Catalytic Asymmetric Synthesis of Pyrroloindolines by a Formal [3+2] Cycloaddition Reaction

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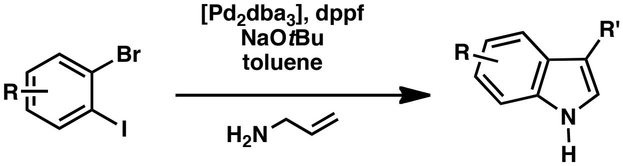
General. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), and toluene were dried by passing through activated alumina columns. Deuterated methylene chloride (CD_2Cl_2) for the experiments resubjecting the pyrroloindoline products to reaction conditions was dried by passing through a plug of activated alumina. Dimethylformamide (DMF) was dried over activated molecular sieves, dichloroethane (DCE) was distilled over calcium hydride. All other commercially obtained reagents were used as received unless specifically indicated. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash column chromatography was performed either as described by Still et al. (Still, W. C., Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.) using silica gel (partical size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Diastereomeric ratios were determined by integration of NMR spectra or HPLC or SFC analysis. Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively), a Varian 400 (at 400 MHz and 100 MHz respectively) or a Varian Inova 500 (at 500 MHz and 125 MHz respectively), and are reported relative to internal chloroform (^{1}H, $\delta = 7.26$, ^{13}C, $\delta = 77.0$). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). Preparatory HPLC was performed with either an Agilent 1100 or 1200 Series HPLC utilizing an Agilent Zorbax RX-SIL 5μm column (9.4 x 250 mm). Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing Chiralcel AD or OD-H columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm. Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralcel AD-H, OJ-H columns (4.6 mm x 25 cm). Melting points were determined using a Büchi B-545 capillary melting point apparatus and the values reported are uncorrected. HRMS were acquired using either an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode, or obtained from the Caltech Mass Spectral Facility.

Abbreviations used: dppp: 1,3-Bis(diphenylphosphino)propane; dppf: 1,1'-Bis(diphenylphosphino)ferrocene; BINOL: 1,1'-Bi(2-naphthol); IPA: isopropanol; DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene; dba: dibenzylidineacetone.

Comprehensive List of Citations for Pyrroloindoline Synthesis:

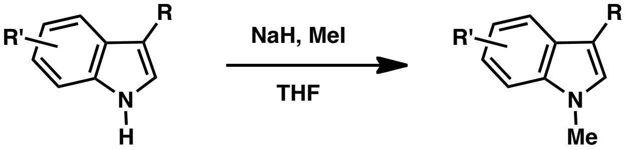
Substrate Synthesis.

General Procedure A. Amination-Heck cascade for synthesis of indole derivatives.



Procedure was adapted from Jørgensen *et al.*[1] To a 50 mL Schlenk tube was added [Pd_2dba_3], dppf, NaO*t*Bu (20.8 mmol, 2.5 equiv) and toluene (10 mL). The mixture was stirred for 5 minutes, then the bromoiodide (8.3 mmol, 1.0 equiv) and allylamine (8.3 mmol, 1.0 equiv) were added. The tube was sealed, heated to 140 °C over 30 minutes and stirred at 140 °C for 21 h. The reaction was then cooled to room temperature, diluted with 40 mL hexanes, filtered through a plug of celite, and concentrated under reduced pressure. The crude residue was purified by flash chromatography.

General Procedure B. *N*-methylation of indole derivatives.



In a flame-dried flask, the indole (1.7 mmol, 1.0 equiv) was dissolved in 11 mL THF. Sodium hydride (60% w/w, 2.5 mmol, 1.5 equiv) was added in one portion, then methyl iodide (3.4 mmol, 2.0 equiv) was added dropwise. The reaction was stirred at room temperature until consumption of starting material was observed by TLC. The reaction was diluted with ethyl acetate and the excess NaH was quenched with water. The organic layer was separated, and the aqueous layer was extracted 3× with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography.

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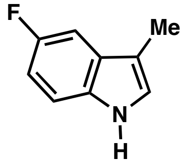
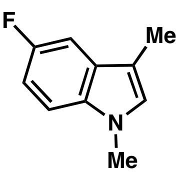
[1] Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jørgensen, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 888.

5-Fluoro-3-methyl-1*H*-indole.



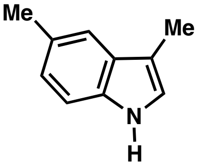
Prepared from 3.75 mmol of 2-bromo-4-fluoro-1-iodobenzene, 0.63 mol % [Pd_2dba_3] and 2.5 mol % dppf using general procedure A. The product was purified by flash chromatography (10% ethyl acetate/hexanes) to yield 5-fluoro-3-methyl-1*H*-indole (0.22 g, 38% yield). Spectral data matches that reported in the literature[1].

5-Fluoro-1,3-dimethyl-1*H*-indole 12b.



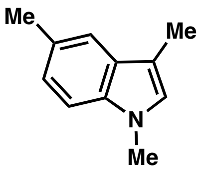
Prepared from 1.07 mmol of 5-fluoro-3-methyl-1*H*-indole using general procedure B. The product was purified by flash chromatography (3% ethyl acetate/hexanes) to yield **12b** (0.97 g, 55% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.13 (m, 2H), 7.00 – 6.92 (m, 1H), 6.86 (s, 1H), 3.72 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 132.4, 128.8, 127.2, 111.6, 109.8, 109.5, 100.8, 32.6, 9.6. IR (NaCl/thin film): 2918, 1581, 1493, 1457, 1423, 1225, 1062, 786 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $[M+H]^+$ 164.0870, found 164.0873.

3,5-dimethyl-1*H*-indole.



Prepared from 2.88 mmol of 2-bromo-1-iodo-4-methylbenzene[2], 2.5 mol % [Pd_2dba_3] and 10 mol % dppf using general procedure A. The product was purified by flash chromatography (5→13% ethyl acetate/hexanes) to yield 3,5-dimethyl-1*H*-indole (0.11 g, 14% yield). Spectral data matches that reported in the literature.[1]

1,3,5-trimethyl-1*H*-indole 12c.



Prepared from 0.70 mmol of 3,5-dimethyl-1*H*-indole using general procedure B. The product was purified by flash chromatography (2% ethyl acetate/hexanes) to yield **12c** (0.048 g, 43% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.34 (m, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.05 (dd, J = 8.3, 1.4 Hz, 1H), 6.78 (s, 1H), 3.71 (s, 3H), 2.49 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 128.8, 127.6, 126.6, 123.0, 118.6, 109.5, 108.7, 32.5, 21.5, 9.5. IR (NaCl/thin film): 2918, 1494, 1460, 1388, 1298, 1250, 1149, 1058, 885, 866, 784 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $[M+H]^+$ 160.1121, found 160.1116.

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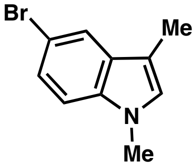
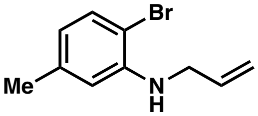
[2] van Klink, G.P.M.; de Boer, H.J.R.; Schat, G.; Akkerman, O.S.; Bickelhaupt, F.; Spek, A.L. *Organometallics* **2002**, *21*, 2119.

5-Bromo-1,3-dimethyl-1*H*-indole 12d.



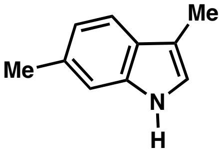
Prepared from 0.95 mmol of 5-bromo-3-methyl-1*H*-indole[3] using general procedure B. The product was purified by flash chromatography (5% ethyl acetate/hexanes) to yield **12d** (0.20 g, 90% yield) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 1.5 Hz, 1H), 7.30 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 1H), 6.82 (s, 1H), 3.70 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 130.3, 127.7, 124.1, 121.5, 111.9, 110.5, 109.7, 32.6, 9.4. IR (NaCl/thin film): 2918, 1563, 1479, 1422, 1279, 812, 785 cm^{-1}; HRMS (APCI) calc'd for $[M+H]^+$ 224.0069, found 224.0070.

***N*-allyl-2-bromo-5-methylaniline.**



Procedure was adapted from Sørensen and Pombo-Villar.[4] To a solution of 2-bromo-5-methylaniline (10.8 mmol, 1.0 equiv) in 29 mL THF at –78°C was added MeLi (2.9 M solution in dimethoxymethane, 11.8 mmol, 1.1 equiv), and stirred for 30 minutes. Allyl bromide was added dropwise, followed by stirring at –78 °C for 10 minutes, then at room temperature for 5 hours. Then saturated $NaHCO_{3\,(aq)}$ solution was added, and the aqueous layer was extracted with ethyl acetate 3×. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield *N*-allyl-2-bromo-5-methylaniline (1.63 g, 67% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 1.5 Hz, 1H), 6.41 (ddd, *J* = 8.0, 2.0, 0.6 Hz, 1H), 5.97 (ddt, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.31 (ddd, *J* = 17.2, 3.3, 1.7 Hz, 1H), 5.21 (dq, *J* = 10.3, 1.5 Hz, 1H), 4.41 (s, 1H), 3.83 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 138.4, 134.7, 132.0, 118.8, 116.3, 112.4, 106.5, 46.2, 21.5. IR (NaCl/thin film): 3411, 2920, 1596, 1506, 1416, 1016, 921, 787 cm^{-1}. HRMS (MM: ESI–APCI) calc'd for $[M+H]^+$ 226.0226, found 226.0216.

3,6-dimethyl-1*H*-indole.



Procedure was adapted from Sørensen and Pombo-Villar.[4] A solution of *N*-allyl-2-bromo-5-methylaniline (1.6 mmol, 1.0 equiv), $Pd(OAc)_2$ (0.16 mmol, 0.1 equiv), dppp (0.16 mmol, 0.1 equiv), Bu_4NCl (1.6 mmol, 1.0 equiv), and NaOAc (6.2 mmol, 4.0 equiv) in 24 mL DMF was heated to 120 °C in a flask equipped with a reflux condenser for 16h. The reaction was cooled to room temperature, saturated $NaHCO_{3\,(aq)}$ solution and 100 mL water were added,

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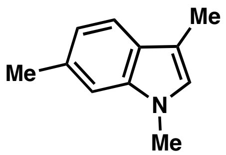
[3] Petit, S.; Duroc, Y.; Larue, V.; Giglione, Léon, C.; Soulama, C.; Denis, A.; Dardel, F. Meinnel, T.; Artaud, I. *ChemMedChem* **2009**, *4*, 261.

[4] Sørensen, U.S.; Pombo-Villar, E. *Helv. Chim. Acta.* **2004**, *87*, 82.

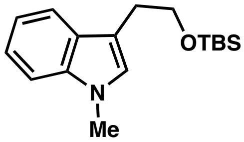
and the aqueous layer was extracted with ethyl acetate 3×. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5→10% ethyl acetate/hexanes) to yield 3,6-dimethyl-1*H*-indole (0.19 g, 85% yield) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (br s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.13-7.11 (m, 1H), 6.94 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 6.87 (dd, *J* = 2.1 Hz, 1.1 Hz, 1H), 2.45 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 131.6, 126.2, 120.9, 120.8, 118.5, 111.6, 110.9, 21.7, 9.7. IR (NaCl/thin film): 3409, 2922, 1452, 1329, 1086, 908, 803. 733 cm^{-1}. HRMS (MM: ESI–APCI) calc'd for $[M+H]^+$ 146.0964, found 146.0970.

1,3,6-trimethyl-1*H*-indole 12e.



Prepared from 0.70 mmol of 3,6-dimethyl-1*H*-indole using general procedure B. The product was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield **12e** (62 mg, 56% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 1H), 7.07 (s, 1H), 6.94 (dd, *J* = 8.0, 0.7 Hz, 1H), 6.75 (d, *J* = 0.9 Hz, 1H), 3.70 (s, 3H), 2.50 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 131.1, 126.5, 125.8, 120.2, 118.6, 109.9, 109.0, 32.4, 21.9, 9.6. IR (NaCl/thin film): 3027, 2917, 2860, 1625, 1478, 1388, 1369, 1328, 1248, 799 cm^{-1}; HRMS (MM: ESI–APCI) calc'd for $[M+H]^+$ 160.1121, found 160.1114.

1-methyl-3-*t*-butyldimethylsiloxyethyl-1*H*-indole 12f.



Prepared from 2.66 mmol of 3-*t*-butyldimethylsiloxyethyl-1*H*-indole[5] using general procedure B. The product was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield **12f** (0.67 g, 87% yield) as an orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.31 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.26 – 7.23 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.13 (ddd, *J* = 7.9, 6.9, 1.0 Hz, 1H), 6.91 (s, 1H), 3.90 (t, J = 7.2 Hz, 2H), 3.76 (s, 3H), 3.02 (ddd, *J* = 7.9, 7.1, 0.8 Hz, 2H), 0.95 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 128.1, 126.9, 121.4, 119.0, 118.6, 111.5, 109.1, 64.1, 32.5, 29.0, 26.0, 18.4, -5.3; IR (NaCl/thin film): 3056, 2954, 2929, 2857, 1472, 1251, 1095, 836, 737 cm^{-1}; HRMS (ESI) calc'd for $[M+H]^+$ 290.1940, found 290.1933.

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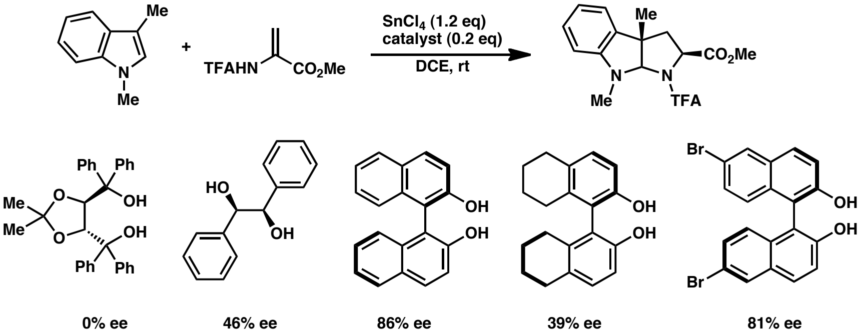
[5] Hirose, T.; Sunazuka, T.; Yamamoto, D.; Kojima, N.; Shirahata, T.; Harigaya, Y.; Kuwajima, I.; Ōmura, S. *Tetrahedron*, **2005**, *61*, 6015.

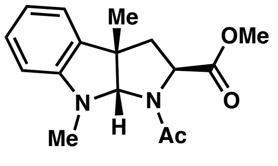
General Procedure C. Formal [3+2] cycloaddition of indoles and acrylates.

To a flame-dried flask was added indole (0.20 mmol, 1.00 equiv), acrylate (0.20 mmol, 1.00 equiv), and (*R*)-BINOL (0.04 mmol, 0.20 equiv). The flask was charged with CH_2Cl_2 (1.5 mL), followed by addition of $SnCl_4$ (0.24 mmol, 1.20 equiv unless specifically indicated, 1 M in CH_2Cl_2), then stirred at room temperature. The reaction was quenched by diluting with 1 mL MeCN and 1 mL 1 M HCl, followed by addition of 5 mL H_2O. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with either saturated $NaHCO_{3(aq)}$ or 1 M $NaOH_{(aq)}$ (10 mL). The aqueous layer was back extracted with EtOAc (10 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash chromatography.

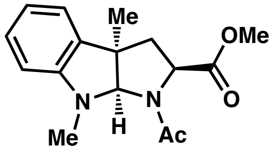
Initial Screen of Chiral Diol Additives.



Pyrroloindoline 7a.



(a) *exo* diastereomer



(b) *endo* diastereomer

Screen varying (*R*)–BINOL loading. All reactions were run at room temperature for 3 h in DCE with 1,3-dimethyl-1*H*-indole[6] (**6**, 0.2 mmol, 1 equiv), methyl 2-acetamidoacrylate[7] (**8**, 0.2 mmol, 1 equiv) and $SnCl_4$ (1.2 equiv, 1 M in CH_2Cl_2) Purified by flash chromatography (0→50% ethyl acetate/hexanes). The diastereomeric ratio was determined by ^1H NMR analysis of the crude reaction mixture. The diastereomers were separated by flash chromatography (30→50% ethyl acetate/hexanes). The enantiomeric excess was determined for both diastereomers by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in hexanes, λ = 254 nm).

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[6] Rodriguez, J. G.; Lafuente, A.; Garcia-Almaraz, P.. *J. Heterocycl. Chem.* **2000**, *37*, 1281.

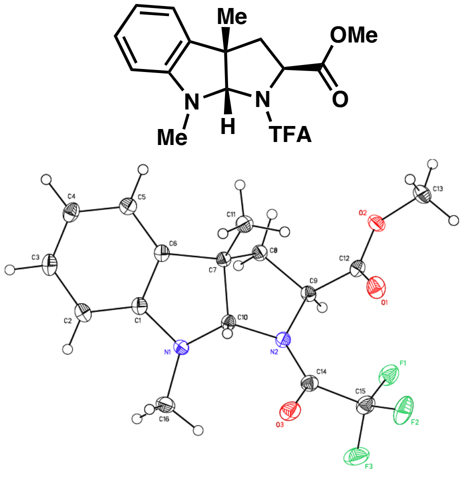
[7] Methyl 2-acetamidoacrylate is commercially available, or can be prepared according to Crestey, F.; Collot, V.; Steibing, S.; Rault, S. *Synthesis* **2006**, *20*, 3506.

entry	R^1, R^2	pdt	BINOL (equiv)	solvent	yield (%)	d.r.	ee (%)
1	Me, Me (**8**)	**7a**	0.0	DCE	64	6:1	--
2	Me, Me (**8**)	**7a**	1.1[e]	DCE	86	4:1	64/83
3	Me, Me (**8**)	**7a**	0.3	DCE	96	5:1	62/81
4	Me, Me (**8**)	**7a**	0.2	DCE	94	5:1	63/83
5	Me, Me (**8**)	**7a**	0.1	DCE	93	5:1	61/79
6	Me, Me (**8**)	**7a**	0.05	DCE	82	5:1	51/72

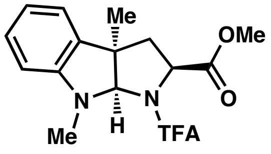
Exo diastereomer: pale yellow oil. t_R(major) = 9.5 min t_R(minor) = 6.2 min. ^{1}H NMR (400 MHz, CDCl$_3$; compound exists as a 1:1 mixture of rotamers) δ 7.10 – 7.01 (m, 1H), 6.95 (d, J = 7.3 Hz, 0.5H), 6.91 (d, J = 7.3 Hz, 0.5H), 6.68 (t, J = 7.4 Hz, 0.5H), 6.62 (t, J = 7.4 Hz, 0.5H), 6.43 (d, J = 7.8 Hz, 0.5H), 6.38 (d, J=7.8 Hz, 0.5H), 5.47 (s, 0.5H), 5.04 (s, 0.5H), 4.43 (dd, J = 10.0, 1.9 Hz, 0.5H), 4.30 (dd, J = 9.7, 4.7 Hz, 0.5H), 3.73 (s, 1.5H), 3.66 (s, 1.5H), 2.98 (s, 1.5H), 2.80 (s, 1.5H), 2.44 (dd, J = 13.4, 10.0 Hz, 0.5H), 2.32 (dd, J = 13.3, 9.8 Hz, 0.5H), 2.22 (s, 0.5H), 2.18 (dd, J = 13.5, 2.0 Hz, 0.5H), 1.97 – 1.90 (m, 2H), 1.46 (s, 1.5H), 1.32 (s, 1.5H); ^{13}C NMR (100 MHz, CDCl$_3$; compound exists as a 1:1 mixture of rotamers) δ 172.8, 171.7, 171.5, 169.4, 149.4, 148.5, 134.2, 128.04, 128.02, 121.0, 120.8, 118.6, 117.6, 107.7, 107.1, 91.8, 90.8, 60.5, 59.6, 52.2, 51.8, 51.6, 49.2, 43.4, 41.0, 35.9, 33.8, 22.5, 22.3, 21.9; IR (NaCl/thin film): 2954, 2877, 1746, 1660, 1608, 1489, 1393, 1299, 1200, 1178, 744 cm^{-1}; $[\alpha]_D^{25}$ –69.7° (c = 0.85, CH$_2$Cl$_2$); HRMS (FAB+) calc'd for [M+H]$^+$ 289.1552, found 289.1559.

Endo diastereomer: bright yellow oil. t_R(major) = 4.0 min t_R(minor) = 4.7 min. ^{1}H NMR (400 MHz, CDCl$_3$; compound exists as a 3:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.11 (t, J = 7.6 Hz, 1H§), 7.06 (t, J = 7.8 Hz, 1H*), 7.01 (d, J = 7.1 Hz, 1H§), 6.96 (d, J = 7.2 Hz, 1H*), 6.68 (t, J = 7.4 Hz, 1H§), 6.61 (t, J = 7.3 Hz, 1H*), 6.40 (d, J = 7.8 Hz, 1H§), 6.32 (d, J = 7.8 Hz, 1H*), 5.55 (s, 1H*), 5.09 (s, 1H§), 4.98 (dd, J= 8.8, 5.8 Hz, 1H§), 4.46 (d, J = 8.3 Hz, 1H*), 3.46 (s, 3H§), 3.25 (s, 3H*), 2.99 (s, 3H*), 2.91 (s, 3H§), 2.68 (d, J = 13.6 Hz, 1H*), 2.44 – 2.16 (m, 1H*, 5H§), 2.05 (s, 3H*), 1.42 (s, 3H§), 1.41 (s, 3H*); ^{13}C NMR (100 MHz, CDCl$_3$; ; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 171.4§, 171.1*, 170.7*, 169.6§, 150.6*, 149.0§, 133.1§, 132.4*, 128.7*, 128.6§, 122.3*, 121.8§, 118.0§, 117.1*, 106.4§, 105.6*, 91.1§, 86.4*, 61.1*, 59.1§, 52.3§, 52.2*, 52.1§, 50.8*, 42.6*, 41.7§, 32.2*, 31.6§, 24.7*, 22.8§, 22.4*, 21.9§; IR (NaCl/thin film): 2953, 2869, 1740, 1656, 1610, 1493, 1407, 1302, 1236, 1204, 744 cm^{-1}; $[\alpha]_D^{25}$ +146.5° (c = 0.79, CH$_2$Cl$_2$) ; HRMS (FAB+) calc'd for [M+H]$^+$ 289.1552 , found 289.1549.

