

Supporting Information

Directing Activator-Assisted Regio- and Oxidation State-Selective Aerobic Oxidation of Secondary C(sp³)-H Bonds in Aliphatic Alcohols

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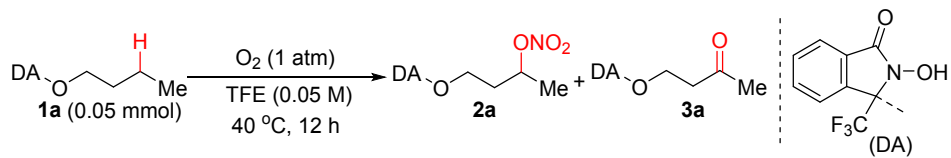
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1. General Method

¹H NMR spectra were recorded on JEOL ECX500 (500 MHz for ¹H NMR and 125 MHz for ¹³C NMR), and JEOL ECS400 (400 MHz for ¹H NMR, 100 MHz for ¹³C NMR and 400 MHz for ¹⁹F NMR) spectrometer. Proton and carbon chemical shifts are reported relative to the solvent used as an internal reference. Fluorine chemical shifts are reported relative to trifluoroacetic acid ($\delta -76.55$ ppm) as an external reference. Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. ESI-MS spectra were measured on a JEOL JMS-T100LC AccuTOF spectrometer (for HRMS). Column chromatographies were performed with silica gel Merck 60 (230-400 mesh ASTM). The ratios of regioisomers were determined by HPLC analysis (JASCO HPLC systems; pump: PU-2080; detector: UV-2075, measured at 254 nm; column: CHIRALPAK AD-H or Inertsil[®] diol column; mobile phase: 2-propanol/ⁿhexane or chloroform/ⁿhexane). All reactions other than substrates synthesis were carried out in normal solvents without any purification (purchased from Aldrich or Wako Pure Chemical Industries, Ltd.) unless otherwise noted. Other reagents of which preparation is not described in this manuscript were purchased from Aldrich, Tokyo Chemical Industry Co., Ltd. (TCI), Kanto Chemical Co., Inc., and Wako Pure Chemical Industries, Ltd., and used without further purification. NMR yields were calculated by ¹H NMR of crude products using 1,1,2,2-tetrachloroethane as an internal standard.

2. Experimental Details

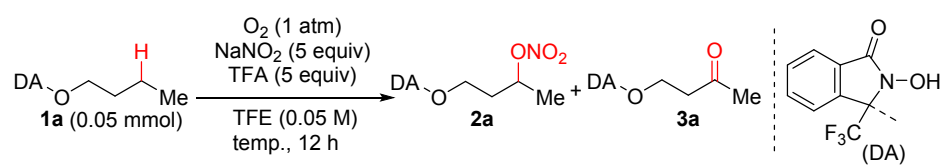
Table S1. NO_x source screening



Entry	reactant (equiv)	combined yield (%) ^[a]	ratio (2a/3a)
1	NO gas (ca. 3)	46	0.6
2	HNO ₃ (3)	23	1.3
3	^t BuONO (1) ^[b]	54	1.0
4	^t BuONO (2) ^[b]	51	1.4
5	^t BuONO (3) ^[b]	43	1.8
6	KNO ₂ (5) + TFA (5)	50	1.2
7	AgNO ₂ (5) + TFA (5)	50	1.3
8	NaNO ₂ (5) + TFA (5)	63	1.5
9	NaNO ₂ (10) + TFA (50) ^[c]	45	2.7
10	KNO ₂ (10) + TFA (10) ^[c]	61	1.6
11	AgNO ₂ (10) + TFA (10) ^[c]	74	1.6
12	NaNO ₂ (10) + TFA (10) ^[c]	72	1.6
13	AgNO ₃ (5) + TFA (5)	trace	-
14	NaNO ₃ (5) + TFA (5)	trace	-
15	NaNO ₂ (5)	32	1.3
16	TFA (5)	trace	-

[a] NMR Yield. [b] Slowly added over 8 h. [c] TFA was slowly added over 8 h. TFA = trifluoroacetic acid, TFE = 2,2,2-trifluoroethanol

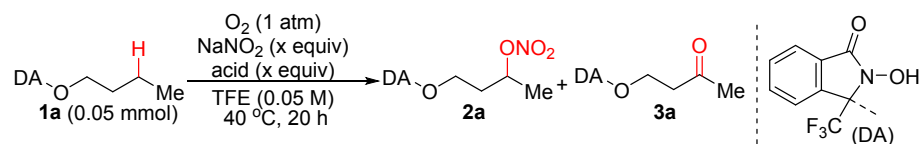
Table S2. Temperature effect



Entry	temp. (°C)	combined yield (%) ^[a]	ratio (2a/3a)
1	23	15	2.0
2	40	63	1.5
3	50	62	1.4
4	60	62	1.0

[a] NMR yield. TFA = trifluoroacetic acid, TFE = 2,2,2-trifluoroethanol

Table S3. Brønsted acid screening



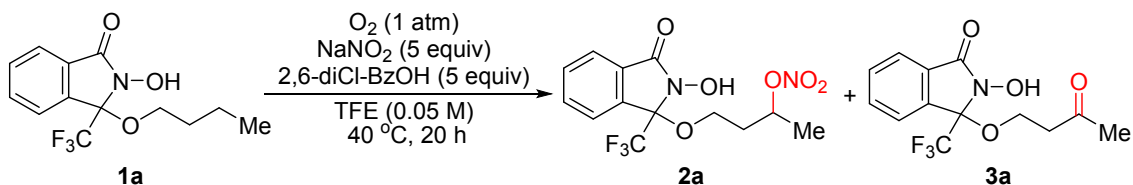
Entry	acid (x equiv)	combined yield (%) ^[a]	ratio (2a/3a)
1	MeSO ₃ H (10)	41	1.0
2	H ₂ SO ₄ (10)	30	2.5
3	BzOH (10)	43	2.1
4	BzOH (5)	71	1.7
5	BzOH (3)	62	1.8
6	4-F-BzOH (5)	63	1.6
7	3-Cl-BzOH (5)	76	1.7
8	2-Cl-BzOH (5)	70	1.8
9	3-NO ₂ -BzOH (5)	77	1.6
10	4-MeO-BzOH (5)	78	1.6
11	3,5-diCl-BzOH (5)	69	1.8
12	2,6-diCl-BzOH (5)	78	1.8
13	2-NO ₂ -BzOH (5)	78	1.8
14	3-NO ₂ -BzOH (5)	77	1.7
15	ClCH ₂ CO ₂ H (5)	61	1.9
16	Cl ₂ CHCO ₂ H (5)	48	1.9
17	Cl ₃ CCO ₂ H (5)	72	1.6

[a] NMR Yield. TFE = 2,2,2-trifluoroethanol.

