 4.23 (d, $J=9.3$ Hz, 1 H), 4.52 (m, 2 H), 5.12 (dd, $J=10.3, 1.5$ Hz, 1 H), 5.29 (d, $J=17.4$ Hz, 1 H), 5.75 (m, 1 H), 5.89 (s, 1 H), 6.59 (d, $J=9.1$ Hz, 1 H), 7.47 (m, 3 H), 8.02 (d, $J=8.1$ Hz, 1 H), 8.06 (d, $J=6.1$ Hz, 1 H); MS: $(\text{M}+\text{Na})^+$ 724.

Example 256: Preparation of Compound 256

**Compound 256**

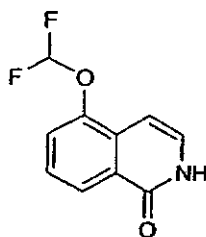
Compound 256 was prepared by following Scheme 1 of Example 250 except 2-difluoromethoxycinnamic acid was used in place of 3-phenyl-but-2-enoic acid in step

15 1.

Step 1:

Modifications: 10.7 g 2-difluoromethoxycinnamic acid used, 2 g product obtained (18% yield).

Product:

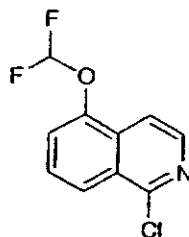


- 5 Data: ^1H NMR (400 MHz, CD_3SOCD_3) δ ppm 6.06 (m, 2 H), 6.42 (m, 2 H), 6.71 (s, 2 H), 7.35 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 212.

Step 2:

- Modifications: 300 mg 5-difluoromethoxy-2H-isoquinolin-1-one used, 300 mg
10 product obtained (92% yield).

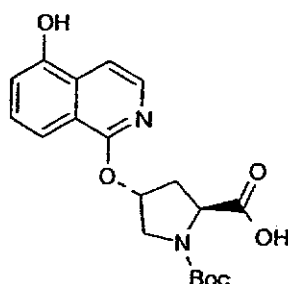
Product:



- Data: ^1H NMR (400 MHz, CDCl_3) δ ppm 6.70 (t, $J=72.87$ Hz, 1 H), 7.48 (m, 1 H),
7.64 (m, 1 H), 7.92 (d, $J=5.87$ Hz, 1 H), 8.21 (d, $J=8.56$ Hz, 1 H), 8.35 (d, $J=5.62$ Hz,
15 1 H).

Step 3:

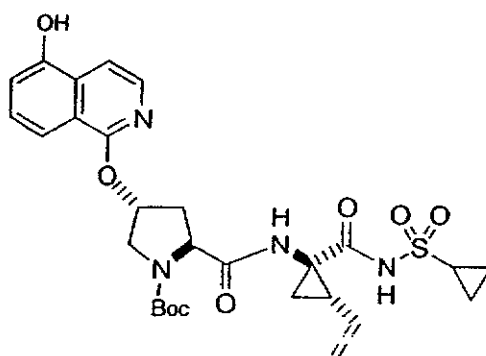
- Modifications: 230 mg 1-chloro-5-difluoromethoxy-isoquinoline used, 360 mg
product obtained (96% yield).
20 Product:



Step 4:

Modifications: 37 mg 4-(5-hydroxy-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester used, 57 mg product obtained (99% yield).

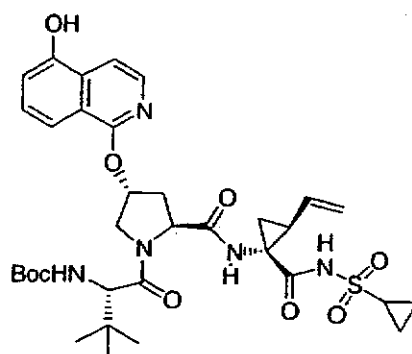
Product:



10 Step 5:

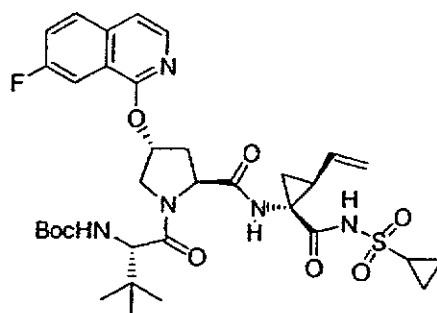
Modifications: 57 mg 2-(1-cyclopropanesulfonylamino-2-vinyl-cyclopropylcarbamoyl)-4-(5-hydroxy-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester used, 10 mg product obtained (15% yield).

Product:

**Compound 256**

Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 0.93 (m, 4 H), 1.13 (s, 9 H), 1.31 (m, 1 H), 1.49 (s, 9H), 1.89 (dd, $J=7.8, 5.4$ Hz, 1 H), 2.16 (q, $J=8.8$ Hz, 1 H), 2.40 (m, 1 H), 2.81 (m, 1 H), 2.90 (m, 1 H), 3.76 (m, 2 H), 4.30 (m, 1 H), 4.59 (dd, $J=10.2, 7.7$ Hz, 1 H), 5.07 (dd, $J=10.3, 1.7$ Hz, 1 H), 5.26 (dd, $J=17.2, 1.3$ Hz, 1 H), 5.77 (dt, $J=17.2, 9.6$ Hz, 1 H), 5.93 (s, 1 H), 7.24 (d, $J=8.6$ Hz, 1 H), 7.51 (m, 2 H), 7.63 (t, $J=8.0$ Hz, 1 H), 7.98 (d, $J=6.1$ Hz, 1 H), 8.24 (d, $J=8.3$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 700.

10 Example 257: Preparation of Compound 257

**Compound 257**

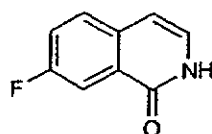
Compound 257 was prepared by following Scheme 1 of Example 250 except 4-fluorocinnamic acid was used in place of 3-phenyl-but-2-enoic acid in step 1.

15 Step 1:

Modifications: 16.6 g 4-fluorocinnamic acid used, 8.2 g product obtained (49% yield).

Product:

344



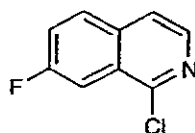
Data: ^1H NMR (400 MHz, CD_3COCD_3) δ ppm 6.57 (d, $J=7.09$ Hz, 1 H), 7.21 (d, $J=7.09$ Hz, 1 H), 7.50 (m, 1 H), 7.72 (dd, $J=8.68$, 5.26 Hz, 1 H), 7.90 (dd, $J=9.54$, 2.93 Hz, 1 H).

5

Step 2:

Modifications: 8.15 g 7-fluoro-2H-isoquinolin-1-one used, 7.6 g product obtained (84% yield).

Product:



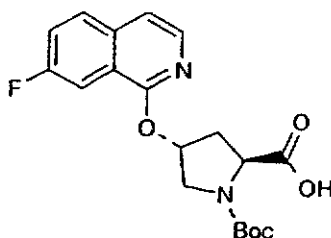
10

Data: ^1H NMR (400 MHz, CDCl_3) δ ppm 7.52 (td, $J=8.6$, 2.6 Hz, 1 H), 7.59 (d, $J=5.6$ Hz, 1 H), 7.86 (dd, $J=9.1$, 5.4 Hz, 1 H), 7.95 (dd, $J=9.5$, 2.5 Hz, 1 H), 8.26 (d, $J=5.6$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 182.

15 Step 3:

Modifications: 191 mg 1-chloro-7-fluoro-isoquinoline used, 350 mg product obtained (93% yield).

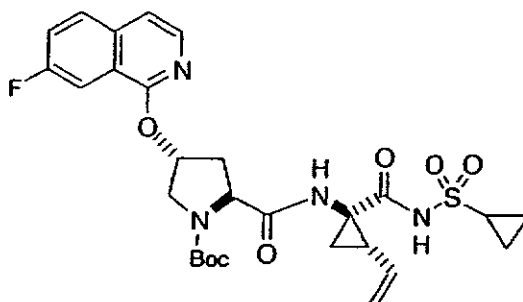
Product:

20 Data: MS: $(\text{M}+\text{Na})^+$ 399.

Step 4:

Modifications: 75 mg 4-(7-fluoro-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester used, 100 mg product obtained (85% yield)

Product:

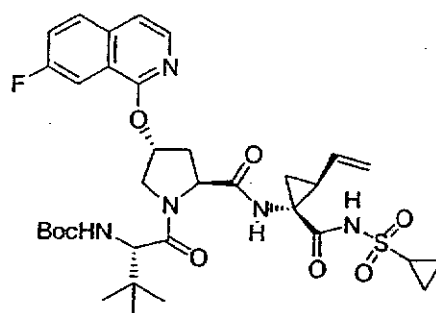


Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.16 (m, 4 H), 1.41 (m, 10 H), 1.88 (dd, $J=8.1, 5.4$ Hz, 1 H), 2.28 (m, 2 H), 2.56 (m, 1 H), 2.94 (m, 1 H), 3.87 (m, 2 H), 4.41 (dd, $J=9.7, 7.0$ Hz, 1 H), 5.12 (d, $J=10.8$ Hz, 1 H), 5.31 (d, $J=17.1$ Hz, 1 H), 5.78 (m, 2 H), 7.36 (d, $J=5.9$ Hz, 1 H), 7.54 (m, 1 H), 7.78 (dd, $J=9.3, 2.5$ Hz, 1 H), 7.90 (dd, $J=9.1, 5.1$ Hz, 1 H), 7.96 (d, $J=5.9$ Hz, 1 H); MS: $(\text{M}+\text{Na})^+$ 611.

Step 5:

Modifications: 95 mg 2-(1-cyclopropanesulfonylamino-carbonyl-2-vinyl-cyclopropylcarbamoyl)-4-(7-fluoro-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester used, 55 mg product obtained (44% yield).

Product:

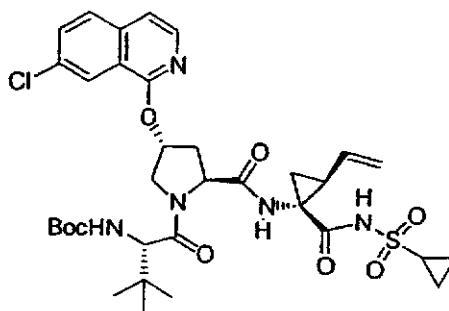


Compound 257

Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.05 (m, 12 H), 1.22 (m, 10 H), 1.44 (dd, $J=9.3, 5.4$ Hz, 1 H), 1.88 (dd, $J=8.2, 5.5$ Hz, 1 H), 2.27 (m, 2 H), 2.63 (dd, $J=13.8, 7.0$ Hz, 1 H), 2.94 (m, 1 H), 4.07 (dd, $J=11.5, 3.2$ Hz, 1 H), 4.22 (d, $J=9.5$ Hz, 1 H), 4.47 (d, $J=11.7$ Hz, 1 H), 4.55 (dd, $J=10.6, 7.5$ Hz, 1 H), 5.12 (d, $J=10.3$ Hz, 1 H), 5.29 (d, $J=17.1$ Hz, 1 H), 5.75 (m, 1 H), 5.87 (s, 1 H), 6.61 (d, $J=9.5$ Hz, 1 H), 7.36

(d, $J=5.9$ Hz, 1 H), 7.52 (td, $J=8.9, 2.5$ Hz, 1 H), 7.79 (dd, $J=9.4, 2.6$ Hz, 1 H), 7.88 (dd, $J=8.7, 5.5$ Hz, 1 H), 7.96 (d, $J=5.9$ Hz, 1 H); MS: $(M+Na)^+$ 724.

Example 258: Preparation of Compound 258



5

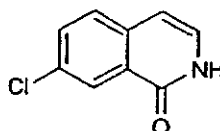
Compound 258

Compound 258 was prepared by following Scheme 1 of Example 250 except that 4-chlorocinnamic acid was used in place of 3-phenyl-but-2-enoic acid in step 1.

10 Step 1:

Modifications: 9.13 g 4-chlorocinnamic acid used, 4 g product obtained (44% yield).

Product:

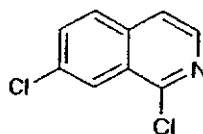


15 Data: ^1H NMR (400 MHz, CD_3SOCD_3) δ ppm 6.58 (d, $J=7.1$ Hz, 1 H), 7.20 (dd, $J=7.1, 5.9$ Hz, 1 H), 7.72 (m, 2 H), 8.10 (m, 1 H).

Step 2:

Modifications: 3.5 g 7-chloro-2H-isoquinolin-1-one used, 2.8 g product obtained (72% yield).

20 Product:

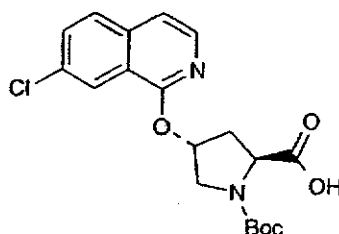


Data: ^1H NMR (500 MHz, CDCl_3) δ ppm 7.59 (d, $J=5.5$ Hz, 1 H), 7.69 (dd, $J=8.9$, 2.1 Hz, 1 H), 7.80 (d, $J=8.6$ Hz, 1 H), 8.29 (d, $J=5.5$ Hz, 1 H), 8.34 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 198.

5 Step 3:

Modifications: 208 mg 1,7-dichloro-isoquinoline used, 350 mg product obtained (89% yield).

Product:

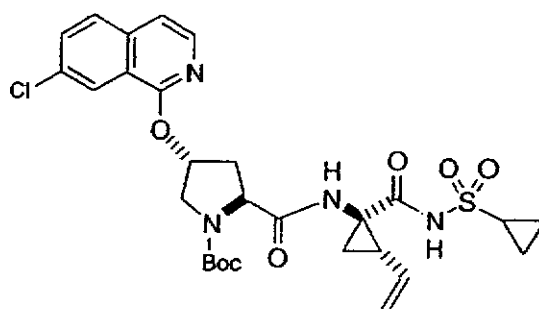


10 Data: MS: $(\text{M}+\text{Na})^+$ 415.

Step 4:

Modifications: 79 mg 4-(7-chloro-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester used, 119 mg product obtained (99% yield).

15 Product:

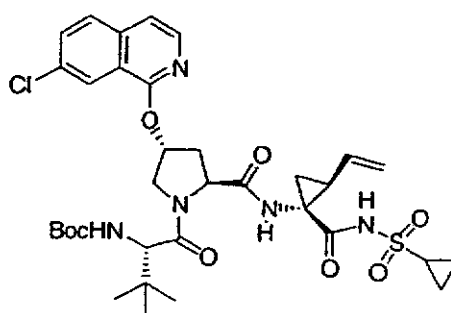


Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.17 (m, 4 H), 1.43 (m, 10 H), 1.88 (dd, $J=8.3$ 5.4 Hz, 1 H), 2.29 (m, 2 H), 2.57 (dd, $J=13.7$, 6.9 Hz, 1 H), 2.95 (m, 1 H), 3.87 (m, 2 H), 4.42 (dd, $J=9.9$, 6.9 Hz, 1 H), 5.13 (d, $J=10.3$ Hz, 1 H), 5.31 (dd, $J=17.1$, 1.2 Hz, 1 H), 5.78 (m, 2 H), 7.35 (d, $J=5.9$ Hz, 1 H), 7.69 (dd, $J=8.7$, 2.1 Hz, 1 H), 7.84 (d, $J=8.8$ Hz, 1 H), 7.99 (d, $J=5.9$ Hz, 1 H), 8.12 (d, $J=1.7$ Hz, 1 H); MS: $(\text{M}+\text{Na})^+$ 627.

Step 5:

Modifications: 115 mg 2-(1-cyclopropanesulfonylamino-2-vinyl-cyclopropylcarbamoyl)-4-(7-chloro-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester used, 36 mg product obtained (25% yield).

