3,8-Diazabicyclo[3.2.1]octan-2-one Peptide Mimetics: Synthesis of a Conformationally Restricted Inhibitor of Farnesyltransferase

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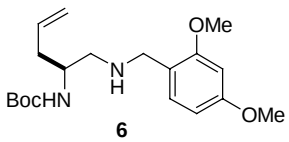
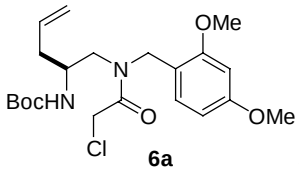
Supplementary Material

General Experimental Information: Proton NMR spectra were recorded on Varian Unity 400 or VRX-400 spectrometers (400 MHz), or Varian Unity or Varian Plus (500 MHz) spectrometers. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane as an internal standard. Low resolution electrospray mass spectra were recorded on a Micromass ZMD spectrometer using a Waters 2690 HPLC (2.1 x 100 mm C18 column, H_2O/MeCN w/0.05% TFA) for sample introduction. High resolution mass spectra were recorded on a Bruker 3T Fourier transform ion cyclotron resonance mass spectrometer equipped with electrospray ionization. The MH^+ signal of the analyte of interest is mass measured against the internal calibrant, polypropylene glycol (average mass 425). Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a sodium lamp. Silica gel 60 (230-400) mesh from EM Science was used for flash column chromatography, and analytical thin layer chromatography was performed on EM Science Kieselgel 60 F254 plates. Solvents and reagents were obtained from commercial sources and used without further purification. The reported yields are the actual isolated yields of purified material, and are not optimized. In the following paragraphs, the experimental procedures and spectroscopic data for the compounds included in the Letter are included. In those instances where a given compound structure does not appear in the graphics for the paper, it is assigned a number which correlates it to the previous illustrated structure.



6

Preparation of (1*S*)-*tert*-butyl-1-{[(2,4-dimethoxybenzyl)amino]methyl}but-3-enylcarbamate (6). To a solution of 2,4-dimethoxybenzylamine hydrochloride (5.15 g, 25.3 mmol) and (S)-*N*-Boc-allylglycinal **5**[1] (4.58 g, 23.0 mmol) in 50 mL of 1,2-dichloroethane at 0 °C was added 4Å powdered molecular sieves (6 g), followed by sodium triacetoxyborohydride (6.79 g, 32.2 mmol). The reaction was allowed to warm to room temperature, then stirred for 14 hours. The mixture was poured into EtOAc, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (4-5% MeOH/CH_2Cl_2) provided the titled product as a yellow oil (7.21 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.1 Hz, 1H), 6.45 (bs, 1H), 6.43 (bd, *J* = 8 Hz, 1H), 5.74 (m, 1H), 5.04-5.10 (m, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 3.77-3.83 (m, 2H), 3.72 (d, *J* = 13.2 Hz, 1H), 2.66-2.69 (m, 2H), 2.26-2.29 (m, 2H), 1.43 (s, 9H); HRMS (ES) exact mass calcd for $C_{19}H_{31}N_2O_4$ ($M+H^+$): 351.2278; found 351.2289.



6a

Preparation of (1*S*)-*tert*-butyl-1-{[(chloroacetyl)(2,4-dimethoxybenzyl)amino]-methyl}but-3-enylcarbamate (6a). To a solution of the amine **6** (8.79 g, 25.1 mmol) in 50 mL of EtOAc and 50 mL of saturated $NaHCO_3$ solution at 0 °C was added chloroacetyl chloride (4.00 mL, 50.2 mmol). After 20 minutes, the layers were separated, and the aqueous layer was extracted with EtOAc. The combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The titled product was obtained (9.93 g, 93%) as an orange oil which was used in the next reaction without further purification. HRMS (ES) exact mass calcd for $C_{21}H_{32}N_2O_5Cl$ ($M+H^+$): 427.1994; found 427.2020.

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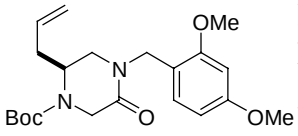
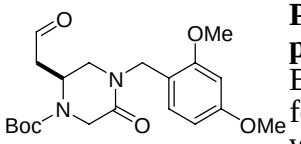
(1) Ohfune, Y.; Nishio, H. *Tetrahedron Lett*. **1984**, *25*, 4133-4136.



