Supporting Information for: Combining Asymmetric Catalysis with Natural Product Functionalization through Enantioselective α-Fluorination

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Contents:

General:

Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions under nitrogen. All solvents and acid chlorides were dried and distilled by standard methods. ^{1}H and ^{13}C NMR spectra were acquired on a 400 Mhz NMR and ^{19}F spectra were taken on a 300 Mhz NMR in $CDCl_3$ or DMSO-D_6. The ^{1}H (400 MHz), ^{13}C (101 MHz), and ^{19}F (282 MHz) chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard, $CFCl_3$, or with the solvent reference relative to TMS employed as an internal standard. NMR data is reported in the following format: chemical shift (multiplicity, integration, coupling constants [Hz]). Diastereoselectivity was determined by ^{1}H and ^{19}F NMR. All measurements were recorded at 25 °C unless otherwise stated.

Syntheses of Drug Nucleophiles:

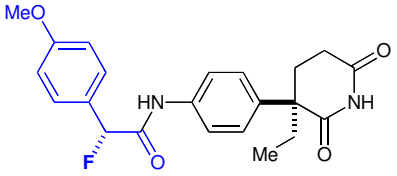
Diphenyldiazomethane was synthesized according to Andrews[i] and reacted with 6-aminopenicillanic acid by the procedure of Jensen et al.[ii] Dihydroartemisinin was synthesized according to Posner et Al. by reduction with DIBAL in 99% yield and 81% de. The two diastereomers formed from the reduction could not be separated by column chromatography and were used further as a mixture of diastereomers.[iii] Diacetylnormorphine was obtained from a known literature procedure in 3 steps.[iv] Glutathione was derivatized by a Fisher esterification with ethanol. All other natural product nucleophiles were used without further modification.

General Procedure for the Syntheses of Fluorinated Products:

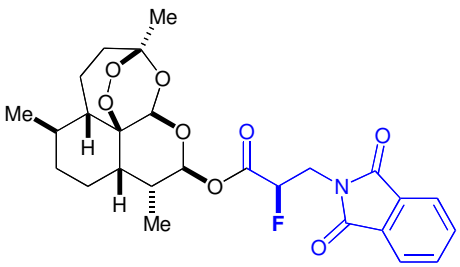
To a dry 10 mL round bottom flask equipped with a stir bar was added *trans*-$(PPh_3)_2PdCl_2$ (3.5 mg, 0.0083 mmol, 0.05 eq) and benzoylquinidine (BQd) (7.1 mg, 0.016 mmol, 0.1 eq), and kept under an atmosphere of nitrogen. THF (1 mL) was added, and the mixture was cooled to -78 °C. Hünig's base (0.03 mL, 0.18 mmol, 1.1 eq) was added neat to the mixture. There upon, a solution of N-fluorobenzenesulfonimide (NFSi, 52.3 mg, 0.16 mmol, 1.0 eq) in 0.33 mL THF was added, followed by a solution of *p*-methoxyphenylacetyl chloride (0.021 mL, 0.16 mmol, 1.0 eq) in 0.66 mL THF. The reaction was maintained at -78 °C for 8 h. 4-Dimethylaminopyridine (DMAP, 2.0 mg, 0.016 mmol, 0.1 eq) and (R)-(+)-aminoglutethimide (12.8 mg, 0.055 mmol, 0.33 eq) were added as a solution in THF (0.50 mL), and the reaction was warmed to room

temperature overnight. The product was then subjected to column chromatography on silica gel with a mixture of ethyl acetate/hexanes as the eluent (unless otherwise noted).

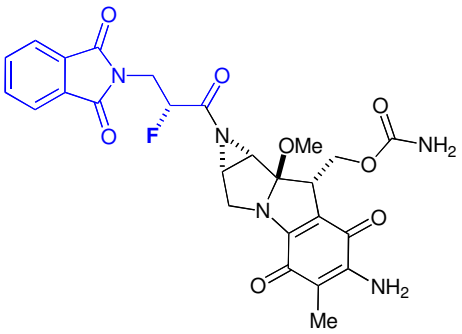
Compound Characterization:



