Supporting Information

Organocatalytic One Pot Asymmetric Synthesis of 4*H*,5*H*-Pyrano[2,3-c]pyrazoles

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Contents

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1. General Methods

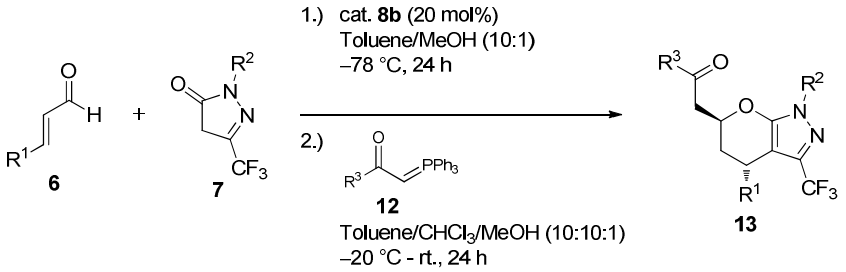
- **Preparative column chromatography**: Merck silica gel 60, particle size 0.040-0.063 mm (230-240 mesh, flash).
- **Analytical TLC:** SIL G-25 UV254 from MACHEREY&NAGEL. Visualization of the developed TLC plates was performed with ultraviolet irradiation (254 nm) or by staining with basic potassium permanganate solution.
- **Optical rotation** values were measured on a Perkin-Elmer 241 polarimeter.
- **Microanalyses** were performed with a Vario EL element analyzer.
- **Mass spectra** were acquired on a Finnigan SSQ7000 (EI/CI) spectrometer and high resolution mass spectra on a Finnigan MAT 95 (EI/CI) or on a ThermoFisher Scientific LTQOrbitrap XL (ESI). All signals over 10% relative intensity are listed.
- **IR spectra** were taken on a Perkin-Elmer FT-IR Spectrum 100 using a Diamant/KRS5 ATR.
- **^{1}H-, ^{13}C- and ^{19}F-NMR** spectra were recorded at ambient temperature on Varian Mercury 300, VNMRS 600 and Inova 400 instruments with tetramethylsilane as an internal standard.
- **Analytical HPLC** was performed on a Hewlett-Packard 1100 Series instrument using chiral stationary phases (Daicel AD, Daicel IA, Daicel OD).

2. Materials

- Trifluoromethylpyrazolones **7a** and **7b** were purchased from Fluorochem and ABCR and were used as received.
- Catalysts **10-11** were purchased from Sigma Aldrich and were used as received.
- Aldehydes **6a-f** were purchased from Sigma Aldrich, distilled and stored in the fridge previous to use.
- Aldehydes **6g**,[1] **6h**,[2] **6i**[3] were synthesized according to the literature procedures.
- Organocatalysts **8a-c**[4] and **8d**[5] were prepared according to the literature procedure.
- The **racemic products** were prepared using morpholine instead of **8b** as the catalyst and chloroform as sole solvent.[6]
- $CHCl_3$ (spectroscopy grade) was purchased from a commercial source and used as received. All other solvents were of technical grade and dried using common purification techniques.

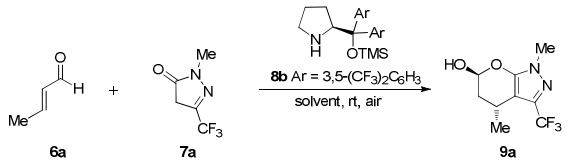
(1) Bulger, P. G.; Moloney, M. G.; Trippier, P. C. *Org. Biomol. Chem.* **2003,** *1,* 3726-3737.
(2) Boone, M. A.; McDonald, F. E.; Lichter, J.; Lutz, S.; Cao, R.; Hardcastle, K. I. *Org. Lett.* **2009,** *11,* 851.
(3) Belardi, J. K.; Curtis, L. A.; Clareen, S. S.; Shimp, H. L.; Leimkuhler, C. E.; Simonowicz, N. L; Casillas, E. *Synth. Commun.* **2005,** *35,* 1633-1640.
(4) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem*. **2005,** *117,* 804–807; *Angew. Chem. Int. Ed. Engl.* **2005,** *44,* 794.
(5) Sparr, C. Tanzer, E.-M.; Bachmann, J.; Gilmour, R. *Synthesis* **2010,** 1394–1397.
(6) Morpholine led to complex mixtures of products, when a toluene/methanol mixture was used as solvent.

3. General Procedure for the Asymmetric Michael/Wittig/oxa-Michael One Pot Reaction



A solution of trifluoromethyl pyrazolone **7** (1.0 mmol, 1.0 equiv.) and catalyst **8b** (0.20 mmol, 0.2 equiv.) in toluene/methanol 10:1 (3 mL) was cooled to −78 °C. Subsequently, a solution of the aldehyde **6** was added dropwise. After the mixture was stirred for 24 h chloroform (4 mL) was added and the temperature was raised to -20 °C. Finally, phosphorus ylide **12** was added in one portion and the reaction was continued stirring for 24 h while the reaction was allowed to reach room temperature. The crude product was transferred on a small amount of silica and then directly purified by column chromatography gaining the products **13** as an inseparable mixture of diastereomers.

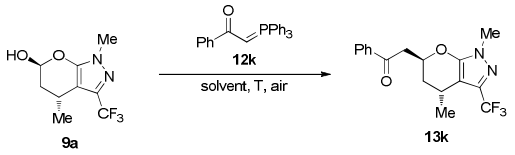
4. Solvent Screening of the Asymmetric Michael/Acetalization Cascade Reaction[a]



entry	cat. (mol%)	solvent	yield[b] (%)	er[c]
1	**8b** (2.5)	$CHCl_3$	76	83:17
2	**8b** (2.5)	CH_2Cl_2	82	83:17
3	**8b** (2.5)	Toluene	94	83:17
4	**8b** (2.5)	THF	37	76:24
5	**8b** (2.5)	CH_3CN	32	71:29
6	**8b** (2.5)	EtOAc	41	71:29
7	**8b** (2.5)	MeOH	34	66:34
8	**8b** (2.5)	DMSO	37	70:30
9	**8b** (2.5)	1,4-Dioxane	44	76:24

[a] Reaction conditions: **6a** (1.0 mmol), **7a** (1.0 mmol), solvent (4.0 mL). [b] Yields of **9a** were determined via 1H NMR spectroscopy using 4,4'-di-tert-butylbiphenyl (DTBP) as internal standard; sum of isomers. [c] Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase after converting **9a** to **13k**.

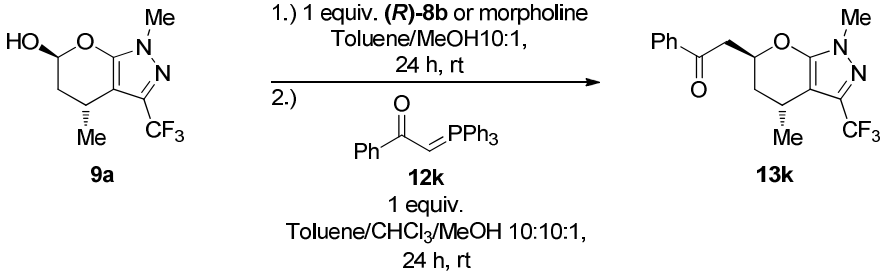
5. Optimization of the Ring opening/Wittig/oxa-Michael Cascade[a]



entry	solvent	T / °C	t / h	yield[b] (%)	dr[c]
1	$CDCl_3$	rt	24	76	73:27
2	EtOH	rt	24	75	71:29
3	Acetone	rt	24	78	77:23
4	CH_2Cl_2	rt	24	85	76:24
5	DMSO	rt	24	62	74:26
6	THF	rt	24	65	78:22
7	Toluene	rt	24	86	71:29
8	Toluene	reflux	2	n.d.	70:30
9	Toluene/MeOH10:1	rt	9	67	72:28

[a] Reaction conditions: **9a** (1.0 mmol), **12k** (1.0 mmol), solvent (8.0 mL). [b] Yields of isolated **13k**; sum of diastereomers. [c] Diastereomeric ratio was determined by HPLC analysis or 1H NMR spectroscopy. n.d. = not determined.

6. Epimerization/Decomposition Experiment of Compound ***9a***

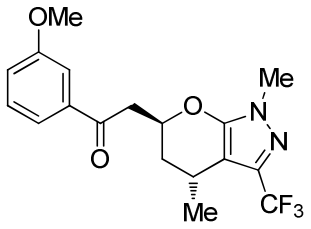


A solution of acetal **9a** (0.25 mmol) in toluene/methanol 10:1 (1 mL) was treated with **(*R*)-8b** (0.25 mmol) or morpholine (0.25 mmol) and stirred at ambient temperature for 24 h. Subsequently, chloroform (1 mL) and the Wittig reagent **12k** (0.25 mmol) were added while the reaction mixture was stirred for additional 24 h. Finally, compounds **13k** was directly purified by column chromatography (Et_2O/n-pentane 1:1) yielding the corresponding product as a colorless oil.

entry	catalyst	yield[a] (%)	dr[b]	er[b] (*trans*)	er[b] (*cis*)
1	none	76	71:29	89:11	88:12
2	**(*R*)-8b**	25	72:28	75:25	71:29
3	morpholine	38	71:29	89:11	88:12

[a] Yields of isolated **13k**; sum of diastereomers. [b] The diastereomeric and enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase.

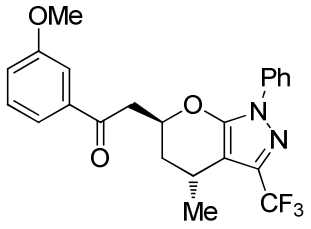
7. Analytical data



13a

2-((4*R*,6*S*)-1,4-Dimethyl-3-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)-1-(3-methoxyphenyl)ethanone (13a) was purified by flash chromatography (*n*-pentane/Et_2O 1:1) yielding an inseparable mixture of diastereomers of **13a** as a colorless oil. For analytical purposes a sample of the *trans*-diastereomer was obtained via preparative HPLC (LiChrosorb Si 60 7µm 250x25 mm, *n*-pentane/diethylether 6:4, 18 mL/min), t_R = 18.58 min (*trans*), t_R ~ 19.00 min (*cis*).[7] The *ee* (*trans* 92%, *cis* 92%) was determined by HPLC on a chiral stationary phase (Daicel AD, *n*-heptane/*i*PrOH 95:5, 0.7 mL/min), t_R = 15.93 min (*trans*, major), 21.49 min (*trans*, minor), t_R = 23.53 min (*cis*, major), 25.77 min (*cis*, minor). R_f = 0.21 (**13a**), (*n*-pentane/Et_2O 2:1);

trans-Diastereomer: $[\alpha]_D^{25}$ = +19.2 (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{24}$ = +62.8 (*c* = 1.0, $CHCl_3$); IR (ATR): 3219, 2953, 1685, 1583, 1489, 1433, 1354, 1259, 1165, 1117, 1030, 892, 851, 776, 725 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.9 Hz, 3H), 1.85 (dt, *J* = 14.4 Hz, 2.5Hz, 1H), 1.90 (ddd, *J* = 15.9 Hz, 10.4 Hz, 5.5 Hz, 1H), 3.00 – 3.07 (m, 1H), 3.20 (dd, *J* = 16.8 Hz, 5.9 Hz, 1H), 3.59 (s, 3H), 3.60 (dd, *J* = 16.8 Hz, 6.4 Hz, 1H), 3.87 (s, 3H), 4.93 - 4.99 (m, 1H), 7.16 (ddd, *J* = 8.4 Hz, 2.5 Hz, 1.0 Hz, 1H), 7.41 (t, *J* = 8.2 Hz, 1H), 7.52 (dd, *J* = 2.5 Hz, 1.5 Hz, 1H), 7.56 (dt, *J* = 7.9 Hz, 1.0 Hz, 1H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 22.2, 23.0, 33.8, 35.1, 43.3, 55.4, 72.7, 100.4, 112.4, 119.9, 120.7, 121.6 (q, *J* = 269.6 Hz, CF_3) 129.7, 136.9 (q, *J* = 36.9 Hz), 138.0, 150.0, 159.9, 196.2 ppm; ^{19}F NMR (564 MHz, $CDCl_3$): δ = 61.9 ppm; MS (EI, 75 eV): *m/z* 368 (M^+, 26%), 135 (100), 107 (14); HRMS (ESI): *m/z* calcd for $C_{18}H_{20}F_3N_2O_3^+$: 369.1421 [M+H^+]; found: 369.1409.



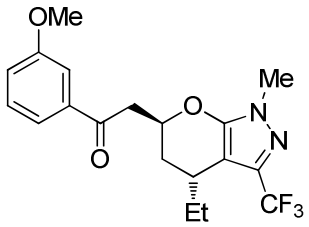
13b

1-(3-Methoxyphenyl)-2-((4*R*,6*S*)-4-methyl-1-phenyl-3-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)ethanone (13b) was purified by flash chromatography (*n*-pentane/Et_2O 2:1) yielding an inseparable mixture of diastereomers of **13b** as a colorless oil. For analytical purposes a sample of the *trans*-diastereomer was obtained via preparative HPLC (LiChrosorb Si 60 7µm 250x25 mm,

(7) The c*is*-diastereomer was only observed as a shoulder of the major peak and could not be completely separated.

n-pentane/diethylether 6:4, 18 mL/min), t_R = 12.14 min (*trans*), t_R ~ 12.70 min (*cis*).[7] The *ee* (*trans* 87%, *cis* 85%) was determined by HPLC on a chiral stationary phase (Daicel IA, *n*-heptane/*i*PrOH 9:1, 1.0 mL/min), t_R = 6.33 min (*trans*, major), 7.01 min (*cis*, minor), t_R = 8.11 min (*trans*, minor), 9.59 min (*cis*, major). R_f = 0.48 (**13b**), (*n*-pentane/Et_2O 2:1);

trans-Diastereomer: $[\alpha]_D^{26}$ = +1.8 (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{26}$ = –31.9 (*c* = 1.0, $CHCl_3$); IR (ATR): 3072, 2966, 2875, 1951, 1875, 1686, 1593, 1517, 1481, 1397, 1350, 1261, 1131, 1023, 874, 840, 761, 690, 634, 565, 505 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.9 Hz, 3H), 1.90 (dt, *J* = 13.4 Hz, 2.5Hz, 1H), 1.97 (ddd, *J* = 15.9 Hz, 10.4 Hz, 5.5 Hz, 1H), 3.05 – 3.15 (m, 1H), 3.22 (dd, *J* = 16.4 Hz, 6.0 Hz, 1H), 3.61 (dd, *J* = 16.8 Hz, 6.9 Hz, 1H), 3.83 (s, 3H), 4.97 - 5.05 (m, 1H), 7.14 (dd, *J* = 8.4 Hz, 1.9 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 8.4 Hz, 2H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.50 (dd, *J* = 2.5 Hz, 1.5 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.65 (dd, *J* = 8.9 Hz, 1.5 Hz, 2H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 22.3, 23.1, 34.8, 43.3, 55.4. 73.5, 101.7, 112.4, 120.0, 120.8, 121.0, 121.5 (q, *J* = 269.6 Hz, CF_3), 126.7, 128.9, 129.7, 137.7, 138.0, 138.7 (q, *J* = 36.9 Hz), 149.9, 159.9, 196.4 ppm; ^{19}F NMR (564 MHz, $CDCl_3$): δ = 62.1 ppm; MS (CI, 100 eV): *m/z* 432 ($M+H^+$, 15%), 255 (17), 205 (15), 204 (100), 177 (84); HRMS (ESI): *m/z* calcd for $C_{23}H_{22}F_3N_2O_3^+$: 431.1577 [$M+H^+$]; found: 431.1577.



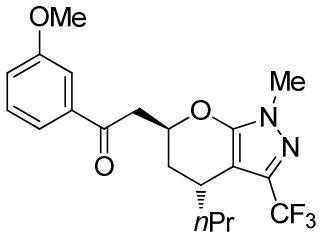
13c

2-((4*R*,6*S*)-4-Ethyl-1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)-1-(3-methoxyphenyl)ethanone (13c) was purified by flash chromatography (*n*-pentane/Et_2O 1:1) yielding inseparable mixture of diastereomers of **13c** as a colorless oil. For analytical purposes a sample of the *trans*-diastereomer was obtained via preparative HPLC (LiChrosorb Si 60 7µm 250x25 mm, *n*-pentane/diethylether 6:4, 18 mL/min), t_R = 17.79 min (*trans*), t_R ~ 17.00 min (*cis*).[8] The *ee* (*trans* 94%, *cis* 95%) was determined by HPLC on a chiral stationary phase (Daicel AD, *n*-heptane/EtOH 97:3, 0.3 mL/min), t_R = 34.91 min (*trans*, major), 49.73 min (*cis*, minor), t_R = 51.95 min (*trans*, minor), 56.84 min (*cis*, major). R_f = 0.21 (**13c**), (*n*-pentane/Et_2O 2:1);

trans-Diastereomer: $[\alpha]_D^{25}$ = +9.8 (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{25}$ = +43.9 (*c* = 1.0, $CHCl_3$); IR (ATR): 2956, 1685, 1585, 1548, 1491, 1429, 1354, 1256, 1161, 1116, 1040, 991, 887, 785, 730, 684 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.4 Hz, 3H), 1.45 - 1.55 (m, 1H), 1.74 (ddd, *J* = 16.4 Hz, 10.9 Hz, 5.5 Hz, 1H), 1.80 – 1.86 (m, 1H), 2.09 (dt, *J* = 14.4 Hz, 2.0 Hz, 1H), 2.75 – 2.80 (m, 1H), 3.22 (dd, *J* = 16.8 Hz, 6.0 Hz, 1H), 3.59 (s, 3H), 3.60 (dd, *J* = 16.8 Hz, 6.4 Hz, 1H), 3.88 (s, 3H), 4.89 -4.95 (m, 1H), 7.16 (dd, *J* = 7.9 Hz, 2.5 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.52 (t, *J* = 2.0 Hz, 1H), 7.57 (d, *J* = 7.4 Hz, 1H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 11.6, 28.7, 30.0, 30,9, 33.8, 43.5, 55.5, 72.9, 99.8, 112.4, 120.0, 120.7, 121.8 (q, *J* = 268.3 Hz, CF_3), 129.7, 137.1 (q, *J* = 38.2 Hz), 138.1, 150.1, 160.0, 196.3 ppm; ^{19}F NMR (564 MHz, $CDCl_3$): δ = 61.7

(8) The c*is*-diastereomer was only observed as a shoulder of the major peak and could not be completely separated.

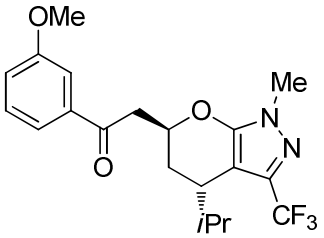
ppm; MS (EI, 75 eV): *m/z* 383 (M^+, 56%), 203 (41), 135 (100), 107 (14); HRMS (ESI): *m/z* calcd for $C_{19}H_{22}F_3N_2O_3^+$: 383.1577 [M+H^+]; found: 383.1577.



13d

1-(3-Methoxyphenyl)-2-((4*R*,6*S*)-1-methyl-4-propyl-3-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)ethanone (13d) was purified by flash chromatography (*n*-pentane/Et_2O 1:1) yielding an inseparable mixture of diastereomers of **13d** as a colorless oil. For analytical purposes a sample of the *trans*-diastereomer was obtained via preparative HPLC (LiChrosorb Si 60 7µm 250x25 mm, *n*-pentane/diethylether 6:4, 18 mL/min), t_R = 17.16 min (*trans*), t_R ~ 17.00 min (*cis*).[9] The *ee* (*trans* 95%, *cis* >99%) was determined by HPLC on a chiral stationary phase (Daicel AD, *n*-heptane/*i*PrOH 95:5, 0.7 mL/min), t_R = 13.14 min (*trans*, major), 16.74 min (*trans*, minor), t_R = 18.38 min (*cis*, major), 30.88 min (*cis*, minor). R_f = 0.21 (**13d**), (*n*-pentane/Et_2O 2:1);

trans-Diastereomer: $[\alpha]_D^{24}$ = +8.5 (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{24}$ = +37.9 (*c* = 1.0, $CHCl_3$); IR (ATR): 2930, 2869, 2322, 2110, 1740, 1685, 1585, 1546, 1492, 1429, 1396, 1354, 1257, 1162, 1118, 1037, 991, 930, 854, 783, 730, 683 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 6.9 Hz, 3H), 1.33 – 1.40 (m, 1H), 1.46 – 1.55 (m, 2H), 1.65 – 1.80 (m, 2H), 2.06 (dt, *J* = 14.4 Hz, 2.0 Hz, 1H), 2.85 – 2.90 (m, 1H), 3.21 (dd, *J* = 16.8 Hz, 6.4 Hz, 1H), 3.59 (s, 3H), 3.61 (dd, *J* = 16.8 Hz, 6.4 Hz, 1H), 3.88 (s, 3H), 4.89 – 4.95 (m, 1H), 7.16 (dd, *J* = 7.4 Hz, 1.5 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.52 (t, *J* = 2.0 Hz, 1H), 7.57 (dt, *J* = 8.4 Hz, 1.0 Hz, 1H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 13.9, 20.1, 28.0, 31.4, 33.8, 38.0, 43.5, 55.5, 72.8, 99.9, 112.4, 120.0, 120.7, 121.7 (q, *J* = 269.6 Hz, CF_3), 129.7, 136.9 (q, *J* = 36.9 Hz), 138.1, 150.1, 160.0, 196.4 ppm; ^{19}F NMR (564 MHz, $CDCl_3$): δ = 61.6 ppm; MS (CI, 100 eV): *m/z* 397 ($M+H^+$, 100%), 396 (11), 377 (55), 61 (16); elemental analysis calcd (%) for $C_{20}H_{23}F_3N_2O_3$: C 60.60, H 5.85, N 7.07; found: C 60.64, H 6.18, N 7.33.



13e

2-((4*R*,6*S*)-4-Isopropyl-1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)-1-(3-methoxyphenyl)ethanone (13e) was purified by flash chromatography (*n*-pentane/Et_2O 1:1) yielding an inseparable mixture of diastereomers of **13e** as a colorless oil. For analytical purposes samples of the *trans*-

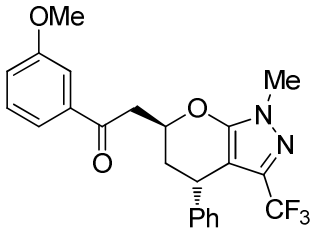
(9) The c*is*-diastereomer was only observed as a shoulder of the major peak and could not be completely separated.

diastereomer and *cis*-diastereomers were obtained via preparative HPLC (LiChrosorb Si 60 7µm 250x25 mm, *n*-pentane/diethylether 6:4, 18 mL/min), t_R = 17.10 min (*trans*), t_R = 16.30 min (*cis*). The *ee* (*trans* 93%, *cis* 95%) was determined by HPLC on a chiral stationary phase (Daicel AD, *n*-heptane/*i*PrOH 95:5, 1.0 mL/min), t_R = 7.18 min (*trans*, major), 10.09 min (*cis*, major), t_R = 10.48 min (*trans*, minor), 14.00 min (*cis*, minor). R_f = 0.17 (**13e**), (*n*-pentane/Et_2O 2:1);

trans-Diastereomer: $[\alpha]_D^{24}$ = +8.4 (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{24}$ = +45.9 (*c* = 1.0, $CHCl_3$); IR (ATR): 2957, 2325, 2099, 1684, 1582, 1483, 1430, 1358, 1259, 1119, 1035, 874, 784, 734, 686, 540 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 1.65 (ddd, *J* = 16.4 Hz, 10.4 Hz, 6.0 Hz, 1H), 2.00 – 2.08 (m, 1H), 2.18 (dt, *J* = 14.4 Hz, 2.5 Hz, 1H), 2.73 – 2.77 (m, 1H), 3.19 (dd, *J* = 16.8 Hz, 6.9 Hz, 1H), 3.56 (dd, *J* = 16.8 Hz, 6.0 Hz, 1H), 3.59 (s, 3H), 3.87 (s, 3H), 4.96 – 5.02 (m, 1H), 7.15 (dd, *J* = 7.4 Hz, 2.0 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.51 (t, *J* = 2.0 Hz, 1H), 7.55 (dt, *J* = 7.9 Hz, 1.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 20.7, 29.0, 31.7, 33.8, 34.3, 43.6, 55.4, 74.1, 98.2, 112.3, 120.0, 120.7, 121.7 (q, *J* = 268.7 Hz, CF_3), 129.7, 137.3 (q, *J* = 36.5 Hz), 137.9, 150.2, 159.9, 196.4 ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = 60.9 ppm; MS (CI, 100 eV): *m/z* 397 ($M+H^+$, 100%), 377 (48).

cis-Diastereomer: $[\alpha]_D^{24}$ = –48.9 (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{24}$ = –180.5 (*c* = 1.0, $CHCl_3$); IR (ATR): 2961, 2325, 2095, 1686, 1582, 1544, 1486, 1428, 1393, 1354, 1294, 1256, 1163, 1115, 1041, 995, 883, 763, 728, 684, 556 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 0.68 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.54 – 1.61 (m, 1H), 2.02 (ddd, *J* = 13.9 Hz, 6.4 Hz, 1.5 Hz, 1H), 2.37 – 2.45 (m, 1H), 3.04 (ddd, *J* = 10.4 Hz, 6.0 Hz, 3.5 Hz, 1H), 3.25 (dd, *J* = 16.8 Hz, 6.0 Hz, 1H), 3.59 (s, 3H), 3.61 (dd, *J* = 16.8 Hz, 6.4 Hz, 1H), 3.88 (s, 3H), 4.72 – 4.78 (m, 1H), 7.16 (dd, *J* = 7.4 Hz, 1.9 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.52 (t, *J* = 1.9 Hz, 1H), 7.58 (dt, *J* = 7.4 Hz, 1.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 20.4, 27.7, 28.3, 33.8, 35.9, 44.0, 55.5, 76.9, 98.8, 112.4, 120.0, 120.8, 121.7 (q, *J* = 268.7 Hz, CF_3), 129.7, 136.8 (q, *J* = 37.1 Hz), 138.0, 151.5, 159.9, 196.2 ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = 61.6 ppm; MS (CI, 100 eV): *m/z* 397 ($M+H^+$, 27%), 377 (11), 231 (27), 221 (40), 205 (10), 201 (13), 178 (12), 177 (100), 135 (36).

Elemental analysis calcd (%) for $C_{20}H_{23}F_3N_2O_3$: C 60.60, H 5.85, N 7.07; found: C 60.59, H 5.48, N 7.21.