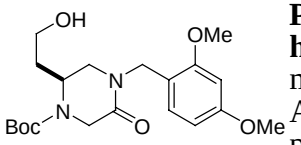
7

Preparation of (*S*)-5-allyl-4-*tert*-butoxycarbonyl-1-(2,4-dimethoxybenzyl)-2-piperazinone (7). To a solution of **6a** (9.93 g, 23.3 mmol) in 60 mL of DMF was added cesium carbonate (15.15 g, 46.6 mmol). The reaction was warmed to 65 °C under argon for 2 hours, then cooled to room temperature. The solution was poured into 90% EtOAc-hexane solution and washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (40-50% EtOAc/hexane) provided **7** as a pale yellow oil (6.84 g, 75%). R*f* 0.23 (40% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.2 Hz, 1H), 6.45 (dd, *J* = 8.2 and 2.4 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 5.60 (m, 1H), 4.98 (bd, *J* = 10.1 Hz, 1H), 4.89 (bd, *J* = 16.9 Hz, 1H), 4.66 (d, *J* = 14.2 Hz, 1H), 4.49 (d, *J* = 14.2 Hz, 1H), 4.30 (bd, *J* = 18.5 Hz, 1H), 4.29 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.78 (d, *J* = 18.5 Hz, 1H), 3.44 (dd, *J* = 12.6 and 4.4 Hz, 1H), 3.15 (bd, *J* = 12.6 Hz, 1H), 2.26 (m, 1H), 2.13 (m, 1H), 1.45 (s, 9H); HRMS (ES) exact mass calcd for $C_{21}H_{31}N_2O_5$ ($M+H^+$): 391.2227; found 391.2243.



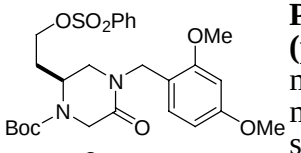
7a

Preparation of (*S*)-4-*tert*-butoxycarbonyl-1-(2,4-dimethoxybenzyl)-5-(2-oxoethyl)-2-piperazinone (7a). To a solution of olefin **7** (209 mg, 0.536 mmol) in 8 mL of *t*-BuOH:THF:H_2O (10:3:1) was added *N*-methylmorpholine-*N*-oxide (80 mg, 0.59 mmol), followed by 0.25M aqueous OsO_4 solution (0.10 Ml, 0.025 mmol). After 7 hours, water was added (5 mL). Followed by solid $NaHCO_3$ (450 mg, 5.36 mmol) and $NaIO_4$ (570 mg, 2.68 mmol). After 1.5 hours, the solution was poured into EtOAc, extracted with aq. NaCl solution, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide **7a** as a pale orange foam (201 mg, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 6.42-6.47 (m, 2H), 4.80 (d, *J* = 14.1 Hz, 1H),4.63 (m, 1H), 4.30 (d, *J* = 14.1 Hz, 1H), 4.20 (m, 1H), 3.87 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.57 (dd, *J* = 13.3 and 4.0 Hz, 1H), 3.15 (bd, *J* = 13 Hz, 1H), 2.52 (m, 1H), 2.45 (m, 1H), 1.44 (s, 9H); *m/z* (ES^+) 393.3 (MH^+).



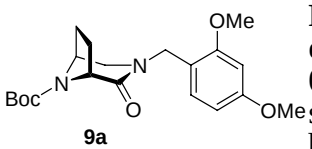
7b

Preparation of (*S*)-4-*tert*-butoxycarbonyl-1-(2,4-dimethoxybenzyl)-5-(2-hydroxyethyl)-2-piperazinone (7b). To a solution of the aldehyde **7a** (200 mg, 0.510 mmol) in 3 mL of ethanol at 0 °C was added sodium borohydride (19 mg, 0.50 mmol). After one hour, the reaction was quenched with saturated aqueous NH_4Cl solution, poured into EtOAc, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled product. Purification by silica gel chromatography (3-5% MeOH/CH_2Cl_2) provided **7b** as a pale yellow foam (185 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.8 Hz, 1H), 6.45 (dd, J = 8 and 2.4 Hz, 1H), 6.44 (bs, 1H), 4.68 (d, *J* = 14.2 Hz, 1H), 4.47 (d, *J* = 14.2 Hz, 1H), 4.41 (m, 1H), 4.25 (d, *J* = 18.5 Hz, 1H), 3.87 (m, 1H), 3.80 (s, 6H), 3.80 (m, 1H), 3.73 (d, *J* = 18.5 Hz, 1H), 3.54-3.62 (m, 1H), 3.30-3.40 (m, 2H), 3.15 (bd, *J* = 11.5 Hz, 1H), 1.64 (m, 1H), 1.47 (s, 9H), 1.40-1.50 (m, 1H); HRMS (ES) exact mass calcd for $C_{20}H_{31}N_2O_6$ ($M+H^+$): 395.2176; found 395.2195.



