Electronic Supplementary Information

Tuning the Electronic Transition Energy of Indole via Substitution: Application to Identify Tryptophan-Based Chromophores That Absorb and Emit Visible Light

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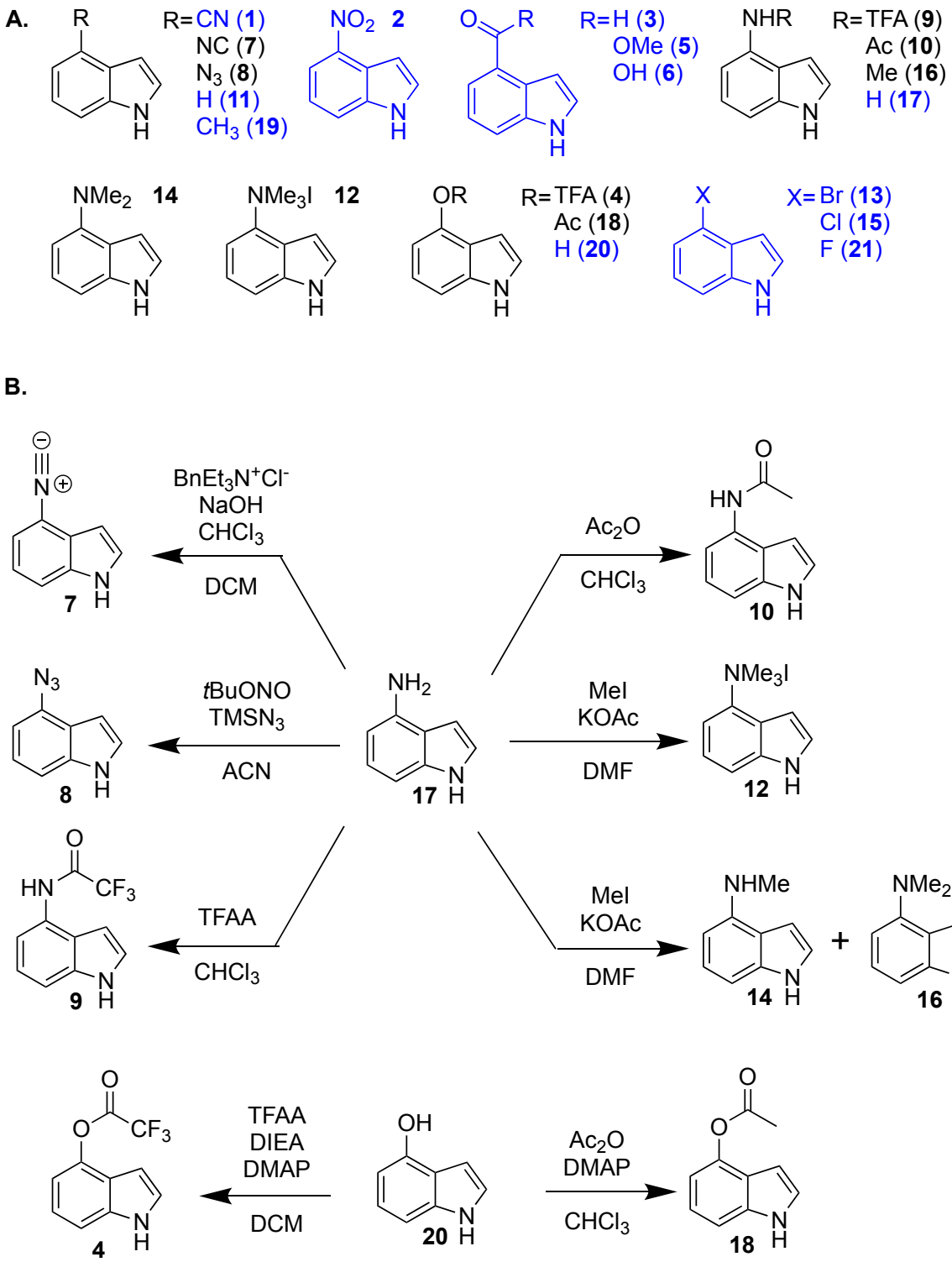
General Synthetic Information

All reactions were carried out in flame-dried glassware under Ar(g) atmosphere using standard Schlenk line technique, unless otherwise noted. All solvents were reagent grade. Anhydrous DCM and THF were obtained from a Pure Solve TM PS-400. Anhydrous, oxygen-free THF was obtained from a purple sodium-benzophenone ketyl still. Anhydrous methanol was prepared by drying over 3 Å molecular sieves for 2 days prior to use. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 0.25 mm silica gel HL TLC plates purchased from Sorbent Technologies. In aqueous work-up, all organic solutions were dried over magnesium sulfate and filtered through a cotton plug using a water aspirator prior to rotary evaporation. Flash column chromatography (FCC) was performed using SiliaFlash® P60 silica gel (particle size 0.040 – 0.062 mm) supplied by Silicycle. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Infrared spectra were recorded on a Jasco Model FT/IR-480 Plus spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-500 spectrometer. NMR spectra were processed and analyzed using MestReNova software from Mestrelab Research. Chemical shifts are reported as δ values relative to the NMR solvent (chloroform: δ 7.26 ppm for ^{1}H and δ 77.16 ppm for ^{13}C; CD_3OD: δ 3.31 ppm for ^{1}H and δ 49.00 ppm for ^{13}C). NMR spectra baseline corrections were performed using an automated polynomial fit function. Optical rotations were measured on a Jasco P-2000 polarimeter. Accurate mass measurement data were acquired on Waters instruments. Waters software calibrates and reports by use of neutral atomic masses. The mass of the electron is not included.

Reagents

4-Bromoindole (96.72% purity), indole-4-carboxaldehyde (98.55% purity), indole-4-carboxylic acid (98.73% purity), 4-cyanoindole (99.31% purity), 4-fluoroindole (99.71% purity), 4-methylindole (97.90% purity), 4-nitroindole (98% purity), and 4-bromo-L-tryptophan (98.5% ee) were purchased from Chem-Impex Int'l Inc. 4-Chloroindole (97% purity), methyl indole-4-carboxylate (99% purity), and 4-hydroxyindole (98% purity) were purchased from Alfa Aesar. 4-Aminoindole (97% purity) was purchased from Ark Pharm, Inc. Unless otherwise stated, commercial reagents were used without purification. "Freshly distilled" reagents were obtained via short-path distillation at atmospheric pressure under Ar immediately prior to use in the reaction.



Scheme S1 A. Assembled 4X-indole library (commercially available derivatives highlighted in blue). **B.** Synthesis of 4X-indoles not commercially available.

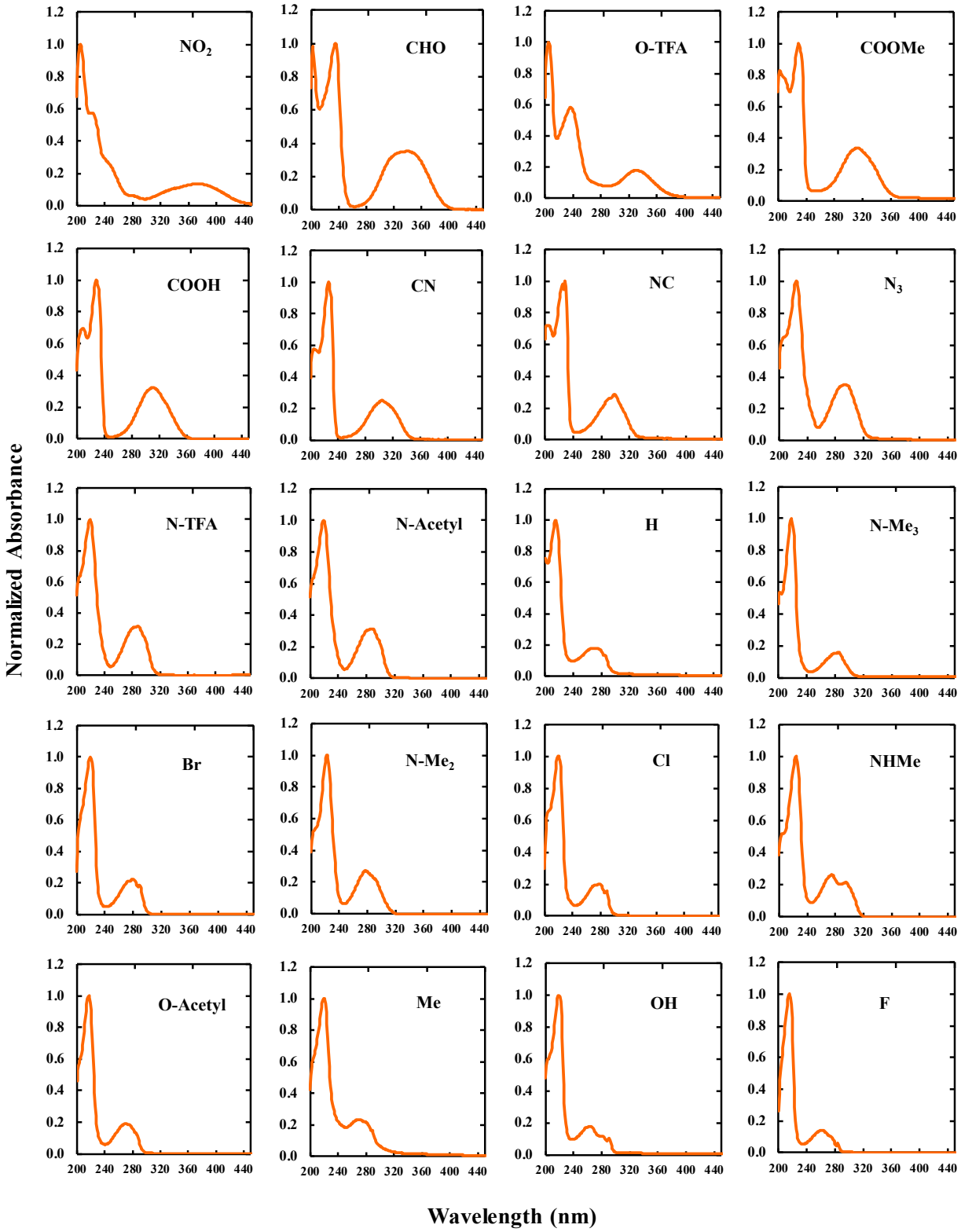


Fig. S1 Normalized absorption spectra of 4X-indoles in ethanol where the substituent X is indicated.

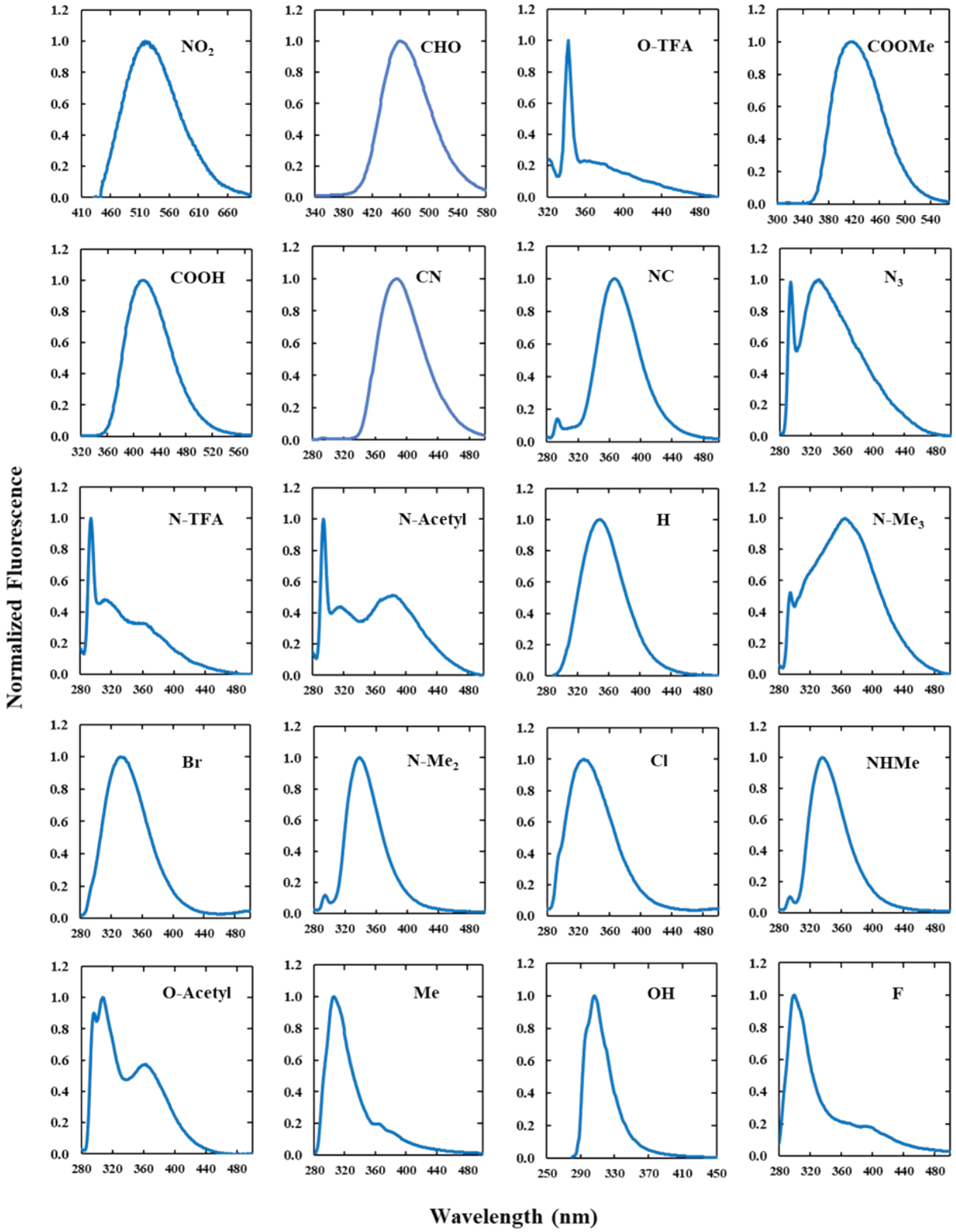


Fig. S2 Normalized fluorescence spectra of 4X-indoles in ethanol where the substituent X is indicated. The sharp peaks in some of the spectra correspond to Raman scatterring of the solvent. An excitaion wavelength of 270 nm (350 nm) was used for X-indoles whose absorption spectra are similar to that of indole (4CN-indole).