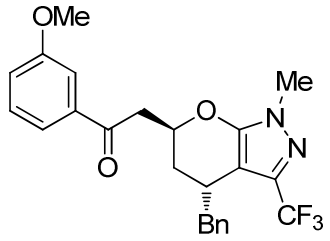


13f

1-(3-Methoxyphenyl)-2-((4*R*,6*S*)-1-methyl-4-phenyl-3-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)ethanone (13f) was purified by flash chromatography (*n*-pentane/Et_2O 1:1) yielding an inseparable mixture of diastereomers of **13f** as a colorless oil. For analytical purposes a sample of the *trans*-diastereomer was obtained via preparative HPLC (LiChrosorb Si 60 7µm 250x25 mm, *n*-pentane/diethylether 65:35, 18 mL/min), t_R = 25.84 min (*trans*), t_R = 26.50 min (*cis*). The *ee* (*trans* 76%) was determined by HPLC on a chiral stationary phase (Daicel AD, *n*-heptane/*i*PrOH 95:5, 1.0 mL/min),

t_R = 13.34 min (*trans*, major), 17.46 min (*trans*, minor), t_R = 25.47 min (*cis*, unseparated). R_f = 0.26 (**13f**), (*n*-pentane/Et_2O 2:1);

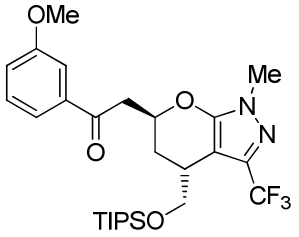
trans-Diastereomer: $[\alpha]_D^{26}$ = +3.3 (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{26}$ = +4.9 (*c* = 1.0, $CHCl_3$); IR (ATR): 2944, 2321, 2099, 1686, 1588, 1548, 1494, 1430, 1350, 1256, 1161, 1119, 1035, 878, 757, 697 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 2.11 (dt, *J* = 14.4 Hz, 2.5 Hz, 1H), 2.22 (ddd, *J* = 14.4 Hz, 10.9 Hz, 6.0 Hz, 1H), 3.07 (dd, *J* = 16.8 Hz, 4.5 Hz, 1H), 3.54 (dd, *J* = 16.8 Hz, 7.4 Hz, 1H), 3.64 (s, 3H), 3.83 (s, 3H), 4.26 (d, *J* = 3.5 Hz, 1H), 4.79 – 4.84 (m, 1H), 7.11 – 7.15 (m, 3H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.45 (t, *J* = 2.5 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 33.9, 34.1, 36.8, 43.0, 55.4, 72.5, 96.1, 112.4, 119.9, 120.7, 121.3 (q, *J* = 269.6 Hz, CF_3), 126.7, 127.6, 128.4, 129.6, 137.6 (q, *J* = 38.2 Hz), 138.0, 143.8, 151.2, 159.9, 195.8 ppm; ^{19}F NMR (564 MHz, $CDCl_3$): δ = 62.3 ppm; MS (CI, 100 eV): *m/z* 431 ($M+H^+$, 100%), 412 (11), 411 (41); elemental analysis calcd (%) for $C_{23}H_{21}F_3N_2O_3$: C 64.18, H 4.92, N 6.51; found: C 64.22, H 5.11, N 6.38.



13g

2-((4*R*,6*S*)-4-Benzyl-1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)-1-(3-methoxyphenyl)ethanone (13g) was purified by flash chromatography (*n*-pentane/Et_2O 1:1) yielding an inseparable mixture of diastereomers of **13g** as a colorless oil. For analytical purposes a sample of the *trans*-diastereomer was obtained via preparative HPLC (LiChrosorb Si 60 7µm 250x25 mm, *n*-pentane/diethylether 6:4, 18 mL/min), t_R = 19.21 min (*trans*), t_R = 17.55 min (*cis*). The *ee* (*trans* 93%, *cis* >99%) was determined by HPLC on a chiral stationary phase (Daicel OD, *n*-heptane/*i*PrOH 97:3, 0.7 mL/min), t_R = 25.36 min (*trans*, major), 28.29 min (*trans*, minor), t_R = 32.16 min (*cis*, minor), 53.64 min (*cis*, major). R_f = 0.21 (**13g**), (*n*-pentane/Et_2O 2:1);

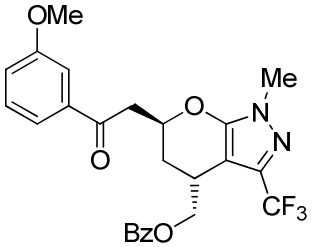
trans-Diastereomer: $[\alpha]_D^{24}$ = –11.1 (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{24}$ = –21.2 (*c* = 1.0, $CHCl_3$); IR (ATR): 3025, 2935, 2111, 1684, 1586, 1547, 1493, 1429, 1354, 1257, 1162, 1116, 1044, 1001, 941, 854, 782, 728, 694 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 1.57 (ddd, *J* = 14.4 Hz, 11.4 Hz, 6.0 Hz, 1H), 1.94 (dt, *J* = 14.4 Hz, 1.5 Hz, 1H), 2.63 (dd, *J* = 13.9 Hz, 11.4 Hz, 1H), 3.08 – 3.13 (m, 1H), 3.15 – 3.21 (m, 2H), 3.57 (dd, *J* = 16.8 Hz, 6.0 Hz, 1H), 3.63 (s, 3H), 3.87 (s, 3H), 4.94 – 5.00 (m, 1H), 7.15 (dd, *J* = 8.4 Hz, 2.5 Hz, 1H), 7.22 (t, *J* = 6.9 Hz, 1H), 7.25 (d, *J* = 6.4 Hz, 2H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.50 (t, *J* = 1.9 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 1H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 30.2, 30.7, 33.8, 42.0, 43.6, 55.4, 72.7, 99.2, 112.4, 119.9, 120.7, 121.8 (q, *J* = 269.6 Hz, CF_3), 126.3, 128.4, 129.3, 129.7, 137.0 (q, *J* = 38.2 Hz), 137.9, 139.4, 150.4, 159.9, 196.0 ppm; ^{19}F NMR (564 MHz, $CDCl_3$): δ = 61.5 ppm; MS (CI, 100 eV): *m/z* 445 ($M+H^+$, 100%), 425 (33), 353 (12), 135 (17), 61 (25); elemental analysis calcd (%) for $C_{24}H_{23}F_3N_2O_3$: C 64.86, H 5.22, N 6.30; found: C 64.84, H 5.67, N 6.21.



13h

1-(3-Methoxyphenyl)-2-((4*R*,6*S*)-1-methyl-3-(trifluoromethyl)-4-(((triisopropylsilyl)oxy)methyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)ethanone (13h) was purified by flash chromatography (*n*-pentane/Et_2O 1:1) yielding an inseparable mixture of diastereomers of **13h** as a colorless oil. For analytical purposes a sample of the *trans*-diastereomer was obtained via preparative HPLC (LiChrosorb Si 60 7µm 250x25 mm, *n*-pentane/diethylether 6:4, 18 mL/min), t_R = 14.26 min (*trans*), t_R ~ 14.20 min (*cis*).[10] The *ee* (*trans* 97%, *cis* >99%) was determined by HPLC on a chiral stationary phase (Daicel IA, *n*-heptane/*i*PrOH 95:5, 0.5 mL/min), t_R = 10.53 min (*trans*, minor), 11.37 min (*trans*, major), t_R =12.17 min (*cis*, major), 13.07 min (*cis*, minor). R_f = 0.37 (**13h**), (*n*-pentane/Et_2O 2:1);

trans-Diastereomer: $[\alpha]_D^{26}$ = +22.7 (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{26}$ = +94.6 (*c* = 1.0, $CHCl_3$); IR (ATR): 3222, 2941, 2868, 1688, 1584, 1549, 1461, 1361, 1259, 1173, 1113, 1013, 886, 830, 781, 727, 682 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 1.01 – 1.13 (m, 21H), 1.78 (ddd, *J* = 14.4 Hz, 11.9 Hz, 6.0 Hz, 1H), 2.39 (dt, *J* = 14.4 Hz, 1.9 Hz, 1H), 3.03 – 3.08 (m, 1H), 3.17 (dd, *J* = 16.4 Hz, 5.0 Hz, 1H), 3.54 – 3.60 (m, 4H), 3.62 (t, *J* = 9.9 Hz, 1H), 3.88 (s, 3H), 3.96 (dd, *J* = 9.9 Hz, 4.0 Hz, 1H), 4.99 – 5.05 (m, 1H), 7.15 (dd, *J* = 8.4 Hz, 3.0 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.52 (dd, *J* = 2.5 Hz, 1.5 Hz, 1H), 7.57 (dt, *J* = 7.4 Hz, 1.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.9, 17.9, 29.2, 31.6, 33.9, 43.8, 55.5, 65.4, 73.1, 95.1, 112.5, 119.9, 120.8, 121.5 (q, *J* = 269.5 Hz, CF_3), 129.7, 137.3 (q, *J* = 37.3 Hz), 138.2, 151.2, 160.0, 196.0 ppm; ^{19}F NMR (564 MHz, $CDCl_3$): δ = 61.8 ppm; MS (CI, 100 eV): *m/z* 541 ($M+H^+$, 52%), 498 (15), 497 (48), 368 (17), 367 (80), 346 (21), 345 (100), 135 (32); elemental analysis calcd (%) for $C_{27}H_{39}F_3N_2O_4Si$: C 59.98, H 7.27, N 5.18; found: C 59.82, H 7.35, N 5.57.



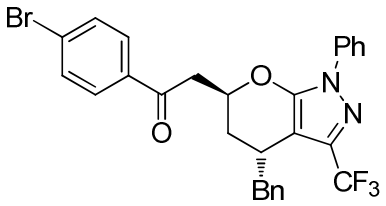
13i

((4*R*,6*S*)-6-(2-(3-Methoxyphenyl)-2-oxoethyl)-1-methyl-3-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-4-yl)methyl benzoate (13i) was purified by flash chromatography (*n*-pentane/Et_2O 1:1) yielding an inseparable mixture of diastereomers of **13i** as a colorless oil. For analytical

(10) The c*is*-diastereomer was only observed as a shoulder of the major peak and could not be completely separated.

purposes a sample of the *trans*-diastereomer was obtained via preparative HPLC (LiChrosorb Si 60 7µm 250x25 mm, *n*-pentane/diethylether 6:4, 18 mL/min), t_R = 28.13 min (*trans*), t_R ~ 27.90 min (*cis*).[11] The *ee* (*trans* 91%) was determined after the separation of the diastereomers by HPLC on a chiral stationary phase (Daicel OD, *n*-heptane/*i*PrOH 7:3, 0.7 mL/min), t_R = 10.77 min (*trans*, minor), 13.48 min (*trans*, major). R_f = 0.25 (**13i**), (*n*-pentane/Et_2O 1:1);

trans-Diastereomer: $[\alpha]_D^{26}$ = +1.0 (*c* = 0.50, $CHCl_3$), $[\alpha]_{365}^{26}$ = –2.2 (*c* = 0.50, $CHCl_3$); IR (ATR): 2947, 2325, 2229, 2189, 2157, 2113, 2077, 2049, 2005, 1963, 1717, 1687, 1585, 1549, 1493, 1432, 1260, 1164, 1112, 1026, 972, 862, 785, 712 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.90 (ddd, *J* = 14.4 Hz, 11.4 Hz, 5.5 Hz, 1H), 2.27 (dt, *J* = 14.9 Hz, 2.0 Hz, 1H), 3.24 (dd, *J* = 16.9 Hz, 5.5 Hz, 1H), 3.39 – 3.44 (m, 1H), 3.60 (dd, *J* = 16.8 Hz, 6.9 Hz, 1H), 3.62 (s, 3H), 3.87 (s, 3H), 3.40 (t, J = 9.9 Hz, 1H), 4.56 (dd, *J* = 11.4 Hz, 4.0 Hz, 1H), 5.05 – 5.10 (m, 1H), 7.15 (dd, *J* = 7.9 Hz, 2.5 Hz, 1H), 7.38 – 7.48 (m, 3H), 7.51 (t, *J* = 1.5 Hz, 1H), 7.54 – 7.59 (m, 2H), 8.06 (dd, *J* = 7.9 Hz, 1.5 Hz, 2H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ 28.6, 29.7, 34.0, 43.5, 55.5, 66.2, 72.9, 94.0, 112.5, 120.0, 120.8, 121.4 (q, *J* = 269.6 Hz, CF_3), 128.4, 129.6, 129.7, 130.0, 133.1, 137.5 (q, *J* = 36.9 Hz), 138.0, 151.2, 160.0, 166.3, 195.7 ppm; ^{19}F NMR (564 MHz, $CDCl_3$): δ = 61.8 ppm; MS (CI, 100 eV): *m/z* 489 ($M+H^+$, 34%), 469 (28), 368 (19), 367 (100), 366 (13), 135 (15), 123 (35), 61 (28); elemental analysis calcd (%) for $C_{25}H_{23}F_3N_2O_5$: C 61.47, H 4.75, N 5.74; found: C 61.21, H 4.85, N 5.41.



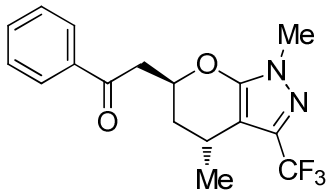
13j

2-((4*R*,6*S*)-4-Benzyl-1-phenyl-3-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)-1-(4-bromophenyl)ethanone (13j) was purified by flash chromatography (*n*-pentane/Et_2O 2:1) yielding an inseparable mixture of diastereomers of **13j** as a colorless solid. For analytical purposes a sample of the *trans*-diastereomer was obtained via preparative HPLC (LiChrosorb Si 60 7µm 250x25 mm, *n*-pentane/diethylether 6:4, 18 mL/min), t_R = 11.18 min (*trans*), t_R = 12.84 min (*cis*). The *ee* (*trans* 96%, *cis* 86%) was determined by HPLC on a chiral stationary phase (Daicel IA, *n*-heptane/EtOH 97:3, 0.5 mL/min), t_R = 20.50 min (*trans*, major), 21.81 min (*trans*, minor), t_R = 24.51 min (*cis*, major), 25.83 min (*cis*, minor). R_f = 0.71 (**13j**), (*n*-pentane/Et_2O 2:1);

trans-Diastereomer: m.p. 138 – 142 °C (MTBE/*n*-pentane); $[\alpha]_D^{25}$ = –55.7 (*c* = 0.70, $CHCl_3$), $[\alpha]_{365}^{25}$ = –209.1 (*c* = 0.70, $CHCl_3$); IR (ATR): 3066, 3025, 2953, 2921, 2321, 2086, 1688, 1591, 1515, 1481, 1454, 1399, 1351, 1266, 1207, 1158, 1120, 1069, 1013, 920, 890, 835, 812, 756, 735, 691 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 1.65 (ddd, *J* = 14.4 Hz, 11.9 Hz, 5.5 Hz, 1H), 2.01 (d, *J* = 14.4 Hz, 1H), 2.69 (dd, 13.4 Hz, 11.4 Hz, 1H), 3.14 – 3.21 (m, 2H), 3.25 (dd, *J* = 13.9 Hz, 3.5 Hz, 1H), 3.57 (dd, *J* = 16.8 Hz, 6.4 Hz, 1H), 4.98 – 5.04 (m, 1H), 7.21 – 7.38 (m, 8H), 7.61 (d, *J* = 8.9 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 30.0, 30.7, 42.0, 43.3, 73.5, 100.5, 121.2, 121.8 (q, *J* =

(11) The c*is*-diastereomer was only observed as a shoulder of the major peak and could not be completely separated.

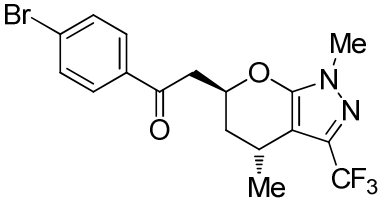
269.6 Hz, CF_3), 126.5, 127.0, 128.6, 128.9, 129.0, 129.4, 129.7, 132.1, 135.3, 137.7, 138.8 (q, J = 38.2 Hz), 139.2, 150.2, 195.3 ppm; ^{19}F NMR (564 MHz, $CDCl_3$): δ = 61.4 ppm; MS (CI, 100 eV): *m/z* 557 (100), 555 ($M+H^+$, 95%), 537 (33), 536 (13), 535 (36), 465 (19), 463 (19), 265 (46), 62 (20); elemental analysis calcd (%) for $C_{28}H_{22}BrF_3N_2O_2$: C 60.55, H 3.99, N 5.04; found: C 60.35, H 4.03, N 4.73.



13k

2-((4*R*,6*S*)-1,4-Dimethyl-3-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)-1-phenylethanone (13k) was purified by flash chromatography (*n*-pentane/Et_2O 1:1) yielding an inseparable mixture of diastereomers of **13k** as a colorless oil. For analytical purposes a sample of the *trans*-diastereomer was obtained via preparative HPLC (LiChrosorb Si 60 7µm 250x25 mm, *n*-pentane/diethylether 6:4, 18 mL/min), t_R = 15.17 min (*trans*), t_R ~ 15.90 min (*cis*).[12] The *ee* (*trans* 91%, *cis* 95%) was determined by HPLC on a chiral stationary phase (Daicel AD, *n*-heptane/*i*PrOH 95:5, 0.7 mL/min), t_R = 12.33 min (*trans*, major), 15.92 min (*trans*, minor), t_R = 17.46 min (*cis*, major), 19.16 min (*cis*, minor). R_f = 0.28 (**13k**), (*n*-pentane/Et_2O 2:1);

trans-Diastereomer: $[\alpha]_D^{25}$ = +26.4 (*c* = 1.17, $CHCl_3$), IR (ATR): 2960, 2327, 2095, 1686, 1585, 1546, 1498, 1430, 1395, 1355, 1261, 1162, 1116, 1032, 963, 899, 854, 746, 690, 649, 567 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.31 (d, J = 6.9 Hz, 3H), 1.86 (dt, J = 13.9 Hz, 2.5 Hz, 1H), 1.91 (ddd, J = 14.4 Hz, 10.4 Hz, 5.5 Hz, 1H), 3.01 – 3.07 (m, 1H), 3.21 (dd, J = 16.8 Hz, 6.0 Hz, 1H), 3.58 (s, 3H), 3.62 (dd, J = 16.8 Hz, 6.4 Hz, 1H), 4.94 – 4.99 (m, 1H), 7.51 (t, J = 7.4 Hz, 2H), 7.62 (tt, J = 6.9 Hz, 1.5 Hz, 1H), 8.00 (dd, J = 8.4 Hz, 1.0 Hz, 2H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 22.3, 23.0, 33.8, 35.2, 43.2, 72.8, 100.4, 121.6 (q, J = 269.6 Hz, CF_3), 128.2, 128.8, 133.6, 136.7, 137.0 (q, J = 38.2 Hz), 150.1, 196.5 ppm; ^{19}F NMR (564 MHz, $CDCl_3$): δ = 61.9 ppm; MS (CI, 100 eV): *m/z* 339 ($M+H^+$, 100%), 338 (14), 320 (11), 319 (45); elemental analysis calcd (%) for $C_{17}H_{17}F_3N_2O_3$: C 60.35, H 5.06, N 8.28; found: C 60.29, H 5.28, N 8.61.



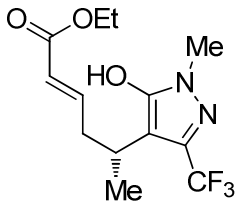
13l

1-(4-Bromophenyl)-2-((4*R*,6*S*)-1,4-dimethyl-3-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-yl)ethanone (13l) was purified by flash chromatography (*n*-pentane/Et_2O 1:1) yielding an inseparable mixture of diastereomers of **13l** as a colorless oil. For analytical purposes a sample of the *trans*-

(12) The c*is*-diastereomer was only observed as a shoulder of the major peak and could not be completely separated.

diastereomer was obtained via preparative HPLC (LiChrosorb Si 60 7µm 250x25 mm, *n*-pentane/diethylether 6:4, 18 mL/min), t_R = 15.10 min (*trans*), t_R ~ 15.90 min (*cis*).[12] The *ee* (*trans* 87%, *cis* 87%) was determined by HPLC on a chiral stationary phase (Daicel AD, *n*-heptane/*i*PrOH 95:5, 0.7 mL/min), t_R = 15.41 min (*trans*, major), 18.41 min (*trans*, minor), t_R = 20.20 min (*cis*, major), 23.58 min (*cis*, minor). R_f = 0.29 (**13l**), (*n*-pentane/Et_2O 2:1);

trans-Diastereomer: $[\alpha]_D^{24}$ = +14.4 (*c* = 0.95, $CHCl_3$), $[\alpha]_{365}^{24}$ = +70.8 (*c* = 0.95, $CHCl_3$); IR (ATR): 3457, 3074, 2922, 2575, 2423, 2289, 1919, 1691, 1579, 1383, 1252, 1021, 913, 808, 727, 662, 602 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.9 Hz, 3H), 1.84 (dt, *J* = 13.9 Hz, 2.5 Hz, 1H), 1.90 (ddd, *J* = 13.9 Hz, 10.4 Hz, 5.5 Hz, 1H), 3.01 – 3.07 (m, 1H), 3.17 (dd, *J* = 16.8 Hz, 6.0 Hz, 1H), 3.56 (dd, *J* = 16.8 Hz, 6.4 Hz, 1H), 3.57 (s, 3H), 4.92 – 4.97 (m, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 22.3, 23.0, 33.8, 35.2, 43.2, 72.6, 100.4, 121.6 (q, *J* = 268.3 Hz, CF_3), 128.9, 129.6, 132.1, 135.4, 137.0 (q, *J* = 38.2 Hz), 150.0, 195.4 ppm; ^{19}F NMR (564 MHz, $CDCl_3$): δ = 61.9 ppm; MS (CI, 100 eV): *m/z* 420 (100), 419 (48), 418 ($M+H^+$, 87%), 417 (18), 401 (14), 400 (84), 399 (15), 398 (81), 339 (16), 320 (11), 217 (23), 203 (10), 185 (46), 183 (47); HRMS (ESI): *m/z* calcd for $C_{17}H_{17}BrF_3O_2N_2^+$: 417.0420 [$M+H^+$]; found: 417.0421.

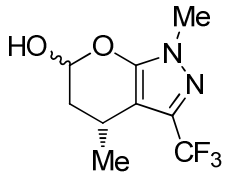


13m'

(*R*,*E*)-Ethyl 5-(5-hydroxy-1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)hex-2-enoate (13m') was purified by flash chromatography (*n*-pentane/Et_2O 1:2 – 1:5) yielding an inseparable mixture of E/Z-isomers of **13m'** (E/Z 18:1) as a colorless oil.

R_f = 0.23 (**13m'**), (*n*-pentane/Et_2O 1:5); $[\alpha]_D^{25}$ = –10.1 (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{25}$ = +109.8 (*c* = 1.0, $CHCl_3$); IR (ATR): 2968, 2089, 1698, 1567, 1483, 1376, 1271, 1162, 1121, 1040, 981, 857, 725 cm^{-1}; E-Isomer: ^1H NMR (600 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 7.4 Hz, 3H), 1.28 (t, *J*=7.2 Hz, 3H), 2.40 - 2.47 (m, 1H), 2.51 - 2.57 (m, 1H), 2.92 – 3.00 (m, 1H), 3.64 (s, 3H), 4.16 (q, *J* = 7.1 Hz, 2H), 5.74 (d, *J* = 15.9 Hz, 1H), 6.77 (dt, *J* = 15.4, 7.4 Hz, 1H) ppm;[13] ^{13}C NMR (151 MHz, $CDCl_3$): δ = 16.0, 20.1, 28.2, 34.0, 38.6, 60.8, 106.4, 121.5 (q, *J* = 268.3 Hz, CF_3), 122.3, 137.2 (q, *J* = 36.9 Hz), 148.2, 149.8, 167.6 ppm; ^{19}F NMR (564 MHz, $CDCl_3$): δ = 61.9 ppm; MS (CI, 100 eV): *m/z* 307 ($M+H^+$, 64%), 237 (100), 221 (44), 193 (16), 167 (21); HRMS (ESI): *m/z* calcd for $C_{13}H_{18}F_3N_2O_3^+$: 307.1264 [$M+H^+$]; found: 307.1264.

(13) The signal for OH was not observed.



9a

(4*R*)-1,4-Dimethyl-3-(trifluoromethyl)-1,4,5,6-tetrahydropyrano[2,3-c]pyrazol-6-ol (9a) was purified by flash chromatography (*n*-pentane/Et_2O 1:5) yielding an inseparable mixture of **9a** and **9a'** as an off-white solid.

R_f = 0.25 (**9a**), (*n*-pentane/Et_2O 1:5); m.p. 82-86 °C (Et_2O/*n*-pentane); $[\alpha]_D^{26}$ = +17.1 (*c* = 1.0, $CHCl_3$), $[\alpha]_{365}^{26}$ = +50.6 (*c* = 1.0, $CHCl_3$); IR (ATR): 3197, 2954, 2884, 1579, 1553, 1498, 1431, 1400, 1338, 1258, 1167, 1117, 1048, 1017,984, 948, 872, 841, 745, 718, 700 cm^{-1}; *trans*-Diastereomer:[14] ^1H NMR (300 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 6.9 Hz, 3H), 1.72 (ddd, *J* = 13.9, 7.5, 1.9 Hz, 1H), 2.06 (dt, *J* = 13.9, 5.6 Hz, 1H), 3.05-3.15 (m, 1H), 3.63 (s, 3H), 5.37 (br s, OH), 5.72 (dd, *J*=5.3, 1.9 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 21.4, 33.6, 36.5, 95.5, 100.3, 121.5 (q, *J* = 269.3 Hz, CF_3), 136.8 (q, *J* = 38.3 Hz), 148.9 ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ = 61,7 ppm; MS (CI, 100 eV): *m/z* 237 ($M+H^+$, 100%), 217 (52), 193 (12); elemental analysis calcd (%) for $C_9H_{11}F_3N_2O_2$: C 45.77, H 4.69, N 11.86; found: C 45.78, H 4.43, N 11.87.

(14) The signals were assigned via 2D NMR techniques (COSY, HMQC, HMBC).