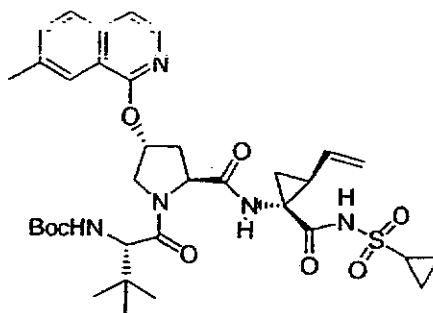
5 Product:



Compound 258

Data: MS: (M+Na)⁺ 740.

10 Example 259: Preparation of Compound 259



Compound 259

Compound 259 was prepared by following Scheme 1 of Example 250 except that 4-methylcinnamic acid was used in place of 3-phenyl-but-2-enoic acid in step 1.

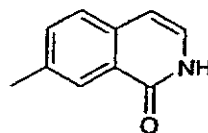
15

Step 1:

Modifications: 25 g 4-methylcinnamic acid used, 15.3 g product obtained (62% yield).

Product:

349



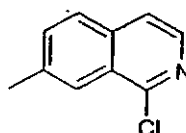
Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 2.50 (s, 3 H), 6.54 (d, $J=7.1$ Hz, 1 H), 7.13 (d, $J=7.1$ Hz, 1 H), 7.49 (m, 2 H), 8.22 (s, 1 H), 11.49 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 160.

5

Step 2:

Modifications: 15.3 g 7-methyl-2H-isoquinolin-1-one used, 5.15 g product obtained (30% yield).

Product:



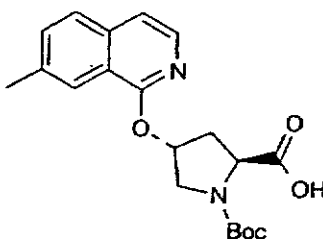
10

Data: ^1H NMR (400 MHz, CDCl_3) δ ppm 2.58 (s, 3 H), 7.56 (m, 2 H), 7.73 (d, $J=8.3$ Hz, 1 H), 8.09 (s, 1 H), 8.20 (d, $J=5.6$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 178.

Step 3:

15 Modifications: 205 mg 1-chloro-7-methyl-isoquinoline used, 350 mg product obtained (89 % yield).

Product:

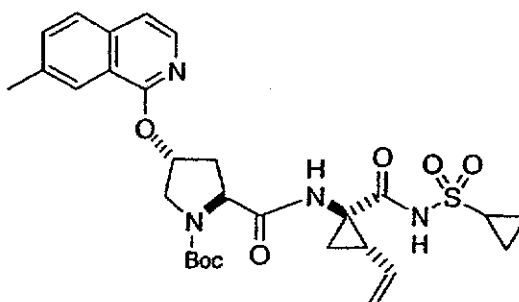


Data: MS: $(\text{M}+\text{H})^+$ 373.

20 Step 4:

Modifications: 75 mg 4-(7-methyl-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester used, 107 mg product obtained (95% yield).

Product:

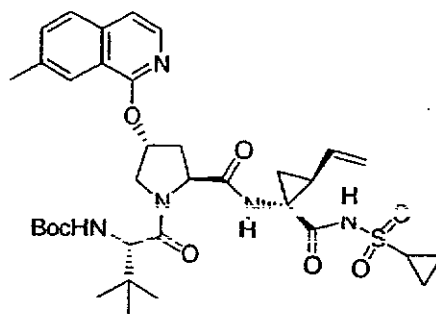


Data: MS: (M+Na)⁺ 607.

Step 5:

- 5 Modifications: 107 mg 2-(1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-(7-methyl-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester used, 53 mg product obtained (41% yield).

Product:

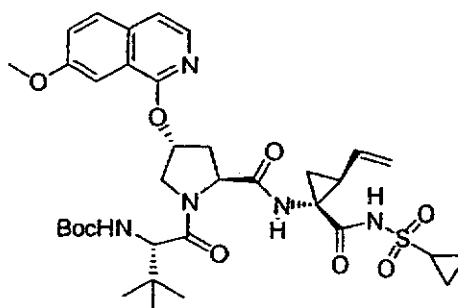


Compound 259

10

Data: ¹H NMR (400 MHz, CD₃OD) δ ppm 1.02 (m, 12 H), 1.18 (s, 9 H), 1.24 (m, 1 H), 1.45 (dd, *J*=9.4, 5.5 Hz, 1 H), 1.88 (dd, *J*=8.2, 5.5 Hz, 1 H), 2.28 (m, 2 H), 2.50 (s, 3 H), 2.61 (dd, *J*=13.8, 6.7 Hz, 1 H), 3.34 (s, 1 H), 4.09 (dd, *J*=11.7, 3.2 Hz, 1 H), 4.23 (s, 1 H), 4.42 (d, *J*=12.0 Hz, 1 H), 4.57 (dd, *J*=10.0, 7.1 Hz, 1 H), 5.12 (dd, *J*=10.3, 1.5 Hz, 1 H), 5.30 (d, *J*=17.1 Hz, 1 H), 5.76 (m, 1 H), 5.87 (s, 1 H), 7.28 (d, *J*=5.9 Hz, 1 H), 7.55 (d, *J*=8.3 Hz, 1 H), 7.71 (d, *J*=8.3 Hz, 1 H), 7.89 (d, *J*=5.9 Hz, 1 H), 7.93 (s, 1 H); MS: (M+H)⁺ 698.

15

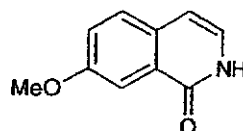
Example 260: Preparation of Compound 260**Compound 260**

Compound 260 was prepared by following Scheme 1 of Example 250 except that 4-methoxycinnamic acid was used in place of 3-phenyl-but-2-enoic acid in step 1.

Step 1:

Modifications: 33 g using 4-methoxycinnamic acid used, 7 g product obtained (33% yield).

Product:

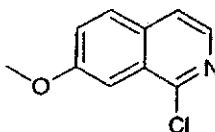


Data: ^1H NMR (500 MHz, CD_3COCD_3) δ ppm 3.90 (s, 3 H), 6.49 (d, $J=7.0$ Hz, 1 H), 7.10 (d, $J=7.3$ Hz, 1 H), 7.28 (dd, $J=8.6, 2.8$ Hz, 1 H), 7.57 (d, $J=8.9$ Hz, 1 H), 7.71 (d, $J=2.8$ Hz, 1 H).

Step 2:

Modifications: 4 g 7-methoxy-2H-isoquinolin-1-one used, 3 g product obtained (68 % yield).

Product:

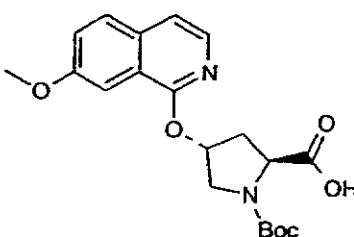


Data: ^1H NMR (400 MHz, CDCl_3) δ ppm 3.98 (s, 3 H), 7.38 (dd, $J=8.9, 2.6$ Hz, 1 H), 7.52 (m, 2 H), 7.73 (d, $J=8.8$ Hz, 1 H), 8.16 (d, $J=5.4$ Hz, 1 H).

Step 3:

- 5 Modifications: 533 mg 1-chloro-7-methoxy-isoquinoline used, 1115 mg product obtained (100 % yield).

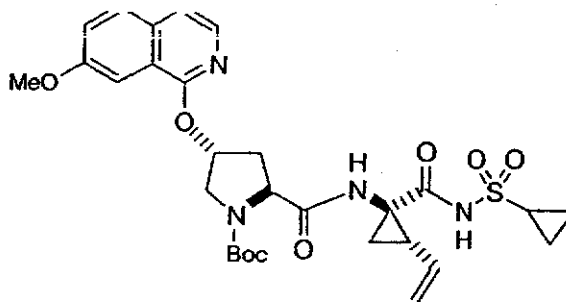
Product:



10 Step 4:

Modifications: 78 mg 4-(7-methoxyisoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester used, 108 mg product obtained (99 % yield).

Product:

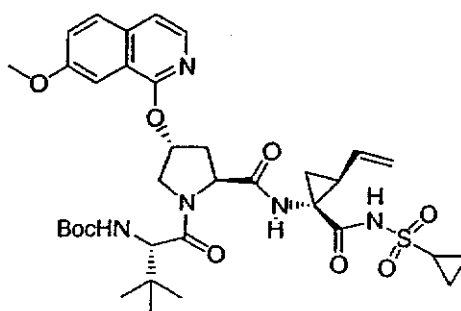


- 15 Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.17 (m, 4H), 1.40 (m, 1 H), 1.43 (s, 9 H), 1.85 (dd, $J=8.1, 5.4$ Hz, 1 H), 2.21 (m, 2 H), 2.51 (dd, $J=13.7, 6.6$ Hz, 1 H), 2.93 (s, 1 H), 3.80 (m, 2 H), 3.94 (s, 3 H), 4.41 (dd, $J=10.0, 6.6$ Hz, 1 H), 4.57 (s, 1 H), 5.11 (d, $J=11.3$ Hz, 1 H), 5.29 (d, $J=17.1$ Hz, 1 H), 5.77 (m, 2 H), 7.01 (d, $J=7.8$ Hz, 1 H), 7.22 (d, $J=5.6$ Hz, 1 H), 7.32 (d, $J=8.1$ Hz, 1 H), 7.58 (t, $J=8.0$ Hz, 1 H), 7.87 (d, $J=5.9$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 601.
- 20

Step 5:

Modifications: 100 mg 2-(1-cyclopropanesulfonylamino-2-vinyl-cyclopropylcarbamoyl)-4-(7-methoxy-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester used, 30 mg product obtained (25% yield).

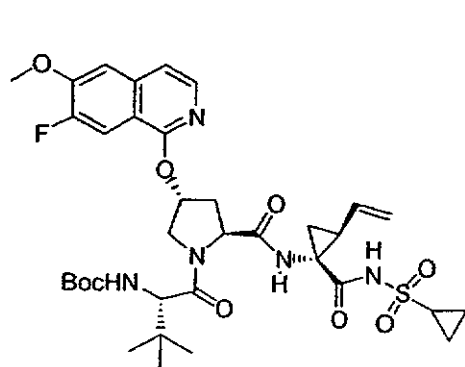
5 Product:



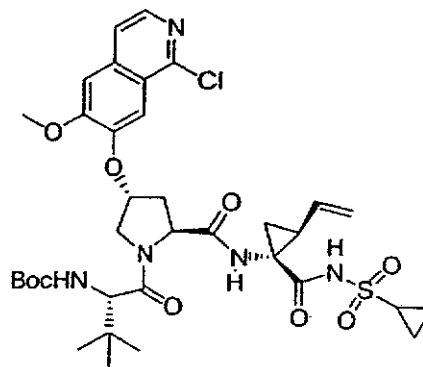
Compound 260

Data: ^1H NMR (400 MHz, CD_3SOCD_3) δ ppm 0.90 (m, 2 H), 0.95 (s, 9 H), 1.05 (m, 1 H), 1.12 (s, 9 H), 1.35 (m, 2 H), 1.70 (m, 1 H), 2.18 (m, 1 H), 2.92 (m, 1 H), 3.86 (s, 3 H), 4.00 (m, 2 H), 4.27 (d, $J=12.0$ Hz, 1 H), 4.45 (t, $J=8.6$ Hz, 1 H), 5.09 (d, $J=10.8$ Hz, 1 H), 5.23 (d, $J=16.9$ Hz, 1 H), 5.62 (m, 1 H), 5.79 (s, 1 H), 6.55 (d, $J=8.1$ Hz, 1 H), 7.35 (d, $J=6.6$ Hz, 1 H), 7.39 (d, $J=2.5$ Hz, 1 H), 7.43 (dd, $J=8.8, 2.2$ Hz, 1 H), 7.84 (d, $J=8.8$ Hz, 1 H), 7.88 (d, $J=5.9$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 714.

15 Example 261 and 262: Preparation of Compounds 261 and 262



Compound 261



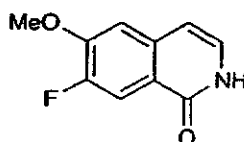
Compound 262

Compounds 261 and 262 were prepared by following Scheme 1 of Example 250 except that 4-fluoro-3-methoxycinnamic acid was used in place of 3-phenyl-but-2-enoic acid in step 1.

5 Step 1:

Modifications: 19.6 g 4-fluoro-3-methoxycinnamic acid used, 9.5 g product obtained (48% yield).

Product:

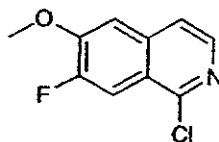


- 10 Data: ^1H NMR (400 MHz, CD_3COCD_3) δ ppm 4.00 (s, 1 H), 6.49 (d, $J=7.34$ Hz, 1 H), 7.19 (d, $J=7.09$ Hz, 1 H), 7.29 (d, $J=8.07$ Hz, 1 H), 7.86 (d, $J=11.74$ Hz, 1 H).

Step 2:

- 15 Modifications: 9 g 7-fluoro-6-methoxy-2H-isoquinolin-1-one used, 7 g product obtained (70% yield).

Product:

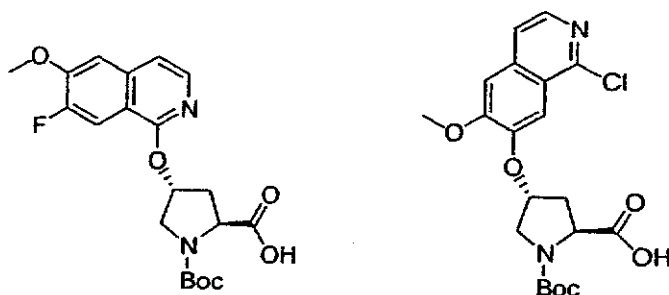


- 20 Data: ^1H NMR (400 MHz, CDCl_3) δ ppm 4.04 (s, 3 H), 7.17 (d, $J=8.07$ Hz, 1 H), 7.48 (d, $J=5.62$ Hz, 1 H), 7.94 (d, $J=11.49$ Hz, 1 H), 8.20 (d, $J=5.62$ Hz, 1 H).

Step 3:

Modifications: 222 mg 1-chloro-7-fluoro-6-methoxy-isoquinoline used, 406 mg products obtained.

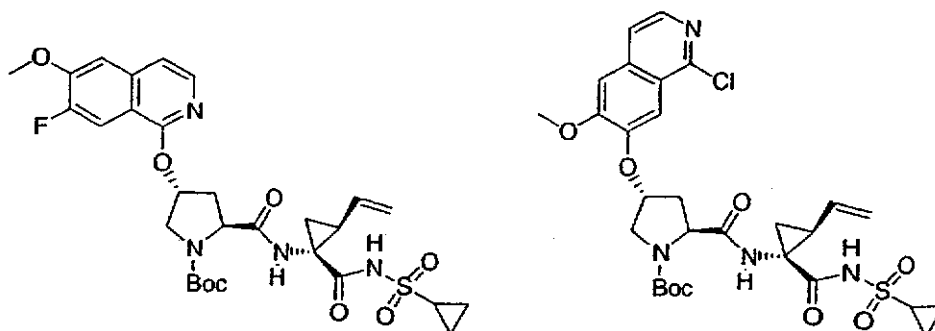
Products:



Step 4:

- Modifications: 400 mg mixture of 4-(7-fluoro-6-methoxy-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester and 4-(1-chloro-6-methoxy-isoquinolin-7-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester used, 700 mg products obtained.