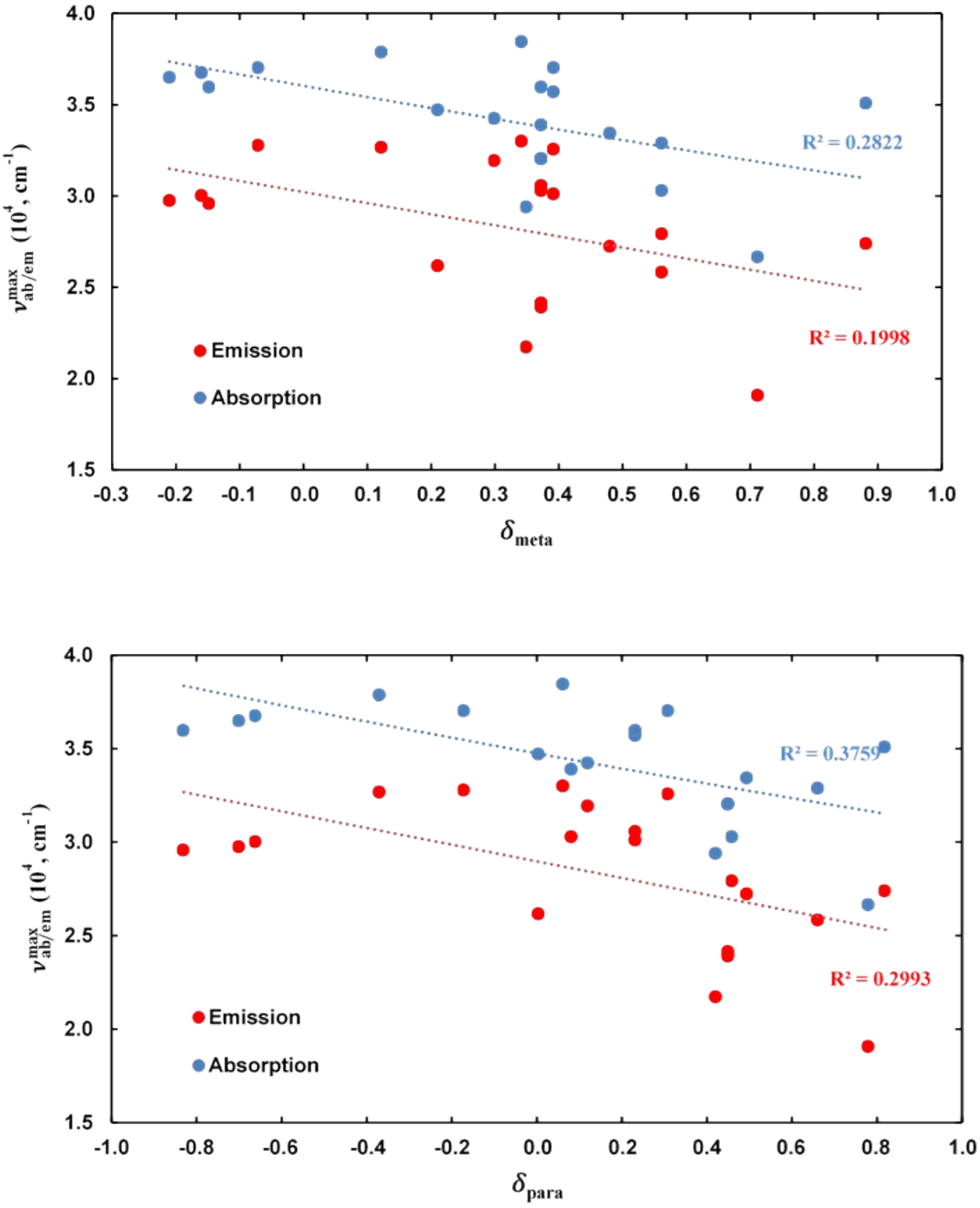


Fig. S3 Dependence of the frequency of the maximum absorbance/emission of 4X-indoles on the values of X's δ_{meta} (top) or δ_{para} (bottom) constants.

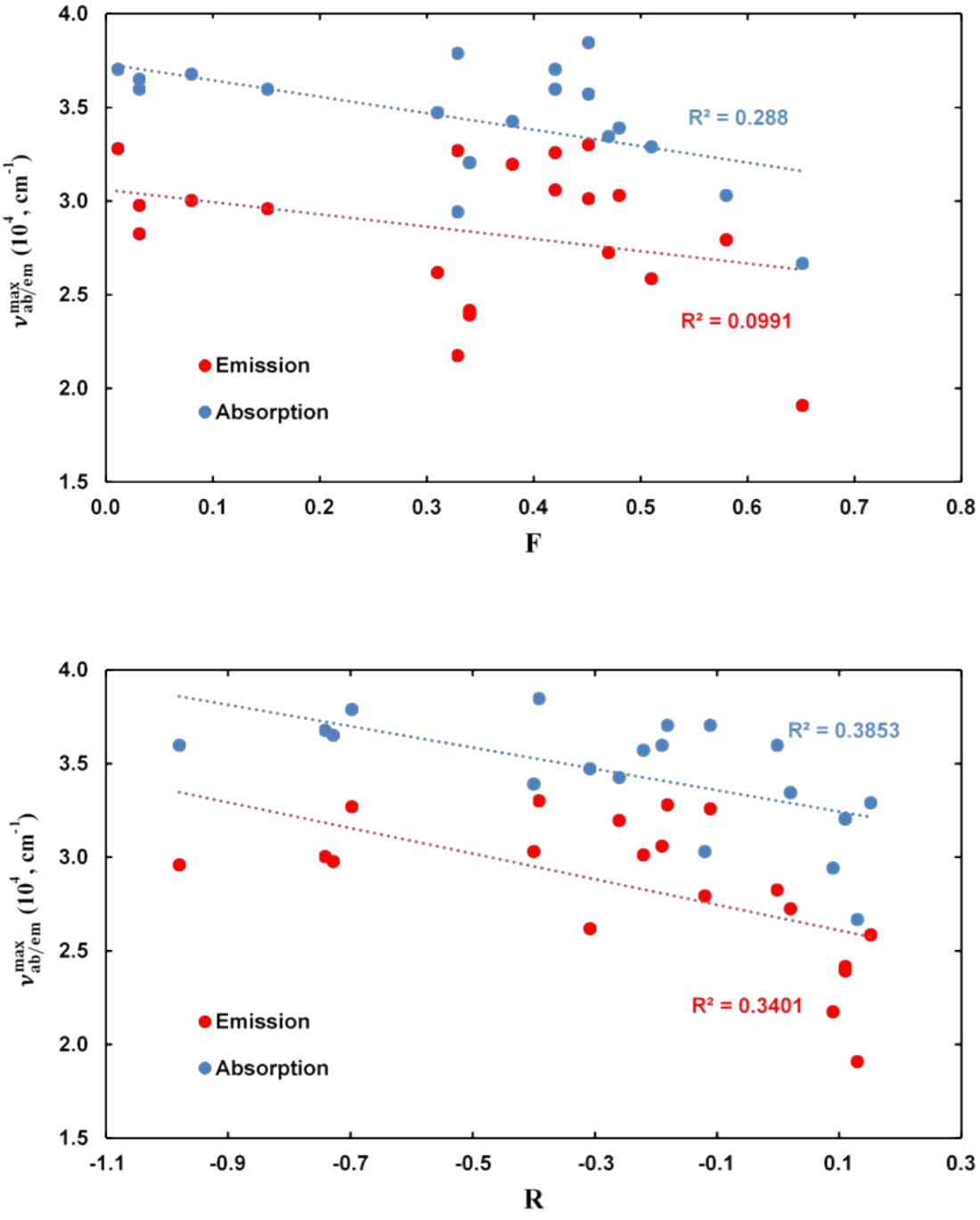
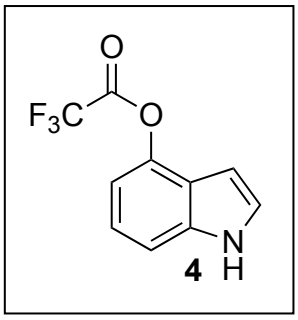


Fig. S4 Dependence of the frequency of the maximum absorbance/emission of 4X-indoles on the values of X's field component, F (top) or resonance component, R (bottom).

4X-Indole Synthetic Procedures and Analytical Data

O-Trifluoroacetyl-4-hydroxyindole (4)



A 25 mL RBF equipped with a small magnetic stir bar under an Ar atmosphere was charged with 4-hydroxyindole **20** (24.8 mg, 0.186 mmol, 1.0 equiv.). The black solid was partially dissolved using anhydrous DCM (5 mL, ~40 mM). Catalytic DMAP (1 flake) and DIEA was added to the solution at RT. The reaction was subsequently chilled to 0 °C using an ice water bath and freshly distilled trifluoroacetic anhydride (TFAA) (50 μL, 0.360 mmol, 1.9 equiv.) was added dropwise with vigorous stirring. Complete dissolution and the appearance of an orange color was noticed at the end of the addition. The reaction was maintained at 0 °C for 1 h and thereafter quenched by the slow addition of pH 7 phosphate buffer (10 mL). The biphasic solution was extracted using DCM (2x10 mL) and the combined org. extracts were dried over $MgSO_4$ and concentrated under reduced pressure. FCC (20% EtOAc/Hex) afforded *O*-TFA-4-hydroxyindole **4** (8.1 mg, 19% yield) as a white solid.

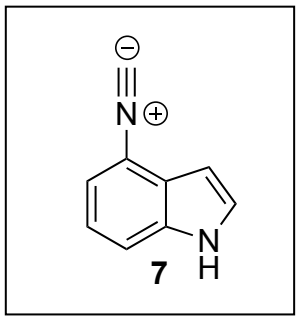
Analytical data for 4

^{1}H NMR (500 MHz, $CDCl_3$): δ=8.04 (d, 1H, 8.3 Hz), 7.42 (m, 1H), 7.29 (app. t, 1H, 8.1 Hz), 6.89 (d, 1H, 4.0 Hz), 6.78 (d, 1H, 7.9 Hz), 5.19 (bs, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ=49.0, 137.6, 127.5, 122.8, 119.3, 114.6, 111.3, 110.1, 109.1.

HRMS (ESI): *m/z* Calc. for $C_{10}H_5F_3NO_2^-$ $[M-H]^-$: 228.0272, Observed: 228.0290.

1-H-4-Isocyanoindole (7)



A 20 mL scintillation vial equipped with a small magnetic stir bar was charged with 4-aminoindole **17** (60.8 mg, 0.461 mmol, 1.0 equiv.). The black solid was suspended in DCM (1.0 mL, ~0.5 M) under ambient conditions. A catalytic amount of benzyltriethylammonium chloride (5 mg, 0.023 mmol, 0.05 equiv.) was added to the suspension at RT followed by NaOH (aq.) (111 mg, 2.78 mmol, 6.0 equiv., 50% w/w solution), at which point, full dissolution and a deep blue color was observed. After stirring for 5 m, $CHCl_3$ (220 μL, 2.78 mmol, 6.0 equiv.) was added at RT. Significant precipitation and the appearance of a brown color were immediately observed. The vial was subsequently sealed with a urea cap and the reaction allowed to stir overnight. The following morning, the reaction was quenched by dilution with H_2O (20 mL) and extracted with DCM (3x20 mL). The combined org. extracts were dried over $MgSO_4$ and concentrated under reduced pressure. NMR analysis of the crude material revealed **7** was present along with unreacted **16** (1.0:1.6, respectively) and significant decomposition. Two rounds of FCC (*1st*: 30% EtOAc/Hex; *2nd*: 20% EtOAc/Hex) afforded 1H-4-isocyanoindole **7** (10 mg, 15% yield) as a yellow solid.

