11-Step Total Synthesis of Araiosamines

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SUPPORTING INFORMATION

Experimental Procedures and Characterization Data

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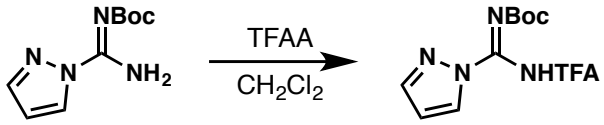
General Experimental. All reactions were carried out under an inert argon atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Dry acetonitrile (MeCN), dichloromethane (DCM), diethyl ether (Et_2O), tetrahydrofuran (THF), toluene (PhMe), dimethylformamide (DMF), and triethylamine (Et_3N) were obtained by passing the previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica plates (60F-254), using UV light as the visualizing agent and an acidic solution of *p*-anisaldehyde and heat, or $KMnO_4$ and heat as developing agents. Flash silica gel chromatography was performed using E. Merck silica gel (60, particle size 0.043– 0.063 mm). NMR spectra were recorded on Bruker DRX-600 and AMX-400 instruments and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$ ^{1}H NMR δ = 7.26 ppm, ^{13}C NMR δ = 77.16 ppm; acetone-d_6 ^{1}H NMR δ = 2.05 ppm, ^{13}C NMR δ = 29.84, 206.26 ppm; CD_3OD ^{1}H NMR δ = 3.31 ppm, ^{13}C NMR δ = 49.00 ppm; $(CD_3)_2SO$ ^{1}H NMR δ = 2.50 ppm, ^{13}C NMR δ = 39.52 ppm). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time-of-flight (ESI-TOF) reflectron experiments. The UCSD small molecule X-ray facility collected and analyzed all X-ray diffraction data.

***N*-Boc-*N'*-TFA-pyrazole-1-carboxamidine (26)**



[ref. 1] **26**

Procedure for the preparation of guanidinylation reagent (26): a round-bottom flask with a magnetic stirrer was charged with dichloromethane (50 mL) and *tert*-butyl-(amino(1*H*-pyrazol-1-yl)methylene)carbamate[1] (10 g, 47.6 mmol).The solution was cooled to 0°C before trifluoroacetic anhydride (TFAA) (6.72 mL, 47.6 mmol) was added dropwise. The resulting mixture was warmed up to ambient temperature over 5 minutes and the solvent was subsequently removed *in vacuo.* Purification of the residue by recrystallization (CH_2Cl_2) yielded **26** (12.2g, 84%) as a colorless crystalline solid.

Physical state: colorless solid;

TLC: R_f = 0.31 (30% EtOAc in hexanes);

^{1}H NMR (600 MHz, acetone-d_6) δ 10.06 (br, 1H), 8.45 (dd, *J* = 2.9, 0.7 Hz, 1H), 7.90 (dd, *J* = 1.6, 0.7 Hz, 1H), 6.69 (dd, *J* = 2.9, 1.6 Hz, 1H), 1.51 (s, 9H);

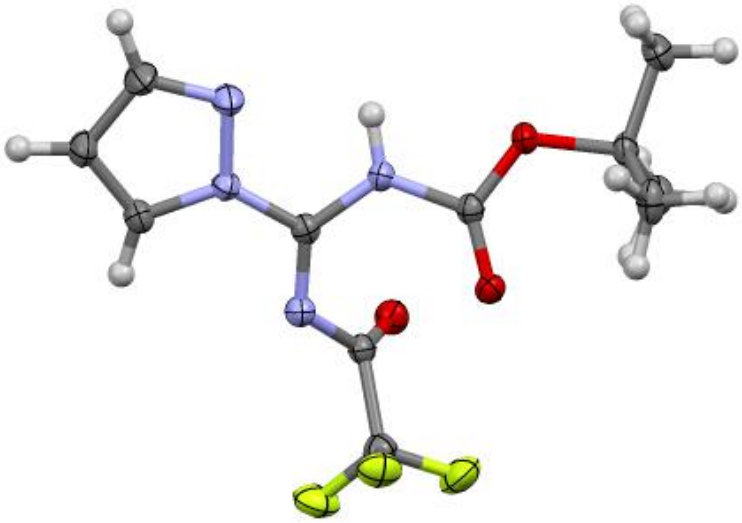
^{13}C NMR (151 MHz, acetone-d_6); δ 164.4 (q, *J* = 38.4 Hz),150.7, 145.3, 142.1, 130.6, 116.7 (q, *J* = 275.4 Hz), 112.1, 85.0, 27.9 (3C);

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.28 (dd, *J* = 2.8, 0.7 Hz, 1H), 7.72 (dd, *J* = 1.6, 0.6 Hz, 1H), 6.53 (dd, *J* = 2.9, 1.6 Hz, 1H), 1.51 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$); δ 164.1 (q, *J* = 38.7 Hz),149.1, 143.9, 139.2, 129,4, 115.9 (q, *J* = 287.4 Hz), 111.1, 85.3, 27.9 (3C);

HRMS (m/z): calcd for $C_{11}H_{13}F_3N_4O_3Na$ $[M+Na]^+$ 329.0832, found 329.0825.

X-ray structure of compound 26, for details see baran593.cif



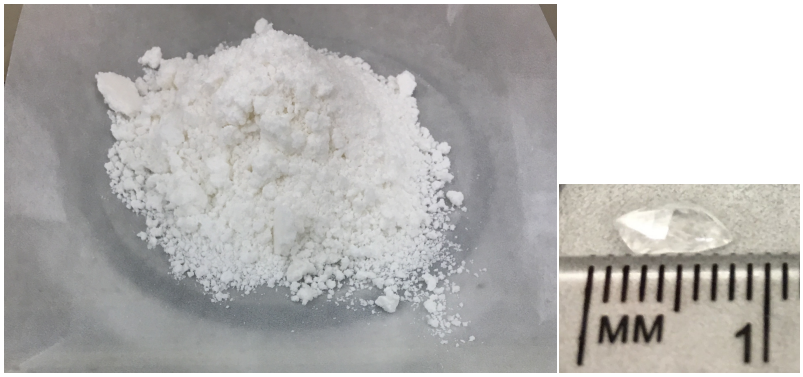


Figure S1. Pictures of Compound 26 synthesized on 30g scale (left) and as a single crystal (right)

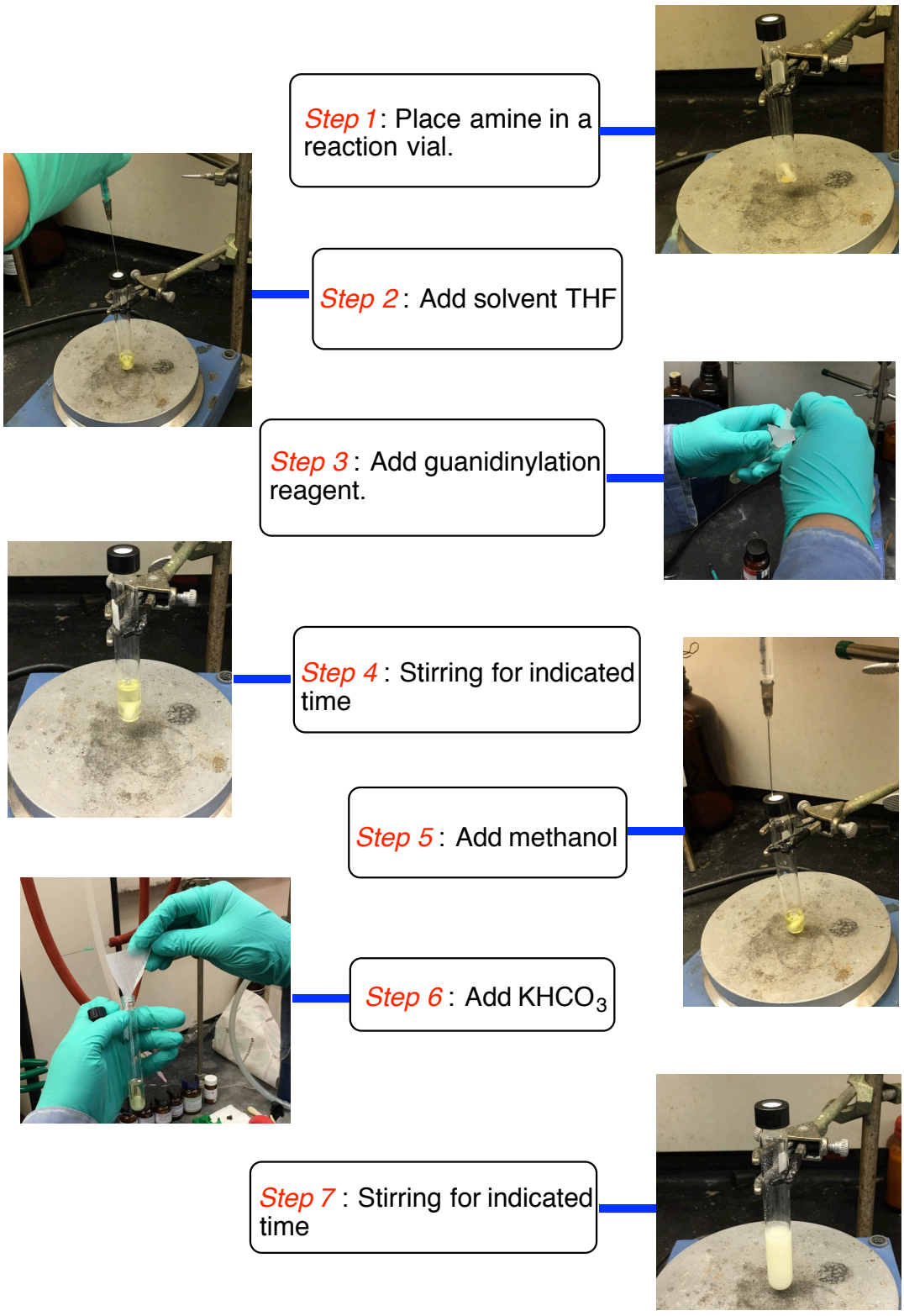
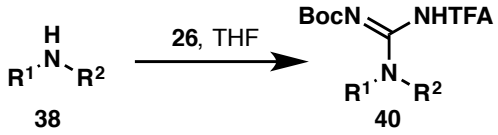
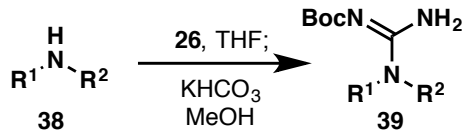


Figure S2. General operation process for the *N*-Boc-guanidinylation of amines.

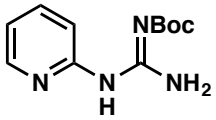


Procedure for preparations of *N*-Boc,*N'*-TFA-guanidines from primary and secondary amines To a solution of amine (0.20 mmol) in THF (2 mL) was added *N*-Boc-*N'*-TFA-pyrazole-1-carboxamidine (**26**) (0.25 mmol). The mixture was stirred at room temperature until the complete disappearance of starting material by TLC and was concentrated *in vacuo*. The crude was purified by FCC (SiO_2) to yield the desired product.



Procedure for the *N*-Boc-guanidinylation of primary and secondary amines To a solution of amine (0.20 mmol) in THF (2 mL) was added *N*-Boc-*N'*-TFA-pyrazole-1-carboxamidine (**26**) (0.25 mmol). The mixture was stirred at room temperature until the complete disappearance of starting material as indicated by TLC and was then treated with $KHCO_3$ (2.5 mmol) and MeOH (1 mL). The resulting solution was stirred until the complete cleavage of the TFA group by TLC or LC/MS and was partitioned between EtOAc (5 mL) and brine (5 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude was purified by FCC (SiO_2) to yield the desired product.

2-aminopyridine-*N*-Boc-guanidine (39a)



Yield: 77% from 2-aminopyridine;

Physical state: white solid;

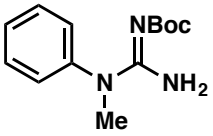
TLC: R_f = 0.41 (40% EtOAc in hexanes);

^{1}H NMR (600 MHz, acetone-d_6) δ 10.12 (br, 1H), 8.26 (d, J = 4.4 Hz, 1H), 7.73 – 7.76 (m, 1H), 7.07 (t, J = 8.3 Hz, 1H), 7.01 (t, J = 6.3 Hz, 1H), 1.42 (s, 9H);

^{13}C NMR (151 MHz, acetone-d6); δ 162.8, 159.7, 156.4, 147.1, 139.1, 118.3, 115.4, 78.5, 28.5 (3C);

HRMS (m/z): calcd for $C_{11}H_{17}N_4O_2$ $[M+H]^+$ 237.1346, found 237.1346.

***N*-methyl-aniline-Boc-guanidine (39b)**



Yield: 98% from N-methylaniline;

Physical state: colorless solid;

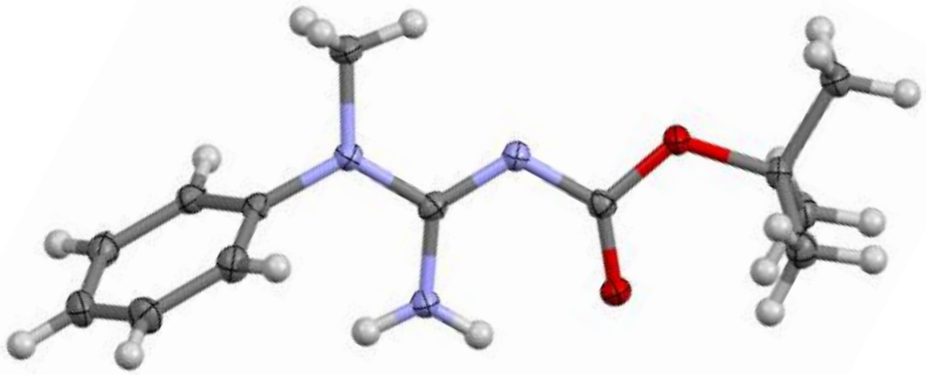
TLC: R_f = 0.33 (30% EtOAc in hexanes);

^{1}H NMR (600 MHz, acetone-d_6) δ 7.47 – 7.50 (m, 2H), 7.34 – 7.38 (m, 3H), 3.29 (s, 3H), 1.43 (s, 9H);

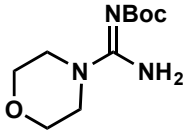
^{13}C NMR (151 MHz, acetone-d_6); δ 164.9, 161.7, 143.7, 130.9 (2C), 128.4, 128.5 (2C), 77.2, 38.6, 28.7(3C);

HRMS (m/z): calcd for $C_{13}H_{20}N_3O_2$ $[M+H]^+$ 250.1550, found 250.1550.

X-ray Structure of Compound 39b, for details see baran604.cif



***tert*-butyl-(amino(morpholino)methylene)carbamate (39c)**



Yield: 83% from morpholine;

Physical state: colorless solid;

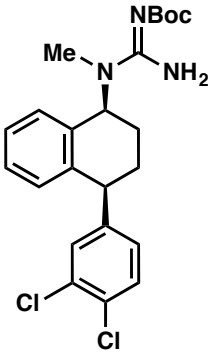
TLC: R_f = 0.52 (EtOAc);

^{1}H NMR (600 MHz, acetone-d_6) δ 7.82 (br, 2H), 3.63 – 3.66 (m, 4H), 3.53 – 3.55 (m, 4H), 1.43 (s, 9H);

^{13}C NMR (151 MHz, acetone-d_6); δ 165.3, 161.7, 77.0, 65.6 (2C), 44.8 (2C), 28.7 (3C);

HRMS (m/z): calcd for $C_{10}H_{20}N_3O_3$ $[M+H]^+$ 230.1499, found 230.1499.

Compound 39d



Yield: 86% from Sertraline;

Physical state: white solid;

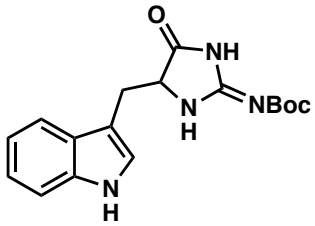
TLC: R_f = 0.39 (30% EtOAc in hexanes);

^{1}**H NMR** (600 MHz, acetone-d_6) δ 7.49 (d, J = 8.3Hz, 1H), 7.27 – 7.32 (m, 1H), 7.27 (d, J = 2.0 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.16 (d, J = 7.8 Hz, 1H), 6.99 – 7.04 (m, 2H), 4.31 – 4.38 (m, 1H), 2.77 (s, 3H), 2.29 – 2.38 (m, 1H), 2.06 – 2.12 (m, 2H), 1.70 – 1.76 (m, 2H), 1.42 (s, 9H)

^{13}**C NMR** (151 MHz, acetone-d_6); δ 164.2, 162,4, 148.2, 138.3, 136.9, 131.5, 130.8, 130.7, 130.2, 129.3, 128.8, 127.3, 127.2, 127.0, 76.1, 53.8, 42.7, 30.0, 27.9, 25.6, 21.5 (3C);

HRMS (m/z): calcd for $C_{23}H_{28}Cl_2N_3O_2$ $[M+H]^+$ 448.1553, found 448.1568.

Compound 40



Yield: 90% from tryptophan methyl ester;

Physical state: white foam;

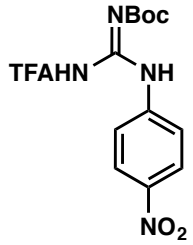
TLC: R_f = 0.26 (EtOAc);

^{1}H NMR (600 MHz, acetone-d_6) δ 10.12 (s, 1H), 8.94 (s, 1H), 7.67 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 1.9 Hz, 1H), 7.08 (ddd, J = 8.0 Hz, 6.9 Hz, 1.1 Hz, 1H), 6.99 (ddd, J = 8.0 Hz, 6.9 Hz, 1.1 Hz, 1H), 4.47 (dd, J = 6.3, 4.5 Hz, 1H), 3.39 – 3.46 (m, 1H), 3.22 (dd, J = 14.8, 6.4 Hz, 1H), 1.42 (s, 9H);

^{13}C NMR (151 MHz, acetone-d_6); δ 176.7, 162.8, 159.5, 136.0, 127.2, 123.4, 120.8, 118.3, 110.7, 108.4, 103.7, 78.7, 59.4, 26.9 (3C), 26.3;

HRMS (m/z): calcd for $C_{17}H_{21}N_4O_3$ $[M+H]^+$ 329.1608, found 329.1584.