Preparation of substrates

Substrates **1a-1k** were prepared according to our reported procedure.¹

Representative procedure for regio- and oxidation state-selective methylene oxygenation



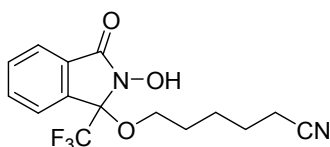
To a dry test tube (ca. 18 mL volume) with a stirring bar, **1a** (28.9 mg, 0.1 mmol), NaNO₂ (34.5 mg, 0.5 mmol) and 2,6-dichlorobenzoic acid (95.5 mg, 0.5 mmol) were added. The tube was capped with a three-way stopcock, and the inside atmosphere was replaced to oxygen (1 atm). Then 2,2,2-trifluoroethanol (2 mL) was added via a syringe. The tube was immediately sealed tightly and the resulting mixture was stirred on a heated metal block (40 °C). During this process, white solid gradually appeared and the reaction mixture turned light yellow. After stirring for 20 h, the mixture was cooled to room temperature and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc/HCO₂H = 80/40/1) to give the oxidation products **2a** (white solid, 15.9 mg) and **3a** (colorless oil, 8.1 mg).

¹ Ozawa, J.; Tashiro, M.; Ni, J.; Oisaki, K.; Kanai, M. *Chem. Sci.* **2016**, 7, 1904.

3. Analytical Data

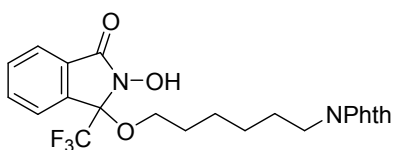
Full spectroscopic data were described for new compounds. Analytically pure samples of each nitrate product diastereomer (dr 1:1) were obtained after preparative HPLC separation.

6-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)hexanenitrile (1g)



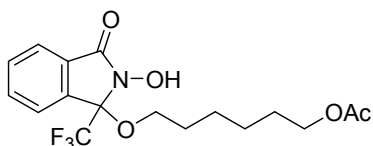
^1H NMR (500 MHz, CDCl_3) δ 9.77 (brs, 1H), 7.80 (d, $J = 7.4$ Hz, 1H), 7.67 (dd, $J = 11.8, 4.2$ Hz, 1H), 7.61 (m, 2H), 3.41 (dt, $J = 8.4, 6.0$ Hz, 1H), 3.01 (dt, $J = 8.4, 6.0$ Hz, 1H), 2.36 (t, $J = 7.0$ Hz, 2H), 1.75 – 1.61 (m, 4H), 1.61 – 1.44 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.80, 134.86, 133.38, 131.64, 129.77, 123.95, 123.92, 121.78 (q, $J = 283.8$ Hz), 119.64, 90.85 (q, $J = 33.4$ Hz), 63.70, 27.99, 25.05, 24.86, 16.93; ^{19}F NMR (400 MHz, CDCl_3) δ -78.96; IR (neat, cm^{-1}) 3194, 2949, 2252, 1717, 1615, 1469, 1197, 1082, 729; HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 351.0927, Found 351.0923.

2-(6-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)hexyl)isoindoline-1,3-dione (1h)



^1H NMR (392 MHz, CDCl_3) δ 9.67 (brs, 1H), 7.88 – 7.74 (m, 3H), 7.74 – 7.50 (m, 5H), 3.64 (t, $J = 6.6$ Hz, 2H), 3.47 – 3.26 (m, 1H), 3.05 – 2.83 (m, 1H), 1.80 – 1.46 (m, 4H), 1.46 – 1.12 (m, 4H); ^{13}C NMR (123 MHz, CDCl_3) δ 168.51, 165.62, 135.12, 133.89, 133.21, 131.97, 131.48, 129.96, 124.00, 123.85, 123.16, 121.85 (q, $J = 285.5$ Hz), 90.91 (q, $J = 32.9$ Hz), 64.08, 37.77, 28.79, 28.36, 26.34, 25.30; ^{19}F NMR (400 MHz, CDCl_3) δ -78.79; IR (neat, cm^{-1}) 3163, 2944, 2863, 2254, 1771, 1712, 1200, 909, 733; HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 485.1295, Found 485.1293.

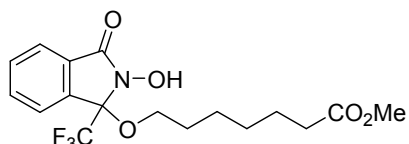
6-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)hexyl acetate (1i)



^1H NMR (500 MHz, CDCl_3) δ 9.84 (brs, 1H), 7.76 (d, $J = 7.4$ Hz, 1H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.59 – 7.50 (m, 2H), 4.07 – 3.85 (m, 2H), 3.44 – 3.28 (m, 1H), 3.00 – 2.85 (m, 1H), 1.97 (s, 3H), 1.71 – 1.45 (m, 4H), 1.45 – 1.09 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 171.56, 165.51, 134.97, 133.13, 131.40, 129.88,

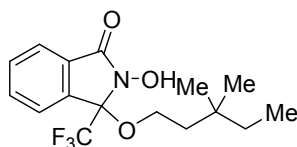
123.84, 123.69, 121.80 (q, $J = 286.6$ Hz), 90.79 (q, $J = 32.8$ Hz), 64.39, 63.95, 28.65, 28.19, 25.34, 25.28, 20.69; ^{19}F NMR (400 MHz, CDCl_3) δ -78.88 ; IR (neat, cm^{-1}) 3153, 2945, 2359, 2253, 1717, 1265, 1201, 910, 733, 650; HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{20}\text{F}_3\text{NO}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 398.1186, Found 398.1192.

methyl 7-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)heptanoate (1j)



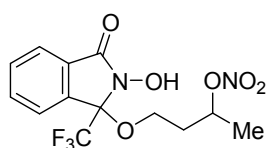
^1H NMR (392 MHz, CDCl_3) δ 7.80 (d, $J = 7.3$ Hz, 1H), 7.68 – 7.56 (m, 3H), 3.64 (s, 3H), 3.43 – 3.26 (m, 1H), 3.01 – 2.88 (m, 1H), 2.81 – 2.22 (m, 2H), 1.67 – 1.50 (m, 4H), 1.44 – 1.16 (m, 4H); ^{13}C NMR (123 MHz, CDCl_3) δ 174.56, 165.70, 135.12, 133.25, 131.51, 129.91, 124.00, 123.90, 121.85 (q, $J = 286.3$ Hz), 90.93 (q, $J = 33.1$ Hz), 64.13, 51.54, 33.86, 28.88, 28.56, 25.36, 24.63; ^{19}F NMR (400 MHz, CDCl_3) δ -78.87 ; IR (neat, cm^{-1}) 3179, 2948, 2864, 2255, 1717, 1470, 1190, 912, 729; HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{20}\text{F}_3\text{NO}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 398.1186, Found 398.1192.

3-((3,3-dimethylpentyl)oxy)-2-hydroxy-3-(trifluoromethyl)isoindolin-1-one (1k)



^1H NMR (500 MHz, CDCl_3) δ 9.68 (brs, 1H), 7.80 (d, $J = 7.3$ Hz, 1H), 7.70 – 7.65 (m, 1H), 7.64 – 7.57 (m, 2H), 3.54 – 3.40 (m, 1H), 3.09 – 2.94 (m, 1H), 1.71 – 1.46 (m, 2H), 1.24 – 1.08 (m, 2H), 0.80 (s, 3H+3H), 0.76 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (123 MHz, CDCl_3) δ 165.83, 135.27, 133.23, 131.49, 129.98, 123.99, 123.92, 121.88 (q, $J = 286.4$ Hz), 91.05 (q, $J = 66.3, 33.5$ Hz), 61.63, 39.75, 34.47, 32.14, 26.78, 26.75, 8.26; ^{19}F NMR (400 MHz, CDCl_3) δ -78.94 ; IR (neat, cm^{-1}) 3154, 2962, 2254, 1716, 1202, 909, 734; HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{20}\text{F}_3\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 354.1287, Found 354.1296.