Pyrroloindoline 7b.



(a) ***exo*** **diastereomer**



(b) ***endo*** **diastereomer**

Prepared from 1,3-dimethyl-1*H*-indole **6** and methyl 2-trifluoroacetamidoacrylate[8] **9** using general procedure C (with DCE as the solvent). The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (20→35% ethyl acetate/hexanes) to yield 53.0 mg (77% yield) of **7b** in a 6:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→8% ethyl acetate/hexanes).

Exo diastereomer: pale yellow oil that crystallized upon standing in the fridge to give crystals suitable for single crystal X-ray diffraction. The enantiomeric excess was determined to be 86% by chiral SFC analysis (AD-H, 2.5 mL/min, 7% IPA in CO_2, λ = 254 nm): t_R(major) = 2.8 min t_R(minor) = 2.4 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 2.4:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.18 (t, *J* = 7.6 Hz, 1H*, 1H§), 7.03 (d, *J* = 7.2 Hz, 1H*, 1H§), 6.82 (br s, *J* = 7.4 Hz, 1H§), 6.77 (t, *J* = 7.3 Hz, 1H*), 6.56 (br s, 1H§), 6.51 (d, *J* = 7.8 Hz, 1H*), 5.62 (s, 1H*), 5.34 (br s, 1H§), 4.72 (d, *J* = 9.2 Hz, 1H*), 4.44 (br s, 1H§), 3.82 (br s, 3H*), 3.77 (br s, 3H§), 3.08 (br s, 3H*), 2.87 (br s, 3H§), 2.60 (dd, *J* = 13.0, 9.9 Hz, 1H*), 2.55 – 2.44 (br m, 1H§), 2.37 (d, *J* = 12.7 Hz, 1H*), 2.13-2.00 (br m, 1H§), 1.51 (s, 3H§), 1.40 (s, 3H*); ^{13}C NMR (100 MHz, $CDCl_3$; ; compound exists as a 2.4:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.6*, 170.5§, 159.2* (q, $J_{C\text{-}F}$ = 37.2 Hz), 149.4*, 149.2§, 134.2*§, 128.8*§, 121.5*§, 119.9§, 118.7*, 116.1* (q, $J_{C\text{-}F}$ = 288.4 Hz), 109.4§, 108.0*, 93.3*, 91.7§, 61.3§, 60.3*, 53.0*, 52.6§, 49.2*§, 44.0*, 40.6§, 36.8*, 34.4§, 23.5*, 22.8§; IR (NaCl/thin film): 2959, 1751, 1696, 1610, 1490, 1435, 1204, 1155, 988, 744 cm^{-1}; melting point: 105.5 – 107.5 °C; $[\alpha]_D^{25}$ = –118.1 (*c* = 0.78, CH_2Cl_2). HRMS (ESI) calc'd for $[M+H]^+$ 343.1270, found 343.1267.

Endo diastereomer: pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.13 (t, *J* = 7.7 Hz, 1H§), 7.10 (t, *J* = 7.7 Hz, 1H*), 7.04 (d, *J* = 7.5 Hz, 1H§), 6.98 (d, *J* = 7.3 Hz, 1H*), 6.73 (t, *J* = 7.4

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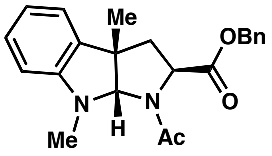
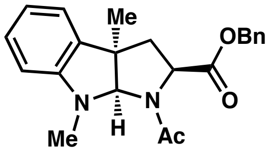
[8] Synthesis of methyl 2-trifluoroacetamidoacrylate: Navarre, L.; Martinez, R.; Genet, J.; Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159.

Hz, 1H§), 6.66 (t, *J* = 7.4 Hz, 1H*), 6.43 (d, *J* = 7.8 Hz, 1H§), 6.37 (d, *J* = 7.8 Hz, 1H*), 5.59 (s, 1H*), 5.33 (s, 1H§), 5.07 (dd, *J* = 9.4, 5.2 Hz, 1H§), 4.74 (d, *J* = 8.2 Hz, 1H*), 3.57 (s, 3H§), 3.16 (s, 3H*), 3.05 (s, 3H*), 2.80 (s, 3H§), 2.80 (d, *J* = 12.7 Hz, 1H*), 2.42 (dd, *J* = 13.3, 5.3 Hz, 1H§), 2.37 (dd, *J* = 12.9, 8.3 Hz, 1H*), 2.26 (dd, *J* = 13.2, 9.7 Hz, 1H§), 1.45 (s, 3H*), 1.43 (s, 3H§); ^{13}C NMR (125 MHz, CDCl$_3$; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.9*, 156.8* (q, *J*$_{\text{C-F}}$ = 36.9 Hz), 150.4*, 148.5§, 133.0§, 131.8*, 129.1*, 128.7§, 122.5*, 121.6§, 118.6§, 117.8*, 116.1* (q, *J*$_{\text{C-F}}$ = 288.7 Hz), 106.9§, 105.7*, 90.8§, 88.5*, 60.3§, 60.1*, 52.5*, 52.2§, 50.4*§, 42.9*, 41.1§, 32.1*§, 25.1*, 22.2§; IR (NaCl/thin film): 2954, 2923, 1741, 1694, 1608, 1494, 1435, 1206, 1147, 998, 860, 844, 742 cm^{-1}; $[\alpha]_D^{25}$ = +201.5 (*c* = 0.11, CH$_2$Cl$_2$). HRMS (ESI) calc'd for [M+H]$^+$ 343.1270, found 343.1278.

Pyrroloindoline 7c.



(a) ***exo*** **diastereomer**



(b) ***endo*** **diastereomer**

Prepared from 1,3-dimethyl-1*H*-indole **6** and benzyl 2-acetamidoacrylate[9] **10** using general procedure C (with DCE as the solvent). The reaction was allowed to run for 4 h. The product **7c** was formed in a 2:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the crude reaction mixture), and purified by flash chromatography (20→35% ethyl acetate/hexanes) to yield 41.3 mg (57% yield) of the *exo* diastereomer and 17.3 mg (24% yield) of the *endo* diastereomer. *Exo diastereomer:* pale yellow oil. The enantiomeric excess was determined to be 74% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO$_2$, λ = 254 nm): t_R(major) = 24.6 min t_R(minor) = 19.1 min. ^{1}H NMR (300 MHz, CDCl$_3$; compound exists as a 1.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.43 – 7.29 (m, 5H*, 5H§), 7.19 – 7.09 (m, 1H*, 1H§), 7.01 (d, *J* = 7.3 Hz, 1H§), 6.96 (d, *J* = 7.3 Hz, 1H*), 6.76 (t, *J* = 8.4 Hz, 1H§), 6.70 (t, *J* = 7.4 Hz, 1H*), 6.50 (d, *J* = 8.2 Hz, 1H§), 6.46 (d, *J* = 8.0 Hz, 1H*), 5.54 (s, 1H*), 5.28 (d, *J* = 12.0 Hz, 1H*), 5.21 (d, *J* = 9.7 Hz, 1H§), 5.20 (s, 1H*, 1H§), 5.09 (s, 1H§), 4.51 (dd, *J* = 10.1, 2.1 Hz, 1H*), 4.45 (dd, *J* = 9.8, 4.8 Hz, 1H§), 3.06 (s, 3H*), 2.89 (s, 3H§), 2.53 (dd, *J* = 13.4, 10.0 Hz, 1H*), 2.42 (dd, *J* = 13.3, 9.7 Hz, 1H§), 2.31 (s, 3H§), 2.22 (dd, *J* = 13.5, 2.0 Hz, 1H*), 2.01 (dd, *J* = 13.3, 4.8 Hz, 1H§), 1.95 (s, 3H*), 1.49 (s, 3H§), 1.32 (s, 3H*); ^{13}C NMR (100 MHz, CDCl$_3$; compound exists as a 1.1:1 mixture of rotamers, the major rotamer is denoted

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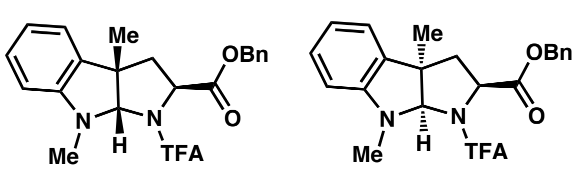
[9] Synthesis of benzyl 2-acetamidoacrylate: Liu, G.; Xin, Z.; Liang, H.; Abad-Zapatero, C.; Hajduk, P.J.; Janowick, D.A.; Szczepankiewicz, B.G.; Pei, Z.; Hutchins, C.W.; Ballaron, S.J.; Stashko, M.A.; Lubben, T.H.; Berg, C.E.; Rondinone, C.M.; Trevillyan, J.M.; Jirousek, M.R. *J. Med. Chem.* **2003**, *46*, 3437.

by *, minor rotamer denoted by §) δ 172.6*, 172.0§, 171.6*, 170.0§, 149.9*, 148.9§, 135.7§, 134.9*, 134.7*, 134.6§, 128.8§, 128.7*, 128.7*, 128.5§, 128.5*, 128.2*, 128.2§, 121.5§, 121.2*, 119.1§, 118.1*, 108.1§, 107.7*, 92.4§, 91.4*, 67.6*, 66.9§, 61.1*, 60.2§, 52.3§, 49.7*, 43.8*, 41.4§, 36.5*, 34.3§, 23.0§, 22.7*, 22.7*, 22.4§; IR (NaCl/thin film): 3032, 2962, 2877, 1745, 1661, 1609, 1489, 1390, 1175, 1117, 744 cm^{-1}; $[\alpha]_D^{25}$ = –66.9 (*c* = 0.98, CH_2Cl_2). HRMS (ESI) calc'd for $[M+H]^+$ 365.1865, found 365.1875.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 82% by chiral SFC analysis (AD-H, 2.5 mL/min, 10% IPA in CO_2, λ = 254 nm): t_R(major) = 11.1 min t_R(minor) = 12.6 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.36 – 7.28 (m, 3H*, 3H§), 7.23 – 7.20 (m, 2H§), 7.19 – 7.15 (m, 2H*), 7.12 (td, *J* = 7.7, 1.3 Hz, 1H§), 7.08 (td, *J* = 7.7, 1.3 Hz, 1H*), 7.01 (dd, *J* = 7.3, 0.9 Hz, 1H§), 6.98 (dd, *J* = 7.3, 0.9 Hz, 1H*), 6.69 (td, *J* = 7.4, 0.9 Hz, 1H§), 6.64 (td, *J* = 7.4, 0.9 Hz, 1H*), 6.36 (d, *J* = 7.8 Hz, 1H§), 6.28 (d, *J* = 7.8 Hz, 1H*), 5.56 (s, 1H*), 5.09 (s, 1H§), 5.05 (dd, *J* = 9.0, 6.0 Hz, 1H§), 4.92 (d, *J* = 12.4 Hz, 1H§), 4.88 (d, *J* = 12.4 Hz, 1H§), 4.69 (d, *J* = 12.2 Hz, 1H*), 4.55 (d, *J* = 12.2 Hz, 1H*), 4.51 (dd, *J* = 8.5, 1.9 Hz, 1H*), 2.93 (s, 3H*), 2.81 (s, 3H§), 2.73 (dd, *J* = 12.8, 1.8 Hz, 1H*), 2.37 (dd, *J* = 13.0, 6.0 Hz, 1H§), 2.33 (dd, *J* = 12.8, 8.5 Hz, 1H*), 2.31 (s, 3H§), 2.26 (dd, *J* = 13.0, 9.0 Hz, 1H§), 2.05 (s, 3H*), 1.42 (s, 3H§), 1.41 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 170.8*, 170.5*, 169.6§, 150.4*, 148.9§, 135.5§, 134.9*, 133.1§, 132.5*, 128.8*, 128.6§, 128.5*, 128.4§, 128.4*, 128.2*, 128.1§, 128.0§, 122.4*, 121.8§, 118.0§, 117.2*, 106.5§, 105.7*, 91.3§, 86.5*, 67.3*, 66.7§, 61.3*, 59.3§, 52.3§, 50.8*, 42.6*, 41.8§, 32.3*, 31.6§, 24.8*, 22.7§, 22.5*, 21.9§; IR (NaCl/thin film): 2956, 1741, 1656, 1608, 1493, 1404, 1301, 1219, 1194, 1152, 1105, 992, 743 cm^{-1}; $[\alpha]_D^{25}$ = +114.4 (*c* = 0.57, CH_2Cl_2). HRMS (ESI) calc'd for $[M+H]^+$ 365.1865, found 365.1862.

Pyrroloindoline 7d.



(a) ***exo*** **diastereomer** **(b)** ***endo*** **diastereomer**

Prepared from 1,3-dimethyl-1*H*-indole (**6**, 0.15 mmol) and benzyl 2-trifluoroacetamidoacrylate[10] (**11**, 0.15 mmol) using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified

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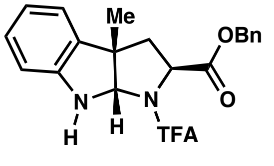
[10] Synthesis of benzyl 2-trifluoroacetamido acrylate: Crossley, M.; Stamford, A. *Aust. J. Chem.* **1994**, *47*, 1695.

by flash chromatography (5→8% ethyl acetate/hexanes) to yield 54 mg (86% yield) of **7d** in a 4:1 ratio of diastereomers (determined by NMR analysis of the crude reaction mixture). The diastereomers were separated by flash chromatography (5→8% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral SFC analysis (OJ-H, 2.5 mL/min, 3% IPA in CO_2, λ = 254 nm)

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 94%. t_R(major) = 12.5 min t_R(minor) = 10.7 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.53-7.36 (m, 5H*, 5H§), 7.23 (br t, *J* = 7.6 Hz, 1H*, 1H§), 7.11 (br d, *J* = 6.7 Hz, 1H§), 7.07 (br d, *J* = 7.2 Hz, 1H*), 6.93 – 6.86 (m, 1H§), 6.83 (br t, *J* = 7.3 Hz, 1H*), 6.64 (br d, *J* = 7.3 Hz, 1H§), 6.57 (br d, *J* = 7.8 Hz, 1H*), 5.69 (s, 1H*), 5.42 (s, 1H§), 5.36 – 5.21 (m, 2H*, 2H§), 4.82 (br d, *J* = 9.2 Hz, 1H*), 4.57 (m, 1H§), 3.14 (br s, 3H*), 2.94 (br s, 3H§), 2.60 (br dd, *J* = 13.3, 9.7 Hz, 1H*), 2.60 – 2.52 (m, 1H§), 2.41 (br d, *J* = 14.7 Hz, 1H*), 2.12 (br dd, *J* = 12.7, 6.0 Hz, 1H§), 1.54 (s, 3H§), 1.34 (s, 3H*); ^{13}C NMR (100 MHz, $CDCl_3$; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 171.9*, 169.6§, 158.9 (q, $J_{C\text{-}F}$ = 37.0 Hz)*, 157.3 (q, $J_{C\text{-}F}$ = 38.1 Hz)§, 149.2*, 149.0§, 135.1§, 134.5*, 134.2*, 134.0§, 128.6*, 128.6*, 128.5*, 128.4§, 128.2§, 128.1§, 121.3*, 119.8§, 188.5*, 116.0 (q, $J_{C\text{-}F}$ = 288.6 Hz)*, 109.3§, 107.8*, 93.1*, 91.6§, 67.8*, 67.1§, 61.2§, 60.2 (q, $J_{C\text{-}F}$ = 2.44 Hz)*, 52.9§, 49.0*, 43.6*, 40.2§, 36.5*, 34.2§, 23.1*, 22.5§; IR (NaCl/thin film): 3034, 2966, 1747, 1695, 1610, 1490, 1456, 1432, 1188, 1156, 745 cm^{-1}; $[\alpha]_D^{25}$ –90.1° (c = 1.11, CH_2Cl_2); HRMS (FAB+) calc'd for $[M+H]^+$ 419.1583, found 419.1562.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 91%. t_R(major) = 5.8 min t_R(minor) = 5.0 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 10.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.43 – 7.30 (m, 3H*, 3H§) 7.22 (dd, *J* = 6.8, 2.8 Hz, 1H§), 7.20-7.09 (m, 2H*, 1H§), 7.04 (d, *J* = 7.3 Hz, 1H§), 7.00 (d, *J* = 7.3 Hz, 1H*), 6.78 – 6.72 (m, 1H§), 6.68 (t, *J* = 7.4 Hz, 1H*), 6.36 (d, *J* = 7.8 Hz, 1H§), 6.27 (d, *J* = 7.8 Hz, 1H*), 5.60 (s, 1H*), 5.32 (s, 1H§), 5.14 (dd, *J* = 9.5, 4.9 Hz, 1H§), 5.04 (d, *J* = 12.4 Hz, 1H§), 4.94 (d, *J* = 12.4 Hz, 1H§), 4.79 (d, *J* = 8.1 Hz, 1H*), 4.63 (d, *J* = 12.1 Hz, 1H*), 4.36 (d, *J* = 12.1 Hz, 1H*), 2.95 (s, 3H*), 2.85 (d, *J* = 12.9 Hz, 1H*), 2.65 (s, 3H§), 2.46 (dd, *J* = 13.3, 5.3 Hz, 1H§), 2.39 (dd, *J* = 13.0, 8.4 Hz, 1H*), 2.28 (dd, *J* = 13.3, 9.7 Hz, 1H§), 1.46 (s, 3H*), 1.43 (s, 3H§); ^{13}C NMR (125 MHz, $CDCl_{3;}$; compound exists as a 10.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.3§, 169.2*, 156.9 (q, $J_{C\text{-}F}$ = 36.7 Hz)§, 150.3*, 148.5§, 135.2§, 134.6*, 133.1§, , 131.8*, 129.1*, 128.7§, 128.5§, 128.44*, 128.40*, 128.3*, 128.2§, 122.5*, 121.6§, 118.6§, 117.7*, 116.1 (q, J=288.8)*, 107.0§, 105.9*, 90.9§, 88.6*, 67.6*, 67.2§, 60.5§, 60.3 (q, $J_{\text{C-F}}$ = 3.1 Hz)* , 52.2§, 50.4*, 42.9*, 41.1§, 32.0*, 29.7§, 25.2*, 22.3§; IR (NaCl/thin film): 3034, 2960, 1752, 1741, 1697, 1609, 1494, 1442, 1211, 1149, 742 cm^{-1}; $[\alpha]_D^{25}$ +187.7° (c = 0.78, CH_2Cl_2) ; HRMS (FAB+) calc'd for $[M+H]^+$ 418.1504, found 418.1517.

Pyrroloindoline product from reaction with 3-methyl-1*H*-indole.

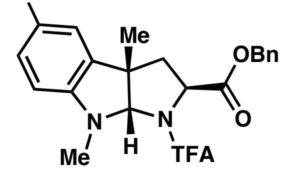


exo diastereomer

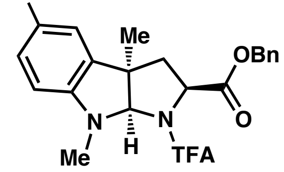
Prepared from 3-methyl-1*H*-indole (0.15 mmol) and benzyl 2-trifluoroacetamidoacrylate (**11**, 0.15 mmol) using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (0→20% ethyl acetate/hexanes) to yield 10.7 mg (18% yield) of pyrroloindoline in an 8:1 ratio of diastereomers (determined by NMR analysis of the pure product). The diastereomers were separated by prepatory HPLC (5→12% ethyl acetate/hexanes).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 95% by chiral SFC analysis (OJ-H, 2.5 mL/min, 7% IPA in hexanes, λ = 254 nm): t_R(major) = 9.6 min t_R(minor) = 7.4 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 1:1 mixture of rotamers) δ 7.43 – 7.31 (m, 5H), 7.12 (t, J = 8.1 Hz, 0.5H), 7.10 (t, J = 8.1 Hz, 0.5H), 7.05 (d, J = 4.1 Hz, 0.5H), 7.04 (d, J = 3.9 Hz, 0.5H), 6.82 (t, J = 7.5 Hz, 0.5H), 6.77 (t, J = 7.5 Hz, 0.5H), 6.64 (d, J = 7.8 Hz, 0.5H), 6.60 (d, J = 7.8 Hz, 0.5H), 5.63 (s, 0.5 H), 5.57 (s, 0.5H), 5.30 (s, 0.5H), 5.23 (s, 1H), 5.22 (d, J = 12.2 Hz, 0.5H), 5.17 (d, J = 12.2 Hz, 0.5H), 4.76 (s, 0.5H), 4.68 – 4.62 (m, 0.5H), 4.50 (t, J = 7.7 Hz, 0.5H), 2.72 (dd, J = 13.5, 9.2 Hz, 0.5H), 2.58 (dd, J = 13.1, 8.5 Hz, 0.5H), 2.33 (dd, J = 13.4, 3.9 Hz, 0.5H), 2.17 (dd, J = 13.1, 6.9 Hz, 0.5H), 1.44 (s, 1.5H), 1.31 (s, 1.5H) ; ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 1:1 mixture of rotamers) δ 171.5, 170.2, 156.8 (q, $J_{\text{C-F}}$ = 38.7 Hz), 146.8, 146.3, 135.2, 134.7, 133.2, 133.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 122.3, 122.1,120.2, 119.3, 116.1 (q, $J_{\text{C-F}}$ = 287.2), 115.7 (q, $J_{\text{C-F}}$ = 287.2), 109.9, 109.3, 86.5, 84.5, 68.10, 67.5, 61.3, 59.6, 54.5, 50.3, 43.7, 40.3, 24.2, 23.9 ; IR (NaCl/thin film): 3390, 3034, 2961, 2920, 1748, 1687, 1610, 1486, 1469, 1456, 1189, 1158, 745 cm^{-1}; $[\alpha]_D^{25}$ –111.8° (c = 0.22, CH_2Cl_2); HRMS (EI+) calc'd for $M^{+\bullet}$ 404.1348, found 404.1344.

Pyrroloindoline 13a.