Compound 41



Yield: 80% from 4-nitroaniline;

Physical state: yellow foam;

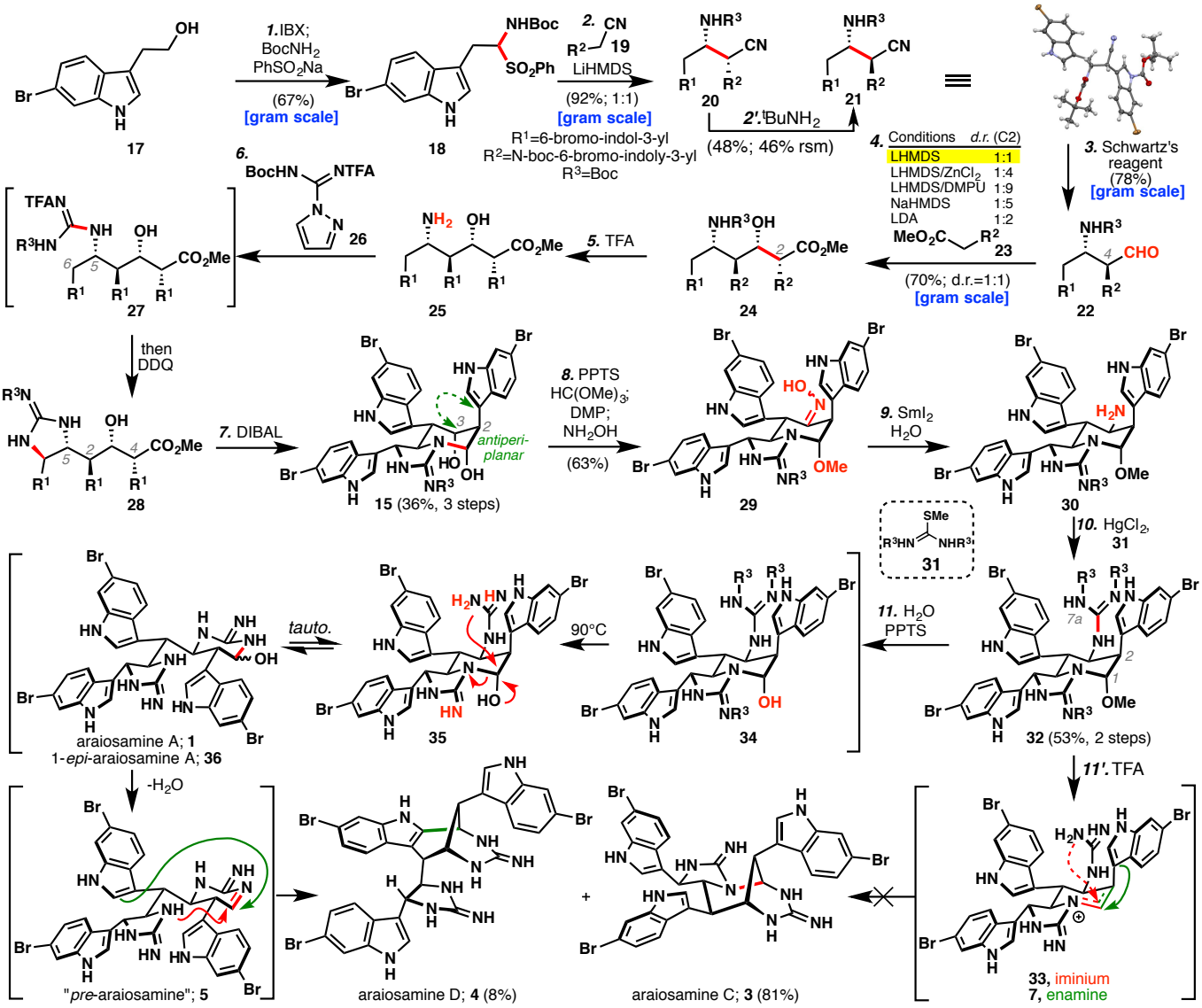
TLC: R_f = 0.54 (20% EtOAc in hexanes);

^{1}H NMR (600 MHz, acetone-d_6) δ 11.27 (br, 1H), 8.29 – 8.35 (m, 2H), 8.02 – 8.08 (m, 2H), 1.60 (s, 9H);

^{13}C NMR (151 MHz, acetone-d_6) δ 166.6 (q, J = 40.7 Hz), 155.9, 152.0, 144.6, 141.2, 123.9 (2C), 123.1(2C), 115.8 (q, J = 429 Hz), 85.1, 28.6 (3C);

HRMS (m/z): calcd for $C_{14}H_{16}F_3N_4O_5$ $[M+H]^+$ 377.1067, found 377.1083.

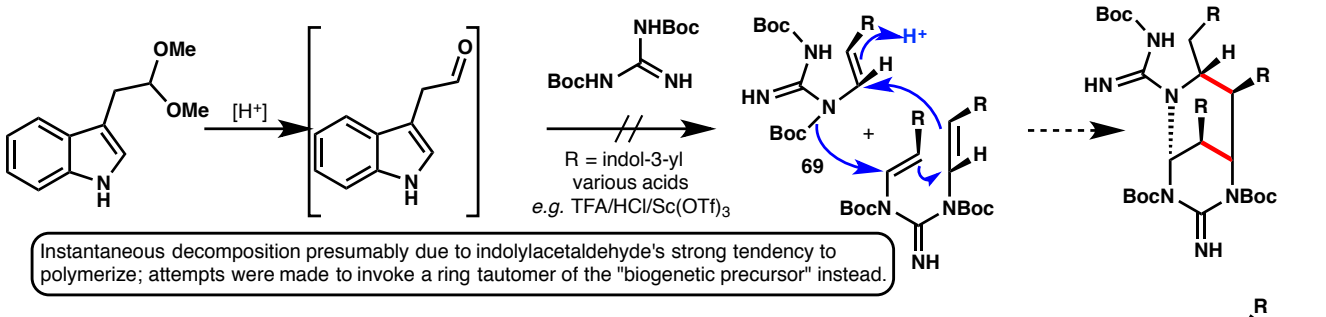
In this section the final synthetic route is depicted along with an in-depth look at some of the failed routes and thoughts that went into the evolution of our final strategy. For the purposes of contextualizing the current studies, we define a reaction step as one in which a substrate is converted to a product in a single reaction flask (irrespective of the number of transformations) without intermediate workup in a separate flask or purification. If the substrate leaves the flask, this must constitute the end of a step. Some of the earlier strategies are explored on model systems with non-brominated indoles.



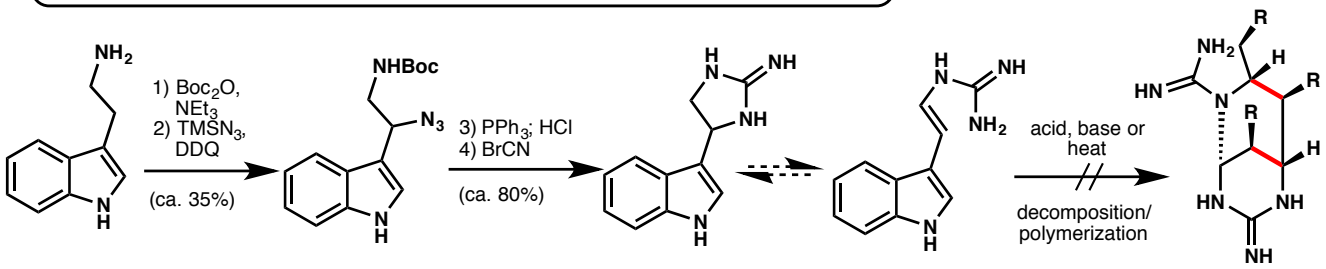
[a] Reagents and conditions: (1) **17** (1 equiv), IBX (1.5 equiv), MeCN, 82°C, then *tert*-butyl carbamate (1 equiv), sodium benzenesulfinate (1.1 equiv), THF/H_2O/formic acid, 25°C (67%, one pot); (2) **19** (3 equiv), LiHMDS (3 equiv), THF, -78°C (92%, 1:1); (2') MeOH/^{t}BuNH$_2$ (10:1); (3) Schwartz's reagent (2.6 equiv), CH_2Cl_2, 25°C (78%); (4) **23** (3 equiv), LiHMDS (4 equiv), THF, -78°C (70%, d.r.=1:1); (5) TFA/CH_2Cl_2 (1:3) 0°C to 25°C; (6) **26** (1 equiv), THF, 25°C then DDQ (1.5 equiv), MeCN, 25°C; (7) DIBAL (ca. 3 equiv), CH_2Cl_2, -78°C (36%, over 3 steps); (8) PPTS (1 equiv), MeOH/HC(OMe)$_3$ (2:1), 25°C; DMP (2 equiv), THF, 25°C then NH$_2$OH•HCl (11 equiv), NaOAc (5.5 equiv), EtOH, 50°C (63%, one pot); (9) SmI_2, THF/H_2O (6:1), 25°C; (10) *N,N'*-Di-Boc-*S*-methylisothiourea (**31**) (2.4 equiv), $HgCl_2$ (2.9 equiv), DMF, 25°C (53%, 2 steps); (11') TFA/CH_2Cl_2 (1:1), (11) PPTS (4.4 equiv), MeCN/H_2O (1:2), 25°C to 90°C (**3**, 81%; **4**, 8%, one pot); IBX=2-iodoxybenzoic acid, LiHMDS=lithium bis(trimethylsilyl) amide, Schwartz's reagent=$ZrCp_2(H)Cl$, TFA=trifluoroacetic acid, DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DIBAL=diisobutylaluminum hydride, PPTS=pyridinium *p*-toluenesulfonate, DMP=1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one.

Approaches towards araiosamines C-D via trimerization

1) Trimerization attempts via "biogenetic precursor"

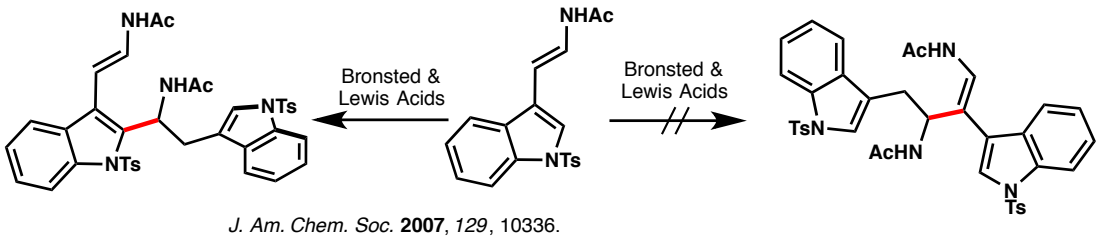


Instantaneous decomposition presumably due to indolylacetaldehyde's strong tendency to polymerize; attempts were made to invoke a ring tautomer of the "biogenetic precursor" instead.



2) Trimerization/dimerization attempts using enamides

Inspiration for this strategy came from Terada's work on enecarbamate trimerization. It was surmised that formation of the 6-membered ring would provide a driving force for trimerization over polymerization. But with substituted simple enecarbamates, dimerization products were obtained instead. Therefore, a stepwise dimerization approach was deemed more feasible.



Other modalities of dimerization also noted; alkynyl enamides were pursued as indole surrogates. However, desired C-C bond forming reactions were not observed.

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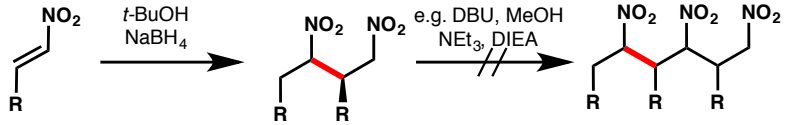
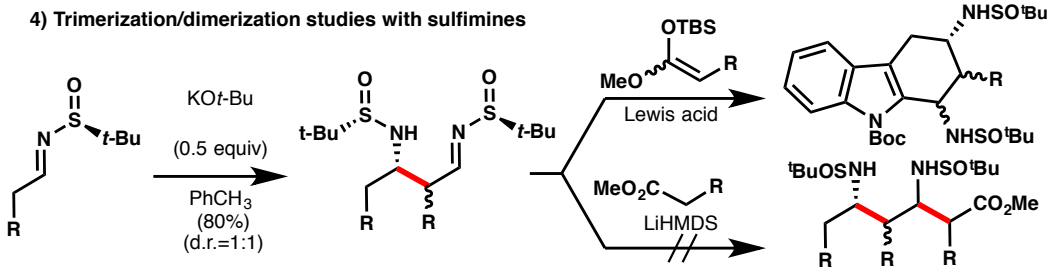
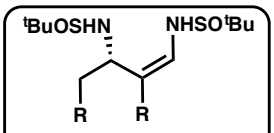
3) Trimerization/dimerization via "umpolung approach"



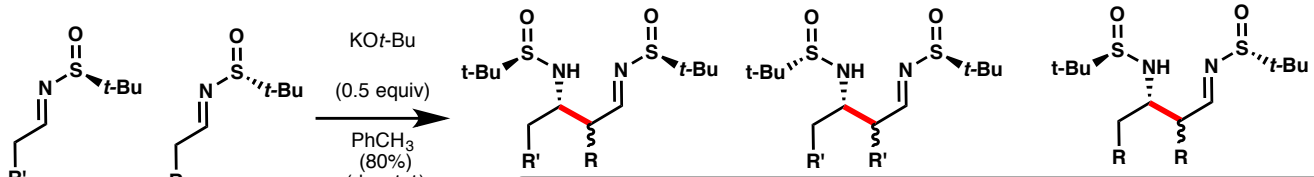
To circumvent the polymerization/ instability problem, an umpolung approach was devised which seeks to forge the skeleton through consecutive "Henry-type" reactions. While dimerization was successful, attempts to elaborate the dimer further was foiled by competing "retro-Henry-type" processes.

4) Trimerization/dimerization studies with sulfimines





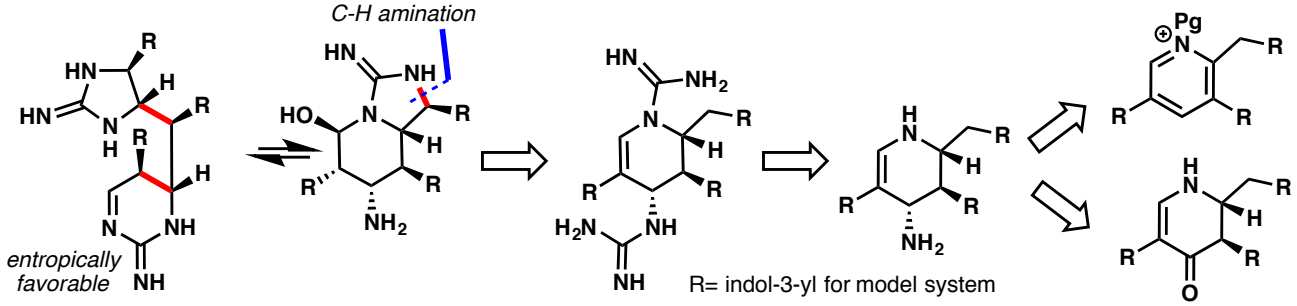
frequently observed by TLC under acid/base but reverts back to starting material on quenching.



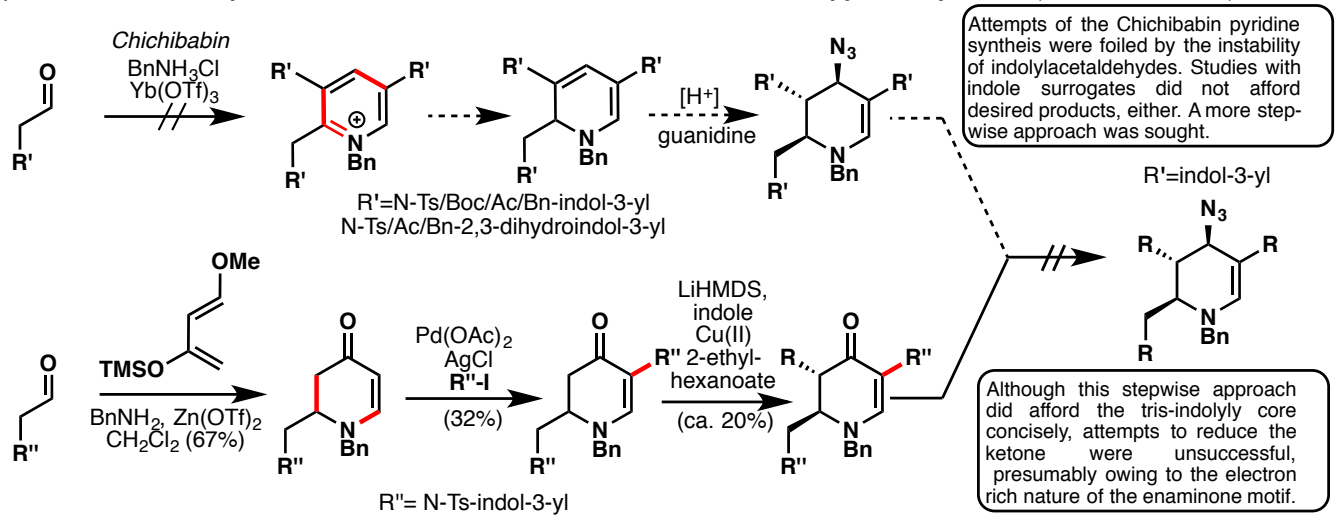
R=N-Boc-indol-3-yl; R'=N-Boc-6-bromoindol-3-yl

The desired stereochemical outcome requires the formation of a "mixed" Ellman imine dimer. However, crossover experiments were unsuccessful and the route was abandoned.

Attempts to construct araiosamine skeleton via the cyclic logic



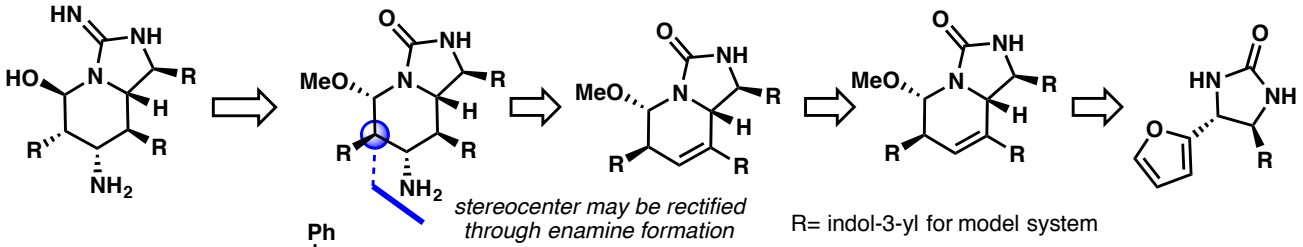
1) unsuccessful attempts to construct araiosamine skeleton with Chichibabin pyridine synthesis (with model indoles)

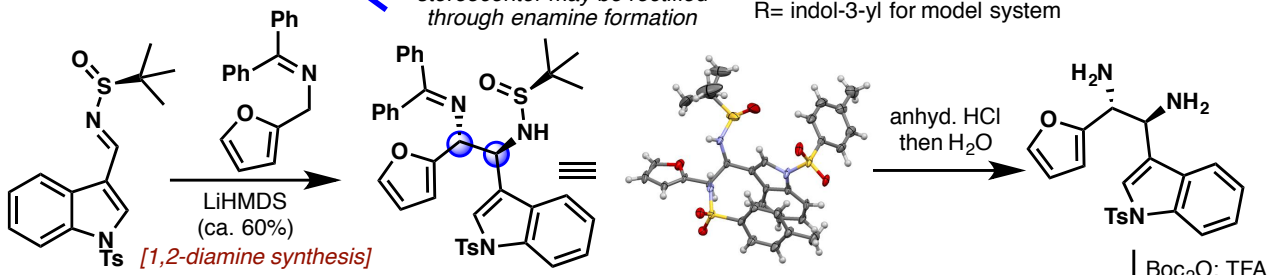


Attempts of the Chichibabin pyridine syntheis were foiled by the instability of indolylacetaldehydes. Studies with indole surrogates did not afford desired products, either. A more step-wise approach was sought.

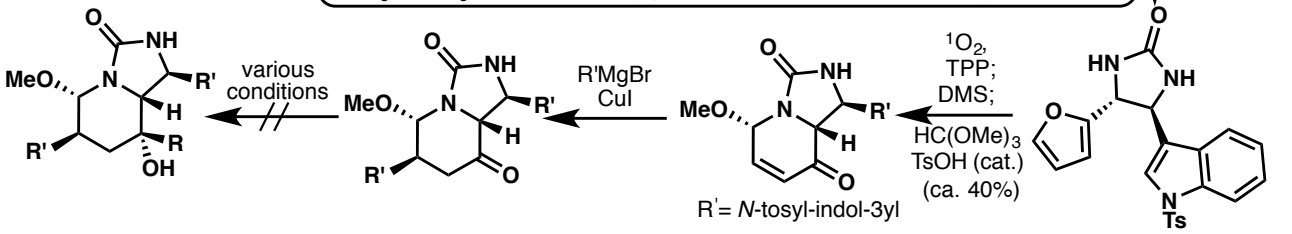
Although this stepwise approach did afford the tris-indolyly core concisely, attempts to reduce the ketone were unsuccessful, presumably owing to the electron rich nature of the enaminone motif.