4-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxybutan-2-yl nitrate (2a)

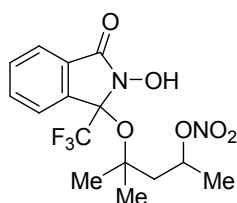


HPLC: Inertsil[®] diol column, eluent: hexane/IPA = 60/1, flow rate: 9.5 mL/min, retention time 117 min and 130 min.

[for less polar diastereomer] white solid; ^1H NMR (500 MHz, CDCl_3) δ 9.37 (brs, 1H), 7.81 (d, $J = 7.1$ Hz, 1H), 7.69 – 7.61 (m, 2H), 7.53 (d, $J = 7.4$ Hz, 1H), 5.44 – 5.28 (m, 1H), 3.59 – 3.41 (m, 1H), 3.17 – 3.01 (m, 1H), 2.12 – 1.99 (m, 1H), 1.98 – 1.83 (m, 1H), 1.43 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.84, 134.68, 133.72, 131.87, 129.70, 124.11, 123.67, 121.74 (q, $J = 285.0$ Hz), 90.76 (q, $J = 33.3$ Hz), 77.74, 59.69, 33.35, 18.74; ^{19}F NMR (400 MHz, CDCl_3) δ -78.90; IR (neat, cm^{-1}) 2926, 1716, 1623, 1507, 1279, 1199, 864; HRMS (ESI): m/z calcd for $\text{C}_{13}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 373.0618, Found 373.0600.

[for more polar diastereomer] white solid; ^1H NMR (500 MHz, CDCl_3) δ 8.63 (brs, 1H), 7.88 – 7.79 (m, 1H), 7.71 – 7.65 (m, 1H), 7.66 – 7.46 (m, 2H), 5.37 – 5.25 (m, 1H), 3.52 – 3.40 (m, 1H), 3.15 – 3.03 (m, 1H), 2.07 – 1.82 (m, 2H), 1.41 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.55, 134.64, 133.52, 131.88, 129.75, 124.29, 123.96, 78.20, 60.18, 33.48, 18.90; ^{19}F NMR (400 MHz, CDCl_3) δ -78.90; IR (neat, cm^{-1}) 2987, 1716, 1624, 1507, 1266, 1200, 897; HRMS (ESI): m/z calcd for $\text{C}_{13}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 373.0618, Found 373.0600.

4-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yloxy)-4-methylpentan-2-yl nitrate (2b)

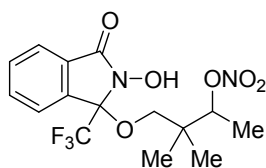


HPLC: Inertsil[®] diol column, eluent: hexane/IPA = 60/1, flow rate: 9.5 mL/min, retention time 74 min and 79 min.

[for less polar diastereomer] white solid; ^1H NMR (400 MHz, CDCl_3) δ 8.82 (brs, 1H), 7.82 (d, $J = 7.2$ Hz, 1H), 7.71 – 7.59 (m, 3H), 5.68 – 5.53 (m, 1H), 2.03 (dd, $J = 15.3, 3.2$ Hz, 1H), 1.82 (dd, $J = 15.3, 7.5$ Hz, 1H), 1.47 (d, $J = 6.3$ Hz, 3H), 1.10 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.14, 137.38, 133.10, 131.58, 129.35, 125.04, 124.07, 80.55, 78.34, 47.50, 27.88, 26.90, 20.29; ^{19}F NMR (400 MHz, CDCl_3) δ -79.95; IR (neat, cm^{-1}) 3054, 2986, 1716, 1623, 1265, 896, 741, 705; HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 401.0931, Found 401.0944.

[for more polar diastereomer] white solid; ^1H NMR (400 MHz, CDCl_3) δ 7.84 (d, $J = 6.8$ Hz, 1H), 7.69 – 7.61 (m, 3H), 5.64 – 5.56 (m, 1H), 1.92 (dd, $J = 15.1, 4.3$ Hz, 1H), 1.82 (dd, $J = 15.1, 6.6$ Hz, 1H), 1.47 (d, $J = 6.3$ Hz, 3H), 1.23 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.95, 136.76, 132.76, 131.64, 129.78, 125.39, 124.14, 80.90, 78.27, 48.51, 29.47, 24.42, 20.22; ^{19}F NMR (400 MHz, CDCl_3) δ -80.23; IR (neat, cm^{-1}) 2925, 2852, 1716, 1623, 1267, 1196, 874, 741; HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 401.0931, Found 401.0944.

4-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yloxy)-3,3-dimethylbutan-2-yl nitrate (2c)

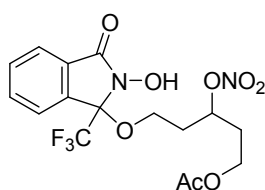


HPLC: Inertsil[®] diol column, eluent: hexane/IPA = 60/1, flow rate: 9.5 mL/min, retention time 64 min and 78 min.

[for less polar diastereomer] white solid; ¹H NMR (400 MHz, CDCl₃) δ 9.47 (brs, 1H), 7.79 (d, *J* = 7.1 Hz, 1H), 7.71 – 7.59 (m, 2H), 7.47 (d, *J* = 7.4 Hz, 1H), 5.31 (q, *J* = 6.5 Hz, 1H), 3.15 (d, *J* = 8.4 Hz, 1H), 2.86 (d, *J* = 8.4 Hz, 1H), 1.37 (d, *J* = 6.5 Hz, 3H), 1.09 (s, 3H), 0.91 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 165.84, 134.61, 133.77, 131.77, 129.63, 124.02, 123.67, 121.78 (q, *J* = 283.8 Hz), 90.54 (q, *J* = 33.4 Hz), 82.79, 69.03, 38.01, 21.62, 19.53, 13.38; ¹⁹F NMR (400 MHz, CDCl₃) δ -79.05; IR (neat, cm⁻¹) 2973, 1716, 1624, 1277, 1200, 877, 737; HRMS (ESI): *m/z* calcd for C₁₅H₁₇F₃N₂O₆Na [M+Na]⁺ 401.0931, Found 401.0916.

[for more polar diastereomer] white solid; ¹H NMR (400 MHz, CDCl₃) δ 8.97 (brs, 1H), 7.84 (d, *J* = 7.1 Hz, 1H), 7.72 – 7.54 (m, 3H), 5.22 (q, 6.4 Hz, 1H), 3.35 – 3.23 (m, 1H), 2.76 – 2.63 (m, 1H), 1.31 (d, *J* = 6.4 Hz, 3H), 1.00 (s, 3H), 0.99 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.57, 134.66, 133.46, 131.79, 129.84, 124.21, 123.85, 121.81 (q, *J* = 290.9 Hz), 90.52 (q, *J* = 33.4 Hz), 83.13, 69.32, 38.04, 21.42, 20.00, 13.71; ¹⁹F NMR (400 MHz, CDCl₃) δ -78.96; IR (neat, cm⁻¹) 2925, 1716, 1625, 1278, 1200, 877, 737; HRMS (ESI): *m/z* calcd for C₁₅H₁₇F₃N₂O₆Na [M+Na]⁺ 401.0931, Found 401.0952.