Analytical data for 7

Rf: 0.52 (30% EtOAc/Hex), visualized with UV and 4-Anisaldehyde stain (bright orange);

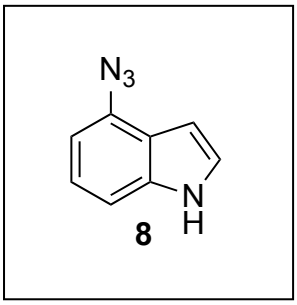
^{1}H NMR (500 MHz, $CDCl_3$): δ=8.43 (bs, 1H), 7.45 (d, 1H, 7.7 Hz), 7.32 (t, 1H, 2.8 Hz), 7.20-7.13 (m, 2H), 6.72 (t, 1H, 2.2 Hz);

^{13}C NMR (125 MHz, $CDCl_3$): δ=147.6, 136.6, 126.0, 124.8, 121.9, 118.3, 112.7, 106.7, 100.7;

IR (neat): ν_{max}=3326, 2361, 2344, 2121, 1360, 1340, 752;

HRMS (ESI): *m/z* Calc. for $C_9H_7N_2^+$ $[M+H]^+$:143.0609, Observed: 143.0637.

4-Azido-1H-indole (8)



A 20 mL scintillation vial equipped with a small magnetic stir bar was charged with 4-aminoindole **17** (125 mg, 0.947 mmol, 1.0 equiv.). The black solid was dissolved using ACN (2.0 mL, ~0.5 M) under ambient conditions. The resultant dark black solution was cooled to 0 °C using an ice water bath. *tert*-Butyl nitrite (189 μL, 1.42 mmol, 1.5 equiv., 90%) and $TMSN_3$ (158 μL, 1.14 mmol, 1.2 equiv., 95%) were sequentially added dropwise to the chilled solution with vigorous stirring. The vial was subsequently sealed with a urea cap and the ice bath removed after 5 m. The reaction was allowed to stir for 5 h at RT before quenching by the addition of SiO_2 and concentrating the resultant slurry under vacuum. The SiO_2 dry-loaded crude product was directly subjected to FCC (20% EtOAc/Hex) which afforded 4-azidoindole **8** (90 mg, 60% yield) as a dark green solid.

Analytical data for 8

Rf: 0.64 (30% EtOAc/Hex); visualized with UV and 4-Anisaldehyde stain (bright pink);

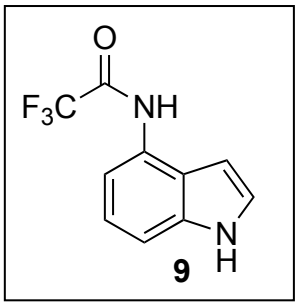
^{1}H NMR (500 MHz, $CDCl_3$): δ=8.21 (bs, 1H), 7.22-7.16 (m, 3H), 6.86 (m, 1H), 6.66 (t, 1H, 2.2 Hz);

^{13}C NMR (125 MHz, $CDCl_3$): δ=137.2, 132.4, 124.2, 122.9, 121.2, 109.2, 108.1, 100.0;

IR (neat): 3406, 2112, 2058, 1616, 1579, 1499, 1356, 1296, 1259, 747, 730;

HRMS (ESI): *m/z* Calc. for $C_8H_6N_2^+$ $[M-N_2]^+$: 130.0530, Observed: 130.0523.

N-Trifluoroacetyl-1H-4-aminoindole (9)



A 20 mL scintillation vial equipped with a small magnetic stir bar was charged with 4-aminoindole **17** (67.4 mg, 0.511 mmol, 1.0 equiv.). The black solid was suspended in $CHCl_3$ (5.1 mL, 0.1 M) under ambient conditions. Freshly distilled TFAA (210 μL, 1.53 mmol, 3.0 equiv.) was added dropwise to the stirring suspension (exothermic!). The vial was subsequently sealed with a urea cap and allowed to stir for 4 h at RT. The reaction was thereafter quenched by slowly pipetting the contents into a vigorously stirring biphasic solution of pH 7 phosphate buffer (25 mL) and DCM (25 mL). The org. layer was isolated and the aq. layer further extracted with DCM (2x25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. FCC (30% EtOAc/Hex) afforded *N*-trifluoroacetyl-1H-4-aminoindole **9** (45 mg, 39% yield) as a flakey, greenish-grey solid.

Analytical data for 9

Rf: 0.47 (30% EtOAc/Hex); visualized with UV and 4-Anisaldehyde stain (bright orange);

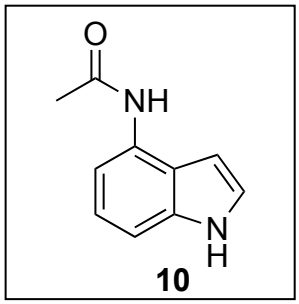
^{1}H NMR (500 MHz, $CDCl_3$): δ=8.46 (bs, 1H), 8.10 (bs, 1H), 7.69 (d, 1H, 7.7 Hz), 7.31 (d, 1H, 8.1 Hz), 7.24 (app. t, 1H, 2.6 Hz), 7.21 (t, 1H, 7.9 Hz), 6.48 (br. t, 1H, 2.6);

^{13}C NMR (125 MHz, $CDCl_3$): δ=155.0 (q, 37.0 Hz), 154.8, 136.7, 126.8, 125.0, 122.6, 120.6, 116.1 (q, 288.6 Hz), 112.8, 112.4, 110.1, 98.3;

IR (neat): ν_{max}=3408, 1714, 1628, 1544, 1506, 1440, 1357, 1247, 1155, 1115, 750, 688;

HRMS (ESI): *m/z* Calc. for $C_{10}H_8F_3N_2O^+$ $[M+H]^+$: 229.0589, Observed: 229.0589.

N-Acetyl-1H-4-aminoindole (10)



10

A 20 mL scintillation vial equipped with a small magnetic stir bar was charged with 4-aminoindole **17** (43.2 mg, 0.327 mmol, 1.0 equiv.). The black solid was suspended in $CHCl_3$ (3.3 mL, 0.1 M) under ambient conditions. To the suspension was added freshly distilled Ac_2O (80 µL, 0.847 mmol, 2.6 equiv.). The vial was subsequently sealed with a urea cap and heated to 60 °C with stirring. After 1 h, the reaction was allowed to return to RT and subsequently quenched by slowly pipetting the contents into a vigorously stirring biphasic solution of pH 7 phosphate buffer (25 mL) and DCM (25 mL). The org. layer was isolated and the aq. layer further extracted with DCM (2x25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. FCC (60% EtOAc/Hex) afforded *N*-acetyl-1H-4-aminoindole **10** (46 mg, 81% yield) as an amorphous, white solid.

Analytical data for 10

Rf: 0.45 (60% EtOAc/Hex); visualized with UV and 4-Anisaldehyde stain (bright orange);

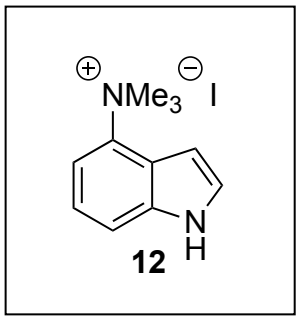
^{1}H NMR (500 MHz, CD_3OD): δ=7.37 (d, 1H, 7.7 Hz), 7.21 (m, 2H), 7.06 (app. t, 1H, 7.8 Hz), 6.57 (d, 1H, 3.0 Hz), 2.21 (s, 3H);

^{13}C NMR (125 MHz, CD_3OD): δ=172.0, 138.6, 130.8, 125.2, 123.0, 122.3, 113.7, 109.6, 99.9, 23.5;

IR (neat): ν_{max}=3447, 1631, 747;

HRMS (ESI): *m/z* Calc. for $C_{10}H_{10}N_2O^+$ $[M+H]^+$: 175.0859, Observed: 175.0871.

N,N,N-Trimethylammonium-1H-indol-4-ammonium iodide (12)



12

A 20 mL scintillation vial equipped with a small magnetic stir bar was charged with 4-aminoindole **17** (26.9 mg, 0.204 mmol, 1.0 equiv.). The black solid was dissolved in anhydrous DMF (2.0 mL, 0.1 M) under ambient conditions. To the stirring solution at RT was added anhydrous KOAc (200 mg, 2.04 mmol, 10 equiv.) and MeI (130 μL, 2.04 mmol, 10 equiv.). The vial was subsequently sealed with a urea cap and allowed to stir for 3 h at RT. The reaction was then directly concentrated to near dryness using a rotary evaporator (15 torr, water bath temp. ~60 °C) and the product was precipitated from solution by the addition of DCM (10 mL). The precipitate was collected via vacuum filtration, the filter cake washed with additional DCM (3x5 mL) and the obtained white solid placed under high vacuum overnight to remove residual DMF (gradually acquiring a green appearance). NMR analysis of the crude product indicated that *N*,*N*,*N*-trimethylammonium-1H-indol-4-ammonium iodide **12** was isolated (59 mg, 92% yield) as an analytically pure green, flakey solid.

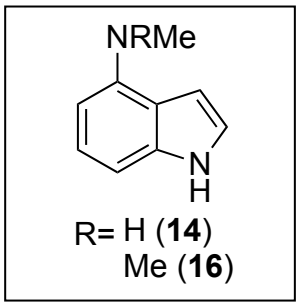
Analytical data for 12

^{1}H NMR (500 MHz, CD_3OD): δ=7.69 (d, 1H, 8.1 Hz), 7.59 (d, 1H, 3.5 Hz), 7.48 (d, 1H, 8.1 Hz), 7.29 (app. t, 1H, 8.0 Hz), 6.94 (dd, 1H, 0.7 Hz, 3.3 Hz) 3.85 (s, 9H);

^{13}C NMR (125 MHz, CD_3OD): δ=140.3, 139.6, 128.5, 122.1, 119.3, 115.9, 111.5, 100.9, 56.9;

HRMS (ESI): *m/z* Calc. for $C_{11}H_{15}N_2^+$ $[M]^+$: 175.1235, Observed: 175.1219.

***N*-Methyl-1H-4-aminoindole (14) & *N,N*-dimethyl-1H-4-aminoindole (16)**



A 20 mL scintillation vial equipped with a small magnetic stir bar was charged with 4-aminoindole **17** (66.2 mg, 0.502 mmol, 1.0 equiv.). The black solid was dissolved in anhydrous DMF (1.0 mL, 0.5 M) under ambient conditions. To the solution was added anhydrous KOAc (148 mg, 1.51 mmol, 3.0 equiv.) and MeI (47 μL, 0.753 mmol, 1.5 equiv.) sequentially. The vial was subsequently sealed with a urea cap and allowed to stir for 30 m at RT. The reaction was thereafter quenched by the addition of sat. aq. $NaHCO_3$ (25 mL) and extraction with DCM (3x30 mL). The combined org. extracts were dried over $MgSO_4$ and concentrated under vacuum. The crude solid was placed under high vacuum overnight to remove residual DMF. NMR analysis of the crude product revealed a 2.2:1.0 ratio of the monomethyl (**14**) and dimethyl (**16**) products, respectively. Two rounds of FCC (*1st*: 30% EtOAc/Hex; *2nd*: 20% Acetone/Hex) afforded *N,N*-dimethyl-1H-4-aminoindole **16** (12.4 mg, 15% yield) as an amorphous, greenish-grey solid and *N*-methyl-1H-4-aminoindole **14** (28.4 mg, 39% yield) as an amorphous, black solid contaminated with 5% of **16**.

Analytical data for 14

Rf: 0.50 (30% EtOAc/Hex), visualized with UV and 4-Anisaldehyde stain (dim orange);

^{1}H NMR (500 MHz, $CDCl_3$): δ=8.11 (bs, 1H), 7.13 (app. t, 1H, 7.9 Hz), 7.08 (app. t, 1H, 2.6 Hz), 6.84 (d, 1H, 8.2 Hz), 6.45 (m, 1H), 6.31 (d, 1H, 7.6 Hz), 4.04 (bs, 1H), 3.01 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ=142.7, 136.4, 123.6, 122.0, 116.8, 101.4, 99.0, 98.7, 31.0;

IR (neat): ν_{max}=3407, 1635, 1507, 1363, 738;

HRMS (ESI): *m/z* Calcd for $C_9H_{10}N_2^+$ $[M+H]^+$:147.0922, Observed: 147.0926.