2) Alternative approaches based on the "cyclic logic" (with model indoles)

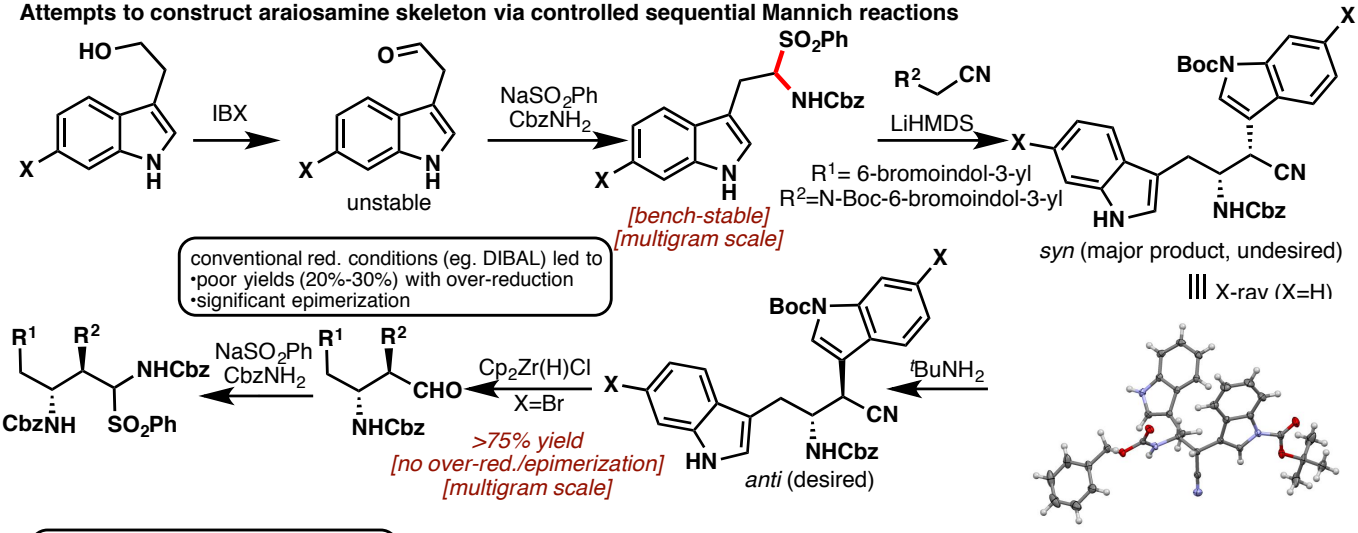


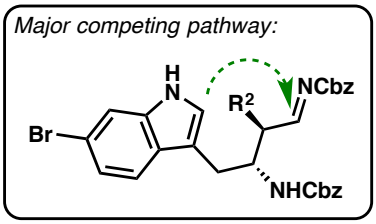


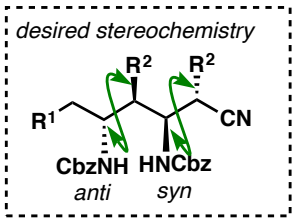
Attempts to install an indole via 1,2-addition led to recovered starting material. Addition of $CeCl_3$ or $LaCl_3$ did not result in any products and the route was eventually abandoned.

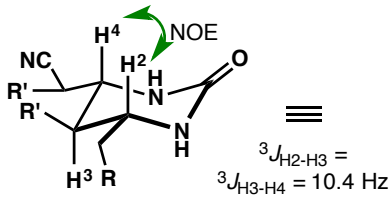


Attempts to construct araiosamine skeleton via controlled sequential Mannich reactions

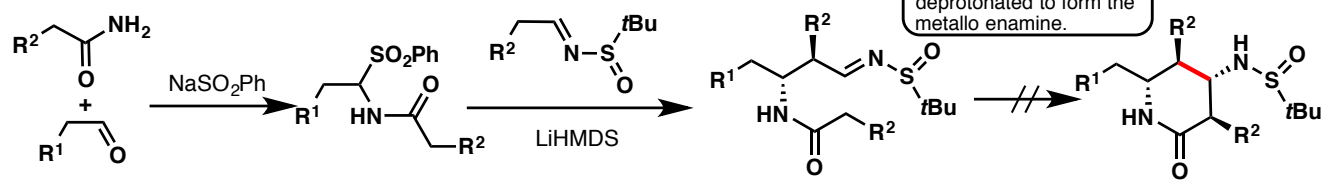




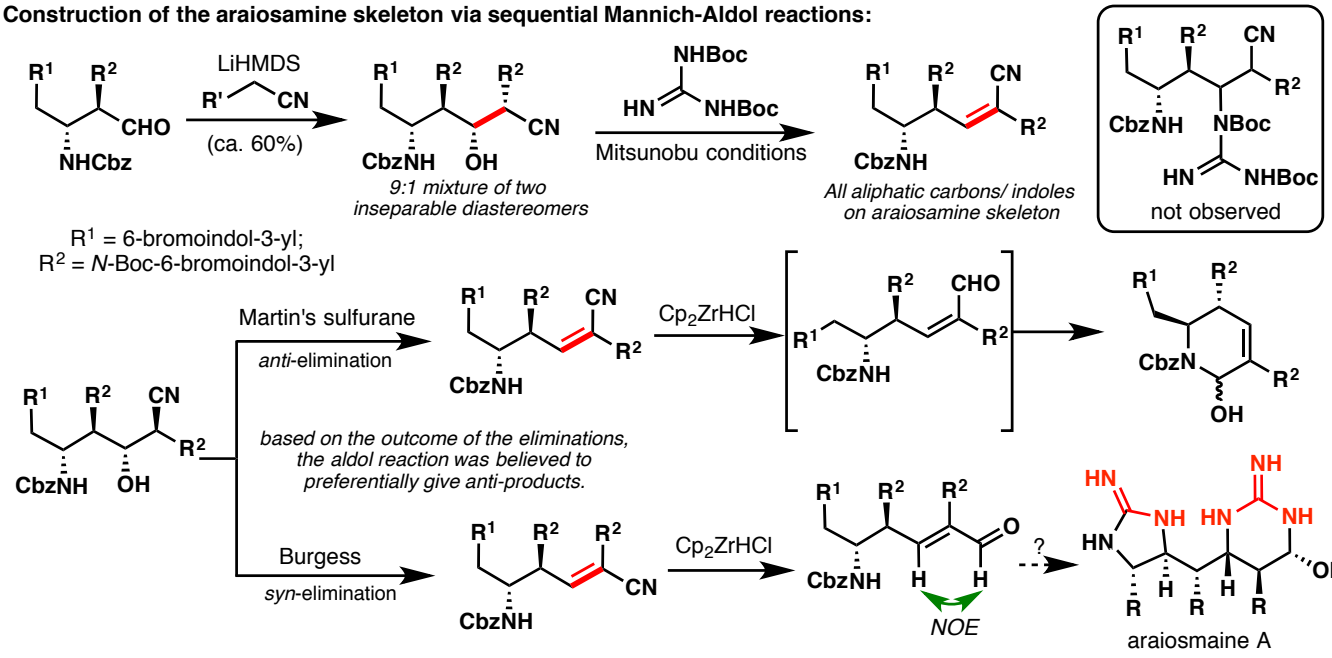




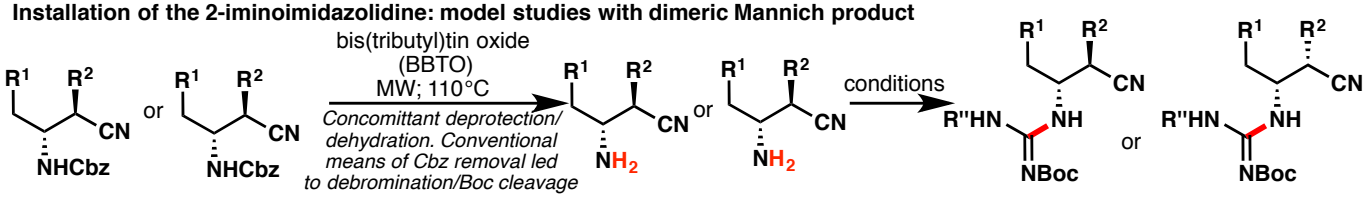
it was hypothsized that the desired stereochemical outcome may be more tenable in a cyclic template, an intramolecular Mannich reaction was therefore devised:



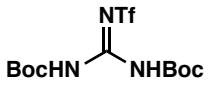
Construction of the araiosamine skeleton via sequential Mannich-Aldol reactions:



Installation of the 2-iminoimidazolidine: model studies with dimeric Mannich product

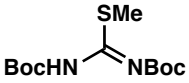


Guanidinylation reagent surveyed:



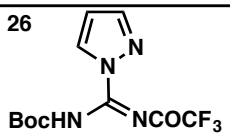
poor reactivity

poor reactivity

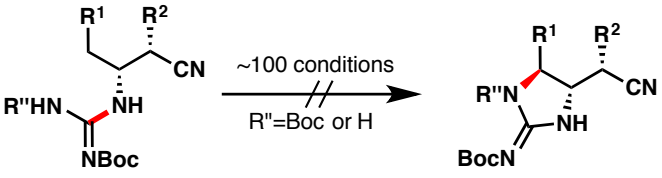


poor yield
better yield only with $HgCl_2$ activation

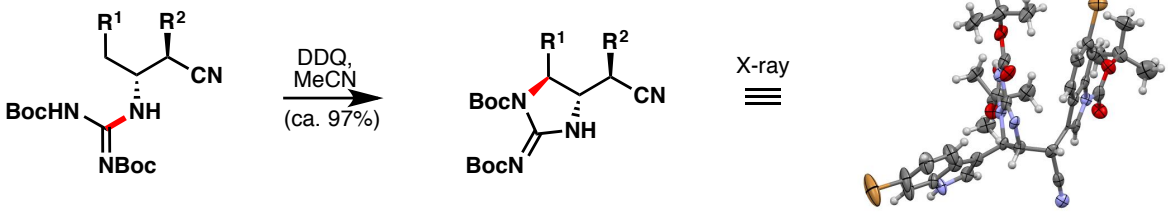
26



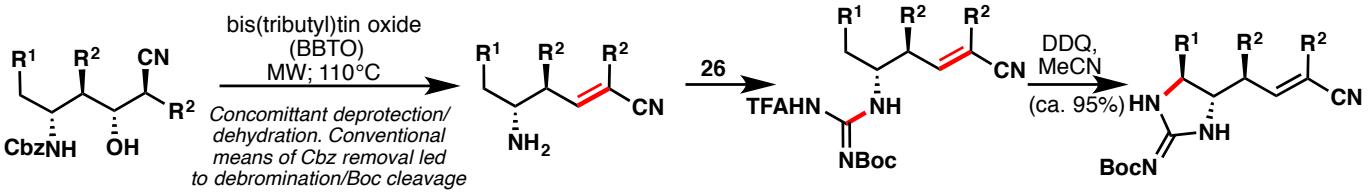
[high reactivity/stability]
(TFA can be removed through in situ treatment with $KHCO_3$ to afford mono-boc-guanidine in ca. 90% for both diastereomers)



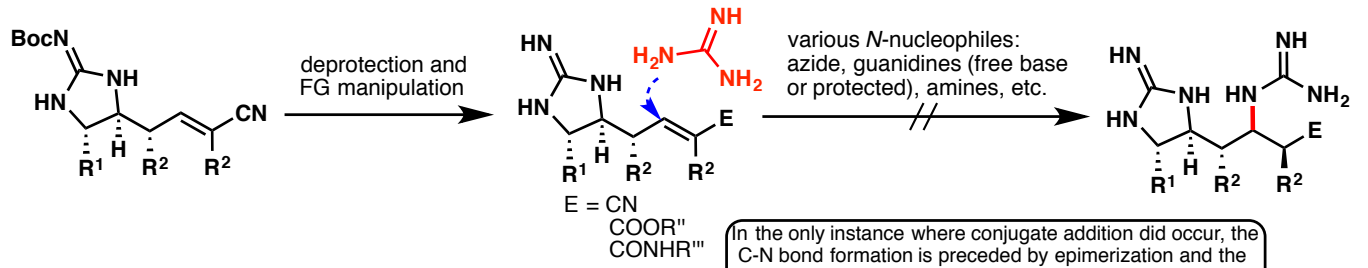
Oxidants screened include CAN, DDQ, $PhNO/ZrCl_4$ Bobbit salt, electrochemical oxidation, PIDA, Swern oxidation, Mukaiyama reagent, etc. Products were only observed with DDQ, albeit in low yields (~20%) and as mixture of diastereomers.



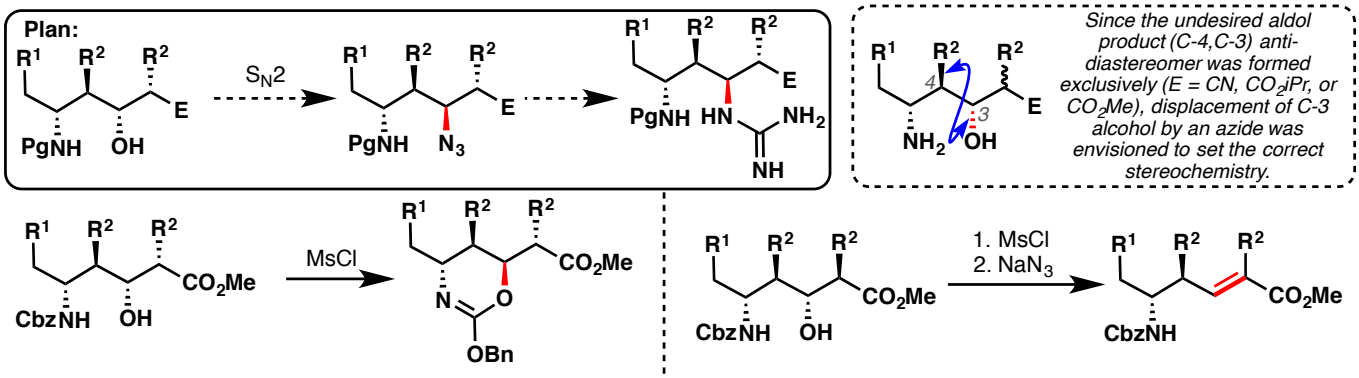
Installation of the 2-iminoimidazolidine



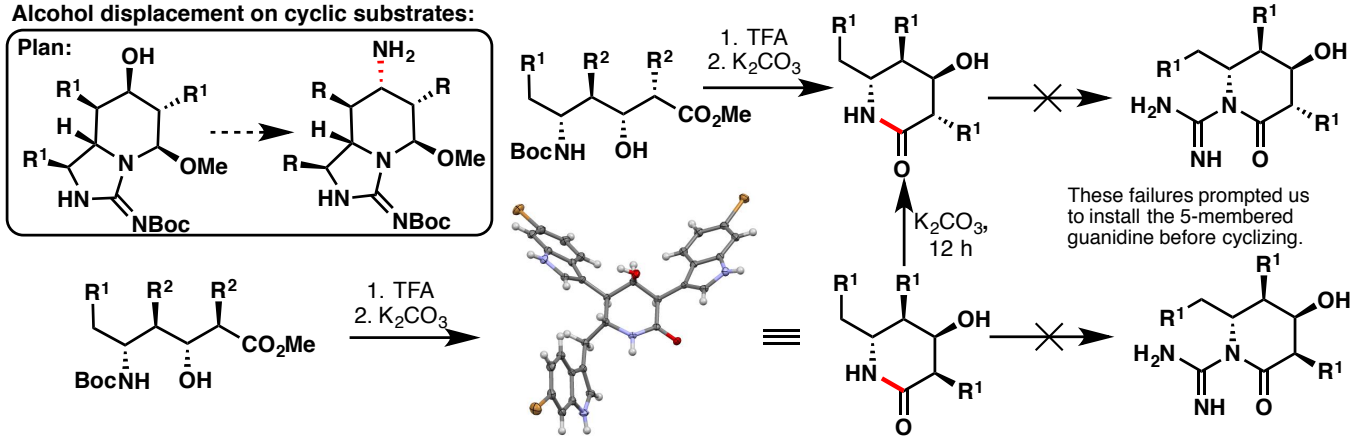
Attempts to install the 2nd guanidine through conjugate addition



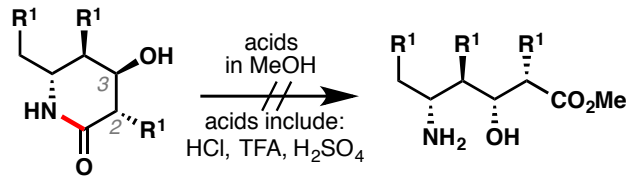
Attempts to install the 2nd guanidine via alcohol displacement on acyclic substrates:



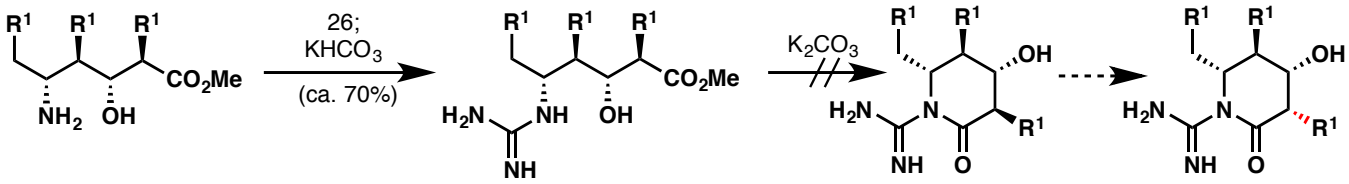
Alcohol displacement on cyclic substrates:



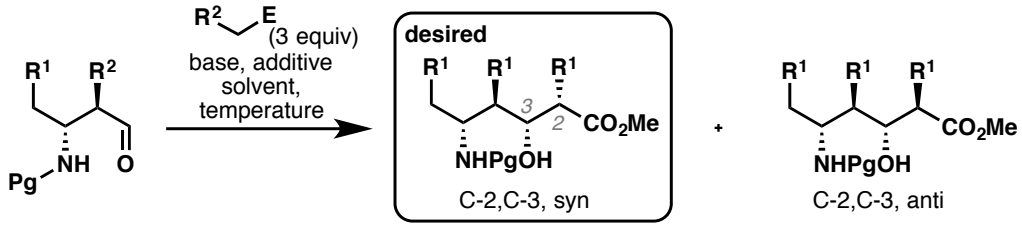
Searching for the viable substrate for the installation of the final guanidine



Initial explorations on the cyclic lactams prompted us to pursue the incorporation of aminoimidozolidine ring before ring cyclization which requires abundant supplies of the correct aldol diastereomer. Since both aldol diastereomers can be funneled to the desired C-2, C-3 relative stereochemistry, methanolysis of the lactam ring appears as an attractive approach towards acyclic tris-indole aldol product.