5-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yloxy)-3-(nitrooxy)pentyl acetate (2d)



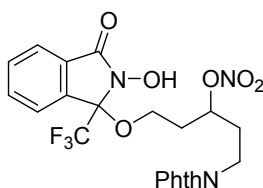
HPLC: Inertsil[®] diol column, eluent: hexane/IPA = 20/1, flow rate: 9.5 mL/min, retention time 93 min and 98 min.

[for less polar diastereomer] colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 9.47 (brs, 1H), 7.83 (d, *J* = 7.2 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.56 (d, *J* = 7.4 Hz, 1H), 5.54–5.37 (m, 1H), 4.31 – 4.11 (m, 2H), 3.60 – 3.42 (m, 1H), 3.19 – 3.06 (m, 1H), 2.20 – 2.03 (m, 6H), 2.02 – 1.93 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 171.13, 165.78, 134.51, 133.70, 131.90, 129.73, 124.17, 123.79, 121.72 (q, *J* = 286.4 Hz), 90.76 (q, *J* = 33.4 Hz), 78.40, 60.20, 59.54, 31.89, 31.68, 20.79; ¹⁹F NMR (400 MHz, CDCl₃) δ -78.90; IR (neat, cm⁻¹) 2986, 1734, 1716, 1635, 1276, 1200, 766, 710; HRMS (ESI): *m/z* calcd for C₁₆H₁₇F₃N₂O₈Na [M+Na]⁺ 445.0829, Found 445.0845.

[for more polar diastereomer] colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.85 (d, *J* = 7.4 Hz, 1H),

7.72 – 7.59 (m, 3H), 5.42 – 5.38 (m, 1H), 4.25 – 4.16 (m, 2H), 3.54 – 3.43 (m, 1H), 3.21 – 3.11 (m, 1H), 2.21 – 2.14 (m, 1H), 2.11 – 1.96 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.13, 165.77, 134.47, 133.53, 131.90, 129.77, 124.28, 124.01, 121.73 (q, $J = 286.6$ Hz), 90.72 (q, $J = 33.4$ Hz), 79.15, 60.21, 60.17, 32.00, 32.00, 20.79; ^{19}F NMR (400 MHz, CDCl_3) δ -78.90; IR (neat, cm^{-1}) 2897, 1734, 1717, 1634, 1265, 1200, 740, 704; HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 445.0829, Found 445.0831.

1-(1,3-dioxoisindolin-2-yl)-5-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yloxy)pentan-3-yl nitrate (2e)

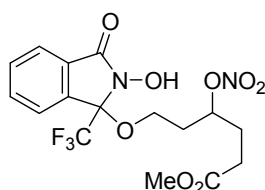


HPLC: Inertsil[®] diol column, eluent: hexane/IPA = 10/1, flow rate: 9.5 mL/min, retention time 107 min and 116 min.

[for less polar diastereomer] colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.89 – 7.81 (m, 3H), 7.76 – 7.73 (m, 2H), 7.67 – 7.48 (m, 3H), 5.35 – 5.22 (m, 1H), 3.90 – 3.77 (m, 2H), 3.52 – 3.33 (m, 1H), 3.19 – 3.03 (m, 1H), 2.27 – 2.14 (m, 1H), 2.12 – 2.06 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.40, 165.48, 134.46, 134.25, 133.61, 131.89, 131.79, 129.86, 124.25, 123.96, 123.51, 122.84, 90.81 (q, $J = 33.3$ Hz), 78.80, 59.60, 34.01, 31.64, 30.86; ^{19}F NMR (400 MHz, CDCl_3) δ -78.71; IR (neat, cm^{-1}) 2919, 1716, 1635, 1276, 1189, 1125, 723; HRMS (ESI): m/z calcd for $\text{C}_{22}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 532.0938, Found 532.0929.

[for more polar diastereomer] white solid; ^1H NMR (500 MHz, CDCl_3) δ 8.66 (brs, 1H), 7.88 – 7.83 (m, 3H), 7.76 – 7.71 (m, 2H), 7.67 – 7.60 (m, 2H), 7.55 (d, $J = 7.1$ Hz, 1H), 5.35 – 5.25 (m, 1H), 3.94 – 3.75 (m, 2H), 3.50 – 3.46 (m, 1H), 3.19 – 3.10 (m, 1H), 2.23 – 2.17 (m, 1H), 2.15 – 2.02 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.43, 165.35, 134.33, 134.17, 133.52, 131.91, 131.87, 129.78, 124.33, 124.10, 123.41, 80.11, 60.48, 34.02, 31.93, 31.57; ^{19}F NMR (400 MHz, CDCl_3) δ -78.68; IR (neat, cm^{-1}) 2927, 1716, 1635, 1265, 1202, 909, 738; HRMS (ESI): m/z calcd for $\text{C}_{22}\text{H}_{18}\text{F}_3\text{N}_3\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 532.0938, Found 532.0954.

methyl 6-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yloxy)-4-(nitrooxy)hexanoate (2f)



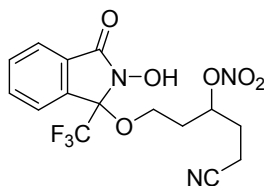
HPLC: Inertsil[®] diol column, eluent: hexane/IPA = 20/1, flow rate: 9.5 mL/min, retention time

87 min and 95 min.

[for less polar diastereomer] colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 8.45 (brs, 1H), 7.88 (d, $J = 7.6$ Hz, 1H), 7.72 – 7.62 (m, 2H), 7.58 (d, $J = 6.8$ Hz, 1H), 5.38 – 5.32 (m, 1H), 3.73 (s, 3H), 3.47 – 3.41 (m, 1H), 3.26 – 3.12 (m, 1H), 2.57 – 2.35 (m, 2H), 2.20 – 2.09 (m, 1H), 2.09 – 1.97 (m, 1H), 1.95 – 1.82 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.74, 165.21, 134.36, 133.55, 131.88, 129.99, 124.32, 124.09, 79.98, 59.51, 52.31, 32.10, 29.19, 27.18; ^{19}F NMR (400 MHz, CDCl_3) δ –78.53; IR (neat, cm^{-1}) 3055, 1716, 1624, 1265, 1020, 740, 706; HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 445.0829, Found 445.0831.

[for more polar diastereomer] colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, $J = 6.8$ Hz, 1H), 7.72 – 7.61 (m, 3H), 5.24 – 5.13 (m, 1H), 3.73 (s, 3H), 3.46 – 3.40 (m, 1H), 3.28 – 3.23 (m, 1H), 2.51 – 2.48 (m, 2H), 2.39 – 2.32 (m, 1H), 2.04 – 1.93 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.81, 165.28, 134.25, 133.42, 131.88, 130.03, 124.38, 124.21, 81.37, 60.38, 52.23, 31.98, 29.26, 27.65; ^{19}F NMR (400 MHz, CDCl_3) δ –78.50; IR (neat, cm^{-1}) 3055, 1716, 1624, 1265, 1200, 896, 740, 705; HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 445.0829, Found 445.0831.