Analytical data for 16

Rf: 0.55 (30% EtOAc/Hex), visualized with UV and 4-Anisaldehyde stain (dim orange);

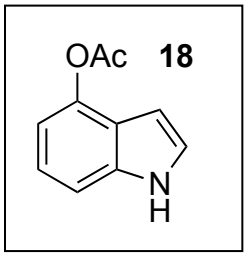
^{1}H NMR (500 MHz, $CDCl_3$): δ=8.15 (bs, 1H), 7.13 (app. t, 1H, 2.5 Hz), 7.12 (app. t, 1H, 7.9 Hz), 7.00 (d, 1H, 8.1 Hz), 6.67 (m, 1H), 6.54 (d, 1H, 7.6 Hz), 3.02 (s, 6H);

^{13}C NMR (125 MHz, $CDCl_3$): δ=146.8, 137.3, 122.9, 122.2, 120.5, 105.7, 104.6, 102.2, 43.4;

IR (neat): ν_{max}=3147, 1577, 1366, 900, 737;

HRMS (ESI): *m/z* Calcd for $C_{10}H_{13}N_2^+$ $[M+H]^+$:161.1079, Observed: 161.1080.

O-Acetyl-4-hydroxyindole (18)



A 20 mL scintillation vial equipped with a small magnetic stir bar was charged with 4-hydroxyindole **20** (34.1 mg, 0.256 mmol, 1.0 equiv.). The black solid was partially dissolved using $CHCl_3$ (2.6 mL, 0.1 M) under ambient conditions. Catalytic DMAP (1 flake) and freshly distilled Ac_2O (60 μL, 0.635 mmol, 2.5 equiv.) were added to the stirring black solution at RT. The vial was subsequently sealed with a urea cap and heated to 60 °C. After 2 h, additional Ac_2O (100 μL, 1.06 mmol, 4.2 equiv.) was added at RT. After an additional 2 h at 60 °C, the reaction was cooled to RT and quenched by slowly pipetting the contents into a vigorously stirring biphasic solution of pH 7 phosphate buffer (25 mL) and DCM (25 mL). The org. layer was isolated and the aq. layer further extracted with DCM (2x25 mL). The combined organic extract was dried over $MgSO_4$ and concentrated under reduced pressure. FCC (30% EtOAc/Hex) afforded *O*-acetyl-4-hydroxyindole **18** (44 mg, 98% yield) as a flakey, red solid.

Analytical data for 18

Rf: 0.44 (30% EtOAc/Hex), visualized with UV and 4-Anisaldehyde stain (bright orange);

^{1}H NMR (500 MHz, $CDCl_3$): δ=8.29 (bs, 1H), 7.22(d, 1H, 8.10 Hz), 7.16 (t, 1H, 7.85 Hz), 7.10 (t, 1H, 2.67 Hz), 6.87 (d, 1H, 7.63 Hz), 6.42 (bs, 1H), 2.40 (s, 1H);

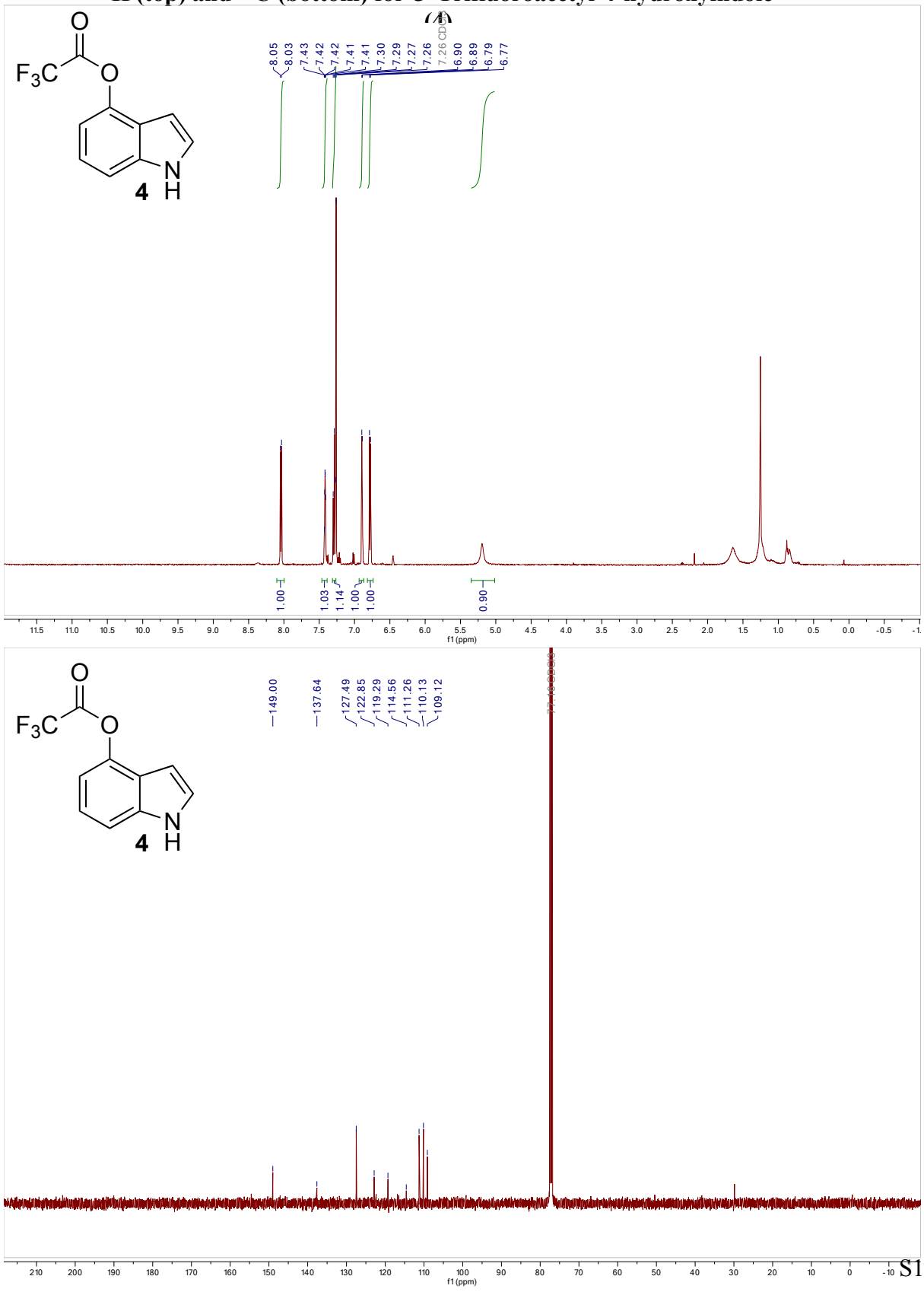
^{13}C NMR (125 MHz, $CDCl_3$): δ=169.7, 143.7, 137.8, 124.7, 122.2, 121.3, 111.9, 109.3, 99.3, 21.2;

IR ($CHCl_3$): ν_{max}=3376, 1752, 1624, 1579, 1498, 1425, 1352, 1222, 1199, 1083, 1027, 899, 756, 581, 516;

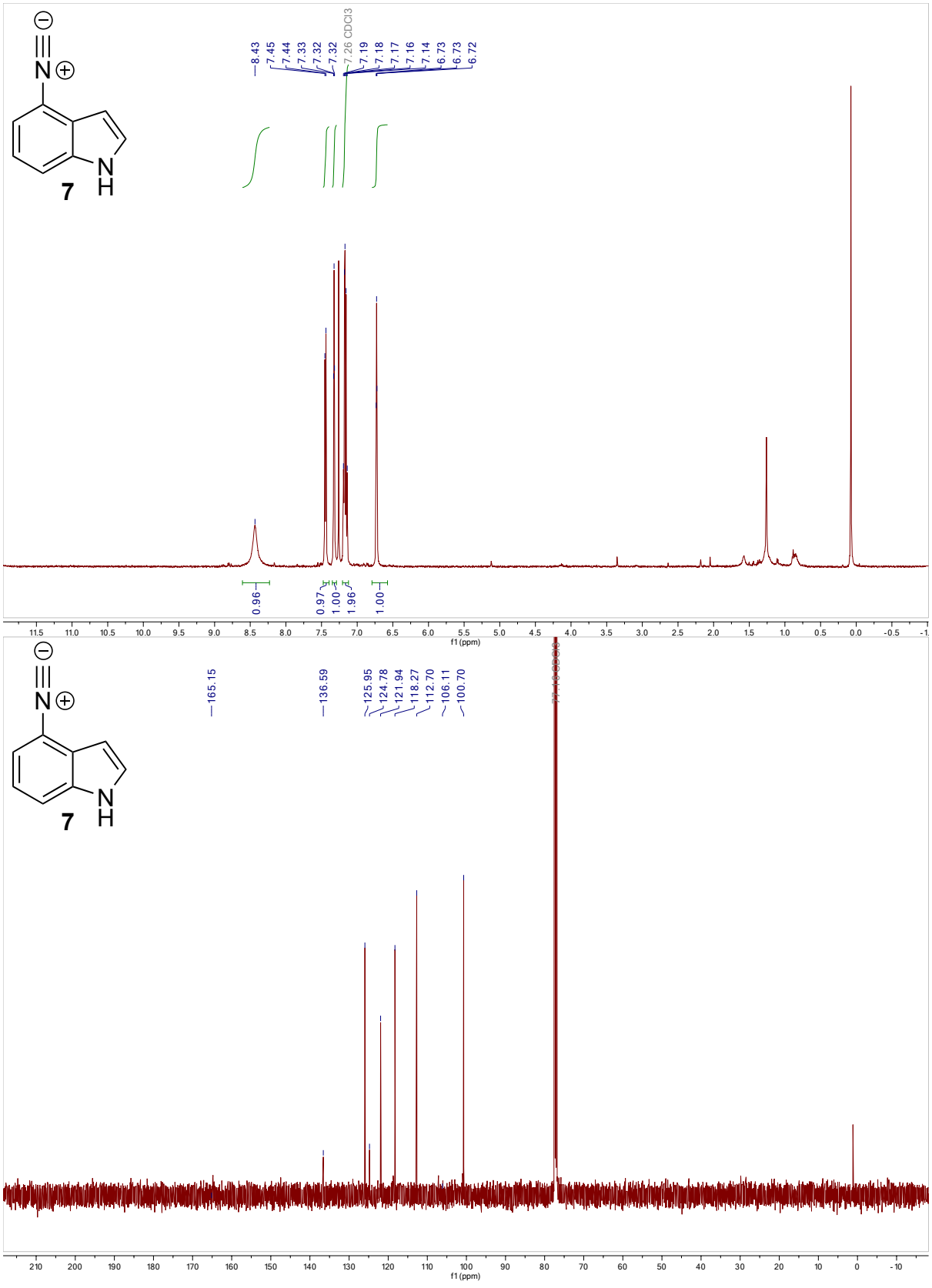
HRMS (ESI): *m/z* Calcd for $C_{10}H_9NMNaO_2^+$ $[M+Na]^+$: 198.0531, Observed: 198.0540.