8. NMR Spectra

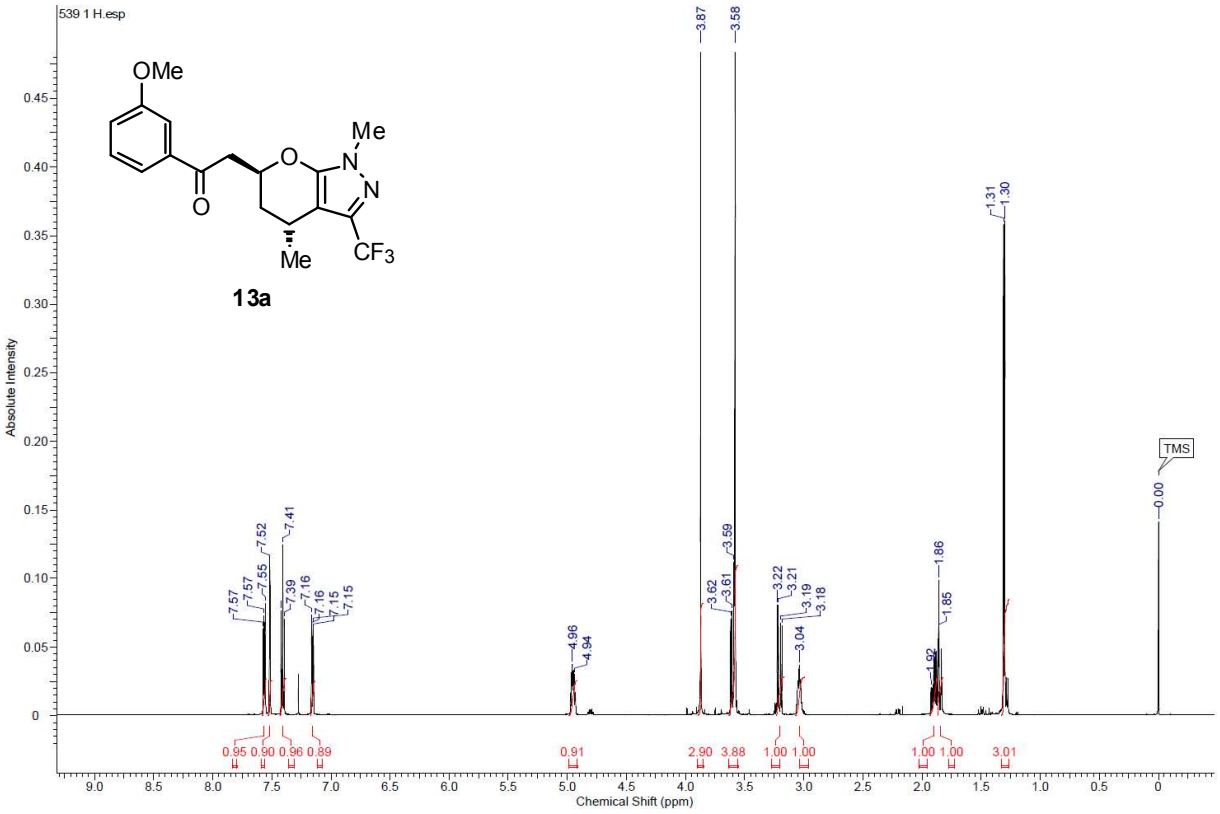


Figure S1. 1H NMR spectrum (600 MHz, $CDCl_3$) of ***trans*-13a**.

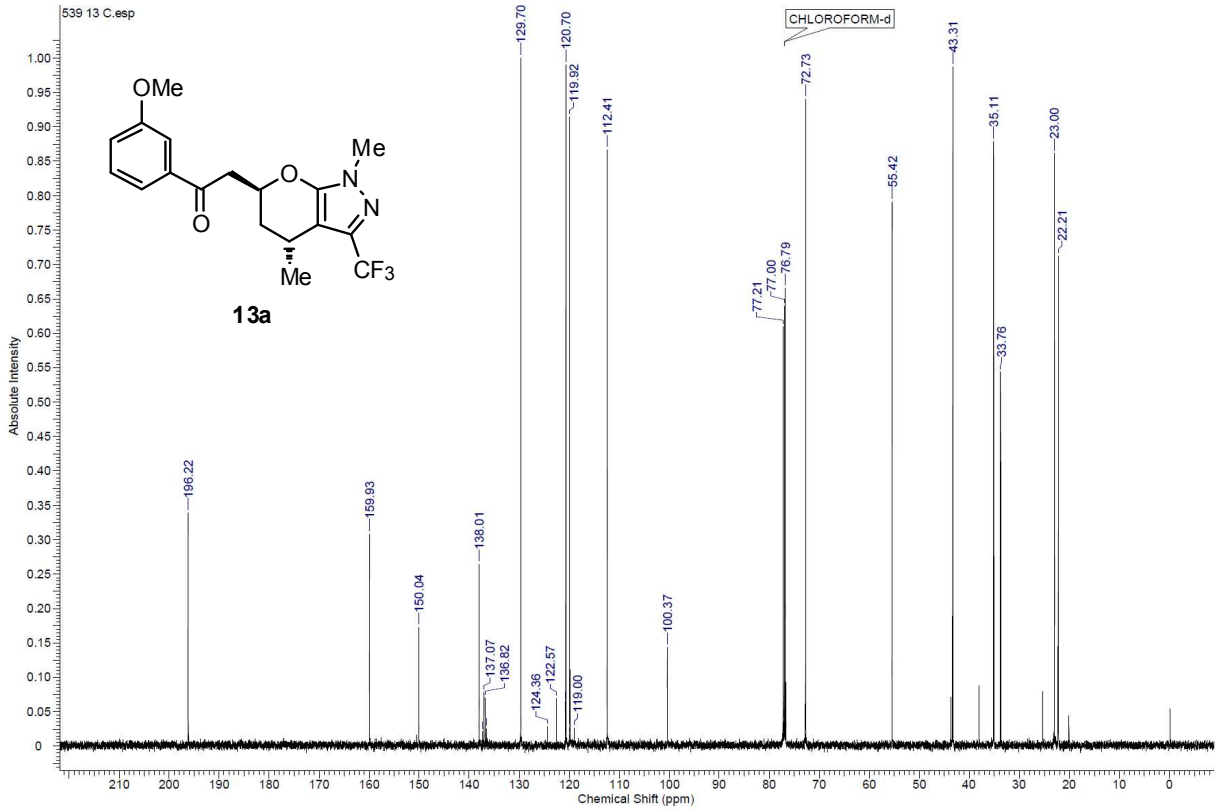


Figure S2. 13C NMR spectrum (151 MHz, $CDCl_3$) of ***trans*-13a**.

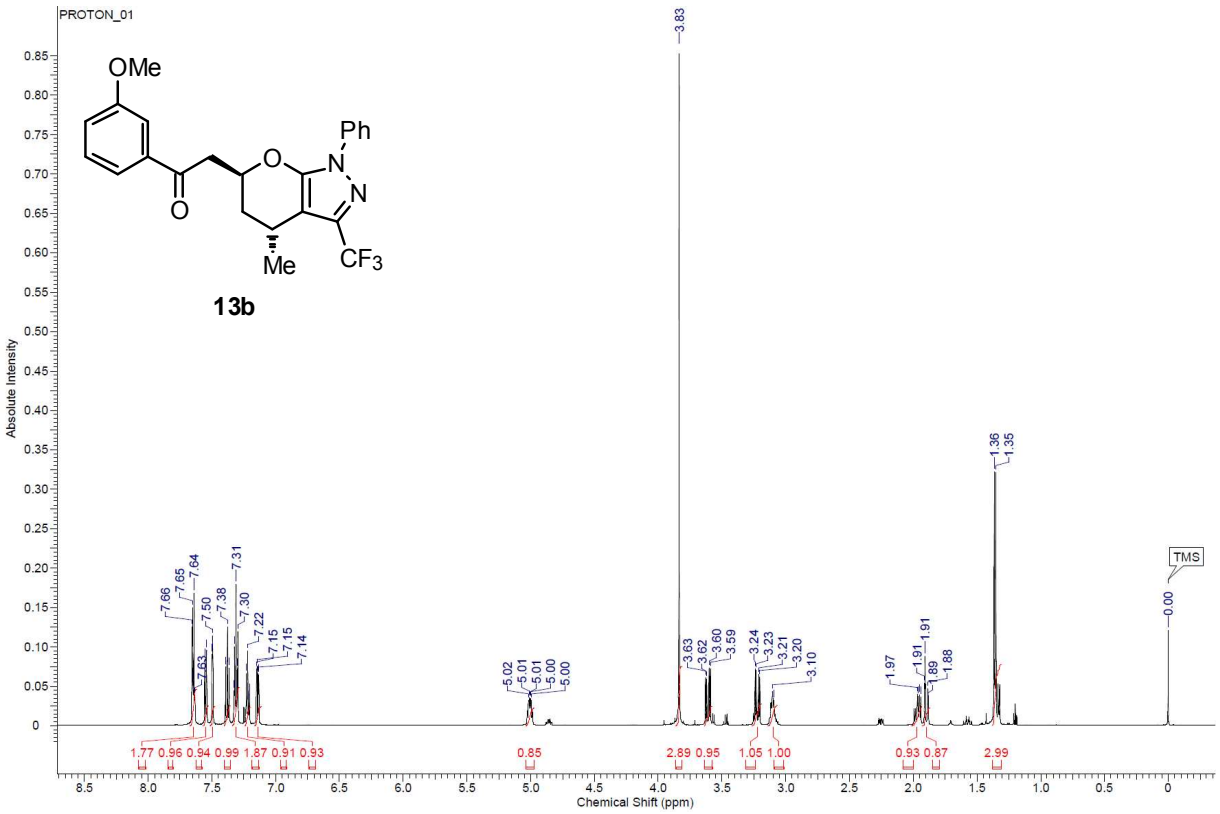


Figure S3. 1H NMR spectrum (600 MHz, $CDCl_3$) of ***trans*-13b**.

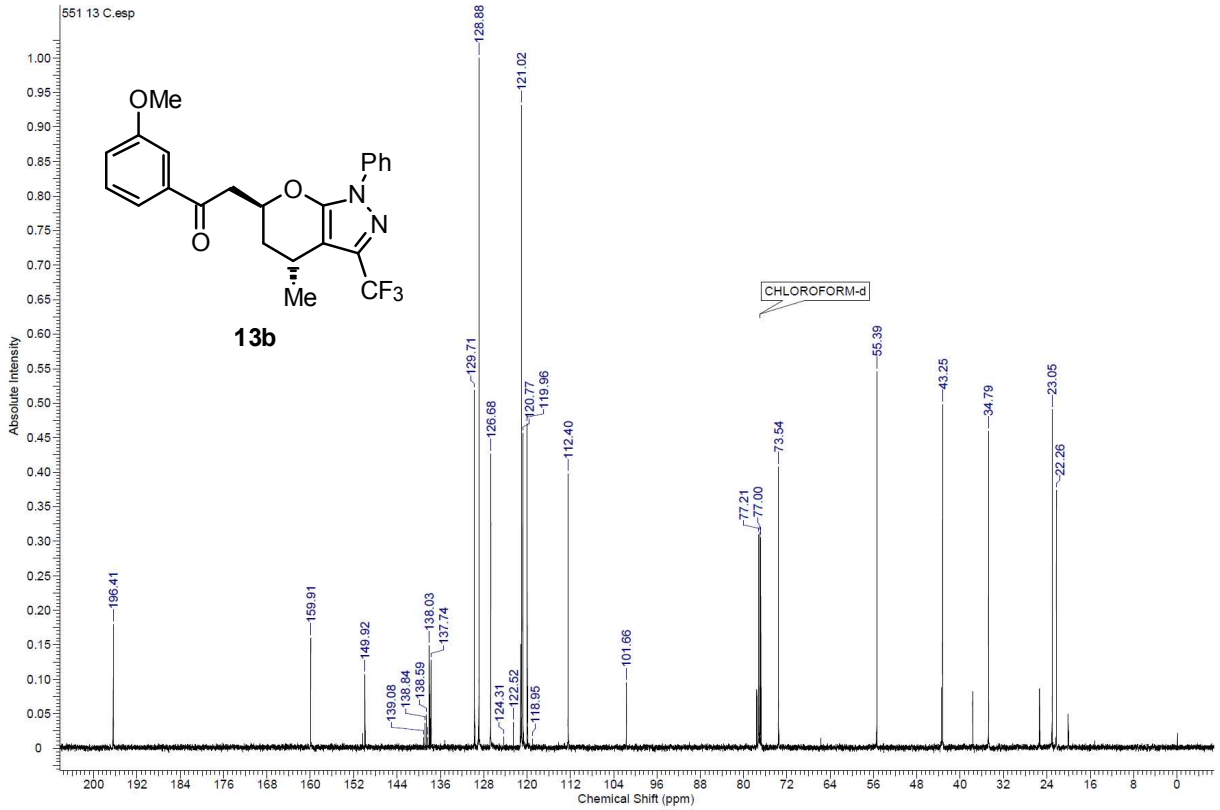


Figure S4. 13C NMR spectrum (151 MHz, $CDCl_3$) of ***trans*-13b**.

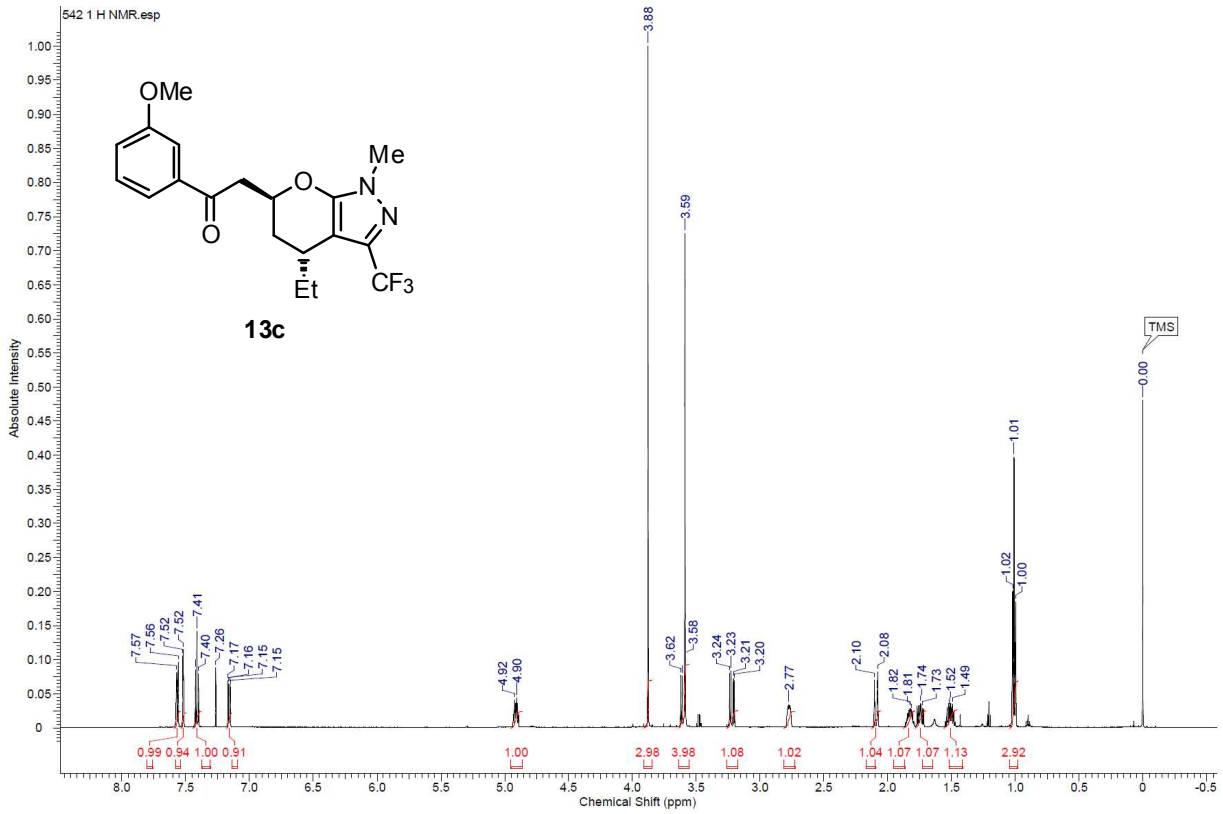


Figure S5. 1H NMR spectrum (600 MHz, $CDCl_3$) of ***trans*-13c**.

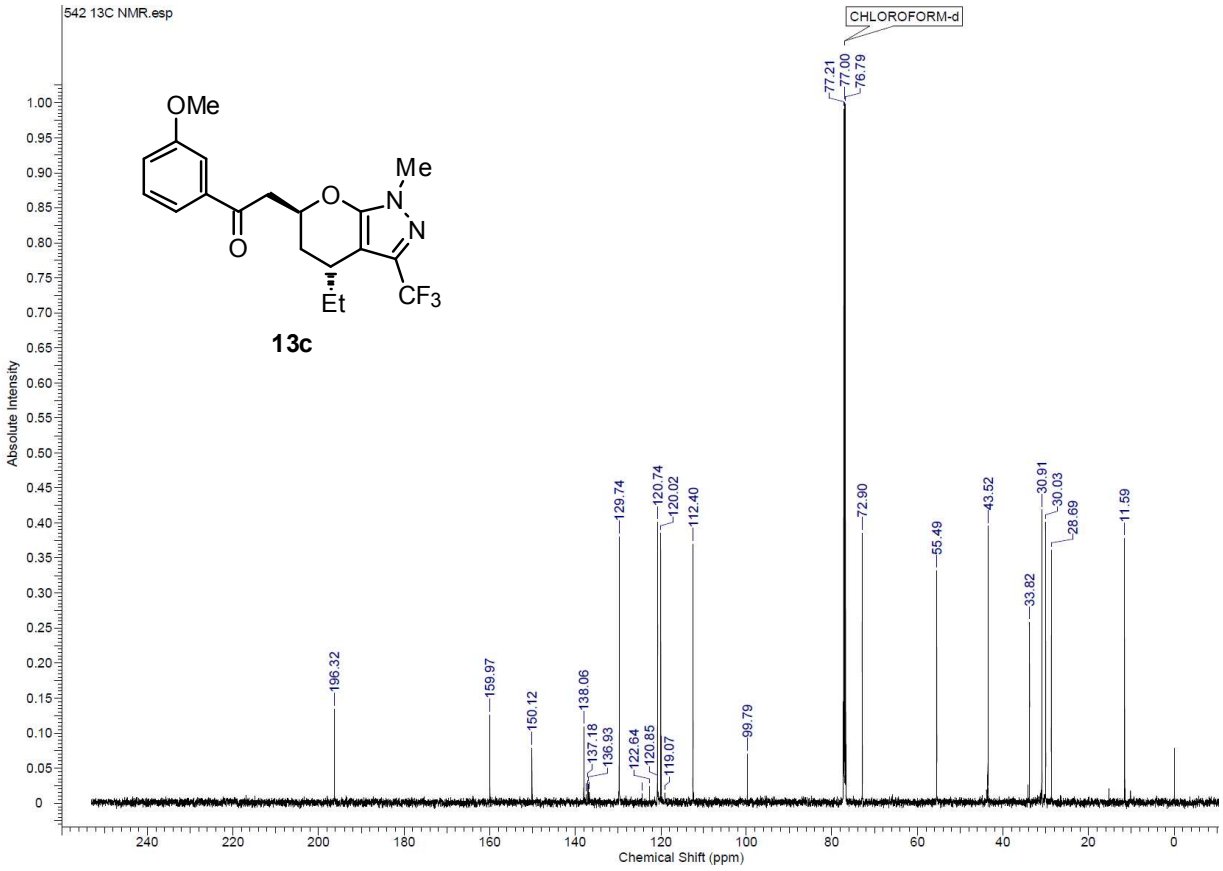


Figure S6. 13C NMR spectrum (151 MHz, $CDCl_3$) of ***trans*-13c**.

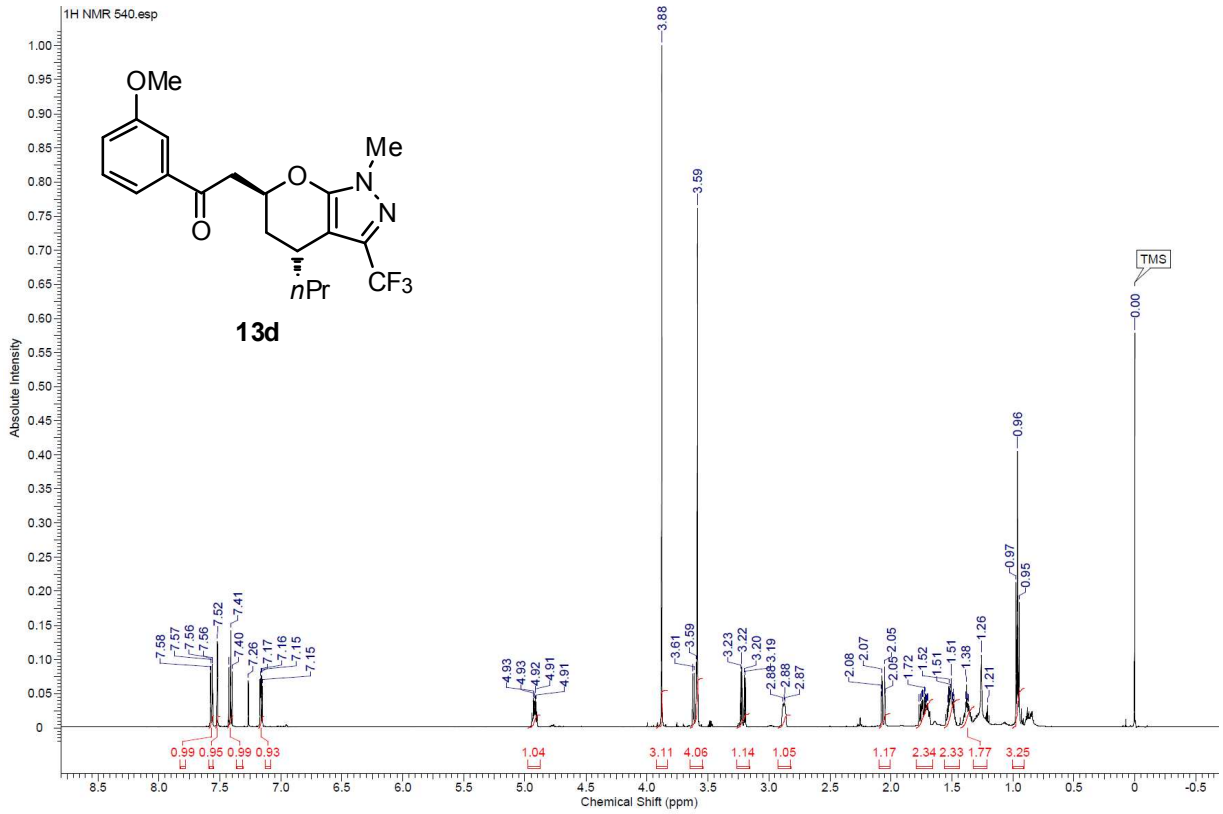


Figure S7. 1H NMR spectrum (600 MHz, $CDCl_3$) of ***trans*-13d**.

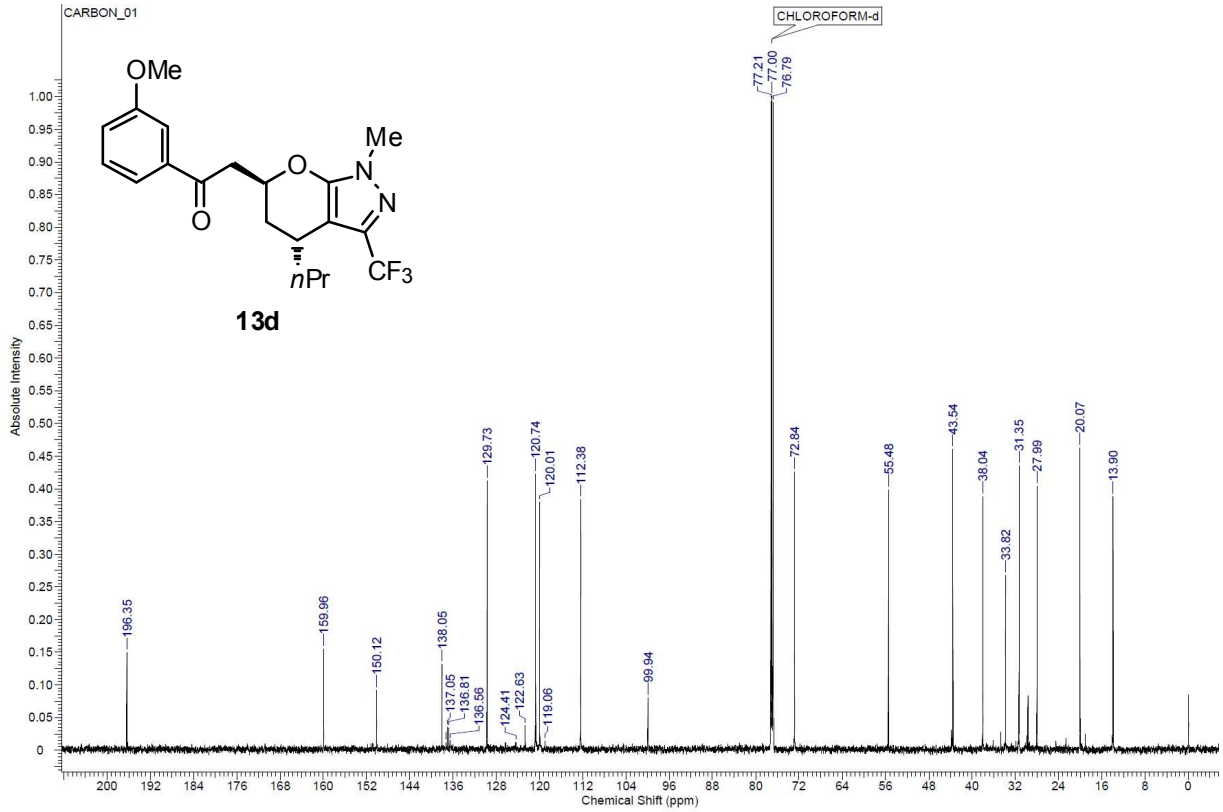


Figure S8. 13C NMR spectrum (151 MHz, $CDCl_3$) of ***trans*-13d**.

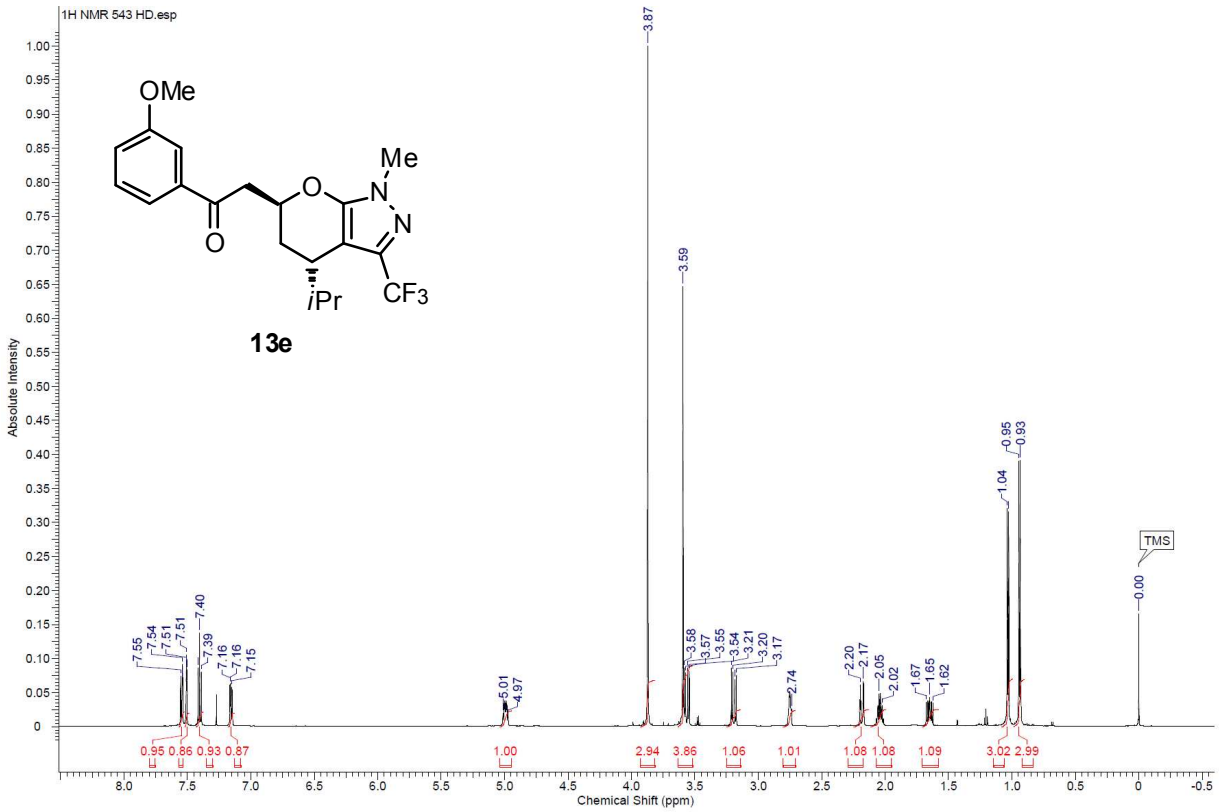


Figure S9. 1H NMR spectrum (600 MHz, $CDCl_3$) of ***trans*-13e**.