(a) *exo* diastereomer



(b) *endo* diastereomer

Prepared from 5-methoxy-1,3-dimethyl-1*H*-indole[11] and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to

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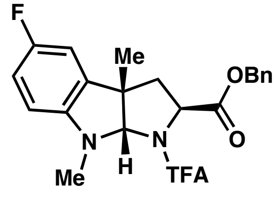
[11] Underwood, R.; Prasad, K.; Repic, O.; Hardtmann, G.E.. *Synth. Commun.* **1992**, *22*, 343.

run for 4 h. The crude residue was purified by flash chromatography (5→10% ethyl acetate/hexanes) to yield 83.1 mg (93% yield) of **13a** in a 3:1 ratio of diastereomers (determined by HPLC analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→10% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral HPLC analysis (OD-H, 1 mL/min, 10% IPA in hexanes, λ = 254 nm).

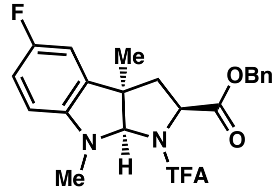
Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 93%. t_R(major) = 11.3 min t_R(minor) = 9.9 min. ^{1}H NMR (400 MHz, CDCl$_3$; compound exists as a 1.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.46 – 7.29 (m, 5H*, 5H§), 6.72 (d, *J* = 8.4 Hz, 1H*, 1H§), 6.63 (d, *J* = 13.4 Hz, 1H*, 1H§), 6.55 (d, *J* = 8.4 Hz, 1H§), 6.44 (d, *J* = 8.5 Hz, 1H*), 5.53 (br s, 1H*), 5.24 (br s, 2H*, 1H§), 5.19 (br s, 2H§), 4.76 (br d, *J* = 9.3 Hz, 1H*), 4.44 (t, *J* = 7.8 Hz, 1H§), 3.75 (br s, 3H*, 3H§), 3.04 (br s, 3H*), 2.86 (br s, 3H§), 2.61 – 2.48 (m, 1H*, 1H§), 2.31 (d, *J* = 13.4 Hz, 1H*), 2.09 – 1.99 (m, 1H§), 1.45 (br s, 3H§), 1.26 (br s, 3H*); ^{13}C NMR (100 MHz, CDCl$_{3;}$; compound exists as a 1.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.9§, 159.0* (q, $J_{\text{C-H}}$ = 36.8 Hz), 154.7§, 153.6*, 143.7*§, 135.8§, 135.8*, 135.2§, 134.6*, 128.8§, 128.8*, 128.7*, 128.6§, 128.4§, 128.3*, 116.1* (q, $J_{\text{C-F}}$ = 288.6 Hz), 113.4§, 113.1*, 111.5*, 109.0*, 108.8§, 94.2*, 92.4§, 68.1*, 67.3§, 61.2§, 60.4*, 55.9*, 53.6§, 49.3§, 43.8*, 39.9§, 38.1*, 36.9§, 23.5§, 23.4*; IR (NaCl/thin film): 2963, 2833, 1748, 1694, 1497, 1432, 1156, 1030, 991, 754 cm^{-1}; $[\alpha]_D^{25}$ = –78.1 (*c* 1.07, CH$_2$Cl$_2$); HRMS (ESI) calc'd for [M+H]$^+$ 449.1683, found 449.1676.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 92%. t_R(major) = 6.6 min t_R(minor) = 7.4 min. ^{1}H NMR (500 MHz, CDCl$_3$; compound exists as a 6.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.37 – 7.29 (m, 3H*, 3H§), 7.24 – 7.21 (m, 2H§), 7.19 – 7.12 (m, 2H*), 6.68 (dd, *J* = 8.4, 2.5 Hz, 1H*, 1H§), 6.67 (d, *J* = 2.5 Hz, 1H§), 6.63 (d, *J* = 2.5 Hz, 1H*), 6.31 – 6.26 (m, 1H§), 6.19 (d, *J* = 8.4 Hz, 1H*), 5.57 (s, 1H*), 5.22 (br d, *J* = 1.8 Hz, 1H§), 5.13 (dd, *J* = 9.7, 5.3 Hz, 1H§), 5.07 (d, *J* = 12.3 Hz, 1H§), 4.97 (d, *J* = 12.3 Hz, 1H§), 4.78 (d, *J* = 8.4 Hz, 1H*), 4.66 (d, *J* = 12.1 Hz, 1H*), 4.46 (d, *J* = 12.1 Hz, 1H*), 3.75 (s, 3H§), 3.72 (s, 3H*), 2.92 (s, 3H*), 2.81 (d, *J* = 13.0 Hz, 1H*), 2.59 (d, *J* = 1.3 Hz, 3H§), 2.45 (dd, *J* = 13.3, 5.3 Hz, 1H§), 2.36 (dd, *J* = 13.0, 8.4 Hz, 1H*), 2.26 (dd, *J* = 13.3, 9.7 Hz, 1H§), 1.44 (s, 3H*), 1.40 (s, 3H§); ^{13}C NMR (125 MHz, CDCl$_3$; compound exists as a 6.1:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.4§, 169.1*, 156.9* (q, $J_{\text{C-F}}$ = 36.7 Hz), 153.4§, 152.8*, 144.7*, 142.7§, 135.3§, 134.7*, 134.5§, 133.2*, 128.5*, 128.4*, 128.3*, 128.3§, 128.1§, 116.2* (q, $J_{C\text{-}F}$ = 288.8 Hz), 113.5*, 112.8§, 110.0*, 109.4§, 107.7§, 106.4*, 91.6§, 89.4*, 67.7*, 67.2§, 60.5§, 60.2*, 56.0*, 56.9§, 52.2§, 50.6*, 42.8*, 40.8§, 32.6*, 32.0§, 25.1*, 22.2§; IR (NaCl/thin film): 2957, 1750, 1697, 1500, 1446, 1282, 1210, 1157, 1031, 994, 850 cm^{-1}; $[\alpha]_D^{25}$ = +162.4 (*c* 1.41, CH_2Cl_2); HRMS (ESI) calc'd for $[M+H]^+$ 449.1683, found 449.1682.

Pyrroloindoline 13b.



(a) *exo* diastereomer



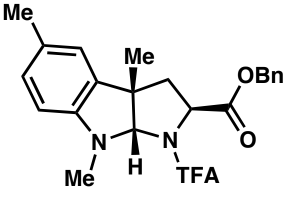
(b) *endo* diastereomer

Prepared from 5-fluoro-1,3-dimethyl-1*H*-indole **12b** and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 5.5 h. The crude residue was purified by flash chromatography (5→12% ethyl acetate/hexanes) to yield 53.0 mg (61% yield) of **13b** in a 3:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→8% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral HPLC analysis (OD-H, 1 mL/min, 3% IPA in hexanes, λ = 254 nm).

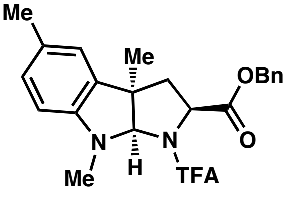
Exo diastereomer: pale yellow oil. The ee was determined to be 93%. t_R(major) = 14.7 min t_R(minor) = 18.0 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.3:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.38 (br s, 5H*, 5H§), 6.85 (br t, *J* = 7.8 Hz, 1H*, 1H§), 6.75 (br s, 1H§), 6.71 (br d, *J* = 7.8 Hz, 1H*), 6.50 (br s, 1H§), 6.39 (dd, *J* = 8.4, 3.8 Hz, 1H*), 5.58 (br s, 1H*), 5.34 – 5.16 (m, 2H*, 3H§), 4.75 (br d, *J* = 9.3 Hz, 1H*), 4.47 (br t, *J* = 6.8 Hz, 1H§), 3.04 (br s, 3H*), 2.85 (br s, 3H§), 2.55 (dd, *J* = 13.2, 9.9 Hz, 1H*), 2.55 – 2.45 (m, 1H§), 2.31 (br d, *J* = 13.4 Hz, 1H*), 2.10 – 1.97 (m, 1H§), 1.45 (br s, 3H§), 1.24 (s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 2.3:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 171.9*, 169.7§, 159.1* (q, $J_{C\text{-}F}$ = 37.1 Hz), 157.0* (d, $J_{C\text{-}F}$ = 236.5 Hz), 145.6*, 145.4§, 135.7* (d, $J_{C\text{-}F}$ = 7.3 Hz), 135.1§, 134.6*, 128.9*, 128.8*, 128.7*, 128.6§, 128.5§, 128.4§, 116.2* (q, $J_{C\text{-}F}$ = 267.0 Hz), 114.9§, 114.7* (d, $J_{C\text{-}F}$ = 23.0 Hz), 110.5§, 109.3* (d, $J_{C\text{-}F}$ = 24.3 Hz), 108.6* (d, $J_{C\text{-}F}$ = 7.8 Hz), 93.9*, 92.2§, 68.2*, 67.5§, 61.3§, 60.3*, 53.2§, 49.2*, 43.7*, 40.1§, 37.6*, 35.6§, 23.3*, 22.9§; IR (NaCl/thin film): 2966, 1748, 1698, 1495, 1434, 1350, 1270, 1157, 994, 843 cm^{-1}; $[\alpha]_D^{25}$ = –81.7 (*c* 1.14, CH_2Cl_2); HRMS (ESI) calc'd for $[M+H]^+$ 437.1483, found 437.1476.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 90%. t_R(major) = 9.1 min t_R(minor) = 10.5 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.37 – 7.30 (m, 3H*, 3H§), 7.24 – 7.20 (m, 2H§), 7.18 – 7.12 (m, 2H*), 6.83 – 6.74 (m, 1H*, 2H§), 6.71 (dd, J = 8.0, 2.6 Hz, 1H*), 6.23 (dd, J = 8.5, 4.0 Hz, 1H§), 6.14 (dd, J = 8.5, 4.0 Hz, 1H*), 5.60 (s, 1H*), 5.29 (d, J = 1.7 Hz, 1H§), 5.14 (dd, J = 9.6, 5.0 Hz, 1H§), 5.06 (d, J = 12.2 Hz, 1H§), 4.97 (d, J = 12.2 Hz, 1H§), 4.79 (d, J = 8.5 Hz, 1H*), 4.70 (d, J = 12.0 Hz, 1H*), 4.50 (d, J = 12.1 Hz, 1H*), 2.93 (s, 3H*), 2.78 (d, J = 13.1 Hz, 1H*), 2.60 (d, J = 1.3 Hz, 3H§), 2.45 (dd, J = 13.3, 5.0 Hz, 1H§), 2.37 (dd, J = 13.1, 8.5 Hz, 1H*), 2.26 (dd, J = 13.4, 9.7 Hz, 1H§), 1.44 (s, 3H*), 1.41 (s, 3H§); ^{13}C NMR (125 MHz, CDCl$_3$; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.2§, 169.0*, 156.9* (q, $J_{\text{C-F}}$ = 36.7 Hz), 156.3* (q, $J_{\text{C-F}}$ = 235.3 Hz), 146.5*, 144.7§, 135.2§, 134.5*, 133.3* (d, $J_{\text{C-F}}$ = 7.2 Hz), 128.5*, 128.4*, 128.2§, 116.1* (q, $J_{\text{C-F}}$ = 288.6 Hz), 115.0* (d, $J_{\text{C-F}}$ = 23.0 Hz), 114.5§ (d, $J_{\text{C-F}}$ = 23.1 Hz), 110.2* (d, $J_{\text{C-F}}$ = 24.4 Hz), 109.6* (d, $J_{\text{C-F}}$ = 24.6 Hz), 107.3§ (d, $J_{\text{C-F}}$ = 7.7 Hz), 106.0* (d, $J_{\text{C-F}}$ = 7.9 Hz), 91.3§, 89.1*, 67.8*, 67.3§, 60.4§, 60.2*, 52.2§, 50.4*, 42.8§, 40.9§, 32.4*, 31.5§, 25.1*, 22.3§; IR (NaCl/thin film): 2961, 1749, 1698, 1498, 1439, 1270, 1207, 1157, 995, 852, 752 cm^{-1}; $[\alpha]_D^{25}$ = +156.8 (c 1.16, CH$_2$Cl$_2$); HRMS (ESI) calc'd for [M+H]$^+$ 437.1483, found 437.1490.

Pyrroloindoline 13c.



(a) *exo* diastereomer



(b) *endo* diastereomer

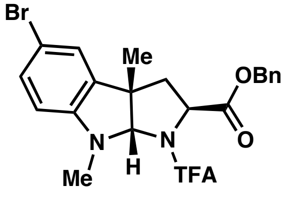
Prepared from 5-methyl-1,3-dimethyl-1*H*-indole **12c** and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 4 h. The crude residue was purified by flash chromatography (5→15% ethyl acetate/hexanes) to yield 72.9 mg (84% yield) of **13c** in a 5:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→10% ethyl acetate/hexanes).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 94% by chiral SFC analysis (OJ-H, 2.5 mL/min, 2% IPA in CO$_2$, λ = 254 nm): t_R(major) = 20.5 min t_R(minor) = 16.6 min. ^{1}H NMR (400 MHz, CDCl$_3$; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.39 (br s, 5H*, 5H§), 6.97 (br d, J = 7.7 Hz, 1H*, 1H§), 6.85 (br s, 1H§), 6.81 (br s, 1H*), 6.50 (br d, J = 7.6 Hz, 1H§), 6.42 (br d, J = 7.9 Hz, 1H*), 5.56 (br s, 1H*), 5.32 – 5.15 (br m, 2H*, 3H§), 4.76 (br d, J = 9.3 Hz, 1H*), 4.47 (br t, J = 7.5 Hz, 1H§), 3.05 (br s, 3H*), 2.87 (br s, 3H§), 2.61 – 2.46 (m, 1H*, 1H§), 2.30 (d, J = 21.3 Hz, 1H*), 2.27 (s, 3H*, 3H§), 2.09 – 1.98 (br m, 1H§), 1.45 (br s, 3H§), 1.26 (s, 3H§); ^{13}C NMR (100 MHz, CDCl$_3$; compound exists as a 2.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.9§, 159.1* (q, $J_{\text{C-}}$

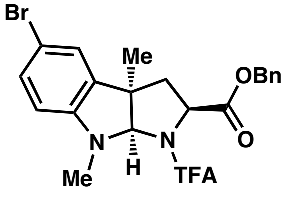
$_{\text{F}}$ = 36.8 Hz), 157.7§ (q, $J_{\text{C-F}}$ = 37.9 Hz), 147.3*§, 135.2§, 134.6*, 134.5*, 134.4§, 129.7§, 129.2§, 129.0*, 128.8*, 128.8*, 128.7*, 128.6*, 128.4*, 128.2§, 122.3*§, 116.1* (q, $J_{\text{C-F}}$ = 288.7 Hz), 110.0§, 108.2*, 93.8*, 92.1§, 68.0*, 67.3§, 61.4§, 60.4*, 53.3§, 49.2*, 43.9*, 40.2§, 37.4*, 35.6§, 23.4*, 23.2§, 20.7*§; IR (NaCl/thin film): 2965, 1748, 1697, 1499, 1456, 1433, 1348, 1194, 1153, 992, 754 cm^{-1}; $[\alpha]_{D}^{25}$ = – 87.1 (*c* 0.90, CH$_2$Cl$_2$); HRMS (APCI) calc'd for [M+H]$^+$ 433.1734, found 433.1713.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 91% by chiral HPLC analysis (OD-H, 1 mL/min, 3% IPA in hexanes, λ = 254 nm): t_{R}(major) = 6.5 min t_{R}(minor) = 7.3 min. ^{1}H NMR (300 MHz, CDCl$_3$; compound exists as a 6.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.40 – 7.29 (m, 3H*, 3H§), 7.23 – 7.18 (m, 2H§), 7.18 – 7.10 (m, 2H*), 6.96 – 6.84 (m, 1H*, 2H§), 6.81 (br s, 1H*), 6.27 (d, *J* = 7.9 Hz, 1H§), 6.18 (d, *J* = 7.9 Hz, 1H*), 5.57 (s, 1H*), 5.25 (br d, *J* = 1.9 Hz, 1H§), 5.12 (dd, *J* = 9.6, 5.4 Hz, 1H§), 5.05 (d, *J* = 12.4 Hz, 1H§), 4.94 (d, *J* = 12.2 Hz, 1H§), 4.78 (d, *J* = 8.4 Hz, 1H*), 4.63 (d, *J* = 12.2 Hz, 1H*), 4.41 (d, *J* = 12.2 Hz, 1H*), 2.92 (s, 3H*), 2.82 (d, *J* = 13.0 Hz, 1H*), 2.61 (d, *J* = 1.4 Hz, 3H§), 2.44 (dd, *J* = 13.3, 5.3 Hz, 1H§), 2.37 (dd, *J* = 13.0, 8.4 Hz, 1H*), 2.26 (s, 3H§), 2.23 (s, 3H*), 1.44 (s, 3H*), 1.41 (s, 3H§); ^{13}C NMR (125 MHz, CDCl$_3$; compound exists as a 6.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.4§, 169.2*, 156.9* (q, $J_{\text{C-F}}$ = 36.6 Hz), 148.2*, 135.3§, 134.7*, 133.3§, 132.0*, 129.3*, 128.9§, 128.5§, 128.5*, 128.4*, 128.3§, 128.2*, 128.1§, 126.9*§, 123.2*, 122.5§, 116.2* (q, $J_{\text{C-F}}$ = 288.8 Hz), 107.0§, 105.9*, 91.3§, 89.0*, 67.6*, 67.2§, 60.5§, 60.2*, 52.2§, 50.4*, 42.9*, 41.1§, 32.2*, 31.4§, 25.2*§, 22.2§, 20.7*; IR (NaCl/thin film): 2958, 1752, 1698, 1619, 1505, 1443, 1210, 1158, 995, 851, 752 cm^{-1}; $[\alpha]_{D}^{25}$ = +176.4 (*c* 0.97, CH$_2$Cl$_2$); HRMS (ESI) calc'd for [M+H]$^+$ 433.1734, found 433.1737.

Pyrroloindoline 13d.



(a) *exo* diastereomer



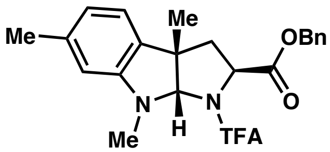
(b) *endo* diastereomer

Prepared from 5-bromo-1,3-dimethyl-1*H*-indole (**12d**) and benzyl 2-trifluoroacetamidoacrylate (**11**) using general procedure C, in DCE with 1.6 equivalents SnCl$_4$. The reaction was allowed to run for 57 h. The crude residue was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 50 mg (51% yield) of **13d** in a 3:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the pure product). The diastereomers were separated by prepatory HPLC (0→10% ethyl acetate/hexanes).

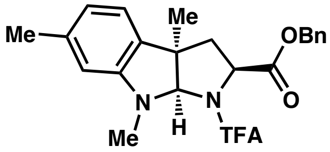
Exo diastereomer: The enantiomeric excess was determined to be 87% by chiral HPLC analysis (OD-H, 2.5 mL/min, 5% IPA in hexanes, λ = 254 nm): t_R(major) = 14.7 min t_R(minor) = 12.5 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.38 (br s, 5H*, 5H§), 7.24 (br d, J = 8.3 Hz, 1H*, 1H§), 7.11 (br s, 1H§), 7.05 (br s, 1H*), 6.41 (br d, J = 7.1 Hz, 1H§), 6.35 (br d, J = 8.3 Hz, 1H*), 5.60 (br s, 1H*), 5.34 (br s, 1H§), 5.28 – 5.15 (m, 2H*, 2H§), 4.74 (br d, J = 9.0 Hz, 1H*), 4.50 (br t, J = 7.0 Hz, 1H§), 3.03 (br s, 3H*), 2.83 (br s, 3H§), 2.53 (br dd, J = 12.9, 10.2 Hz, 1H*), 2.47 (br t, J = 11.1 Hz, 1H§), 2.30 (br d, J = 13.4 Hz, 1H*), 2.02 (br dd, J = 12.2, 6.5 Hz, 1H§), 1.45 (br s, 1H§), 1.23 (br s, 3H*); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 3.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 171.9*, 169.6§, 159.18 (q, $J_{C\text{-}F}$ = 37.1 Hz)*, 157.42 (d, $J_{C\text{-}F}$ = 39.7 Hz)§, 148.4*, 148.0§, 136.4*, 136.2§, 135.0§, 134.5*, 131.5§, 131.4*, 128.9*, 128.8*, 128.7*, 128.4§, 124.7*, 116.0 (q, $J_{C\text{-}F}$ = 288.5 Hz)*, 111.5§, 110.5*, 110.2§, 109.4*, 93.1*, 91.5§, 68.2*, 67.5§, 61.4§, 60.2*, 52.9§, 49.1*, 43.7*, 40.4§, 36.7*, 33.9§, 23.2*, 22.3§; IR (NaCl/thin film): 3034, 2965, 2931, 1747, 1698, 1602, 1489, 1205, 1154, 806, 751 cm^{-1}; $[\alpha]_D^{25}$ –86.4° (c = 0.60, CH_2Cl_2); HRMS (FAB+) calc'd for $[M+H]^+$ 498.0589, found 498.0576.

Endo diastereomer: The enantiomeric excess was determined to be 85% by chiral HPLC analysis (OD-H, 2.5 mL/min, 5% IPA in hexanes, λ = 254 nm): t_R(major) = 7.3 min t_R(minor) = 8.1 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 12.5:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.39 – 7.30 (m, 3H*, 3H§), 7.23 – 7.13 (m, 3H*, 3H§), 7.11 (s, 1H§), 7.08 (s, 1H*), 6.19 (d, J = 8.5 Hz, 1H§), 6.13 (d, J = 8.3 Hz, 1H*), 5.59 (s, 1H*), 5.33 (s, 1H§), 5.14 (dd, J = 10.0, 4.9 Hz, 1H§), 5.06 (d, J=11.9 Hz, 1H§), 4.93 (dd, J = 11.9 Hz, 1H§), 4.79 (d, J = 8.4 Hz, 1H*), 4.64 (d, J = 12.0 Hz, 1H*), 4.56 (d, J=12.0, 1H*), 2.94 (s, 3H*), 2.78 (d, J = 13.2 Hz, 1H*), 2.61 (s, 3H§), 2.45 (dd, J = 13.7, 3.9 Hz, 1H§), 2.37 (dd, J = 13.1, 8.4 Hz, 1H*), 2.26 (dd, J = 14.3, 9.9 Hz, 1H§), 1.44 (s, 3H*), 1.41 (s, 3H§); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 12.5:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.0*, 156.9 (q, $J_{C\text{-}F}$ = 37.0 Hz)*, 149.4*, 134.4*, 134.2*, 131.8*, 131.4§, 125.5*, 124.9§, 116.1(q, $J_{C\text{-}F}$ = 288.6 Hz)*, 108.9*, 108.3§, 107.5§, 107.3*, 90.6§, 88.5*, 67.9*, 67.4§, 60.4§, 60.2*, 50.4*, 42.8*, 41.1§, 32.1*, 25.3*, 22.5§; IR (NaCl/thin film): 3034, 2962, 2930, 1749, 1698, 1602, 1493, 1442, 1261, 1211, 1151, 804, 750 cm^{-1}; $[\alpha]_D^{25}$ + 156.3° (c = 0.24, CH_2Cl_2) ; HRMS (FAB+) calc'd for $[M+H]^+$ 498.0589, found 498.0606.