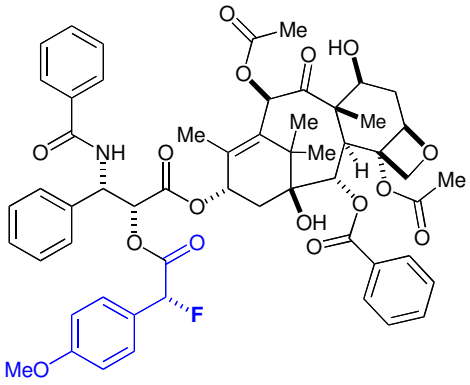
(R)-2-fluoro-2-(4-methoxyphenyl)-*N*-(R)-(+)-aminoglutethimide (3a): yellow solid: % yield = 98, % de = 99; mp = 55-60 ºC; $[\alpha]^{20}_{D}$ = -3.42º (c = 0.0120, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (@ 25 ºC) δ □□□br s, 1H), 8.20 (s, 1H), 7.65 (d, 2H), 7.40 (d, 2H), 7.25 (d, 2H), 6.95 (d, 2H), 5.85 (d, 1H, J = 49.8 Hz), 3.80 (s, 3H), 2.55 (d, 1H), 2.40-2.30 (m, 2H), 2.30-2.10 (m, 1H), 1.95-1.80 (m, 1H), 1.25 (t, 1H), 0.85 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 175.3, 172.5, 161.0, 160.1, 136.5, 134.5, 129.5, 129.5, 127.8, 120.4, 114.5, 92.2 (d, J = 190.4 Hz), 56.0, 52.0, 34.0, 29.5, 27.0, 9.0; ^{19}F NMR ($CDCl_3$) δ –169.9 (ddd, J = 49.8, 15.5, 5.8 Hz); IR (cm^{-1}, CaF_2, CH_2Cl_2) 1706; HRMS (ESI+) calc for $C_{22}H_{23}FN_2O_4Na^+$: 421.153407, found 421.152714.



(R)-dihydroartemisinin-3-(1,3-dioxoisoindolin-2-yl)-2-fluoropropanoate (3b): mixture of diastereomers (could not be separated by column chromatography; major diastereomer shown above); white amorphous solid: % yield = 75, % de = 81; $[\alpha]^{20}_{D}$ = 47.7º (c = 0.390, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (@ 25 ºC) δ 7.85 (m, 2H), 7.72 (m, 2H), 6.26 (d, 0.1 H from minor diastereomer), 5.85 (d, 1H), 5.40 (s, 1H), 5.40-5.25 (m, 1H, J = 48 Hz), 4.25-4.15 (m, 2H), 2.65 (m, 1H), 2.35 (td, 1H), 1.9-1.57 (m, 4H), 1.55 (s, 1H), 1.40 (s, 6H), 1.40-1.20 (m, 3H), 1.00-0.90 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 167.7, 166.3, 166.1, 134.4, 134.3, 132.0, 131.9, 123.7, 123.7, 104.7, 92.6 (d, J = 189.1 Hz), 85.1 (d, J = 192.9 Hz), 80.5, 53.5, 51.7, 45.4, 39.0, 38.8, 37.5, 36.3, 34.2, 31.8, 26.0, 24.7, 22.1, 20.3, 12.4; ^{19}F NMR ($CDCl_3$) δ –198.5 (dt, J= 48 Hz), -196.5 (dq, J = 48 Hz); IR (cm^{-1}, CaF_2, CH_2Cl_2) 1778.2, 1723.7; HRMS (ESI+) calc for $C_{26}H_{30}FNO_8Na^+$: 526.184766, found 526.185400