8

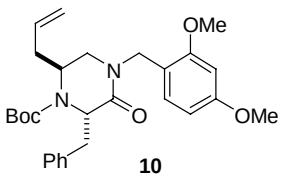
Preparation of (*S*)-4-*tert*-butoxycarbonyl-1-(2,4-dimethoxybenzyl)-5-[2-(phenylsulfonyloxy)ethyl]-2-piperazinone (8). To a solution of the alcohol **7b** (45.1 mg, 0.114 mmol) in 0.5 mL of dichloromethane at 0 °C was added triethylamine (0.032 mL, 0.23 mmol), followed by benzenesulfonyl chloride (0.016 mL, 0.126 mmol). The solution was warmed to room temperature. After one hour, the reaction was diluted with EtOAc, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled product. Purification by silica gel chromatography (2-4% MeOH/CH_2Cl_2) provided **8** as a pale white foam (50.4 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.3 Hz, 2H), 7.66 (bt, *J* = 7.6 Hz, 1H), 7.55 (bt, *J* = 7.7 Hz, 2H), 7.19 (d, *J* = 8.9 Hz, 1H), 6.46 (bs, 1H), 6.45 (m, 1H), 4.73 (d, *J* = 14.2 Hz, 1H), 4.38 (d, *J* = 14.2 Hz, 1H), 4.20-4.56 (m, 2H), 3.90 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.64-3.74 (m, 2H), 3..47 (dd, *J* = 13.1 and 4.0 Hz, 1H), 3.11 (bd, *J* = 13 Hz, 1H) 1.84 (m, 1H), 1.62 (m, 1H), 1.42 (s, 9H); *m/z* (ES^+) 535.25 (MH^+).



9a

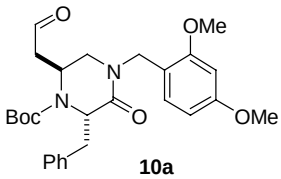
Preparation of 1(*R*),5(*S*)-8-*tert*-butoxycarbonyl-3-(2,4-dimethoxybenzyl)-3,8-diaza-2-oxobicyclo[3.2.1]octane (9a). To a solution the benzenesulfonate **8** (48.0 mg, 0.0899 mmol) in 0.5 mL of THF at -78 °C under argon was added dropwise LiHMDS solution (1M THF, 0.187 mL, 0.187 mmol). The reaction was placed in a 0 °C ice bath, and stirred for 40 minutes. The reaction was quenched with saturated aqueous NH_4Cl solution, and partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution. The aqueous layer

was extracted with EtOAc, and the combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (2% MeOH/CH_2Cl_2) provided **9a** as a white foam (29.1 mg, 86%). $[\alpha]_D^{23}$ –8.6 (*c* 0.011, $CHCl_3$); R*f* 0.30 (50% EtOAc/hexane); ^{1}H NMR (400 MHz, d_6-DMSO, 363K) δ 6.90 (d, *J* = 8.3 Hz, 1H), 6.55 (d, *J* = 2.3 Hz, 1H), 6.44 (dd, *J* = 8.3 and 2.3 Hz, 1H), 4.39 (d, *J* = 14.9 Hz, 1H), 4.28 (m, 1H), 4.24 (d, *J* = 14.9 Hz, 1H), 4.20 (d, *J* = 6.5 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.43 (dd, *J* = 11.6 and 4.2 Hz, 1H), 2.86 (d, *J* = 11.6 Hz, 1H), 1.99-2.24 (m, 2H), 1.90 (m, 1H), 1.66 (m, 1H), 1.36 (s, 9H); HRMS (ES) exact mass calcd for $C_{20}H_{29}N_2O_5$ (M+H$^+$): 377.2071; found 377.2093.