Pyrroloindoline 13e.



(a) *exo* diastereomer



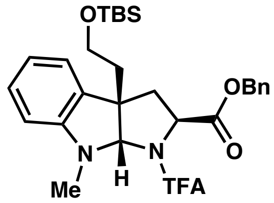
(b) *endo* diastereomer

Prepared from 6-methyl-1,3-dimethyl-1*H*-indole **12e** and benzyl 2-trifluoroacetamidoacrylate using general procedure C. The reaction was allowed to run for 6 h. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 78.3 mg (91% yield) of **13e** in a 4:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→10% ethyl acetate/hexanes). The enantiomeric excesses of both diastereomers were determined by chiral HPLC analysis (OD-H, 1 mL/min, 3% IPA in hexanes, $\lambda = 254$ nm).

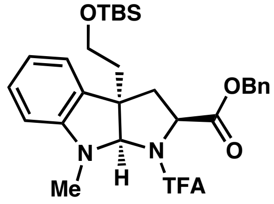
Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 94%. t_R(major) = 14.5 min t_R(minor) = 12.9 min. ^{1}H NMR (500 MHz, CDCl$_3$; compound exists as a 2.2:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.40 (br s, 5H*, 5H§), 6.93 (br d, J = 7.1 Hz, 1H§), 6.89 (br d, J = 7.4 Hz, 1H*), 6.65 (br d, J = 6.8 Hz, 1H§), 6.58 (br d, J = 7.3 Hz, 1H*), 6.42 (br s, 1H§), 6.35 (br s, 1H*), 5.60 (br s, 1H*), 5.32 (br s, 1H§), 5.29 – 5.14 (m, 2H*, 2H§), 4.76 (br d, J = 9.2 Hz, 1H*), 4.50 (br t, J = 7.2 Hz, 1H§), 3.07 (br s, 3H*), 2.88 (br s, 3H§), 2.61 – 2.42 (m, 1H*, 1H§), 2.32 (br s, J = 5.8 Hz, 4H*, 3H§), 2.10 – 1.98 (m, 1H§), 1.46 (s, 3H§), 1.27 (s, 3H*); ^{13}C NMR (125 MHz, CDCl$_3$; compound exists as a 2.2:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.1*, 169.9§, 159.2* (q, $J_{C\text{-}F}$ = 37.0 Hz), 157.7§ (q, $J_{C\text{-}F}$ = 38.4 Hz), 149.6*, 149.5§, 139.0§, 138.8*, 135.2§, 134.7*, 131.7*, 131.4§, 128.9*, 128.8*, 128.7*, 128.6*, 128.5§, 128.4§, 121.3§, 121.2*, 120.7§, 119.3*, 116.1* (q, $J_{C\text{-}F}$ = 288.4 Hz), 116.0§ (q, $J_{C\text{-}F}$ = 286.5 Hz), 110.5§, 108.9*, 93.6*, 92.0§, 68.1*, 67.4§, 61.5§, 60.5*, 52.9§, 49.0*, 43.9*, 40.4§, 36.8*, 34.7§, 23.5*, 23.0§, 21.7*§; IR (NaCl/thin film): 2964, 1748, 1697, 1616, 1499, 1456, 1423, 1160, 1004, 752 cm^{-1}; $[\alpha]_D^{25} = -85.6$ (c 0.93, CH$_2$Cl$_2$); HRMS (EI+) calc'd for M$^{+\bullet}$ 432.1661, found 432.1663.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 90%. t_R(major) = 7.8 min t_R(minor) = 8.3 min. ^{1}H NMR (500 MHz, CDCl$_3$; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.38 – 7.29 (m, 3H*, 3H§), 7.21 (dd, J = 6.6, 2.9 Hz, 2H§), 7.16 – 7.10 (m, 2H*), 6.92 (d, J = 7.4 Hz, 1H§), 6.86 (d, J = 7.4 Hz, 1H*), 6.55 (d, J = 7.4 Hz, 1H§), 6.49 (dd, J = 7.4, 0.6 Hz, 1H*), 6.17 (s, 1H§), 6.06 (s, 1H*), 5.57 (s, 1H*), 5.28 (d, J = 1.9 Hz, 1H§), 5.12 (dd, J = 9.6, 5.2 Hz, 1H§), 5.03 (d, J = 12.3 Hz, 1H§), 4.95 (d, J = 12.3 Hz, 1H§), 4.78 (d, J = 8.4 Hz, 1H*), 4.67 (d, J = 12.1 Hz, 1H*), 4.33 (d, J = 12.2 Hz, 1H*), 2.91 (s, 3H*), 2.82 (d, J = 12.9 Hz, 1H*), 2.62 (d, J = 1.4 Hz, 3H§), 2.43 (dd, J = 13.3, 5.2 Hz, 1H§), 2.36 (dd, J = 12.9, 8.3 Hz, 1H*), 2.30 (s, 3H§), 2.28 (s, 3H*), 2.24 (dd, J = 13.3, 9.6 Hz, 1H§), 1.43 (s, 3H*), 1.40 (s, 3H§); ^{13}C NMR (125 MHz, CDCl$_3$; compound exists as a 9.0:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.4§, 169.3*, 156.9* (q, $J_{\text{C-F}}$ = 36.8 Hz), 150.4*, 148.7§, 139.0*, 138.7§, 135.2§, 134.7*, 130.3§, 129.0*, 128.5§, 128.4*, 128.4*, 128.3§, 128.2*, 122.3*, 121.3§, 119.1§, 118.4*, 116.2* (q, $J_{\text{C-F}}$ = 288.7 Hz), 108.0§, 106.8*, 91.1§, 88.9*, 67.6*, 67.2§, 60.5§, 60.3*, 52.0§, 50.2*, 42.9*, 41.1§, 32.0*, 31.0§, 25.3*§, 22.4§, 21.8*; IR (NaCl/thin film): 2923, 1740, 1698, 1612, 1501, 1440, 1214, 1150, 1011, 849, 746 cm^{-1}; $[\alpha]_D^{25}$ = +165.5 (c 0.53, CH$_2$Cl$_2$); HRMS (ESI) calc'd for $[M+H]^+$ 433.1739, found 433.1756.

Pyrroloindoline 13f.



(a) ***exo*** **diastereomer**



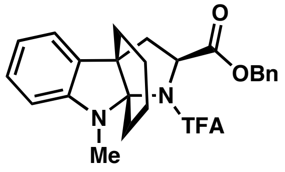
(b) ***endo*** **diastereomer**

Prepared from 1-methyl-3-*t*-butyldimethylsiloxyethyl-1*H*-indole (**12f**) and benzyl 2-trifluoroacetamidoacrylate (**11**) using general procedure C. The reaction was allowed to run for 20 h. The crude residue was purified by flash chromatography (0→5% ethyl acetate/hexanes) to yield 61 mg (54% yield) of **13f** in a 6:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the purified product). The diastereomers were separated by preparatory HPLC (0→5% ethyl acetate/hexanes).

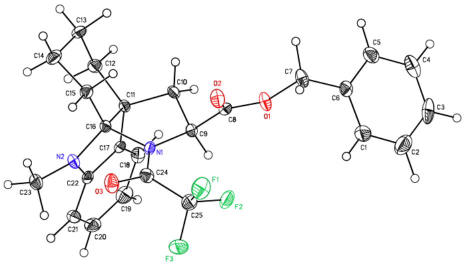
Exo diastereomer: The enantiomeric excess was determined to be 92% by chiral HPLC analysis (OD-H, 1 mL/min, 0.6% EtOH in hexanes, λ = 254 nm): t_R(major) = 10.7 min t_R(minor) = 12.1 min. ^{1}H NMR (500 MHz, CDCl$_3$; compound exists as a 1.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.38 (br s, 5H*, 5H§), 7.17 (t, J = 7.6 Hz, 1H*, 1H§), 7.00 (br d, J = 6.7 Hz, 1H*, 1H§), 6.87-6.78 (br m, 1H§), 6.76 (br t, J = 6.7 Hz, 1H*), 6.59 (br d, J = 6.0 Hz, 1H§), 6.51 (br d, J = 7.4 Hz, 1H*), 5.89 (br s, 1H*), 5.79 (br s, 1H§), 5.30 – 5.10 (m, 2H*, 2H§), 4.61 (br s, 1H*), 4.32 (br s, 1H§), 3.60 (br d, J = 22.3 Hz, 2H§), 3.49 (br s, 2H*), 3.10 (s, 3H*), 2.94 (br s, 3H§), 2.74 – 2.64 (m, 1H*), 2.63 – 2.52 (m, 1H§), 2.39 (br d, J = 10.1 Hz, 1H*), 2.18 (br t, J = 9.9 Hz, 1H§), 1.97 (br s, 2H§), 1.82 (br td, J = 13.6, 7.9 Hz, 2H*), 0.86 (br s, 9H*, 9H§), 0.02 – -0.06 (m, 6H*, 6H§); ^{13}C NMR (100 MHz, CDCl$_3$; compound exists as a 1.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.9§, 159.0 (q, $J_{\text{C-F}}$ = 37.9 Hz)*, 157.7 (q, $J_{\text{C-F}}$ = 38.1 Hz)§, 150.5§, 150.0*, 135.2§, 134.7*, 131.7§, 131.5*, 128.8*§, 128.6*§, 128.4*§, 122.4*§, 119.9§, 118.4*, 116.0 (q, $J_{\text{C-F}}$ = 288.0 Hz)*, 110.0§, 108*, 90.8*, 89.5§, 67.9*, 67.3§, 60.5§, 59.6*, 56.4§, 52.3*, 43.5*, 39.9§, 39.1§, 39.0*, 36.4*, 35.7§, 25.8*, 18.1§, -5.6*§; IR (NaCl/thin film): 3035, 2955, 2930, 2857, 2884, 1750, 1694, 1492, 1432, 1257, 1201, 1158, 1106, 837 cm^{-1}; $[\alpha]_D^{25}$ = –95.3° (c =1.38, CH_2Cl_2); HRMS (FAB+) calc'd for $[M+H]^+$ 562.2475, found 562.2468.

Endo diastereomer: The enantiomeric excess was determined to be 90% by chiral HPLC analysis (AD-H, 1 mL/min, 0.5% EtOH in hexanes, λ = 254 nm): t_R(major) = 6.5 min t_R(minor) = 5.8 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 16.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.38 – 7.29 (m, 3H*, 3H§), 7.20 – 7.07 (m, 3H*, 3H§), 6.96 (d, *J* = 7.2 Hz, 1H*, 1H§), 6.69 (t, *J* = 7.5 Hz, 1H§), 6.65 (t, *J* = 7.4 Hz, 1H*), 6.27 (d, *J* = 8.2 Hz, 1H§), 6.25 (d, *J* = 7.9 Hz, 1H*), 5.90 (s, 1H§), 5.83 (s, 1H*), 5.12 (dd, *J* = 9.3, 3.0 Hz, 1H§), 4.86 (d, 12.2 Hz, 1H§), 4.79 (d, *J*= 12.2 Hz, 1H§), 4.77 (d, *J* = 8.2 Hz, 1H*), 4.60 (d, *J* = 12.1 Hz, 1H*), 4.33 (d, *J* = 12.2 Hz, 1H*), 3.65 – 3.49 (m, 2H*, 2H§), 2.92 (s, 3H*), 2.88 (d, *J* = 13.1 Hz, 1H*), 2.67 (s, 3H§), 2.58 (dd, *J* = 13.1, 3.3 Hz, 1H§), 2.49 (dd, *J* = 13.1, 8.4 Hz, 1H*), 2.28 (dd, *J* = 13.7, 10.1 Hz, 1H§), 2.07 – 1.84 (m, 2H*, 2H§), 0.87 (s, 9H*), 0.80 (s, 9H§), 0.00 (d, *J* = 4.0 Hz, 6H*), -0.09 (d, *J* = 13.9 Hz, 6H§); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a 16.7:1 mixture of rotamers, only the major rotamer is reported) δ 169.3, 156.8 (q, $J_{C\text{-}F}$ = 37.9 Hz), 151.2, 134.7, 129.6, 129.2, 128.43, 128.37, 128.2, 123.5, 117.5, 116. 2 (q, $J_{C\text{-}F}$ = 289.0 Hz), 107.5, 105.9, 87.1, 67.5, 59.9, 59.4, 53.0, 42.2, 40.4, 31.9, 25.9, 18.2, -5.6 (*J* = 6.1 Hz); IR (NaCl/thin film): 3034, 2954, 2930, 2857, 1742, 1699, 1609, 1494, 1441, 1255, 1207, 1146, 1104, 837, 745 cm^{-1}; $[\alpha]_D^{25}$ +148.5° (c = 0.33, CH_2Cl_2); HRMS (FAB+) calc'd for $[M+H]^+$ 562.2475, found 562.2458.

Pyrroloindoline 13g.



exo diastereomer



Prepared from 9-methyl-2,3,4,9-tetrahydro-1*H*-carbazole[12] and benzyl 2-trifluoroacetamidoacrylate (**11**) using general procedure C. The reaction was allowed to run for 11 h. The crude residue was purified by

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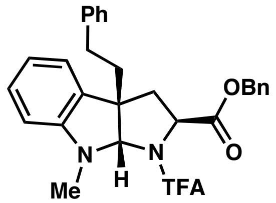
[12] Pitts, M.R.; Harrison, J.R.; Moody, C.J. *J. Chem. Soc., Perkin Trans. 1* **2001**, *9*, 955

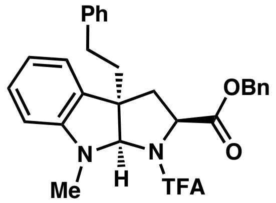
flash chromatography (5→20% ethyl acetate/hexanes) to yield 60 mg (65% yield) of **13g** in a >18:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the pure product). The diastereomers were separated by prep HPLC (0→10% ethyl acetate/hexanes).

Exo diastereomer: pale yellow oil. The oil was crystallized from ethyl acetate/hexanes to give crystals suitable for single crystal X-ray diffraction. The enantiomeric excess was determined to be 86% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in hexanes, λ = 254 nm): t_R(major) = 4.5 min t_R(minor) = 6.9 min. ^{1}H NMR (300 MHz, $CDCl_3$; compound exists as a >20:1 mixture of rotamers) δ 7.44 – 7.29 (m, 5H), 7.16 (t, J = 7.2 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 6.72 (t, J = 7.4 Hz, 1H), 6.51 (d, J = 7.8 Hz, 1H), 5.20 (dd, J = 29.3, 12.1 Hz, 2H), 4.43 (t, J = 8.2 Hz, 1H), 3.20 (d, J = 15.5 Hz, 1H), 3.10 (s, 3H), 2.75 (dd, J = 13.0, 8.6 Hz, 1H), 2.28 (dd, J = 13.0, 9.3 Hz, 1H), 2.02 – 1.75 (m, 2H), 1.75 – 1.55 (m, J = 12.9 Hz, 1H), 1.53 – 1.38 (m, 1H), 1.36 – 1.07 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$; compound exists as a >20:1 mixture of rotamers) δ 172.4, 157.7 (q, $J_{C\text{-}F}$ = 36.3 Hz), 148.0, 134.9, 133.7, 128.7, 128.6, 128.4, 120.8, 118.0, 115.8 (q, $J_{C\text{-}F}$ = 289.8 Hz), 112.3, 107.1, 95.6, 67.6, 58.4 (q, $J_{C\text{-}F}$ = 3.5 Hz), 52.3, 35.2, 33.9, 30.7, 26.8, 21.5, 20.4 ; IR (NaCl/thin film): 3034, 2928, 2857, 1749, 1693, 1609, 1490, 1214, 1186, 1160, 741 cm^{-1}; melting point: 106 – 108 °C; $[\alpha]_D^{25}$ = –92.6° (c = 1.40, CH_2Cl_2); HRMS (ESI+) calc'd for $[M+H]^+$ 459.1890, found 459.1892.

Pyrrolidinoindoline 13h.



(a) *exo* diastereomer



(b) *endo* diastereomer

Prepared from 3-phenethyl-1-methyl-1*H*-indole[13] and benzyl 2-trifluoroacetamidoacrylate (**11**) using general procedure C, with 1.6 equivalents $SnCl_4$. The reaction was allowed to run for 9.5 h. The crude residue was purified by flash chromatography (5→20% ethyl acetate/hexanes) to yield 81 mg (80% yield) of **13h** in a 4:1 ratio of diastereomers (determined by ^{1}H NMR analysis of the crude reaction mixture). The diastereomers were separated by preparatory HPLC (0→6% ethyl acetate/hexanes). The enantiomeric excess of both diastereomers was determined by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in hexanes, λ = 254 nm).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 92%. t_R(major) = 33.3 min t_R(minor) = 28.0 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ

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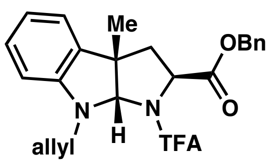
[13] Ferreira, E. PhD. Dissertation, California Institute of Technology, 2005.

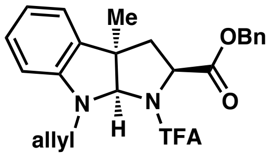
^{1}H NMR (500 MHz, CDCl$_3$) δ 7.39 – 7.28 (m, 5H*, 5H§), 7.28 – 7.16 (m, 4H*, 4H§), 7.12 – 7.06 (br s, 3H§), 7.02 (m, 3H*), 6.90-6.81 (br s, 1H§), 6.81 (t, J = 6.9 Hz, 1H*), 6.63 – 6.57 (m, J = 9.8 Hz, 1H§), 6.55 (br d, J = 7.5 Hz, 1H*), 5.70 (br s, 1H*), 5.45 (br s, 1H§), 5.25-5.15 (m, 2H*, 2H§), 4.69 (br d, J = 7.4 Hz, 1H*), 4.39 (br s, 1H§), 3.12 (br s, 3H*), 2.90 (br s, 3H§), 2.78 – 1.73 (m, 6H*, 6H§); ^{13}C NMR (125 MHz, CDCl$_3$; compound exists as a 2.6:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.8§, 159.0 (q, $J_{\text{C-F}}$ = 36.7 Hz)*, 157.60 (q, $J_{\text{C-F}}$ = 32.9 Hz)§, 150.3*§, 141.0*§, 135.1§, 134.5*, 132.0*, 131.6§, 129.1§, 128.9§, 128.8§, 128.7*, 128.4*, 128.2*, 126.0*§, 122.3§, 121.9*, 120.1§, 118.9*, 116.0 (q, $J_{\text{C-F}}$ = 288.4 Hz)*, 109.7§, 108.3*, 90.4*, 89.2§, 68.1*, 67.4§, 60.7§, 59.5*, 57.5§, 53.7*, 43.5*, 40.0§, 39.0*, 38.6§, 36.9*, 35.1§, 31.9*§ ; IR (NaCl/thin film): 3030, 2921, 2852, 1747, 1694, 1607, 1492, 1455, 1433, 1190, 1152, 750 cm^{-1}; $[\alpha]_D^{25}$ –113.8° (c =1.17, CH$_2$Cl$_2$); HRMS (ESI) calc'd for $[M+H]^+$ 509.2047, found 509.2052.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 90%. t_R(major) = 11.6 min t_R(minor) = 17.5 min. ^{1}H NMR (500 MHz, CDCl$_3$; compound exists as a 14.5:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.37 – 7.30 (m, 3H*, 3H§), 7.23 (d, J = 7.6 Hz, 2H*, 2H§), 7.19 – 7.12 (m, 4H*, 4H§), 7.07 (d, J = 7.3 Hz, 2H*, 2H§), 7.03 (d, J = 7.2 Hz, 1H*, 1H§), 6.76 (t, J = 7.3 Hz, 1H§), 6.71 (t, J = 7.3 Hz, 1H*), 6.33 (d, J = 7.8 Hz, 1H§), 6.28 (d, J = 7.8 Hz, 1H*), 5.70 (s, 1H*), 5.49 (s, 1H§), 5.13 (dd, J = 9.4, 3.5 Hz, 1H§), 4.91 (d, J = 12.2 Hz, 1H§), 4.83 (d, J = 12.2 Hz, 1H§), 4.80 (d, J = 8.2 Hz, 1H*), 4.63 (d, J = 12.1 Hz, 1H*), 4.37 (d, J = 12.1 Hz, 1H*), 2.94 (s, 3H*), 2.86 (d, J = 12.9 Hz, 1H*), 2.65 (s, 3H§), 2.59 (td, J = 12.9, 5.3 Hz, 1H*), 2.53 – 2.46 (m, 1H§), 2.45 – 2.32 (m, 2H*), 2.27 (dd, J = 13.2, 9.6 Hz, 1H§), 2.23 – 2.18 (m, 1H§), 2.15 – 1.89 (m, 2H*, 2H§); ^{13}C NMR (125 MHz, CDCl$_{3;}$; compound exists as a 14.5:1 mixture of rotamers, only the major rotamer is reported) δ 169.2, 156.8 (q, $J_{\text{C-F}}$ = 36.9 Hz), 151.3, 141.2, 134.7, 129.6, 129.4, 128.5, 128.43, 128.41, 128.3, 128.2, 126.0, 123.1, 117.8, 116.2 (q, J = 288.9 Hz), 105.9, 86.9, 67.7, 60.0 (q, $J_{\text{C-F}}$ = 3.2 Hz). 54.3, 47.5, 42.2, 41.0, 31.9, 31.1; IR (NaCl/thin film): 2919, 2850, 1738, 1694, 1607, 1493, 1455, 1441, 1204, 1142, 744 cm^{-1}; $[\alpha]_D^{25}$ +119.6° (c = 0.87, CH$_2$Cl$_2$); HRMS (ESI) calc'd for $[M+H]^+$ 509.2047, found 509.2048.