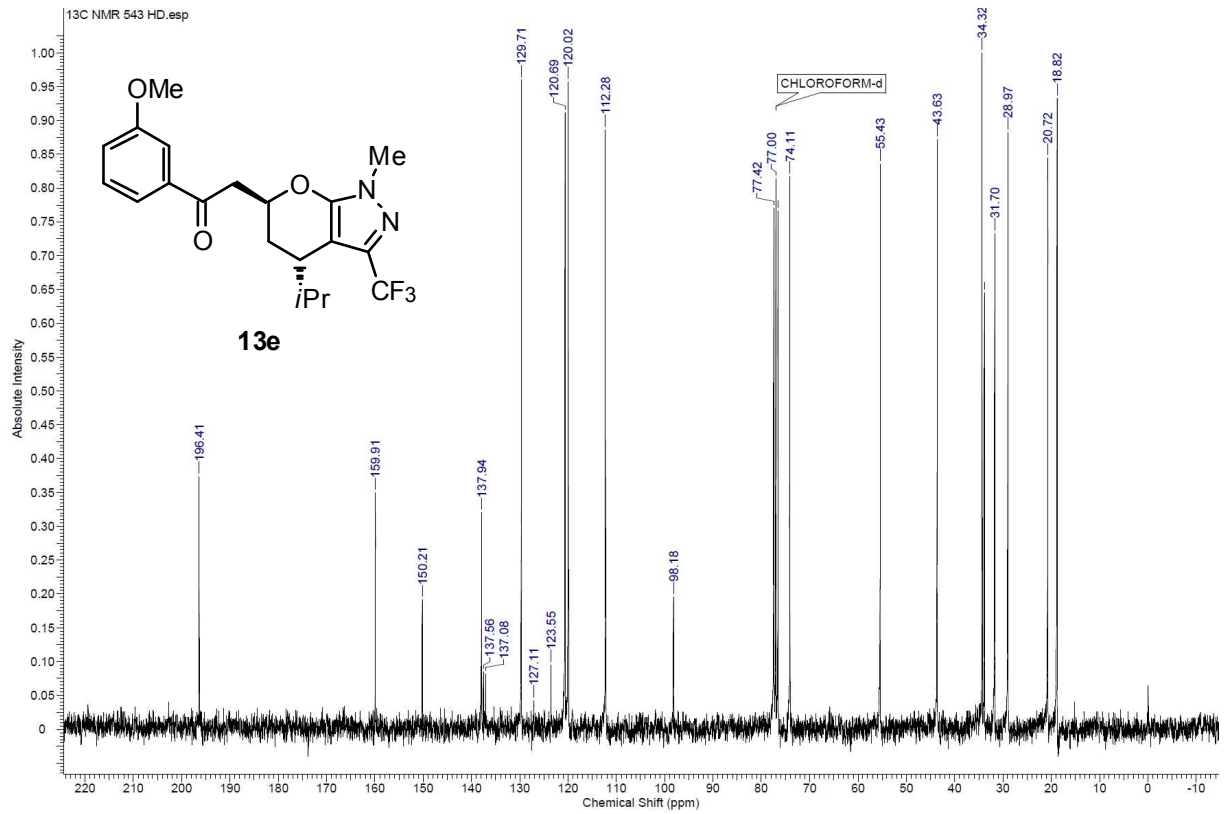


Figure S10. 13C NMR spectrum (75 MHz, $CDCl_3$) of ***trans*-13e**.

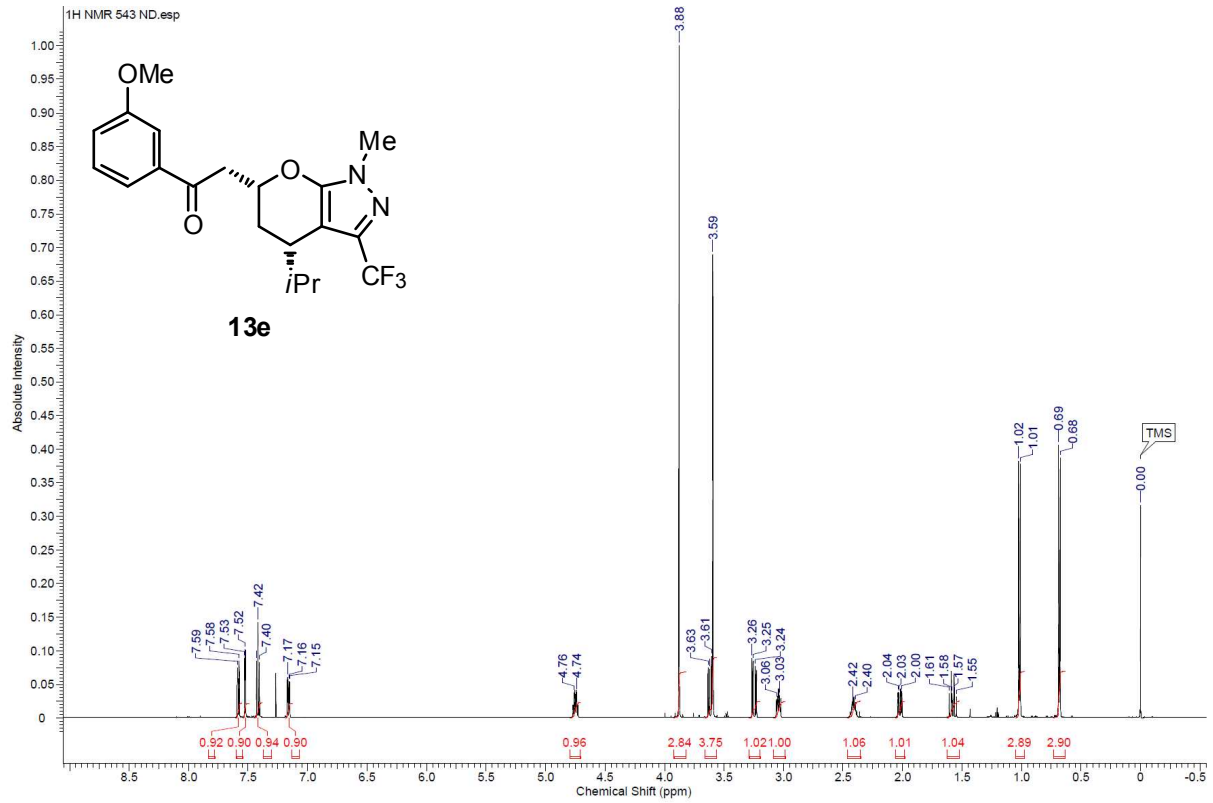


Figure S11. 1H NMR spectrum (600 MHz, $CDCl_3$) of ***cis*-13e**.

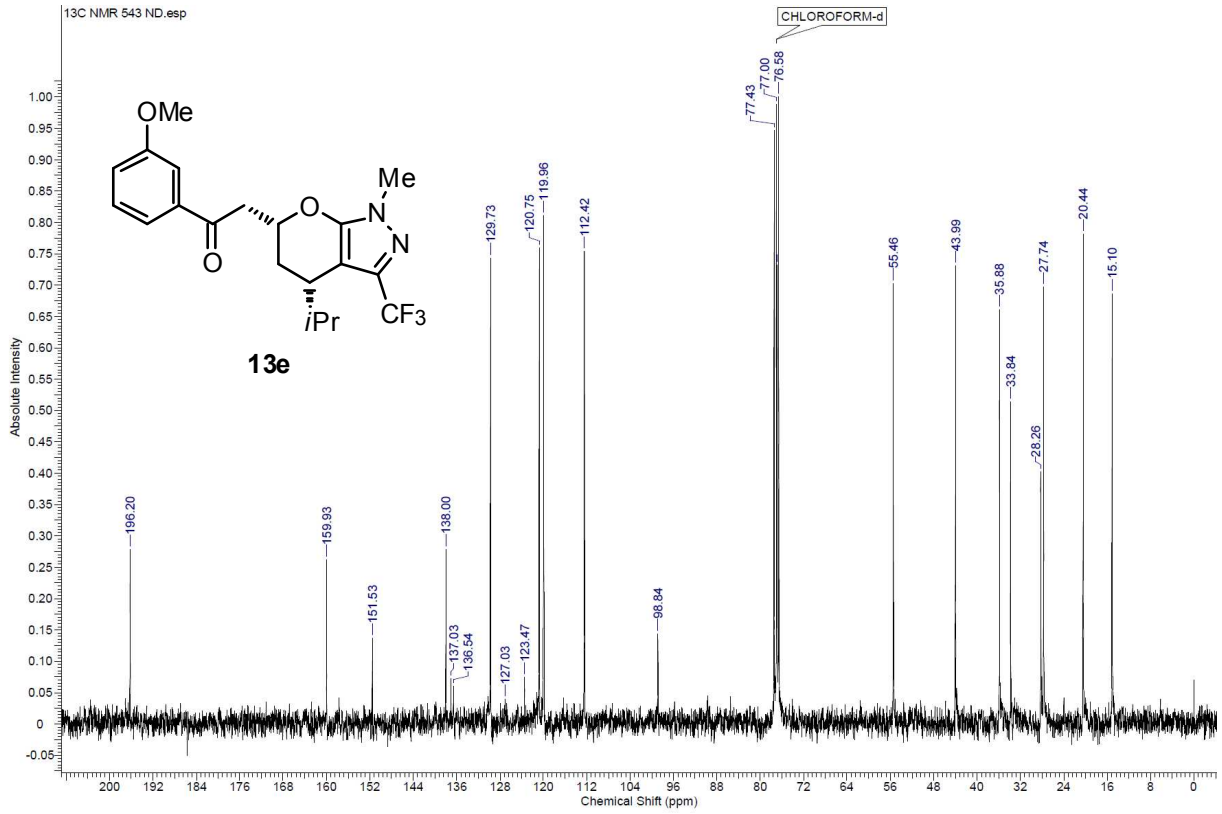


Figure S12. 13C NMR spectrum (75 MHz, $CDCl_3$) of ***cis*-13e**.

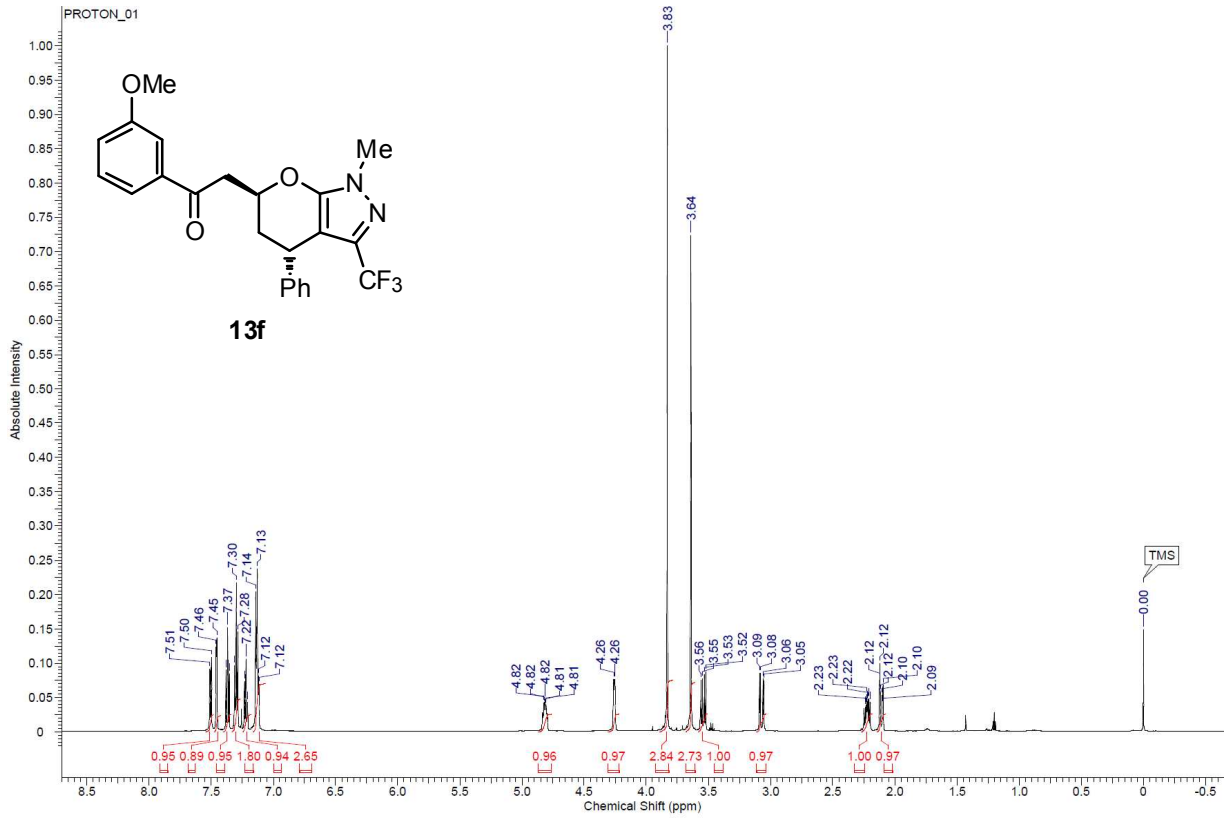


Figure S13. 1H NMR spectrum (600 MHz, $CDCl_3$) of ***trans*-13f**.

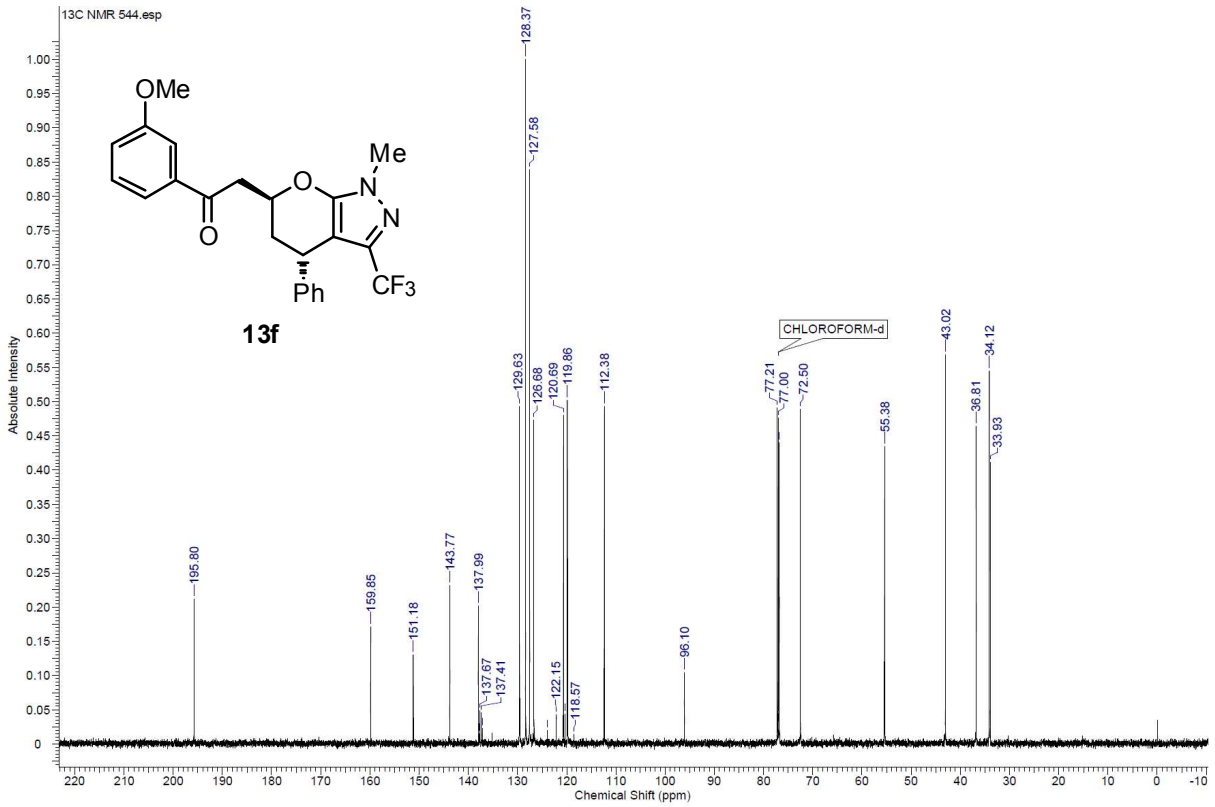


Figure S14. 13C NMR spectrum (151 MHz, $CDCl_3$) of ***trans*-13f**.

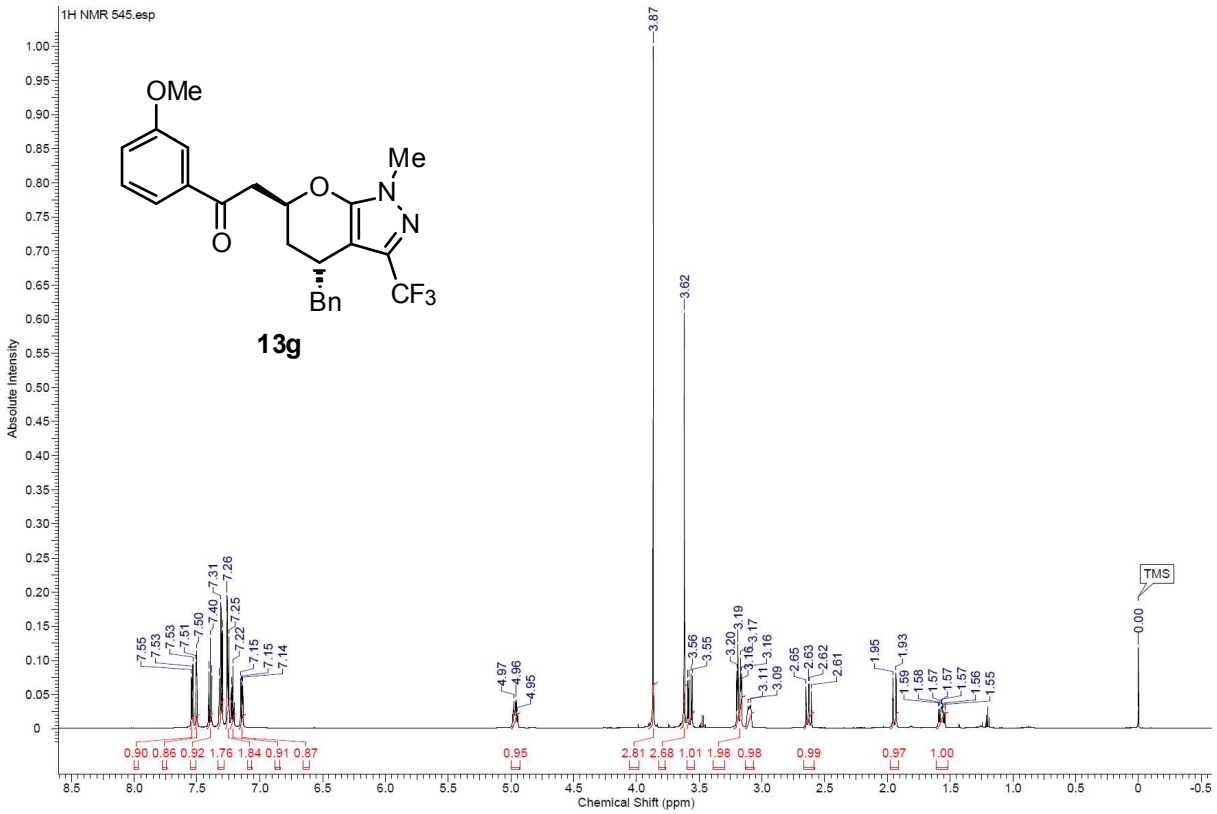


Figure S15. 1H NMR spectrum (600 MHz, $CDCl_3$) of ***trans*-13g**.

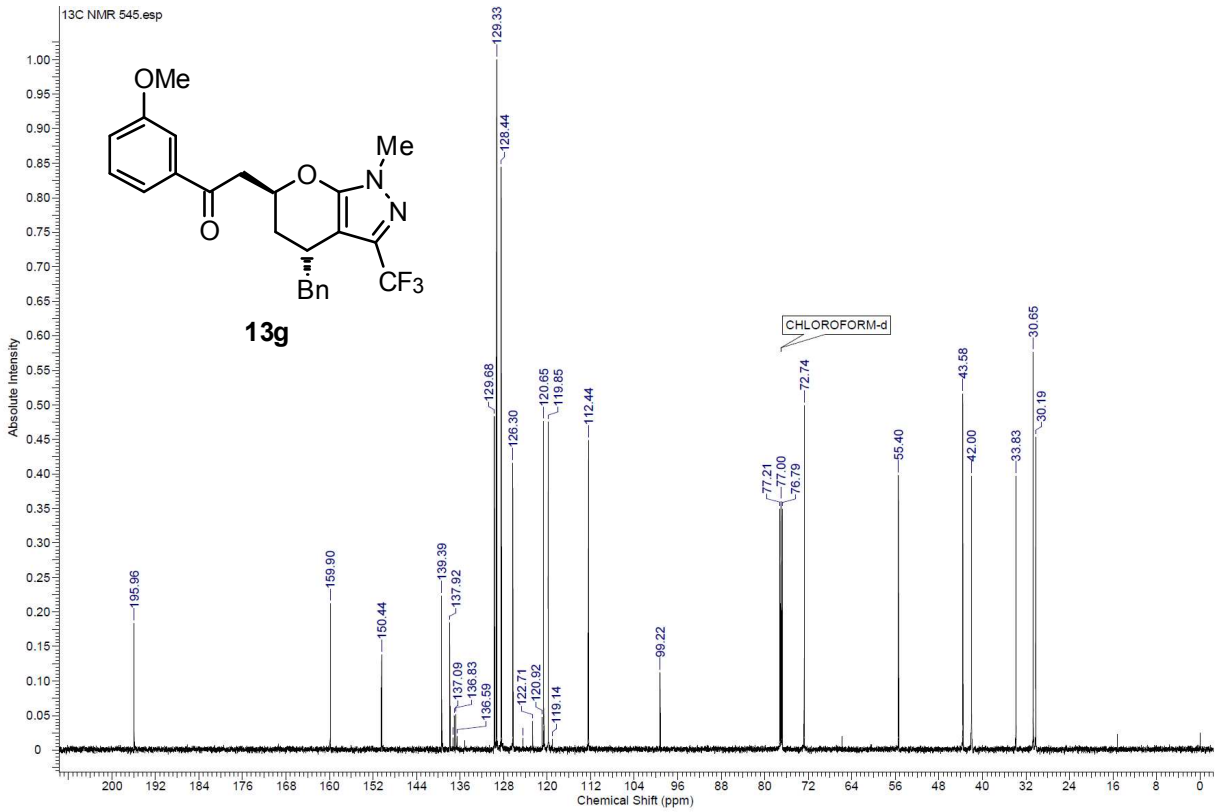


Figure S16. 13C NMR spectrum (151 MHz, $CDCl_3$) of ***trans*-13g**.

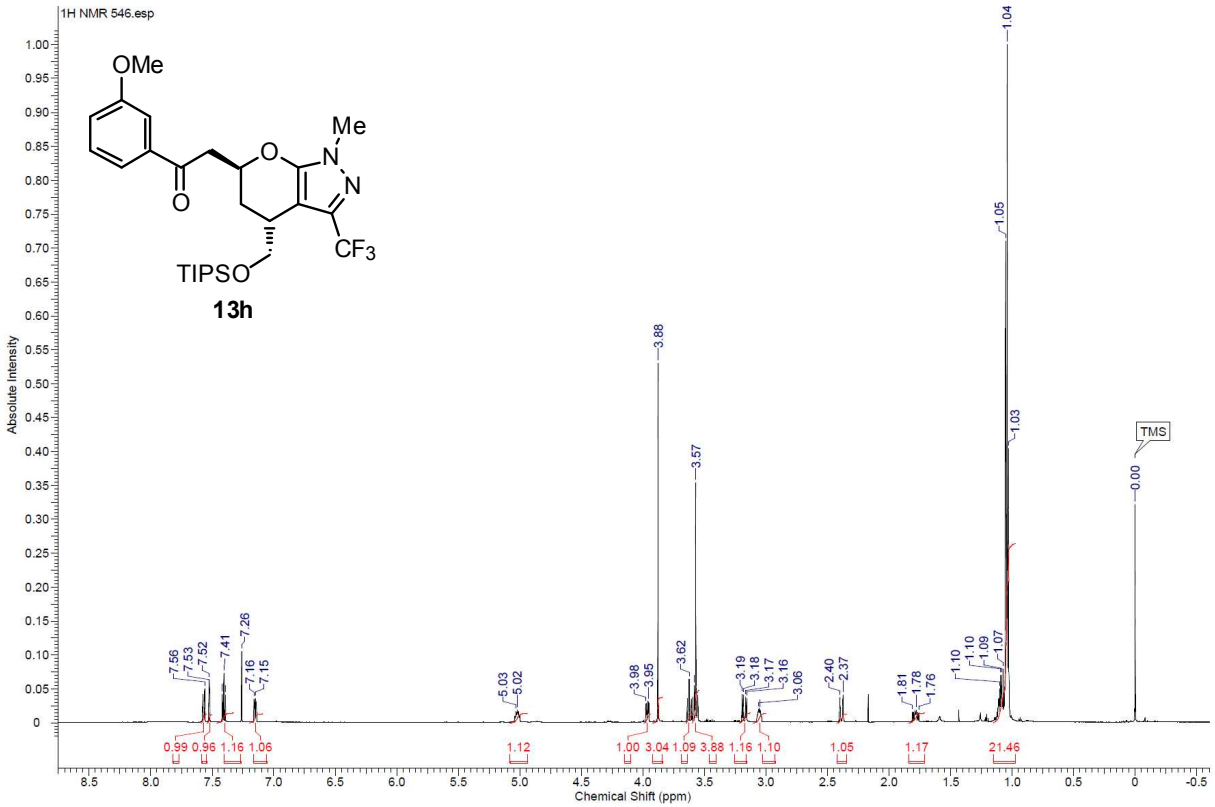


Figure S17. 1H NMR spectrum (600 MHz, $CDCl_3$) of ***trans*-13h**.