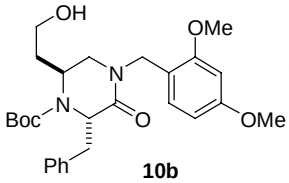
10

Preparation of 5(*S*),3(*S*)-5-allyl-3-benzyl-4-*tert*-butoxycarbonyl-1-(2,4-dimethoxybenzyl)-2-piperazinone (10). To a solution the piperazinone **7** (317 mg, 0.813 mmol) in 1.5 mL of THF at -78 °C under argon was added dropwise LiHMDS solution (1M THF, 0.894 mL, 0.894 mmol). After 20 minutes, benzyl bromide was added (0.106 mL, 0.894 mmol), and the reaction was stirred for 3.5 hours. The solution was quenched with saturated aqueous NH_4Cl solution, and partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (2% MeOH/CH_2Cl_2) provided recovered **7** (74 mg, 23%) and **10** as a white foam (221 mg, 74% based on recovered **7**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1H), 7.17 (bt, J = 7 Hz, 1H), 7.11 (bt, J = 7 hz, 2H), 6.96 (m, 2H), 6.47 (dd, *J* = 8.3 and 2.3 Hz, 1H), 6.41 (d, *J* = 2.3 Hz, 1H), 5.41 (m, 1H), 4.87 (bd, *J* = 10.1 Hz, 1H), 4.68 (bd, *J* = 17.1 Hz, 1H), 4.52 (m, 1H), 4.46 (m, 1H), 4.31 (m, 1H), 3.81 (s, 3H), 3.70 (s, 3H), 3.59 (m, 1H), 3.33 (m, 1H), 3.08 (d, *J* = 13.5 and 3.1 Hz, 1H), 2.70-2.84 (m, 1H), 2.10-2.26 (m, 1H), 1.79-1.96 (m, 2H), 1.52 (s, 9H); *m/z* (FAB$^+$) 481.2 (MH$^+$).



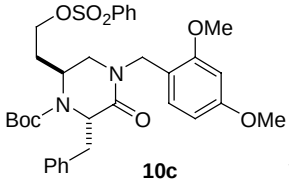
10a

Preparation of 5(*S*),3(*S*)-3-benzyl-4-*tert*-butoxycarbonyl-1-(2,4-dimethoxybenzyl)-5-(2-oxoethyl)-2-piperazinone (10a). To a solution of olefin **10** (197 mg, 0.410 mmol) in 10 mL of *t*-BuOH:THF:H_2O (10:3:1) was added *N*-methylmorpholine-*N*-oxide (61 mg, 0.45 mmol), followed by 0.25M aqueous OsO_4 solution (0.33 mL, 0.082 mmol). After 2.5 hours, water was added (5 mL). Followed by solid $NaHCO_3$ (344 mg, 4.10 mmol) and $NaIO_4$ (438 mg, 2.05 mmol). After 2 hours, the solution was poured into EtOAc, extracted with aq. NaCl solution, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide **10a** as a pale orange foam (220 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.28 (m, 1H), 7.16-7.24 (m, 3H), 7.02 (bd, *J* = 7 Hz, 2H), 6.45 (dd, *J* = 8.3 and 2.3 Hz, 1H), 6.38 (d, *J* = 2.3 Hz, 1H), 4.75 (d, J = 13.9 Hz, 1H), 4.52 (m, 1H), 4.18 (m, 1H), 3.95-4.05 (m, 2H), 3.79 (s, 3H), 3.70 (s, 3H), 3.35-3.40 (m, 1H), 3.11 (dd, J = 13.5 and 3.3 Hz, 1H), 2.92 (m, 1H), 2.52 (m, 1H), 2.09-2.18 (m, 1H), 1.48 (s, 9H).