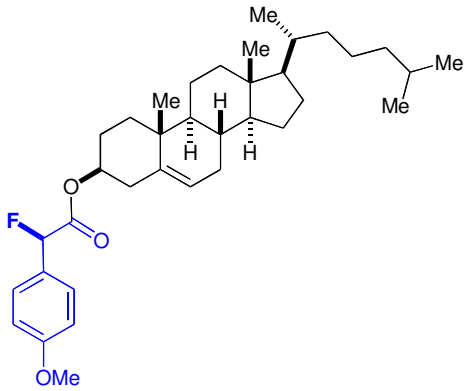


(R)-3-(1,3-dioxoisoindolin-2-yl)-2-fluoro-*N*-azirino-(mitomycin c)propanamide (3c): purple solid: % yield = 58.7, % de = 99; mp = 229 ºC (decomp.); ^{1}H NMR ($CDCl_3$) (@ 25 ºC) δ 7.90-7.75 (m, 5H), 7.6 (br s, 2H), 6.50 (br s, 2H), 5.35 (dt, 1H, J = 48 Hz), 4.80 (dd, 1H), 4.25 (d, 1H), 4.15-4.00 (m, 2H), 3.90 (s, 1H), 3.80 (t, 1H), 3.60 (d, 1H), 3.50 (s, 1H), 3.35 (s, 3H), 3.15 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.9, 176.3, 175.6, 167.0, 156.2, 153.8, 148.4, 134.3, 130.9, 122.7, 109.2, 105.1, 102.6, 88.1 (d, J = 189.3 Hz), 60.1, 48.9, 41.7, 41.2, 8.1; ^{19}F NMR ($CDCl_3$) δ –193.4 (quintet, J= 24 Hz); IR (cm^{-1}, CaF_2, DMSO) 1703, 1692; HRMS (ESI+) calc for $C_{26}H_{24}FN_5O_8Na^+$: 576.150112, found 576.150017**. Optical rotation could not be obtained for this compound due to the opaque nature of the solution. The product was obtained by filtering through a fritted funnel, washing with CH_2Cl_2, and collecting the solid residue. Residual solvent peak in the ^{13}C spectra obscures some peaks.**

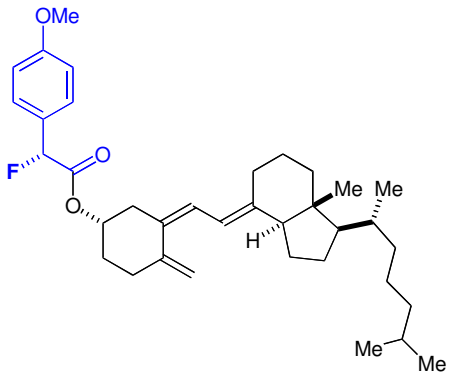


(R)-2'-Taxol-2-fluoro-2-(4-methoxyphenyl)acetate (3d): yellow solid: % yield = 43, % de = 99; mp = 138-140 ºC; $[\alpha]^{20}_{D}$ = -45.3º (c = 0.0130 , CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (@ 25 ºC) δ 8.13 (d, 2H), 8.00-7.25 (m, 16H), 6.65 (d, 2H), 6.65 (d, 1H), 6.26 (s, 1H), 6.21 (t, 1H), 5.90 (dd, 1H), 5.80 (d, 1H), 5.65 (d, 1H), 5.50 (d, 1H), 4.90 (d, 1H), 4.45 (m, 1H), 4.32 (d, 1H), 4.20 (d, 1H), 3.80 (s, 3H), 2.55-2.40 (m, 5H), 2.40-2.10 (m, 5H), 1.89 (m, 3H), 1.70 (s, 3H), 1.67 (s, 2H), 1.24 (s, 3H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 203.0, 171.3, 169.8, 167.8, 167.1, 167.0, 166.9, 161.0, 161.0, 142.7, 136.7, 133.8, 133.5, 132.9, 132.1, 132.1, 130.3, 129.3, 129.2, 129.2, 128.8, 128.7, 128.7, 127.1, 126.6, 114.4, 88.9 (d, J = 189.1 Hz), 84.5, 81.2, 79.2,

76.5, 75.6, 75.1, 75.1, 72.2, 72.1, 58.6, 55.4, 53.5, 52.7, 45.6, 43.2, 35.6, 26.9, 24.9, 22.8, 22.2, 20.9, 14.8, 9.7; ^{19}F NMR ($CDCl_3$) δ –174.8 (d, J = 48.5 Hz); IR (cm^{-1}, CaF_2, CH_2Cl_2) 1710, 1724; HRMS (ESI+) calc for $C_{56}H_{58}FNO_{16}Na^+$: 1042.363184, found 1042.363991