Pyrroloindoline 13i.



(a) *exo* diastereomer



(b) *endo* diastereomer

Prepared from 1-allyl-3-methyl-1*H*-indole[14] and benzyl 2-trifluoroacetamidoacrylate using general procedure C, with 1.6 equivalents $SnCl_4$. The reaction was allowed to run for 15 h. The crude residue was purified by flash chromatography (0→10% ethyl acetate/hexanes) to yield 79.7 mg (90% yield) of **13i** in a 3:1 ratio of diastereomers (determined by SFC analysis of the purified products, before the diastereomers were separated). The diastereomers were separated by flash chromatography (0→10% ethyl acetate/hexanes).

Exo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 93% by chiral SFC analysis (OJ-H, 2.5 mL/min, 6% IPA in CO_2, $\lambda = 254$ nm): t_R(major) = 5.7 min t_R(minor) = 4.3 min. ^{1}H NMR (400 MHz, $CDCl_3$; compound exists as a 5.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.40 (br s, 5H*, 5H§), 7.14 (t, *J* = 7.7 Hz, 1H*, 1H§), 7.09 – 6.95 (br m, 1H§), 7.00 (br d, *J* = 7.2 Hz, 1H*), 6.90 – 6.71 (br m, 1H§), 6.76 (br t, *J* = 7.3 Hz, 1H*), 6.68 – 6.44 (br m, 1H§), 6.54 (br d, *J* = 7.9 Hz, 1H*), 5.82 (br ddd, *J* = 21.5, 10.5, 5.7 Hz, 1H*, 1H§), 5.73 (br s, 1H*), 5.52 (br s, 1H§), 5.34 – 5.09 (m, 4H*, 4H§), 4.75 (br d, *J* = 9.2 Hz, 1H*), 4.40 (br s, 1H§), 4.26 (br d, *J* = 13.1 Hz, 1H*), 4.04 (br dd, *J* = 16.3, 5.9 Hz, 1H*, 1H§), 3.83 (br s, 1H§), 2.60 (br dd, *J* = 13.3, 9.8 Hz, 1H*, 1H§), 2.36 (br d, *J* = 13.4 Hz, 1H*), 2.20 – 2.03 (m, 1H§), 1.46 (s, *J* = 10.6 Hz, 3H§), 1.27 (s, *J* = 8.7 Hz, 3H*); ^{13}C NMR (100 MHz, $CDCl_3$; compound exists as a 5.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 172.0*, 169.8§, 158.9* (q, $J_{C\text{-}F}$ = 37.0 Hz), 148.4*§, 134.8*, 134.6*, 133.8*, 133.4§, 128.8*, 128.7*, 128.7*, 121.5*, 120.3§, 118.7*, 117.7§, 116.7*, 116.0* (q, $J_{C\text{-}F}$ = 288.5 Hz), 110.8§, 108.4*, 91.3*, 89.7§, 68.0*, 67.4§, 61.1§, 60.0*, 53.6§, 51.8*, 50.5§, 49.4*, 44.1*, 40.7§, 23.5*§; IR (NaCl/thin film): 3035, 2968, 1748, 1694, 1609, 1488, 1424, 1339, 1257, 1148, 1026, 921, 744 cm^{-1}; $[\alpha]_D^{25} = -94.3$ (*c* 1.14, CH_2Cl_2); HRMS (ESI) calc'd for $[M+H]^+$ 445.1734, found 445.1750.

Endo diastereomer: pale yellow oil. The enantiomeric excess was determined to be 89% by chiral SFC analysis (OJ-H, 2.5 mL/min, 2% IPA in CO_2, $\lambda = 254$ nm): t_R(major) = 5.9 min t_R(minor) = 5.1 min. ^{1}H NMR (500 MHz, $CDCl_3$; compound exists as a 15.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 7.36 – 7.30 (m, 3H*, 3H§), 7.19 (dd, *J* = 6.5, 3.0 Hz, 2H§), 7.16 – 7.11 (m, 2H*), 7.08 (td, *J* = 7.7, 1.3 Hz, 1H*, 1H§), 7.04 (d, *J* = 7.4 Hz, 1H§), 6.99 (dd, *J* = 7.4, 0.9 Hz, 1H*), 6.73 (t, *J* = 7.0 Hz, 1H§), 6.68 (td, *J* = 7.4, 0.9 Hz, 1H*), 6.35 (d, *J* = 7.4 Hz,

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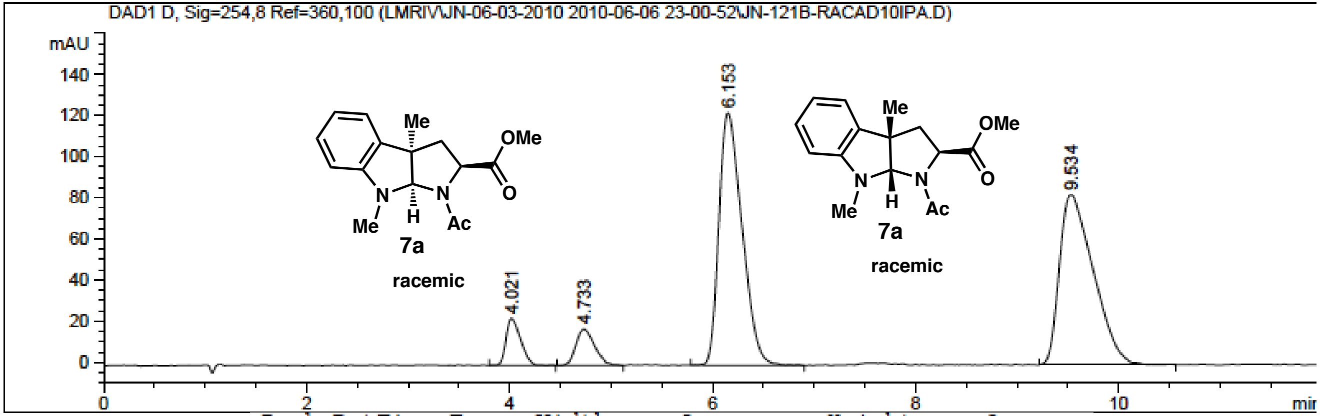
[14] Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L.S. *J. Org. Chem.* **1980**, *45*, 2709.

1H§), 6.34 (d, *J* = 7.8 Hz, 1H*), 5.77 (dddd, *J* = 17.1, 10.4, 5.5, 5.1 Hz, 1H*), 5.73 – 5.67 (m, 1H§), 5.58 (s, 1H*), 5.55 – 5.53 (m, 1H§), 5.22 (dq, *J* = 17.1, 1.6 Hz, 1H*), 5.16 (dd, *J* = 9.6, 4.3 Hz, 1H§), 5.14 – 5.10 (m, 2H§), 5.05 (dq, *J* = 10.2, 1.5 Hz, 1H*), 4.97 (d, *J* = 12.3 Hz, 1H§), 4.91 (d, *J* = 12.3 Hz, 1H§), 4.80 (d, *J* = 8.5 Hz, 1H*), 4.68 (d, *J* = 12.1 Hz, 1H*), 4.36 (d, *J* = 12.1 Hz, 1H*), 4.15 (ddt, *J* = 16.7, 5.9, 1.5 Hz, 1H*), 4.01 (ddt, *J* = 16.7, 5.0, 1.6 Hz, 1H*), 3.68 – 3.64 (m, 1H§), 2.88 (d, *J* = 13.0 Hz, 1H*), 2.53 (dd, *J* = 13.3, 4.3 Hz, 1H§), 2.40 (dd, *J* = 13.0, 8.5 Hz, 1H*), 2.26 (dd, *J* = 13.3, 9.6 Hz, 1H§), 1.44 (s, 1H§), 1.43 (s, 1H*); ^{13}C NMR (125 MHz, CDCl$_3$; compound exists as a 15.7:1 mixture of rotamers, the major rotamer is denoted by *, minor rotamer denoted by §) δ 169.3*, 156.9* (q, $J_{C\text{-}F}$ = 36.9 Hz), 149.3*, 147.7§, 134.7*, 134.1*, 133.2§, 132.4§, 132.0*, 128.9*, 128.6§, 128.5§, 128.5*, 128.4*, 128.3*, 128.2§, 122.6*, 121.7§, 118.7§, 118.0*, 117.1§, 116.3*, 116.2* (q, $J_{C\text{-}F}$ = 288.7 Hz), 108.0§, 106.9*, 88.1*, 67.6*, 67.3§, 60.4§, 60.2*, 52.7§, 50.6*, 48.8*, 42.5*, 41.5§, 25.8*, 23.1§; IR (NaCl/thin film): 2962, 1739, 1697, 1608, 1491, 1447, 1269, 1211, 1145, 851, 742 cm^{-1}; $[\alpha]_D^{25}$ = +166.6 (*c* 1.52, CH$_2$Cl$_2$); HRMS (ESI) calc'd for [M+H]$^+$ 445.1734, found 445.1740.

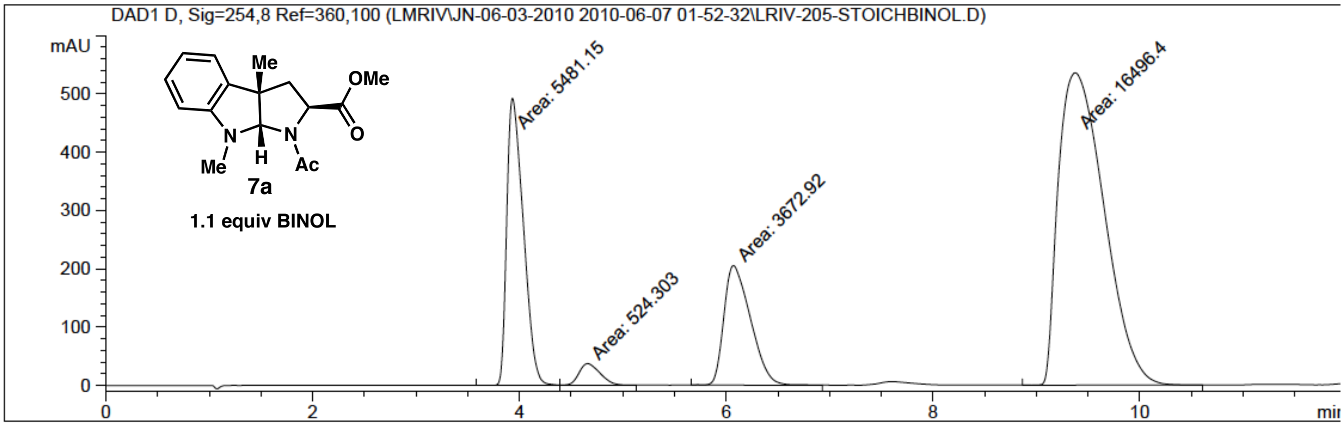
Chromatograms of racemic and enantiomerically enriched pyrroloindolines.

7a (Table 1, entries 2-6): racemic



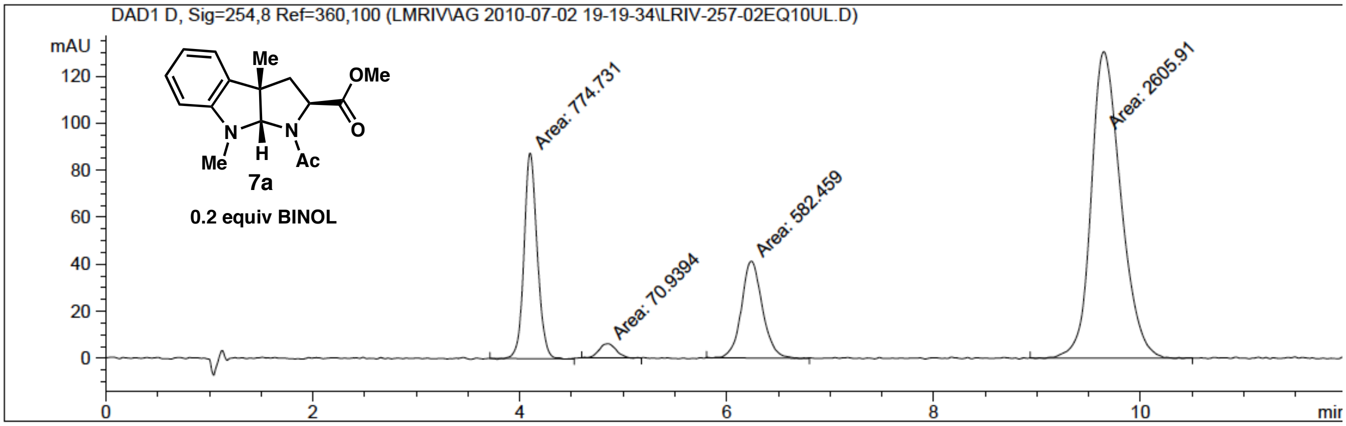
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.021 BB    0.1585  233.11978   22.95946   5.3721
   2   4.733 BB    0.2032  229.21661   17.68176   5.2822
   3   6.153 BB    0.2451 1949.83508  122.89280  44.9330
   4   9.534 BB    0.3471 1927.25183   82.93414  44.4126
```

7a (Table 1, entry 2): enantioenriched, *exo:* 64% ee, *endo*: 83% ee



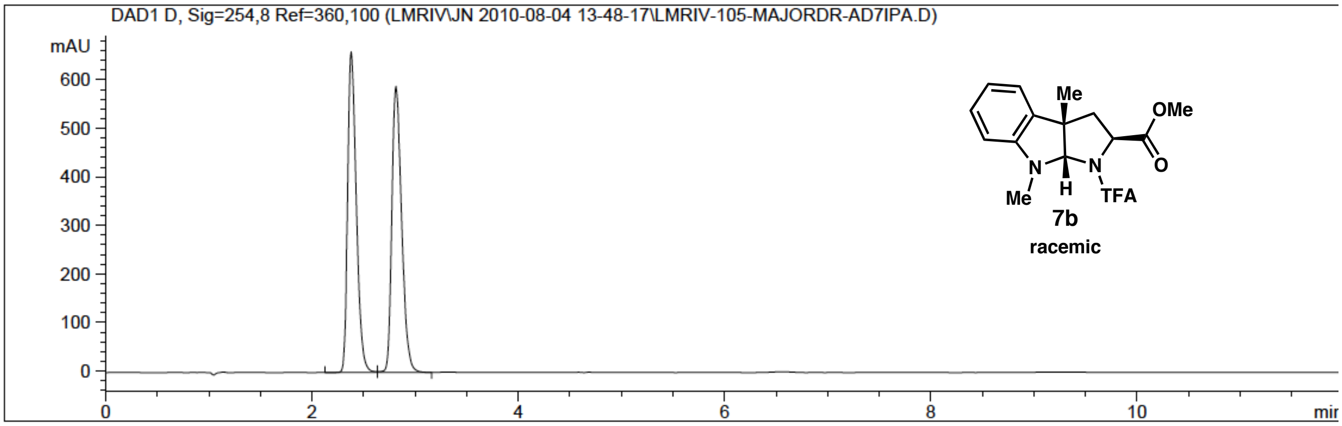
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   3.934 MF    0.1852 5481.14941  493.18698  20.9406
   2   4.658 FM    0.2354  524.30292   37.12406   2.0031
   3   6.070 MM    0.2985 3672.91748  205.08722  14.0323
   4   9.375 MM    0.5132 1.64964e4   535.76978  63.0240
```

7a (Table 1, entry 4): enantioenriched, *exo:* 63% ee, *endo*: 83% ee



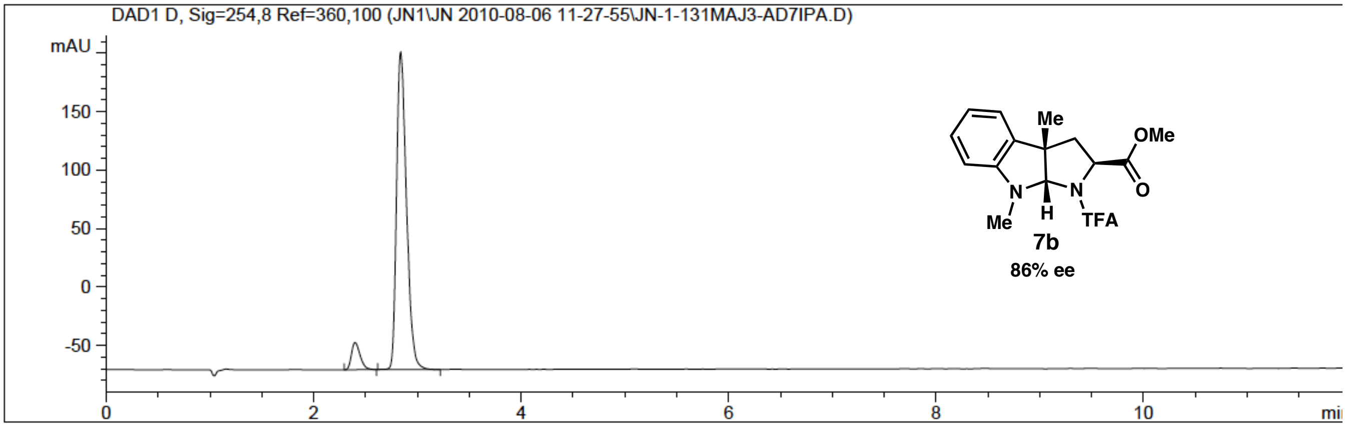
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   4.100 MM    0.1473  774.73053   87.65621  19.2048
   2   4.852 MM    0.1955   70.93945    6.04832   1.7585
   3   6.238 MM    0.2351  582.45917   41.28461  14.4386
   4   9.647 MM    0.3330 2605.91260  130.42717  64.5981
```

***exo*-7b (Table 1, entry 7):** racemic



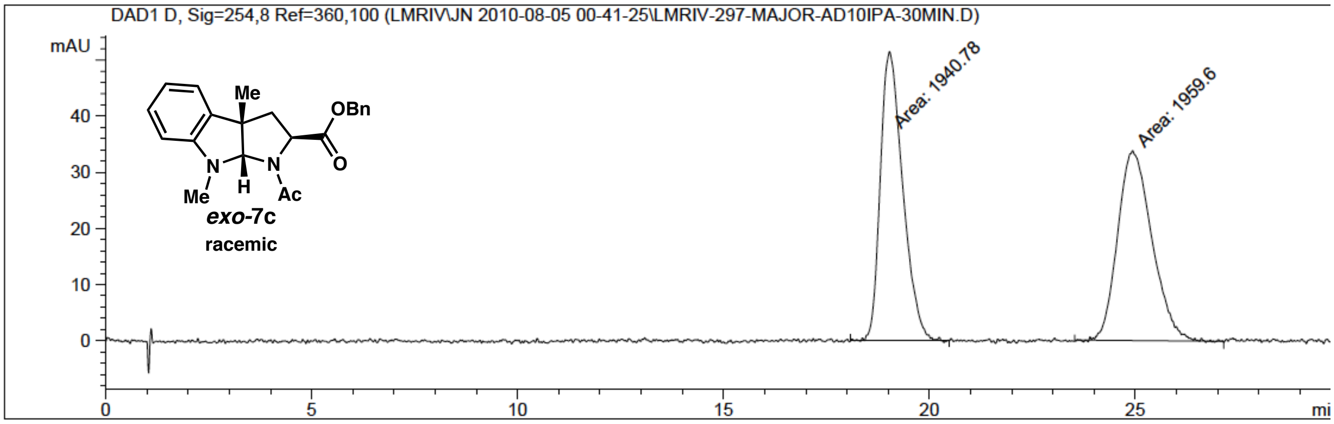
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   2.381 BV    0.0886 3856.54150  655.60498 49.8096
   2   2.815 VB    0.1009 3886.01978  589.71381 50.1904
```

***exo*-7b (Table 1, entry 7):** enantioenriched, 86% ee



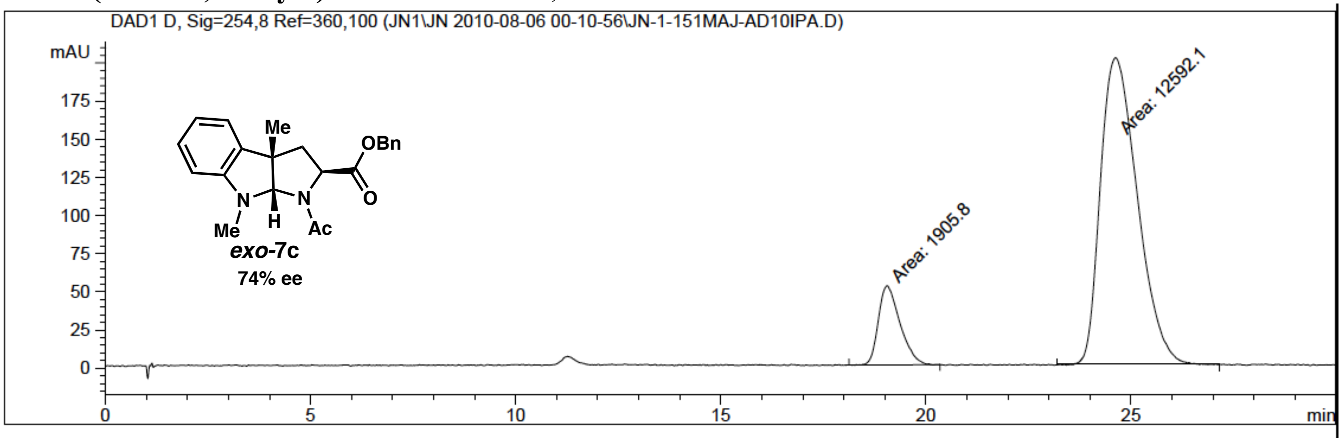
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   2.399 BB    0.0925  136.26041   23.19655   6.9999
   2   2.839 BB    0.1061 1810.34204  270.34299  93.0001
```

***exo*-7c (Table 1, entry 8):** racemic



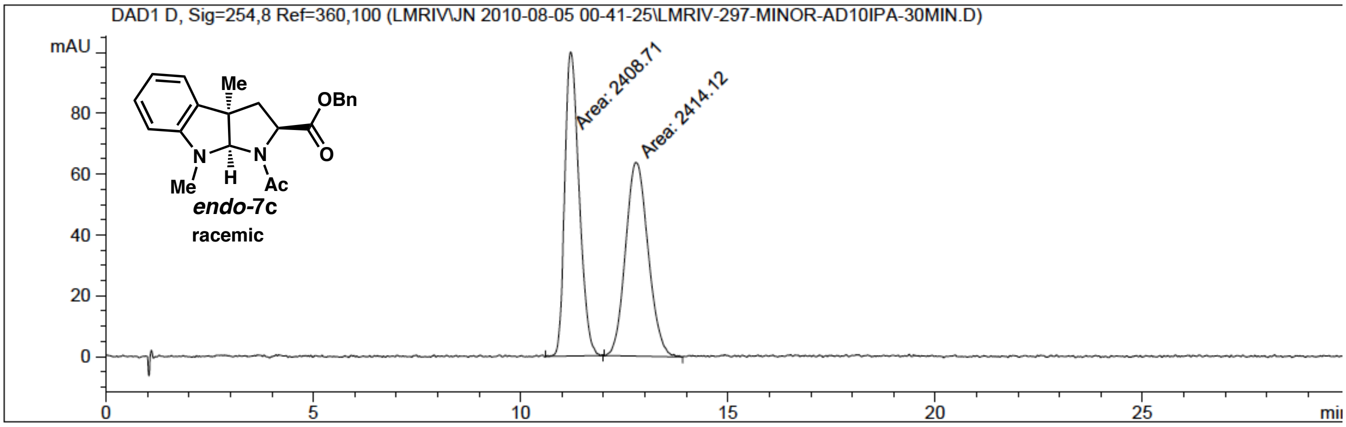
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  19.033 MM     0.6293 1940.77502   51.40419  49.7587
  2  24.937 MM     0.9651 1959.59827   33.84022  50.2413
```