1-cyano-5-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yloxy)pentan-3-yl nitrate (2g)

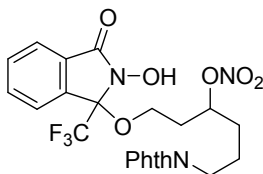


HPLC: Inertsil[®] diol column, eluent: hexane/IPA = 5/1, flow rate: 9.5 mL/min, retention time 43 min and 45 min.

[for less polar diastereomer] colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.85 (d, $J = 7.3$ Hz, 1H), 7.72 – 7.63 (m, 2H), 7.59 (d, $J = 7.3$ Hz, 1H), 5.45 – 5.35 (m, 1H), 3.56 – 3.44 (m, 1H), 3.21 – 3.10 (m, 1H), 2.54 (t, $J = 7.1$ Hz, 2H), 2.30 – 2.20 (m, 1H), 2.18 – 2.05 (m, 2H), 2.04 – 1.98 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.79, 134.32, 133.82, 132.02, 129.62, 124.29, 123.83, 118.37, 79.09, 59.51, 31.57, 28.28, 13.39; ^{19}F NMR (400 MHz, CDCl_3) δ –78.93; IR (neat, cm^{-1}) 3053, 2986, 1716, 1623, 1265, 1201, 896, 739; HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 412.0727, Found 412.0727.

[for more polar diastereomer] colorless oil; ^1H NMR (400 MHz, CDCl_3) δ 9.01 (brs, 1H), 7.86 (d, $J = 7.3$ Hz, 1H), 7.73 – 7.62 (m, 3H), 5.38 – 5.30 (m, 1H), 3.55 – 3.36 (m, 1H), 3.22 – 3.17 (m, 1H), 2.54 (t, $J = 7.7$ Hz, 2H), 2.35 – 2.20 (m, 1H), 2.17 – 2.10 (m, 1H), 2.10 – 1.97 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.75, 134.27, 133.69, 132.04, 129.65, 124.39, 124.03, 121.66 (q, $J = 290.2$ Hz), 118.45, 90.65 (q, $J = 33.4$ Hz), 79.78, 60.07, 31.58, 28.67, 13.31; ^{19}F NMR (400 MHz, CDCl_3) δ –78.93; IR (neat, cm^{-1}) 3055, 2925, 1716, 1624, 1265, 1201, 896, 742; HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 412.0727, Found 412.0727.

6-(1,3-dioxoisindolin-2-yl)-1-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yloxy)hexan-3-yl nitrate (2ha)

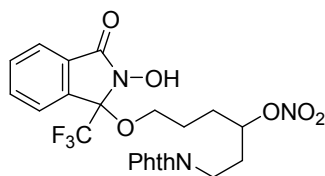


HPLC: Inertsil[®] diol column, eluent: hexane/IPA = 5/1, flow rate: 9.5 mL/min, retention time 41 min and 45 min.

[for less polar diastereomer] colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 9.09 (brs, 1H), 7.92 – 7.86 (m, 2H), 7.83 (d, *J* = 7.4 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.69 – 7.60 (m, 2H), 7.54 (d, *J* = 7.4 Hz, 1H), 5.45 – 5.32 (m, 1H), 3.74 (t, *J* = 6.4 Hz, 2H), 3.46 (dt, *J* = 9.3, 5.0 Hz, 1H), 3.09 (td, *J* = 9.3, 3.7 Hz, 1H), 2.07 – 2.01 (m, 1H), 1.95 – 1.88 (m, 1H), 1.86 – 1.71 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 168.57, 165.52, 134.54, 134.17, 133.61, 131.85, 131.84, 129.84, 124.15, 123.84, 123.43, 90.81 (q, *J* = 33.1 Hz), 80.31, 59.58, 37.24, 31.97, 29.98, 24.09; ¹⁹F NMR (400 MHz, CDCl₃) δ –78.74; IR (neat, cm⁻¹) 2927, 1716, 1625, 1267, 1191, 866, 738; HRMS (ESI): *m/z* calcd for C₂₃H₂₀F₃N₃O₈Na [M+Na]⁺ 546.1095, Found 546.1107.

[for more polar diastereomer] colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 8.94 (brs, 1H), 7.91 – 7.81 (m, 3H), 7.75 – 7.67 (m, 3H), 7.65 – 7.60 (m, 2H), 5.32 – 5.21 (m, 1H), 3.79 – 3.66 (m, 2H), 3.64 – 3.42 (m, 1H), 3.19 – 3.08 (m, 1H), 2.07 – 1.91 (m, 2H), 1.91 – 1.69 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 168.51, 165.49, 134.50, 134.09, 133.48, 131.90, 131.84, 129.86, 124.25, 124.02, 123.37, 90.72 (q, *J* = 32.4 Hz), 81.25, 60.33, 37.29, 31.92, 30.16, 24.14; ¹⁹F NMR (400 MHz, CDCl₃) δ –78.80; IR (neat, cm⁻¹) 2923, 1713, 1628, 1277, 1190, 877, 721; HRMS (ESI): *m/z* calcd for C₂₃H₂₀F₃N₃O₈Na [M+Na]⁺ 546.1095, Found 546.1072.

6-(1,3-dioxoisindolin-2-yl)-1-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yloxy)hexan-3-yl nitrate (2hb)

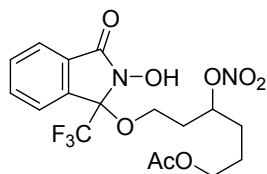


HPLC: Inertsil[®] diol column, eluent: hexane/IPA = 5/1, flow rate: 9.5 mL/min, retention time 41 min and 48 min.

[diastereo mixture (dr1:1)] colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.89 – 7.84 (m, 3H), 7.77 – 7.71 (m, 2H), 7.70 – 7.58 (m, 3H), 5.21 – 5.02 (m, 1H), 3.92 – 3.73 (m, 2H), 3.41 – 3.37 (m, 1H), 3.12 – 2.99 (m, 1H), 2.13 – 2.02 (m, 2H), 2.02 – 1.92 (m, 1H), 1.92 – 1.71 (m, 3H); ¹³C NMR (125 MHz,

CDCl₃) δ 168.51, 168.45, 165.36, 134.80, 134.30, 134.23, 133.37, 131.81, 131.76, 131.72, 130.01, 124.10, 123.56, 123.50, 90.88 (q, $J = 33.0$ Hz), 81.57, 81.17, 63.85, 62.97, 34.10, 34.05, 31.45, 31.33, 29.43, 28.75, 24.34; ¹⁹F NMR (400 MHz, CDCl₃) δ -78.68, -78.77; IR (neat, cm⁻¹) 2924, 1716, 1624, 1266, 1190, 875, 738, 705; HRMS (ESI): m/z calcd for C₂₃H₂₀F₃N₃O₈Na [M+Na]⁺ 546.1095, Found 546.1075.

6-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yloxy)-4-(nitrooxy)hexyl acetate (2ia)

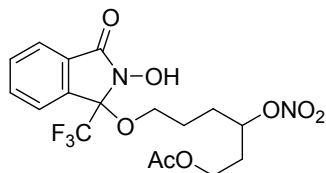


HPLC: Inertsil[®] diol column, eluent: hexane/IPA = 5/1, flow rate: 9.5 mL/min, retention time 14 min; AD-H column, eluent: hexane/IPA = 10/1, flow rate: 9.5 mL/min, retention time 54 min.