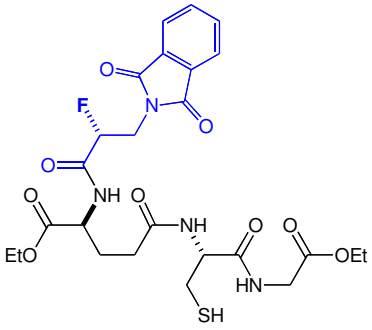


(R)-cholesterol-2-fluoro-2-(4-methoxyphenyl)acetate (3e): off-white solid: % yield = 77, % de = 99; mp = 107-109 ºC; $[\alpha]^{20}_D$ = -54.1º (c = 0.00600, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (@ 25 ºC) δ 7.30 (d, 2H), 6.90 (d, 2H), 5.65 (d, 1H, J = 48 Hz), 5.35, (d, 1H), 4.70 (m, 1H), 3.80 (s, 3H), 2.35 (d, 2H), 2.05-1.90 (m, 2H), 1.90-1.65 (m, 3H) 1.60-0.80 (m, 34H), 0.65 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.4, 168.0, 160.5, 139.1, 128.5, 123.0, 114.1, 114.1, 89.1 (d, J = 186.1), 75.4, 56.6, 56.1, 55.3, 49.9, 42.2, 39.6, 39.5, 37.6, 36.8, 36.5, 36.1, 35.7, 31.8, 31.8, 28.2, 28.0, 27.6, 24.2, 23.8, 22.8, 22.5, 21.0, 19.2, 19.2, 18.7, 11.8; ^{19}F NMR ($CDCl_3$) δ –174.1 (d, J= 47.4 Hz); IR (cm^{-1}, CaF_2, CH_2Cl_2) 1751; HRMS (ESI+) calc for $C_{36}H_{53}FO_3Na^+$: 575.387095, found 575.387446

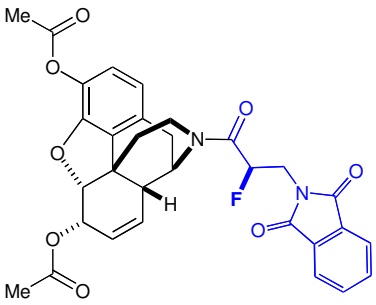


(R)-vitamin D3-2-fluoro-2-(4-methoxyphenyl)acetate (3f): waxy oil: % yield = 75, % de = 99; $[\alpha]^{20}_D$ = 13.3º (c = 0.010, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (@ 25 ºC) δ 7.30 (d, 2H), 6.85 (d, 2H), 6.00 (dd, 1H), 5.65 (d, 1H, J = 48Hz), 5.00 (s, 1H), 4.70 (s, 1H), 3.90 (s, 3H), 2.75-2.5 (dd, 1H), 2.50-0.60 (m, 36H), 0.50 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.4, 168.0, 160.5, 139.1, 128.5, 123.0, 114.1, 114.1, 89.1 (d, J = 186.1), 75.4, 56.6, 56.1, 55.3, 49.9, 42.2, 39.6, 39.5, 37.6, 36.8, 36.5, 26.1, 35.7,

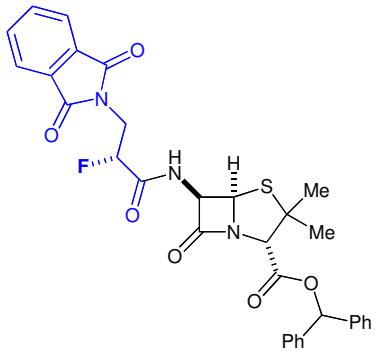
31.8, 31.8, 28.2, 28.0, 27.6, 24.2, 23.8, 22.8, 22.5, 21.0, 19.2, 19.2, 18.7, 11.8; ^{19}F NMR ($CDCl_3$) δ –174.1 (d, J= 47.4 Hz); IR (cm^{-1}, CaF_2, CH_2Cl_2) 1752; HRMS (ESI+) calc for $C_{36}H_{51}FO_3Na^+$ = 573.371445, found 573.372069



(R)-3-(1,3-dioxoisoindolin-2-yl)-2-fluoro-*N*-(glutathione diethyl ester)propanamide (3g): white solid: % yield = 40, % de = 99; mp = 134-136 ºC; $[\alpha]^{20}_D$ = 43.9º (c = 0.120, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (@ 25 ºC) δ 7.88 (m, 2H), 7.75 (m, 2H), 7.07 (d, 1H), 5.25 (m, 1H, J = 48 Hz), 4.64 (m, 1H), 4.31-4.04 (m, 6H), 2.40 (m, 2H), 2.27 (m, 1H), 2.07 (m, 1H), 1.64 (s, 1H), 1.28 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 172.7, 171.0, 167.8, 167.3, 167.2, 134.3, 132.1, 123.7, 88.1 (d, J = 193.3 Hz), 62.0, 60.9, 51.6, 51.6, 39.6, 39.4, 30.4, 29.8, 27.3, 14.3, 14.2; ^{19}F NMR ($CDCl_3$) δ -195.7 (m, J = 3.3, 8.0, 3.3, 4.6, 3.4, 3.1 Hz); IR (cm^{-1}, CaF_2, CH_2Cl_2) 1712, 1664, 1546; HRMS (ESI+) calc for $C_{25}H_{31}FN_4O_9SNa^+$: 605.168799, found 445.137261 (cleavage of CH_2-CHF bond and a proton lost, $C_{16}H_{25}FN_3O_7SNa^+$, calc 445.129497)