^{1}H & ^{13}C NMR Spectra for Synthesized 4X-Indole Derivatives

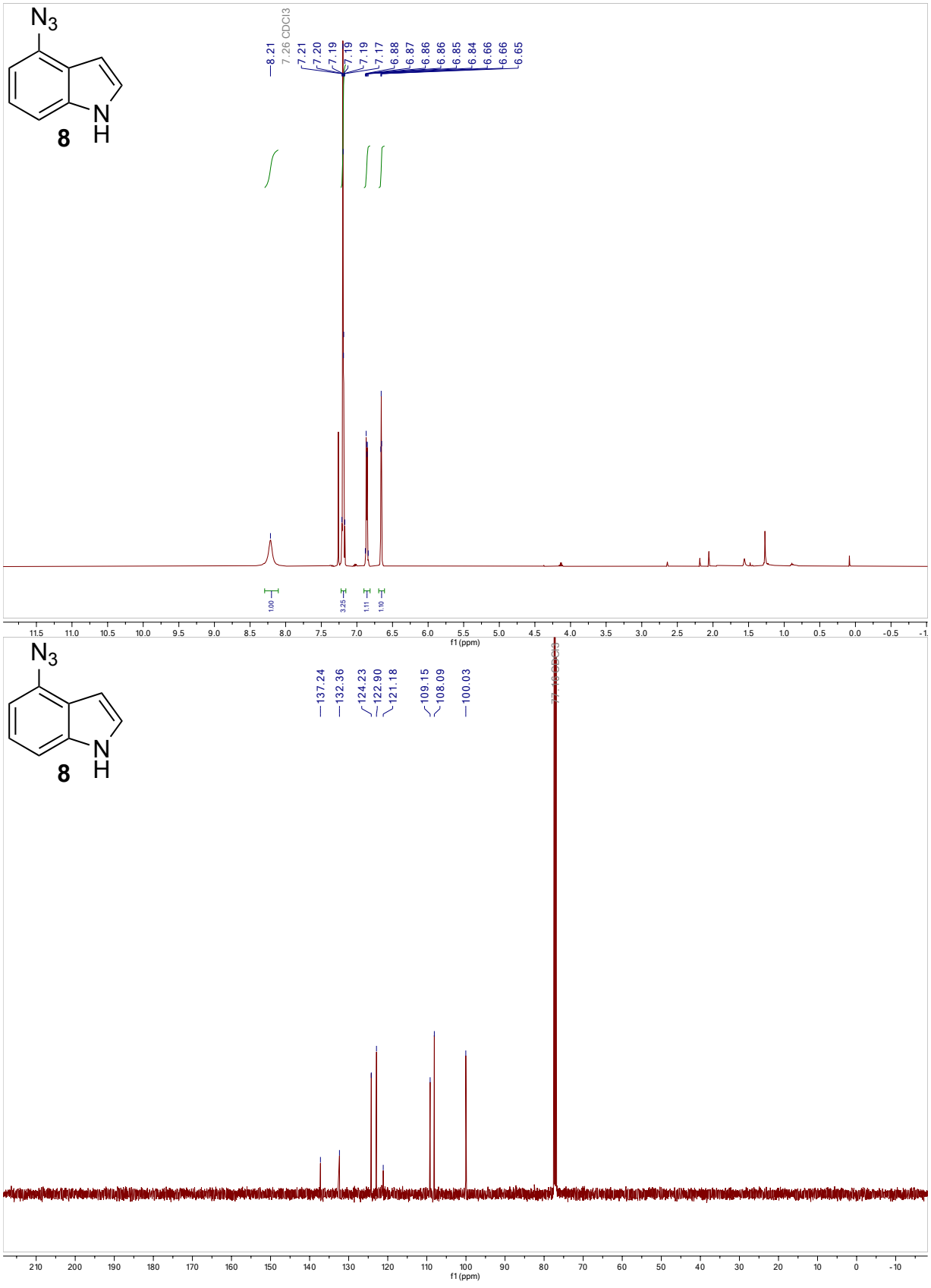
^{1}H (top) and ^{13}C (bottom) for *O*-Trifluoroacetyl-4-hydroxyindole



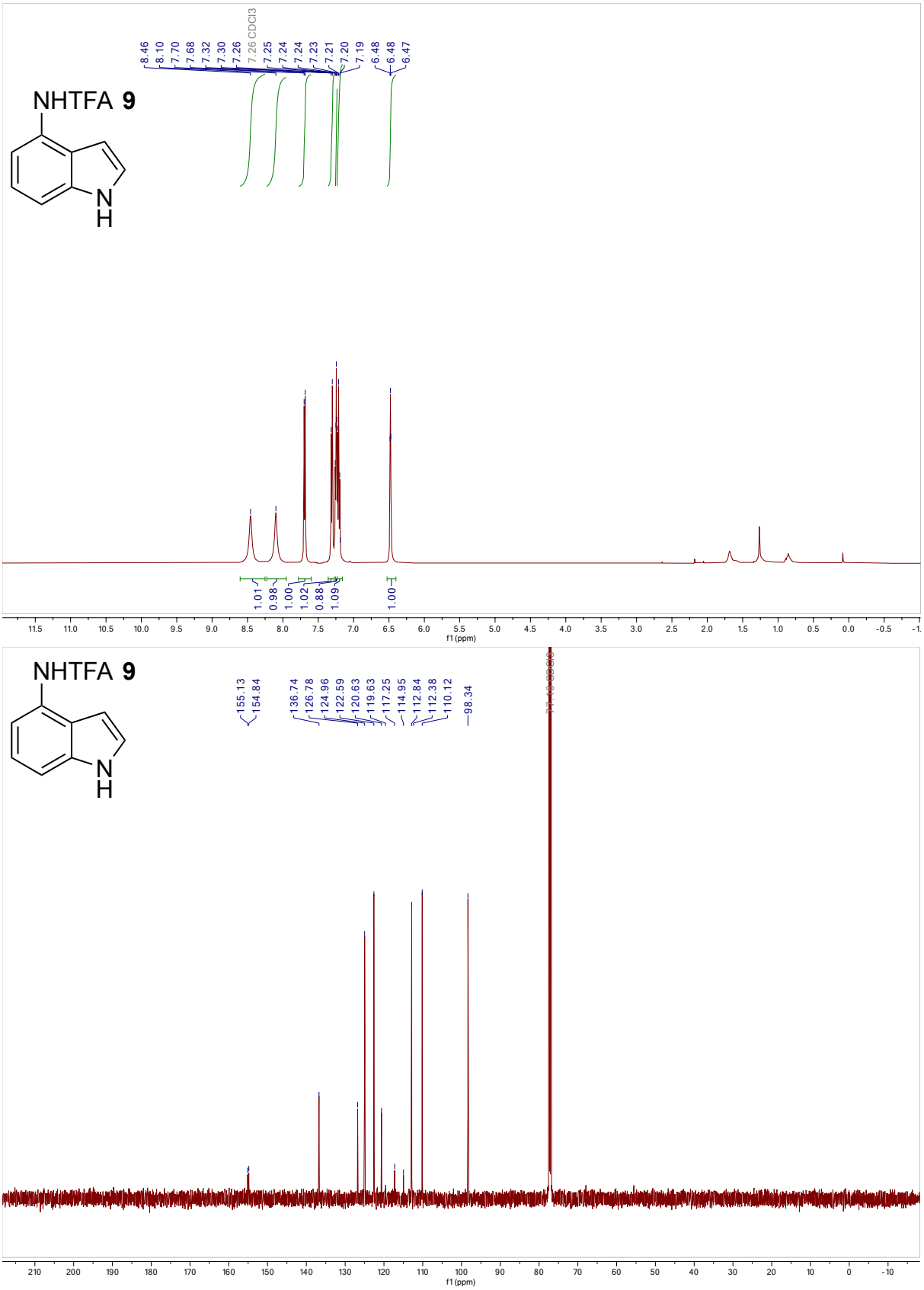
^{1}H (top) and ^{13}C (bottom) for 1-H-4-Isocyanoindole (7)



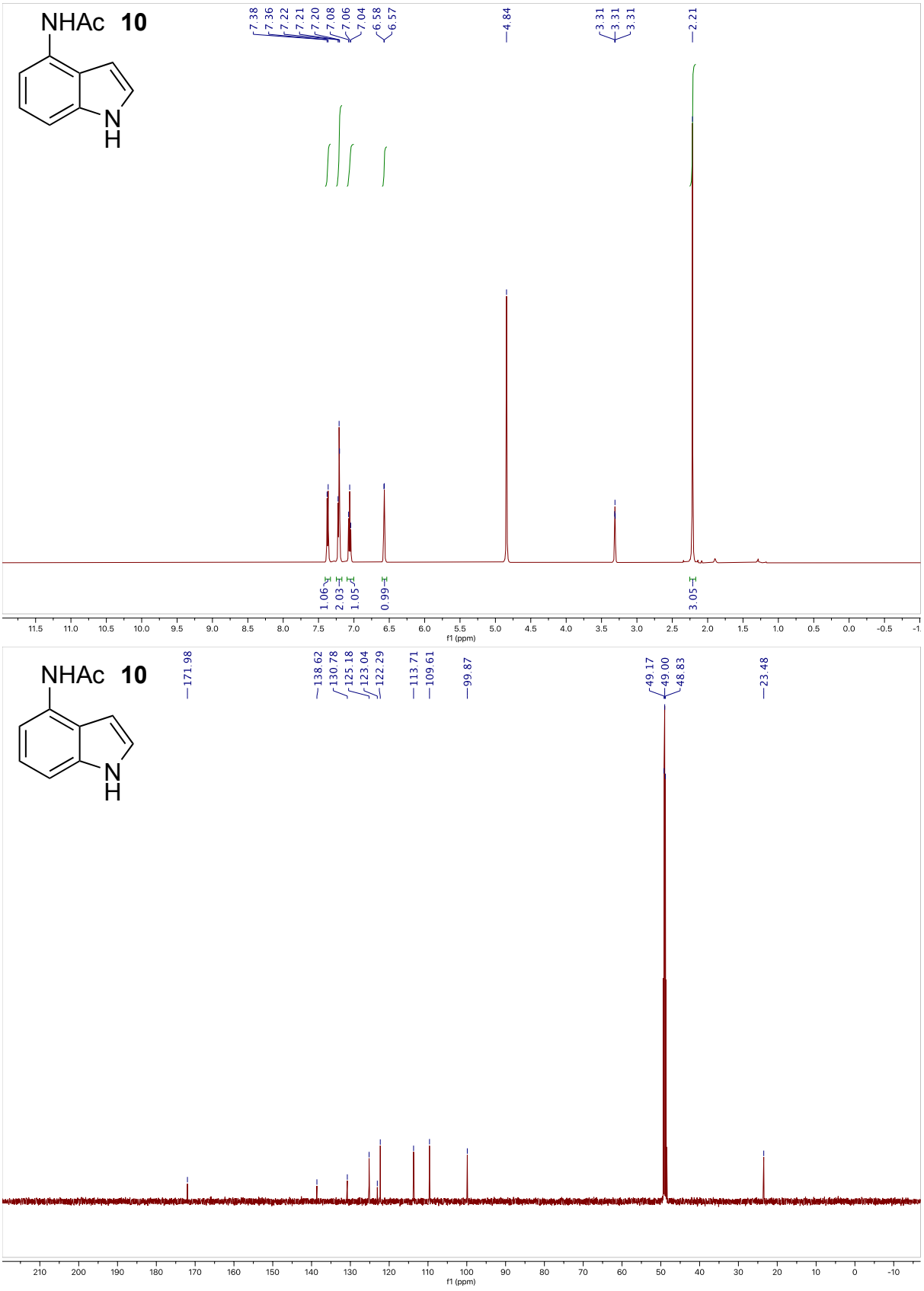
^{1}H (top) and ^{13}C (bottom) for 4-Azido-1H-indole



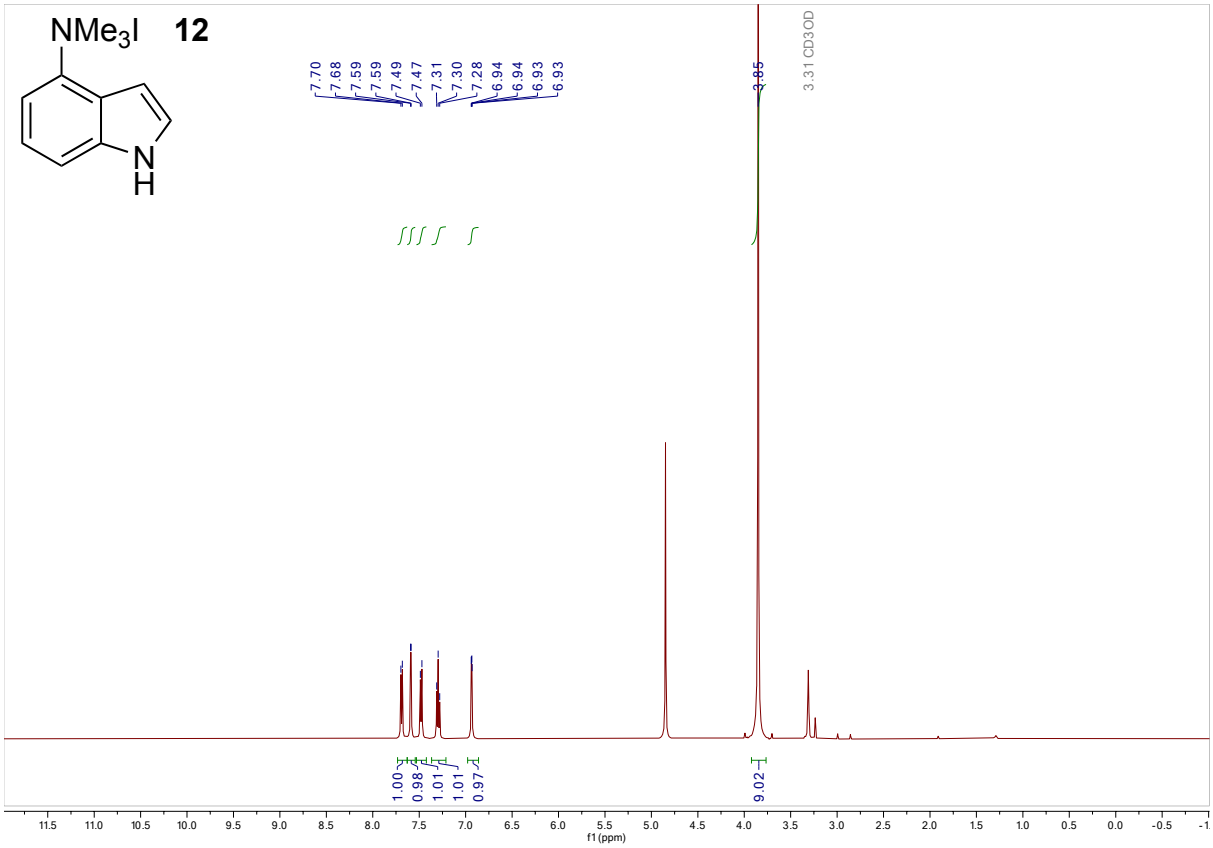
^{1}H (top) and ^{13}C (bottom) for *N*-Trifluoroacetyl-1H-4-aminoindole (9)