[for less polar diastereomer] colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, $J = 7.3$ Hz, 1H), 7.74 – 7.60 (m, 1H), 7.55 (d, $J = 7.4$ Hz, 1H), 5.43 – 5.31 (m, 1H), 4.15 – 4.01 (m, 2H), 3.55 – 3.44 (m, 1H), 3.16 – 3.05 (m, 1H), 2.14 – 2.02 (m, 1H), 2.07 (s, 3H) 1.96 – 1.88 (m, 1H), 1.88 – 1.82 (m, 1H), 1.82 – 1.71 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.35, 165.76, 134.56, 133.69, 131.87, 129.74, 124.13, 123.77, 121.74 (q, $J = 285.9$ Hz), 90.76 (q, $J = 33.5$ Hz), 80.63, 63.73, 59.67, 31.81, 29.40, 24.07, 20.87; ¹⁹F NMR (400 MHz, CDCl₃) δ -78.90; IR (neat, cm⁻¹) 2959, 1733, 1716, 1635, 1270, 1191, 872, 732; HRMS (ESI): m/z calcd for C₁₇H₁₉F₃N₂O₈Na [M+Na]⁺ 459.0986, Found 459.0977.

[for more polar diastereomer] colorless oil; ¹H NMR (500 MHz, CDCl₃) δ 8.97 (brs, 1H), 7.85 (d, $J = 7.4$ Hz, 1H), 7.71 – 7.60 (m, 3H), 5.32 – 5.25 (m, 1H), 4.14 – 4.00 (m, 2H), 3.53 – 3.41 (m, 1H), 3.19 – 3.11 (m, 1H), 2.06 (s, 3H), 2.04 – 1.93 (m, 2H), 1.93 – 1.86 (m, 1H), 1.84 – 1.71 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.34, 165.65, 134.51, 133.52, 131.90, 129.79, 124.28, 124.00, 121.77 (q, $J = 286.5$ Hz), 90.70 (q, $J = 33.5$ Hz), 81.53, 63.75, 60.37, 31.89, 29.63, 24.15, 20.87; ¹⁹F NMR (400 MHz, CDCl₃) δ -78.90; IR (neat, cm⁻¹) 2986, 1732, 1716, 1631, 1265, 1201, 876, 703; HRMS (ESI): m/z calcd for C₁₇H₁₉F₃N₂O₈Na [M+Na]⁺ 459.0986, Found 459.0992.

6-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yloxy)-3-(nitrooxy)hexyl acetate (2ib)

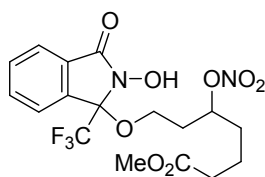


HPLC: Inertsil[®] diol column, eluent: hexane/IPA = 5/1, flow rate: 9.5 mL/min, retention time 18 min; AD-H column, eluent: hexane/IPA = 10/1, flow rate: 9.5 mL/min, retention time 35 min.

[for less polar diastereomer] colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.85 (d, $J = 7.6$ Hz, 1H), 7.71 – 7.60 (m, 3H), 5.24 – 5.17 (m, 1H), 4.27 – 4.14 (m, 2H), 3.42 – 3.32 (m, 1H), 3.12 – 3.03 (m, 1H), 2.08 (s, 3H), 2.07 – 1.99 (m, 2H), 1.96 – 1.86 (m, 1H), 1.86 – 1.67 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.27, 165.44, 134.83, 133.49, 131.79, 129.83, 124.17, 124.01, 81.01, 63.14, 60.31, 31.84, 29.04, 24.42, 20.84; ^{19}F NMR (400 MHz, CDCl_3) δ –78.84; IR (neat, cm^{-1}) 2923, 2851, 1716, 1624, 1266, 1189, 746; HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 459.0986, Found 459.0992.

[for more polar diastereomer] colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.84 (d, $J = 7.4$ Hz, 1H), 7.72 – 7.58 (m, 3H), 5.30 – 5.21 (m, 1H), 4.18 (t, $J = 6.1$ Hz, 2H), 3.41 – 3.31 (m, 1H), 3.13 – 3.04 (m, 1H), 2.07 (s, 3H), 2.05 – 1.99 (m, 2H), 1.89 – 1.81 (m, 2H), 1.76 – 1.70 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.18, 165.53, 134.79, 133.45, 131.78, 129.85, 124.11, 123.98, 81.41, 63.77, 60.28, 31.79, 29.52, 24.43, 20.82; ^{19}F NMR (400 MHz, CDCl_3) δ –78.90; IR (neat, cm^{-1}) 3054, 1716, 1624, 1265, 1200, 896, 744, 642; HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 459.0986, Found 459.0975.

methyl 7-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yloxy)-5-(nitrooxy)heptanoate (2ja)

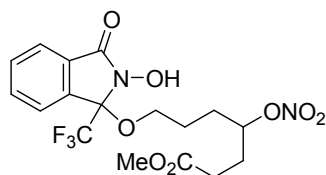


HPLC: AD-H column, eluent: hexane/IPA = 20/1, flow rate: 9.5 mL/min, retention time 55 min and 65 min and 115 min.

[for less polar diastereomer] colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.86 (d, $J = 7.4$ Hz, 1H), 7.71 – 7.62 (m, 2H), 7.56 (d, $J = 7.3$ Hz, 1H), 5.33 – 5.30 (m, 1H), 3.71 (s, 3H), 3.50 – 3.42 (m, 1H), 3.17 – 3.06 (m, 1H), 2.44 – 2.33 (m, 2H), 2.05 – 1.95 (m, 2H), 1.17 – 1.69 (m, 4H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.11, 165.29, 134.53, 133.60, 131.86, 129.90, 124.20, 123.88, 80.73, 59.53, 51.97, 33.13, 31.40, 31.38, 19.95; ^{19}F NMR (400 MHz, CDCl_3) δ –78.74; IR (neat, cm^{-1}) 2926, 1716, 1625, 1472, 1276, 1198, 1082, 877, 731; HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 459.0986, Found 445.0983.

[for more polar diastereomer] colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 8.62 (brs, 1H), 7.86 (d, $J = 7.4$ Hz, 1H), 7.72 – 7.59 (m, 3H), 5.25 – 5.16 (m, 1H), 3.69 (s, 3H), 3.48 – 3.38 (m, 1H), 3.18 – 3.09 (m, 1H), 2.42 – 2.26 (m, 2H), 2.12 – 2.00 (m, 1H), 2.00 – 1.92 (m, 1H), 1.91 – 1.80 (m, 1H), 1.79 – 1.70 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.80, 165.43, 134.54, 133.49, 131.87, 129.86, 124.30, 124.05, 81.50, 60.32, 51.80, 33.30, 32.04, 31.66, 20.05; ^{19}F NMR (400 MHz, CDCl_3) δ –78.87; IR (neat, cm^{-1}) 2987, 1716, 1625, 1474, 1265, 1200, 896, 739, 705; HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 459.0986, Found 445.0988.

methyl 7-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yloxy)-4-(nitrooxy)heptanoate (2jb)

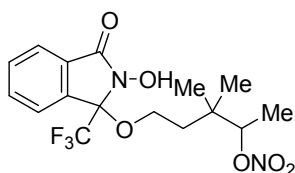


HPLC: AD-H column, eluent: hexane/IPA = 20/1, flow rate: 9.5 mL/min, retention time 65 min, 68 min and 97 min.

