

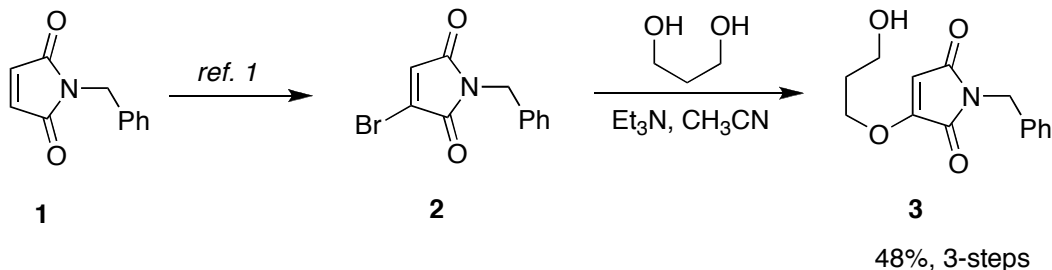
Supplementary Information

Towards the Total Synthesis of FD-838: Modular Enantioselective Assembly of the Core

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Supplementary Information

Alcohol 2



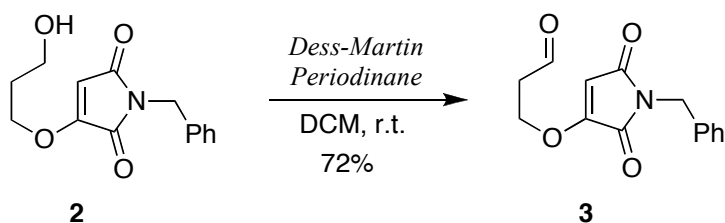
To a solution of bromomaleimide **2**¹ (5.80 g, 23.03 mmol, 1.0 equiv.) and 1,3-propanediol (3.33 mL, 46.1 mmol, 2 equiv.) in acetonitrile (50 mL) was added triethylamine (4.81 mL, 34.5 mmol, 1.5 equiv.). The resulting mixture was heated to reflux and monitored by TLC until all the maleimide was consumed. The reaction mixture was partitioned between EtOAc and water. The aqueous layer was extracted twice more with EtOAc, or until no more product could be observed in the EtOAc phase by TLC. The organic layers were combined, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The resulting purple oil was purified by flash column chromatography using 100% EtOAc to give alcohol **3** (2.99 g, 11.0 mmol, 48 % yield).

¹H NMR (CDCl₃, 400 MHz): δ 1.76-1.80 (t, OH, *J* = 4.7 Hz), 2.00-2.08 (dt, 1 H, *J* = 5, 6.1 Hz), 3.75-3.81 (dt, 1 H, *J* = 4.7, 5 Hz), 4.12-4.17 (dt, 1 H, *J* = 6.1, 1.3 Hz), 4.61 (s, 2 H), 5.39 (d, 1 H, *J* = 1.3 Hz), 7.22-7.35 (m, 5 H).

¹³C NMR (CDCl₃, 100 MHz): δ 31.2, 41.4, 58.1, 69.6, 96.8, 128.0, 128.6, 128.9, 136.5, 160.3, 165.7, 170.3.

HRMS: [M+H] *calculated*: 262.1074, *found*: 262.1063.

Aldehyde 3



To a solution of alcohol **2** (2.45 g, 9.39 mmol) in DCM (60 mL) in a 250 mL round-bottomed flask equipped with an air-cooled condenser (reaction is slightly exothermic) was added Dess-Martin periodinane (1.25 equiv, 4.97 g, 11.73 mmol) portionwise over 5 to 10 minutes. The reaction is stirred at ambient temperature, and the disappearance of the alcohol is monitored by TLC (typically 30 minutes to 1 h). After the reaction is deemed complete, the mixture is diluted with hexanes (60 mL) and filtered through a pad of celite to remove the solids. The filtrate is placed in a separatory funnel and extracted with 1 N HCl, saturated aqueous NaHCO₃ and brine. The organic phase is dried over Na₂SO₄, and