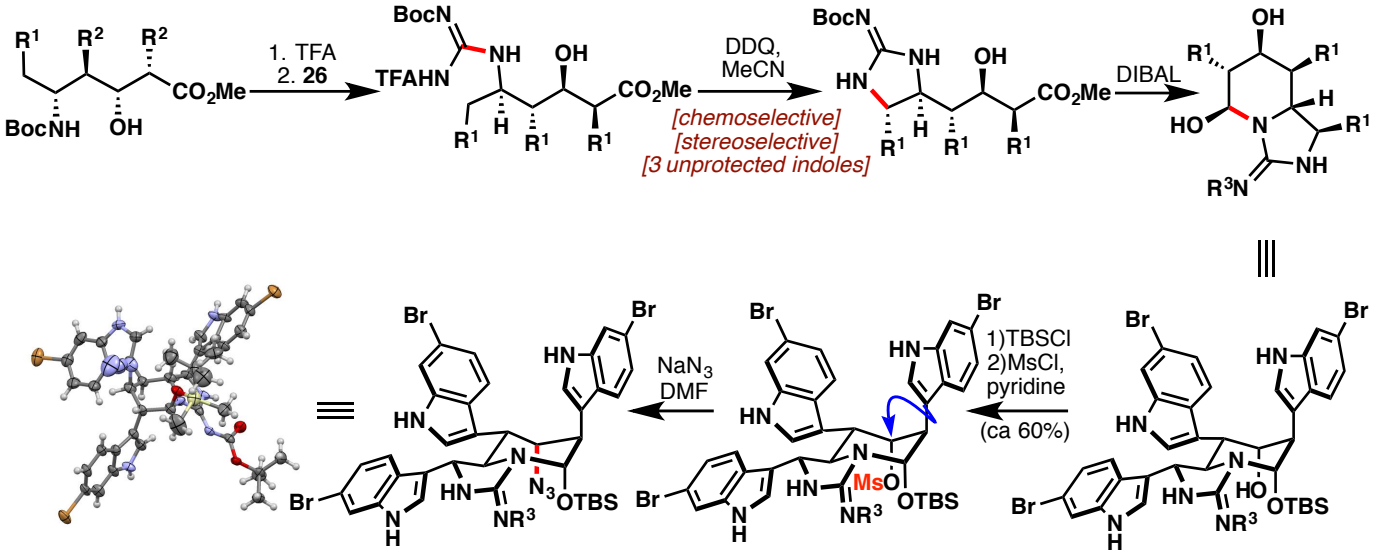
Attempts to optimize the diastereoselectivity of the aldol reaction



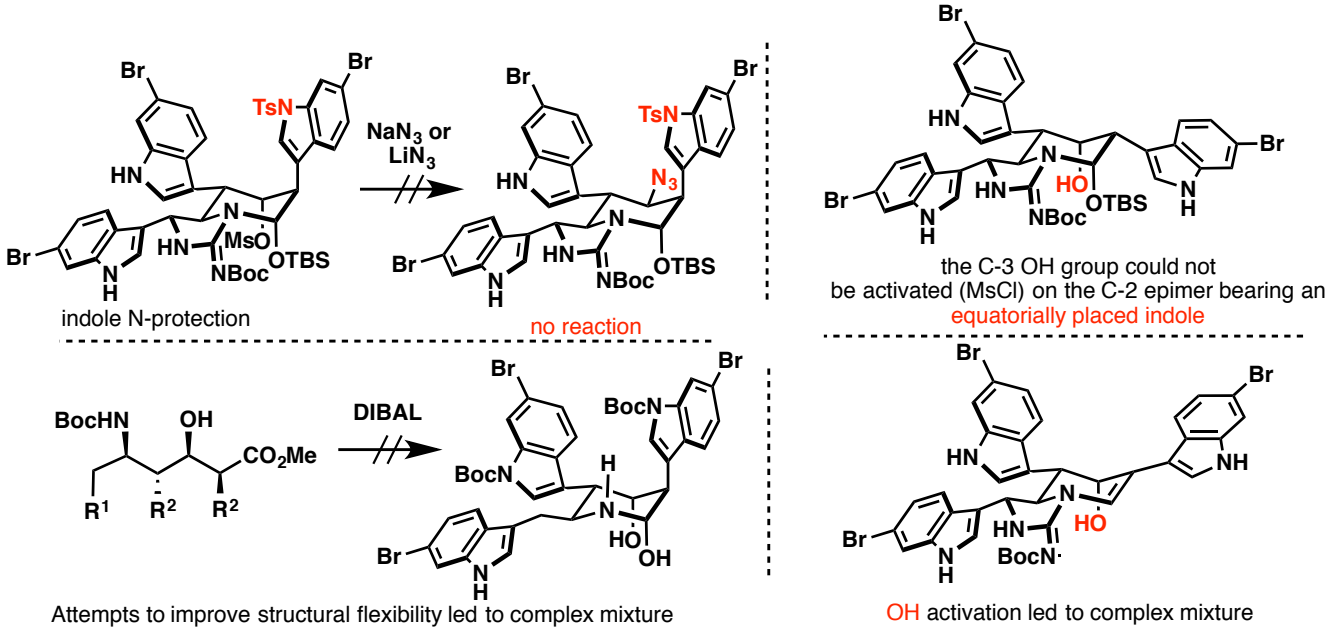
Pg	E	base*	additive	solvent	temperature	d.r. (syn/anti)	remark
Cbz	CN	LiHMDS	None	THF	-78°C	1:10	None
Cbz	CO_2Me	LiHMDS	None	THF	-78°C	1:1.5	None
Teoc	CO_2Me	LiHMDS	None	THF	-78°C	1:1.5	None
Boc	CO_2Me	LiHMDS	None	THF	-78°C	1:1	None
Boc	CN	LiHMDS	None	THF	-78°C	1:9	None
Boc	CO_2iPr	LiHMDS	None	THF	-78°C	1:2	None
Boc	CO_2Me	LiHMDS (3 eq)	None	THF	-78°C	1:5	None
Boc	CO_2Me	LiHMDS (6 eq)	None	THF	-78°C	1:1	low yield
Boc	CO_2Me	LiHMDS	None	THF	-78°C to 0°C	1:1	decomposition
Boc	CO_2Me	LiHMDS	DMPU	THF	-78°C	1:9	None
Boc	CO_2Me	LiHMDS	$ZnCl_2$	THF	-78°C	1:4	None
Boc	CO_2Me	LiHMDS	$MgCl_2$	THF	-78°C	1:3	None
Boc	CO_2Me	LDA	None	THF	-78°C	1:2	None
Boc	CO_2Me	NaHMDS	None	THF	-78°C	1:5	None
Boc	CO_2Me	KHMDS	None	THF	-78°C	1:4	None
Boc	CO_2Me	KHMDS	None	Toluene	-78°C	1:5	None

* unless otherwise stated, 4 equivalents of base were used with respect to the aldehyde.

Synthesis of N,O-acetal 15 and attempts to displace alcohol

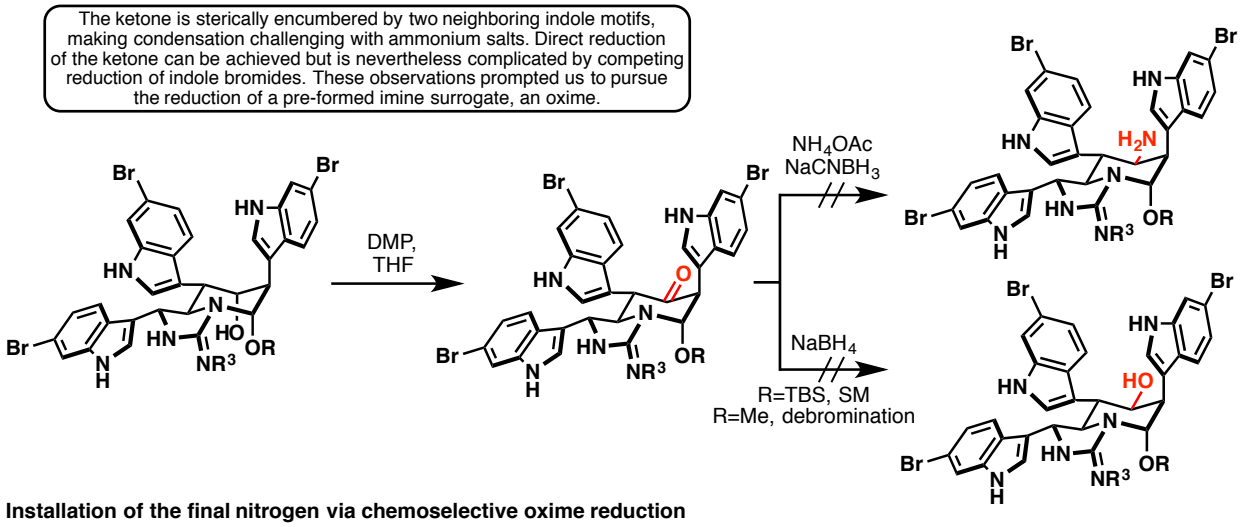


Attempts to suppress neibouring group participation of the axially placed indole

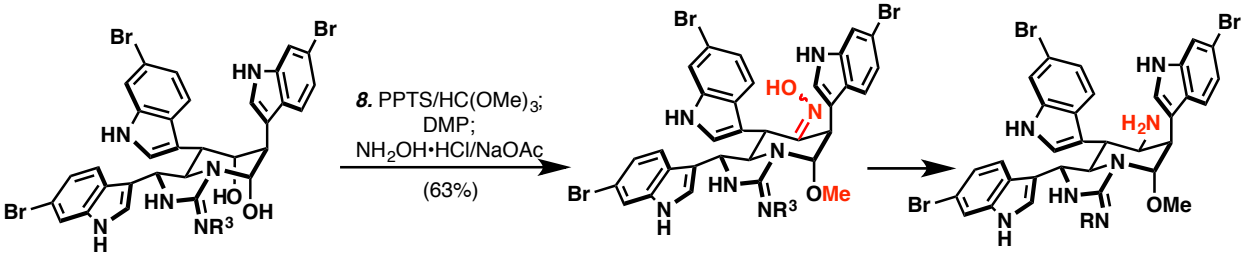


Unsuccessful attempts of ketone reductive amination

The ketone is sterically encumbered by two neighboring indole motifs, making condensation challenging with ammonium salts. Direct reduction of the ketone can be achieved but is nevertheless complicated by competing reduction of indole bromides. These observations prompted us to pursue the reduction of a pre-formed imine surrogate, an oxime.



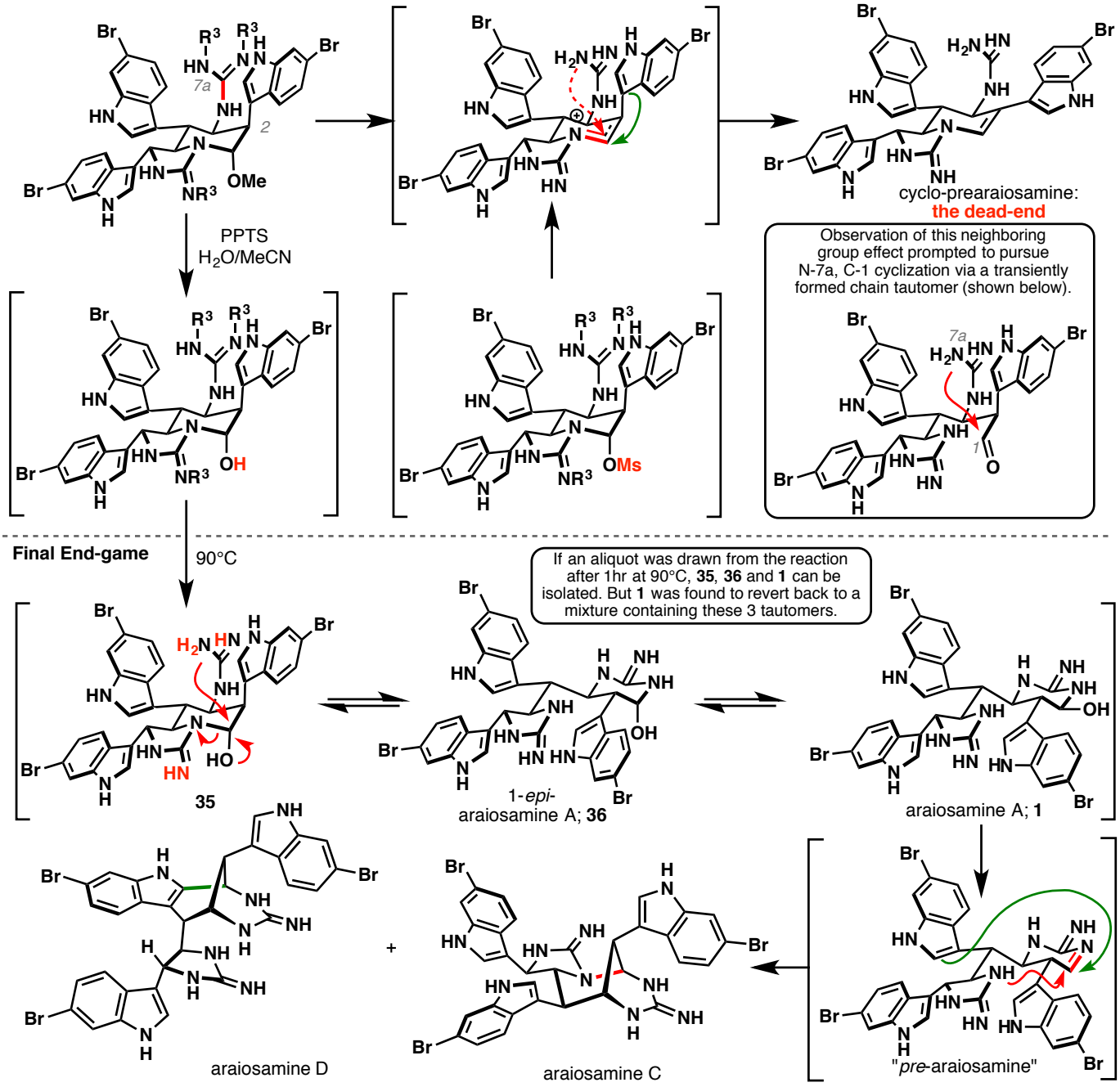
Installation of the final nitrogen via chemoselective oxime reduction



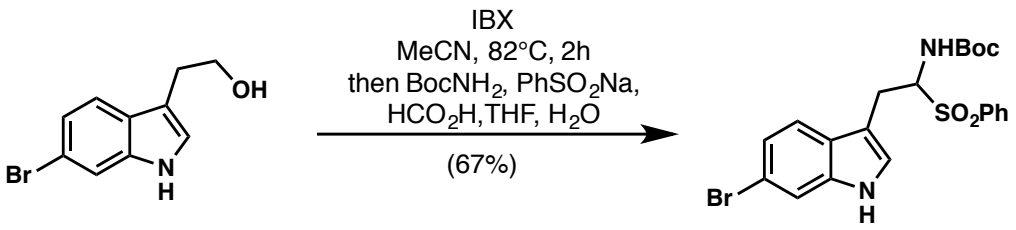
conditions	observations
Zn, HCO_2NH_4, MeOH	No reaction
$NiCl_2$, $NaBH_4$, MeOH	debromination
$ZrCl_4$, $NaBH_4$, MeOH	No reaction
$CuSO_4$, $NaBH_4$, MeOH	No reaction
LAH, THF, reflux	*N,O*-acetal reduced

conditions	observations
MoO_3, $NaBH_4$, MeOH	debromination
Na, *i*-PrOH, reflux	debromination
SmI_2, THF, MeOH	no reaction
SmI_2, H_2O, 0 °C	low conversion
SmI_2, H_2O, rt	**59%, dr > 20:1**

The enamine dead-end: final cyclization foiled by achimeric "assistance"



Compound 18



17; 6-bromo-tryptophol [ref. 2] **18**

Experimental: A flame dried round-bottom flask equipped with a stirrer bar was charged with MeCN (125 mL), 6-bromo-tryptophol (5.00g, 20.8 mmol, 1 equiv.) and IBX (8.75g, 31.3 mmol, 1.5 equiv.). The flask was fitted with a reflux condenser; the mixture was heated to 82 °C and stirred uniformly for 2 h. The reaction then was allowed to cool to room temperature and the volatiles were removed *in vacuo*. The residue was immediately taken up in a mixture of H_2O (50mL) and THF (50mL) and was treated with $BocNH_2$ (2.68g, 22.91 mmol, 1.1 equiv.), $PhSO_2Na$ (4.10g, 24.88 mmol, 1.2 equiv.) and formic acid (5mL). The reaction was stirred for 12h at room temperature. The resulting mixture was diluted with EtOAc (250 mL), filtered to remove any residual solids from the IBX oxidation and washed with H_2O (200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (SiO_2, 30% EtOAc in hexanes) followed by trituration with toluene yielded the desired product (6.69g, 67% yield).

Physical state: white powder;

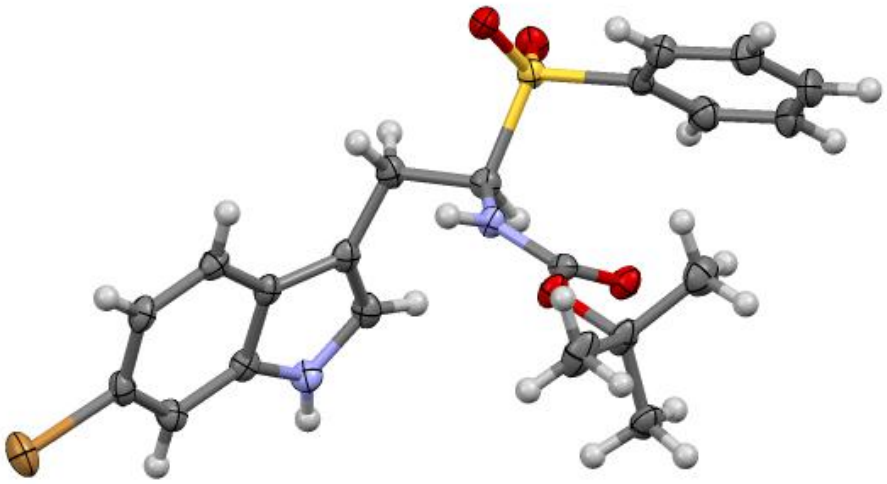
TLC: R_f = 0.29 (40% EtOAc in hexanes);

^{1}H NMR (500 MHz, DMSO-d_6, 60 °C) δ 10.91 (s, 1H), 7.84 – 7.95 (m, 3H), 7.72 (t, J = 7.2 Hz, 1H), 7.63 (t, J = 7.7 Hz, 2H), 7.52 (d, J = 1.7 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.09 – 7.17 (m, 2H), 4.90 – 4.99 (m, 1H), 3.45 (dd, J = 14.8 Hz, 2.8 Hz, 1H), 3.09 (t, J = 13.0 Hz, 1H), 1.11 (s, 9H).

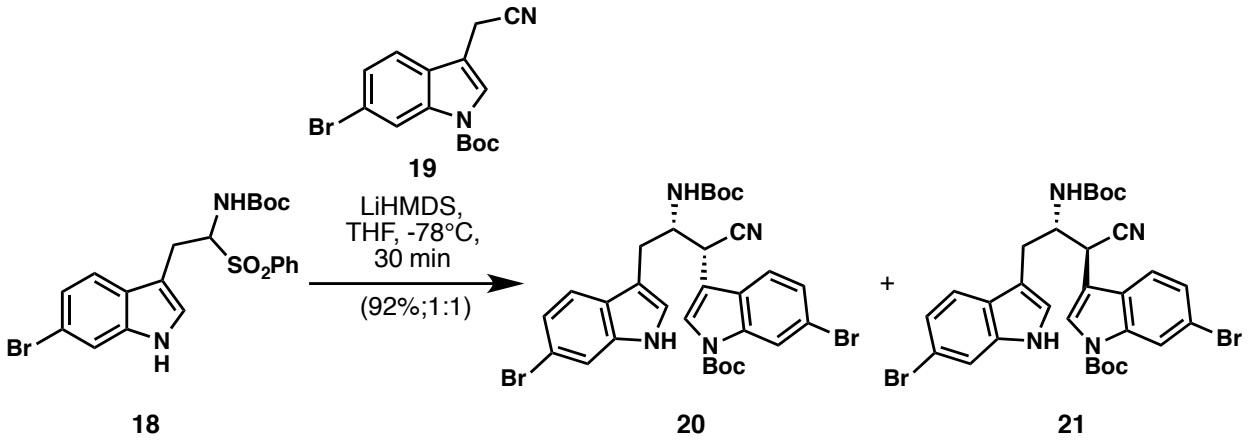
^{13}C NMR (151 MHz, DMSO-d_6, 60°C) δ 155.2, 138.2, 138.0, 134.6, 129.8 (2C), 129.9 (2C), 126.9, 125.7, 122.3, 120.6, 114.9, 114.8, 109.8, 79.8, 73.1, 28.7, 23.0 (3C);

HRMS (m/z): calcd for $C_{21}H_{23}BrN_2O_4SNa$ $[M+Na]^+$ 501.0454, found 501.0454

X-ray Structure of Compound 18, for details, see baran 580.cif

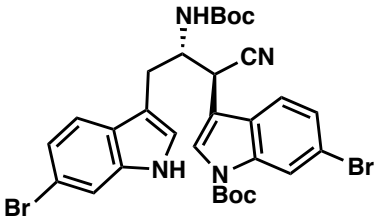


Compounds 20 and 21



Experimental: A flame dried round bottom flask with a stirrer bar was charged with THF (160 mL, 0.1M) and nitrile **19** (prepared according to ref. 3) (5.46 g, 16.28 mmol, 3 equiv.). The mixture was cooled to -78°C with a dry ice-acetone bath and a solution of LiHMDS in THF (1.0M, 18mL, 3.3 equiv.) was added dropwise over 10mins. The mixture was maintained at that temperature for 30mins when a solution of **18** (2.60g, 5.42mmol, 1 equiv.) in THF (55 mL, 0.1M) was added over 10mins. The reaction was stirred for another 30mins at –78°C and was quenched with saturated aqueous NH_4Cl before warming up to room temperature. The resulting mixture was extracted with EtOAc (100 mL x 3). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude was purified via FCC (SiO_2, 20% EtOAc in hexanes) to yield 1.65g of **20** (46% yield) and 1.66g of **21** (46% yield).