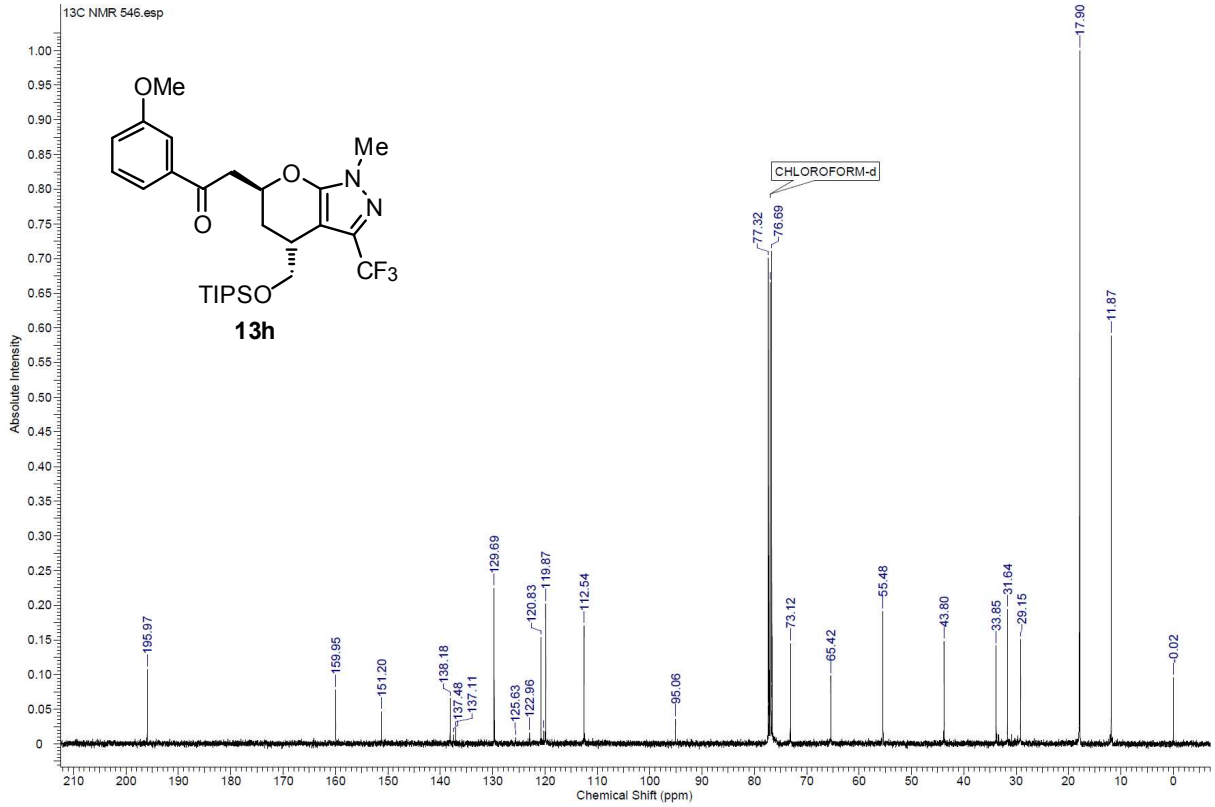


Figure S18. 13C NMR spectrum (100 MHz, $CDCl_3$) of ***trans*-13h**.

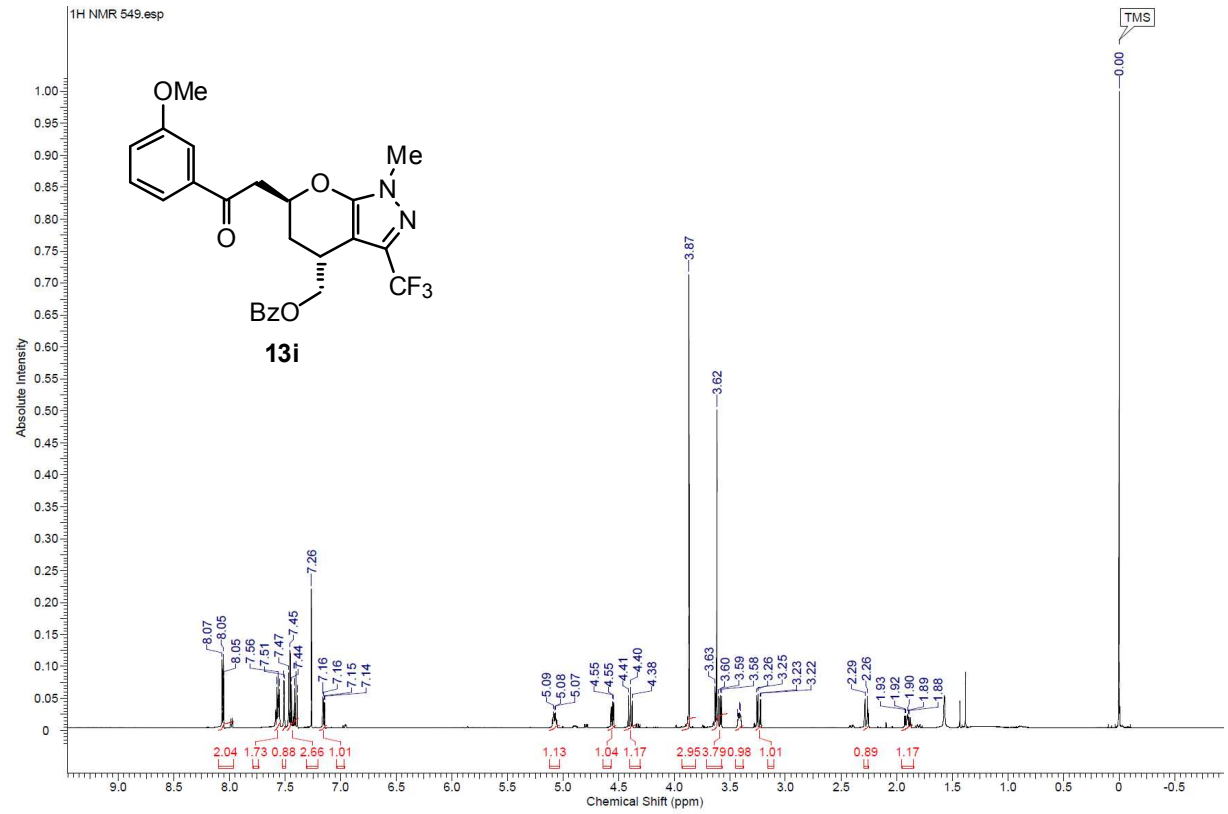


Figure S19. 1H NMR spectrum (600 MHz, $CDCl_3$) of ***trans*-13i**.

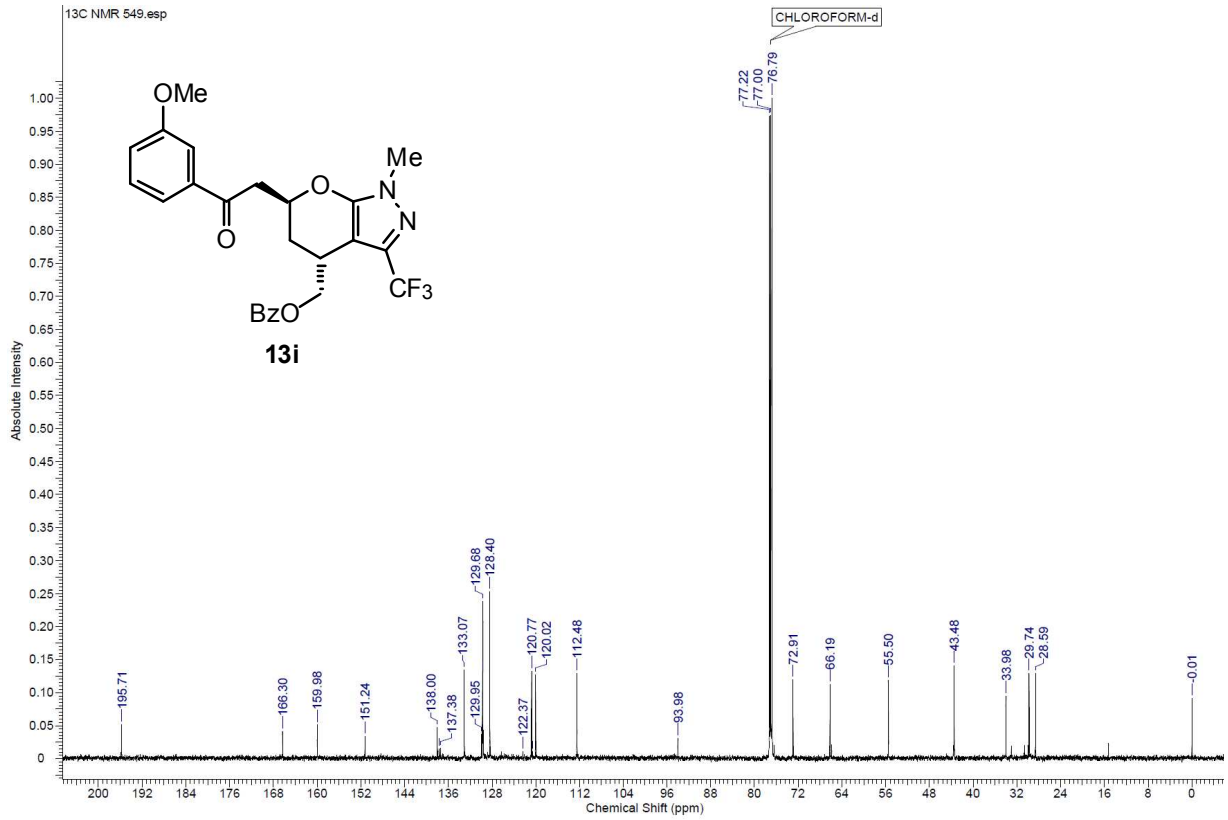


Figure S20. 13C NMR spectrum (151 MHz, $CDCl_3$) of ***trans*-13i**.

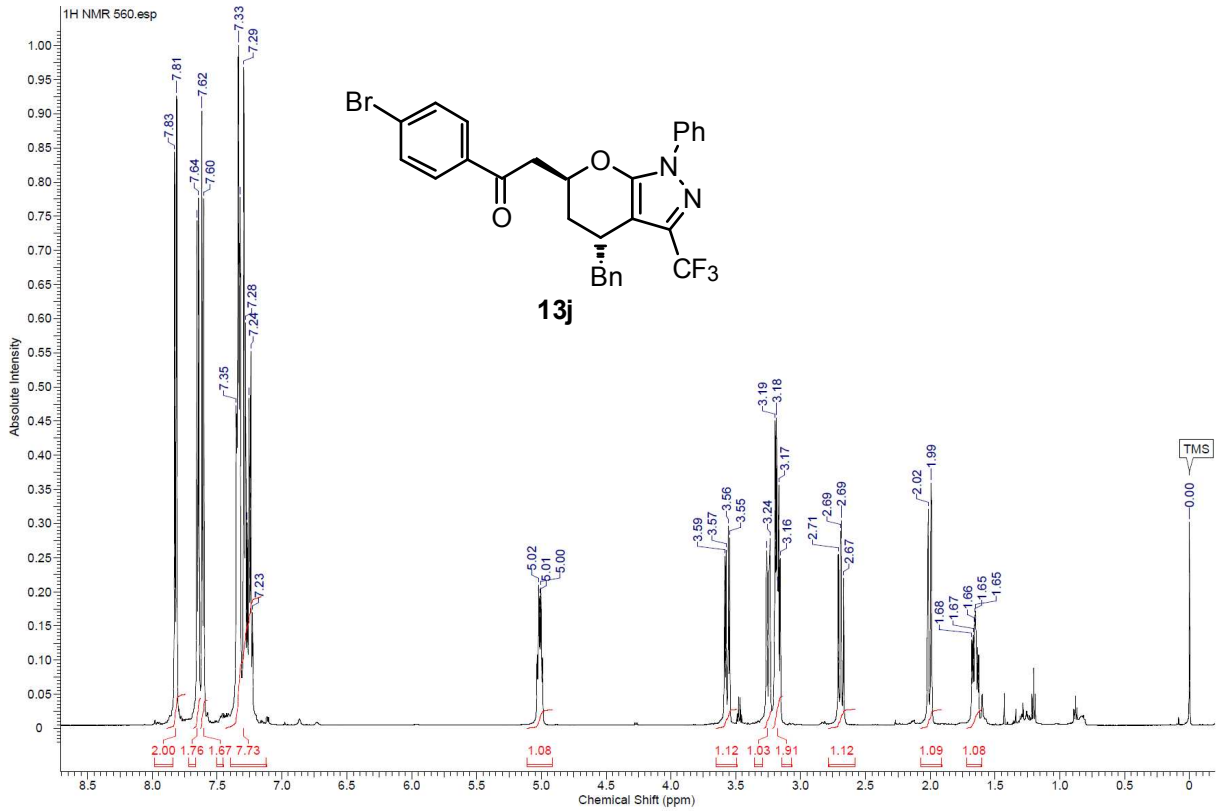


Figure S21. 1H NMR spectrum (600 MHz, $CDCl_3$) of ***trans*-13j**.

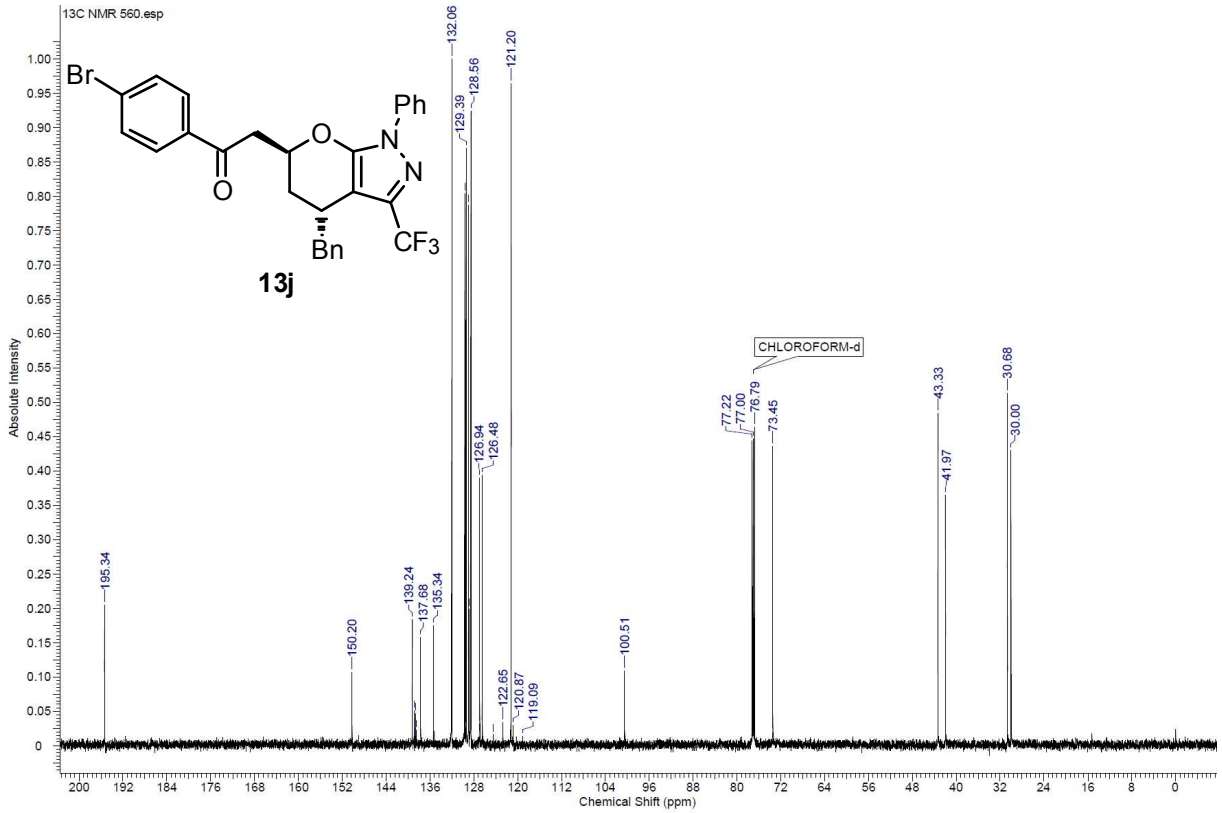


Figure S22. 13C NMR spectrum (151 MHz, $CDCl_3$) of ***trans*-13j**.

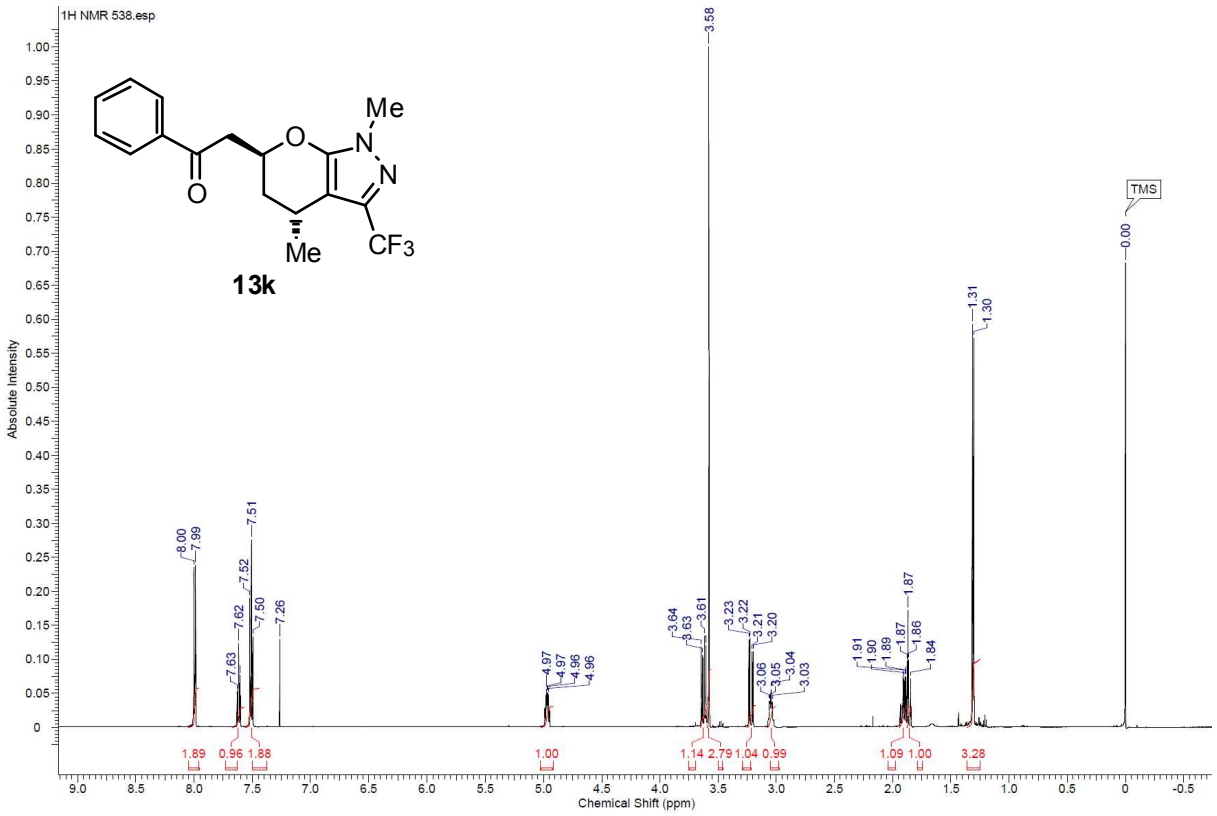


Figure S23. 1H NMR spectrum (600 MHz, $CDCl_3$) of ***trans*-13k**.

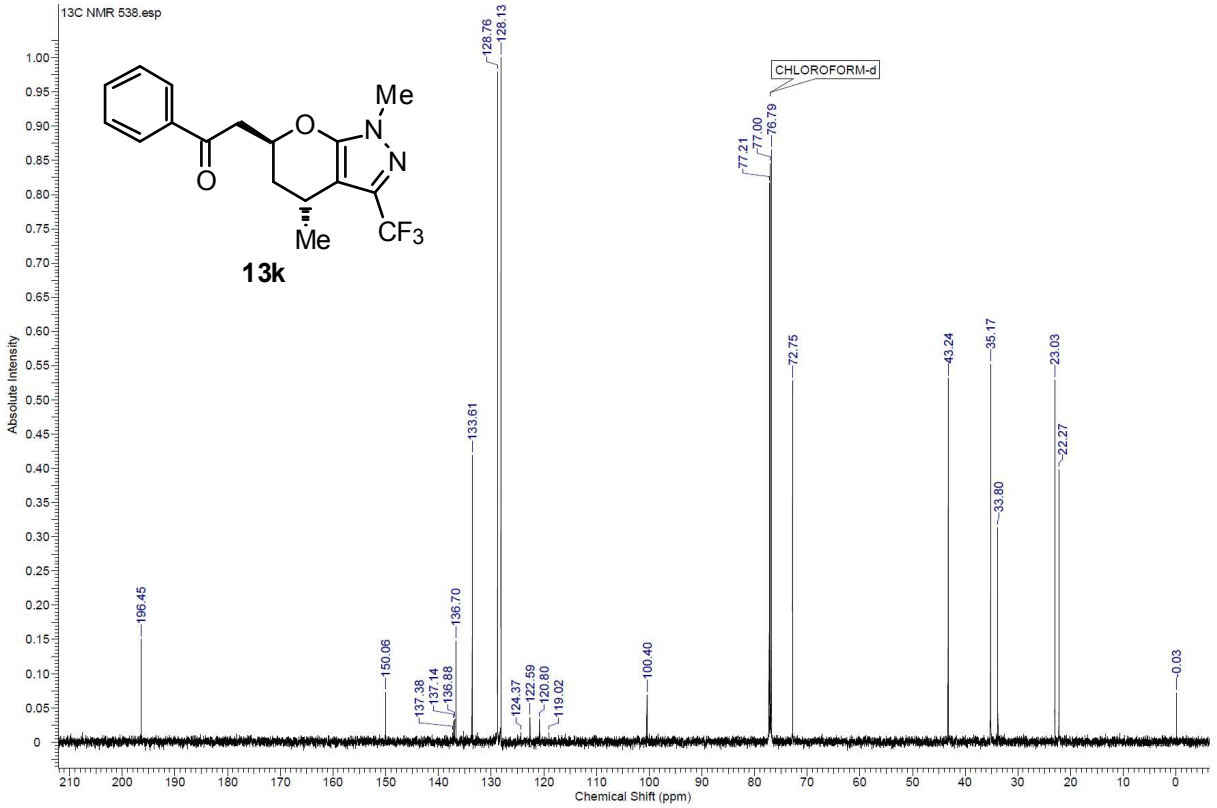


Figure S24. 13C NMR spectrum (151 MHz, $CDCl_3$) of ***trans*-13k**.

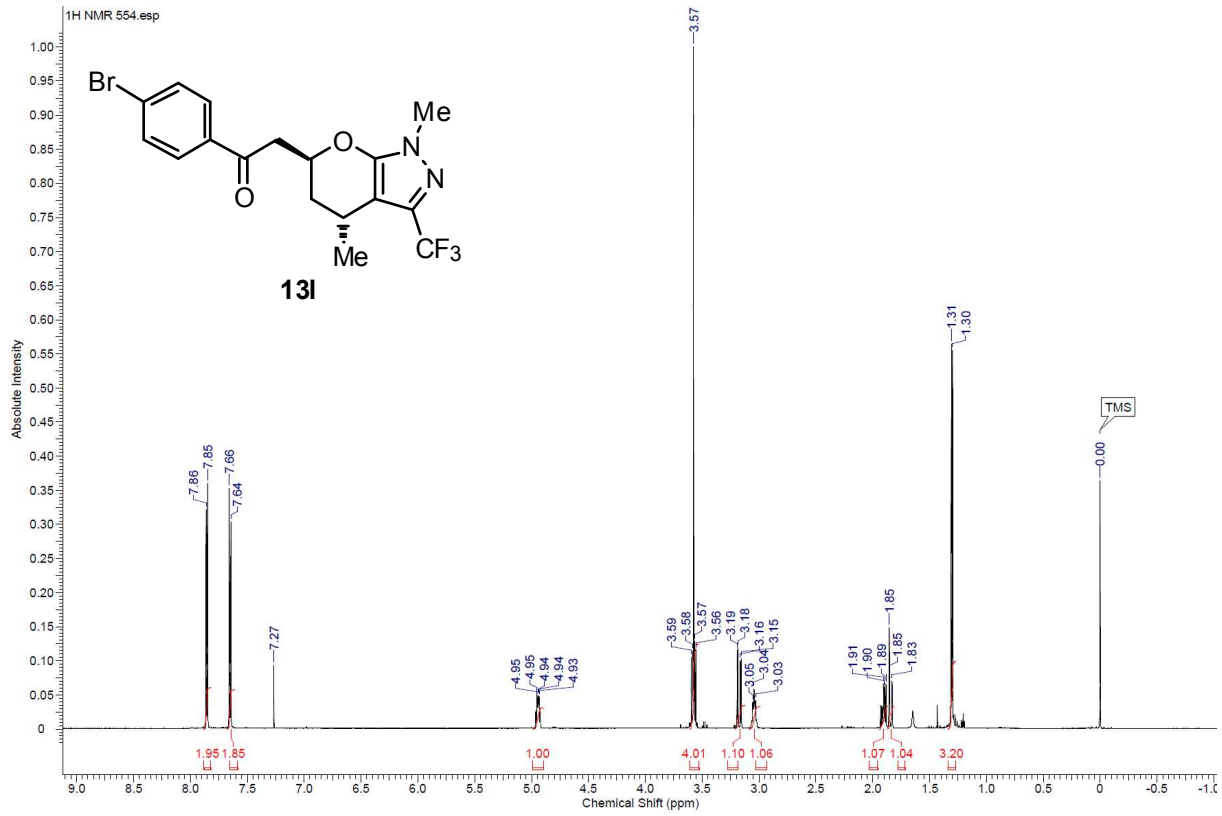


Figure S25. 1H NMR spectrum (600 MHz, $CDCl_3$) of ***trans*-13l**.