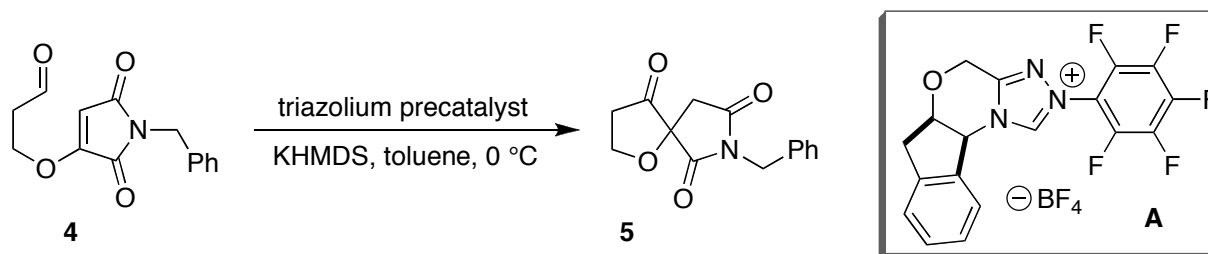
¹ Prepared in nearly quantitative yield over two steps from commercially available *N*-benzyl maleimide. See reference 12.

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concentrated *in vacuo*. The resulting oil was purified by flash column chromatography using a 1:1 mixture of hexanes and EtOAc containing 0.5% HOAc. The collected fractions were combined, washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄ and concentrated *in vacuo* to yield aldehyde **3** as an oil (1.76 g, 6.81 mmol, 72 %). This sensitive aldehyde was used in the next reaction immediately.

¹H NMR (CDCl₃, 400 MHz): δ 3.04 (t, 2 H, *J* = 5.0 Hz), 4.36 (t, 2 H, *J* = 5.0 Hz), 4.64 (s, 2 H), 7.2-7.35 (m, 5 H), 9.81 (s, 1 H).

Spirocycle **5**



To a cooled (0 °C) suspension of triazolium precatalyst **A** (20 mol%, 16 mg, 0.034 mmol) in toluene (2 mL) under positive Argon pressure is added, dropwise *via* a cannula, a freshly prepared, cooled (0 °C) solution of KHMDS (20 mol %, 220 µL of a 0.16 M solution) in toluene. After this mixture has been stirred for 10 minutes, a cooled (0 °C) solution of aldehyde **4** (45 mg, 0.17 mmol) in toluene was added *via* a cannula. The consumption of aldehyde **4** was monitored by TLC. Upon completion of the reaction, the mixture was filtered through a pad of silica gel to remove the solids and eluted with EtOAc. The collected fractions were concentrated *in vacuo* and the resulting oil was purified by flash column chromatography using 1:1 hexanes/EtOAc to yield spirocycle **5** (36 mg, 0.27 mmol, 80 % yield) as a pale-yellow solid in 99% ee (HPLC analysis: Chiracel AD-H, 90:10 Hex:i-PrOH, 1.0 mL/min, 14.1 min (major), 18.2 min (minor)) that could be recrystallized from hexanes/EtOAc.

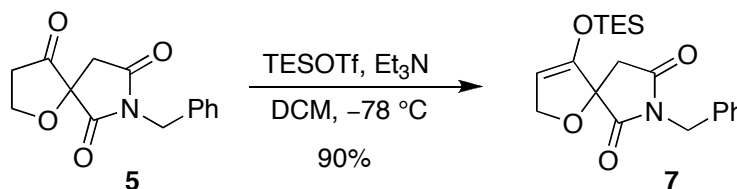
Larger scale reactions could be conducted in an analogous manner, with consistent yields of 60 -70% and 97-99% ee.

¹H NMR (CDCl₃, 400 MHz): δ 2.61-2.72 (ddd, 1 H, *J* = 8.5, 8.5, 18.5 Hz), 2.70-2.75 (d, 1 H, *J* = 18.1 Hz), 2.76-2.84 (ddd, 1 H, *J* = 18.5, 7.9, 4.5 Hz), 2.91-2.96 (d, 1 H, *J* = 18.1 Hz), 4.37-4.44 (ddd, 1 H, *J* = 9.0, 8.5, 4.5 Hz), 4.62-4.69 (ddd, 1 H, *J* = 7.9, 8.5, 9.0 Hz), 4.66 (s, 2 H), 7.25-7.31 (m, 5 H).