Compound 21



Physical state: white foam;

TLC: R_f = 0.50 (30% EtOAc in hexanes);

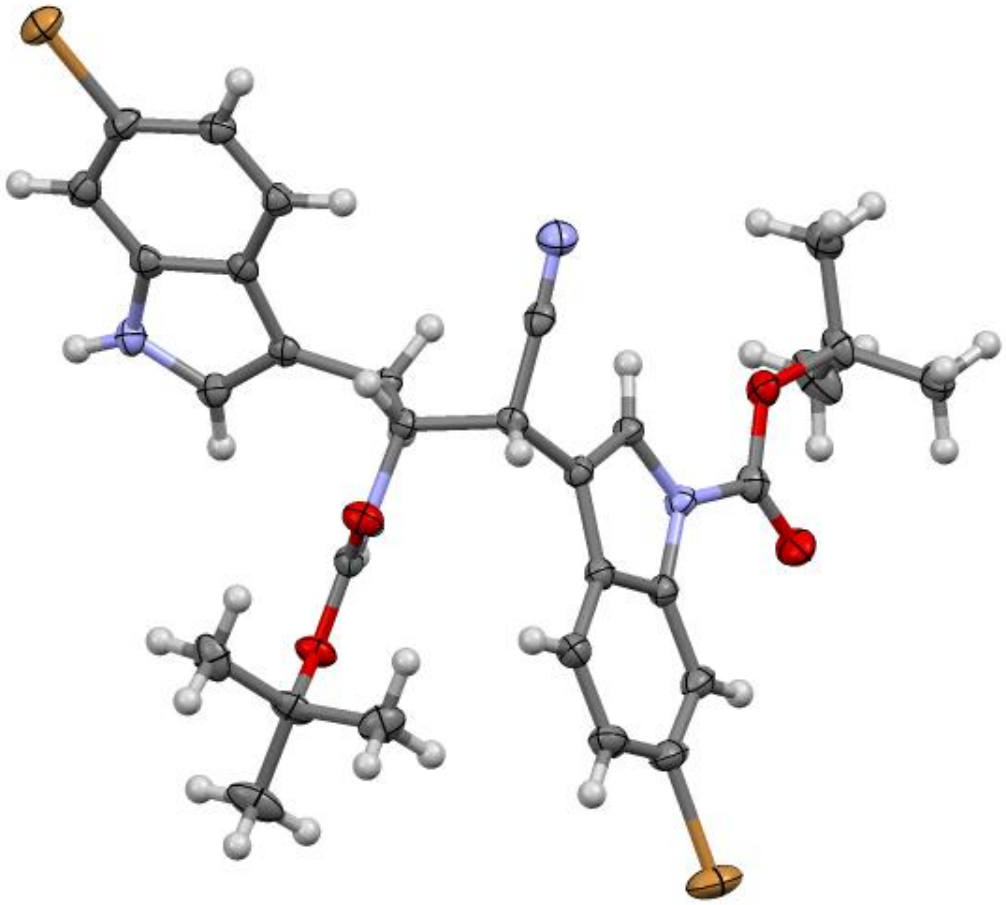
^{1}H NMR (600 MHz, acetone-d_6) δ 10.25 (s, 1H), 8.36 (s, 1H), 7.77 (s, 1H), 7.59 (dd, *J* = 5.0, 3.3Hz, 1H), 7.48 (d, *J* = 8.4Hz, 1H), 7.42 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.27 (d, *J* = 2.3 Hz, 1H), 7.14 (d, *J* = 8.5, 1.8 Hz, 1H), 6.44 (d, *J* = 9.3 Hz, 1H), 4.62 (d, *J* = 5.6 Hz, 1H), 4.52 (tt, *J* = 9.2, 5.6 Hz, 1H), 3.21 (dd, *J* = 14.8, 5.7 Hz, 1H), 3.14 (dd, *J* = 14.8, 8.9 Hz, 1H), 1.69 (s, 9H), 1.27 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.8, 148.3, 137.1, 135.8, 127.2, 126.1, 125.3, 125.1, 124.0, 121.3, 120.3, 119.4, 117.8, 117.7, 117.5, 114.0, 113.8, 113.2, 110.7, 84.2, 77.9, 53.4, 52.5, 33.5, 27.1(3C), 26.8(3C);

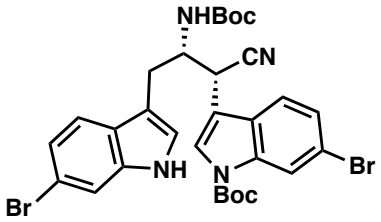
HRMS (m/z): calcd for $C_{30}H_{32}Br_2N_4O_4Na$ $[M+Na]^+$ 693.0683, found 693.0659.

[In the asymmetric route, $[\alpha]_D^{20}$ = 4.3°, (*c* = 1.0, EtOH)]

X-ray structure of compound 21, for details see baran581.cif



Compound 20



Physical state: white foam;

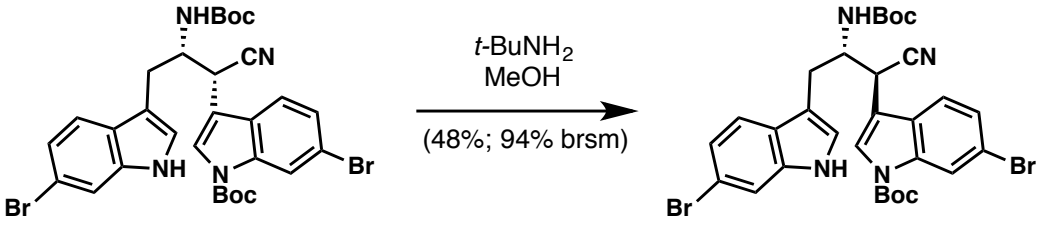
TLC: R_f = 0.44 (30% EtOAc in hexanes);

^{1}H NMR (600 MHz, acetone-d_6) δ 10.19 (s, 1H), 8.36 (s, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.67 – 7.64 (m, 1H), 7.54 – 7.47 (m, 2H), 7.23 (d, *J* = 2.3 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.93 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 4.82 – 4.78 (m, 1H), 4.47 (ddt, *J* = 9.6, 7.7, 5.0 Hz, 1H), 3.19 (qd, *J* = 14.9, 7.0 Hz, 2H), 1.70 (s, 9H), 1.33 (s, 9H);

^{13}C NMR (151 MHz, acetone-d_6) δ 155.1, 148.2, 137.0, 135.8, 126.9, 125.9, 125.4, 124.9, 124.1, 121.0, 120.7, 119.2, 117.9, 117.7, 117.7, 113.9, 113.6, 113.0, 110.4, 84.2, 78.3, 52.3, 33.9, 27.1, 26.8 (3C), 25.6(3C).

HRMS (m/z): calcd for $C_{30}H_{32}Br_2N_4O_4Na$ $[M+Na]^+$ 693.0683, found 693.0691.

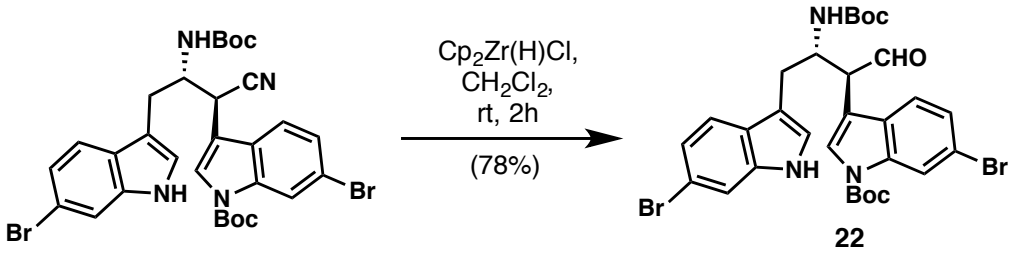
Conversion of compound 20 to compound 21



20 **21**

Experimental: A 100 mL round bottom flask with a magnetic stirrer bar was charged with MeOH (30.0 mL), compound **20** (2.11 g, 3.14 mmol, 1 equiv.) and $^{t}BuNH_2$ (3.0 mL). The reaction was stirred for 30 minutes at ambient temperature and was subsequently quenched with saturated aqueous NH_4Cl (100 mL). The resulting mixture was extracted with EtOAc (100 mL x 2); the combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% EtOAc in hexanes yielded **21** (1.02 g, 48% yield) along with recovered **20** (0.98 g, 46% yield).

Compound 22:



21 **22**

Experimental: A flame dried flask under Ar with a stirrer bar was charged with **21** (1.30 g, 1.93 mmol, 1 equiv.), Schwartz's reagent (1.30 g, 5.0 mmol, 2.6 equiv.) and CH_2Cl_2 (10 mL, 0.19M). The resulting solution was stirred until it turns clear (*ca.* 1.5hrs); the reaction was quenched by loading the mixture evenly onto SiO_2 TLC plates (2000 micron). Purification by FCC (SiO_2, 40% EtOAc in hexanes) afforded **22** (1.00 g, 78% yield).

Physical State: white foam;

TLC: R_f= 0.50 (40% EtOAc in hexanes);

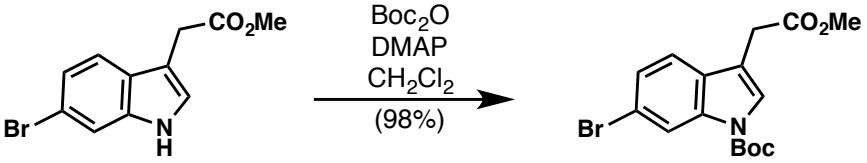
^{1}H NMR (600 MHz, Acetone-d_6) δ 10.16 (s, 1H), 9.82 (d, J = 2.8 Hz, 1H), 8.38 (s, 1H), 7.81 (s, 1H), 7.56 – 7.52 (m, 2H), 7.43 (dt, J = 8.5, 2.1 Hz, 2H), 7.15 (d, J = 2.2 Hz, 1H), 7.10 (dd, J = 8.4, 1.8 Hz, 1H), 6.14 (d, J = 9.0 Hz, 1H), 4.79 – 4.57 (m, 1H), 4.19 (dd, J = 7.9, 2.9 Hz, 1H), 3.06 (dd, J = 14.8, 4.4 Hz, 1H), 2.95 (dd, J = 14.8, 9.3 Hz, 1H), 1.70 (s, 9H), 1.33 (s, 9H);

^{13}C NMR (151 MHz, Acetone-d_6) δ 197.9, 155.0, 148.4, 137.0, 135.7, 128.7, 126.3, 125.2, 125.1, 123.9, 121.1, 120.5, 119.6, 117.6, 117.3, 113.8, 113.6, 113.5, 111.3, 84.0, 77.8, 53.5, 51.2, 27.5, 27.2 (3C), 26.8 (3C);

HRMS (m/z): calcd for $C_{30}H_{34}Br_2N_3O_5$ $[M+H]^+$ 676.0860, found 676.0848.

[In the asymmetric route, $[\alpha]_D^{22} = +11.8°$, (c =1.0, EtOH)]

Compound 23:



[ref. 4] **23**

Experimental: A 250 mL round bottom flask equipped with stir bar was charged with 6-bromo-indol-3-yl acetic acid methyl ester (prepared according to ref. 4) (2.00 g, 7.5 mmol, 1 equiv.), CH_2Cl_2 (15 mL, 0.5 M), DMAP (0.045 g, 0.375 mmol, 0.05 equiv.) and Boc_2O (1.64 g, 7.5 mmol, 1 equiv.). The mixture was stirred for 30 minutes and was concentrated *in vacuo.* Purification of the resulting residue by FCC (SiO_2, 5% EtOAc in hexanes) yielded the desired product (2.68 g, 97%).

Physical state: colorless solid;

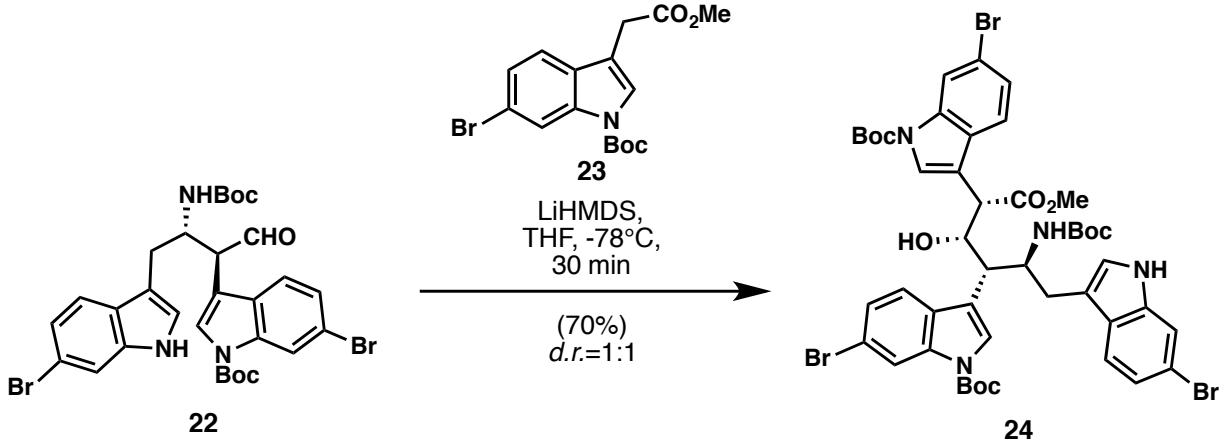
TLC: R_f = 0.37 (10% EtOAc in hexanes);

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.53 (s, 1H), 7.44 – 7.30 (m, 2H), 3.71 (s, 3H), 3.69 (s, 2H), 1.66 (s, 9H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 149.3, 136.2, 129.0, 126.0, 125.0, 120.3, 118.6, 118.3, 113.1, 84.4, 52.4, 31.0, 28.3 (3C).

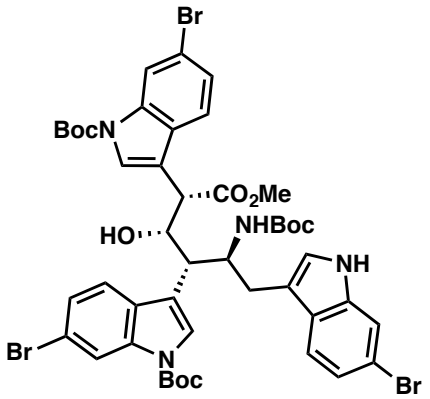
HRMS (m/z): calcd for $C_{16}H_{18}BrNO_4Na$ $[M+Na]^+$ 390.0311, found 390.0310.

Compound 24 and S1:



Experimental: A 250mL round bottom flask equipped with a magnetic stirrer bar was charged under argon with ester **23** (1.64 g, 4.44 mmol, 3 equiv.) (*vide supra*) and THF (50 mL, 0.089M). The solution was cooled to –78°C when a solution of LiHMDS (1.0 M, 5.8 mL, 3.9 equiv.) in THF was added dropwise over 10 mins. The reaction was maintained at -78 °C for 30 mins before a solution of aldehyde **22** (1.00 g, 1.48 mmol, 1 equiv.) in THF (20 mL, 0.074M) was added dropwise at the same temperature. After stirring for another 2 mins at -78 °C, the reaction was quenched with saturated aqueous NH_4Cl (100 mL), warmed up to room temperature and extracted with EtOAc (100 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (SiO_2, 25% EtOAc in hexanes) yielded aldol products **24** (0.540 g, 35%) and its epimer **S1** (0.538 g, 35%). The stereochemistry of **24** and **S1** were assigned by converting them to **S2** and **S3** respectively (*vide infra*).

Compound 24:



Physical state: white foam;

TLC: R_f = 0.33 (30% EtOAc in hexanes);

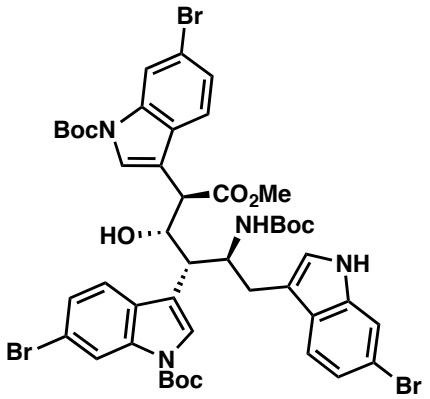
^{1}H NMR (600 MHz, Acetone-d_6) δ 10.04 (s, 1H), 8.31 (s, 2H), 7.53 (d, *J* = 8.8 Hz, 3H), 7.40 (d, *J* = 4.3 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.18 (td, *J* = 8.1, 1.8 Hz, 2H), 7.04 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.99 (d, *J* = 2.2 Hz, 1H), 6.93 (br, 1H), 5.65 (d, *J* = 9.2 Hz, 1H), 5.18 (s, 1H), 4.90 (d, *J* = 5.3 Hz, 1H), 4.58 – 4.36 (m, 1H), 4.10 (d, *J* = 3.7 Hz, 1H), 3.58 (s, 3H), 3.49 – 3.39 (m, 1H), 3.33 (dd, *J* = 14.4, 4.2 Hz, 1H), 1.68 (s, 9H), 1.65 (s, 9H), 1.24 (s, 9H);

^{13}C NMR (151 MHz, Acetone-d_6) δ 173.5, 156.2, 156.2 150.0, 149.8, 138.4, 136.7, 131.2, 130.6, 127.9, 127.2, 126.0, 126.0, 125.6, 125.0, 122.7, 122.2, 122.1, 121.3, 119.6, 118.5, 118.5, 118.1, 118.0, 115.4, 115.1, 114.8, 113.8, 84.9, 78.6, 73.5, 53.3, 53.3, 52.3, 47.5, 43.3, 28.6(3C), 28.2(3C), 28.2(3C), 27.9;

HRMS (m/z): calcd for $C_{46}H_{51}Br_3N_4O_9Na$ $[M+Na]^+$ 1063.1098 found 1063.1073.

[In the asymmetric route, $[\alpha]_D^{23}$ = –76.5°, (*c* = 1.0, EtOH)]

Compound S1:



Physical state: white foam;

TLC: R_f = 0.26 (30% EtOAc in hexanes);

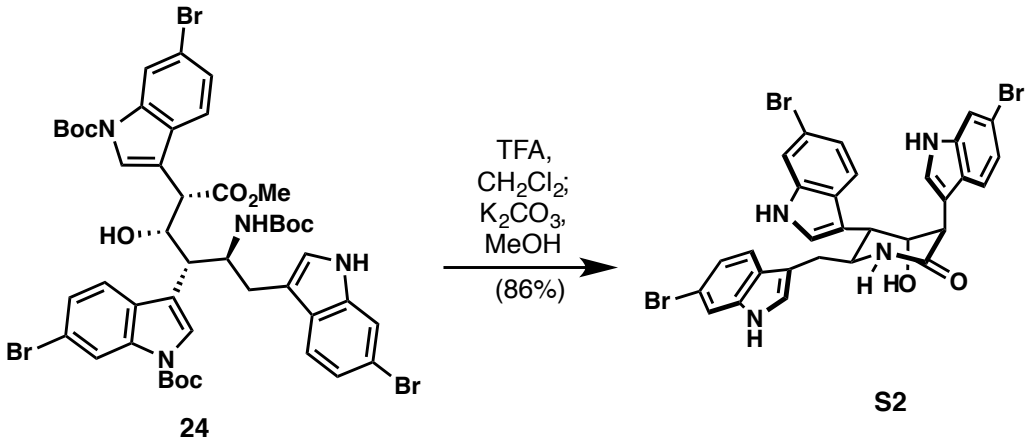
^{1}H NMR (600 MHz, Acetone-d_6) δ 10.07 (s, 1H), 8.05 (s, 1H), 7.99 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 7.31 (s, 1H), 7.25 – 7.16 (m, 1H), 7.14 (d, *J* = 2.2 Hz, 1H), 7.12 – 7.05 (m, 3H), 5.56 (d, *J* = 8.8 Hz, 1H), 5.16 – 4.83 (m, 2H), 4.66 – 4.35 (m, 1H), 4.12 (d, *J* = 8.2 Hz, 1H), 3.63 (s, 3H), 3.59 (dd, *J* = 9.1, 4.8 Hz, 1H), 3.34 (dd, *J* = 14.4, 3.2 Hz, 1H), 2.80 – 2.74 (m, 1H), 1.69 (s, 9H), 1.66 (s, 9H), 1.28 (s, 9H);

^{13}C NMR (151 MHz, Acetone-d_6) δ 172.10, 154.92, 148.14, 147.84, 137.08, 135.02, 134.72,129.45, 127.50, 126.62, 125.42, 124.39, 124.24, 124.07, 123.75, 121.12, 120.86, 120.38, 120.25, 118.21, 116.88, 116.73, 116.58, 116.36, 114.59, 113.70, 113.44, 112.62, 83.51, 83.33, 77.26, 73.35, 51.87, 50.90, 50.86, 42.74, 27.31(3C), 26.98(3C), 26.88(3C), 25.80.