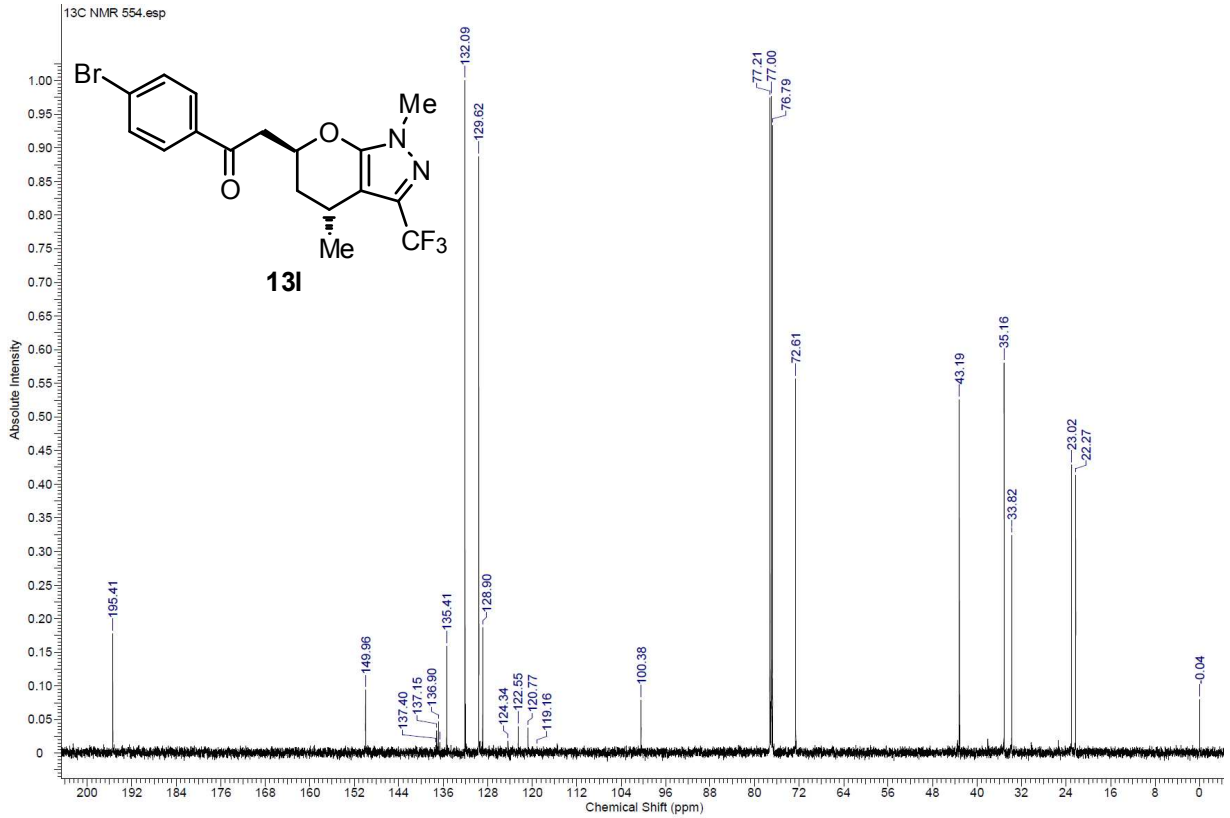


Figure S26. 13C NMR spectrum (151 MHz, $CDCl_3$) of ***trans*-13l**.

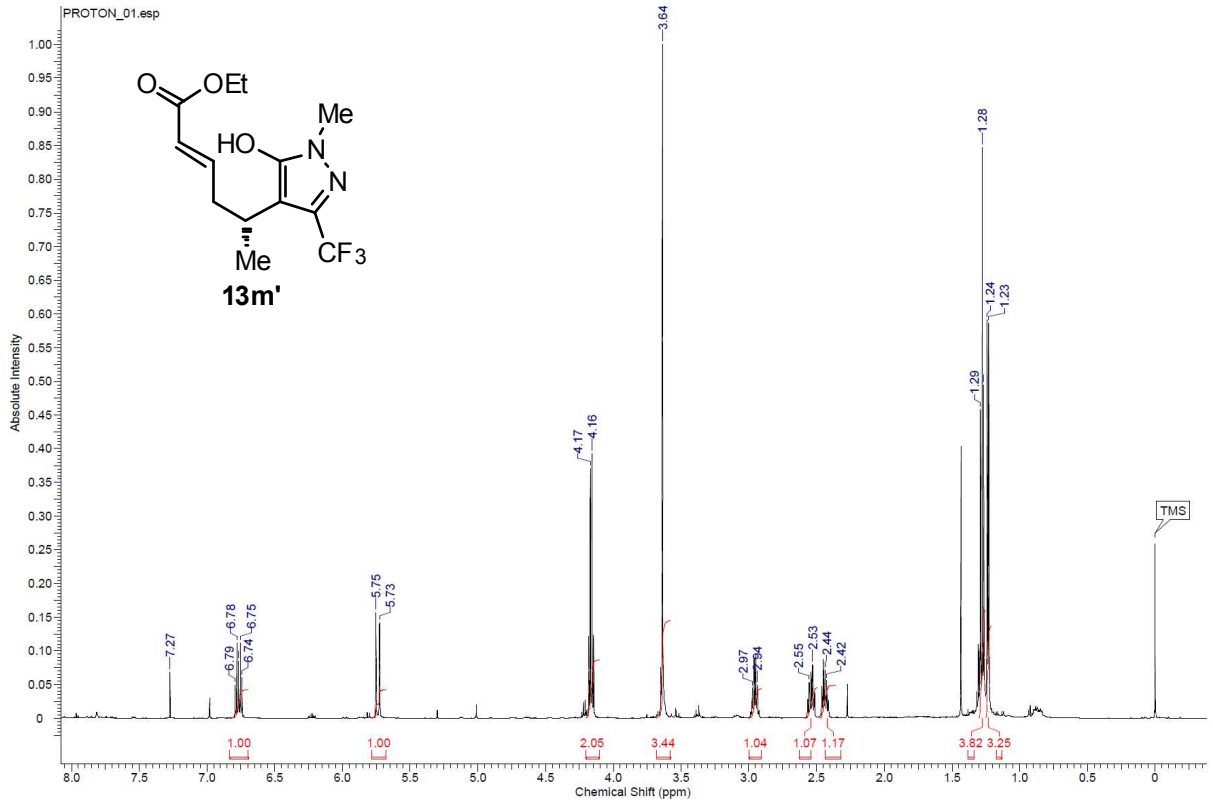


Figure S27. 1H NMR spectrum (600 MHz, $CDCl_3$) of **13m'**; mixture of E/Z isomers.

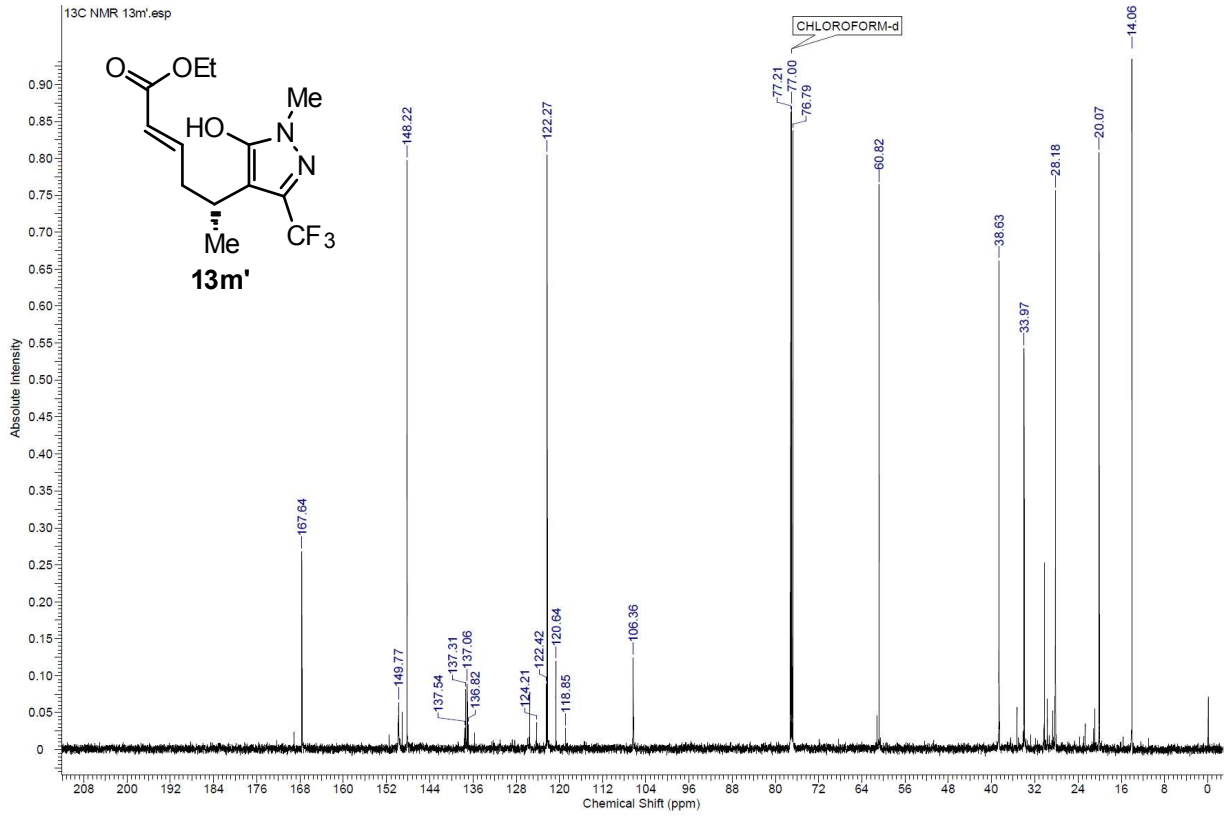


Figure S28. 13C NMR spectrum (151 MHz, $CDCl_3$) of **13m'**; mixture of E/Z isomers.

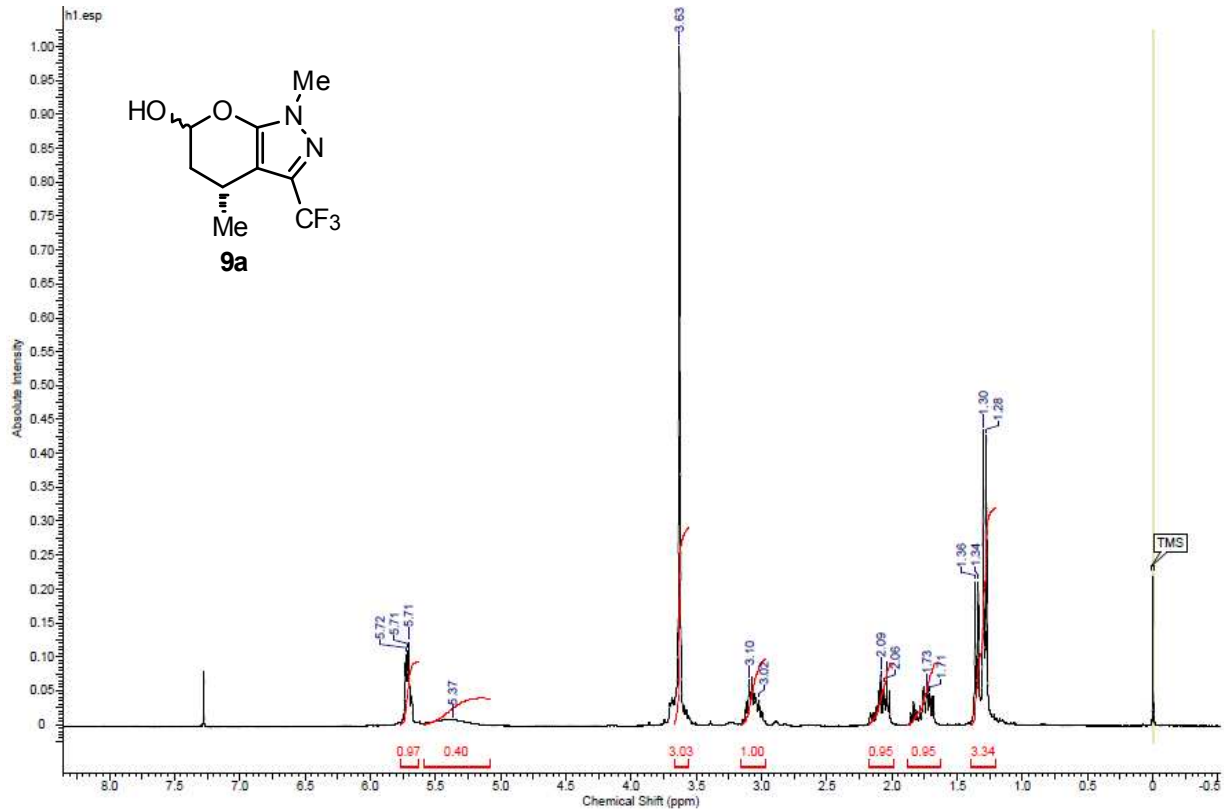


Figure S29. 1H NMR spectrum (300 MHz, $CDCl_3$) of **9a**; mixture of diastereomers.

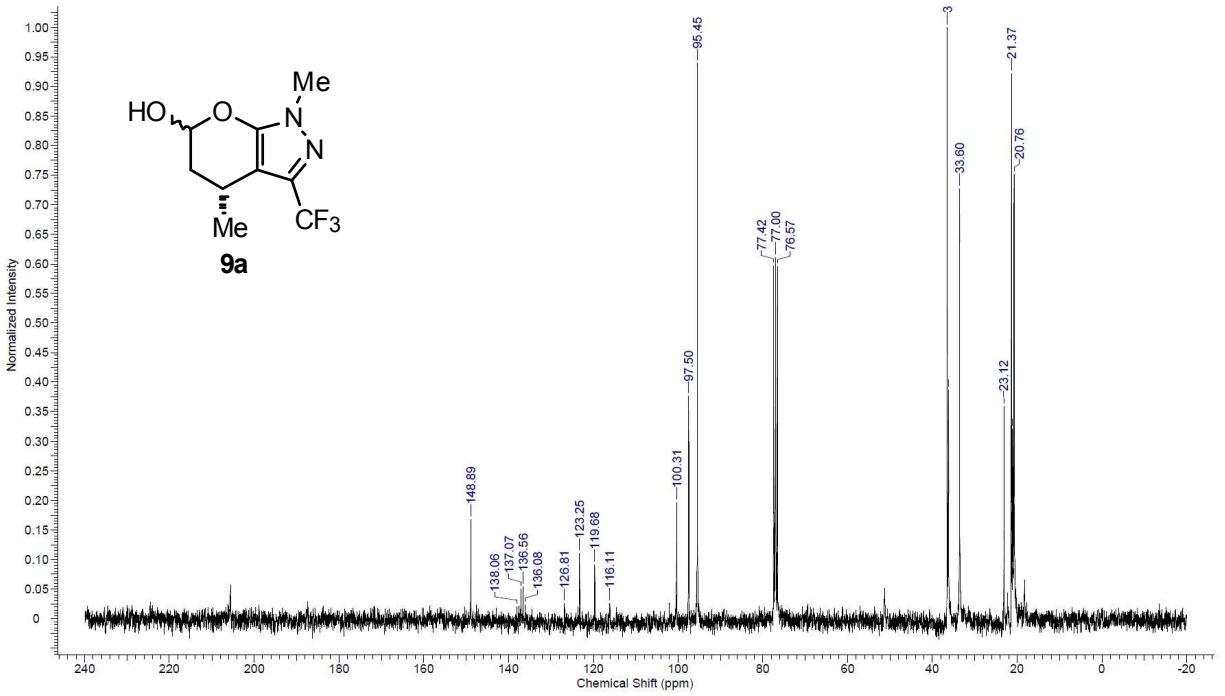
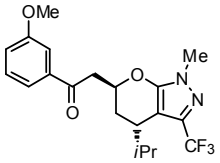


Figure S30. 13C NMR spectrum (75 MHz, $CDCl_3$) of **9a**; mixture of diastereomers.

9. NOESY of Compounds **13e** and **13f**



***trans*-13e**

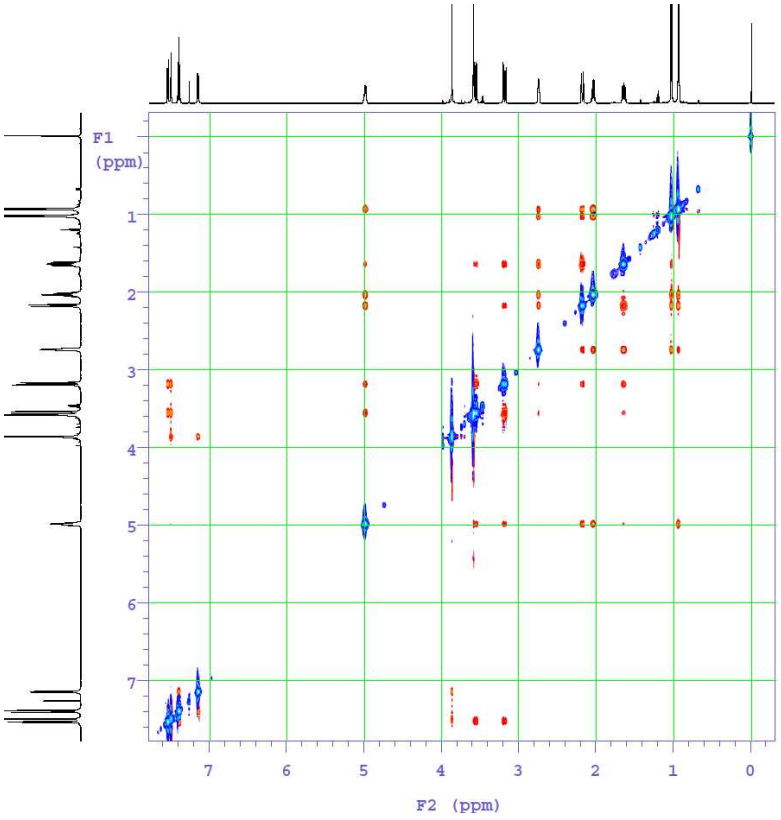
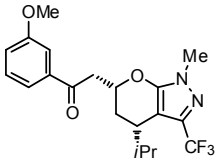


Figure S31. NOESY spectrum (600 MHz, $CDCl_3$) of ***trans*-13e**.



***cis*-13e**

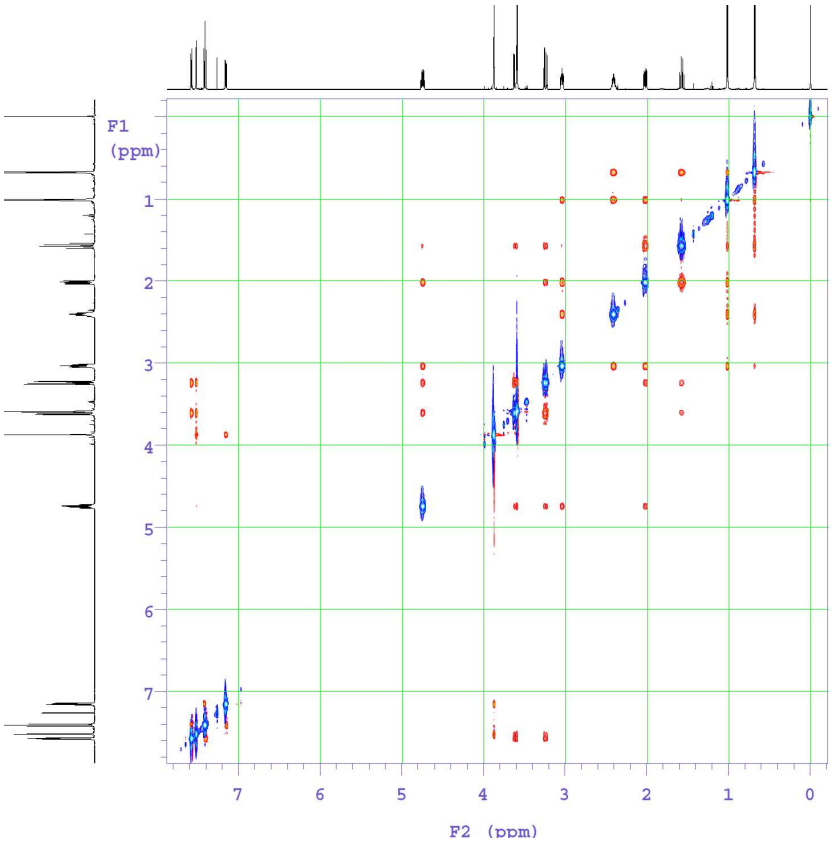


Figure S32. NOESY spectrum (600 MHz, $CDCl_3$) of ***cis*-13e**.

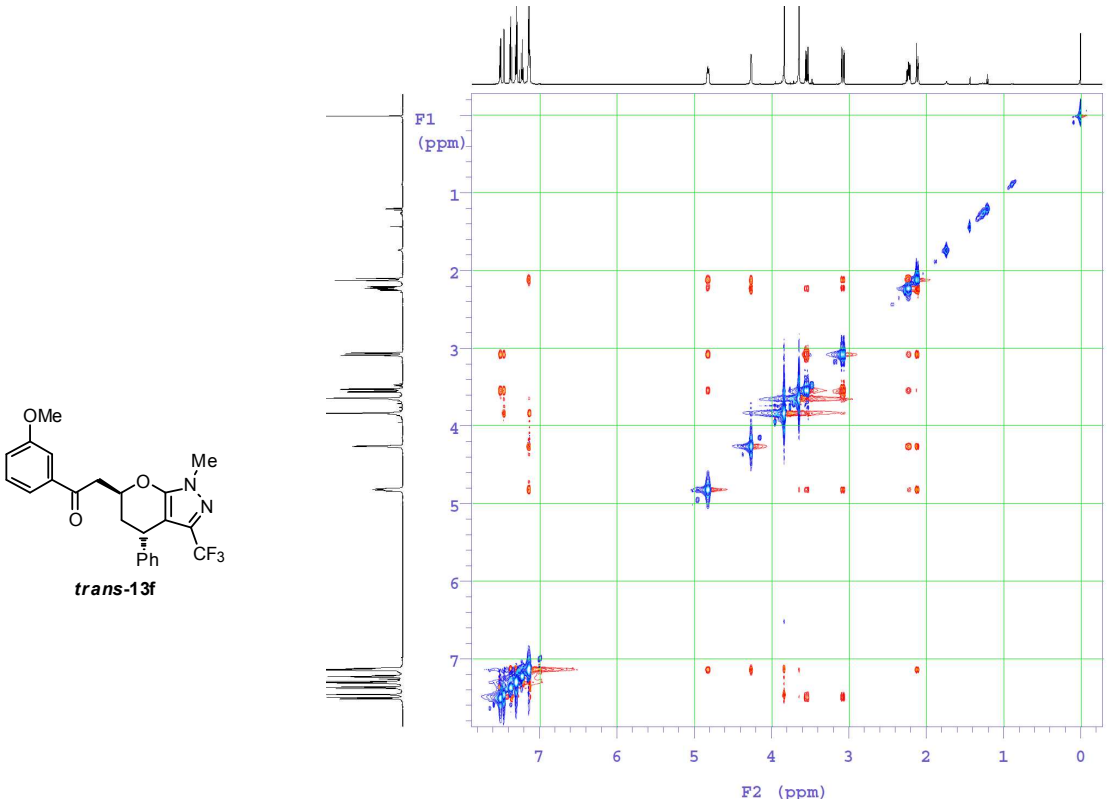
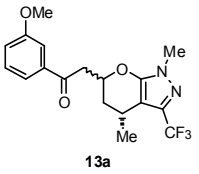
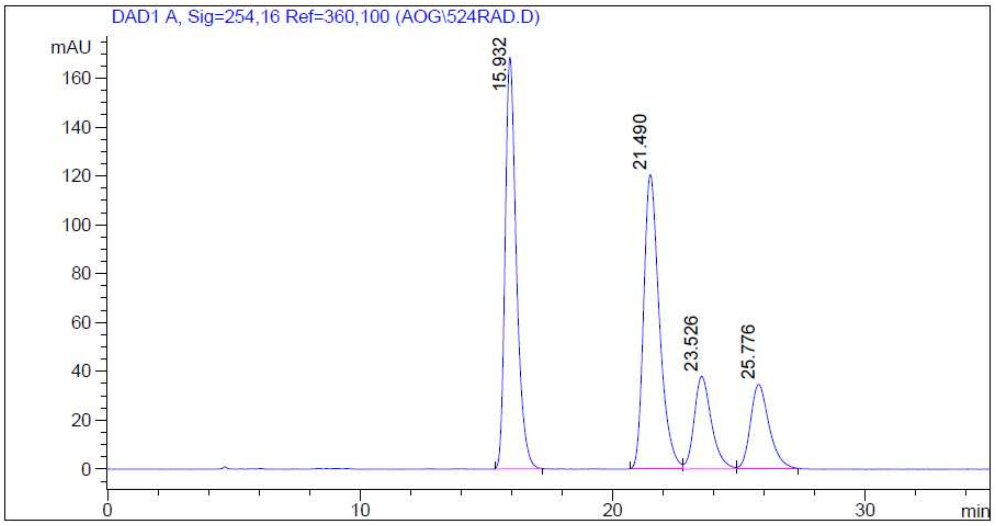


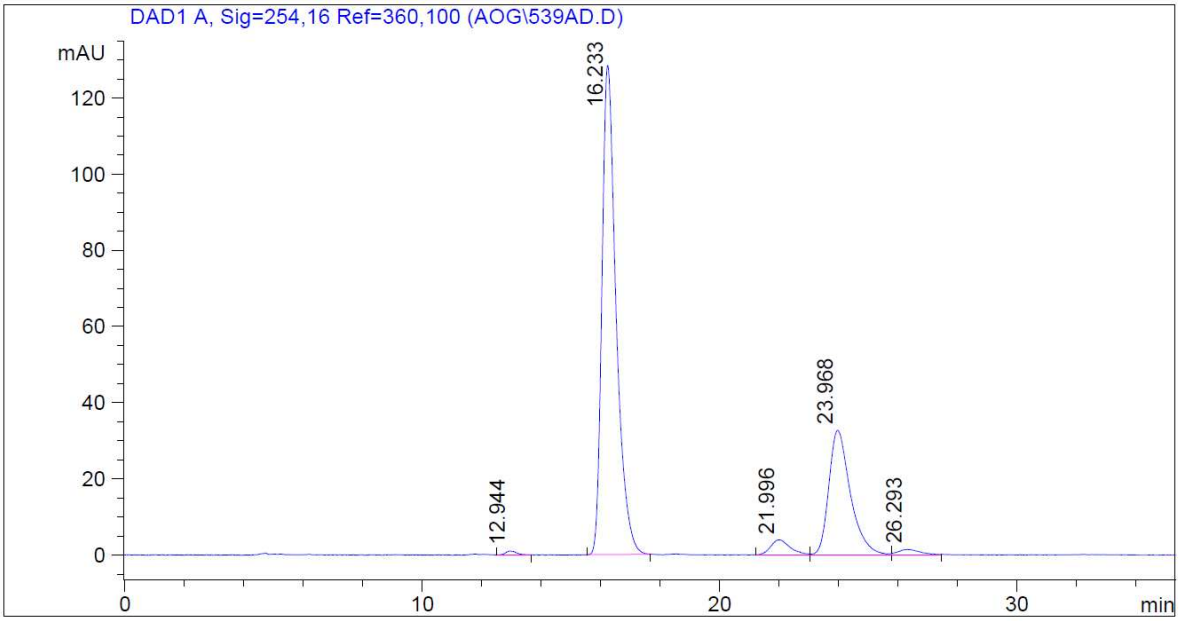
Figure S33. NOESY spectrum (600 MHz, $CDCl_3$) of ***trans*-13f**.