10b

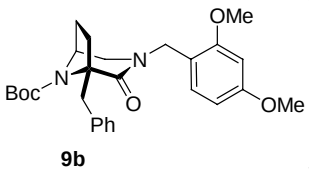
Preparation of 5(*S*),3(*S*)-3-benzyl-4-*tert*-butoxycarbonyl-1-(2,4-dimethoxybenzyl)-5-(2-hydroxyethyl)-2-piperazinone (10b). To a solution of the aldehyde **10a** (220 mg, theor. 0.410 mmol) in 3 mL of ethanol at 0 °C was added sodium borohydride (31 mg, 0.82 mmol). After 20 minutes, the reaction was quenched with saturated aqueous NH_4Cl solution, poured into EtOAc, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled product. Purification by silica gel chromatography (50-70% EtOAc/hexane) provided **10b** as a pale yellow foam (135 mg, 70%). R*f* 0.18 (70% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 1H), 7.14-7.21 (m, 3H), 6.98 (bd, *J* = 6.8 Hz, 2H), 6.45 (dd, *J* = 8.2 and 2.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 4.57 (d, *J* = 13.8 Hz, 1H), 4.45 (m, 1H), 4.16 (d, *J* = 13.8 Hz, 1H), 4.00 (m, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.36-3.47 (m, 3H), 3.29 (m, 1H), 3.11 (dd, *J* = 13.6 and 2.9 Hz, 1H), 2.75 (dd, *J* = 13.4 and 1.8 Hz, 1H), 2.07 (bd, J = 13.4 Hz, 1H), 1.55 (s, 9H), 1.49 (m, 1H), 1.26 (m, 1H); HRMS (ES) exact mass calcd for $C_{27}H_{37}N_2O_6$ (M+H$^+$): 485.2646; found 485.2648.



10c

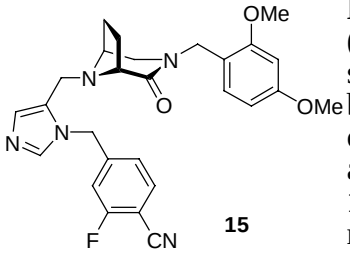
Preparation of 5(*S*),3(*S*)-3-benzyl-4-*tert*-butoxycarbonyl-1-(2,4-dimethoxybenzyl)-5-[2-(phenylsulfonyloxy)ethyl]-2-piperazinone (10c). To a solution of the alcohol **10b** (50.0 mg, 0.103 mmol) in 0.5 mL of dichloromethane at 0 °C was added triethylamine (0.057 mL, 0.41 mmol), followed by benzenesulfonyl chloride (0.040 mL, 0.31 mmol). The solution was warmed to room temperature. After one hour, the reaction was diluted with EtOAc, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the titled product. Purification by silica gel chromatography (40-60% EtOAc/hexane) provided **10c** as a pale white foam (58.0 mg, 90%). R*f* 0.42 (70% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (bd, *J* = 7 Hz, 2H), 7.65 (bt, *J* = 7.4 Hz, 1H), 7.53 (bt, *J* =

7 Hz, 2H), 7.14-7.26 (m, 4H), 6.98 (bd, *J* = 7 Hz, 2H), 6.43-6.46 (m, 2H), 4.70 (m, 1H), 4.48 (dd, *J* = 5.5 and 3.1 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.55-3.64 (m, 2H), 3.34 (m, 1H), 3.08 (dd, *J* = 13.4 and 3.1 Hz, 1H), 2.62-2.82 (m, 1H), 1.60-1.90 (m, 2H), 1.48 (s, 9H); *m/z* (FAB$^+$) 625.3 (MH$^+$).