Product:

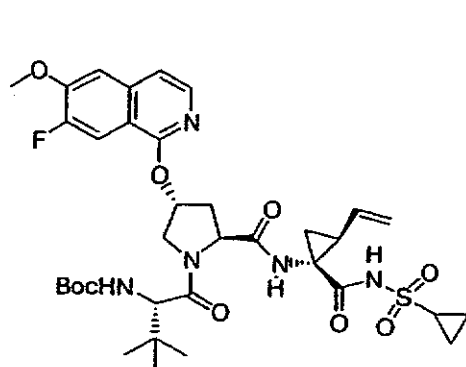


10

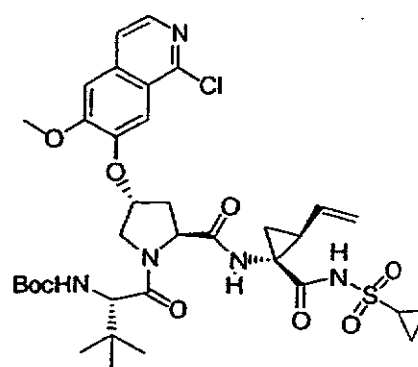
Step 5:

- Modifications: 700 mg mixture of 2-(1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-(7-fluoro-6-methoxy-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester and 4-(1-chloro-6-methoxy-isoquinolin-7-yloxy)-2-(1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropylcarbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester used, 79 mg of compound 261 and 80 mg compound 262 obtained.

Product:



Compound 261

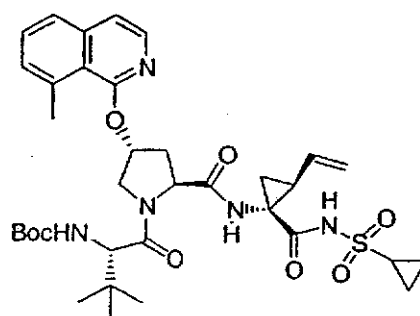


Compound 262

Data of compound 261: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.07 (m, 12 H), 1.25 (m, 10 H), 1.44 (m, 1 H), 1.88 (dd, $J=8.1, 5.6$ Hz, 1 H), 2.25 (m, 2 H), 2.60 (dd, $J=13.7, 6.9$ Hz, 1 H), 2.94 (m, 1 H), 4.02 (m, 4 H), 4.22 (s, 1 H), 4.43 (d, $J=12.2$ Hz, 1 H), 4.53 (dd, $J=10.3, 6.6$ Hz, 1 H), 5.12 (d, $J=10.5$ Hz, 1 H), 5.30 (d, $J=16.6$ Hz, 1 H), 5.75 (m, 1 H), 5.84 (s, 1 H), 7.28 (d, $J=5.9$ Hz, 1 H), 7.37 (d, $J=8.1$ Hz, 1 H), 7.75 (d, $J=11.7$ Hz, 1 H), 7.91 (d, $J=5.9$ Hz, 1 H); MS: $(\text{M}+\text{Na})^+$ 754.

Data of compound 262: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.07 (m, 12 H), 1.25 (m, 10 H), 1.44 (m, $J=9.41, 5.26$ Hz, 1 H), 1.87 (dd, $J=8.51, 5.56$ Hz, 1 H), 2.24 (q, $J=8.72$ Hz, 2 H), 2.57 (dd, $J=13.82, 7.21$ Hz, 1 H), 2.94 (m, 1 H), 3.97 (d, $J=5.14$ Hz, 3 H), 4.09 (m, $J=11.00$ Hz, 1 H), 4.24 (s, 1 H), 4.32 (m, 1 H), 4.50 (m, $J=16.87$ Hz, 1 H), 5.12 (dd, $J=10.52, 1.71$ Hz, 1 H), 5.30 (dd, $J=17.12, 1.47$ Hz, 1 H), 5.38 (s, 1 H), 5.76 (m, 1 H), 7.39 (s, 1 H), 7.63 (s, 1 H), 7.66 (d, $J=5.87$ Hz, 1 H), 8.07 (d, $J=5.62$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 732.

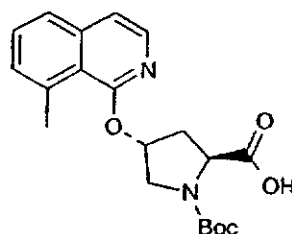
Example 263: Preparation of Compound 263



Compound 263

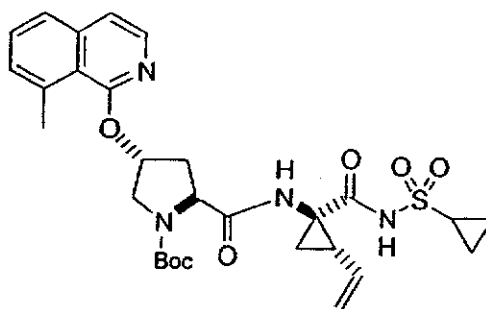
5 Step 3:

Product:



Step 4:

Product:

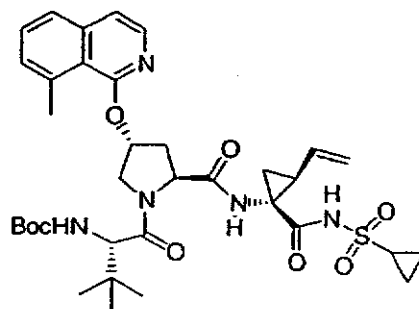


Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.13 (m, 4 H), 1.42 (m, 10 H), 1.87 (dd, $J=8.2, 5.3$ Hz, 1 H), 2.25 (m, 2 H), 2.58 (dd, $J=13.9, 6.9$ Hz, 1 H), 2.83 (s, 3 H), 2.96 (m, 1 H), 3.85 (m, 2 H), 4.38 (dd, $J=10.2, 6.7$ Hz, 1 H), 5.12 (dd, $J=10.4, 1.6$ Hz, 1 H), 5.30 (dd, $J=17.1, 1.2$ Hz, 1 H), 5.76 (m, 2 H), 7.28 (d, $J=5.9$ Hz, 1 H), 7.36 (d, $J=6.9$ Hz, 1 H), 7.53 (t, $J=7.7$ Hz, 1 H), 7.62 (m, 1 H), 7.88 (d, $J=5.6$ Hz, 1 H); MS: $(\text{M}+\text{Na})^+$ 607.

Step 5:

Modifications: 220 mg 2-(1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-(8-methyl-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester used, 90 mg product obtained (35% yield).

5 **Product:**

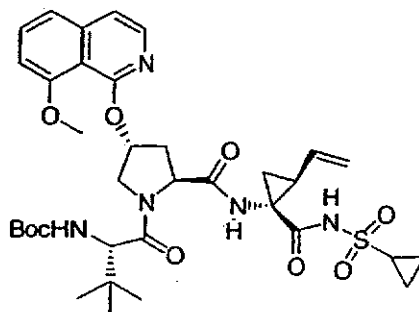


Compound 263

Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.05 (m, 12 H), 1.24 (m, 10 H), 1.44 (dd, $J=9.3, 5.4$ Hz, 1 H), 1.87 (dd, $J=8.1, 5.4$ Hz, 1 H), 2.25 (m, 2 H), 2.60 (dd, $J=13.9, 7.3$ Hz, 1 H), 2.77 (s, 3 H), 2.94 (m, 1 H), 4.04 (dd, $J=11.9, 3.1$ Hz, 1 H), 4.27 (d, $J=9.5$ Hz, 1 H), 4.42 (d, $J=12.0$ Hz, 1 H), 4.54 (dd, $J=10.8, 7.1$ Hz, 1 H), 5.12 (d, $J=10.3$ Hz, 1 H), 5.28 (d, $J=17.1$ Hz, 1 H), 5.75 (m, 1 H), 5.95 (s, 1 H), 6.63 (d, $J=9.1$ Hz, 1 H), 7.28 (m, 2 H), 7.50 (t, $J=7.7$ Hz, 1 H), 7.60 (d, $J=7.8$ Hz, 1 H), 7.89 (d, $J=5.6$ Hz, 1 H); MS: $(\text{M}+\text{Na})^+$ 720.

15

Example 264: Preparation of Compound 264



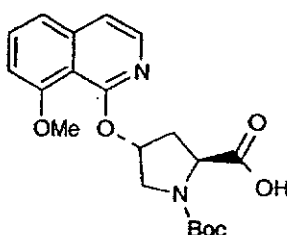
Compound 264

Compound 264 was prepared by following Scheme 1 of Example 250 except step 1 and step 2.

Step 3:

- 5 Modifications: 203 mg 1-chloro-8-methoxy-isoquinoline used, 340 mg product obtained (85% yield).

Product:

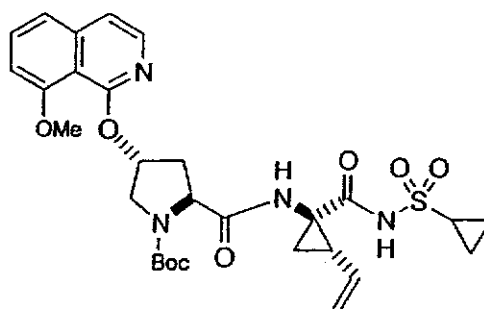


- Data: ^1H NMR (400 MHz, CD_3SOCD_3) δ ppm 1.34, 1.36 (2s, 9 H, rotamers), 2.26 (m, 1 H), 2.49 (m, 1H), 3.67 (m, 2 H), 3.86 (s, 3 H), 4.31 (m, 1 H), 5.67 (br s, 1 H), 7.04 (d, $J=7.8$ Hz, 1 H), 7.30 (d, $J=5.9$ Hz, 1 H), 7.38 (d, $J=8.1$ Hz, 1 H), 7.62 (t, $J=8.0$ Hz, 1 H), 7.93 (d, $J=5.6$ Hz, 1 H), 12.64 (s, 1 H); MS: $(\text{M}+\text{Na})^+$ 411.

Step 4:

- 15 Modifications: 78 mg 8-methoxy-isoquinolin-1-yloxy)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester used, 115 mg product obtained (96% yield).

Product:

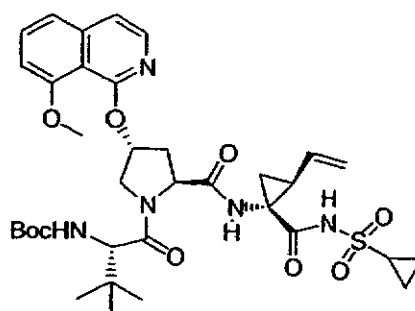
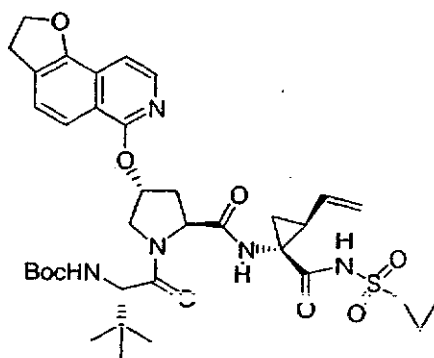
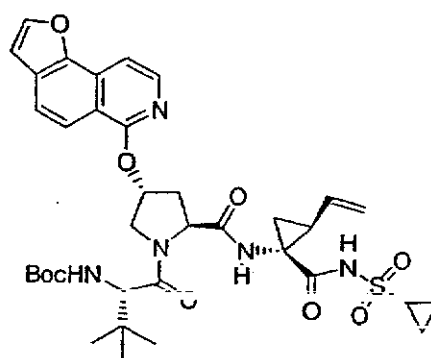


Step 5:

- 20 Modifications: 110 mg 2-(1-cyclopropanesulfonylamino)-2-vinyl-cyclopropylcarbamoyl)-4-(8-methoxy-isoquinolin-1-yloxy)-pyrrolidine-1-carboxylic acid *tert*-butyl ester used, 45 mg product obtained (34% yield).

Product:

360

**Compound 264**Data: MS: (M+H)⁺ 714.**5 Example 265 and 266: Preparation of Compounds 265 and 266****Compound 265****Compound 266**

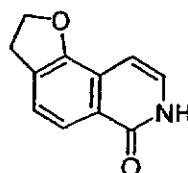
Compounds 265 and 266 were prepared by following Scheme 1 of Example 250 except that 3-(2,3-dihydro-benzofuran-7-yl)-acrylic acid was used in place of 3-phenyl-but-2-enoic acid in step 1.

Step 1:

Modifications: 3.8 g 3-(2,3-dihydro-benzofuran-7-yl)-acrylic acid used, 2 g product obtained (53% yield).

15 Product:

361



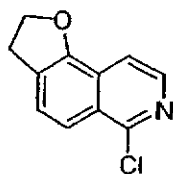
Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 3.37 (t, $J=9.05$ Hz, 1 H), 4.73 (t, $J=9.05$ Hz, 2 H), 6.67 (d, $J=7.09$ Hz, 1 H), 7.10 (d, $J=7.09$ Hz, 1 H), 7.37 (d, $J=8.07$ Hz, 1 H), 7.81 (d, $J=8.07$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 188.

5

Step 2:

Modifications: 1.87 g 2,3-dihydro-7H-furo[2,3-f]isoquinolin-6-one used, 1.84 g product obtained (90% yield).

Product:



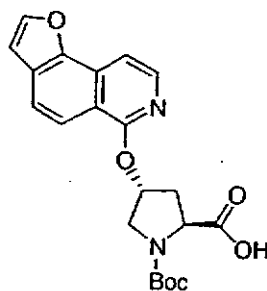
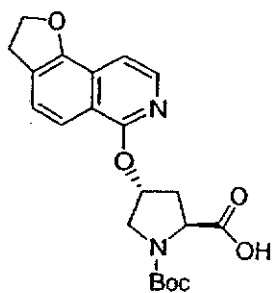
10

Data: ^1H NMR (400 Hz, CDCl_3) δ ppm 3.43 (t, $J=9.05$ Hz, 2 H), 4.82 (t, $J=9.05$ Hz, 2 H), 7.52 (d, $J=8.56$ Hz, 1 H), 7.66 (d, $J=5.62$ Hz, 1 H), 7.84 (d, $J=8.31$ Hz, 1 H), 8.19 (d, $J=5.62$ Hz, 1 H); MS $(\text{M}+\text{H})^+$ 206.

15 Step 3:

Modifications: 206 mg 6-chloro-2,3-dihydro-furo[2,3-f]isoquinoline used, 300 mg products mixture obtained.

Products:

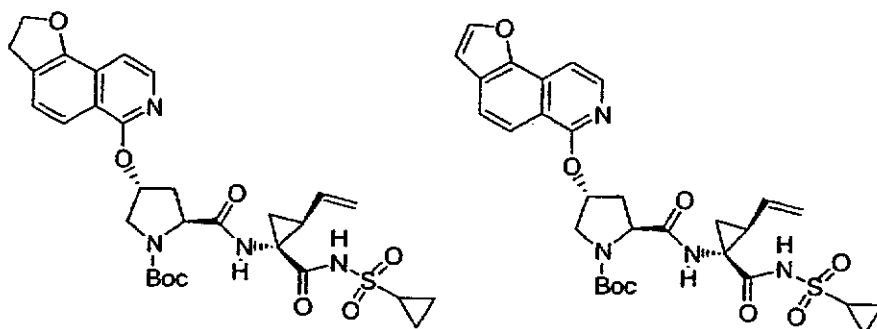


20

Step 4:

Modifications: 240 mg step 3 products mixture used, 350 mg products mixture obtained.

Products:



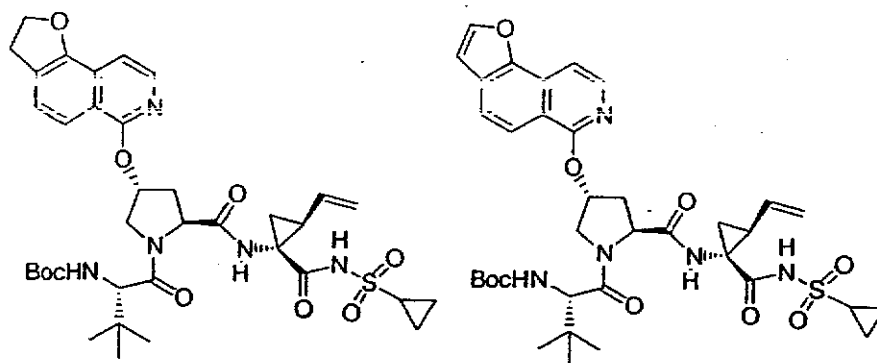
5

Step 5:

Modifications: 331 mg step 4 products mixture used, 240 mg of **compound 265** and 24 mg of **compound 266** obtained.