[for less polar diastereomer] colorless oil; colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.86 (d, $J = 7.3$, 1H), 7.71 – 7.60 (m, 3H), 5.24 – 5.04 (m, 1H), 3.72 (3.71) (s, 3H), 3.40 – 3.29 (m, 1H), 3.13 – 3.03 (m, 1H), 2.49 – 2.35 (m, 2H), 2.15 – 2.05 (m, 1H), 2.03 – 1.91 (m, 1H), 1.85 – 1.79 (m, 1H), 1.77 – 1.67 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.45, 165.55, 134.83, 133.43, 131.76, 129.87, 124.16, 124.04, 83.08, 82.71, 63.71, 62.93, 52.12, 51.99, 29.48, 29.40, 29.20, 28.79, 27.56, 24.47; ^{19}F NMR (400 MHz, CDCl_3) δ -78.77; IR (neat, cm^{-1}) 3054, 2926, 1716, 1635, 1473, 1264, 1200, 1023, 746; HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 459.0986, Found 445.0983.

[for more polar diastereomer] colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.86 (d, $J = 7.6$ Hz, 1H), 7.70 – 7.62 (m, 3H), 5.24 – 5.15 (m, 1H), 3.70 (s, 3H), 3.35 – 3.31 (m, 1H), 3.12 – 3.04 (m, 1H), 2.44 (t, $J = 7.2$ Hz, 2H), 2.13 – 2.04 (m, 1H), 2.00 – 1.94 (m, 1H), 1.84 – 1.80 (m, 2H), 1.75 – 1.70 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.26, 165.41, 134.81, 133.49, 131.78, 129.84, 124.18, 124.03, 83.06, 63.71, 52.02, 29.39, 29.21, 27.54, 24.45; ^{19}F NMR (400 MHz, CDCl_3) δ -78.89; IR (neat, cm^{-1}) 2926, 1716, 1624, 1276, 1200, 1007, 749; HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 459.0986, Found 445.0979.

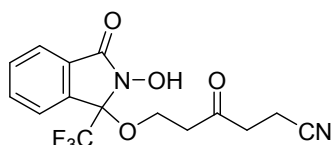
5-(2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yloxy)-3,3-dimethylpentan-2-yl nitrate (2k)



diastereo mixture (dr 1:1); white solid; ^1H NMR (400 MHz, CDCl_3 , with one drop of D_2O) δ 7.84 (d, $J = 7.4$ Hz, 1H), 7.76 – 7.60 (m, 3H), 5.04 (m, 1H), 3.50 – 3.48 (m, 1H), 3.16 – 2.96 (m, 1H), 1.83 – 1.57 (m, 2H), 1.31 (t, $J = 8.0$ Hz, 3H), 0.99 (0.94) (d, $J = 8.0$ Hz, 3H + 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 165.51, 134.82, 133.49, 133.45, 131.75, 129.95, 124.10, 123.94, 86.55, 86.42, 60.83, 60.69, 37.51, 37.42, 36.53, 36.45, 23.42, 23.24, 13.57; ^{19}F NMR (400 MHz, CDCl_3) δ -78.99; IR (neat, cm^{-1}) 1719, 1639, 1490, 1277, 1008, 823, 750; HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 415.1087, Found 415.1107.

Spectral data of ketone products **3a-3f** was in accordance with reported data.¹

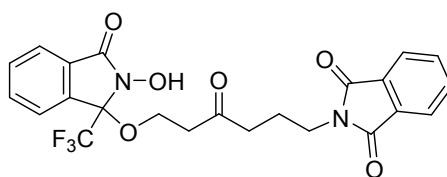
6-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)-4-oxohexanenitrile (3g)



^1H NMR (392 MHz, CDCl_3) δ 8.74 (brs, 1H), 7.87 (d, $J = 7.5$ Hz, 1H), 7.72 – 7.58 (m, 3H), 3.45 – 3.34 (m, 1H), 3.07 – 2.94 (m, 1H), 2.93 (t, $J = 7.1$ Hz, 2H), 2.89 – 2.72 (m, 2H), 2.62 (t, $J = 7.1$ Hz, 2H); ^{13}C NMR (123 MHz, CDCl_3) δ 205.38, 164.40, 133.91, 133.28, 131.88, 130.14, 124.24, 124.17, 121.68 (q, $J = 291.6$ Hz), 118.59, 90.60 (q, $J = 38.2$ Hz), 58.12, 41.22, 38.37, 11.24; IR (neat, cm^{-1}) 3020, 2359, 1732, 1717, 1215, 1121, 759; HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 365.0720, Found 365.0710.

From starting material **1h**, γ -ketone product **3h** were purified by HPLC separation. The δ -ketone product was formed in trace amount.

2-(6-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)-4-oxohexyl)isoindoline-1,3-dione (3h)

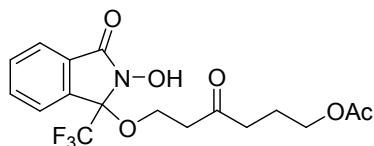


HPLC: Inertsil[®] diol column, eluent: hexane/ $\text{CHCl}_3 = 2/1$, flow rate: 9.5 mL/min, retention time 59 min.

^1H NMR (500 MHz, CDCl_3) δ 8.37 (brs, 1H), 7.90 (dd, $J = 6.5, 1.9$ Hz, 1H), 7.87 – 7.79 (m, 2H), 7.76 – 7.68 (m, 2H), 7.69 – 7.61 (m, 2H), 7.58 (d, $J = 7.2$ Hz, 1H), 3.75 – 3.64 (m, 2H), 3.60 – 3.53 (m, 2H), 3.28 – 3.16 (m, 2H), 3.00 – 2.88 (m, 2H), 2.66 – 2.59 (m, 1H), 2.56 (t, $J = 7.0$ Hz, 2H), 2.10 – 1.90 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 209.73, 168.58, 163.22, 134.11, 132.82, 131.89, 131.69, 130.72, 124.25, 124.02, 123.33, 121.70 (d, $J = 282.2$ Hz), 90.37 (d, $J = 33.4$ Hz), 57.38, 41.20, 40.00, 36.83, 22.43; ^{19}F NMR (400 MHz, CDCl_3) δ -78.56; IR (neat, cm^{-1}) 2930, 2253, 1771, 1715, 1397, 1190, 910, 732; HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 499.1087, Found 499.1071.

From starting material **1i**, γ -ketone product **3i** were obtained after flash column chromatography (hexane/EtOAc = 55/45 to 30/70). The δ -ketone product was formed in trace amount.

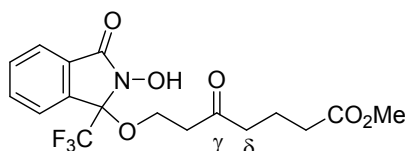
6-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)-4-oxohexyl acetate (3i)



^1H NMR (392 MHz, CDCl_3) δ 8.29 (brs, 1H), 7.97 – 7.88 (m, 1H), 7.71 – 7.56 (m, 3H), 4.07 (td, $J = 6.2$, 3.9 Hz, 2H), 3.57 (t, $J = 10.2$ Hz, 1H), 3.28 – 3.16 (m, 1H), 3.05 – 2.90 (m, 2H), 2.67 – 2.49 (m, 3H), 2.12 – 2.00 (m, 3H), 2.00 – 1.87 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 210.07, 171.13, 163.09, 133.74, 132.84, 131.74, 130.73, 124.32, 123.99, 63.26, 57.21, 41.11, 39.61, 22.54, 20.88; ^{19}F NMR (400 MHz, CDCl_3) δ –78.41; IR (neat, cm^{-1}) 2985, 2306, 2253, 1735, 1716, 1265, 1204, 911, 733; HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{18}\text{F}_3\text{NO}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 412.0978, Found 412.0998.