10. HPLC Chromatograms



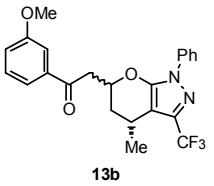
13a



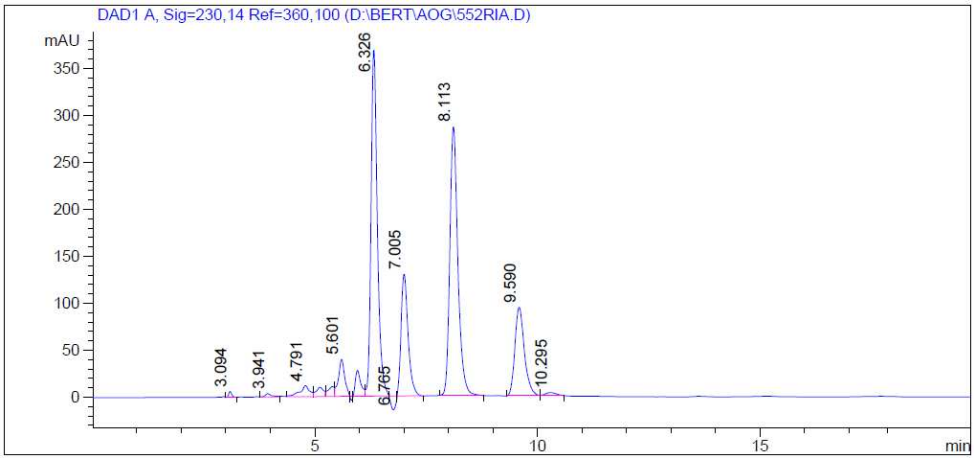


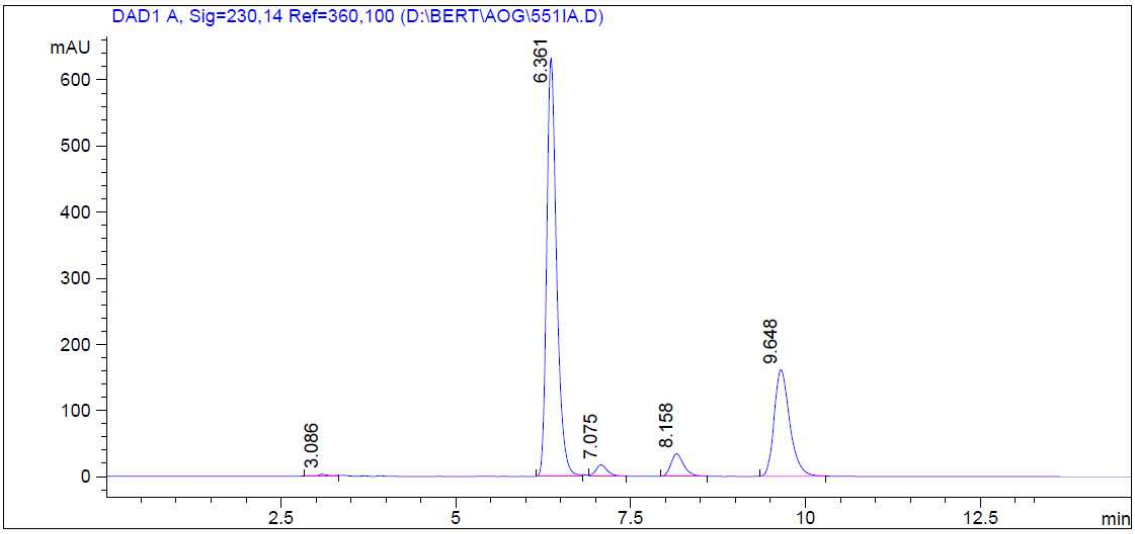
#	Ret. Time (min)	Width	Height (mAU)	Area (mAU*s)	Area %
1	12.94	0.30	1.01	24.35	0.39
2	16.23	0.50	128.46	4257.16	68.93
3	22.00	0.65	3.93	179.03	2.90
4	23.97	0.75	32.72	1643.60	26.61
5	26.29	0.62	1.40	71.68	1.16
Total				6175.81	100.00

Figure S34. HPLC chromatogram of **13a**; comparison of racemic (top) and non-racemic (bottom); mixture of diastreomers.



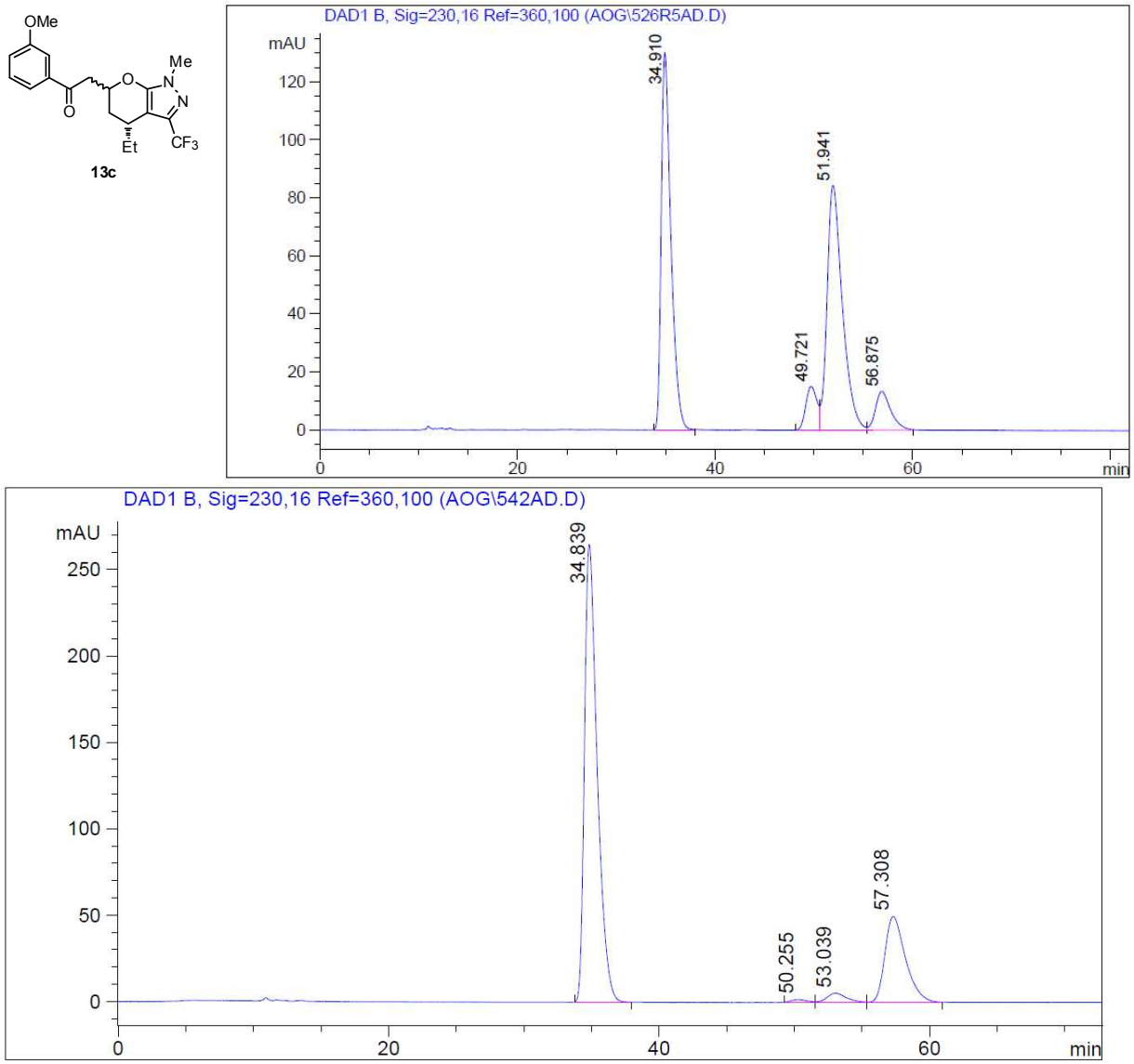
13b





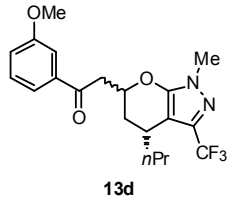
#	Ret. Time (min)	Width	Height (mAU)	Area (mAU*s)	Area %
1	3.09	0.14	3.37	37.05	0.39
2	6.36	0.15	634.33	6248.35	66.28
3	7.08	0.18	17.34	203.76	2.16
4	8.16	0.19	34.13	438.87	4.66
5	9.65	0.24	161.49	2498.67	26.51
Total				9426.70	100.00

Figure S35. HPLC chromatogram of **13b**; comparison of racemic (top) and non-racemic (bottom); mixture of diastreomers.

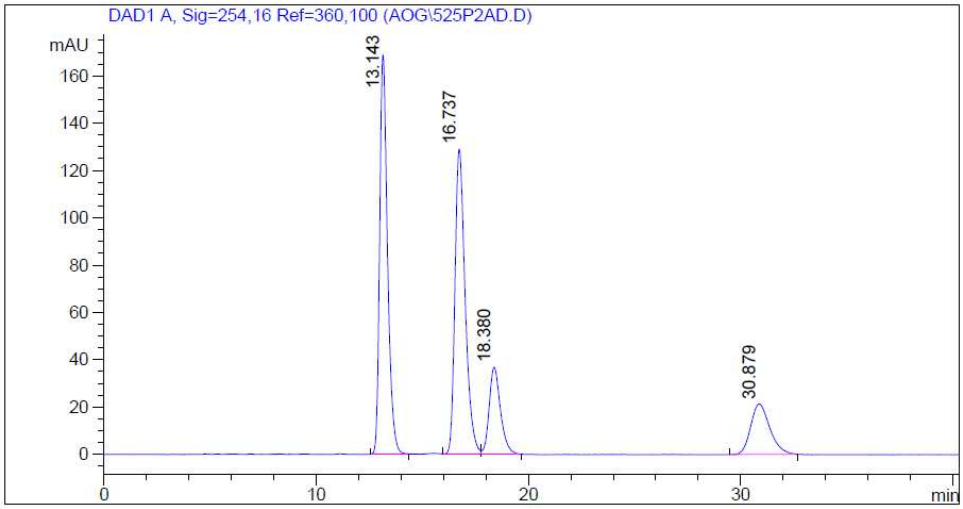


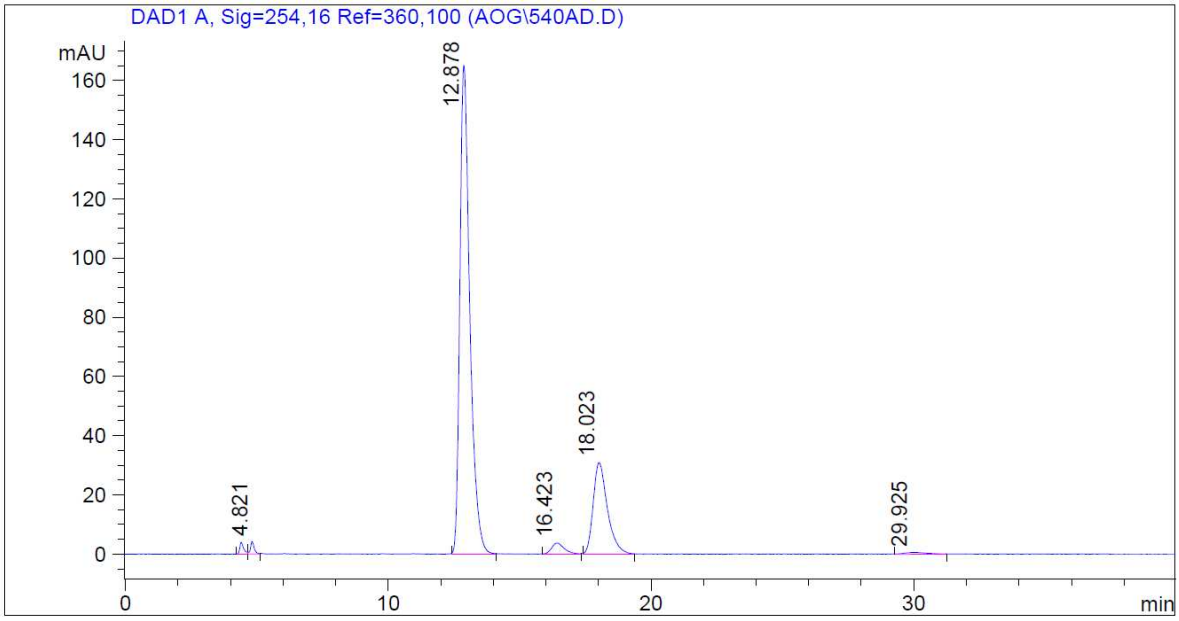
#	Ret. Time (min)	Width	Height (mAU)	Area (mAU*s)	Area %
1	34.84	0.99	264.39	17344.75	74.74
2	50.25	1.27	1.46	114.90	0.50
3	53.04	1.61	5.17	498.69	2.15
4	57.31	1.77	49.56	5249.53	22.62
Total				23207.87	100.00

Figure S36. HPLC chromatogram of **13c**; comparison of racemic (top) and non-racemic (bottom); mixture of diastreomers.



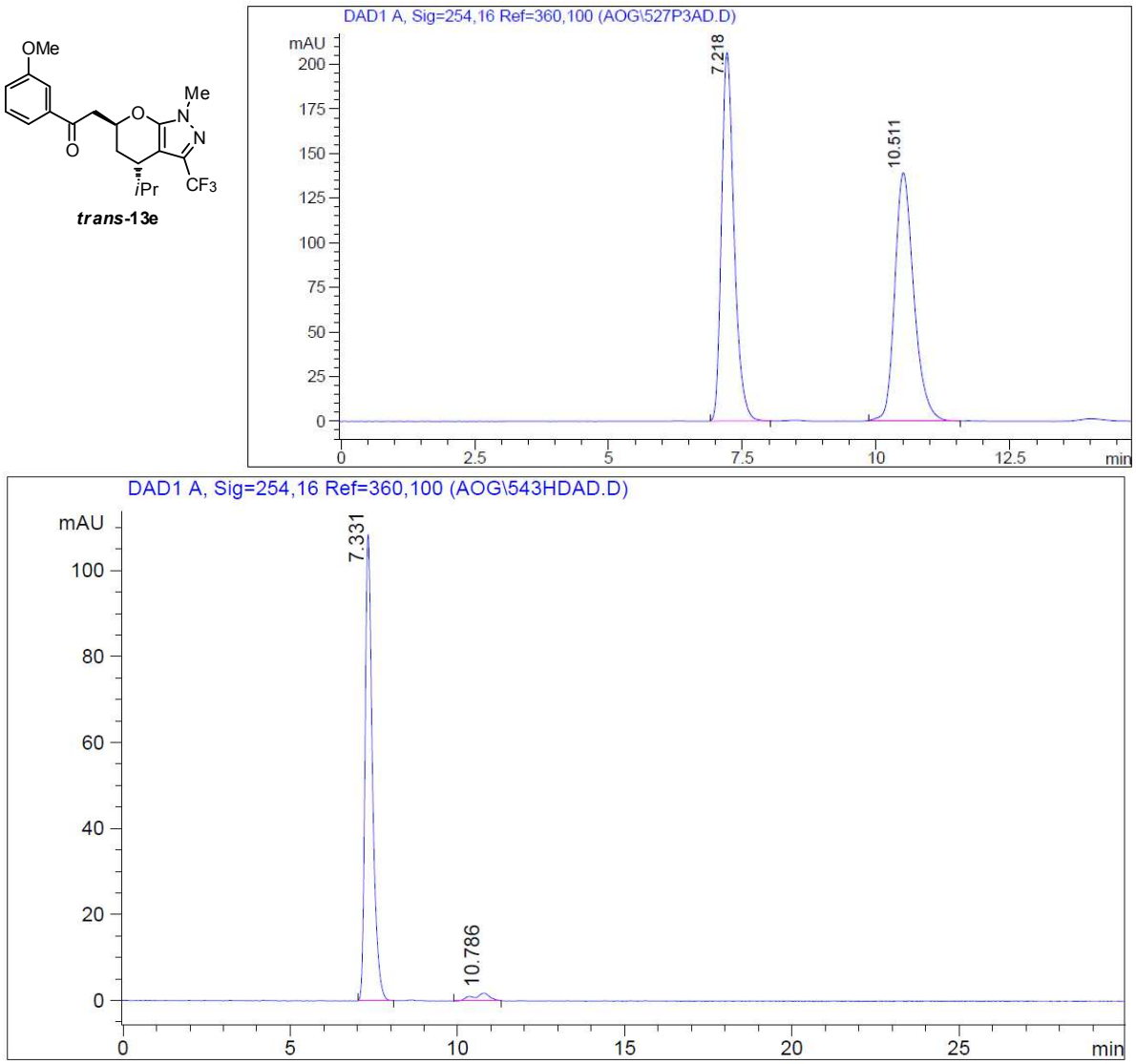
13d





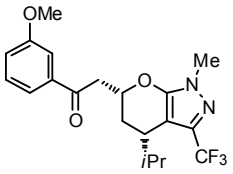
#	Ret. Time (min)	Width	Height (mAU)	Area (mAU*s)	Area %
1	4.41	0.16	3.99	40.77	0.71
2	4.82	0.16	4.08	42.87	0.74
3	12.88	0.40	164.72	4348.09	75.49
4	16.42	0.50	3.70	123.70	2.15
5	18.02	0.57	30.84	1161.59	20.17
6	29.92	1.05	0.67	42.58	0.74
Total				5759.59	100.00

Figure S37. HPLC chromatogram of **13d**; comparison of racemic (top) and non-racemic (bottom); mixture of diastreomers.

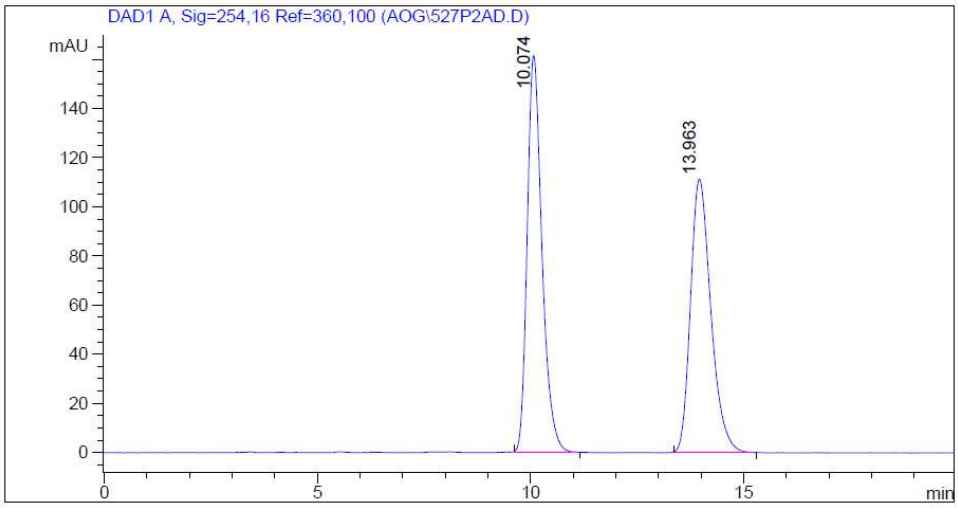


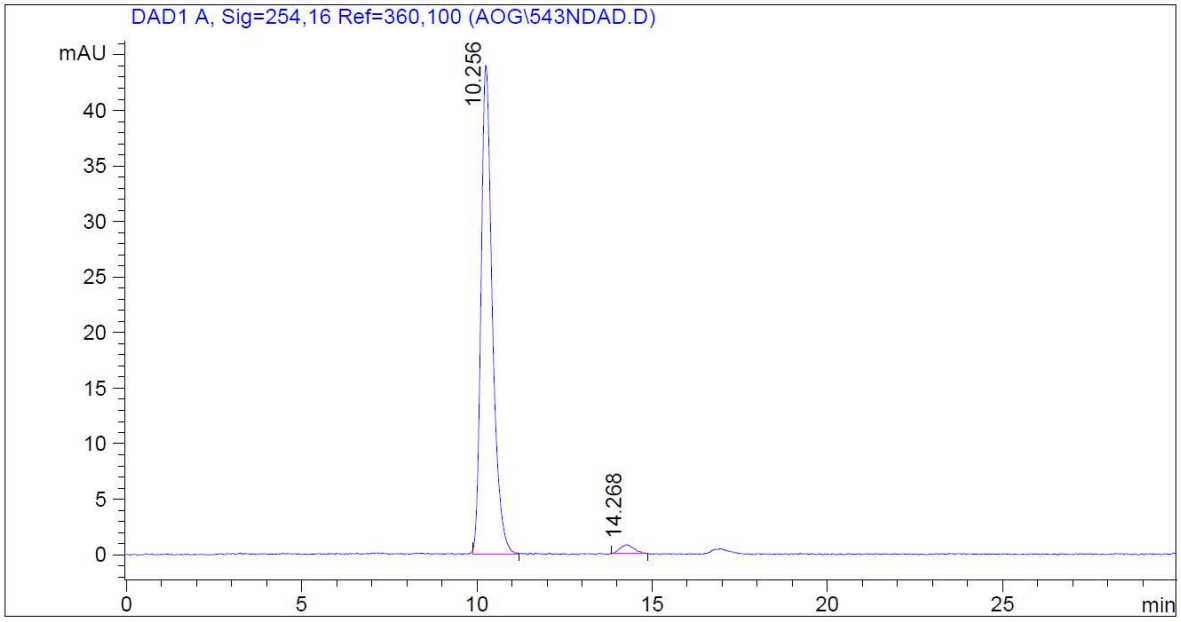
#	Ret. Time (min)	Width	Height (mAU)	Area (mAU*s)	Area %
1	7.33	0.25	107.50	1671.40	96.58
2	10.79	0.47	1.77	59.14	3.42
Total				1730.54	100.00

Figure S38. HPLC chromatogram of ***trans*-13e**; comparison of racemic (top) and non-racemic (bottom).



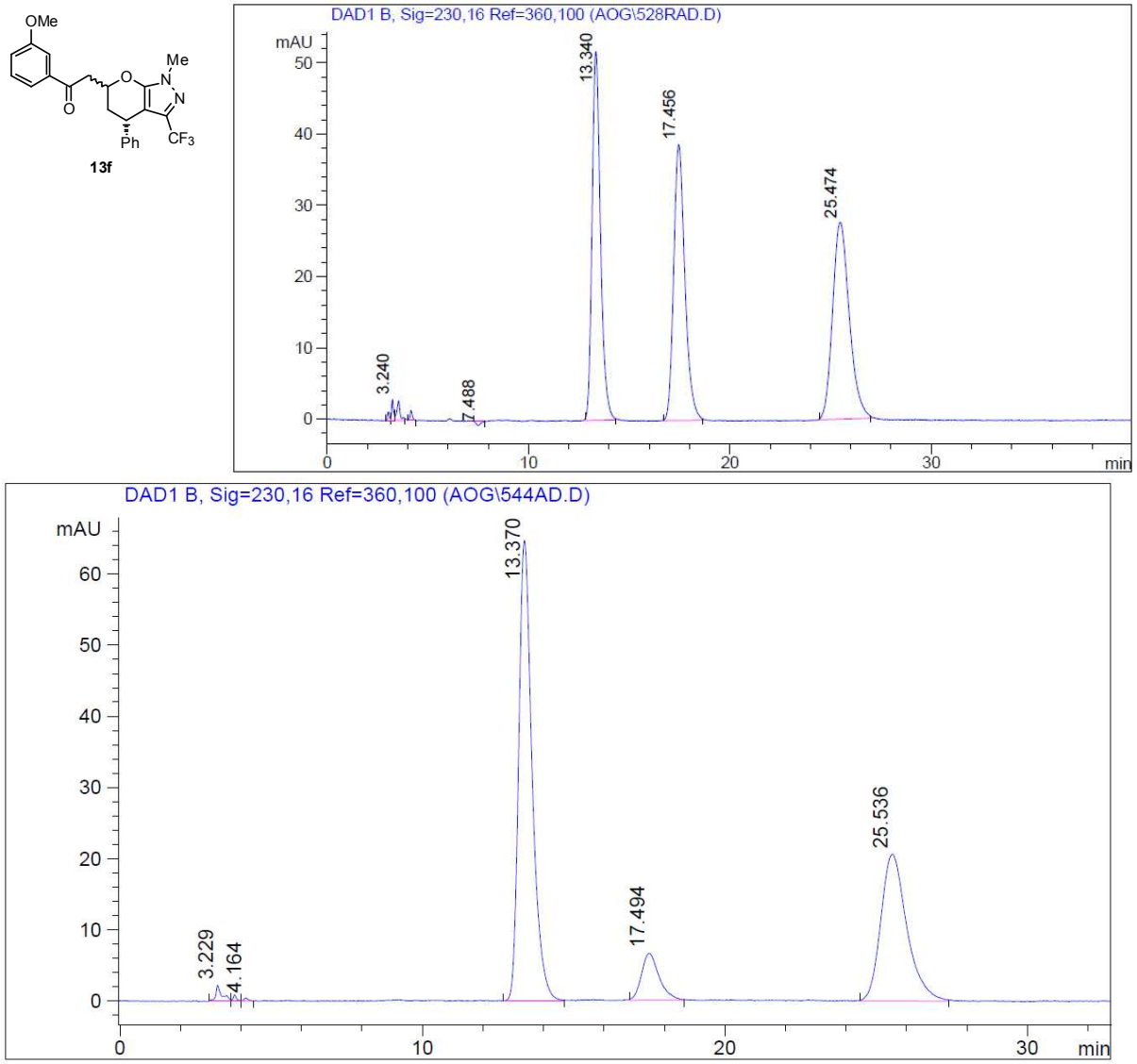
***cis*-13e**





#	Ret. Time (min)	Width	Height (mAU)	Area (mAU*s)	Area %
1	10.26	0.34	43.98	985.36	97.68
2	14.27	0.38	0.82	23.36	2.32
Total				1008.73	100.00

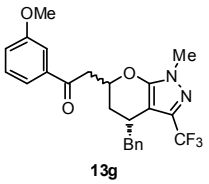
Figure S39. HPLC chromatogram of ***cis*-13e**; comparison of racemic (top) and non-racemic (bottom).