Products:

10



Compound 265

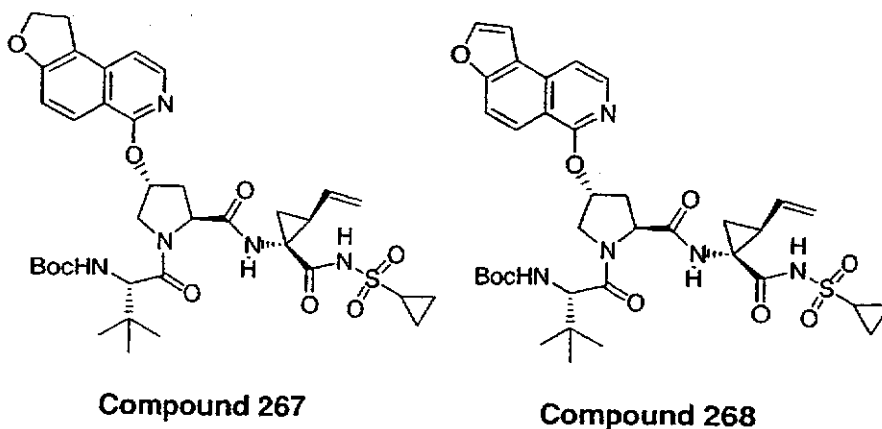
Compound 266

Data of **compound 265**: ^1H NMR (400 Hz, CD_3OD) δ ppm 0.99 (m, 12 H), 1.16 (m, 10 H), 1.36 (m, 1 H), 1.81 (dd, $J=8.07, 5.62$ Hz, 1 H), 2.18 (m, 2 H), 2.54 (dd, $J=13.69, 6.85$ Hz, 1 H), 2.87 (m, 1 H), 3.31 (t, $J=9.05$ Hz, 2 H), 4.01 (m, 1 H), 4.18 (s, 1 H), 4.36 (d, $J=11.74$ Hz, 1 H), 4.46 (dd, $J=10.15, 7.21$ Hz, 1 H), 4.70 (m, 2 H), 5.05 (d, $J=10.27$ Hz, 1 H), 5.23 (d, $J=16.87$ Hz, 1 H), 5.70 (m, 2 H), 7.23 (d, $J=5.87$ Hz, 1 H), 7.31 (d, $J=8.31$ Hz, 1 H), 7.63 (d, $J=8.31$ Hz, 1 H), 7.82 (d, $J=5.87$ Hz, 1 H); MS ($\text{M}+\text{H}$) $^+$ 726.

15

Data of **compound 266**: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.06 (m, 12 H), 1.24 (m, 10 H), 1.44 (dd, $J=10.03$, 5.14 Hz, 1 H), 1.88 (dd, $J=7.83$, 5.38 Hz, 1 H), 2.27 (m, 2 H), 2.65 (dd, $J=12.96$, 6.36 Hz, 1 H), 2.94 (m, 1 H), 4.08 (dd, $J=12.35$, 3.30 Hz, 1 H), 4.25 (s, 1 H), 4.54 (m, 2 H), 5.12 (d, $J=10.27$ Hz, 1 H), 5.29 (d, $J=17.12$ Hz, 1 H), 5.75 (m, 1 H), 5.91 (s, 1 H), 7.05 (d, $J=1.96$ Hz, 1 H), 7.72 (m, 2 H), 8.02 (m, 2 H), 8.11 (d, $J=5.87$ Hz, 1 H), 9.19 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 724.

Example 267 and 268: Preparation of Compounds 267 and 268

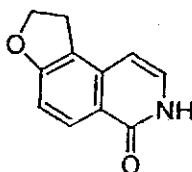


Compounds 267 and 268 were prepared by following Scheme 1 of Example 250 except that 3-(2,3-dihydro-benzofuran-4-yl)-acrylic acid was used in place of 3-phenyl-but-2-enoic acid in step 1.

Step 1:

Modifications: 1.14 g 3-(2,3-dihydro-benzofuran-4-yl)-acrylic acid used, 600 mg product obtained (52% yield).

Product:

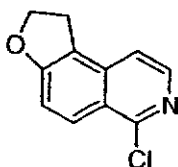


Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 3.35 (t, $J=8.93$ Hz, 2 H), 4.74 (t, $J=8.93$ Hz, 2 H), 6.49 (d, $J=7.09$ Hz, 1 H), 6.95 (d, $J=8.56$ Hz, 1 H), 7.25 (d, $J=7.09$ Hz, 1 H), 8.13 (d, $J=8.80$ Hz, 1 H); MS ($\text{M}+\text{H}$) $^+$ 188.

5 Step 2:

Modifications: 560 mg 1,7-dihydro-2*H*-furo[3,2-*f*]isoquinolin-6-one used, 380 mg product obtained (48% yield).

Product:

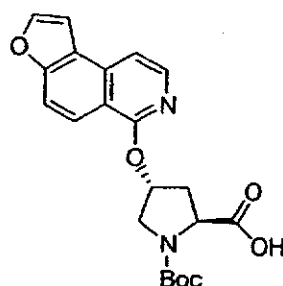
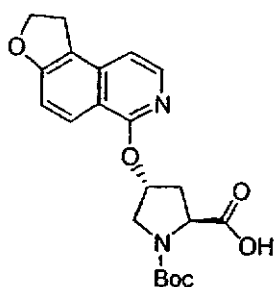


10 Data: ^1H NMR (400 Hz, CDCl_3) δ ppm 3.47 (t, $J=9.05$ Hz, 2 H), 4.84 (t, $J=9.05$ Hz, 2 H), 7.24 (d, $J=8.56$ Hz, 1 H), 7.33 (d, $J=5.87$ Hz, 1 H), 8.20 (m, 2 H); MS ($\text{M}+\text{H}$) $^+$ 206.

Step 3:

15 Modifications: 105 mg 6-chloro-1,7-dihydro-furo[3,2-*f*]isoquinoline used, 390 mg products mixture obtained.

Products:

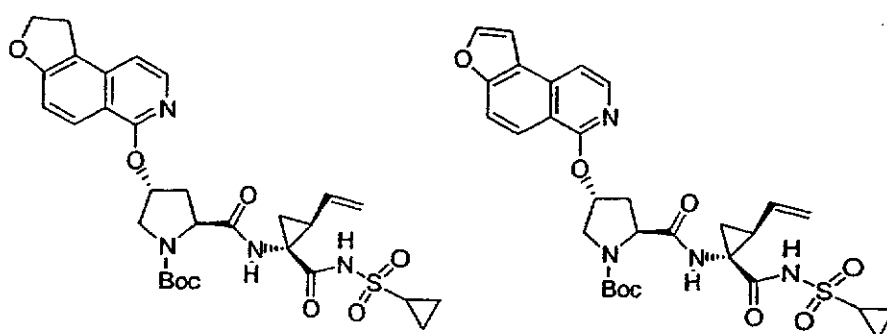


Step 4:

20 Modifications: 216 mg step 3 products mixture used, 330 mg products mixture obtained.

Products:

365

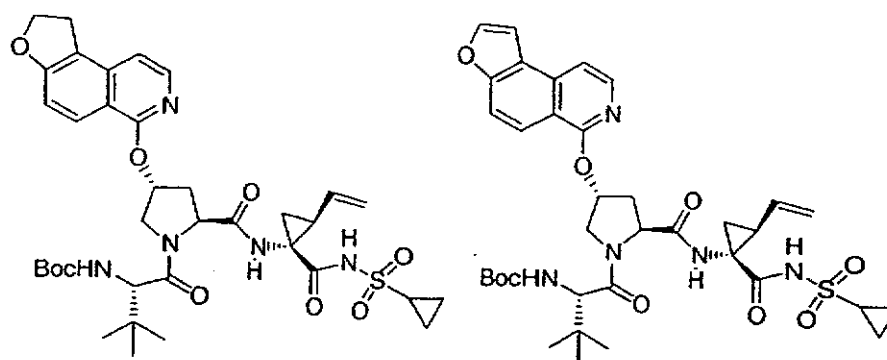


Step 5:

Modifications: 330 mg step 4 products mixture used, 140 mg of **compound 267** and

- 5 25 mg of **compound 268** obtained.

Products:

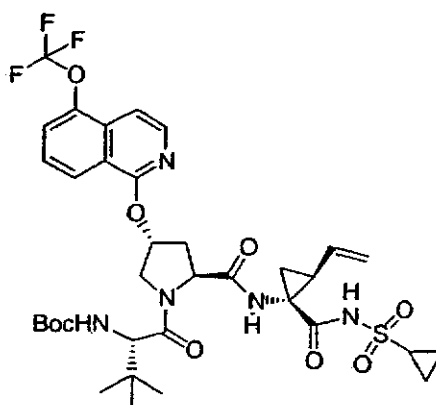
**Compound 267****Compound 268**

- 10 Data of **compound 267**: ^1H NMR (400 Hz, CD_3OD) δ ppm 1.07 (m, 12 H), 1.24 (m, 10 H), 1.43 (m, 1 H), 1.88 (dd, $J=8.07, 5.38$ Hz, 1 H), 2.26 (m, 2 H), 2.61 (dd, $J=13.69, 7.09$ Hz, 1 H), 2.94 (m, 1 H), 3.42 (t, $J=9.05$ Hz, 2 H), 4.05 (dd, $J=11.86, 3.55$ Hz, 1 H), 4.24 (s, 1 H), 4.50 (m, 2 H), 4.77 (t, $J=8.93$ Hz, 2 H), 5.12 (m, 1 H), 5.29 (d, $J=17.12$ Hz, 1 H), 5.76 (m, 2 H), 7.03 (d, $J=8.80$ Hz, 1 H), 7.12 (d, $J=6.11$ Hz, 1 H), 7.91 (d, $J=5.87$ Hz, 1 H), 8.06 (d, $J=8.80$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 726.
- 15

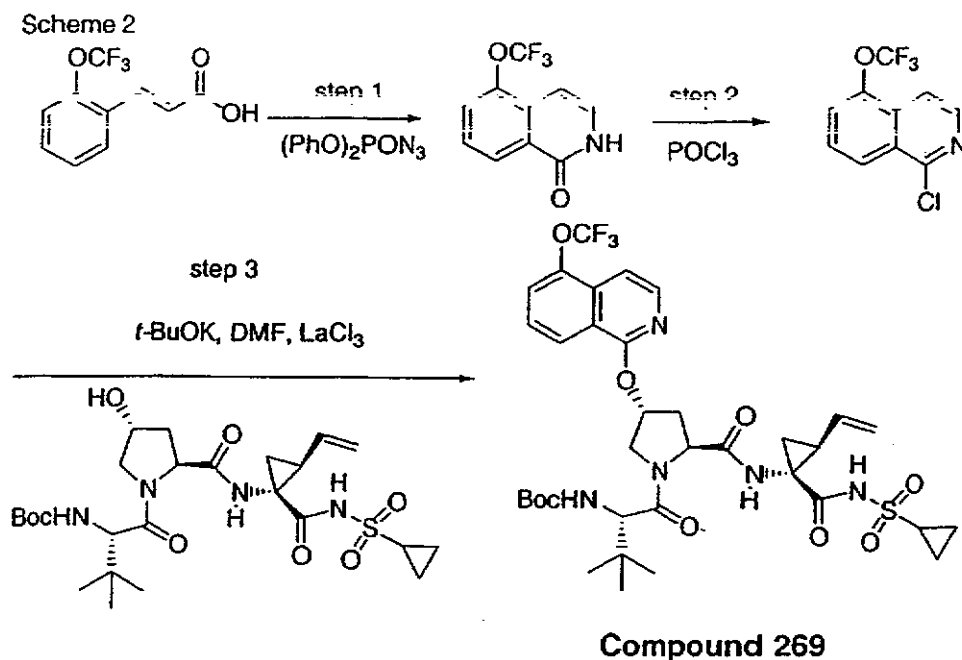
Data of **compound 268**: ^1H NMR (400 Hz, CD_3OD) δ ppm 1.06 (m, 12 H), 1.19 (s, 9 H) 1.26 (m, 1 H), 1.44 (m, 1 H), 1.88 (dd, $J=8.07, 5.62$ Hz, 1 H), 2.24 (d, $J=8.56$ Hz, 2 H), 2.64 (m, 1 H), 2.95 (m, 1 H), 4.07 (m, $J=3.42$ Hz, 1 H), 4.24 (s, 1 H), 4.54 (m, 2 H), 5.12 (d, $J=10.52$ Hz, 1 H), 5.30 (d, $J=17.12$ Hz, 1 H), 5.76 (m, 1 H), 5.91 (s, 1 H),

7.39 (d, $J=1.47$ Hz, 1 H), 7.68 (m, 2 H), 7.96 (d, $J=1.96$ Hz, 1 H), 8.12 (m, 2 H); MS: $(M+H)^+724$.

5 Example 269: Preparation of Compound 269



Compound 269



Step 1:

- 10 A solution of 2-trifluoromethoxycinnamic acid (11.6 g), diphenylphosphoryl azide (13.75 g), and triethylamine (7.07 g) in benzene (50 mL) was stirred for 1 h. After filtration through a silica gel plug washing with benzene and concentration, the

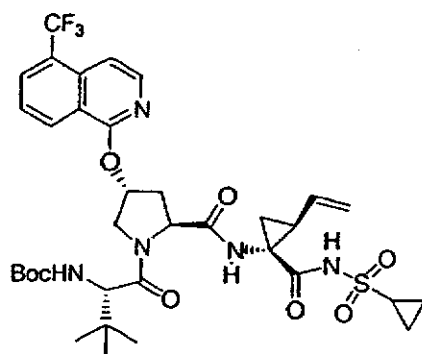
residue was dissolved in diphenylmethane (80 mL) and refluxed for 3 h. After cooling to rt, solids were collected through a plug washing with benzene and dried to give 5.1 g (44%) of the desired product as a solid. ¹H NMR (400 MHz, CD₃OD) δ ppm 6.79 (d, *J*=7.3 Hz, 1 H), 7.29 (d, *J*=7.3 Hz, 1 H), 7.57 (t, *J*=8.1 Hz, 1 H), 7.70 (d, *J*=7.8 Hz, 1 H), 8.30 (d, *J*=8.1 Hz, 1 H); MS: (M+H)⁺ 230.

Step 2:

A solution of 5-trifluoromethoxy-2*H*-isoquinolin-1-one (4.58 g) in POCl₃ (50 mL) was refluxed for 3 h. After cooling and concentration, the residue was based with 5 N NaOH and extracted with CH₂Cl₂. The organic layer was washed with brine and dried over MgSO₄. After concentration, purification by flash chromatography of Biotage with 5% ethyl acetate in hexanes gave 4.347 g (88%) of the desired product as a solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.66 (m, 2 H), 7.87 (d, *J*=5.9 Hz, 1 H), 8.31 (m, 1 H), 8.37 (d, *J*=5.9 Hz, 1 H); MS: (M+H)⁺ 248.

Step 3:

To a suspension of {1-[2-(1-cyclopropanesulfonylamino-carbonyl-2-vinyl-cyclopropylcarbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester (56 mg), 1-chloro-5-trifluoromethoxy-isoquinoline (25 mg), and LaCl₃ (25 mg) in DMF (1 mL) at -78°C was added *tert*-BuOK (0.5 mL, 1 M in THF) and warmed to rt. After stirring for 30 min, the reaction was quenched with saturated NH₄Cl solution and extracted with ethyl acetate. After concentration, purification by prep HPLC gave 35 mg (46%) of the desired compound 269 as a solid. ¹H NMR (400 MHz, CD₃OD) δ ppm 1.03 (m, 12 H), 1.24 (m, 10 H), 1.44 (dd, *J*=9.7, 5.3 Hz, 1 H), 1.88 (dd, *J*=8.1, 5.6 Hz, 1 H), 2.28 (m, 2 H), 2.64 (dd, *J*=13.7, 7.1 Hz, 1 H), 2.94 (m, 1 H), 4.09 (m, 1 H), 4.21 (d, *J*=9.3 Hz, 1 H), 4.53 (m, 2 H), 5.12 (d, *J*=11.5 Hz, 1 H), 5.30 (d, *J*=17.1 Hz, 1 H), 5.75 (m, 1 H), 5.92 (m, 1 H), 6.60 (d, *J*=9.5 Hz, 1 H), 7.49 (d, *J*=6.1 Hz, 1 H), 7.60 (m, 1 H), 7.69 (d, *J*=7.3 Hz, 1 H), 8.11 (d, *J*=6.1 Hz, 1 H), 8.22 (d, *J*=8.3 Hz, 1 H); MS: (M+Na)⁺ 790.