***exo*-7c (Table 1, entry 8):** enantioenriched, 74% ee



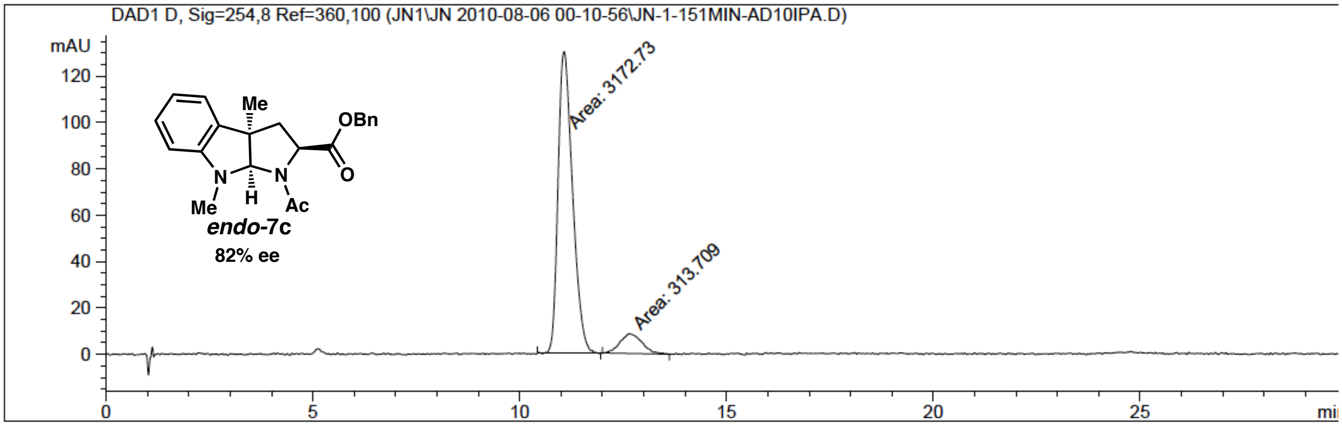
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]         [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  19.055 MM     0.6122 1905.80066   51.88297  13.1454
  2  24.623 MM     1.0448 1.25921e4   200.87437  86.8546
```

***endo*-7c (Table 1, entry 8):** racemic



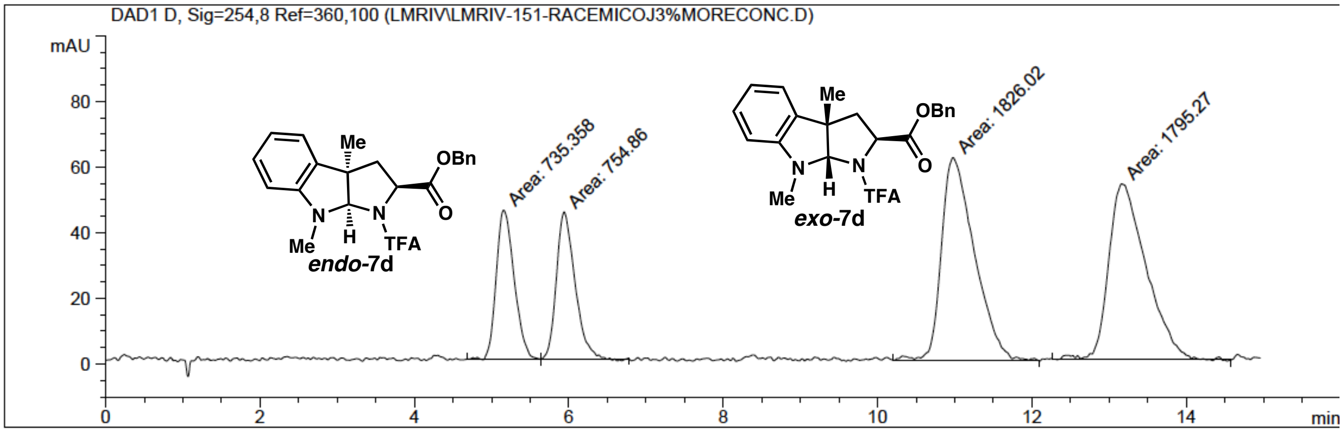
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  11.210 MM    0.4013 2408.70581  100.04025  49.9439
   2  12.782 MM    0.6310 2414.11816   63.76419  50.0561
```

***endo*-7c (Table 1, entry 8):** enantioenriched, 82% ee



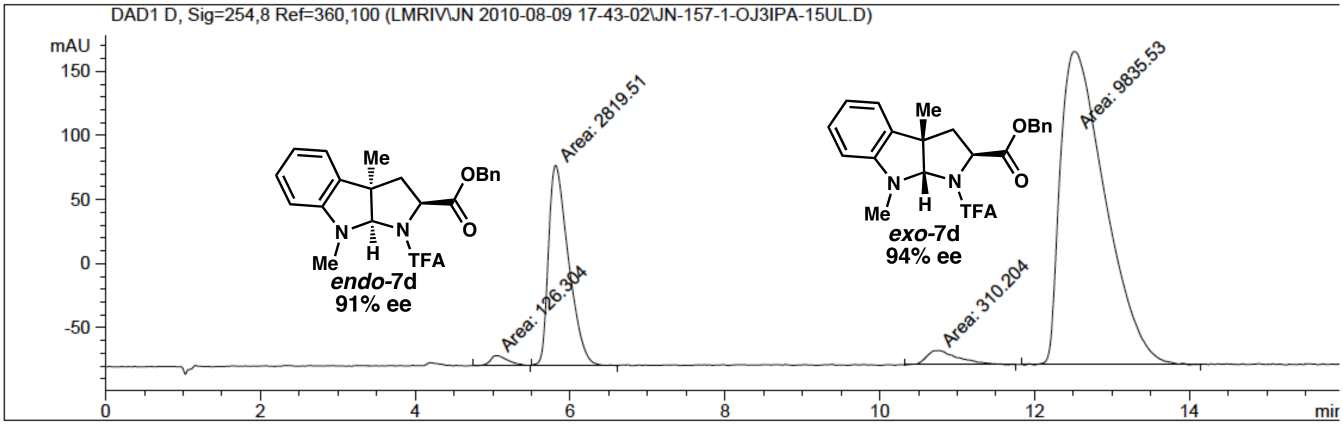
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  11.074 MM    0.4067 3172.73267  130.02379  91.0020
   2  12.646 MM    0.6145  313.70920    8.50807   8.9980
```

7d (Table 1, entry 10): racemic



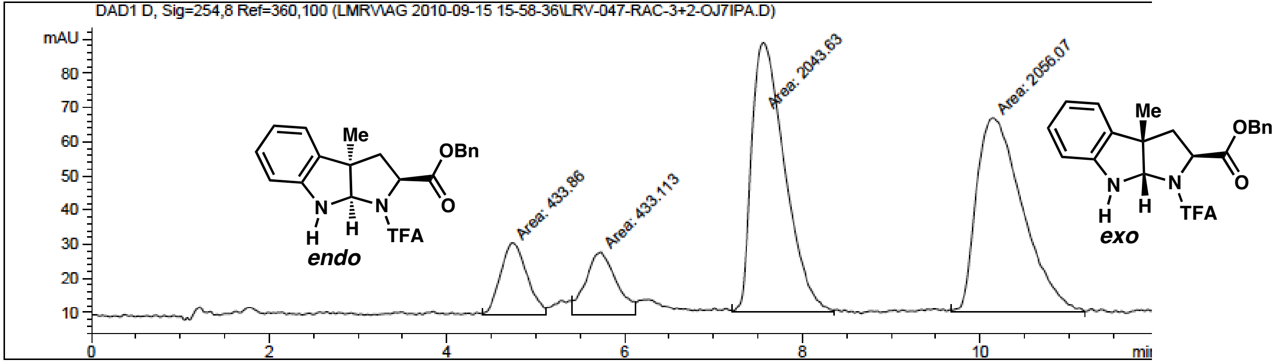
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.156 MF    0.2696  735.35803   45.45393  14.3863
   2   5.940 FM    0.2802  754.85999   44.89612  14.7679
   3  10.979 MM    0.4932 1826.01990   61.70875  35.7237
   4  13.166 MM    0.5603 1795.26794   53.40647  35.1221
```

7d (Table 1, entry 10): enantioenriched, *exo:* 94% ee, *endo*: 91% ee



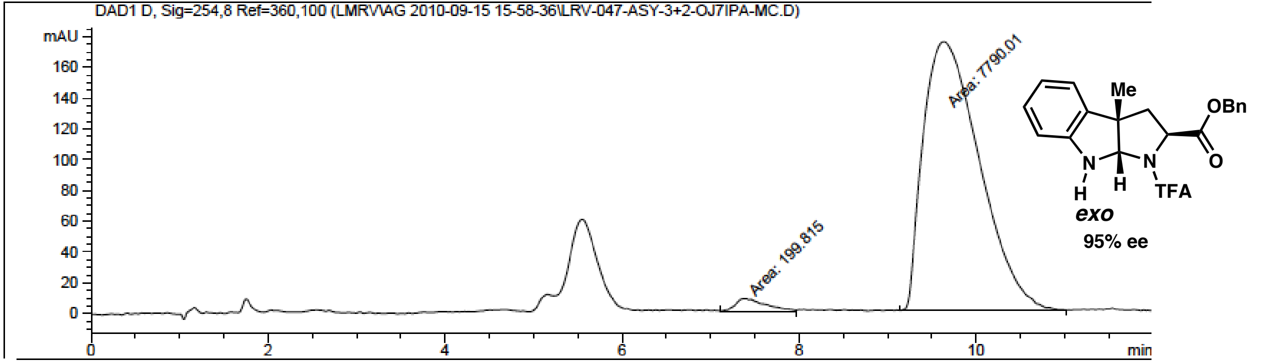
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.044 MM    0.2729  126.30366    7.71386   0.9648
   2   5.812 MM    0.3004 2819.51172  156.42670  21.5369
   3  10.749 MM    0.4705  310.20364   10.98786   2.3695
   4  12.515 MM    0.6705 9835.53320  244.48642  75.1289
```

Pyrroloindoline product from reaction with 3-methyl-1*H*-indole: racemic



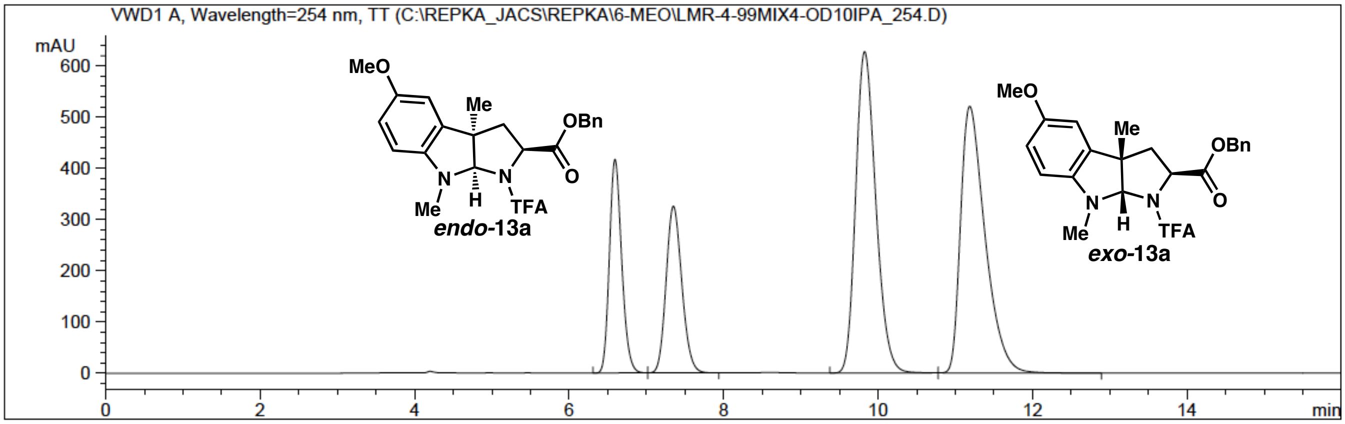
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   4.737 MM    0.3442  433.85974   21.00586   8.7354
   2   5.733 MM    0.3971  433.11276   18.17621   8.7204
   3   7.564 MM    0.4321 2043.62988   78.82232  41.1469
   4  10.149 MM    0.6038 2056.07129   56.75510  41.3974
```

Pyrroloindoline product from reaction with 3-methyl-1*H*-indole: enantioenriched, *exo*: 95% ee



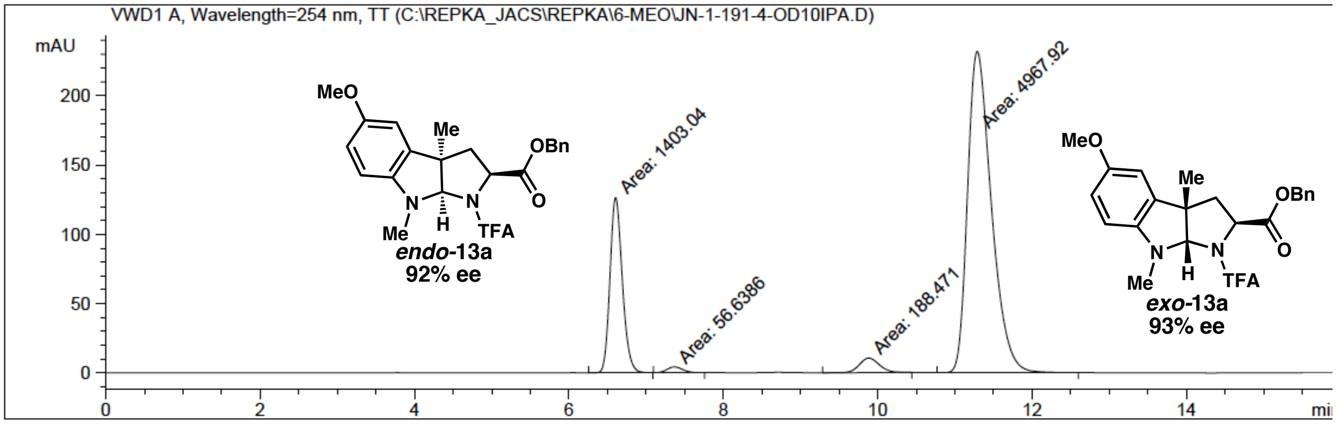
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   7.393 MM    0.4059  199.81528    8.20531   2.5009
   2   9.640 MM    0.7421 7790.00586  174.96088  97.4991
```

13a (Scheme 2): racemic



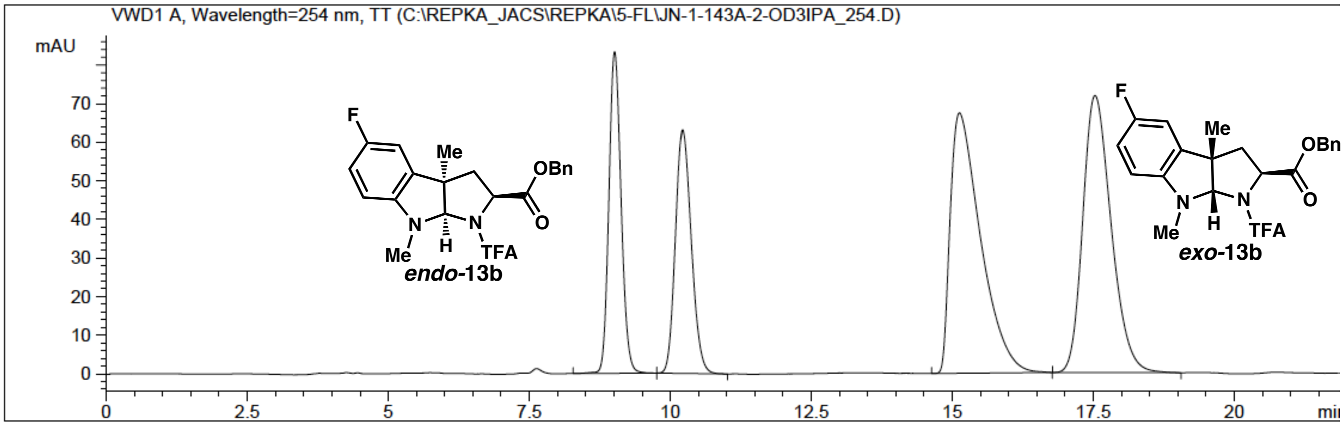
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1   6.594 BB     0.1698 4609.86621  416.95142  14.3772
   2   7.350 BB     0.2192 4610.61719  325.26569  14.3795
   3   9.826 BB     0.2823 1.13860e4   627.58807  35.5104
   4  11.187 BB     0.3325 1.14573e4   520.55212  35.7328
```

13a (Scheme 2): *exo*: 93% ee, *endo*: 92% ee



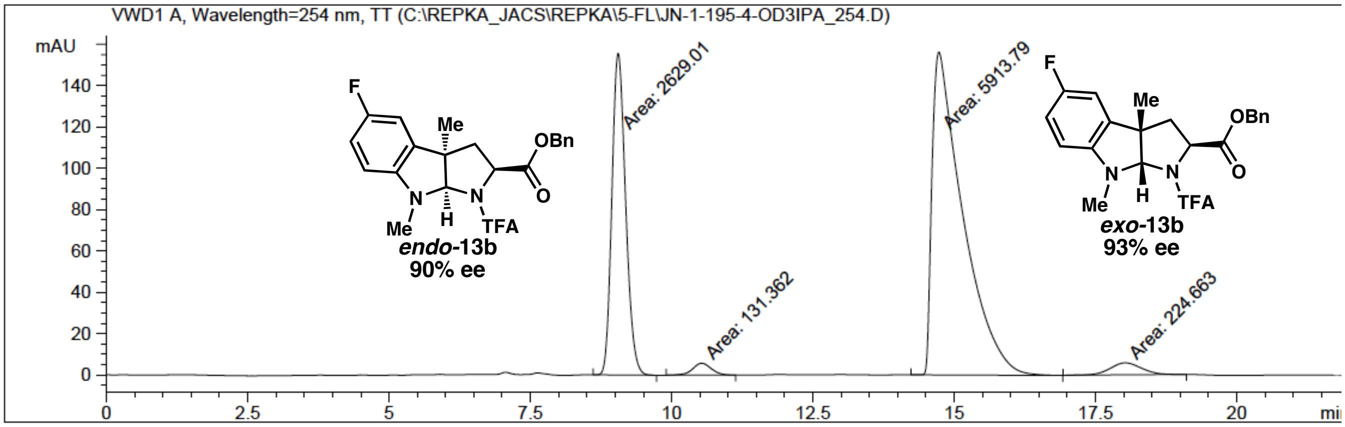
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1   6.605 MM     0.1851 1403.04370  126.31284  21.2066
   2   7.366 MM     0.2282   56.63861    4.13736   0.8561
   3   9.885 MM     0.3007  188.47099   10.44562   2.8487
   4  11.289 MM     0.3574 4967.92139  231.68799  75.0887
```

13b (Scheme 2): racemic



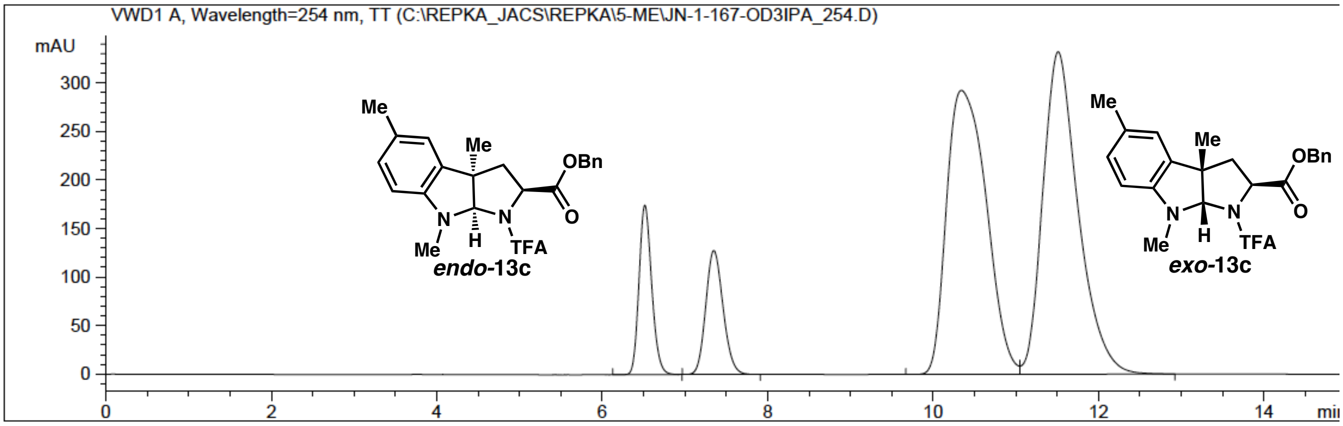
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
  1   9.013 BB    0.2330 1253.27209   83.29908  16.6472
  2  10.220 BB    0.3072 1244.32800   63.10659  16.5284
  3  15.127 BB    0.5588 2519.96948   67.46533  33.4727
  4  17.529 BB    0.5354 2510.85742   71.80063  33.3517
```