HRMS (m/z): calcd for $C_{46}H_{52}Br_3N_4O_9Na$ $[M+Na]^+$ 1063.1098 found 1063.1070.

[In the asymmetric route, $[\alpha]_D^{23}$ = -85.3°, (*c* = 1.0, EtOH)]

Compound S2



Experimental: A culture tube equipped with a magnetic stirrer bar was charged with *syn*-aldol product (**24**) (20 mg, 0.0198 mmol) and dichloromethane (0.50 mL). The solution was cooled to 0 °C when trifluoroacetic acid (0.50 mL) was added. The resulting mixture was warmed up to room temperature and stirred for 2 hours before the volatiles were removed *in vacuo*. To the residue was added MeOH (0.50 mL), followed by K_2CO_3 (20 mg, 0.145 mmol, 7.3 equiv.). The suspension was stirred for 1 hour and was partitioned between H_2O (5 mL) and EtOAc (5 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and was concentrated *in vacuo*. Purification by PTLC (SiO_2, 5% CH_2Cl_2/MeOH) afforded **S2** (12 mg, 86% yield).

Physical state: colorless solid;

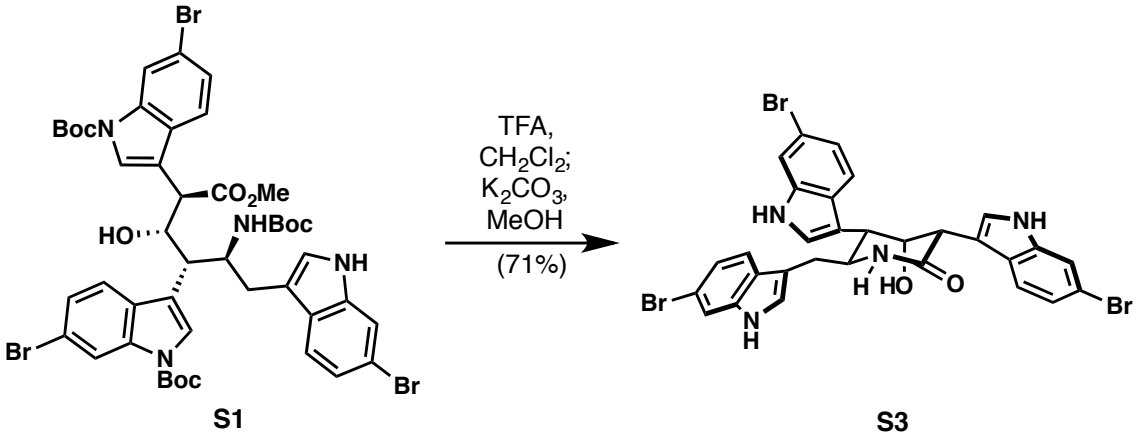
TLC: R_f = 0.15 (5% MeOH in CH_2Cl_2);

^{1}H NMR (600 MHz, MeOD) δ 7.58 (d, *J* = 1.7 Hz, 1H), 7.50 (dd, *J* = 15.1, 1.7 Hz, 2H), 7.36 – 7.29 (m, 2H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.05 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.91 (s, 1H), 6.94 – 6.87 (m, 1H), 6.83 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.47 (d, *J* = 8.5 Hz, 1H), 5.90 (d, *J* = 0.9 Hz, 1H), 4.47 (dt, *J* = 11.0, 4.3 Hz, 1H), 4.08 (t, *J* = 2.2 Hz, 1H), 3.97 – 3.93 (m, 1H), 3.37 – 3.28 (m, 1H), 3.12 (dd, *J* = 14.8, 3.8 Hz, 1H), 2.96 (dd, *J* = 14.8, 4.8 Hz, 1H);

^{13}C NMR (151 MHz, MeOD) δ 173.1, 136.9, 136.8, 136.7, 126.7, 125.4, 124.8, 124.7, 123.1, 122.8, 121.3, 121.2, 120.8, 119.6, 118.7, 118.4, 114.2, 114.0, 114.0, 113.5, 113.3, 111.3, 112.0, 111.6, 109.1, 71.3, 52.0, 48.0, 33.3, 27.3.

HRMS (m/z): calcd for $C_{30}H_{24}Br_3N_4O_2$ $[M+H]^+$ 708.9444 found 708.9417.

Compound S3



S1 **S3**

Experimental: A culture tube equipped with a magnetic stirrer bar was charged with *anti*-aldol product (**S1**) (20 mg, 0.0198 mmol) and dichloromethane (0.50 mL). The solution was cooled to 0 °C when trifluoroacetic acid (0.50 mL) was added. The resulting mixture was warmed up to room temperature and stirred for 2 hours before the volatiles were removed *in vacuo*. To the residue was added MeOH (0.50 mL), followed by K_2CO_3 (20 mg, 0.144 mmol). The suspension was stirred for 1h and was partitioned between H_2O (5 mL) and EtOAc (5 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and was concentrated *in vacuo*. Purification by PTLC (SiO_2, 5% CH_2Cl_2/MeOH) afforded **S3** (10 mg, 71% yield).

Physical state: white solid;

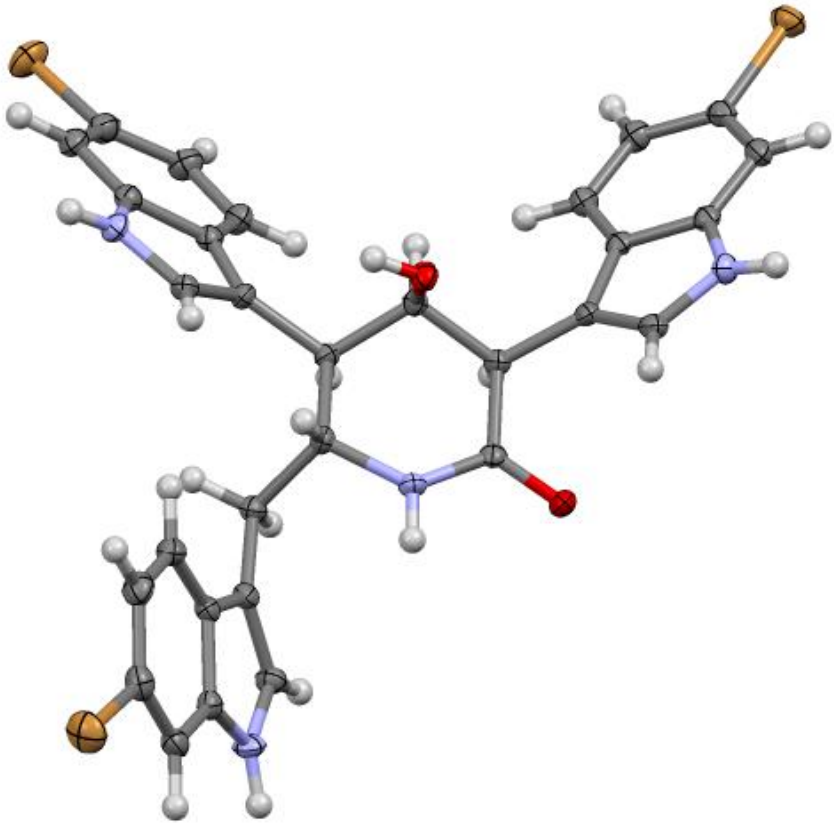
TLC: R_f= 0.23 (5% MeOH in CH_2Cl_2);

^{1}H NMR (600 MHz, MeOD) δ 7.59 (d, *J* = 8.6 Hz, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.50 (d, *J* = 1.7 Hz, 1H), 7.47 – 7.44 (m, 2H), 7.43 (d, *J* = 4.3 Hz, 1H), 7.19 (s, 1H), 7.15 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.09 (s, 1H), 7.05 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.99 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.47 (ddd, *J* = 11.2, 8.1, 3.1 Hz, 1H), 4.17 (d, *J* = 2.9 Hz, 1H), 4.04 (dd, *J* = 2.9, 1.6 Hz, 1H), 3.50 (dd, *J* = 11.0, 1.7 Hz, 1H), 3.12 – 2.98 (m, 1H), 2.84 (dd, *J* = 14.7, 8.2 Hz, 1H);

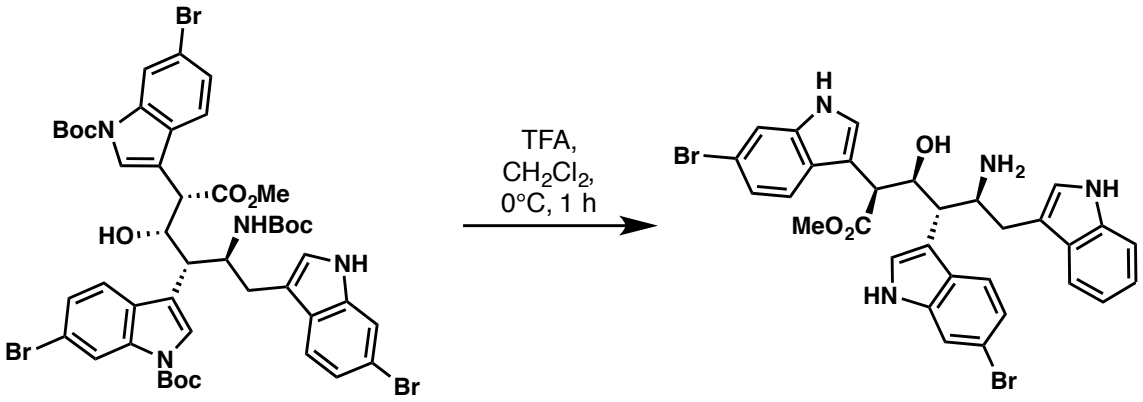
^{13}C NMR (151 MHz, MeOD) δ 173.1, 137.2, 136.8, 136.7, 126.2, 125.9, 125.9, 124.7, 124.0, 123.1, 121.1(2C), 120.8, 120.0, 119.5, 119.2, 114.1, 114.0, 113.6, 113.3, 113.3, 113.1, 113.1, 110.5, 109.5, 72.1, 53.3, 45.6, 41.0, 28.9.

HRMS (m/z): calcd for $C_{30}H_{23}Br_3N_4O_2$ $[M+H]^+$ 708.9444 found 708.9417.

X-ray structure of Compound S3, for details see baran568.cif



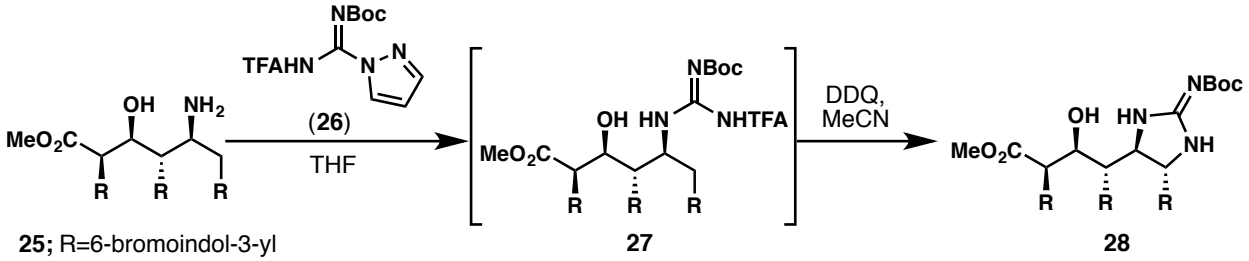
Compound 25 (used without purification):



24 **25**

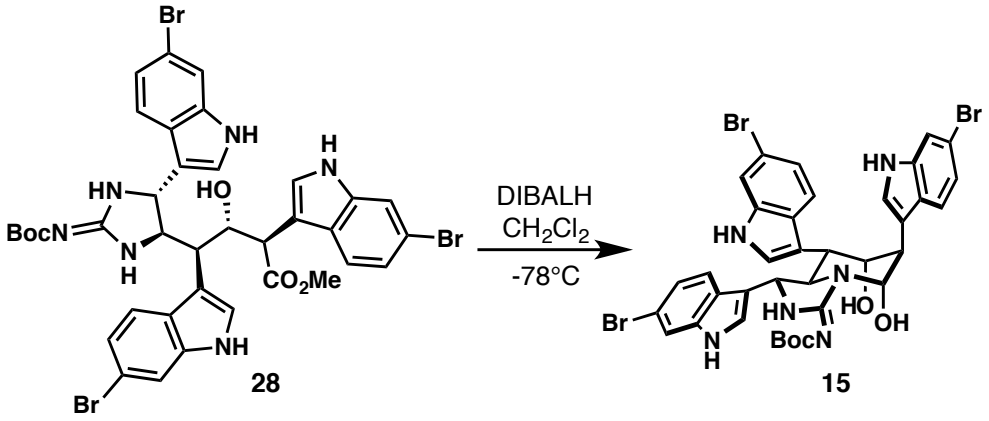
Experimental: A 100mL round bottom flask equipped with stir bar was charged under argon with *syn*-aldol product **24** (600 mg, 0.575 mmol) and CH_2Cl_2 (10 mL). The solution was cooled to 0°C when TFA (3.3 mL) was added dropwise. The reaction was warmed up to room temperature and stirred for an additional 1 hour; the volatiles were then removed *in vacuo*. The resulting residue was taken up in EtOAc (100 mL) and washed with saturated aqueous Na_2CO_3 (100 mL x 2). The combined organic phase was dried with anhydrous Na_2SO_4, concentrated *in vacuo* and the crude compound **25** (450 mg) was directly used in the next step without further purification.

Compound 28 (used without purification)



Experimental: A 50mL round bottom flask equipped with a magnetic stirrer bar was sequentially charged with crude **25** (450 mg), THF (15 mL), and **26** (227 mg, 0.74 mmol). After the reaction was stirred at ambient temperature for 1 hour, the volatiles were removed *in vacuo*. The resulting residue was re-dissolved in MeCN (10 mL) and treated with DDQ (168 mg, 0.47 mmol). The solution was stirred for 1.5 hours at ambient temperature, diluted with EtOAc (100 mL) and thoroughly washed with saturated aqueous $NaHCO_3$ (4 x 100 mL). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and the crude product (350mg) was subjected to the next reaction without further purification.

Compound 15:



Experimental: A solution of DIBAL in hexanes (0.68 mL, 1.0 M) was added dropwise to a solution of crude **28** (205 mg, *ca.* 0.226 mmol) in anhydrous DCM (5 mL) at -78°C. The reaction was stirred at this temperature for 20 min before MeOH (1 mL) was added dropwise. The resulting mixture was warmed to room temperature and partitioned between EtOAc (20 mL) and brine (20 mL). The combined organic phase was dried with anhydrous Na_2SO_4 and was concentrated *in vacuo*. Purification by FCC (SiO2, 50% EtOAc in hexanes) afforded **15** (103 mg, 36% over 3 steps from **24**).

Physical state: colorless solid;

TLC: R_f = 0.33 (EtOAc-hexanes 1:1);

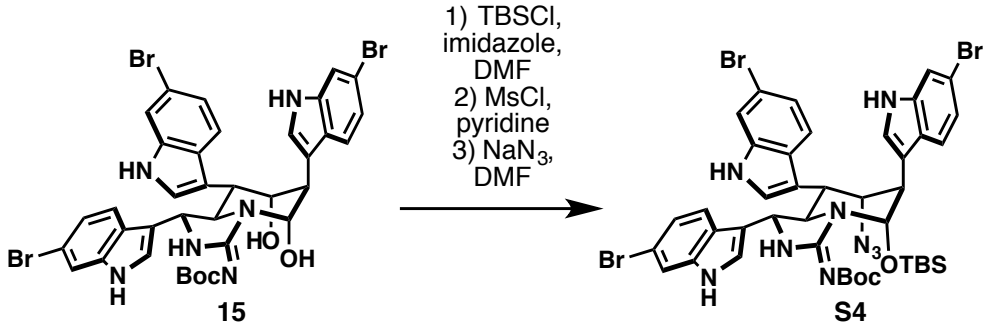
^{1}H NMR (600 MHz, Acetone-d_6) δ 10.49 (s, 1H), 10.10 (s, 1H), 9.99 (s, 1H), 8.28 (s, 1H), 7.68 (d, *J* = 1.7 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.45 (d, *J* = 1.7 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.18 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.10 – 7.02 (m, 2H), 6.91 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.20 (d, *J* = 7.2 Hz, 1H), 5.82 (dd, *J* = 7.2, 3.5 Hz, 1H), 5.02 (d, *J* = 6.2 Hz, 1H), 4.99 – 4.95 (m, 1H), 4.95 – 4.88 (m, 1H), 4.48 (t, *J* = 4.6 Hz, 1H), 3.98 – 3.91 (m, 1H), 3.52 (dd, *J* = 11.0, 2.0 Hz, 1H), 1.42 (s, 9H);

^{13}C NMR (151 MHz, Acetone-d_6) δ 163.5, 160.1, 137.4, 136.9, 136.3, 126.2, 125.5, 124.7, 123.8, 123.8, 123.4, 121.5, 121.5, 121.0, 120.2, 119.4, 119.1, 114.7, 114.3, 114.1, 114.0, 113.9, 113.6, 113.5, 112.5, 111.0, 76.3, 75.9, 73.0, 56.0, 55.6, 43.2, 38.0, 27.3;

HRMS (m/z): calcd for $C_{36}H_{34}Br_3N_6O_4$ $[M+H]^+$ 851.0186 found 851.0172.

[In the asymmetric route, $[\alpha]_D^{22}$ = 25.7°, (*c* =1.0, MeOH)]

Compound S4



Experimental: A solution of **15** (50 mg, 0.058 mmol, 1 equiv.), TBSCl (35 mg, 0.23 mmol, 3.9 equiv.) and imidazole (16 mg, 0.23 mmol, 3.9 equiv.) in DMF (1.0 mL) was stirred under argon at 0 °C for 12 h when LC/MS indicated the complete consumption of starting material. Saturated aqueous solution of $NaHCO_3$ (5 mL) was added and the resulting mixture was extracted with EOAc (3 × 5 mL). After evaporation of the volatiles *in vacuo*, the crude product was dissolved in dry pyridine (1 mL). MsCl (0.05 mL, 0.64 mmol) was added at 0 °C. After stirring at 0 °C for 12 hours, MeOH (0.5 mL) was added, followed by EtOAc (5 mL). The resulting mixture was washed with HCl (1.0 M, 2 × 5 mL) and brine (10 mL). The organic phase was dried over anhydrous Na_2SO_4. Evaporation of the volatile components yielded the crude product which was dissolved in dry DMF (1.5 mL) and treated with sodium azide (10 mg, 0.15 mL). The reaction mixture was stirred under argon at 80 °C for 5 h and was cooled to room temperature when LC/MS indicated complete conversion. The resulting mixture was partitioned between EtOAc (10 mL) and brine (15 mL). The organic phase was dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the resulting residue by PTLC (SiO_2, 50% EtOAc in hexanes) afforded **S4** (37 mg, 65% over 3 steps).