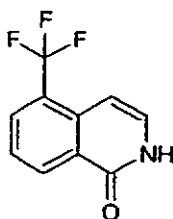
Example 270: Preparation of Compound 270**Compound 270**

Compound 270 was prepared by following Scheme 2 of Example 269 except that 2-trifluoromethylcinnamic acid was used in place of 2-trifluoromethoxycinnamic acid in step 1.

Step 1:

Modifications: 10 g 2-trifluoromethylcinnamic acid used, 5 g product obtained (50% yield).

Product:



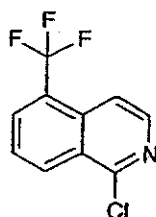
Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 6.83 (m, 1 H), 7.33 (d, $J=7.58$ Hz, 1 H), 7.63 (t, $J=7.83$ Hz, 1 H), 8.09 (d, $J=7.58$ Hz, 1 H), 8.57 (d, $J=8.07$ Hz, 1 H).

Step 2:

Modifications: 4.4 g 5-trifluoromethyl-2H-isoquinolin-1-one used, 3.5 g product obtained (73% yield).

Product:

369



Data: ^1H NMR (400 MHz, CDCl_3) δ ppm 7.75 (t, $J=7.95$ Hz, 1 H), 7.90 (m, 1 H), 8.12 (d, $J=7.34$ Hz, 1 H), 8.41 (d, $J=6.11$ Hz, 1 H), 8.60 (d, $J=8.56$ Hz, 1 H).

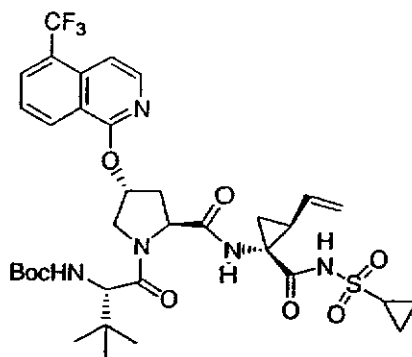
5

Step 3:

Modifications: 46 mg 1-chloro-5-trifluoromethyl-isoquinoline and 111 mg {1-[2-(1-Cyclopropanesulfonylamino-carbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester used, 70 mg product obtained (47% yield).

10

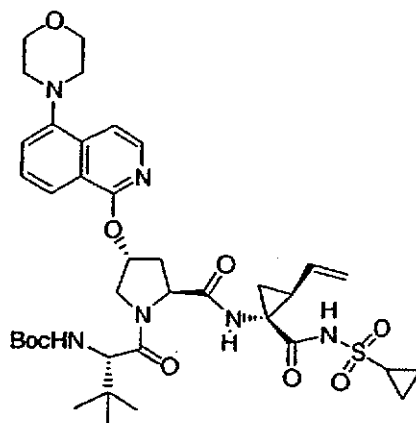
Product:



Compound 270

Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.06 (m, 12 H), 1.23 (m, 10 H), 1.44 (dd, $J=9.54$, 5.38 Hz, 1 H), 1.88 (dd, $J=8.07$, 5.38 Hz, 1 H), 2.28 (m, 2 H), 2.65 (dd, $J=13.82$, 6.97 Hz, 1 H), 2.94 (m, 1 H), 4.07 (m, 1 H), 4.20 (m, 1 H), 4.56 (m, 2 H), 5.12 (m, 1 H), 5.30 (d, $J=17.12$ Hz, 1 H), 5.75 (m, 1 H), 5.90 (s, 1 H), 6.59 (d, $J=9.05$ Hz, 1 H), 7.53 (d, $J=4.40$ Hz, 1 H), 7.65 (t, $J=7.83$ Hz, 1 H), 8.12 (d, $J=7.09$ Hz, 1 H), 8.15 (d, $J=6.36$ Hz, 1 H), 8.50 (d, $J=8.31$ Hz, 1 H); MS: $(\text{M}+\text{Na})^+$ 774.

20

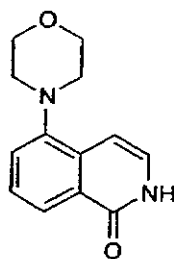
Example 271: Preparation of Compound 271**Compound 271**

Compound 271 was prepared by following Scheme 2 of Example 269 except that 2-chlorocinnamic acid was used in place of 2-trifluoromethoxycinnamic acid in step 1.

Step 1:

Modifications: 7 g 2-chlorocinnamic acid used, 5 g product obtained (71% yield).

Product:



10

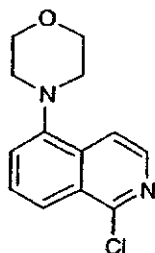
Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 3.02 (m, 4 H), 3.91 (m, 4 H), 6.97 (d, $J=7.34$ Hz, 1 H), 7.18 (d, $J=7.34$ Hz, 1 H), 7.44 (m, 2 H), 8.02 (d, $J=7.83$ Hz, 1 H); MS ($\text{M}+\text{H}$) $^+$ 231.

15 **Step 2:**

Modifications: 2.2 g 5-morpholin-4-yl-2H-isoquinolin-1-one used, 2.1 g product obtained (87% yield).

Product:

371



Data: ^1H NMR (400 MHz, CDCl_3) δ ppm 3.09 (m, 4 H), 3.97 (m, 4 H), 7.32 (d, $J=7.58$ Hz, 1 H), 7.60 (m, 1 H), 7.91 (d, $J=5.87$ Hz, 1 H), 8.06 (d, $J=8.56$ Hz, 1 H), 8.26 (d, $J=5.87$ Hz, 1 H).

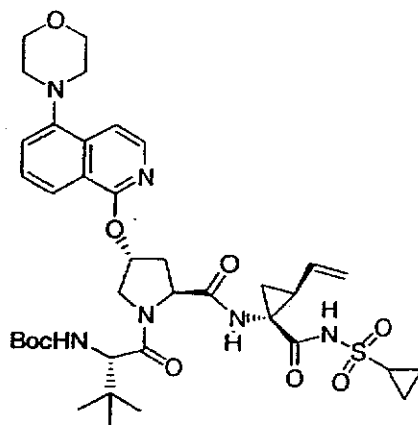
5

Step 3:

Modifications: 50 mg 1-chloro-5-morpholin-4-yl-isoquinoline and 111 mg {1-[2-(1-Cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester used, 40

10 mg product obtained (26% yield).

Product:

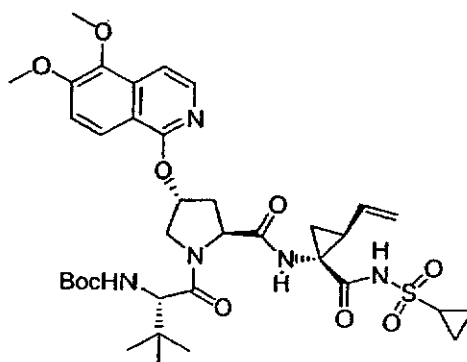


Compound 271

Data: ^1H NMR (500 MHz, CD_3OD) δ ppm 1.07 (m, 12 H), 1.26 (m, 10 H), 1.44 (d, $J=7.93$ Hz, 1 H), 1.88 (dd, $J=7.93, 5.19$ Hz, 1 H), 2.25 (m, 2 H), 2.62 (dd, $J=13.73, 7.02$ Hz, 1 H), 2.94 (m, 1 H), 3.06 (d, $J=3.97$ Hz, 4 H), 3.94 (m, 4 H), 4.07 (d, $J=14.04$ Hz, 1 H), 4.25 (s, 1 H), 4.45 (d, $J=12.21$ Hz, 1 H), 4.52 (m, 1 H), 5.12 (d, $J=9.46$ Hz, 1 H), 5.29 (d, $J=16.79$ Hz, 1 H), 5.75 (m, 1 H), 5.85 (s, 1 H), 7.34 (d,

$J=7.32$ Hz, 1 H), 7.45 (t, $J=7.78$ Hz, 1 H), 7.59 (d, $J=6.10$ Hz, 1 H), 7.91 (d, $J=7.63$ Hz, 1 H), 7.97 (d, $J=5.80$ Hz, 1 H).

Example 272: Preparation of Compound 272



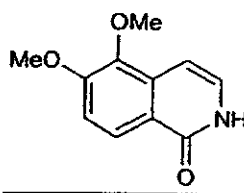
Compound 272

Compound 272 was prepared by following Scheme 2 of Example 269 except that 2,3-dimethoxycinnamic acid was used in place of 2-trifluoromethoxycinnamic acid in step 1.

Step 1:

Modifications: 10.4 g 2,3-dimethoxycinnamic acid used, 4.1 g product obtained (40% yield).

Product:

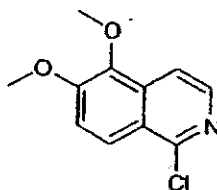


Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 3.86 (s, 3 H), 3.96 (s, 3 H), 6.82 (d, $J=7.2$ Hz, 1 H), 7.10 (d, $J=7.2$ Hz, 1 H), 7.28 (d, $J=8.8$ Hz, 1 H), 8.07 (d, $J=8.8$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 206.

Step 2:

Modifications: 4.1 g 5,6-dimethoxy-2*H*-isoquinolin-1-one used, 4.03 g product obtained (90% yield).

Product:



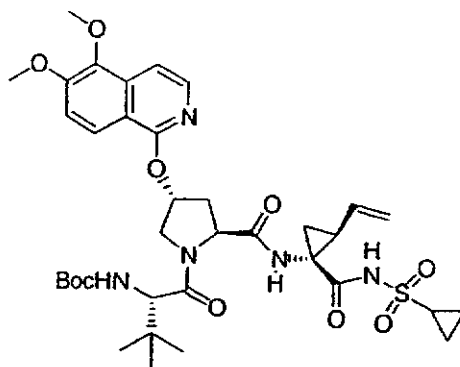
5

Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 3.97 (s, 3 H), 4.05 (s, 3 H), 7.65 (d, $J=9.29$ Hz, 1 H), 7.90 (dd, $J=5.87, 0.98$ Hz, 1 H), 8.12 (m, 2 H).

Step 3:

10 Modifications: 22 mg 1-chloro-5,6-dimethoxy-isoquinoline and 56 mg {1-[2-(1-cyclopropanesulfonylamino-carbonyl)-2-vinyl-cyclopropyl-carbamoyl]-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester used, 31 mg product obtained (42% yield).

Product:



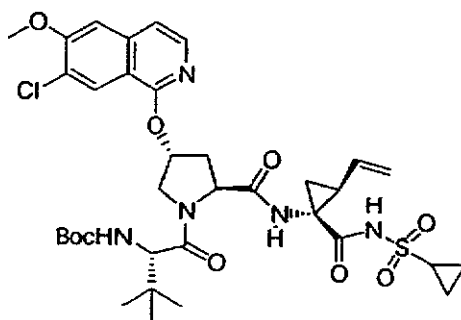
15

Compound 272

20 Data: ^1H NMR (500 MHz, CD_3OD) δ ppm 1.06 (m, 12 H), 1.26 (m, 10 H), 1.44 (s, 1 H), 1.88 (d, $J=7.32$ Hz, 1 H), 2.24 (s, 2 H), 2.60 (m, 1 H), 2.94 (m, 1 H), 3.92 (s, 3 H), 3.99 (s, 3 H), 4.06 (d, $J=11.90$ Hz, 1 H), 4.23 (s, 1 H), 4.43 (d, $J=10.68$ Hz, 1 H), 4.53 (m, 1 H), 5.12 (d, $J=10.38$ Hz, 1 H), 5.30 (d, $J=17.40$ Hz, 1 H), 5.77 (m, 2 H),

7.35 (d, $J=9.16$ Hz, 1 H), 7.46 (d, $J=5.80$ Hz, 1 H), 7.89 (d, $J=5.80$ Hz, 1 H), 7.97 (d, $J=8.85$ Hz, 1 H).

Example 273: Preparation of Compound 273



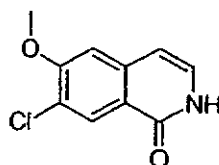
Compound 273

Compound 273 was prepared by following Scheme 2 of Example 269 except that 4-chloro-3-methoxycinnamic acid was used in place of 2-trifluoromethoxycinnamic acid in step 1.

Step 1:

Modifications: 2.5 g 4-chloro-3-methoxycinnamic acid used, 1.2 g product obtained (48% yield).

Product:

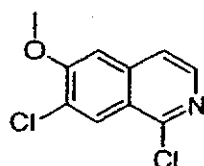


Data: ^1H NMR (400 MHz, CD_3OD) δ 4.00(s, 3 H), 6.64(d, $J=7.09$ Hz, 1 H), 7.15 (d, $J=7.34$ Hz, 1 H), 7.21 (s, 1 H), 8.22 (s, 1 H).

Step 2:

Modifications: 1.05 g 7-Chloro-6-methoxy-2H-isoquinolin-1-one used, 0.8 g product obtained (70% yield).

Product:

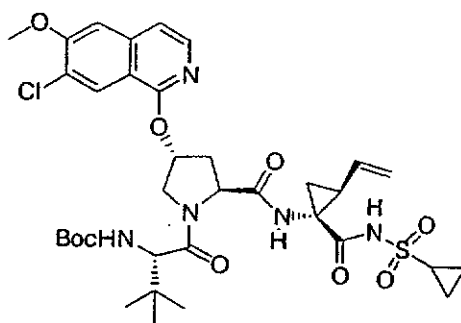


Data: ^1H NMR (400 Hz, CDCl_3) δ ppm 4.05 (s, 3 H), 7.13 (s, 1 H), 7.48 (d, $J=5.38$ Hz, 1 H), 8.21 (d, $J=5.62$ Hz, 1 H), 8.34 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 229.

5 Step 3:

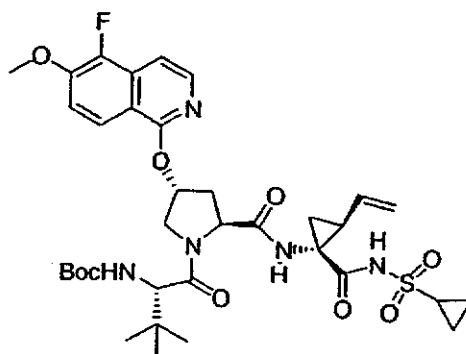
Modifications: 44 mg 1,7-dichloro-6-methoxyisoquinoline and 113 mg {1-[2-(1-cyclopropanesulfonylaminoacetyl)-2-vinyl-cyclopropylcarbamoyl]-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester used, 25 mg product obtained (17% yield)

10 Product:



Compound 273

Data: ^1H NMR (400 Hz, CD_3OD) δ ppm 1.07 (m, 12 H), 1.24 (m, 10 H), 1.44 (dd, $J=9.54, 5.38$ Hz, 1 H), 1.88 (dd, $J=8.07, 5.38$ Hz, 1 H), 2.26 (m, 1 H), 2.60 (m, $J=13.69, 6.85$ Hz, 1 H), 2.94 (m, 2 H), 3.98 (s, 3 H), 4.06 (m, 1 H), 4.20 (m, 1 H), 4.42 (d, $J=12.23$ Hz, 1 H), 4.57 (m, 1 H), 5.12 (d, $J=11.74$ Hz, 1 H), 5.30 (d, $J=17.36$ Hz, 1 H), 5.76 (m, 1 H), 5.86 (s, 1 H), 7.28 (d, $J=5.62$ Hz, 1 H), 7.33 (s, 1 H), 7.92 (d, $J=5.87$ Hz, 1 H), 8.09 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 749.