13b (Scheme 2): *exo*: 93% ee *endo*: 90% ee



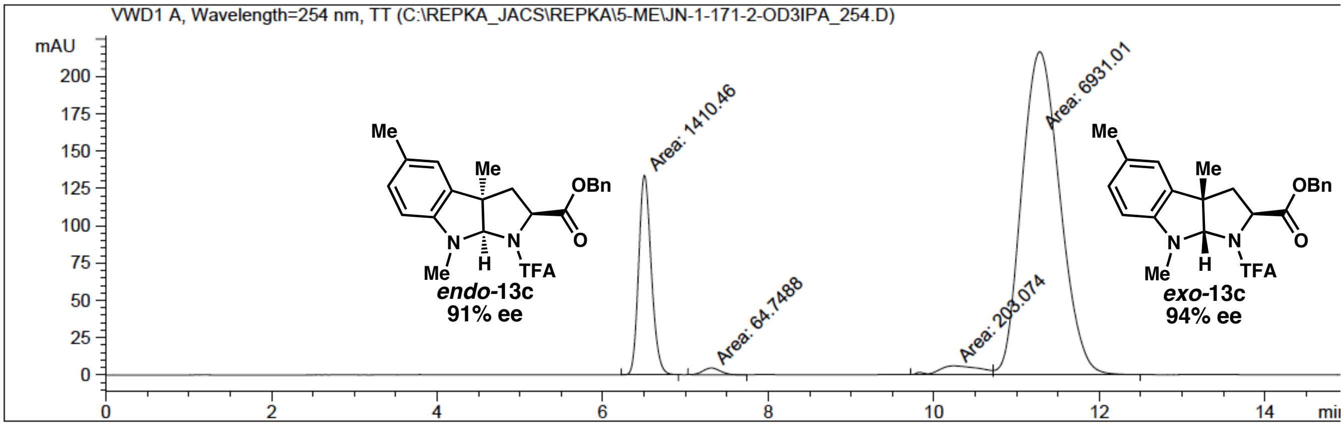
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU   ]     %
----|-------|----|-------|----------|----------|--------|
  1   9.053 MM    0.2815 2629.00732  155.65556  29.5433
  2  10.530 MM    0.3806  131.36226    5.75281   1.4762
  3  14.729 MM    0.6305 5913.78809  156.33769  66.4559
  4  18.025 MM    0.6446  224.66296    5.80853   2.5246
```

13c (Scheme 2): racemic



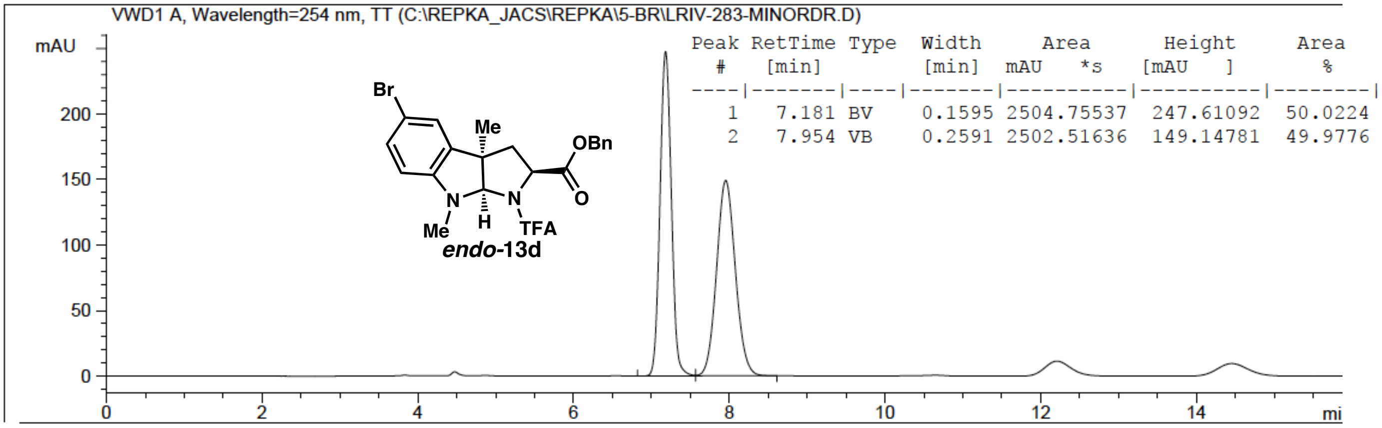
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1   6.515 BB     0.1639 1864.59338  174.59178   7.9727
   2   7.349 BB     0.2261 1861.35925  127.72897   7.9589
   3  10.343 BV     0.5481 9785.77832  292.62845  41.8426
   4  11.512 VV     0.4515 9875.41406  332.30096  42.2258
```

13c (Scheme 2): enantioenriched, *exo:* 94% ee, *endo*: 91% ee



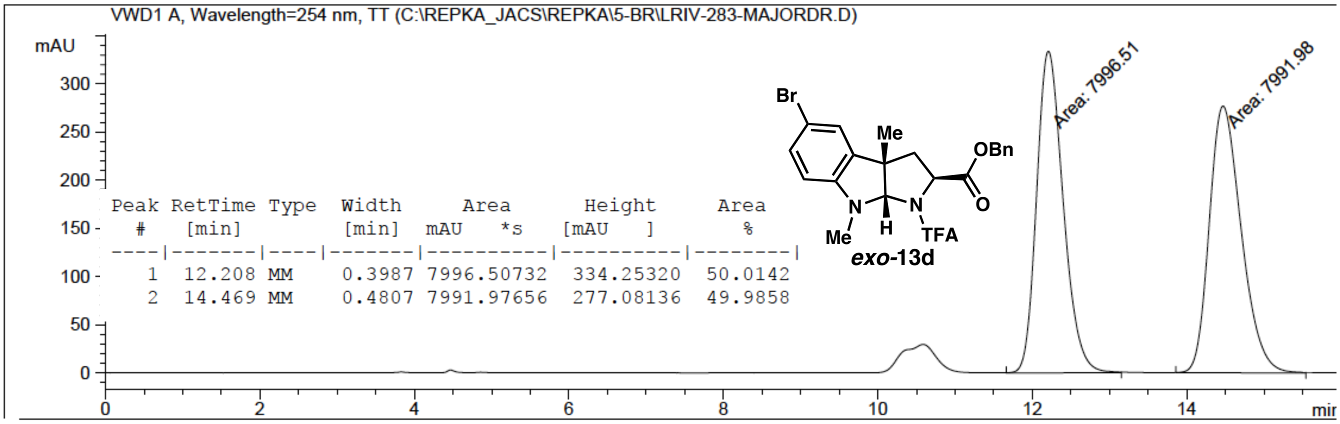
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1   6.505 MM     0.1760 1410.45825  133.56871  16.3830
   2   7.313 MM     0.2416   64.74883    4.46749   0.7521
   3  10.246 MF     0.5768  203.07445    5.86773   2.3588
   4  11.281 FM     0.5342 6931.01367  216.22461  80.5062
```

***endo*-13d (Scheme 2):** racemic



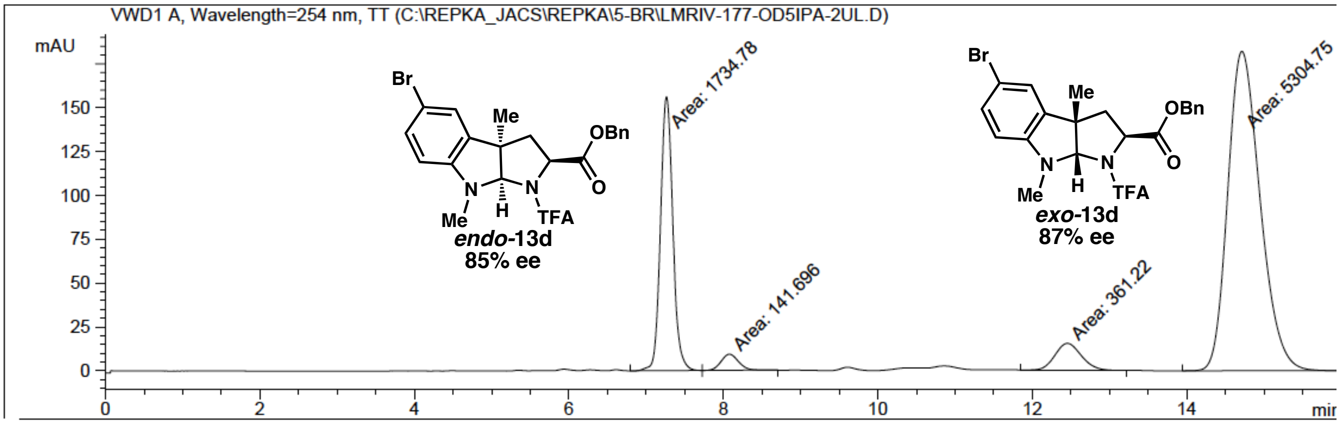
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]       %
----|-------|----|-------|----------|----------|--------|
   1   7.181 BV    0.1595 2504.75537  247.61092  50.0224
   2   7.954 VB    0.2591 2502.51636  149.14781  49.9776
```

***exo*-13d (Scheme 2):** racemic



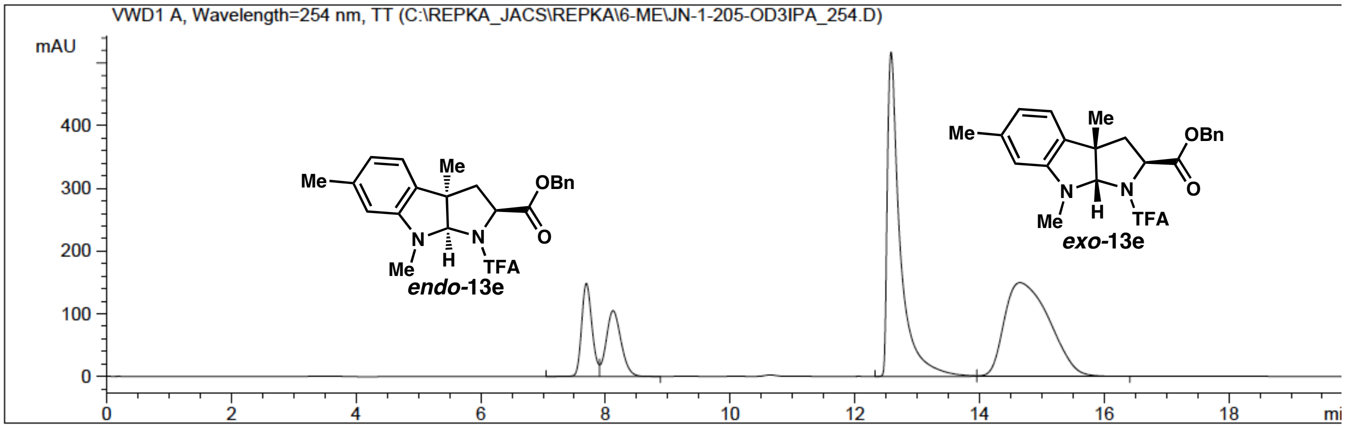
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]       %
----|-------|----|-------|----------|----------|--------|
   1  12.208 MM    0.3987 7996.50732  334.25320  50.0142
   2  14.469 MM    0.4807 7991.97656  277.08136  49.9858
```

13d (Scheme 2): *exo*: 87% ee, *endo:* 85% ee



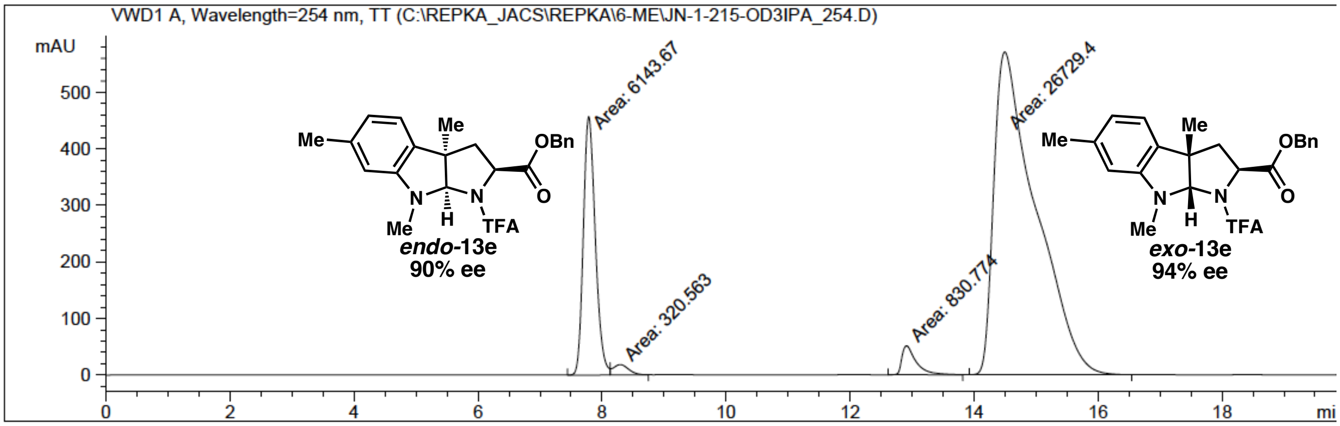
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]       %
----|-------|----|-------|----------|----------|--------|
   1   7.263 MF    0.1852 1734.78003  156.08707  23.0002
   2   8.076 FM    0.2580  141.69585    9.15505   1.8786
   3  12.454 MM    0.3947  361.21967   15.25336   4.7892
   4  14.714 MM    0.4855 5304.75488  182.11263  70.3320
```

13e (Scheme 2): racemic



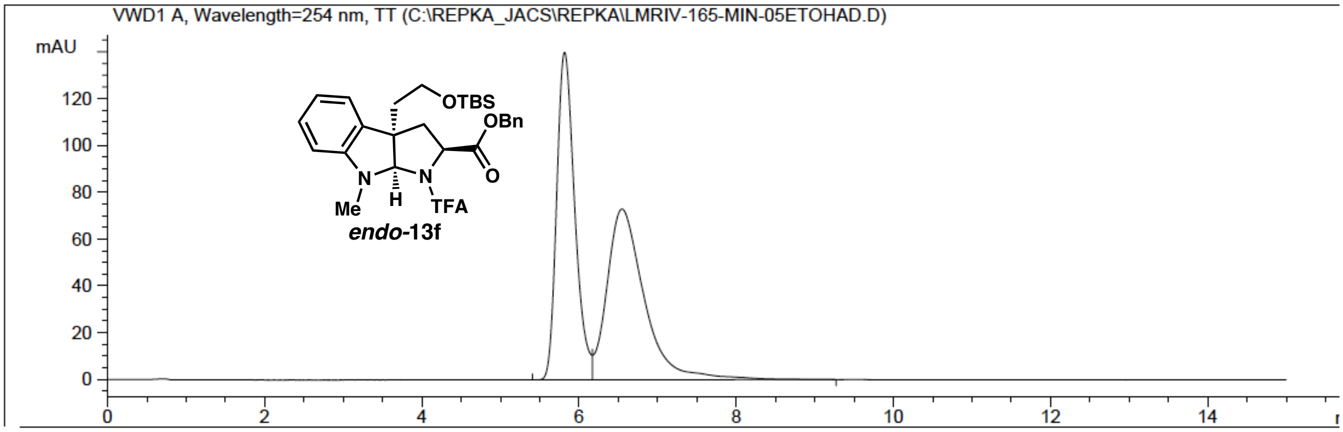
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   7.694 BV    0.1800 1738.04382  148.72224   9.4448
   2   8.122 VB    0.2549 1740.51331  105.22092   9.4582
   3  12.583 BV    0.2060 7424.35889  517.51135  40.3450
   4  14.649 VB    0.7114 7499.26904  149.61671  40.7521
```

13e (Scheme 2): *exo*: 94% ee, *endo*: 90% ee



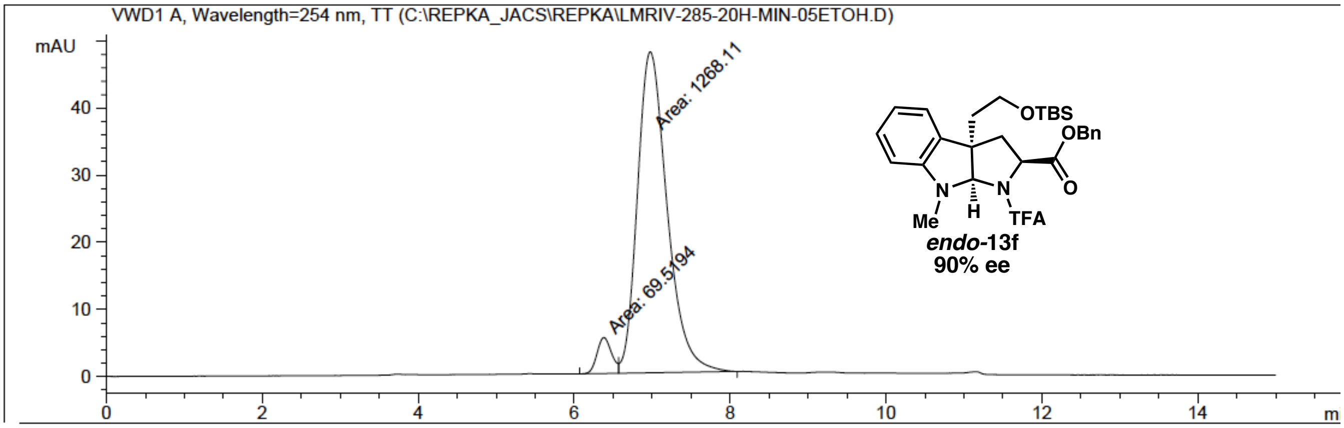
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   7.785 MF    0.2240 6143.67139  457.11594  18.0567
   2   8.294 FM    0.2911  320.56265   18.35141   0.9422
   3  12.912 MM    0.2706  830.77399   51.16518   2.4417
   4  14.496 MM    0.7807 2.67294e4  570.62366  78.5595
```

***endo*-13f (Scheme 2):** racemic



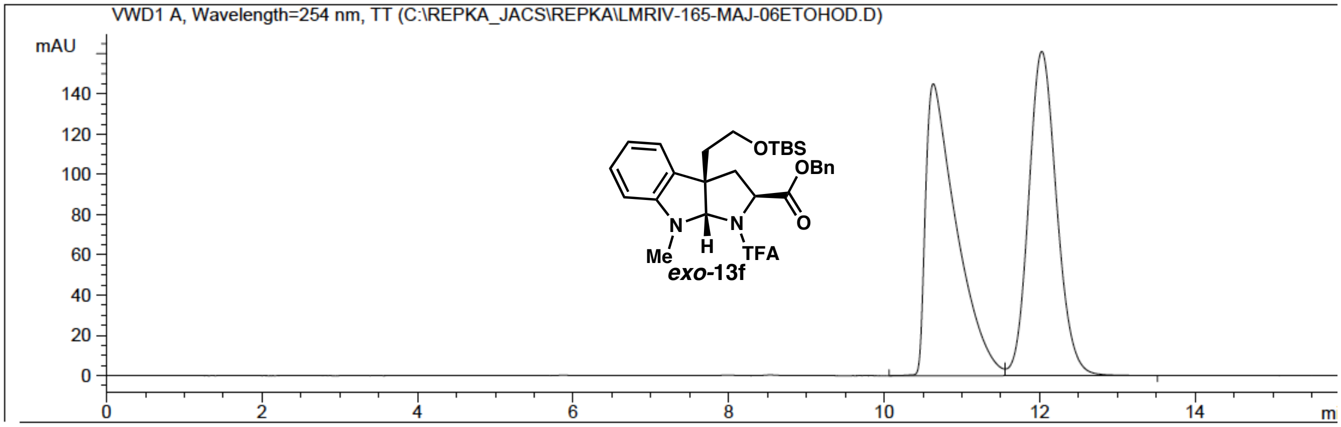
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
  1   5.815 BV    0.2467 2234.77563  139.96280  48.1102
  2   6.546 VB    0.4858 2410.33862   72.97266  51.8898
```

***endo*-13f (Scheme 2):** 90% ee



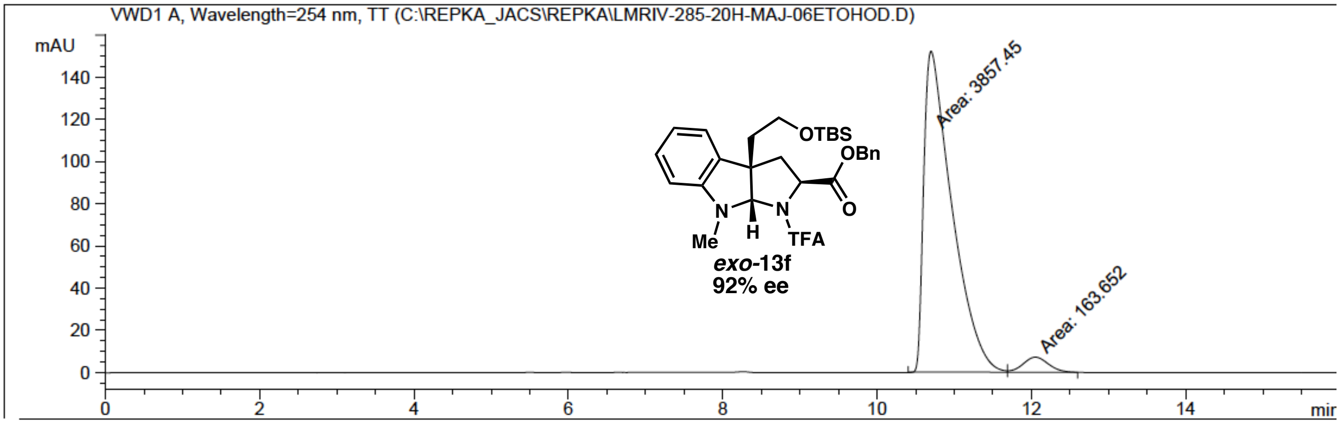
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
  1   6.380 MF    0.2166   69.51939    5.34894   5.1972
  2   6.976 FM    0.4419 1268.11157   47.82830  94.8028
```