(R)-3-(1,3-dioxoisoindolin-2-yl)-2-fluoro-*N*-(normorphine-dimethylester)propanamide (3h): 2:1 mixture of rotamers (2:1); clear oil: % yield = 32, % de = 99; $[\alpha]^{20}_D$ = -68.9º (c = 0.416, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (@ 25 ºC) δ 7.90 (m, 2H), 7.75 (m, 2H), 6.82 (d, 1H), 6.65 (d, 1H), 5.73 (m, 1H), 5.65-5.35 (m, 3H), 5.15 (s, 2H), 4.80-4.30 (m, 2H), 4.20-4.00 (m, 2H), 3.10-2.70 (m, 3H), 2.30 (s, 3H), 2.15 (s, 3H), 2.00 (m, 1H), 1.25 (t, 1H); ^{13}C NMR ($CDCl_3$) δ 170.5, 168.4, 168.3, 168.0, 149.6, 134.4, 134.1, 134.0, 132.2, 132.1, 132.0, 131.0, 130.2, 129.8, 129.5, 128.6, 128.5, 128.2, 127.9, 127.5, 123.7, 123.5, 123.4, 122.8, 122.7, 120.0, 119.8, 88.4, 88.3, 77.4, 77.3, 77.1, 76.8, 67.7, 67.6, 60.5, 47.5, 43.5, 43.3, 40.3, 39.3, 39.2, 35.2, 34.4, 32.2, 30.2, 29.3, 21.1, 20.7, 14.3; ^{19}F NMR ($CDCl_3$) δ -189.7 (m, minor rotamer), -191.1 (m, major rotamer); IR (cm^{-1}, CaF_2, CH_2Cl_2) 1772.3, 1717.7; HRMS (ESI+) calc for $C_{31}H_{27}FN_2O_8Na^+$: 597.164365, found 597.164354



(2S,5R,6R)-benzhydryl-6-((R)-3-(1,3-dioxoisoindolin-2-yl)-2-fluoropropanamido)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (3i): colorless oil: % yield = 74, % de = 99; $[\alpha]^{20}_{D}$ = 130.3º (c = 0.4013 CH_2Cl_2); ^{1}H NMR ($CDCl_3$) (@ 25 ºC) δ 7.30 (m, 12H), 7.00-6.80 (s, 4H), 5.85-5.65 (m, 1H), 5.55 (d, 1H), 4.60 (s, 1H), 3.80 (s, 3H), 1.56 (s, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.2, 167.5, 166.6, 166.5, 166.3, 138.9, 138.8, 134.1, 131.7, 128.5, 128.4, 128.3, 128.1, 127.5, 126.8, 123.5, 88.1 (d, J = 192.8 Hz), 78.4, 70.4, 67.6, 65.1, 58.0, 39.4, 39.1, 32.1, 30.8, 26.4; ^{19}F NMR ($CDCl_3$) δ –196.6 (quintet, J= 24 Hz); IR (cm^{-1}, CaF_2, CH_2Cl_2) 1785, 1741, 1692, 1611, 1512; HRMS (ESI+) calc for $C_{32}H_{28}FN_3O_6SNa^+$: 624.157506, found 624.158161

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[i] Andrews, S. D.; Day, A. C.; Raymond, P.; Whiting, M. C. *Org Synth.* **1988**, *6*, 392.

[ii] Jensen, S. E.; Westlake, W. S.; Bowers, R. J.; Wolfe, S. *J. Antibiot* **1982**, *35*, 1351-1360.

[iii] Posner, G. H.; McRiner, A. J.; Paik, I.; Sur, S.; Borstnik, K.; Xie, S.; Shapiro, T. A.; Alagbala, A.; Foster, B. *J. Med. Chem.* **2004**, *47*, 1299-1301.

[iv] Cooper, G. K.; Rapoport, H. *J. Labelled Compd. Rad.* **1985**, *12*, 1201-1207.