Physical state: white solid;

TLC: R_f = 0.42 (EtOAc-hexanes 1:1);

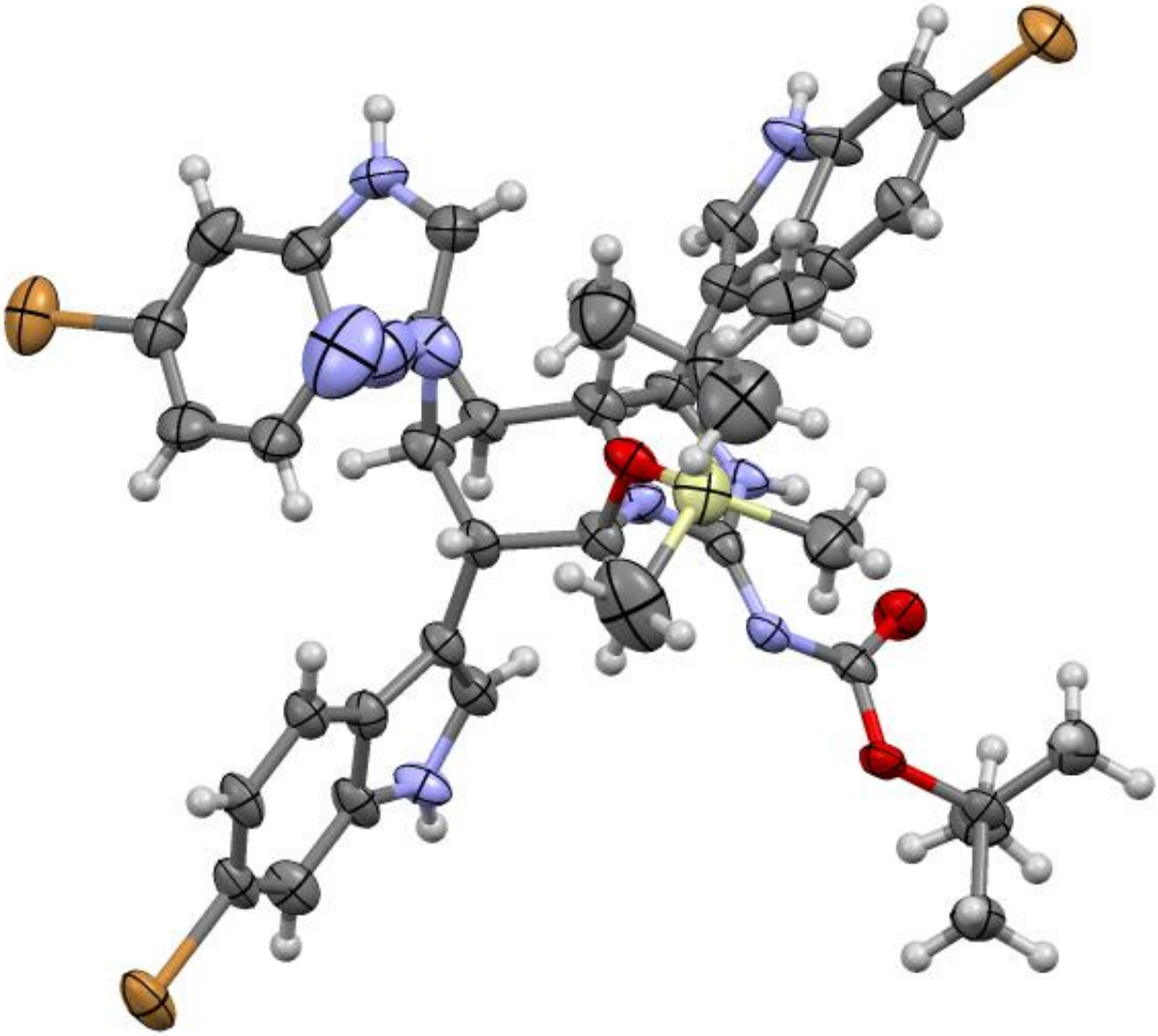
^{1}H NMR (600 MHz, Acetone-d_6) δ 10.57 (s, 1H), 10.20 – 10.09 (m, 2H), 8.23 (s, 1H), 7.71 (d, J = 1.7 Hz, 1H), 7.64 (d, J = 1.9 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 1.7 Hz, 1H), 7.48 (d, J = 1.7 Hz, 1H), 7.24 (dd, J = 8.4, 1.8 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 7.02 (dd, J = 8.5, 1.8 Hz, 1H), 6.91 (dd, J = 8.5, 1.8 Hz, 1H), 6.82 (d, J = 2.3 Hz, 1H), 6.61 (d, J = 2.2 Hz, 1H), 6.25 (s, 1H), 4.95 – 4.91 (m, 1H), 4.80 (dd, J =

11.0, 8.3 Hz, 1H), 4.37 (t, *J* = 2.7 Hz, 1H), 3.98 (dt, *J* = 2.3, 1.0 Hz, 1H), 3.70 (dd, *J* = 10.9, 2.9 Hz, 1H), 1.41 (s, 9H), 1.06 (s, 9H), 0.34 (s, 3H), 0.33 (s, 3H);

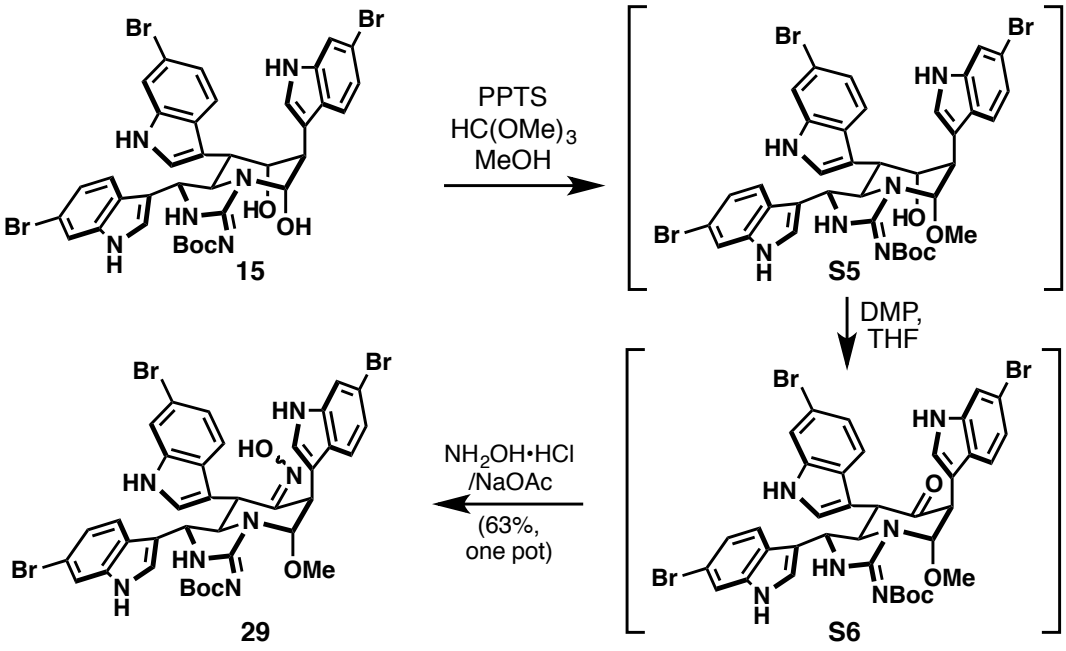
^{13}C NMR (151 MHz, Acetone-d_6) δ 163.3, 159.9, 137.3, 136.9, 136.3, 126.0, 125.0, 124.9, 124.1, 123.8, 123.8, 121.9, 121.3, 121.2, 120.0, 119.0, 119.0, 114.5, 114.1, 114.0, 113.8, 113.6, 112.1, 109.6, 76.2, 75.6, 64.1, 56.2, 55.5, 41.3, 36.8, 27.3(3C), 24.9(3C), 17.4(3C), -5.3, -6.0;

HRMS (m/z): calcd for $C_{42}H_{47}Br_3N_9O_3Si$ $[M+H]^+$ 990.1116 found 990.1118.

X-ray structure of Compound S4, for details see baran573.cif

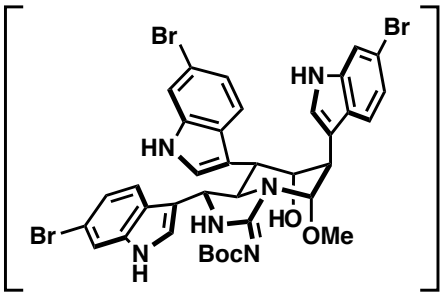


Compound 29



Experimental: Pyridinium *p*-toluenesulfonate (PPTS) (6.8 mg, 0.027 mmol, 1 equiv.) was added to a solution of **15** (23 mg, 0.027 mmol, 1 equiv.) in MeOH (0.5 mL) and trimethyl orthoformate (0.25 mL). The reaction was stirred at room temperature for 12 h before the volatiles were removed *in vacuo*. The resulting residue was charged with THF (0.5 mL) and Dess-Martin Periodinane (23 mg, 0.054 mmol, 2 equiv.). The reaction was concentrated *in vacuo* after stirring for 2 hours at room temperature. The yellow foam thus obtained (crude **S6**) was dissolved in EtOH (0.5 mL) and treated with hydroxylamine hydrochloride (21 mg, 0.3 mmol, 11 equiv.) as well as NaOAc (12 mg, 0.15 mmol, 5.6 equiv.). The resulting mixture was stirred at 50 °C for 30 minutes. After cooling to room temperature, brine (5 mL) was added and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phase was dried with anhydrous Na_2SO_4. Removal of the solvent *in vacuo*, followed by purification of the resulting residue by PTLC (50% EtOAc in hexanes) yielded **29** (15 mg, 63%) as a mixture of rotamers.

Compound S5



Physical state: white foam;

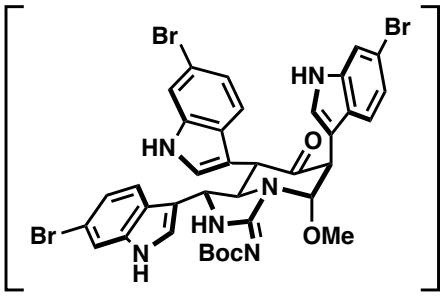
TLC: R_f = 0.44 (EtOAc/hexanes 1:1);

^{1}H NMR (600 MHz, Acetone-d_6) δ 10.51 (s, 1H), 10.15 (d, *J* = 15.1 Hz, 2H), 8.52 (s, 1H), 7.65 (d, *J* = 1.7 Hz, 1H), 7.57 – 7.54 (m, 2H), 7.53 (dd, *J* = 5.0, 1.8 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.17 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.12 (d, *J* = 2.3 Hz, 1H), 7.03 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.99 – 6.95 (m, 2H), 6.59 (d, *J* = 2.4 Hz, 1H), 5.94 (s, 1H), 5.02 (d, *J* = 6.6 Hz, 1H), 4.60 (dd, *J* = 11.3, 6.6 Hz, 1H), 4.31 (d, *J* = 7.7 Hz, 1H), 3.95 – 3.87 (m, 1H), 3.55 (s, 3H), 3.48 (dd, *J* = 11.3, 2.1 Hz, 1H), 1.45 (s, 9H).

^{13}C NMR (151 MHz, Acetone-d_6): δ 164.9, 162.4, 138.7, 138.3, 137.6, 127.9, 126.8, 126.5, 125.0, 124.7, 124.5, 122.9, 122.9, 122.5, 121.1, 120.8, 120.6, 116.9, 115.7, 115.5, 115.3, 115.3, 115.0, 114.9, 114.0, 112.7, 84.3, 77.9, 73.8, 58.7, 56.2, 55.9, 44.1, 39.2, 28.7 (3C).

HRMS (m/z): calcd for $C_{37}H_{36}Br_3N_6O_4$ $[M+H]^+$ 865.0343, found 865.0354.

Compound S6



Physical state: white foam;

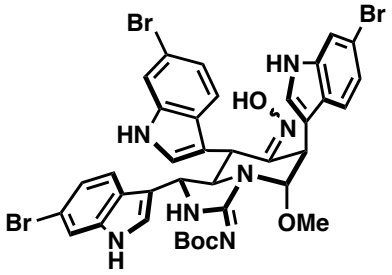
TLC: R_f = 0.44 (EtOAc/hexanes 1:1);

^{1}H NMR (600 MHz, Acetone-d_6): δ 10.71 (s, 1H), 10.35 – 10.25 (m, 1H), 10.19 – 10.15 (m, 1H), 8.63 (s, 1H), 7.87 (dd, *J* = 2.7, 1.1 Hz, 1H), 7.67 (dd, *J* = 1.8, 0.5 Hz, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.15 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.97 (ddd, *J* = 8.5, 4.7, 1.8 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 6.21 (d, *J* = 1.6 Hz, 1H), 5.19 (d, *J* = 5.6 Hz, 1H), 4.52 (dd, *J* = 11.0, 5.6 Hz, 1H), 4.48 (d, *J* = 11.0 Hz, 1H), 4.32 (t, *J* = 1.3 Hz, 1H), 3.53 (s, 3H), 1.50 (s, 9H).

^{13}C NMR (151 MHz, Acetone): δ 203.5, 164.7, 162.1, 138.6, 138.4, 138.3, 128.8, 128.6, 128.4, 127.2, 126.8, 126.7, 124.9, 123.2, 122.9, 122.6, 121.5, 121.45, 120.66, 116.0, 116.0, 115.6, 115.3, 115.2, 115.1, 110.4, 108.2, 85.3, 78.3, 63.1, 56.9, 55.6, 55.0, 49.5, 28.7 (3C).

HRMS (m/z): calcd for $C_{37}H_{34}Br_3N_6O_4$ $[M+H]^+$ 863.0186, found 863.0203.

Compound 29



Physical state: white solid;

TLC: R_f = 0.41 (EtOAc/hexanes 1:1);

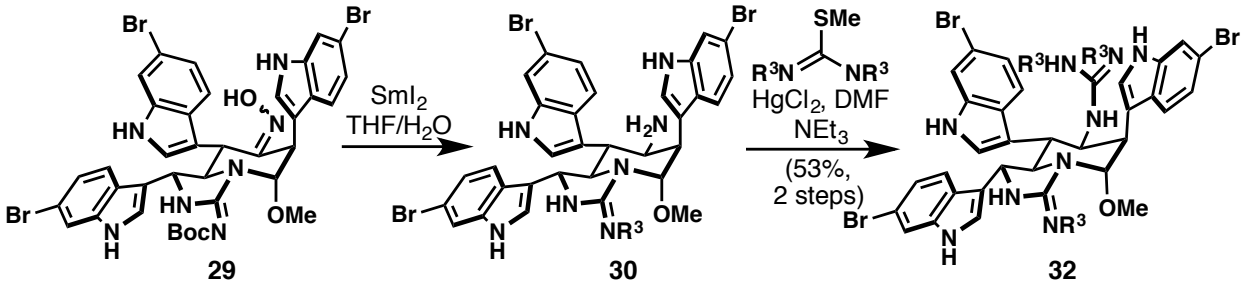
^{1}H NMR (600 MHz, acetone-d_6); δ10.55 (s, 1H), 10.30 – 10.00 (m, 3H), 8.48 (s, 1H), 7.87 – 7.35 (m, 6H), 7.24 – 6.53 (m, 6H), 6.03 (s, 1H), 5.43 (s, 1H), 5.01 (d, J = 6.7 Hz, 1H), 4.62 – 4.41 (br, 1H), 4.13 – 3.96 (br, 1H), 3.53 (s, 3H), 1.45 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$); δ164.8, 162.3, 155.6, 138.6, 138.4, 126.9, 126.3, 125.0, 124.9, 124.7, 123.0, 122.8, 122.2, 122.0, 120.9, 115.9, 115.6, 115.3, 115.0, 114.8, 112.9, 84.2, 82.2, 78.2, 56.9, 55.6, 36.9, 28.8 [spectra data of compound **29** is complicated by the presence of rotamers (see attached spectra)];

HRMS (m/z): calcd for $C_{37}H_{35}Br_3N_7O_4$ $[M+H]^+$ 878.0284, found 878.0295.

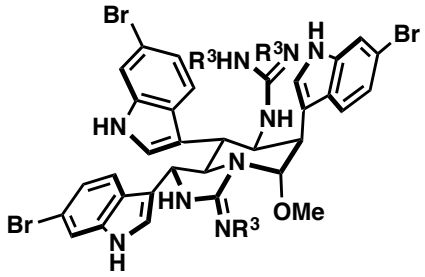
[In the asymmetric route, $[\alpha]_D^{26}$ = +80.3°, (c = 1.0, MeOH)]

Compound 32



Experimental: To a solution of oxime **29** (15mg, 0.017 mmol, 1 equiv.) in THF/H_2O (0.3 mL/0.05 mL) under Ar atmosphere (deoxygenated by sparging with argon) was added a solution of SmI_2 in THF (0.1 mM) dropwise at room temperature until the dark blue color of the reaction mixture did not fade. The resulting mixture was stirred for 15 minutes at room temperature when a saturated aqueous solution of $Na_2S_2O_3$ (3 mL) was added. The mixture was extracted with EtOAc (3 × 5 mL) and the combined organic phase was dried with Na_2SO_4. Evaporation of the solvent *in vacuo* gave crude **30** as colorless foam which was re-dissolved in DMF (0.5 mL) and treated with *N,N′*-Di-Boc-*S*-methylisothiourea (**31**) (11.6 mg, 0.04 mmol, 2.35 equiv.), followed by triethylamine (14 µL, 0.1 mmol, 5.88 equiv.). The mixture was stirred at room temperature for 5 min before $HgCl_2$ (13.5 mg, 0.05 mmol, 2.94 equiv.) was added. A suspension was observed instantly which was filtered through a thin pad of celite. The filtrate was partitioned between brine and EtOAc (10 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and was concentrated *in vacuo*. Purification of the resulting residue by preparative TLC (30% EtOAc in hexanes) afforded **32** (10.0 mg, 53%).

Compound 32



Physical state: colorless foam;

TLC: R_f = 0.30 (EtOAc/hexanes 2:3);

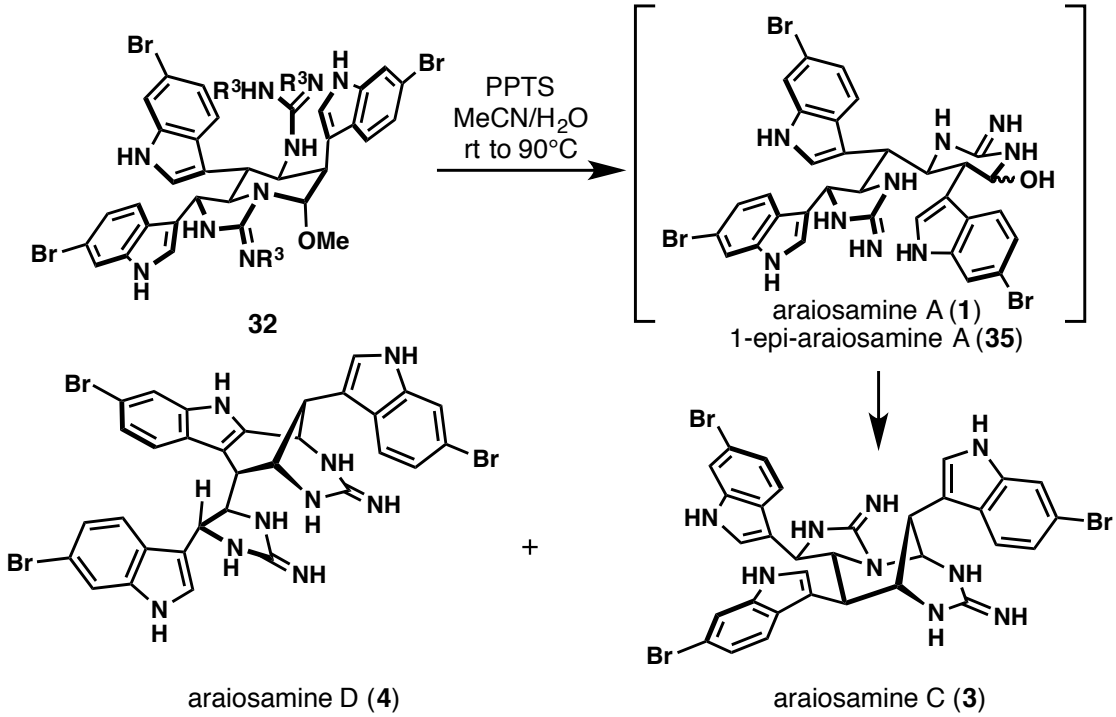
^{1}**H NMR:** (600 MHz, Acetone-d_6) δ 11.25 (s, 1H), 10.57 (s, 1H), 10.13 (s, 1H), 10.06 (s, 1H), 8.51 (s, 1H), 7.92 – 7.25 (m, 7H), 7.20 – 6.89 (m, 5H), 6.51 (s, 1H), 5.73 (s, 1H), 5.48 – 5.28 (br, 1H), 5.20 (d, J = 7.6 Hz, 1H), 4.60 – 4.36 (br, 1H), 4.26 – 4.11 (br, 1H), 3.67 – 3.50 (br. 1H), 3.55 (s, 3H), 1.44 (s, 9H), 1.40 (s, 9H), 1.15 (s, 9H);

^{13}**C NMR:** (151 MHz, Acetone-d_6) δ 164.9, 164.6, 162.6, 156.6, 152.8, 138.7, 137.7, 137.6, 129.0, 128.9, 128.9, 128.7, 128.6, 125.7, 125.6, 125.1, 125.1, 124.7, 124.5, 123.2, 122.9, 122.7, 121.0, 120.7, 115.8, 115.6, 115.4, 115.1, 111.2, 84.3, 83.5, 79.3, 78.1, 57.1, 57.0, 56.1, 55.7, 40.1, 32.8, 28.7, 28.7, 28.0 [spectra data of compound **32** is complicated by the presence of rotamers (see attached spectra)];

HRMS (m/z): calcd for $C_{48}H_{55}Br_3N_9O_7$ $[M+H]^+$ 1106.1769, found 1106.1745.