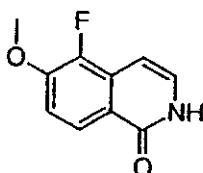
Example 274: Preparation of Compound 274**Compound 274**

Compound 274 was prepared by following Scheme 2 of Example 269 except that 2-fluoro-3-cinnamic acid was used in place of 2-trifluoromethoxycinnamic acid in step 1.

Step 1:

Modifications: 3.92 g 2-fluoro-3-cinnamic acid used, 2.4 g product obtained (61% yield).

Product:



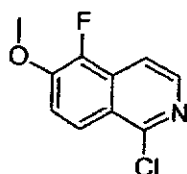
Data: ^1H NMR(400 MHz, CD_3OD) δ ppm 4.00 (s, 3 H), 6.72 (m, 1 H), 7.16 (d, $J=7.34$ Hz, 1 H), 7.35 (t, $J=8.44$ Hz, 1 H), 8.09 (d, $J=8.80$ Hz, 1 H).

Step 2:

Modifications: 1.93 g 5-fluoro-6-methoxy-2H-isoquinolin-1-one used, 1.688 g product obtained (80% yield).

Product:

377



Data: ^1H NMR (CDCl_3) δ ppm 4.08 (s, 3 H), 7.44 (dd, $J=9.29$, 7.83 Hz, 1 H), 7.75 (d, $J=5.87$ Hz, 1 H), 8.12 (d, $J=9.29$ Hz, 1 H), 8.22 (d, $J=5.87$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 212.

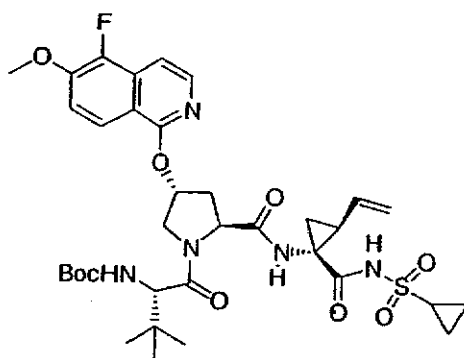
5

Step 3:

Modifications: 41 mg 1-chloro-5-fluoro-6-methoxyisoquinoline and 133 mg {1-[2-(1-cyclopropanesulfonylaminoacetyl)-2-vinylcyclopropylcarbamoyl]-4-hydroxypyrrolidine-1-carbonyl]-2,2-dimethylpropyl}-carbamic acid *tert*-butyl ester used, 70 mg product obtained (48% yield).

10

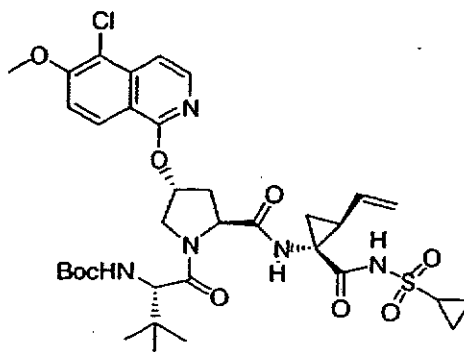
Product:



Compound 274

Data: ^1H NMR (CD_3OD) δ ppm 1.06 (m, 13 H), 1.21 (s, 9 H), 1.44 (dd, $J=9.78$, 5.38 Hz, 1 H), 1.88 (dd, $J=8.19$, 5.50 Hz, 1 H), 2.24 (d, $J=9.29$ Hz, 2 H), 2.62 (d, $J=13.94$ Hz, 1 H), 2.94 (m, 1 H), 4.05 (m, 4 H), 4.22 (d, $J=9.29$ Hz, 1 H), 4.45 (m, 1 H), 4.54 (dd, $J=9.66$, 7.21 Hz, 1 H), 5.12 (d, $J=10.52$ Hz, 1 H), 5.30 (d, $J=16.87$ Hz, 1 H), 5.76 (m, 1 H), 5.86 (s, 1 H), 7.39 (m, 2 H), 7.95 (d, $J=6.11$ Hz, 1 H), 8.00 (d, $J=9.29$ Hz, 1 H).

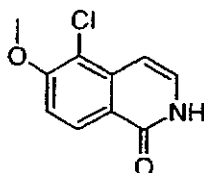
20

Example 275: Preparation of Compound 275**Compound 275**

Compound 2 was prepared by following Scheme 2 of Example 269 except that 2-chloro-3-methoxycinnamic acid was used in place of 2-trifluoromethoxycinnamic acid in step 1.

Step 1:

Modifications: 658 mg 2-chloro-3-methoxycinnamic acid used, 360 mg product obtained (54% yield).

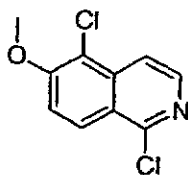
Product:

Data: ^1H NMR(400 MHz, CD_3OD) δ ppm 4.02 (s, 3 H), 6.91 (d, $J=7.34$ Hz, 1 H), 7.23 (d, $J=7.58$ Hz, 1 H), 7.35 (d, $J=9.05$ Hz, 1 H), 8.27 (d, $J=9.05$ Hz, 1 H).

Step 2:

Modifications: 350 mg 5-chloro-6-methoxy-2*H*-isoquinolin-1-one used, 300 mg product obtained (80% yield).

Product:

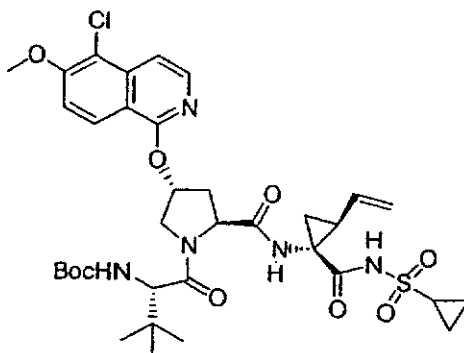


Data: ^1H NMR (400 Hz, CDCl_3) δ ppm 4.09 (s, 3 H), 7.43 (d, $J=9.29$ Hz, 1 H), 7.93 (d, $J=6.11$ Hz, 1 H), 8.30 (m, 2 H); MS ($\text{M}+\text{H}$) $^+$ 229.

5 Step 3:

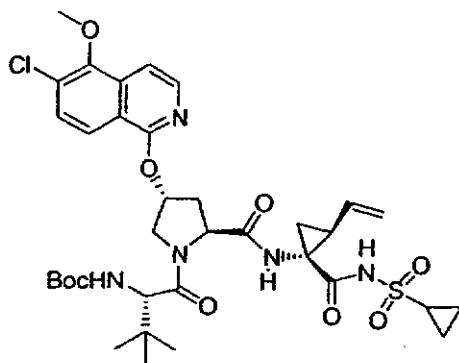
Modifications: 68 mg 1,5-dichloro-6-methoxy-isoquinoline and 167 mg {1-[2-(1-cyclopropanesulfonylamino-carbonyl)-2-vinyl-cyclopropyl-carbamoyl]-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester used, 130 mg product obtained (60% yield).

10 Product:



Compound 275

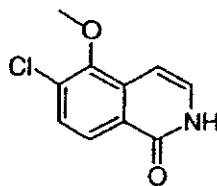
Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.06 (m, 12 H), 1.25 (m, 10 H), 1.46 (d, $J=5.62$ Hz, 1 H), 1.88 (dd, $J=8.07, 5.62$ Hz, 1 H), 2.27 (m, 2 H), 2.62 (m, 1 H), 2.94 (m, 1 H), 4.05 (m, 4 H), 4.22 (d, $J=9.05$ Hz, 1 H), 4.46 (d, $J=11.49$ Hz, 1 H), 4.54 (dd, $J=9.78, 6.36$ Hz, 1 H), 5.13 (d, $J=10.52$ Hz, 1 H), 5.30 (d, $J=15.89$ Hz, 1 H), 5.76 (m, 1 H), 5.86 (s, 1 H), 7.40 (d, $J=9.29$ Hz, 1 H), 7.55 (d, $J=6.36$ Hz, 1 H), 8.01 (d, $J=6.36$ Hz, 1 H), 8.20 (d, $J=9.29$ Hz, 1 H); MS: ($\text{M}+\text{H}$) $^+$ 749.

Example 276: Preparation of Compound 276**Compound 276**

Compound 276 was prepared by following Scheme 2 of Example 269 except that 3-chloro-2-methoxycinnamic acid was used in place of 2-trifluoromethoxycinnamic acid in step 1.

Step 1:

Modifications: 4.24 g 3-chloro-2-methoxycinnamic acid used, 2.4 g product obtained (57% yield)

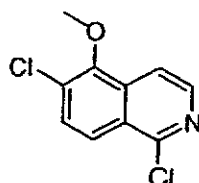
Product:

Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 3.93 (s, 1 H), 6.85 (d, $J=7.34$ Hz, 1 H), 7.24 (d, $J=7.34$ Hz, 1 H), 7.52 (d, $J=8.80$ Hz, 1 H), 8.03 (d, $J=8.80$ Hz, 1 H); MS: (M+H) $^+$ 210.

Step 2:

Modifications: 2.09 g 6-chloro-5-methoxy-2H-isoquinolin-1-one used, 1.9 g product obtained (83% yield).

Product:



Data: ^1H NMR (400 Hz, CDCl_3) δ ppm 4.03 (s, 2 H), 7.63 (d, $J=9.05$ Hz, 1 H), 7.86 (d, $J=5.14$ Hz, 1 H), 8.06 (d, $J=9.05$ Hz, 1 H), 8.32 (d, $J=5.62$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 229.

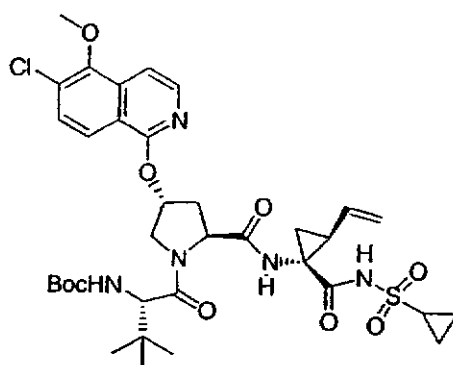
5

Step 3:

Modifications: 91 mg 1,6-dichloro-5-methoxy-isoquinoline and 226 mg {1-[2-(1-cyclopropanesulfonylamino-carbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester used,

10 114 mg product obtained (38% yield).

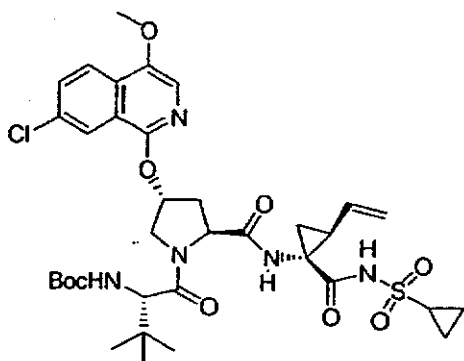
Product:



Compound 276

Data: ^1H NMR (400 Hz, CD_3OD) δ ppm 1.06 (m, 12 H), 1.23 (m, 10 H), 1.44 (t, $J=6.72$ Hz, 1 H), 1.88 (dd, $J=7.95, 5.26$ Hz, 1 H), 2.25 (m, 2 H), 2.62 (dd, $J=13.33, 6.48$ Hz, 1 H), 2.94 (m, 1 H), 3.98 (s, 3 H), 4.03 (m, 1 H), 4.20 (m, 1 H), 4.51 (m, 2 H), 5.12 (d, $J=10.52$ Hz, 1 H), 5.32 (s, 1 H), 5.75 (m, 1 H), 5.87 (s, 1 H), 7.50 (m, 2 H), 7.95 (d, $J=8.80$ Hz, 1 H), 8.06 (d, $J=5.87$ Hz, 1 H); MS (MH^+) 749.

15

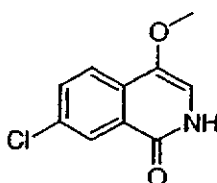
Example 277: Preparation of Compound 277**Compound 277**

Compound 277 was prepared by following Scheme 2 of Example 269 except that 3-
5 (4-chloro-phenyl)-3-methoxy-acrylic acid was used in place of 2-trifluoromethoxycinnamic acid in step 1.

Step 1:

Modifications: 4.24 g 3-(4-chloro-phenyl)-3-methoxy-acrylic acid used, 130 mg
10 product obtained (3% yield)

Product:



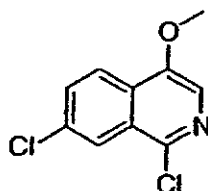
Data: ^1H NMR(400 MHz, CD_3OD) δ ppm 3.96 (s, 3 H), 7.19 (dd, $J=8.80, 2.45$ Hz, 1
H), 7.28 (d, $J=2.45$ Hz, 1 H), 7.34 (s, 1 H), 8.25 (d, $J=9.05$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$
15 210.

Step 2:

Modifications: 105 mg 7-chloro-4-methoxy-2H-isoquinolin-1-one used, 60 mg
product obtained (71% yield).

20 Product:

383

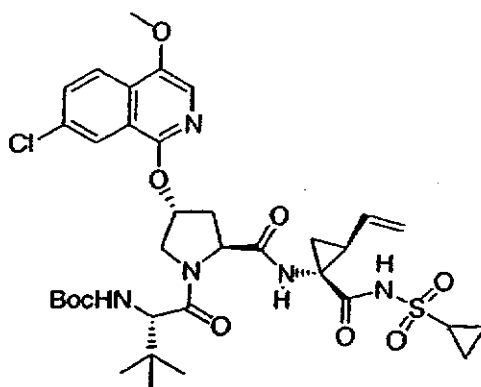


Data: ^1H NMR (400 Hz, CDCl_3) δ ppm 4.05 (s, 3 H), 7.67 (dd, $J=8.80, 1.96$ Hz, 1 H), 7.80 (s, 1 H), 8.16 (d, $J=9.05$ Hz, 1 H), 8.24 (d, $J=1.96$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 229.

5 Step 3:

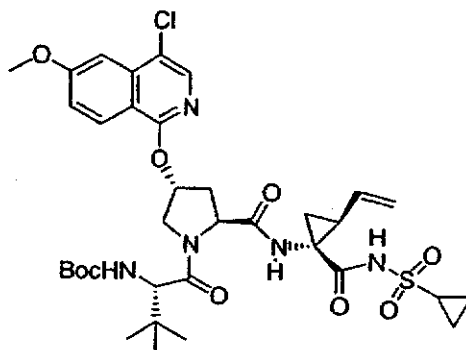
Modifications: 46 mg 1,7-dichloro-4-methoxyisoquinoline and 113 mg {1-[2-(1-cyclopropanesulfonylaminoacetyl)-2-vinylcyclopropylcarbamoyl]-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethylpropyl}-carbamic acid *tert*-butyl ester used, 50 mg product obtained (31% yield).

10 Product:



Compound 277

Data: ^1H NMR (400 Hz, CD_3OD) δ ppm 1.06 (m, 11 H), 1.16 (s, 9 H), 1.24 (m, 2 H), 1.44 (dd, $J=9.54, 5.38$ Hz, 1 H), 1.88 (dd, $J=8.07, 5.62$ Hz, 1 H), 2.28 (m, 2 H), 2.59 (dd, $J=13.69, 6.85$ Hz, 1 H), 2.94 (m, 1 H), 4.00 (s, 3 H), 4.05 (d, $J=11.74$ Hz, 1 H), 4.19 (s, 1 H), 4.43 (d, $J=11.49$ Hz, 1 H), 4.56 (dd, $J=10.03, 6.85$ Hz, 1 H), 5.12 (d, $J=11.49$ Hz, 1 H), 5.30 (d, $J=17.12$ Hz, 1 H), 5.76 (m, 2 H), 7.57 (s, 1 H), 7.67 (d, $J=8.56$ Hz, 1 H), 8.04 (s, 1 H), 8.08 (d, $J=8.80$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 748.