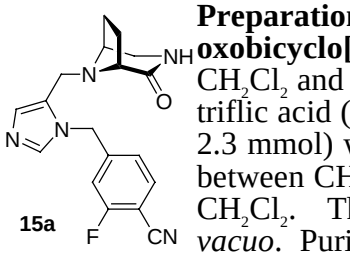
9b

Preparation of 1(*R*),5(*S*)-1-benzyl-8-*tert*-butoxycarbonyl-3-(2,4-dimethoxybenzyl)-3,8-diaza-2-oxobicyclo[3.2.1]octane (9b). A 0.5M solution of LDA in THF was prepared by adding dropwise a solution of *n*-BuLi (1.35 mL, 2.5 M in hexane) to a solution of diisopropylamine (0.50 mL) in THF (5.7 mL) at –78 °C under argon. To a solution the benzenesulfonate **10c** (58.0 mg, 0.0928 mmol) in 0.5 mL of THF at -78 °C under argon was added dropwise LDA solution (0.5M THF, 0.557 mL, 0.288 mmol). The reaction was placed in a 0 °C ice bath, and stirred for two hours. The reaction was quenched with saturated aqueous NH_4Cl solution, and partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc, and the combined organics were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (20-30% EtOAc/hexane) provided **9b** as a white foam (20.1 mg, 63%). $[\alpha]_D^{23}$ –77.6 (*c* 0.010, $CHCl_3$); R*f* 0.30 (50% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (bd, *J* = 7.3 Hz, 2H), 7.24-7.27 (m, 2H), 7.21 (m, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 6.44 (dd, *J* = 8.1 and 2.3 Hz, 1H), 6.43 (bs, 1H), 4.63 (d, *J* = 14.6 Hz, 1H), 4.43 (d, *J* = 14.6 Hz, 1H), 4.33 (dd, *J* = 7.1 and 4.5 Hz, 1H), 3.99 (d, J = 15 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.74 (dd, *J* = 11.8 and 4.1 Hz, 1H), 3.41 (d, *J* = 14.8 Hz, 1H), 2.86 (d, *J* = 11.8 Hz, 1H), 2.09 (m, 1H), 1.97 (m, 1H), 1.87 (m, 1H), 1.52 (m, 1H), 1.42 (s, 9H); *m/z* (ES$^+$) 467.4 (MH$^+$); HRMS (ES) exact mass calcd for $C_{27}H_{34}N_2O_5Na$ (M+Na$^+$): 489.2360; found 489.2369.



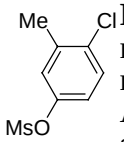
15

Preparation of 1(*R*),5(*S*)-8-[1-(4-cyano-3-fluorobenzyl)-5-imidazolylmethyl]-3-(2,4-dimethoxybenzyl)-3,8-diaza-2-oxobicyclo[3.2.1]octane (15). Through a solution of the carbamate **9a** (81.0 mg, 0.215 mmol) in 5 mL of EtOAc at 0 °C was bubbled anhydrous HCl gas for 3 minutes. After 20 minutes, the solution was concentrated *in vacuo* to provide a white foam (68 mg, 100%). To a solution of this amine hydrochloride and 1-(4-cyano-3-fluorobenzyl)imidazole-5-carboxaldehyde **14** (64 mg, 0.28 mmol) in 1.0 mL of 1,2-dichloroethane was added 4Å powdered molecular sieves (0.10 g), followed by sodium triacetoxyborohydride (82 mg, 0.39 mmol). The reaction was stirred for 24 hours, then diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (4-5% MeOH/CH_2Cl_2) provided **15** as a pale yellow foam (58.5 mg, 56%). *m/z* (ES$^+$) 490.4 (MH$^+$).



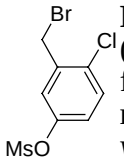
15a

Preparation of 1(*R*),5(*S*)-8-[1-(4-cyano-3-fluorobenzyl)-5-imidazolylmethyl]-3,8-diaza-2-oxobicyclo[3.2.1]octane (15a). To a solution of the amide **15** (58 mg, 0.12 mmol) in 1 mL of CH_2Cl_2 and 0.5 mL of acetonitrile at was added triethylsilane (0.20 mL, 1.2 mmol), followed by triflic acid (0.20 mL, 2.3 mmol). After one week, an additional portion of triflic acid (0.20 mL, 2.3 mmol) was added. After a total of 14 days (75% conversion), the reaction was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$, and the aqueous layer was extracted (4X) with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (3-5% MeOH/CH_2Cl_2) provided the titled product **15a** as an off-white foam (20.6 mg, 69% based on 75% conversion). *m/z* (ES$^+$) 340.2 (MH$^+$).



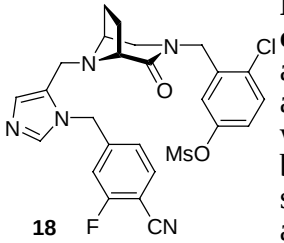
16a

Preparation of 4-chloro-3-methyl-1-phenyl methanesulfonate (16a). To a solution of 4-chloro-3-methylphenol **16** (10.22 g, 71.7 mmol) in 50 mL of CH_2Cl_2 at 0 °C was added triethylamine (19.9 mL, 143 mmol), followed by dropwise addition of methanesulfonyl chloride (6.70 mL, 86.6 mmol). After 30 minutes, the reaction was partitioned between EtOAc and saturated aqueous $NaHCO_3$ solution, and the organic layer was washed with 3N HCl solution and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The titled product **16a** was isolated as a yellow oil (15.8 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.7 Hz, 1H), 7.17 (bs, 1H), 7.07 (dd, *J* = 8.7 and 2.8 Hz, 1H), 3.14 (s, 3H), 2.38 (s, 3H).