From starting material **1j**, γ (**3ja**) and δ (**3jb**) ketone products were obtained after flash column chromatography (hexane/EtOAc = 55/45 to 30/70). The γ/δ ratio is 3/1 by ^1H NMR analysis. The major ketone product **3ja** was purified by preparative HPLC.

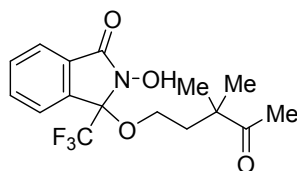
methyl 7-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)-5-oxoheptanoate (3ja)



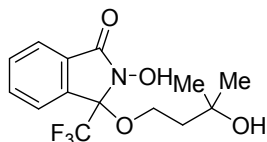
HPLC: Inertsil[®] diol column, eluent: hexane/ CHCl_3 = 2/1, flow rate: 9.5 mL/min, retention time 50 min.

^1H NMR (500 MHz, CDCl_3) δ 8.26 (brs, 1H), 7.93 – 7.89 (m, 1H), 7.71 – 7.60 (m, 2H), 7.59 (d, $J = 7.0$ Hz, 1H), 3.67 (s, 3H), 3.56 (t, $J = 10.2$ Hz, 1H), 3.24 – 3.13 (m, 1H), 3.02 – 2.87 (m, 1H), 2.63 – 2.49 (m, 3H), 2.35 (t, $J = 7.0$ Hz, 2H), 1.97 – 1.87 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 210.37, 173.53, 163.16, 133.77, 132.84, 131.72, 130.72, 124.29, 124.01, 57.30, 51.69, 41.94, 41.07, 32.65, 18.56; ^{19}F NMR (400 MHz, CDCl_3) δ –78.56; IR (neat, cm^{-1}) 3053, 2986, 2305, 2253, 1734, 1716, 1265, 908, 734, 651; HRMS (ESI): m/z calcd for $\text{C}_{17}\text{H}_{18}\text{F}_3\text{NO}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 412.0978, Found 412.0998.

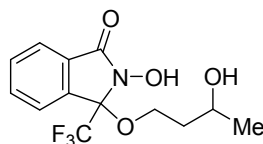
3-((3,3-dimethyl-4-oxopentyl)oxy)-2-hydroxy-3-(trifluoromethyl)isoindolin-1-one (3k)



^1H NMR (392 MHz, CDCl_3) δ 9.20 (brs, 1H), 7.84 (d, $J = 7.3$ Hz, 1H), 7.70 – 7.54 (m, 2H), 3.34 (dt, $J = 9.3$, 5.7 Hz, 1H), 3.06 (dt, $J = 9.3$, 5.7 Hz, 1H), 2.21 (s, 3H), 1.90 (t, $J = 5.7$ Hz, 2H), 1.11 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (99 MHz, CDCl_3) δ 215.51, 165.22, 134.26, 133.20, 131.64, 130.12, 124.37, 124.08, 121.74 (q, $J = 286.6$ Hz), 90.91 (q, $J = 33.0$ Hz), 60.66, 46.41, 39.12, 25.29, 24.54, 24.50; ^{19}F NMR (400 MHz, CDCl_3) δ –78.11; IR (neat, cm^{-1}) 3156, 2973, 2253, 1717, 1470, 1265, 1202, 908, 734; HRMS (ESI): m/z calcd for $\text{C}_{16}\text{H}_{18}\text{F}_3\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 368.1080, Found 368.1092.

2-hydroxy-3-(3-hydroxy-3-methylbutoxy)-3-(trifluoromethyl)isoindolin-1-one (4)

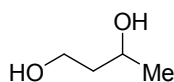
colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 7.86 (d, $J = 7.1$ Hz, 1H), 7.64 (m, 3H), 3.57 – 3.47 (m, 1H), 3.36 – 3.24 (m, 1H), 2.02 – 1.91 (m, 1H), 1.73 – 1.58 (m, 1H), 1.42 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.51, 134.33, 132.96, 131.62, 130.49, 124.18, 124.07, 121.86 (q, $J = 285.0$ Hz), 90.87 (q, $J = 33.8$ Hz), 70.87, 60.72, 40.83, 30.28, 30.12; ^{19}F NMR (400 MHz, CDCl_3) δ –78.53; IR (neat, cm^{-1}) 1716, 1635, 1507, 1457, 1199, 1081, 764; HRMS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{16}\text{F}_3\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 342.0924, Found 342.0945.

2-hydroxy-3-(3-hydroxybutoxy)-3-(trifluoromethyl)isoindolin-1-one (5)

HPLC: Inertsil® diol column, eluent: hexane/IPA = 10/1, flow rate: 9.5 mL/min, retention time 37 min and 56 min.

[for less polar diastereomer] white solid; ^1H NMR (500 MHz, CDCl_3) δ 7.87 (d, $J = 7.8$ Hz, 1H), 7.70 – 7.58 (m, 3H), 4.10 – 3.94 (m, 1H), 3.46 – 3.29 (m, 2H), 1.91 – 1.65 (m, 2H), 1.31 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.53, 134.41, 132.98, 131.64, 130.49, 124.14, 124.08, 121.87 (q, $J = 286.4$ Hz), 90.83 (q, $J = 33.3$ Hz), 67.41, 62.36, 36.85, 23.97; ^{19}F NMR (400 MHz, CDCl_3) δ –78.59; IR (neat, cm^{-1}) 3175, 2934, 1719, 1470, 1190, 1081, 963, 730; HRMS (ESI): m/z calcd for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 328.0767, Found 328.0782.

[for more polar diastereomer] white solid; ^1H NMR (500 MHz, CDCl_3) δ 7.84 (d, $J = 8.0$ Hz, 1H), 7.68 – 7.58 (m, 3H), 4.39 – 4.28 (m, 1H), 3.52 – 3.42 (m, 1H), 3.30 – 3.22 (m, 1H), 2.03 – 1.91 (m, 1H), 1.51 – 1.41 (m, 1H), 1.35 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 164.05, 134.49, 132.80, 131.48, 130.56, 123.99, 121.92 (q, $J = 286.8$ Hz), 90.69 (q, $J = 33.1$ Hz), 63.89, 59.28, 36.88, 23.26; ^{19}F NMR (400 MHz, CDCl_3) δ –78.59; IR (neat, cm^{-1}) 3173, 2934, 1719, 1470, 1190, 1081, 963, 730; HRMS (ESI): m/z calcd for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{NO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 328.0767, Found 328.0782.

butane-1,3-diol (6)

colorless oil; ^1H NMR (500 MHz, CDCl_3) δ 4.11 – 4.00 (m, 1H), 3.93 – 3.77 (m, 2H), 2.47 (brs, 2H), 1.71 – 1.65 (m, 2H), 1.22 (d, $J = 6.1$ Hz, 3H); identical to a commercial source.