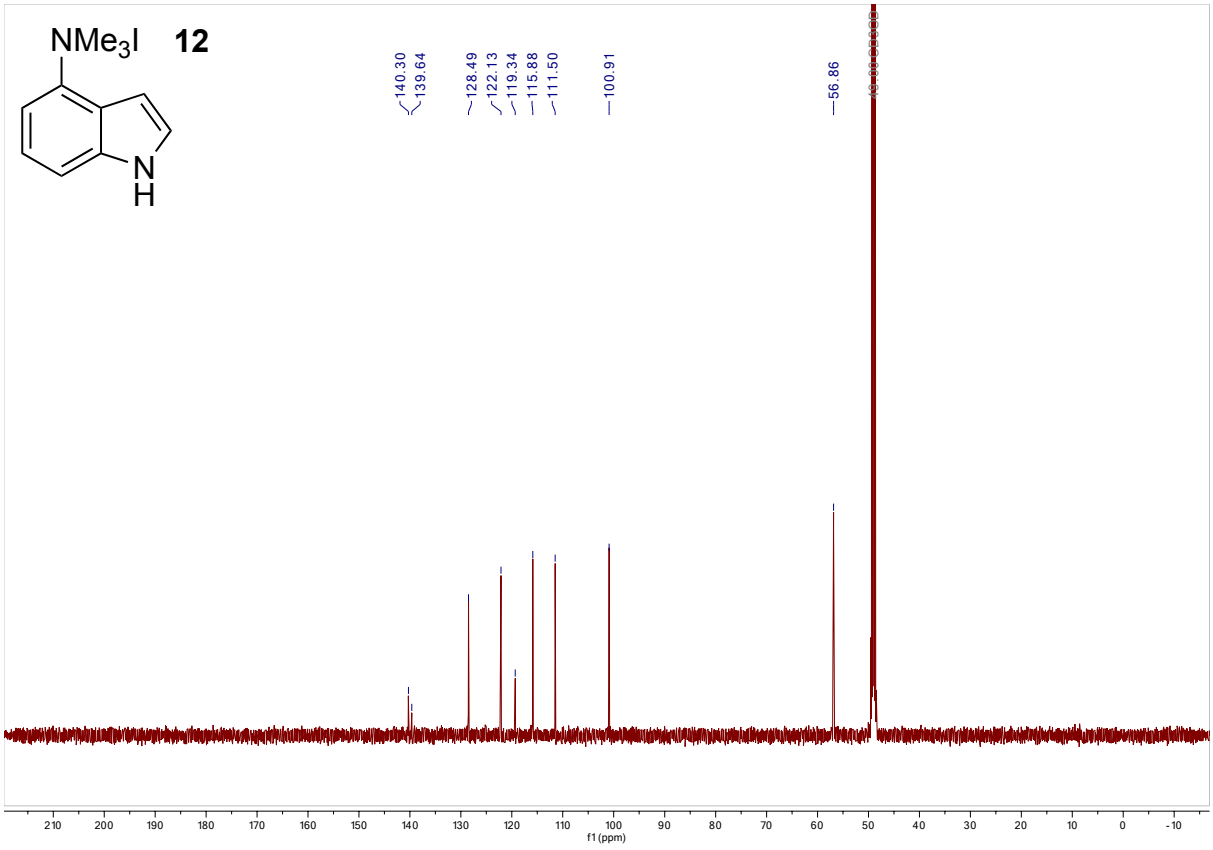


^{1}H (top) and ^{13}C (bottom) for *N*-Acetyl-1H-4-aminoindole (10)

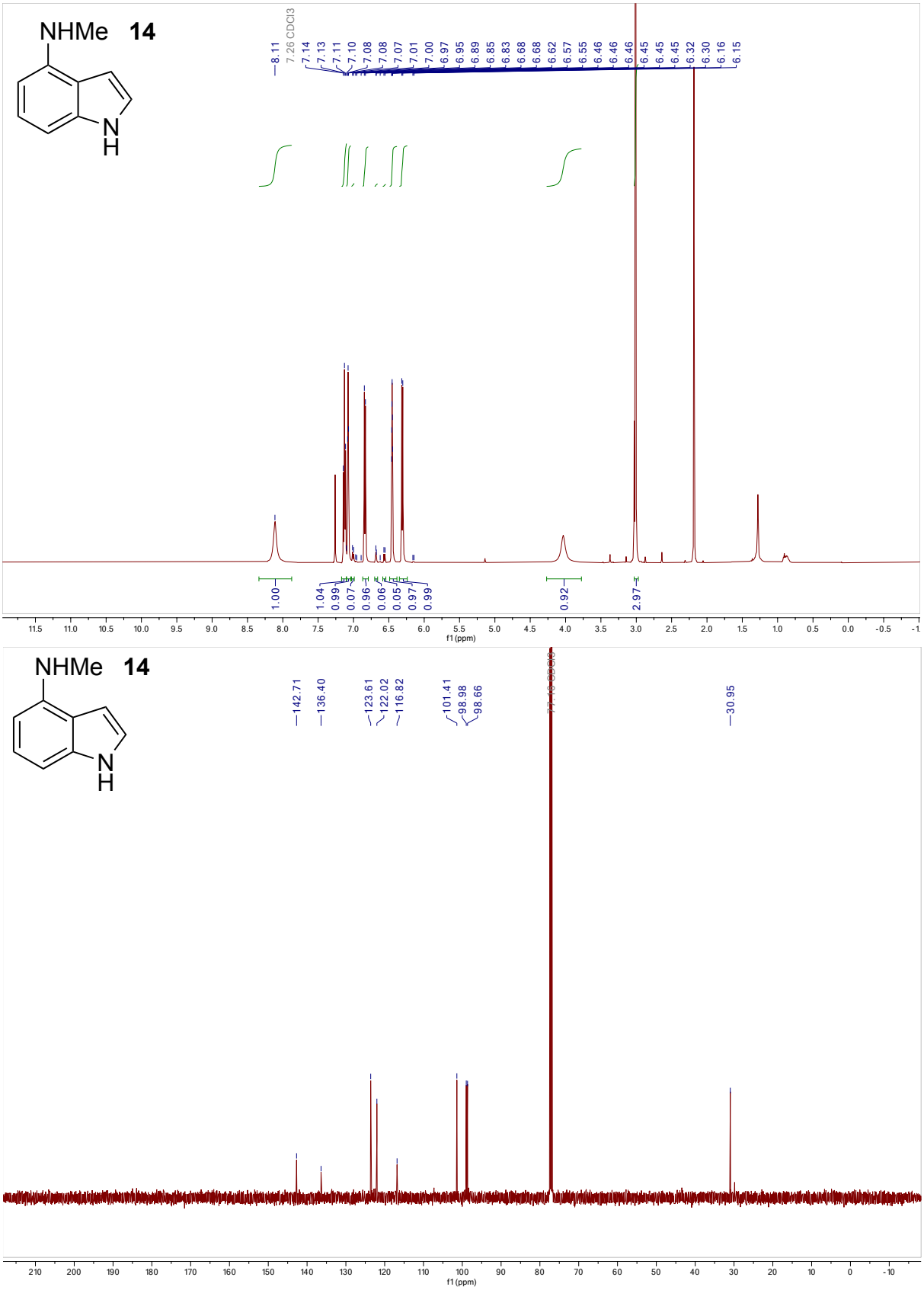


^{1}H (top) and ^{13}C (bottom) for *N,N,N*-Trimethylammonium-1H-indol-4-ammonium iodide (12)