¹³C NMR (CDCl₃, 100 MHz): δ 35.7, 38.2, 42.9, 66.1, 82.3, 128.3, 128.6, 129.0, 135.0, 172.8, 174.0, 210.2

HRMS: [M+H] *calculated*: 260.0917, *found*: 260.0915.

Enol ether **7**



To a cold (-78 °C) solution of ketone **60** (111 mg, 0.43 mmol, 1.0 equiv) and triethylamine (90 µL, 0.64 mmol, 1.5 equiv.) in DCM (5 mL) is added, dropwise *via* a syringe, neat TESOTf (121 mL, 0.54 mmol,

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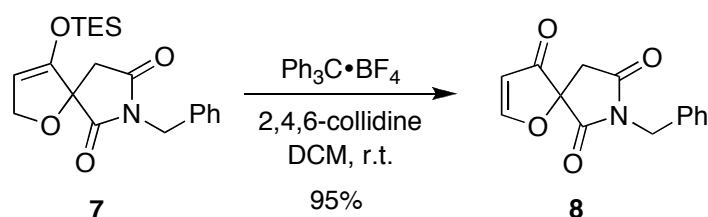
1.25 equiv.). The reaction mixture is maintained at this temperature and consumption of ketone **60** is monitored by TLC analysis. When the reaction is deemed complete, the mixture is diluted with EtOAc and washed with saturated aqueous NaHCO₃, 1 M HCl and brine. The organic phase is dried over Na₂SO₄ and concentrated *in vacuo*. The crude product is purified by column chromatography using 4:1 hexanes/EtOAc to yield enol ether **76** (145 mg, 0.39 mmol, 90 % yield) as a white amorphous solid.

¹H NMR (CDCl₃, 400 MHz): δ 0.55-0.63 (q, 6 H, *J* = 7.9 Hz), 0.81-0.88 (t, 9 H, *J* = 7.9 Hz), 2.74-2.79 (d, 1 H, *J* = 18.1 Hz), 2.92-2.97 (d, 1 H, *J* = 18.1 Hz), 4.62-4.70 (m, 3 H), 4.82-4.87 (d, 1 H, *J* = 10.9 Hz), 4.90 (s, 1 H), 7.20-7.30 (m, 2 H), 7.30-7.36 (m, 2 H).

¹³C NMR (CDCl₃, 100 MHz): δ 4.4, 6.5, 39.5, 42.6, 74.1, 86.5, 97.8, 128.0, 128.8, 128.8, 135.7, 148.5, 173.9, 176.6.

HRMS: [M+H] *calculated*: 388.1934, *found*: 388.1934.

Furanone **8**



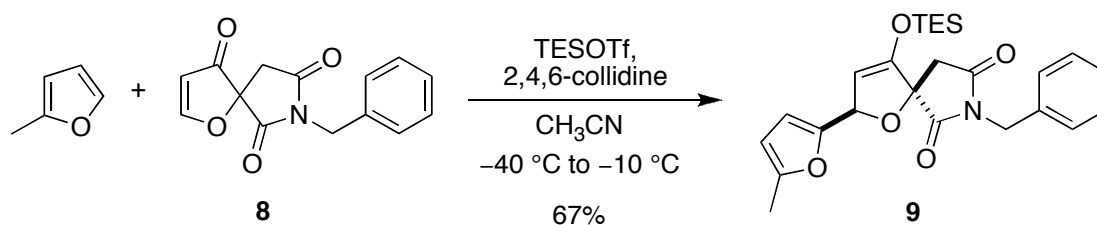
To a solution of enol ether **7** (145 mg, 0.39 mmol, 1.0 equiv.) and 2,4,6-collidine (124 μL, 1.11 mmol, 2.9 equiv.) in DCM (10 mL) at ambient temperature is added solid triphenylcarbenium tetrafluoroborate (525 mg, 1.6 mmol, 4 equiv.). The consumption of enol ether **7** is monitored by TLC and once the reaction is deemed complete (10 to 15 minutes) the mixture is diluted with diethyl ether and washed with water and brine, dried over Na₂SO₄ and concentrated *in vacuo*. The resulting solid mixture is purified by column chromatography on silica gel using 1:1 hexanes/EtOAc to give furanone **8** (104 mg, mmol, 95% yield) as a yellow solid that can be recrystallized from hexanes/EtOAc.