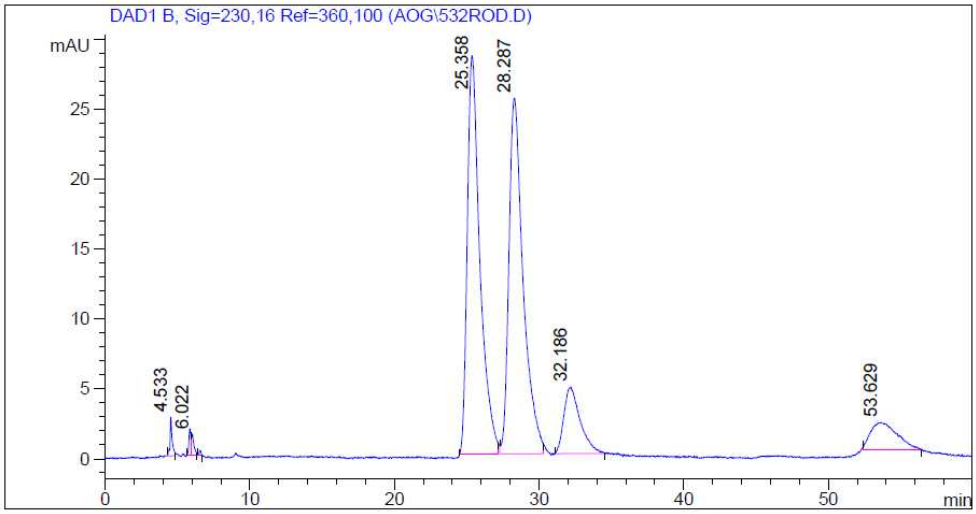
#	Ret. Time (min)	Width	Height (mAU)	Area (mAU*s)	Area %
1	3.23	0.19	2.20	30.93	0.88
2	3.79	0.13	0.87	6.56	0.19
3	4.16	0.16	0.40	4.31	0.12
4	13.37	0.47	64.64	1985.61	56.23
5	17.49	0.58	6.60	267.91	7.59
6	25.54	0.89	20.64	1235.96	35.00
Total				3531.27	100.00

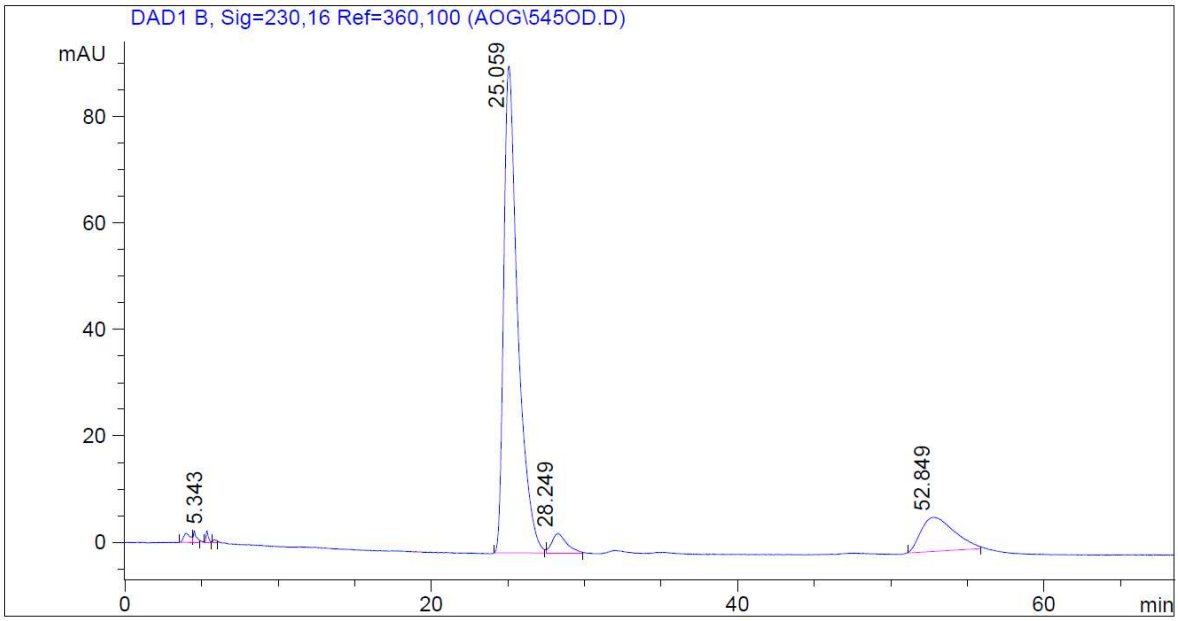
The signal at 25 min belongs to the unseparated mixture of enantiomers of the second diastereomer.

Figure S40. HPLC chromatogram of **13f**; comparison of racemic (top) and non-racemic (bottom); mixture of diastreomers.



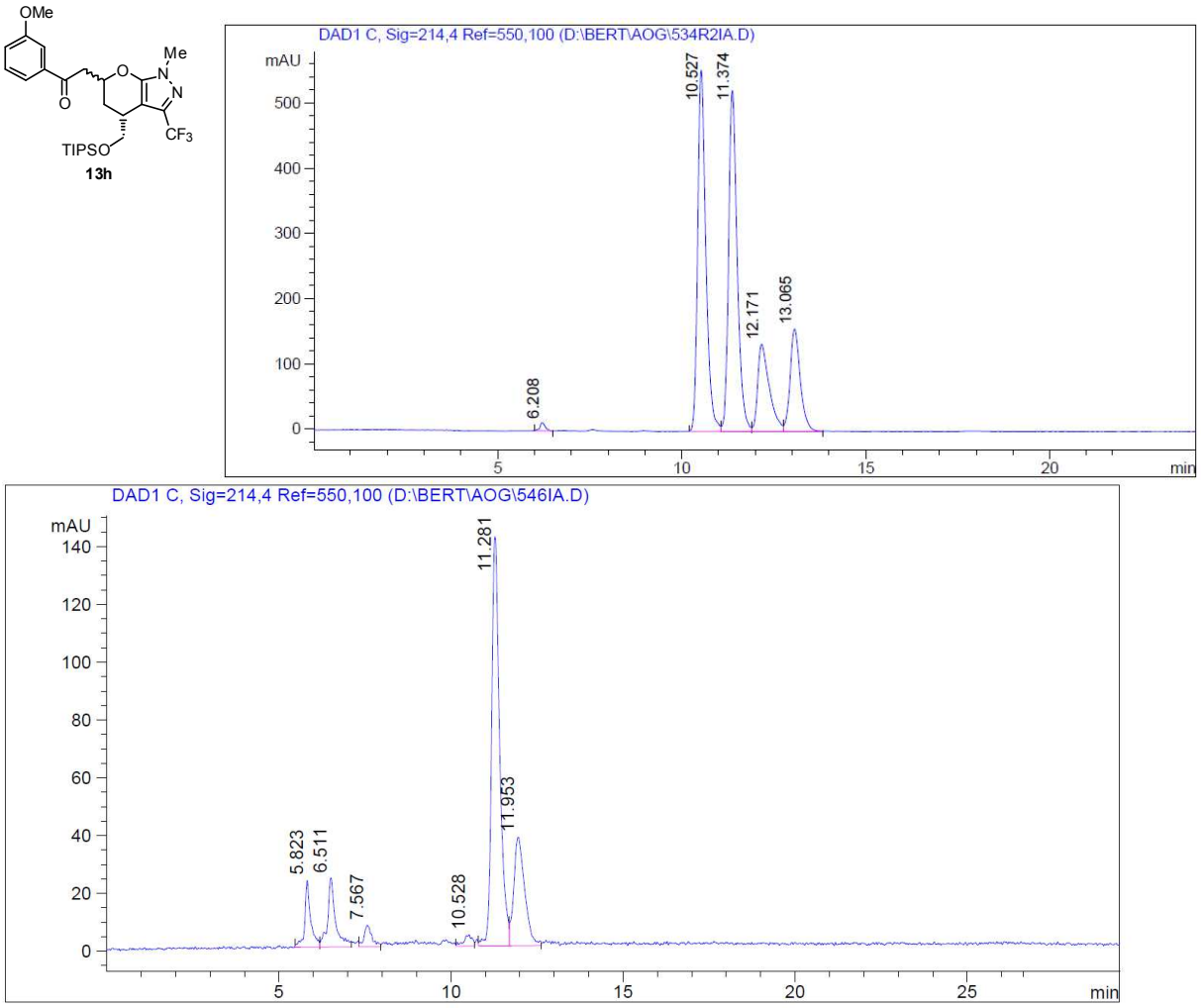
13g





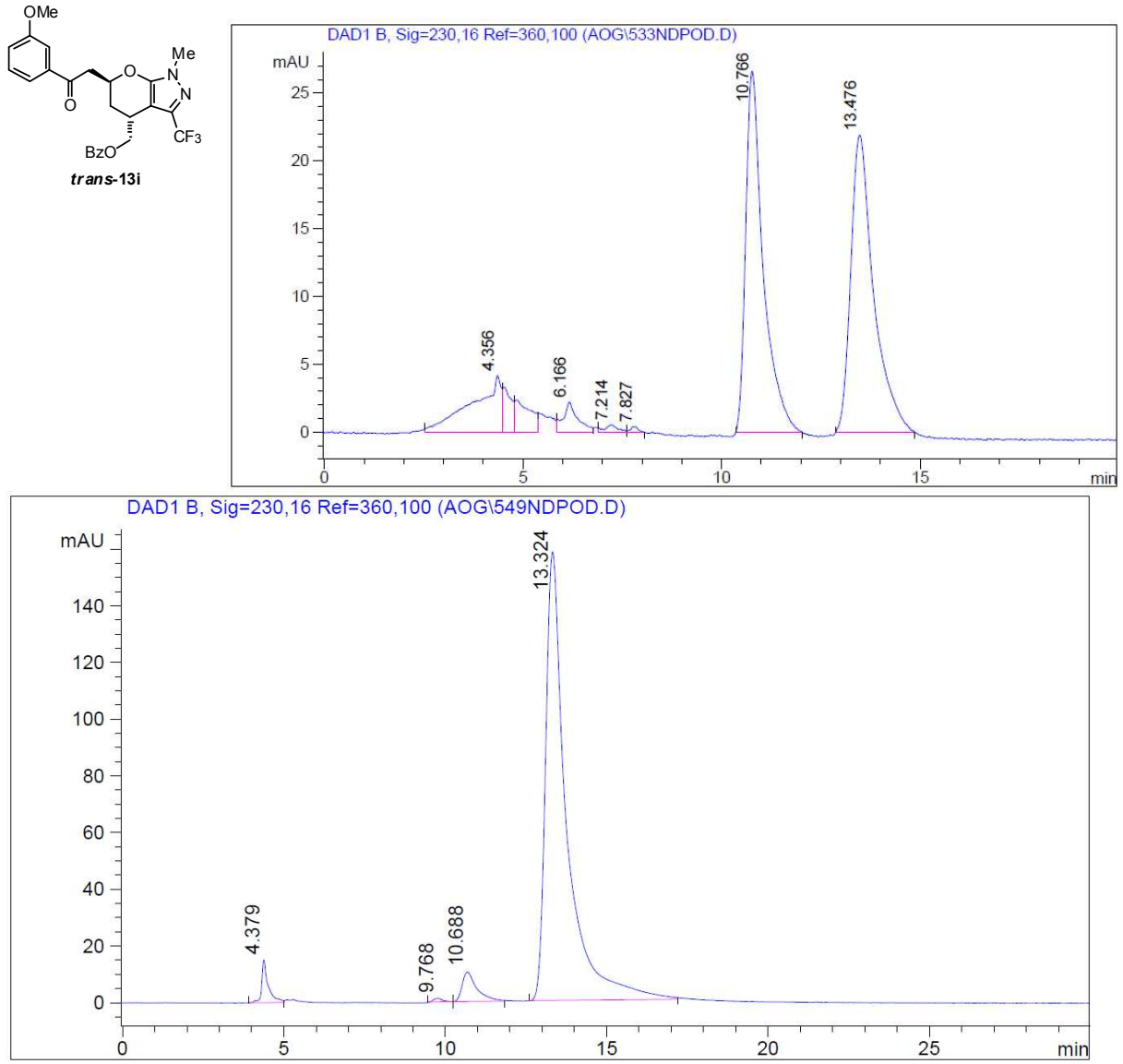
#	Ret. Time (min)	Width	Height (mAU)	Area (mAU*s)	Area %
1	4.00	0.39	1.75	54.29	0.76
2	4.51	0.23	2.24	30.76	0.43
3	5.34	0.16	2.26	25.29	0.35
4	5.83	0.20	0.63	9.18	0.13
5	25.06	0.92	91.48	5845.08	81.39
6	28.25	0.80	3.68	246.29	3.43
7	52.85	1.78	6.43	970.83	13.52
Total				7181.71	100.00

Figure S41. HPLC chromatogram of **13g**; comparison of racemic (top) and non-racemic (bottom); mixture of diastreomers.



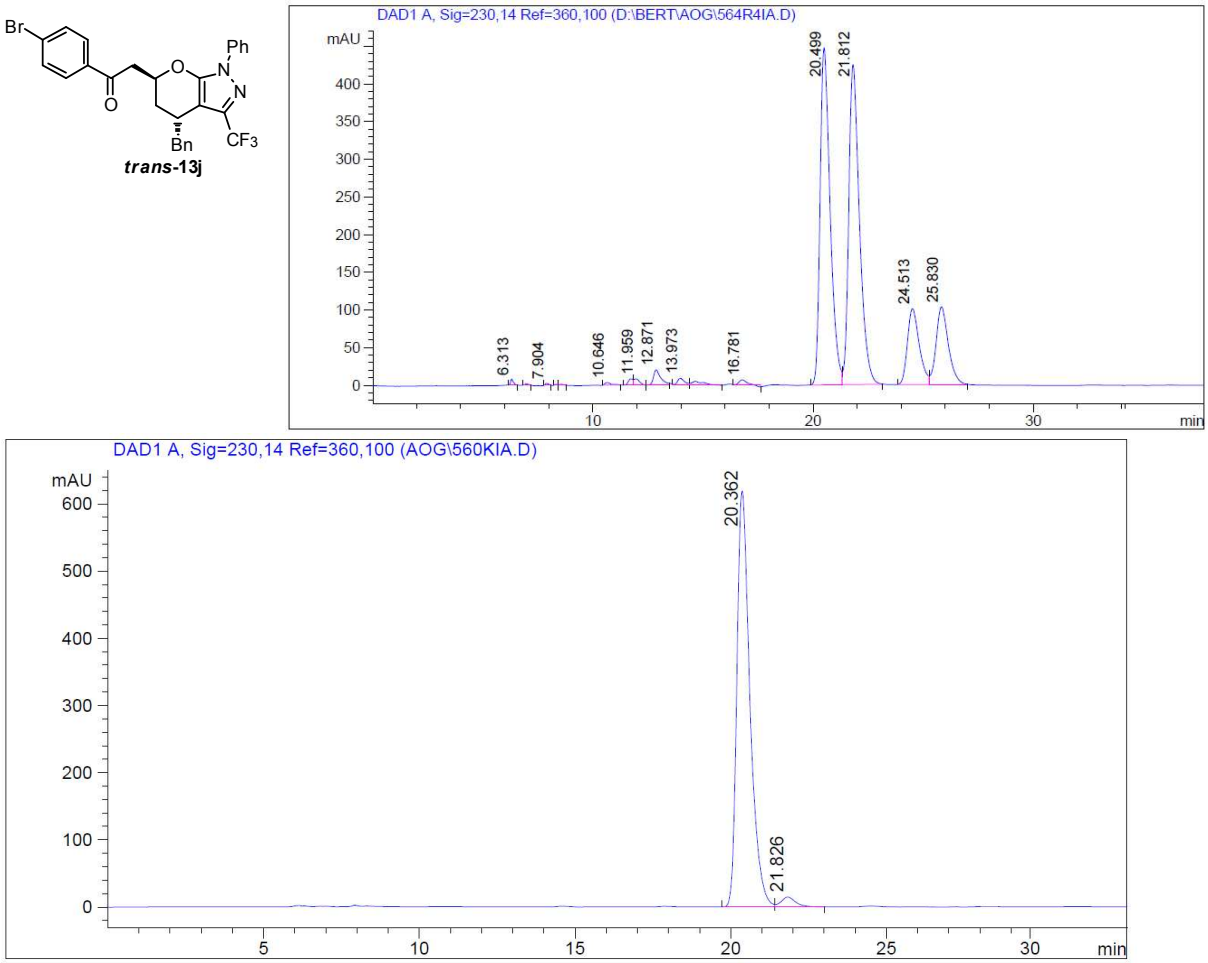
#	Ret. Time (min)	Width	Height (mAU)	Area (mAU*s)	Area %
1	5.82	0.16	23.20	276.07	6.91
2	6.51	0.22	23.88	383.36	9.60
3	7.57	0.22	7.53	119.53	2.99
4	10.53	0.21	3.93	66.87	1.67
5	11.28	0.24	141.57	2316.77	58.02
6	11.95	0.32	37.52	830.42	20.80
Total				3993.02	100.00

Figure S42. HPLC chromatogram of **13h**; comparison of racemic (top) and non-racemic (bottom); mixture of diastreomers.



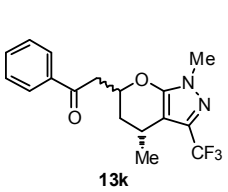
#	Ret. Time (min)	Width	Height (mAU)	Area (mAU*s)	Area %
1	4.38	0.19	15.02	212.92	2.74
2	9.77	0.22	1.17	20.49	0.26
3	10.69	0.52	10.43	327.77	4.23
4	13.32	0.65	158.23	7196.56	92.77
Total				7757.74	100.00

Figure S43. HPLC chromatogram of ***trans*-13i**; comparison of racemic (top) and non-racemic (bottom).

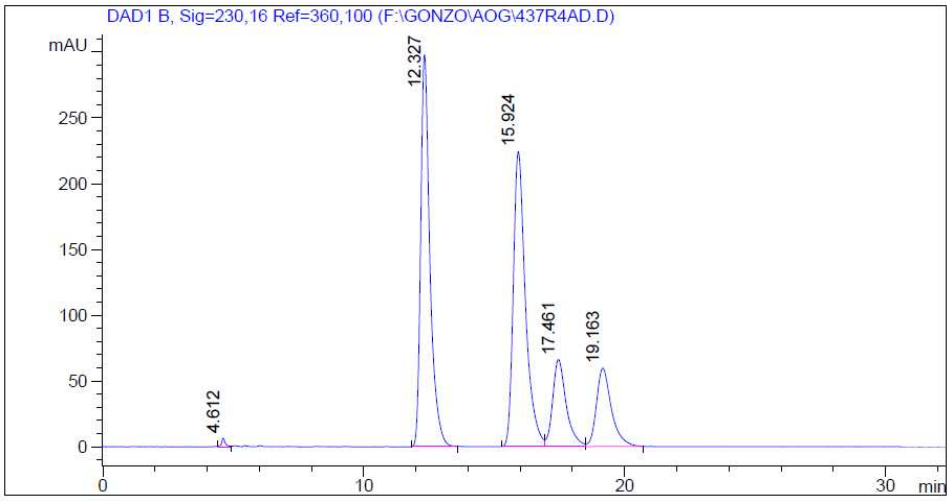


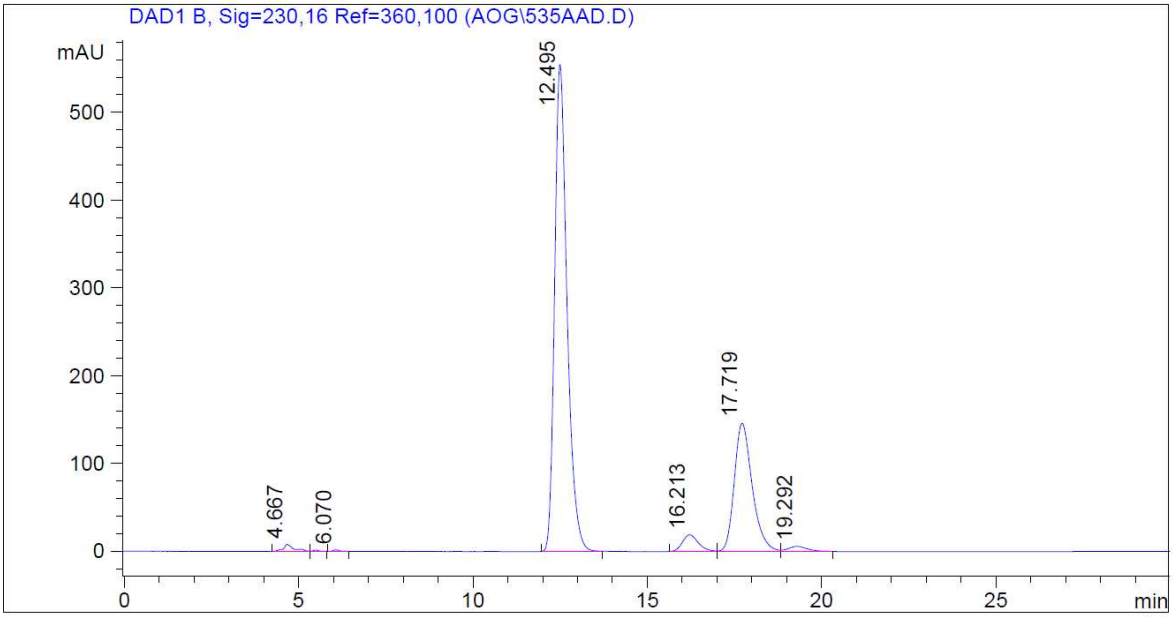
#	Ret. Time (min)	Width	Height (mAU)	Area (mAU*s)	Area %
1	20.36	0.44	618.84	18006.91	97.44
2	21.83	0.48	14.59	473.59	2.56
Total				18480.50	100.00

Figure S44. HPLC chromatogram of ***trans*-13j**; comparison of racemic (top) and non-racemic (bottom).



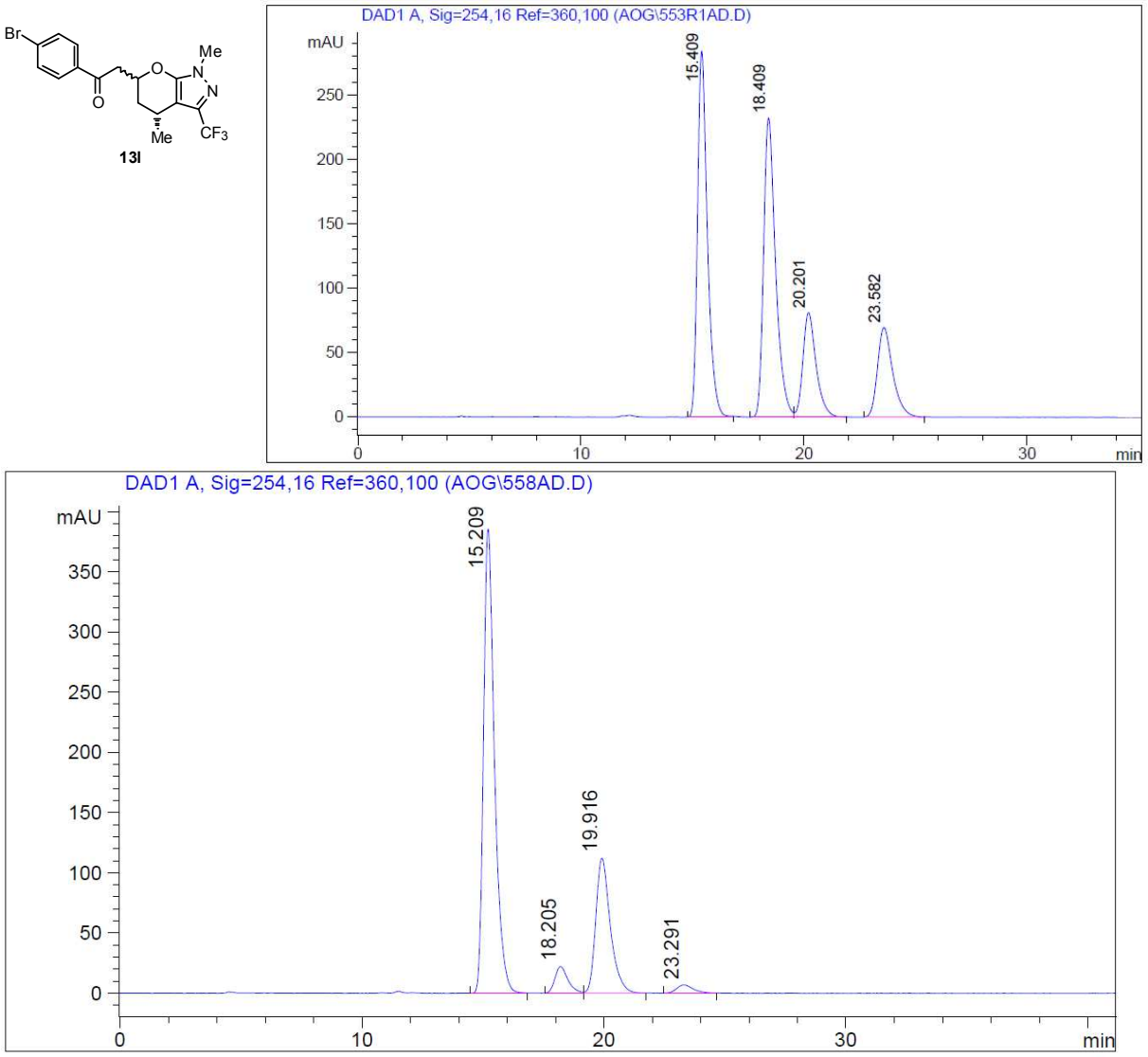
13k





#	Ret. Time (min)	Width	Height (mAU)	Area (mAU*s)	Area %
1	4.67	0.28	8.12	175.28	0.87
2	5.48	0.19	1.75	19.84	0.10
3	6.07	0.18	1.94	23.47	0.12
4	12.50	0.37	554.79	13739.58	68.56
5	16.21	0.49	19.15	615.07	3.07
6	17.72	0.60	146.23	5235.45	26.12
7	19.29	0.65	5.94	231.42	1.15
Total				20040.11	100.00

Figure S45. HPLC chromatogram of **13k**; comparison of racemic (top) and non-racemic (bottom); mixture of diastreomers.



#	Ret. Time (min)	Width	Height (mAU)	Area (mAU*s)	Area %
1	15.21	0.48	385.57	12153.60	67.52
2	18.20	0.56	22.03	823.05	4.57
3	19.92	0.70	112.13	4686.68	26.04
4	23.29	0.71	6.92	336.71	1.87
Total				18000.04	100.00

Figure S46. HPLC chromatogram of **13l**; comparison of racemic (top) and non-racemic (bottom); mixture of diastreomers.