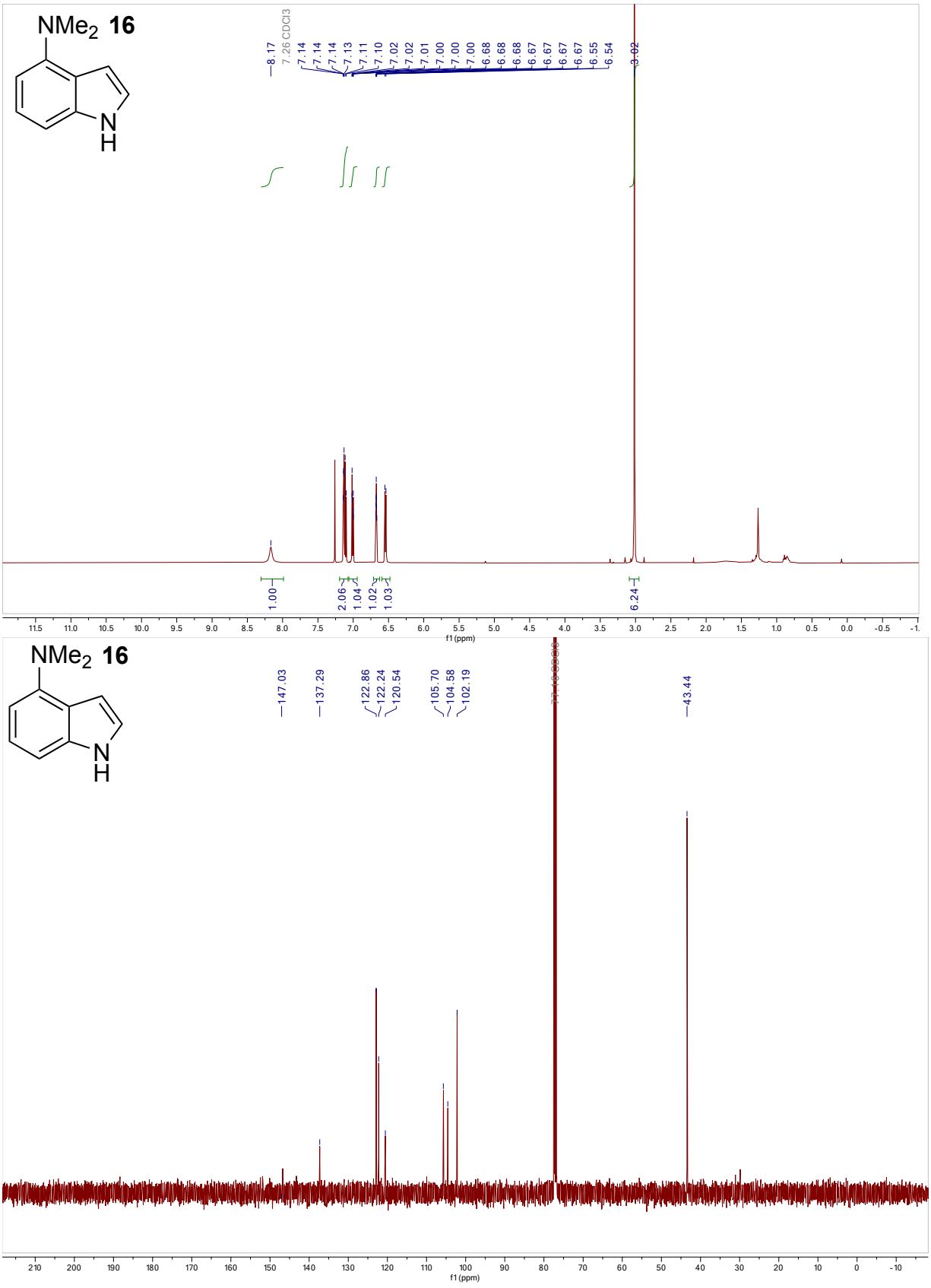




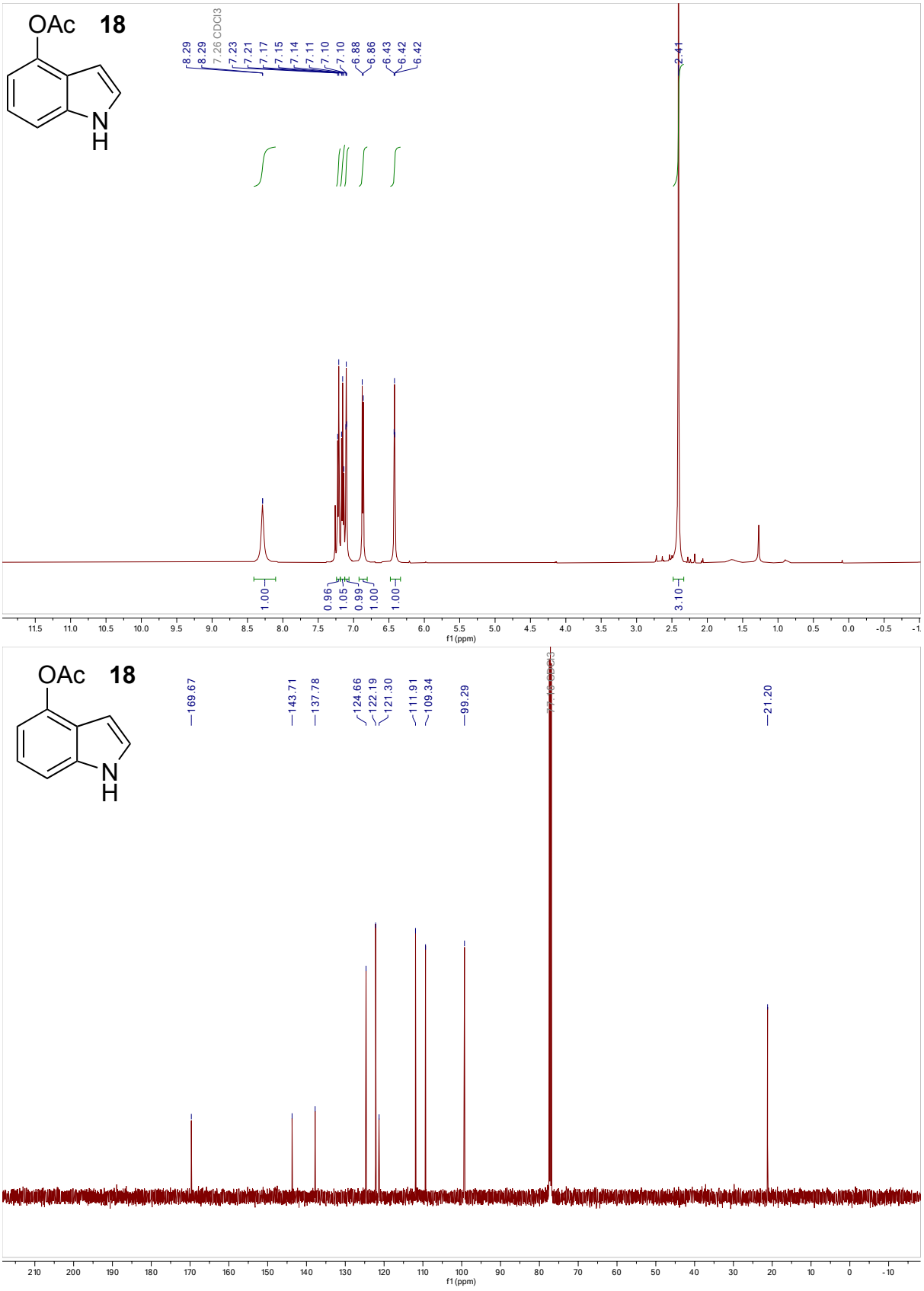
^{1}H (top) and ^{13}C (bottom) for *N*-Methyl-1H-4-aminoindole (14)



^{1}H (top) and ^{13}C (bottom) for *N,N*-Dimethyl-1H-4-aminoindole (16)

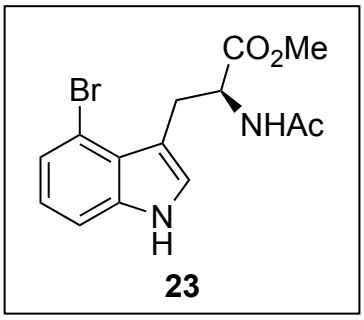


^{1}H (top) and ^{13}C (bottom) for *O*-Acetyl-4-hydroxyindole (18)



4CHO-Trp Synthetic Procedures and Analytical Data

***N*-Acetyl-4-bromo-tryptophan-OMe (23)**



23

A 2-neck, 100 mL RBF equipped with a reflux condenser and stir bar was charged with 4-bromo-L-tryptophan **22** (205 mg, 0.724 mmol, 1.0 equiv.) under a positive pressure of Ar. The solid was suspended in anhydrous methanol (7.2 mL, 0.1 M) to which was added dropwise freshly distilled $SOCl_2$ (106 μL, 1.45 mmol, 2.0 equiv.) at RT with vigorous stirring. The reaction flask was subsequently transferred to an oil bath pre-heated to 40 °C and maintained at this temperature. After 5 h, the oil bath was removed, and the flask allowed to return to RT. The reaction was concentrated to a brown solid under reduced pressure using a rotary evaporator equipped with a base trap. The solid was further dried under high vacuum overnight to remove residual acid.

The atmosphere of the flask was subsequently replaced with Ar and the crude solid suspended in anhydrous DCM (7.2 mL, 0.1 M). The suspension was cooled to 0 °C using an ice water bath. DIEA (260 μL, 1.45 mmol, 2.0 equiv.) and Ac_2O (70 μL, 0.724 mmol, 1.0 equiv.) were added sequentially to the reaction with vigorous stirring. The resultant solution was maintained at 0 °C for 15 m before the ice bath was removed and stirring continued at RT. The reaction was quenched after 1 h by dilution with H_2O (50 mL) and extracted with DCM (1x100 mL). The organic phase was washed with 1N HCl (3x50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. FCC (40% Acetone/Hex) afforded *N*-acetyl-4-bromotryptophan-OMe **23** (143 mg, 58.3% yield) as a yellowish-white solid.

Analytical data for 23

Rf: 0.33 (50% Acetone/Hex); Visualized with UV and 4-Anisaldehyde stain (dim greenish grey);

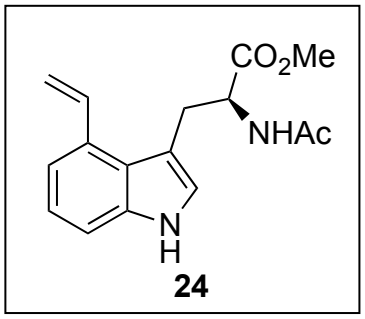
^{1}H NMR (500 MHz, $CDCl_3$): δ=8.94 (bs, 1H), 7.29 (d, 1H, 8.1 Hz), 7.27 (d, 1H, 8.1 Hz), 7.06 (s, 1H), 6.99 (t, 1H, 7.8 Hz), 6.32 (d, 1H, 7.3 Hz), 4.97 (ddd, 1H, 5.4 Hz, 7.3 Hz, 8.1 Hz), 3.72 (s, 3H), 3.66 (dd, 1H, 5.4 Hz, 14. 9 Hz), 3.45 (dd, 1H, 8.1 Hz, 14.9 Hz), 1.91 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.9, 170.1, 137.6, 125.5, 124.7, 124.6, 123.1, 114.0, 111.5, 111.0, 53.9, 52.5, 28.3, 23.3.

IR (neat): 3407, 1653, 752;

HRMS (ESI): m/z Calcd for $C_{14}H_{15}BrN_2NaO_3^+$ [M+Na]$^+$: 361.0164, Found: 361.0176.

_N_-Acetyl-4-ethenyltryptophan-OMe (24)



24

A 2-neck, 25 mL RBF equipped with a reflux condenser and small stir bar was charged with crude N-acetyl-4-bromotryptophan-OMe **23** (55.8 mg, 0.165 mmol, 1.0 equiv.), potassium vinyl trifluoroborate (36.3 mg, 0.271 mmol, 1.6 equiv.), Cs_2CO_3 (174 mg, 0.534 mmol, 3.2 equiv.), and $PdCl_2(dppf)\cdot CH_2Cl_2$ complex (13.9 mg, 0.017 mmol, 10.3 mol %). The atmosphere was replaced with Ar and the solids were subsequently dissolved in oxygen-free THF (3.3 mL) obtained from a purple sodium-benzophenone ketyl still and Millipore H_2O (825 μL) that was sparged with Ar for 20 m immediately prior to use. The flask was transferred to an oil bath pre-heated to 70 °C and the reaction allowed to reflux overnight under Ar. The resultant black solution was allowed to cool to RT the following morning and quenched by dilution with H_2O (50 mL) and extracted using EtOAc (3x30 ml). The combined org. extracts were dried over $MgSO_4$ and concentrated under

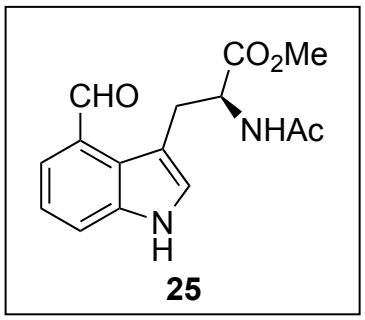
reduced pressure. NMR analysis of the crude product indicated complete consumption of **23**. Crude **24** was used directly in the next reaction without purification.

Analytical data for crude 24

^{1}H NMR (500 MHz, $CDCl_3$): δ=8.61 (bs, 1H), 7.30-7.21 (m, 2H), 7.14 (app. t, 1H, 7.3 Hz), 7.00 (s, 1H), 6.09 (d, 1H, 6.9 Hz), 5.72 (d, 1H, 17.3 Hz), 5.37 (d, 1H, 10.7 Hz), 4.93 (1H, m), 3.70 (s, 3H), 3.49 (dd, 1H, 4.7 Hz, 14.9 Hz), 3.34 (dd, 1H, 7.0 Hz, 14.9 Hz), 1.89 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$): δ=172.9, 170.2, 137.1, 135.7, 131.9, 124.6, 123.9, 122.4, 117.8, 116.0, 111.2, 110.6, 53.6, 52.4, 29.9, 23.2.

***N*-Acetyl-4-formyltryptophan-OMe (25)**



25

A 20 mL scintillation vial equipped with a small stir bar was charged with crude **25** which was subsequently dissolved using THF (2.6 mL) and H_2O (660 μL) under ambient conditions. To the stirring biphasic solution was added K_2OsO_4•$2H_2O$ (8.7 mg, 0.024 mmol, 0.14 equiv.), 2,6-lutidine (77 μL, 0.660 mmol, 4.0 equiv.) and $NaIO_4$ (109 mg, 0.509 mmol, 3.1 equiv.), respectively. The reaction was maintained at RT for 1.5 h before quenching with sat. aq. $NaHCO_3$ (10 mL) and extracting with EtOAc (3x25 mL). The combined org. extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude black oil was purified by FCC (40% to 50% Acetone/Hex) to afford *N*-acetyl-4-formyltryptophan-OMe **25** (22.6 mg, 47.6% yield over 2 steps) as a yellowish-white foam.

Analytical data for 25

^{1}H NMR (500 MHz, $CDCl_3$): δ=10.2 (s, 1H), 9.21 (bs, 1H), 7.64 (m, 2H), 7.30 (t, 1H, 7.7 Hz), 6.76 (d, 1H, 7.9 Hz), 4.78 (m, 1H), 3.71 (s, 3H), 3.64 (AB t, 1H, 9.4 Hz, 14. 9 Hz), 3.56 (AB t, 1H, 5.2 Hz, 14.9 Hz), 1.83 (s, 3H);