¹H NMR (CDCl₃, 400 MHz): δ 2.94–3.00 (d, 1 H, *J* = 18.1 Hz), 3.07-3.13 (d, 1 H, *J* = 18.1 Hz), 4.68 (s, 2 H), 5.75-5.78 (d, 1 H, *J* = 2.3 Hz), 7.22-7.35 (m, 5 H), 8.36-8.39 (d, 1 H, *J* = 2.3 Hz).

¹³C NMR (CDCl₃, 100 MHz): δ 37.0, 43.6, 85.6, 106.6, 128.4, 128.6, 129.0, 134.7, 168.9, 171.8, 179.7, 198.8

HRMS: n/a²

Compound **9**



² A number of attempts to obtain HRMS data for this compound failed. Similarly, a number of attempts to obtain HRMS data for the PMB-protected analog failed.

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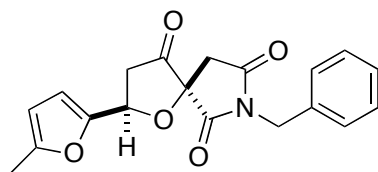
To a cold (-40 °C) solution of furanone **75** (870 mg, 3.385 mmol, 1.0 equiv), 2-methylfuran (5.50 g, 67.7 mmol, 20 equiv), and 2,4,6-collidine (671 mL, 5.08 mmol, 1.5 equiv) in CH₃CN is added dropwise *via* a syringe, TESOTf (995 mL, 4.40 mmol, 1.3 equiv). The reaction is allowed to slowly warm to -10 °C and maintained at this temperature until the reaction is deemed complete by TLC. The reaction is diluted with EtOAc and saturated NaHCO₃ solution and separated. The organic phase is washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The crude material is purified by flash column chromatography on silica gel using 15% EtOAc in Hexanes to give compound **114** (1.035 g, 2.28 mmol, 67%).

¹H NMR (CDCl₃, 400 MHz): δ 0.46-0.53 (q, 2 H, *J*=7.9 Hz), 0.59-0.66 (q, 4 H, *J*=7.9 Hz), 0.84-0.90 (t, 6 H, *J*=7.9 Hz), 0.88-0.94 (t, 3 H, *J*=7.9 Hz), 2.24 (s, 3 H), 2.76-2.82 (d, 1 H, *J*=18.3 Hz), 3.01-3.07 (d, 1 H, *J*=18.3 Hz), 4.66 (s, 2 H), 4.92 (s, 1 H), 5.87-5.90 (d, 1 H, *J*=3.0 Hz), 5.91 (s, 1 H), 6.12-6.15 (d, 1 H, *J*=3.0 Hz), 7.20-7.35 (m, 5 H).

¹³C NMR (CDCl₃, 100 MHz): δ 4.5, 6.5, 6.6, 7.0, 13.8, 39.9, 42.6, 79.0, 86.4, 99.0, 106.5, 109.5, 128.0, 128.8, 135.6, 150.5, 151.9, 153.2, 173.9, 176.2.

HRMS: [M+H] *calculated*: 454.2044, *found*: 454.2038

The corresponding deprotected compound was also obtained (107mg, 0.32 mmol, 8%)