***exo*-13f (Scheme 2):** racemic



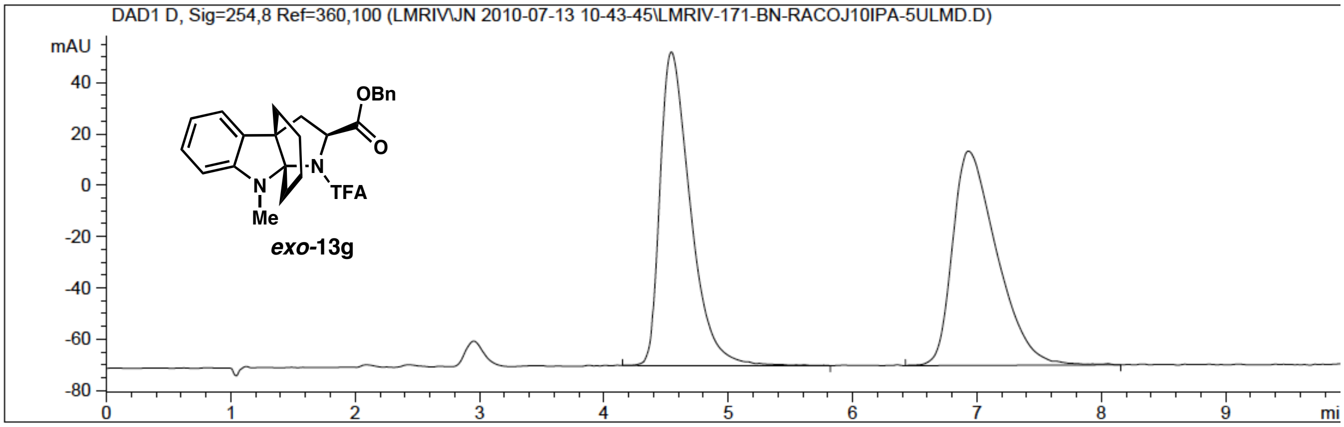
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1  10.632 BV    0.3905 3995.52930  145.07512  49.7976
   2  12.028 VB    0.3841 4028.00830  161.10678  50.2024
```

***exo*-13f (Scheme 2):** 92% ee



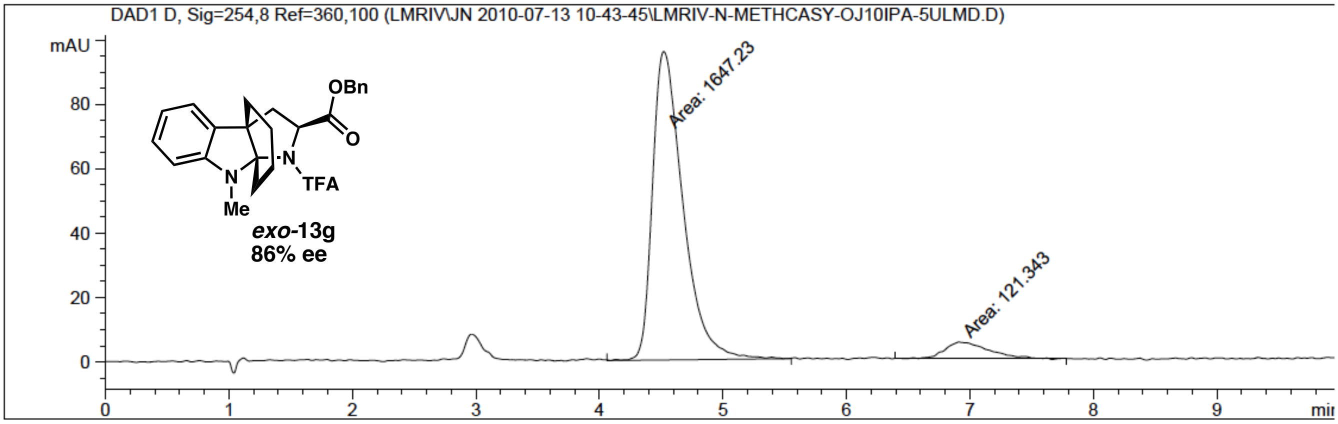
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU    *s   [mAU    ]     %
----|-------|----|-------|----------|----------|--------|
   1  10.700 MF    0.4226 3857.44580  152.13763  95.9302
   2  12.052 FM    0.3805  163.65164    7.16747   4.0698
```

13g (Scheme 2): racemic



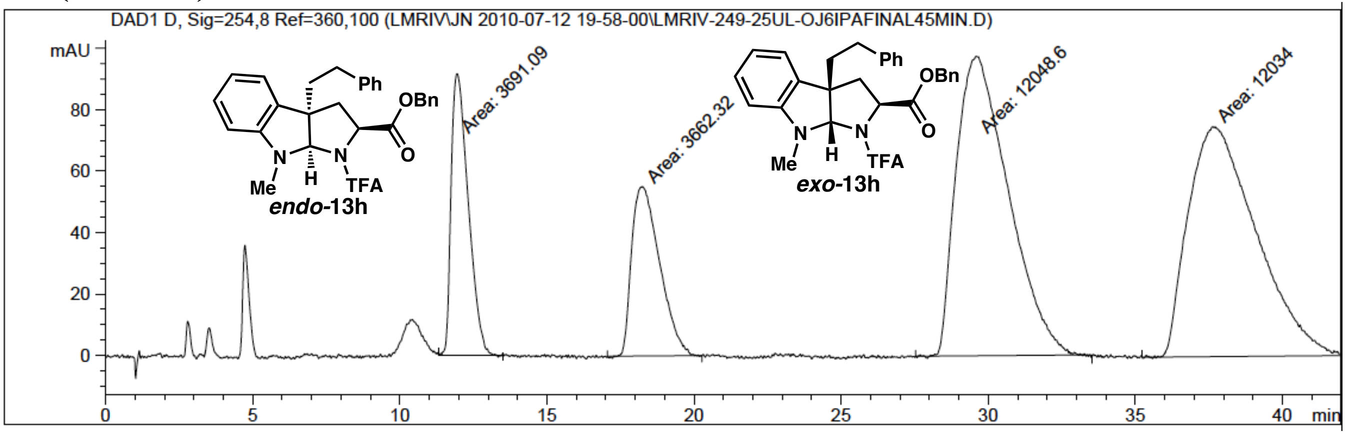
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   4.543 BB    0.2584 2077.59912  122.17298  50.0580
  2   6.933 BB    0.3736 2072.78516   83.50713  49.9420
```

13g (Scheme 2): *exo:* 86% ee



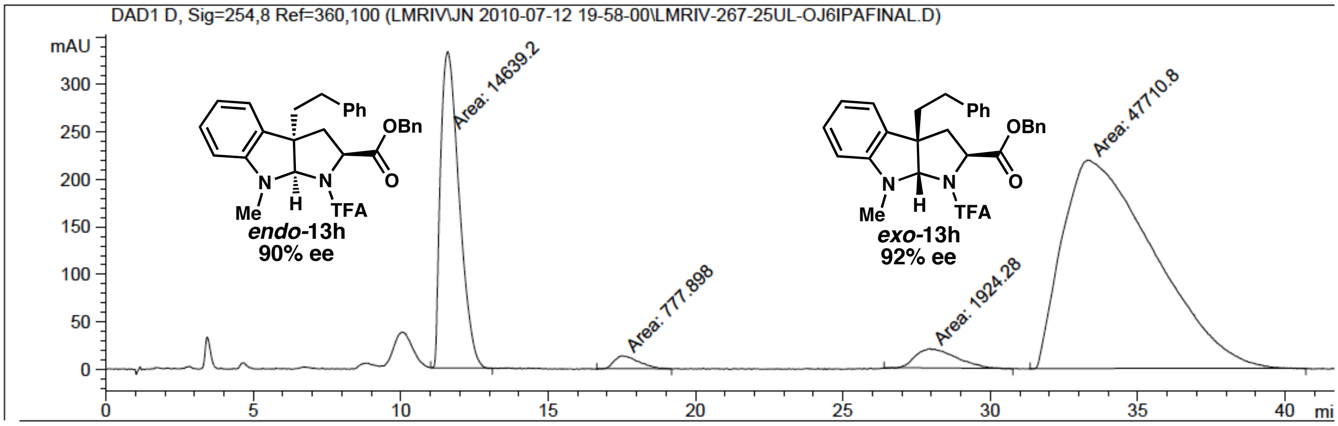
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1   4.522 MM    0.2861 1647.22534   95.95735  93.1389
  2   6.911 MM    0.3977  121.34311    5.08583   6.8611
```

13h (Scheme 2): racemic



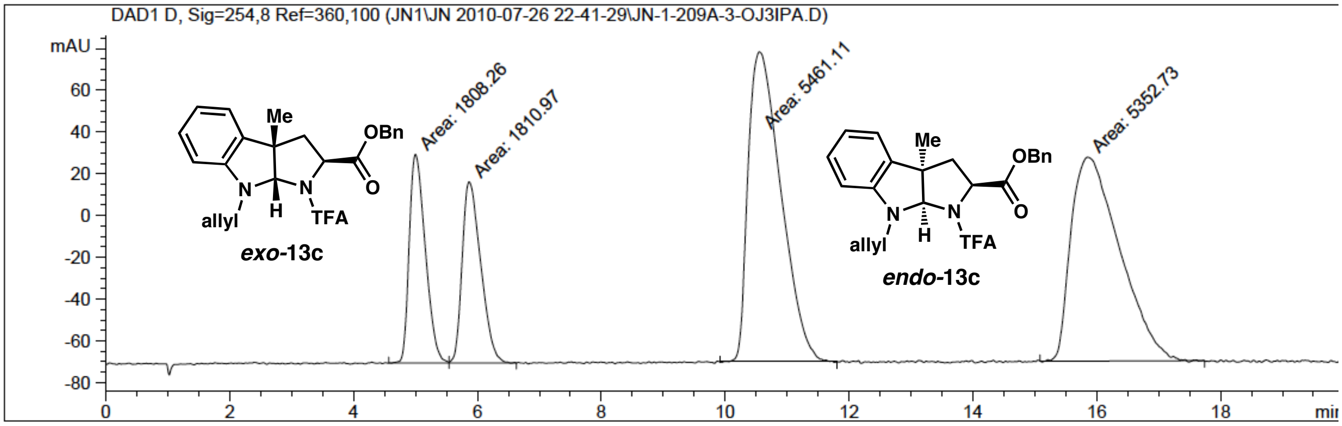
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  11.947 MM     0.6720 3691.09326   91.53949  11.7416
  2  18.252 MM     1.1062 3662.32007   55.18063  11.6501
  3  29.587 MM     2.0594 1.20486e4    97.51013  38.3273
  4  37.639 MM     2.6782 1.20340e4    74.88902  38.2810
```

13h (Scheme 2): *exo:* 92% ee, *endo*: 90% ee



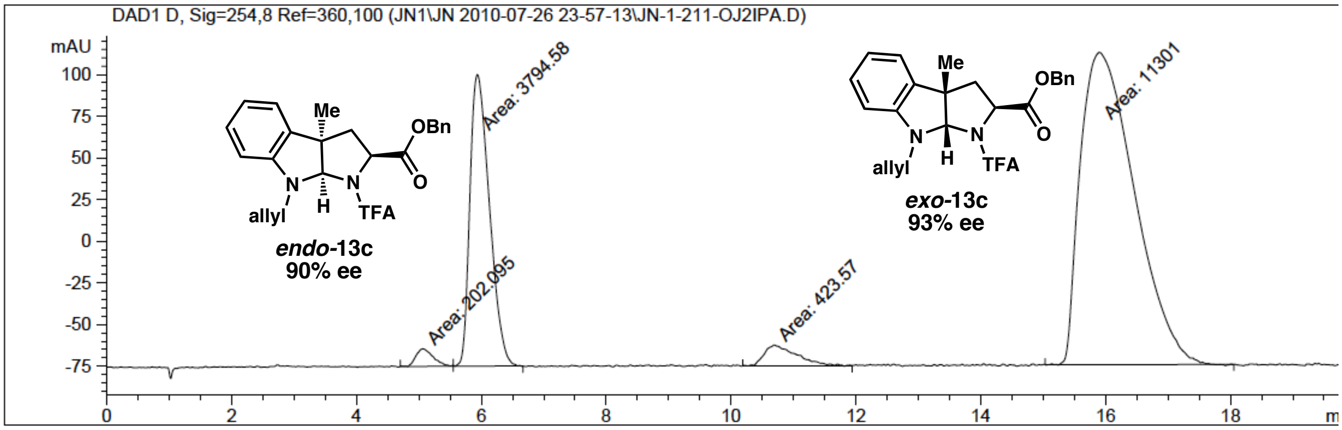
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
  1  11.596 MM     0.7322 1.46392e4  333.24432  22.5038
  2  17.511 MM     0.9481  777.89801  13.67496   1.1958
  3  27.957 MM     1.5821 1924.28345  20.27142   2.9581
  4  33.312 MM     3.6201 4.77108e4  219.65750  73.3423
```

13i (Scheme 2): racemic



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   5.000 MF    0.3012 1808.26282  100.06958  12.5286
  2   5.866 FM    0.3472 1810.96948   86.92387  12.5474
  3  10.557 MM    0.6132 5461.11230  148.42072  37.8375
  4  15.854 MM    0.9124 5352.73047   97.77415  37.0866
```

13i (Scheme 2): *exo*: 93% ee, *endo*: 90% ee

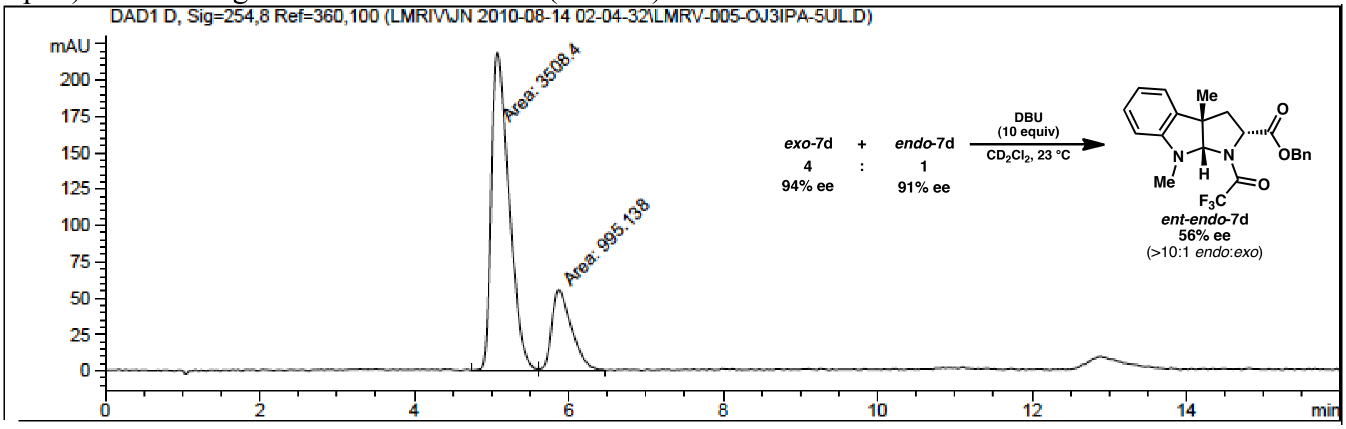


```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   5.064 MF    0.3200  202.09525   10.52417   1.2855
  2   5.937 FM    0.3612 3794.57617  175.06740  24.1367
  3  10.690 MM    0.5781  423.56973   12.21119   2.6943
  4  15.903 MM    1.0047 1.13010e4  187.47484  71.8835
```

General Procedure D. Epimerization Studies.

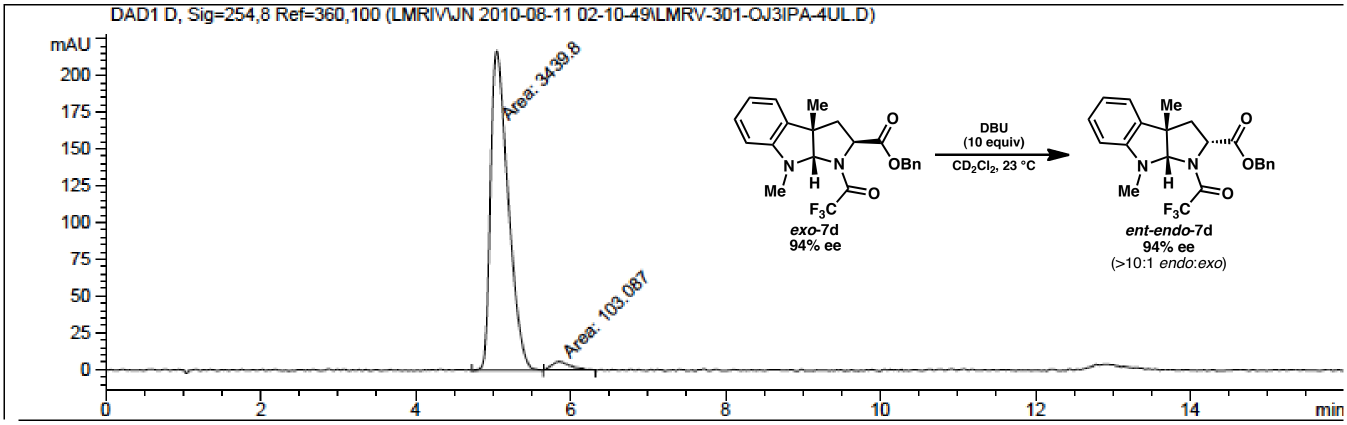
To an NMR tube was added a solution of pyrroloindoline **7d** (0.063 mmol, 1.00 equiv) in CD_2Cl_2 (0.46 mL), followed by DBU (0.63 mmol, 10.00 equiv). The reaction was monitored by ^1H NMR until the ratio of diastereomers reached an equilibrium. At this point the reaction was diluted with 3 mL $CHCl_3$ and 25 mL ethyl acetate and washed with saturated $NaHCO_{3(aq)}$ (3 x 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to give the mixture of pyrroloindoline diastereomers as a pale yellow oil with quantitative recovery of material.

Experiment 1: Treatment of a 4:1 mixture of ***exo*-7d** (94% ee) + ***endo*-7d** (91% ee) with DBU (10 equiv) for 65 h to give >10:1 ***ent-endo*-7d** (56% ee)



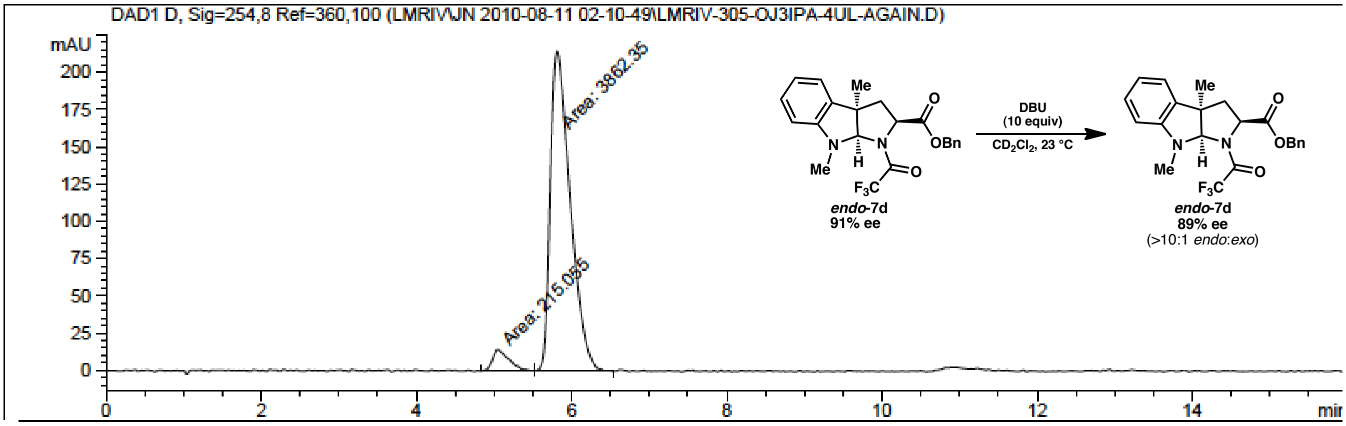
```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   5.078 MM    0.2670 3508.40381  218.96385  77.9032
   2   5.872 MM    0.2984  995.13763   55.57482  22.0968
```

Experiment 2: Treatment of diastereomerically pure ***exo*-7d** (94% ee) with DBU (10 equiv) for 96 h to give >10:1 ***ent-endo-7d*** (94% ee).



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   5.050 MM    0.2637 3439.80371  217.42592  97.0903
   2   5.849 MM    0.2887  103.08688    5.95159   2.9097
```

Experiment 3: Treatment of diastereomerically pure ***endo*-7d** (91% ee) with DBU (10 equiv) for 30 h to return ***endo*-7d** (89% ee).



```
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   5.053 MM    0.2501  215.05467   14.33310   5.2743
   2   5.814 MM    0.2994 3862.34961  215.01805  94.7257
```

Procedure E. Resubjection of pure exo and endo pyrroloindolines to reaction conditions.

To an NMR tube was added a solution of pure pyrroloindoline exo-**7d** (0.073 mmol, 1.00 equiv, 94% ee) in CD_2Cl_2 (297 μL), followed by (*R*)-BINOL (from a 0.0675 M solution in CD_2Cl_2, 0.015 mmol, 0.20 equiv) and $SnCl_4$ (from a 0.72 M solution in CD_2Cl_2, 0.088 mmol, 1.2 equiv). After 4 h at room temperature, the solution was quenched according to general procedure C. The same experiment was performed with pure endo-**7d** (91% ee), except at a concentration of 0.065 M. In both cases, no epimerization or erosion of ee was observed.