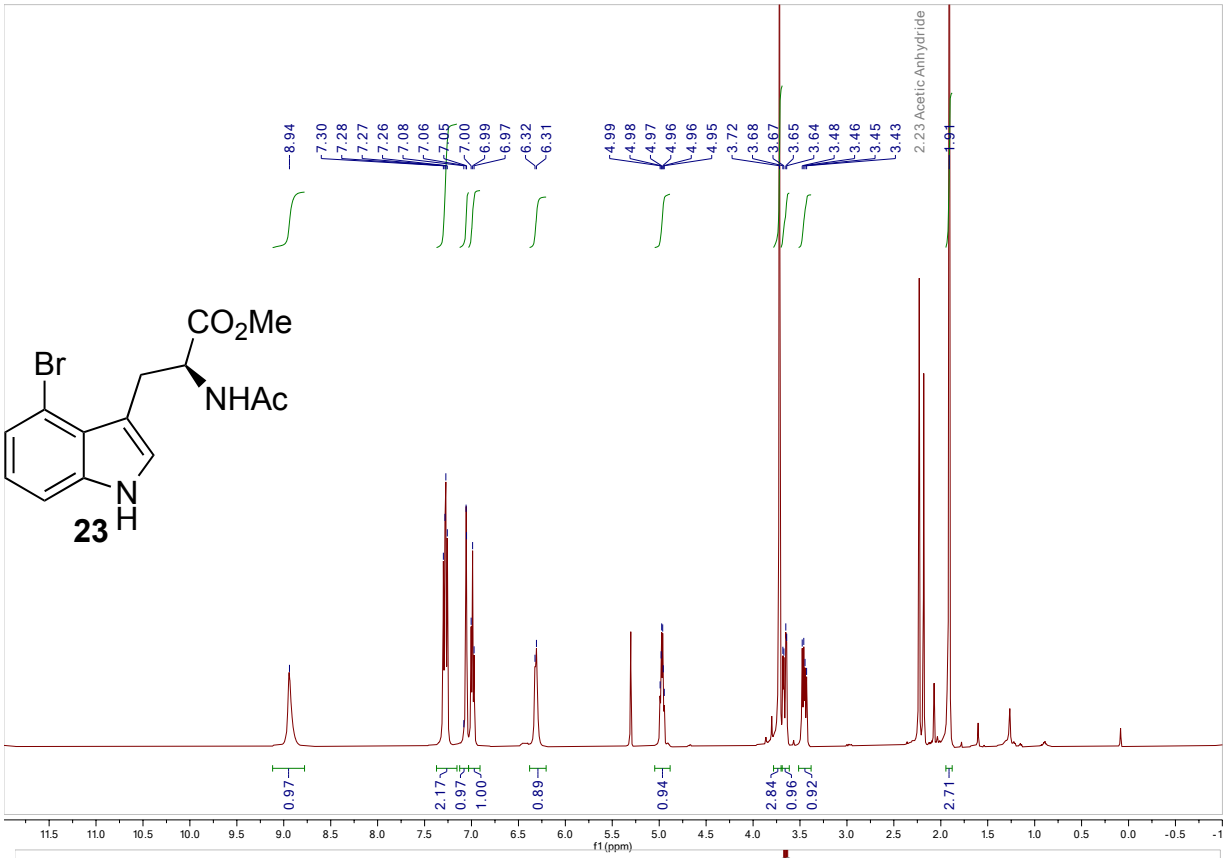
^{13}C NMR (125 MHz, $CDCl_3$): δ=194.4, 172.9, 170.4, 137.8, 130.3, 129.9, 127.7, 124.7, 121.2, 118.8, 112.9, 55.0, 52.4, 30.0, 29.4, 23.2;

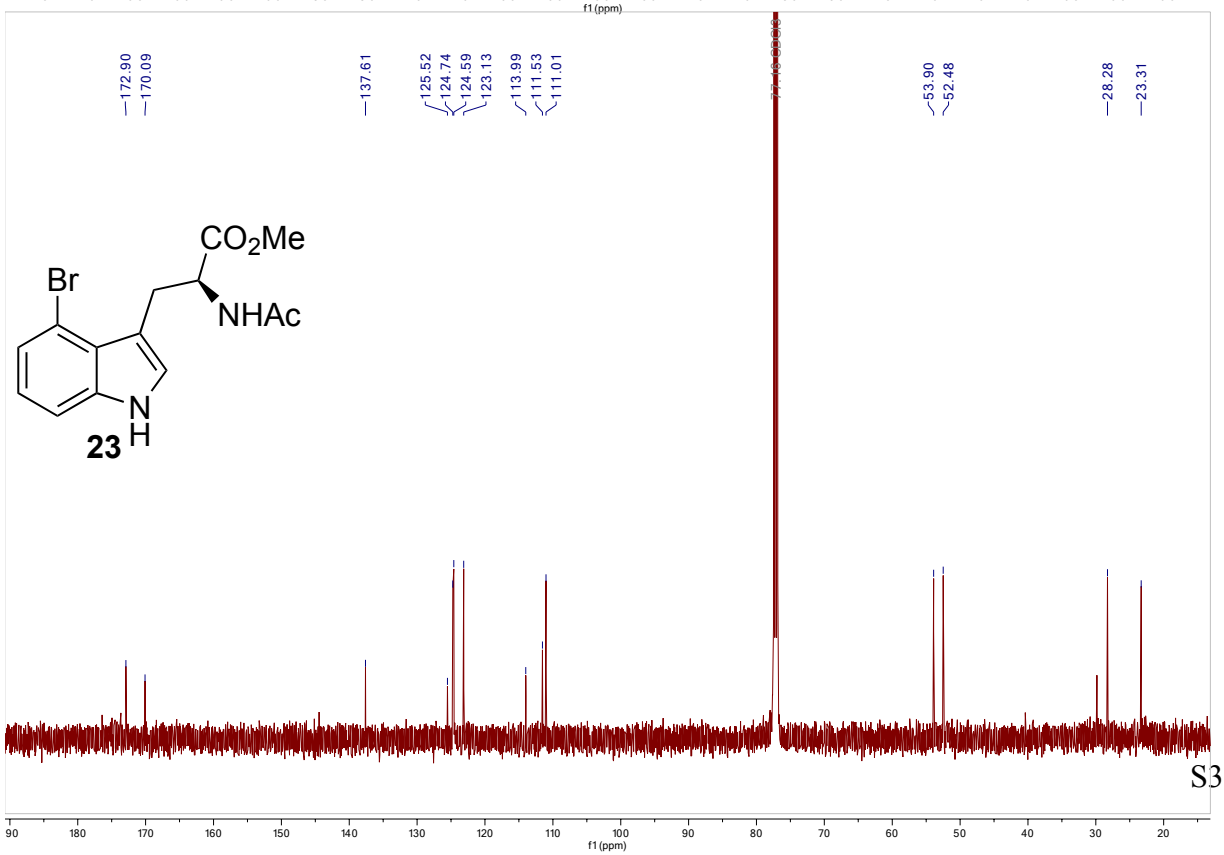
IR (neat): 3438, 2101, 1645, 1437 1214;

HRMS (ESI): m/z Calcd for $C_{15}H_{16}N_2NaO_4^+$ $[M+Na]^+$=311.1008, Found 311.1004;

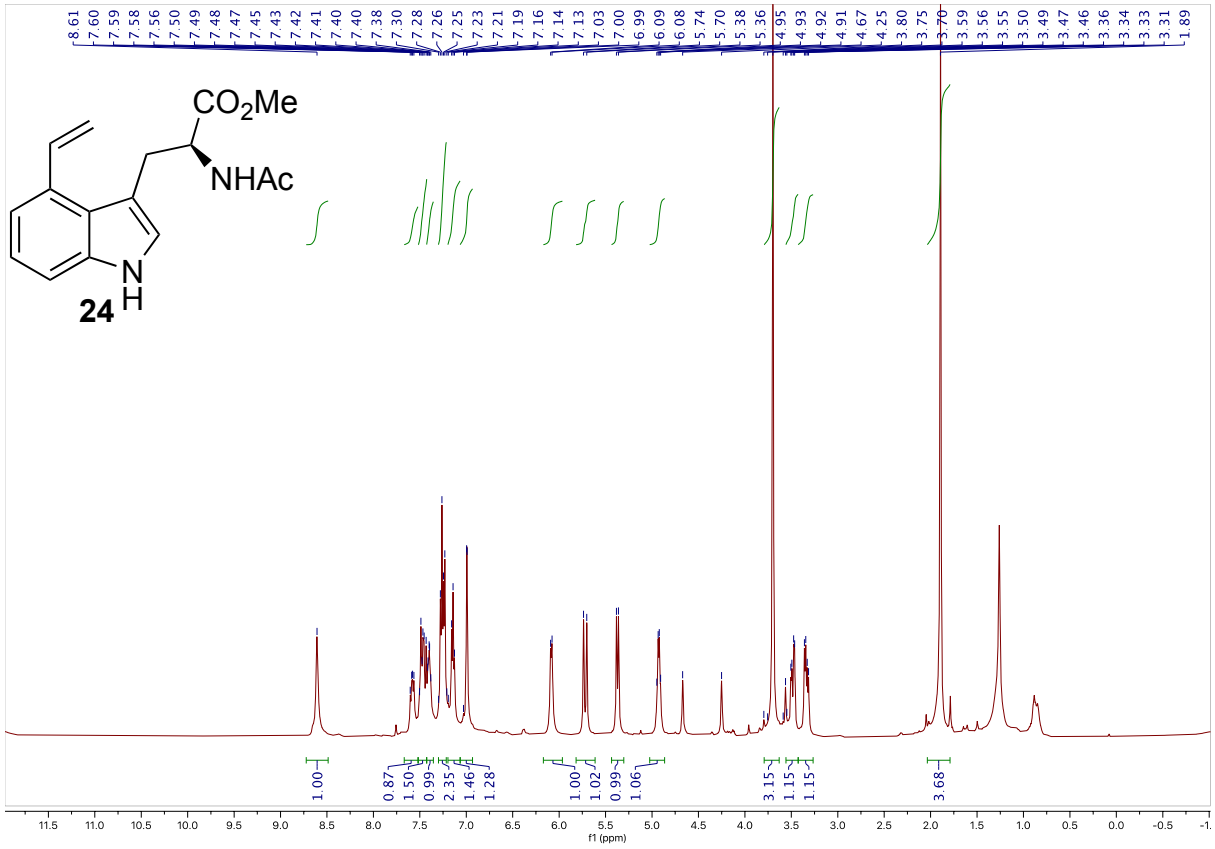
Optical rotation: $[\alpha]_D^{22}$ = -55.98° (c =0.73 w/v, ACN).

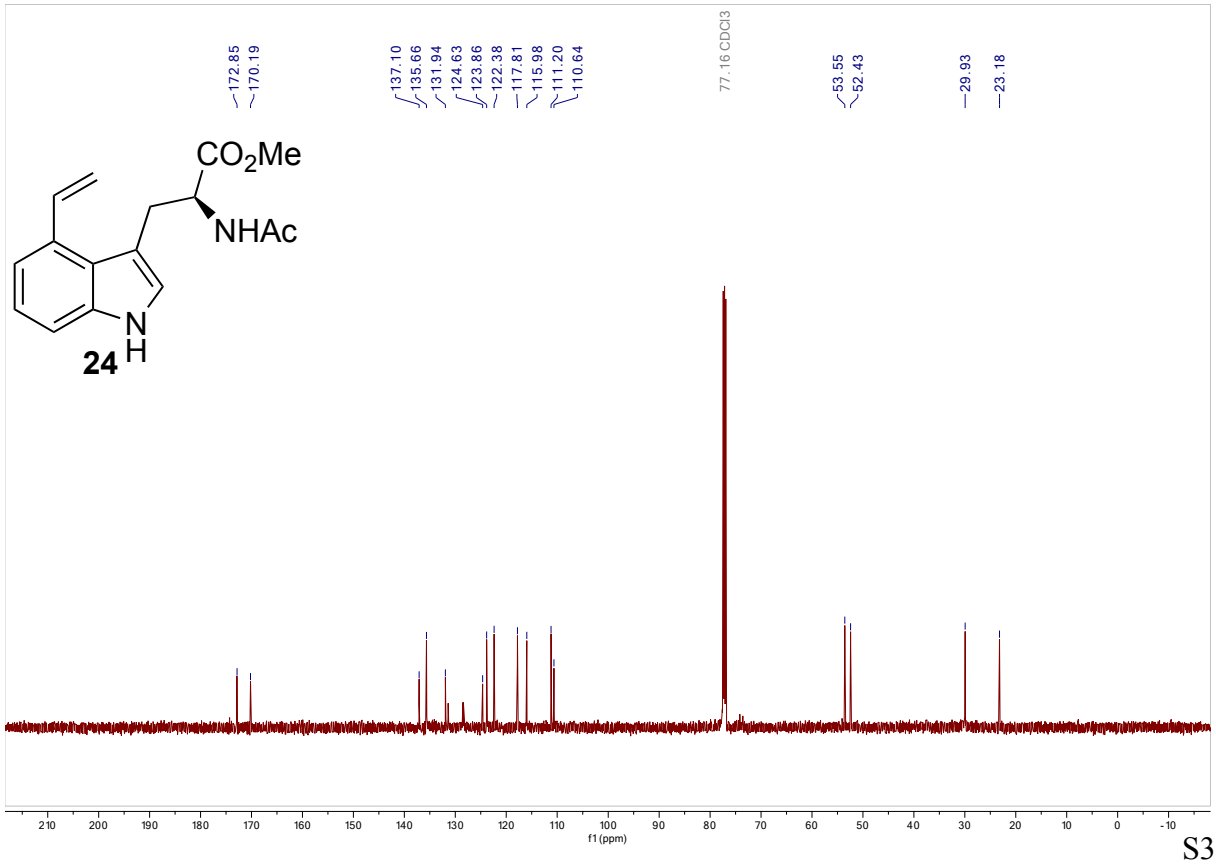
^{1}H & ^{13}C NMR spectra for 4CHO-Trp and Intermediates.
^{1}H (*top*) and ^{13}C (*bottom*) for *N*-Acetyl-4-bromo-tryptophan-OMe (23)





^{1}H (*top*) and ^{13}C (*bottom*) for crude *N*-Acetyl-4-vinyltryptophan-OMe (24)





^{1}H (*top*) and ^{13}C (*bottom*) for *N*-Acetyl-4-formyltryptophan-OMe (25)