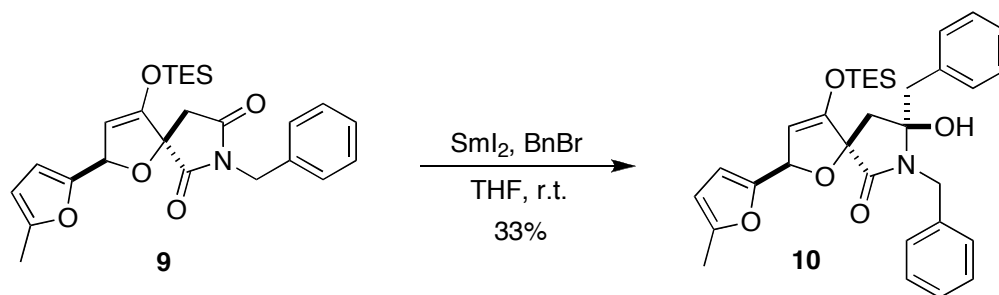


¹H NMR (CDCl₃, 400 MHz): δ 2.27 (s, 3 H), 2.72-2.77 (d, 1 H, *J*=18.3 Hz), 2.92-2.99 (dd, 1 H, *J*=18.5, 7.6 Hz), 2.99-2.04 (d, 1 H, *J*=18.3 Hz), 3.02-3.08 (dd, 1 H, *J*=18.5, 7.6 Hz), 4.84 (s, 2 H), 5.64-5.69 (1 H, dd, *J*=7.6, 7.6 Hz), 5.93-5.95 (d, 1 H, *J*=3 Hz), 6.29-6.31 (d, 1 H, *J*=3 Hz), 7.24-7.30 (m, 5 H).

¹³C NMR (CDCl₃, 100 MHz): δ 13.8, 38.8, 39.6, 43.0, 71.9, 83.5, 106.9, 111.3, 128.3, 128.5, 129.0, 134.9, 48.8, 154.0, 172.8, 173.9, 209.2.

HRMS: [M+H] *calculated*: 340.1179, *found*: 340.1179

Compound 10



A 0.1 M solution of SmI₂ in THF is prepared as follows: To a stirred suspension of samarium filings (225 mg, 1.5 mmol) in THF (15 mL) at ambient temperature under Ar is added 1,2-diiodoethane (422 mg, 1.5 mmol) in one portion. The resulting mixture is allowed to stir for 2 h and a deep blue solution is obtained.

To a solution of compound **9** (100 mg, 0.22 mmol, 1.0 equiv) and benzyl bromide (75 mg, 0.44 mmol, 2.0 equiv) in THF (5 mL) at ambient temperature is added a solution of freshly prepared SmI₂ in THF

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(8.81 mL of a 0.1 M solution, 0.88 mmol, 4 equiv) *via* a syringe. The disappearance of starting material is monitored by TLC analysis. Once the material is consumed, the mixture is diluted with saturated NaHCO₃ and EtOAc and the layers are separated. The organic phase is washed with brine and dried over Na₂SO₄ and concentrated *in vacuo*. The resulting material is purified by flash column chromatography (1 : 4 EtOAc : Hexanes) to yield compound **10** (39 mg, 0.071 mmol, 33%).

This reaction has not been optimized.

¹H NMR (CDCl₃, 400 MHz): δ 0.73-0.82 (q, 6 H, *J* = 7.9 Hz), 0.97-1.04 (t, 9 H, *J* = 7.9 Hz), 1.72-1.78 (d, 1 H, *J* = 14.7 Hz), 2.18 (s, 3 H), 2.42-2.47 (d, 1 H, *J* = 13.5 Hz), 2.61-2.67 (d, 1 H, *J* = 14.7 Hz), 2.63-2.66 (d, 1 H, *J* = 2.0 Hz), 3.11-3.16 (d, 1 H, *J* = 13.5 Hz), 4.41-4.47 (d, 1 H, *J* = 15.6 Hz), 4.84-4.89 (d, 1 H, *J* = 15.6 Hz), 4.94 (s, 1 H), 5.82-5.85 (d, 1 H, *J* = 3.0 Hz), 5.85 (s, 1 H), 6.04-6.07 (d, 1 H, *J* = 3.0 Hz), 7.15-7.35 (m, 10 H).

¹³C NMR (CDCl₃, 100 MHz): δ 4.8, 6.7, 13.8, 43.1, 43.3, 45.4, 78.5, 87.5, 90.1, 99.9, 106.4, 109.2, 127.1, 127.3, 127.8, 128.3, 128.7, 130.6, 135.7, 138.6, 150.8, 152.6, 152.9, 172.3.

HRMS: [M-H₂O+H] *calculated*: 528.2565, *found*: 528.2556