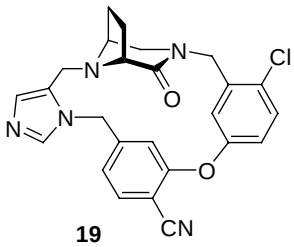
17

Preparation of 3-(bromomethyl)-4-chloro-1-phenyl methanesulfonate (17). To a solution of **16a** (15.8 g, 71.7 mmol) in 100 mL of CCl_4 was added N-bromosuccinimide (19.25 g, 108 mmol), followed by 2,2'-azobisisobutyronitrile (1.82 g, 11.1 mmol). After heating at 80 °C for 14 hours, the reaction was concentrated *in vacuo*, taken up in 30% EtOAc/hexane and filtered, then concentrated *in vacuo* again. Purification by flash chromatography (5-20% EtOAc/hexane) provided **17** as a pale yellow waxy solid (14.9 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.8 Hz, 1H), 7.39 (d, *J* = 2.8 Hz, 1H), 7.20 (dd, *J* = 8.8 and 2.8 Hz, 1H), 4.55 (s, 2H), 3.18 (s, 3H).



18

Preparation of 1(*R*),5(*S*)-8-[1-(4-cyano-3-fluorobenzyl)-5-imidazolylmethyl]-3-[2-chloro-5-(methanesulfonyloxy)benzyl]-3,8-diaza-2-oxobicyclo[3.2.1]octane (18). To a solution of the amide **15a** (20.6 mg, 0.0607 mmol) in 0.5 mL of DMF at 0 °C was added sodium hydride (60% dispersion in oil, 4 mg, 0.09 mmol). The solution was warmed to room temperature for 5 minutes, then cooled to 0 °C. A solution of the bromide **17** (27 mg, 0.091 mmol) in 0.25 mL of DMF was added, and the reaction was stirred for one hour. The reaction was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (2.5-5% MeOH/CH_2Cl_2) provided **18** as a pale yellow foam (18.6 mg, 55%). *m/z* (ES^+) 558.1 (MH^+).



19

Preparation of 20(*R*),23(*S*)-15-chloro-19,20-dihydro-20,23-ethano-19-oxo-5*H*,17*H*-18,21-ethano-6,10:12,16-dimetheno-22*H*-imidazo[3,4-*h*][1,8,11,14]-oxatriaza-cycloeicosine-9-carbonitrile (19). To a solution of **18** (18 mg, 0.033 mmol) in 1.5 mL of DMSO was added cesium carbonate (54 mg, 0.17 mmol). The reaction was warmed to 80 °C under argon for 5 hours, then cooled to room temperature. The solution was diluted with EtOAc and washed with water and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (3-6% MeOH/CH_2Cl_2) was followed by conversion to the HCl salt by taking up in CH_2Cl_2, adding excess ethereal HCl solution, and concentrating *in vacuo* to provide the bis-hydrochloride salt of **19** as a white solid (6 mg, 34%). ^{1}H NMR (as free-base, 500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.0 Hz, 1H), 7.61 (bs, 1H), 7.40 (d, *J* = 8.7 Hz, 1H), 7.22 (bd, *J* = 8 Hz, 1H), 7.12 (dd, *J* = 8.7 and 2.8 Hz, 1H), 6.95 (bs, 1H), 6.92 (bs, 1H), 6.74(d, *J* = 2.8 Hz, 1H), 5.40 (d, *J* -= 15.4 Hz, 1H), 5.12 (d, *J* -= 15.4 Hz, 1H), 4.91 (d, *J* -= 15.4 Hz, 1H), 3.86 (d, *J* -= 15.4 Hz, 1H), 3.61 (d, *J* = 6.4 Hz, 1H), 3.51 (m, 1H), 3.50 (d, *J* = 14.2 Hz, 1H), 3.44 (d, J = 14.2 Hz, 1H), 3.13 (m, 1H), 2.82 (d, *J* = 11.4 Hz, 1H), 2.24 (m, 1H), 2.10 (m, 1H), 1.77-1.84 (m, 2H); HRMS (ES) exact mass calcd for $C_{25}H_{23}N_5O_2$ ($M+H^+$): 460.1535; found 460.1543.