Example 278: Preparation of Compound 278**Compound 278**

Compound 278 was prepared by following Scheme 2 of Example 269 except step 1.

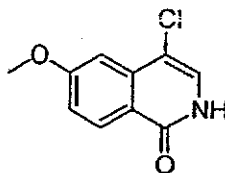
5

Step 1:

Modifications: A mixture of 6-methoxy-2H-isoquinolin-1-one (700 mg) and NCS (532 mg) in MeCN (10 mL) was refluxed for 3 h. Filtration gave 600 mg (72%) of the desired product as a solid.

10

Product:



Data: ^1H NMR(400 MHz, CD_3OD) δ ppm 3.96 (s, 1 H), 7.19 (dd, $J=8.80, 2.45$ Hz, 1 H), 7.28 (d, $J=2.45$ Hz, 1 H), 7.34 (s, 1 H), 8.25 (d, $J=9.05$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 210.

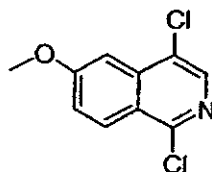
15

Step 2:

Modifications: 500 mg 4-chloro-6-methoxy-2H-isoquinolin-1-one used, 400 mg product obtained.

Product:

385



Data: ^1H NMR (400 Hz, CDCl_3) δ ppm 4.01 (s, 3 H), 7.35 (d, $J=2.45$ Hz, 1 H), 7.41 (d, $J=2.45$ Hz, 1 H), 8.24 (d, $J=9.29$ Hz, 1 H), 8.27 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 229.

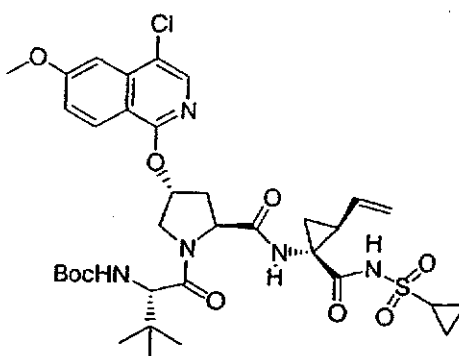
5

Step 3:

Modifications: 42 mg 1,4-dichloro-6-methoxy-isoquinoline and 117 mg {1-[2-(1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester used, 70 mg product obtained (47% yield).

10

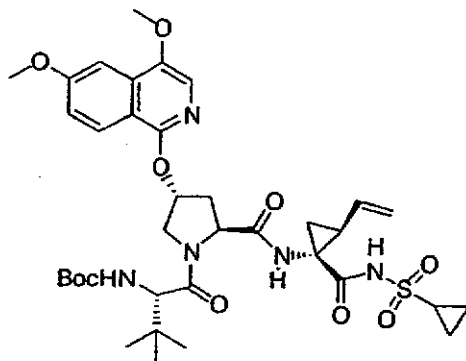
Product:



Compound 278

Data: ^1H NMR (400 Hz, CD_3OD) δ ppm 1.05 (m, 12 H), 1.25 (m, 10 H), 1.44 (m, 1 H), 1.88 (dd, $J=8.07, 5.62$ Hz, 1 H), 2.24 (m, 2 H), 2.61 (dd, $J=13.82, 6.72$ Hz, 1 H), 2.94 (m, 1 H), 3.97 (s, 3 H), 4.04 (dd, $J=11.74, 2.69$ Hz, 1 H), 4.21 (s, 1 H), 4.49 (m, 2 H), 5.12 (d, $J=10.52$ Hz, 1 H), 5.29 (d, $J=17.12$ Hz, 1 H), 5.75 (m, 2 H), 7.19 (d, $J=8.80$ Hz, 1 H), 7.37 (s, 1 H), 8.00 (s, 1 H), 8.13 (d, $J=9.05$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 749.

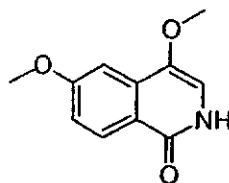
20

Example 279: Preparation of Compound 279**Compound 279**

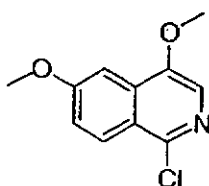
Compound 279 was prepared by following Scheme 2 of Example 269 except that 3-methoxy-3-(3-methoxy-phenyl)-acrylic acid was used in place of 2-trifluormethoxycinnamic acid in step 1.

Step 1:

Modifications: 4.24 g 3-methoxy-3-(3-methoxy-phenyl)-acrylic acid used, 400 mg product obtained (10% yield)

Product:**Step 2:**

Modifications: 400 mg 4,6-dimethoxy-2H-isoquinolin-1-one used, 300 mg product obtained (69% yield).

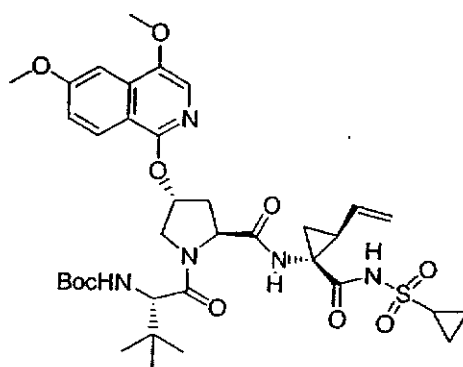
Product:

Data: ^1H NMR (400 Hz, CDCl_3) δ ppm 3.97 (s, 3 H), 4.05 (s, 3 H), 7.31 (dd, $J=9.17$, 2.57 Hz, 1 H), 7.45 (d, $J=2.69$ Hz, 1 H), 7.75 (s, 1 H), 8.16 (d, $J=9.29$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 224.

5 Step 3:

Modifications: 89 mg 1-chloro-4,6-dimethoxy-isoquinoline and 223 mg {1-[2-(1-Cyclopropanesulfonylamino-carbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester used, 160 mg product obtained (54% yield).

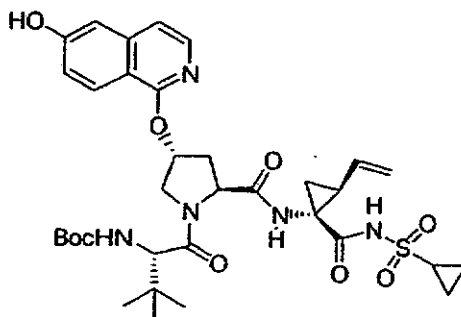
10 Product:



Compound 279

Data: ^1H NMR (400 Hz, CD_3OD) δ ppm 1.07 (m, 12 H), 1.21 (m, 10 H), 1.43 (m, 1 H), 1.87 (dd, $J=8.07$, 5.62 Hz, 1 H), 2.24 (m, 2 H), 2.58 (dd, $J=13.57$, 6.97 Hz, 1 H), 2.94 (m, 1 H), 3.92 (s, 3 H), 3.99 (s, 3 H), 4.04 (dd, $J=11.74$, 2.93 Hz, 1 H), 4.24 (s, 1 H), 4.39 (d, $J=11.98$ Hz, 1 H), 4.50 (m, 1 H), 5.12 (d, $J=10.52$ Hz, 1 H), 5.29 (d, $J=16.87$ Hz, 1 H), 5.75 (m, 2 H), 7.12 (d, $J=9.05$ Hz, 1 H), 7.40 (d, $J=2.20$ Hz, 1 H), 7.48 (s, 1 H), 8.04 (d, $J=9.05$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 744.

Example 280: Preparation of Compound 280



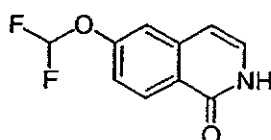
Compound 280

Compound 280 was prepared by following Scheme 2 of Example 269 except that 3-(3-difluoromethoxy-phenyl)-acrylic acid was used in place of 2-trifluoromethoxycinnamic acid in step 1.

Step 1:

Modifications: 4.28 g 3-(3-difluoromethoxy-phenyl)-acrylic acid used, 3.1 g product
10 obtained (72% yield).

1100000.

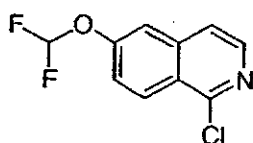


Data: MS: (M+H)⁺ 212.

15 Step 2:

Modifications: 2 g 6-difluoromethoxy-2*H*-isoquinolin-1-one used, 1.5 g product obtained (61% yield).

Product:

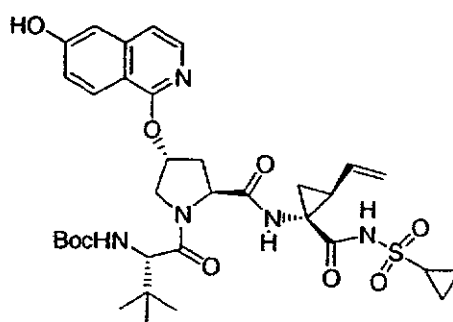


20 Data: ^1H NMR (400 Hz, CDCl_3) δ ppm 6.69 (t, $J=72.75$ Hz, 1 H), 7.49 (m, 2 H), 8.28 (d, $J=5.62$ Hz, 1 H), 8.36 (d, $J=9.05$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 230.

Step 3:

Modifications: 46 mg 1-chloro-6-difluoromethoxy-isoquinoline and 113 mg { 1-[2-(1-Cyclopropanesulfonylaminoacetyl)-2-vinyl-cyclopropylcarbamoyl]-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl }-carbamic acid *tert*-butyl ester used, 8 mg product obtained (5% yield).

Product:

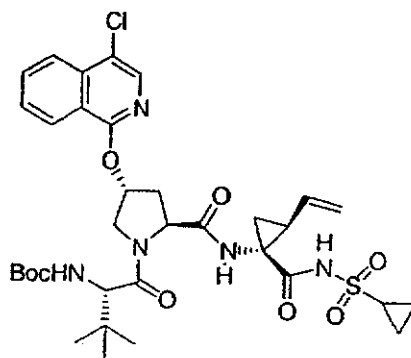


Compound 280

10 Data: ^1H NMR (400 Hz, CD_3OD) δ ppm 1.05 (m, 12 H), 1.23 (m, 10 H), 1.44 (m, 2 H), 1.88 (dd, $J=8.19, 5.50$ Hz, 1 H), 2.30 (m, 2 H), 2.67 (d, $J=13.94$ Hz, 1 H), 2.93 (m, 1 H), 4.07 (d, $J=10.27$ Hz, 1 H), 4.21 (s, 1 H), 4.53 (d, $J=6.85$ Hz, 2 H), 5.13 (m, 1 H), 5.31 (s, 1 H), 5.76 (d, $J=47.93$ Hz, 2 H), 7.11 (m, 2 H), 7.26 (d, $J=6.11$ Hz, 1 H), 7.81 (d, $J=6.11$ Hz, 1 H), 8.16 (m, 1 H); MS: $(\text{M}+\text{H})^+$ 700.

15

Example 281: Preparation of Compound 281



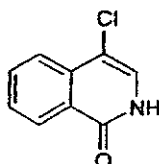
Compound 281

Compound 281 was prepared by following Scheme 2 of Example 269 except that 3-chloro-3-phenyl-acrylic acid was used in place of 2-trifluoromethoxycinnamic acid in step 1.

5 Step 1:

Modifications: 11 g 3-chloro-3-phenyl-acrylic acid used, 3.1 g product obtained (29% yield).

Product:

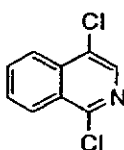


- 10 Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 7.34 (s, 1 H), 7.52 (t, $J=7.58$ Hz, 1 H), 7.77 (t, $J=7.46$ Hz, 1 H), 7.90 (d, $J=8.07$ Hz, 1 H), 8.39 (d, $J=8.07$ Hz, 1 H), 11.37 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 180.

Step 2:

- 15 Modifications: 3.1 g 4-chloro-2H-isoquinolin-1-one used, 2.3 g product obtained (66% yield)

Product:

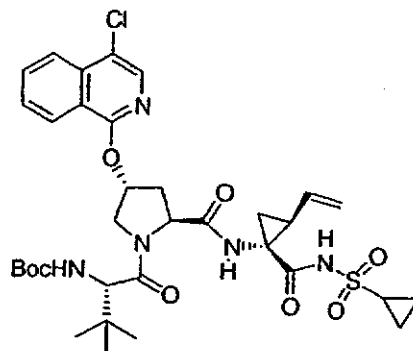


- 20 Data: ^1H NMR (400 MHz, CDCl_3) δ ppm 7.77 (ddd, $J=8.31, 7.09, 1.22$ Hz, 1 H), 7.88 (ddd, $J=8.31, 7.09, 1.22$ Hz, 1 H), 8.23 (d, $J=8.31$ Hz, 1 H), 8.34 (s, 1 H), 8.36 (d, $J=8.56$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 198.

Step 3:

- 25 Modifications: 20 mg 1,4-dichloro-isoquinoline and 56 mg {1-[2-(1-cyclopropanesulfonylamino-carbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester used, 33 mg product obtained (30% yield).

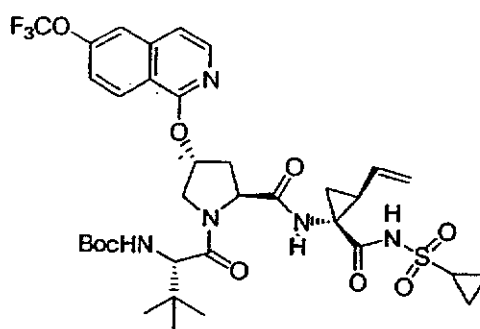
Product:



Compound 281

Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.06 (m, 12 H), 1.24 (m, 10 H), 1.44 (dd, $J=9.41, 5.26$ Hz, 1 H), 1.88 (dd, $J=7.83, 5.62$ Hz, 1 H), 2.27 (m, 2 H), 2.63 (dd, $J=13.82, 6.97$ Hz, 1 H), 2.94 (m, 1 H), 4.06 (dd, $J=11.49, 2.45$ Hz, 1 H), 4.22 (d, $J=9.29$ Hz, 1 H), 4.53 (m, 2 H), 5.12 (d, $J=10.76$ Hz, 1 H), 5.29 (d, $J=17.12$ Hz, 1 H), 5.75 (m, 1 H), 5.85 (s, 1 H), 6.60 (d, $J=8.80$ Hz, 1 H), 7.63 (t, $J=7.58$ Hz, 1 H), 7.86 (t, $J=7.70$ Hz, 1 H), 8.06 (s, 1 H), 8.11 (d, $J=8.56$ Hz, 1 H), 8.25 (d, $J=8.31$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 718.

Example 282: Preparation of Compound 282



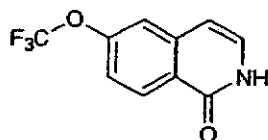
Compound 282

Compound 2 was prepared by following Scheme 2 of Example 269 except that 3-chloro-3-phenyl-acrylic acid was used in place of 2-trifluoromethoxycinnamic acid in step 1.

Step 1:

Modifications: 20 g 3-chloro-3-phenyl-acrylic acid used, 2 g product obtained (8% yield).

Product:



5

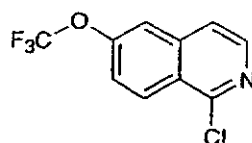
Data: MS: (M+H)⁺ 230.

Step 2:

Modifications: 2 g 6-trifluoromethoxy-2H-isoquinolin-1-one used, 0.7 product obtained (33% yield).

10

Product:



Data: ¹H NMR (400 MHz, CDCl₃) δ ppm 7.51 (d, J=9.29 Hz, 1 H), 7.59 (d, J=5.62 Hz, 1 H), 7.64 (s, 1 H), 8.31 (d, J=5.62 Hz, 1 H), 8.40 (d, J=9.05 Hz, 1 H); MS:

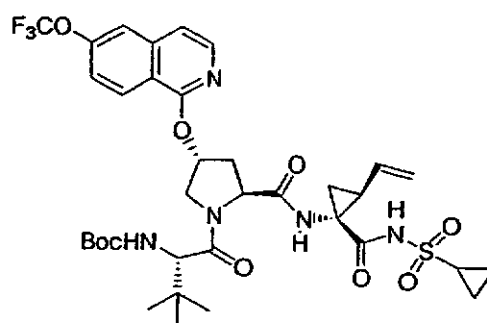
15 (M+H)⁺ 248.

Step 3:

Modifications: 50 mg 1-chloro-6-trifluoromethoxy-isoquinoline and 113 mg {1-[2-(1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester used, 42 mg product obtained (27% yield).

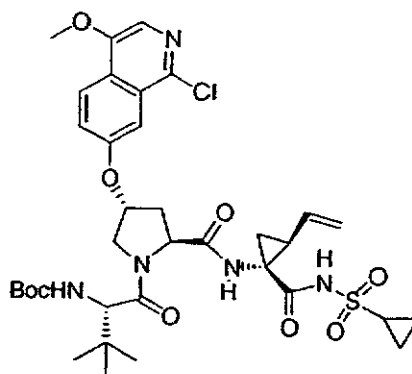
20

Product:

**Compound 282**

Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.05 (m, 12 H), 1.24 (m, 10 H), 1.44 (dd, $J=9.17, 5.50$ Hz, 1 H), 1.88 (dd, $J=8.07, 5.62$ Hz, 1 H), 2.28 (m, 2 H), 2.63 (dd, $J=13.45, 7.09$ Hz, 1 H), 2.94 (m, 1 H), 4.06 (dd, $J=11.25, 2.45$ Hz, 1 H), 4.21 (s, 1 H), 4.53 (m, 2 H), 5.13 (d, $J=10.52$ Hz, 1 H), 5.30 (d, $J=17.12$ Hz, 1 H), 5.75 (m, 1 H), 5.89 (s, 1 H), 7.39 (m, 2 H), 7.72 (s, 1 H), 8.05 (d, $J=5.87$ Hz, 1 H), 8.31 (d, $J=9.05$ Hz, 1 H), 9.18 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 768.

10 Example 283: Preparation of Compound 283

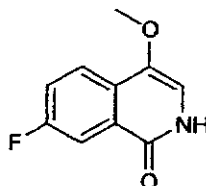
**Compound 283**

Compound 283 was prepared by following Scheme 2 of Example 269 except that 3-(4-fluoro-phenyl)-3-methoxy-acrylic acid was used in place of 2-trifluormethoxycinnamic acid in step 1.

Step 1:

Modifications: 3.82 g 3-(4-Fluoro-phenyl)-3-methoxy-acrylic acid used, 198 mg product obtained (5% yield).

Product:

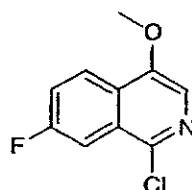


5 Data: MS: (M+H)⁺ 194.

Step 2:

Modifications: 193 mg 7-fluoro-4-methoxy-2*H*-isoquinolin-1-one used, 199 mg product obtained (94% yield).

10 Product:

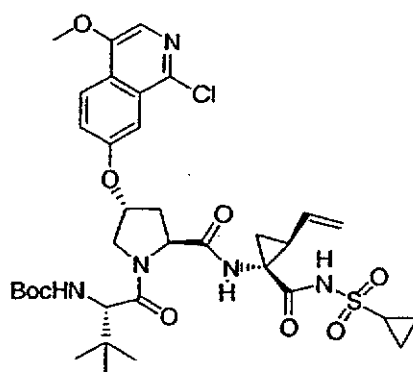


Data: ¹H NMR (400 MHz, CDCl₃) δ ppm 4.05 (s, 3 H), 7.49 (m, 1 H), 7.78 (s, 1 H), 7.86 (dd, *J*=9.66, 2.57 Hz, 1 H), 8.23 (dd, *J*=9.29, 5.38 Hz, 1 H); MS: (M+H)⁺ 212.

15 Step 3:

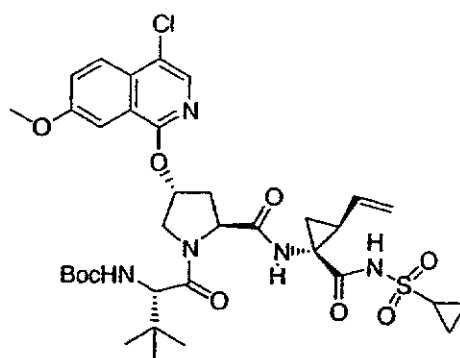
Modifications: 42 mg 1-chloro-7-fluoro-4-methoxy-isoquinoline and 112 mg (1-[2-(1-cyclopropanesulfonylaminocarbonyl-2-vinyl-cyclopropylcarbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl)-carbamic acid *tert*-butyl ester used, 40 mg product obtained (14% yield).

20 Product:

**Compound 283**

Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.06 (m, 12 H), 1.24 (m, 10 H), 1.42 (m, 1 H), 1.87 (dd, $J=7.95, 5.50$ Hz, 1 H), 2.23 (m, 2 H), 2.55 (dd, $J=13.08, 6.48$ Hz, 1 H),
 5 2.93 (m, 1 H), 4.06 (s, 3 H), 4.09 (m, 1 H), 4.23 (s, 1 H), 4.30 (d, $J=11.49$ Hz, 1 H),
 4.46 (m, 1 H), 5.12 (d, $J=10.27$ Hz, 1 H), 5.29 (d, $J=17.36$ Hz, 1 H), 5.40 (s, 1 H),
 5.76 (m, 1 H), 7.46 (d, $J=9.05$ Hz, 1 H), 7.56 (d, $J=2.20$ Hz, 1 H), 7.75 (s, 1 H), 8.18
 (d, $J=9.05$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 749.

10 Example 284: Preparation of Compound 284

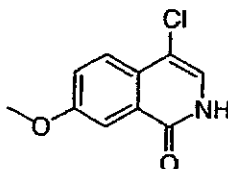
**Compound 284**

Compound 284 was prepared by following Scheme 2 of Example 269 except step 1.

15 Step 1:

Modifications: A mixture of 7-methoxy-2*H*-isoquinolin-1-one (876 mg) and NCS (665 mg) in MeCN (10 mL) was refluxed for 3 h. Filtration gave 500 mg (47%) of the desired product as a solid.

Product:



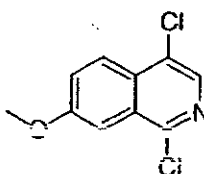
5

Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 4.00 (s, 3 H), 7.58 (m, 2 H), 8.14 (d, $J=10.03$ Hz, 1 H), 8.17 (s, 1 H).

Step 2:

10 Modifications: 418 mg 4-chloro-7-methoxy-2*H*-isoquinolin-1-one used, 410 mg product obtained (90% yield).

Product:

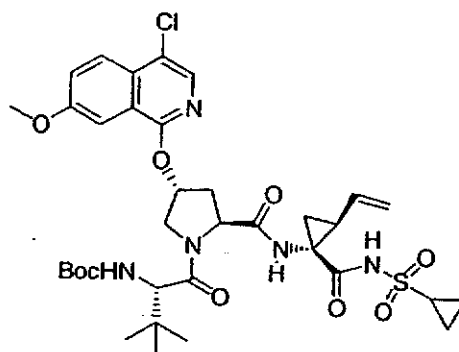


15 Data: ^1H NMR (400 Hz, CDCl_3) δ ppm 4.00 (s, 3 H), 7.49 (dd, $J=9.16, 2.44$ Hz, 1 H), 7.55 (d, $J=2.44$ Hz, 1 H), 8.12 (d, $J=9.16$ Hz, 1 H), 8.21 (s, 1 H); MS: $(\text{M}+\text{H})^+$ 229.

Step 3:

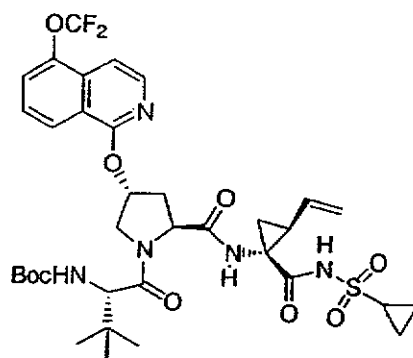
20 Modifications: 42 mg 1,4-dichloro-7-methoxy-isoquinoline and 117 mg {1-[2-(1-cyclopropanesulfonylamino-carbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl}-carbamic acid *tert*-butyl ester used, 50 mg product obtained (33% yield).

Product:

**Compound 284**

Data: ^1H NMR (400 Hz, CD_3OD) δ ppm 1.05 (m, 20 H), 1.24 (m, 2 H), 1.44 (m, 1 H), 1.89 (dd, $J=8.19, 5.50$ Hz, 1 H), 2.28 (m, 2 H), 2.62 (dd, $J=13.69, 6.85$ Hz, 1 H),
 5 2.94 (m, 1 H), 3.92 (s, 3 H), 4.07 (dd, $J=11.98, 3.42$ Hz, 1 H), 4.19 (m, 1 H), 4.44 (d, $J=11.74$ Hz, 1 H), 4.58 (dd, $J=10.27, 7.09$ Hz, 1 H), 5.12 (m, 1 H), 5.31 (d, $J=17.12$ Hz, 1 H), 5.78 (m, 2 H), 7.49 (m, 2 H), 7.91 (s, 1 H), 8.02 (m, 1 H); MS: $(\text{M}+\text{H})^+$ 749.

10 Example 285: Preparation of Compound 285

**Compound 285**

Compound 285 was prepared by following Scheme 2 of Example 269 except that was used in place of 2-difluoromethoxycinnamic acid in step 1.

15

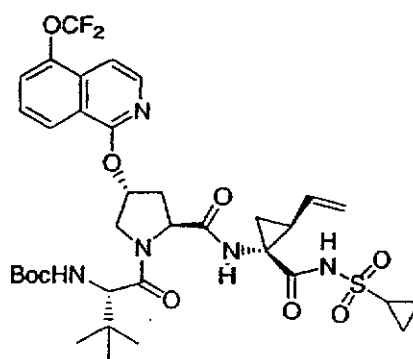
Step 1 and step2:

See compound 256

Step 3:

Modifications: 46 mg 1-chloro-5-difluoromethoxy-isoquinoline and 111 mg (1-[2-(1-cyclopropanesulfonylamino-carbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl)-carbamic acid *tert*-butyl ester used, 40 mg product obtained (27% yield).

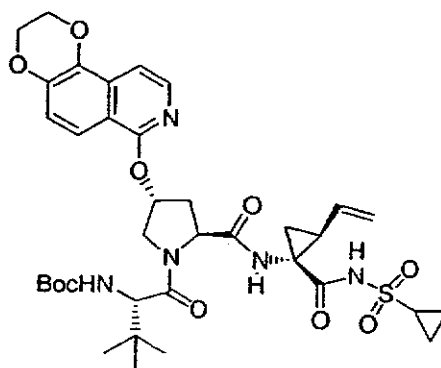
Product:



Compound 285

Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 1.06 (m, 12 H), 1.25 (m, 10 H), 1.44 (m, 1 H), 1.89 (m, 1 H), 2.22 (m, 2 H), 2.62 (m, 1 H), 2.94 (m, 1 H), 4.08 (m, 1 H), 4.23 (d, $J=9.54$ Hz, 1 H), 4.52 (m, 2 H), 5.12 (d, $J=10.76$ Hz, 1 H), 5.29 (d, $J=17.61$ Hz, 1 H), 5.75 (m, $J=10.03$ Hz, 1 H), 5.88 (s, 1 H), 6.60 (s, 1 H), 7.02 (t, $J=73.48$ Hz, 1 H), 7.52 (m, 3 H), 8.07 (m, $J=5.75, 5.75$ Hz, 2 H); MS: $(\text{M}+\text{Na})^+$ 772.

15 Example 286: Preparation of Compound 286



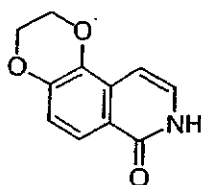
Compound 286

Compound 286 was prepared by following Scheme 2 of Example 269 except that 3-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-acrylic acid was used in place of 2-trifluormethoxycinnamic acid in step 1.

5 Step 1:

Modifications: 4.12 g 3-(2,3-dihydro-benzo[1,4]dioxin-5-yl)-acrylic acid used, 2.2 g product obtained (53% yield).

Product:

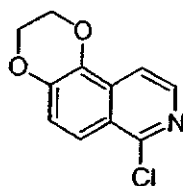


- 10 Data: ^1H NMR (400 MHz, CD_3OD) δ ppm 4.37 (m, 4 H), 6.83 (d, $J=7.09$ Hz, 1 H), 7.02 (d, $J=8.80$ Hz, 1 H), 7.12 (d, $J=7.34$ Hz, 1 H), 7.79 (d, $J=8.80$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 204.

Step 2:

- 15 Modifications: 2.05 g 2,3-dihydro-7H-1,4-dioxo-7-aza-phenanthren-8-one used, 1.5 g product obtained (68% yield).

Product:



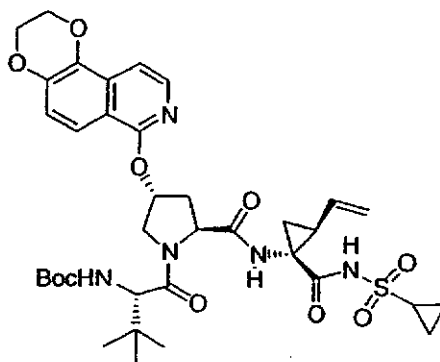
- 20 Data: ^1H NMR (400 Hz, CDCl_3) δ ppm 4.42 (m, 4 H), 7.24 (d, $J=9.05$ Hz, 1 H), 7.77 (d, $J=5.87$ Hz, 1 H), 7.84 (d, $J=9.05$ Hz, 1 H), 8.18 (d, $J=5.87$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 222.

Step 3:

- Modifications: 88 mg 8-Chloro-2,3-dihydro-1,4-dioxo-7-aza-phenanthrene and 223
25 mg (1-[2-(1-Cyclopropanesulfonylamino-carbonyl-2-vinyl-cyclopropyl-carbamoyl)-4-

hydroxy-pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl)-carbamic acid *tert*-butyl ester used, 140 mg product obtained (47% yield).

Product:

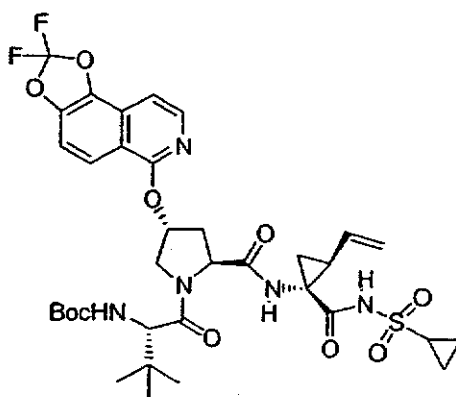


Compound 286

5

Data: ^1H NMR (400 Hz, CD_3OD) δ ppm 1.06 (m, 12 H), 1.24 (m, 10 H), 1.43 (dd, $J=9.05$, 5.14 Hz, 1 H), 1.87 (m, 1 H), 2.22 (d, $J=9.29$ Hz, 2 H), 2.60 (dd, $J=13.45$, 7.09 Hz, 1 H), 2.94 (m, 1 H), 4.05 (dd, $J=11.62$, 2.81 Hz, 1 H), 4.24 (s, 1 H), 4.44 (m, 6 H), 5.13 (d, $J=17.36$ Hz, 1 H), 5.29 (d, $J=17.36$ Hz, 1 H), 5.75 (m, 2 H), 7.04 (d, $J=9.29$ Hz, 1 H), 7.44 (d, $J=5.87$ Hz, 1 H), 7.69 (d, $J=9.05$ Hz, 1 H), 7.88 (d, $J=6.11$ Hz, 1 H); MS: $(\text{M}+\text{H})^+$ 742.

Example 287: Preparation of Compound 287



Compound 287