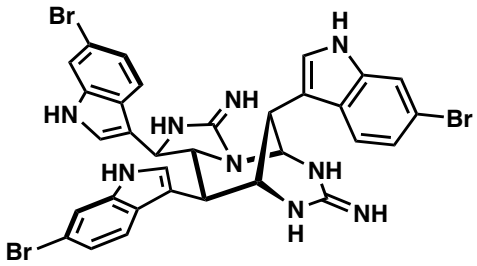
[In the asymmetric route, $[\alpha]_D^{23}$ = +80.7°, (c = 1.0, MeOH)]

araiosamines C (3) and D (4):



Experimental: A culture tube was charged with a solution of **32** (10.0 mg, 0.009 mmol, 1 equiv.) and pyridinium *p*-toluenesulfonate (PPTS) (10.0 mg, 0.040 mmol, 4.4 equiv.) in MeCN/H_2O (1.0 mL/0.2 mL). The reaction mixture was stirred at room temperature for approximately 3 days when LC/MS indicated the complete disappearance of starting material. The reaction mixture was then brought up to 90 °C and stirred at this temperature for 24 hours. After cooled down to room temperature, the volatile components were evaporated *in vacuo*. The crude product was subjected to preparative HPLC (C18 Column, 20% to 75% MeCN in H_2O, 0.1% TFA, 20 minutes ramp) to give araiosamine C (5.7 mg, 81%, R_T = 14.9 min) and araiosamine D (0.6 mg, 8%, R_T = 16.0 min) as colorless amorphous powders.

araiosamine C



araiosamine C (**3**)

Physical state: colorless amorphous powder;

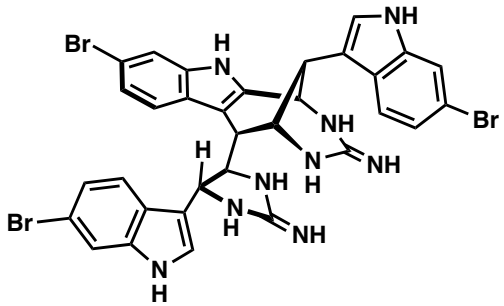
^{1}**H NMR** (600 MHz, MeOD) δ 7.63 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 1.6 Hz, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.43 (d, *J* = 1.6 Hz, 1H), 7.41 (d, *J* = 1.6 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.23 (s, 1H), 7.16 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.12 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.03 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.87 (s, 1H), 6.85 (s, 1H), 5.97 (s, 1H), 5.12 (d, *J* = 9.6 Hz, 1H), 4.76 (dd, *J* = 10.9, 9.6 Hz, 1H), 4.30 (s, 1H), 4.11 (d, *J* = 1.7 Hz, 1H), 3.84 (d, *J* = 10.9 Hz, 1H).

^{13}**C NMR** (151 MHz, MeOD) δ 158.0, 153.2, 139.1, 138.8, 138.7, 126.2, 126.0, 126.0, 125.2, 124.5, 124.0, 123.6, 123.5, 123.4, 121.2, 120.5, 120.5, 116.7, 116.5, 116.3, 115.6, 115.5, 115.4, 113.5, 112.4, 110.1, 60.8, 60.6, 59.1, 55.0, 30.1;

HRMS (m/z): calcd for $C_{32}H_{27}Br_3N_9$ $[M+H]^+$ 773.9939, found 773.9926.

[In the asymmetric route, $[\alpha]_D^{27}$ = +40.4°, (*c* = 1.0, MeOH)]

araiosamine D



araiosamine D (**4**)

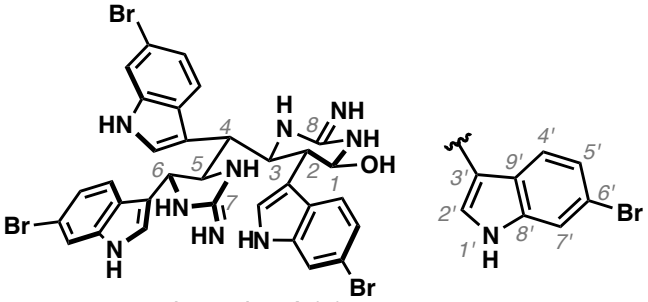
Physical state: colorless amorphous powder.

^{1}**H NMR** (600 MHz, MeOD) δ ^{1}H NMR (600 MHz, Methanol-d_4) δ 7.65 (d, J = 1.8 Hz, 1H), 7.63 (d, J = 1.7 Hz, 1H), 7.56 (d, J = 1.6 Hz, 1H), 7.55 (d, J = 8.9 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.41 (d, J = 8.7 Hz, 1H), 7.40 (s, 1H), 7.27 (s, 1H), 7.24 (dd, J = 8.5, 1.8 Hz, 1H), 7.18 (dd, J = 8.6, 1.8 Hz, 1H), 5.17-5.23 (m, 2H), 4.93 (dd, J = 2.1, 1.1 Hz, 1H), 4.68 (d, J = 3.9 Hz, 1H), 3.92 (dd, J = 4.0, 2.3 Hz, 1H), 3.86 (d, J = 2.5, 1H);

^{13}**C NMR** (151 MHz, MeOD) δ 159.7, 154.6, 139.8, 139.3, 139.3, 138.7, 126.5, 126.4, 126.0, 125.4, 124.3, 124.0, 124.0, 123.5, 122.1, 120.6, 120.5, 116.8, 116.7, 116.6, 116.2, 116.0, 115.5, 113.9, 113.1, 106.4, 65.0, 56.2, 52.3, 46.6, 46.2, 34.8;

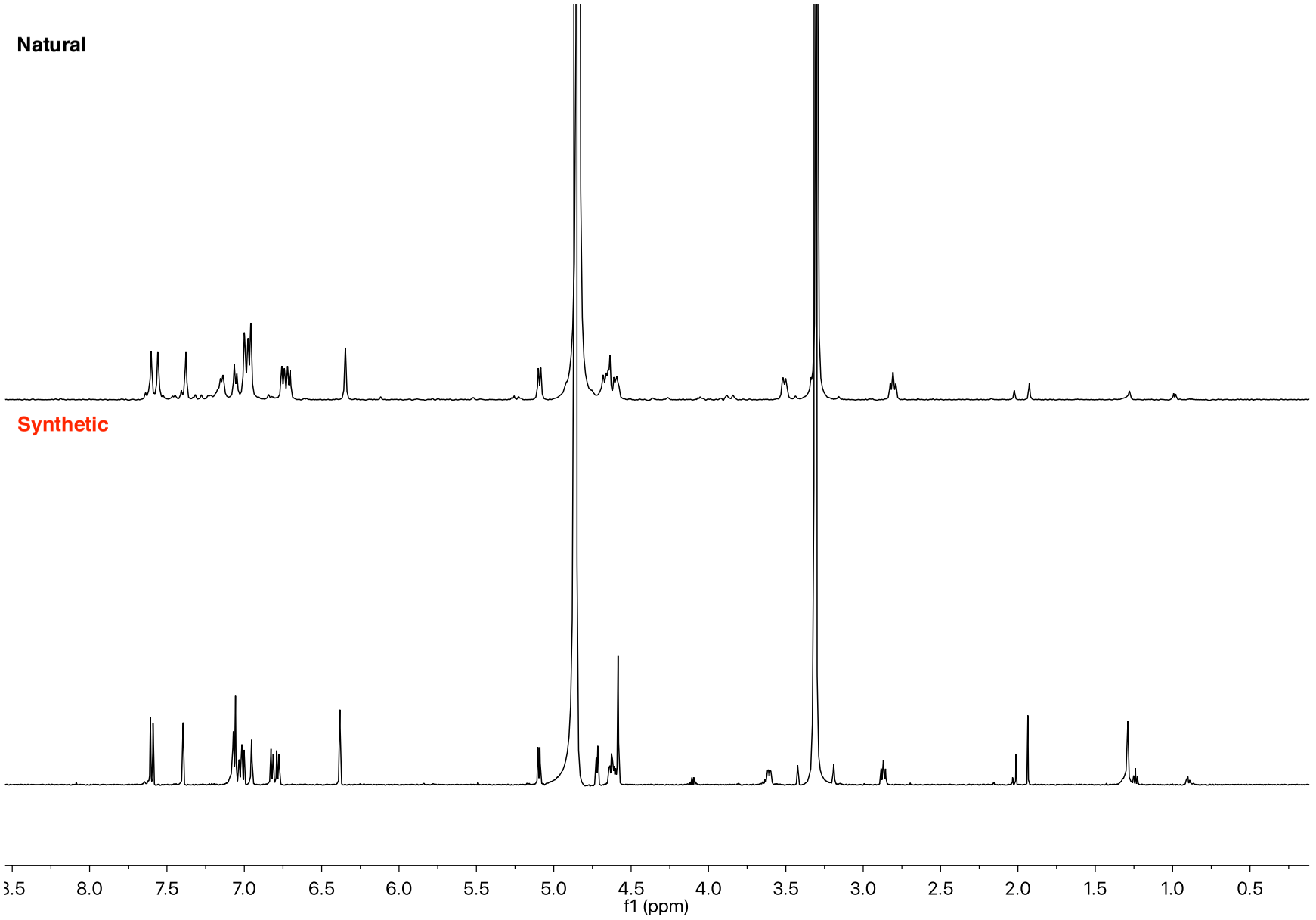
HRMS (m/z): calcd for $C_{32}H_{27}Br_3N_9$ $[M+H]^+$ 773.9939, found 773.9927.

Araiosamine A 1H Spectra Comparison:

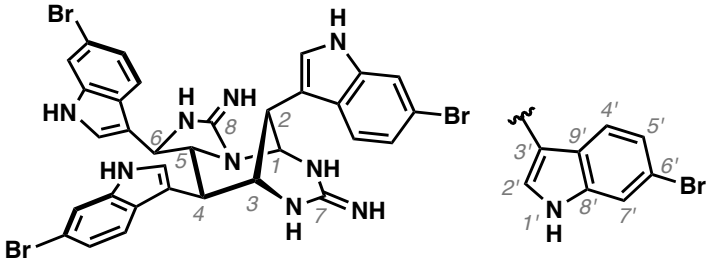


araiosamine A (**1**)

position	**Natural** (500M, MeOD)	**Synthetic** (600M, MeOD)
	δ_H mult (*J* in Hz)	δ_H mult (*J* in Hz)
1	5.09 d (8.3)	5.10 d (7.7)
2	2.81 dd (9.6, 8.3)	2.87 dd (9.8, 7.7)
3	4.67 dd (9.6, 2.0)	4.64 dd (9.9, 4.0)
4	3.52 dd (9.8, 2.0)	3.61 dd (9.9, 4.0)
5	4.60 dd (9.8, 5.5)	4.61 (9.9, 5.5)
6	4.64 d (5.5)	4.72 d (5.5)
2’	6.96 s	6.95 s
4’	7.15 d (8.5)	7.08 m
5’	7.06 d (8.5)	7.06 m
7’	7.60 s	7.61 d (1.4)
2’’	7.00 s	7.00 d (1.7)
4’’	6.75 d (8.5)	6.82 d (8.5)
5’’	6.99 d (8.5)	7.02 d (8.5)
7’’	7.56 s	7.59 d (1.7)
2’’’	6.35 s	6.38 s
4’’’	6.71 d (8.4)	6.78 d (8.5)
5’’’	6.97 d (8.4)	7.03 dd, (8.7, 1.3)
7’’’	7.38 s	7.41 d (1.6)


Natural
Synthetic
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

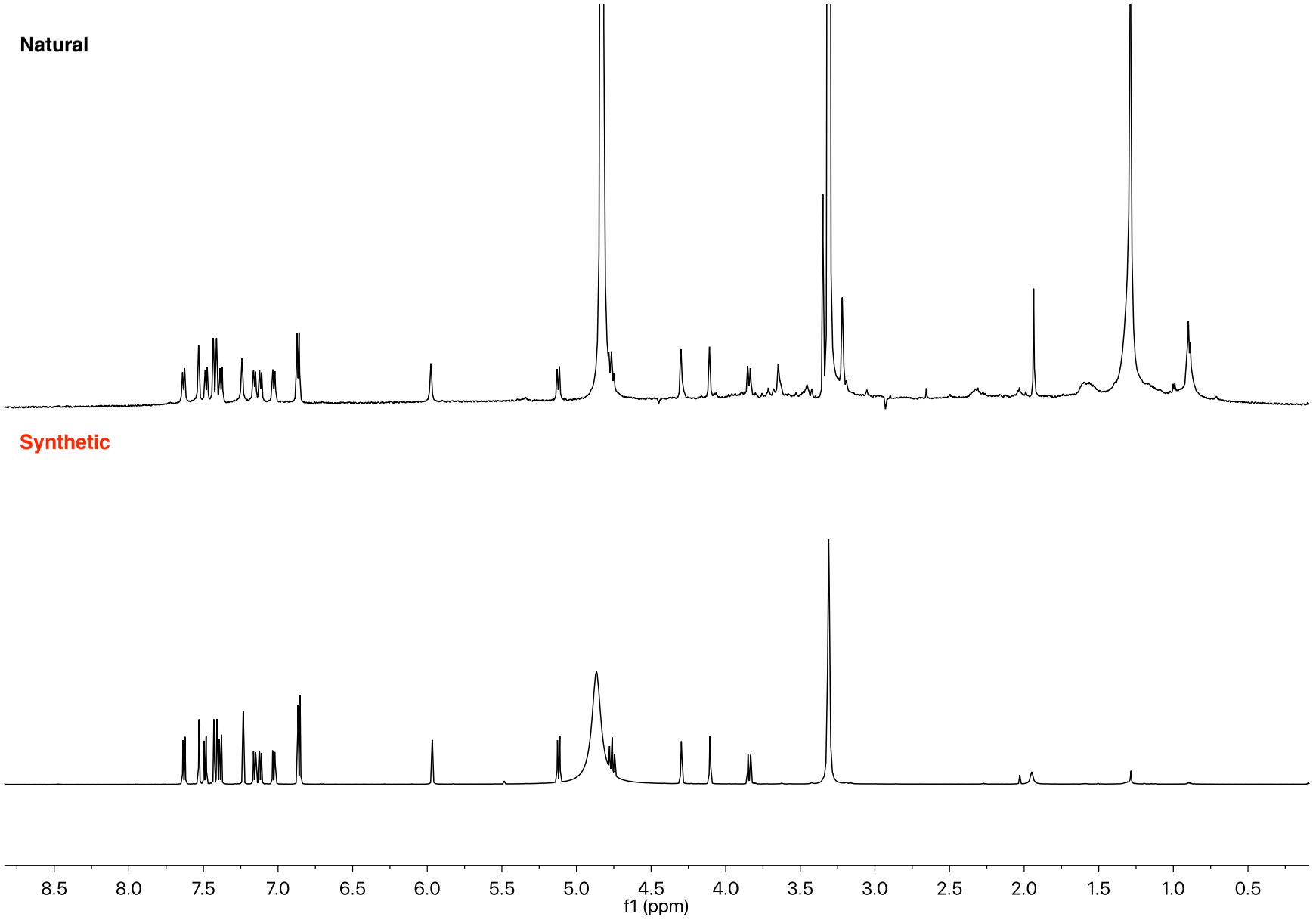
Araiosamine C ^{1}H and ^{13}C spectra comparison:



araiosamine C (**3**)

position	**Natural** (600M, MeOD)		**Synthetic** (600M, MeOD)	
	δ_H mult (*J* in Hz)	δ_C	δ_H mult (*J* in Hz)	δ_C
1	5.97 d (1.1)	58.8	5.97 s	59.1
2	4.29 d (1.1)	30.0	4.30 s	30.1
3	4.10 d (10.5)	54.8	4.11 d (1.7)	55.0
4	3.83 d (10.5)	48.9	3.84 d (10.9)	-
5	4.76 dd (10.5, 9.6)	60.3	4.76 dd (10.9, 9.6)	60.6
6	5.11 d (9.6)	60.6	5.12 d (9.6)	60.8
7		153.0		153.2
8				158.0
2’	7.23 s	124.3	7.23 s	124.5
3’		108.4		110.1
4’	7.47 d (8.4)	120.3	7.49 d (8.5)	120.5
5’	7.11 d (8.4)	123.3	7.12 dd (8.5, 1.7)	123.6
6’		116.3		116.7
7’	7.52 s	115.3	7.53 d (1.6)	115.6
8’		138.3		138.8
9’		125.6		126.0
2’’	6.86 s	123.7	6.85 s	124.0
3’’		113.2		113.5
4’’	7.62 d (8.5)	120.1	7.63 d (8.5)	120.5
5’’	7.15 d (8.5)	123.2	7.16 dd (8.5, 1.7)	123.5
6’’		116.1		116.5
7’’	7.42 s	115.2	7.43 d (1.6)	115.5
8’’		138.3		138.7

9”		125.9		126.2
2”’	6.85 s	125.6	6.85 s	126.0
3”’		112.2		112.4
4”’	7.37 d (8.5)	120.9	7.39 d (8.5)	121.2
5”’	7.02 d (8.5)	123.1	7.03 dd, (8.5, 1.7)	123.4
6”’		115.9		116.3
7”’	7.40 s	115.1	7.41 d (1.6)	115.4
8”’		138.8		139.1
9”’		124.8		125.2


Natural
Synthetic
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8.0
7.5
7.0
6.5
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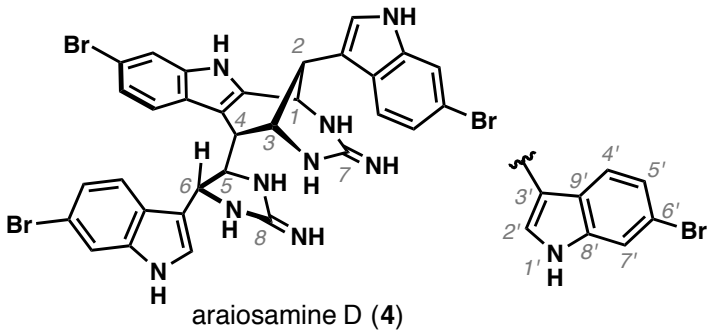
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

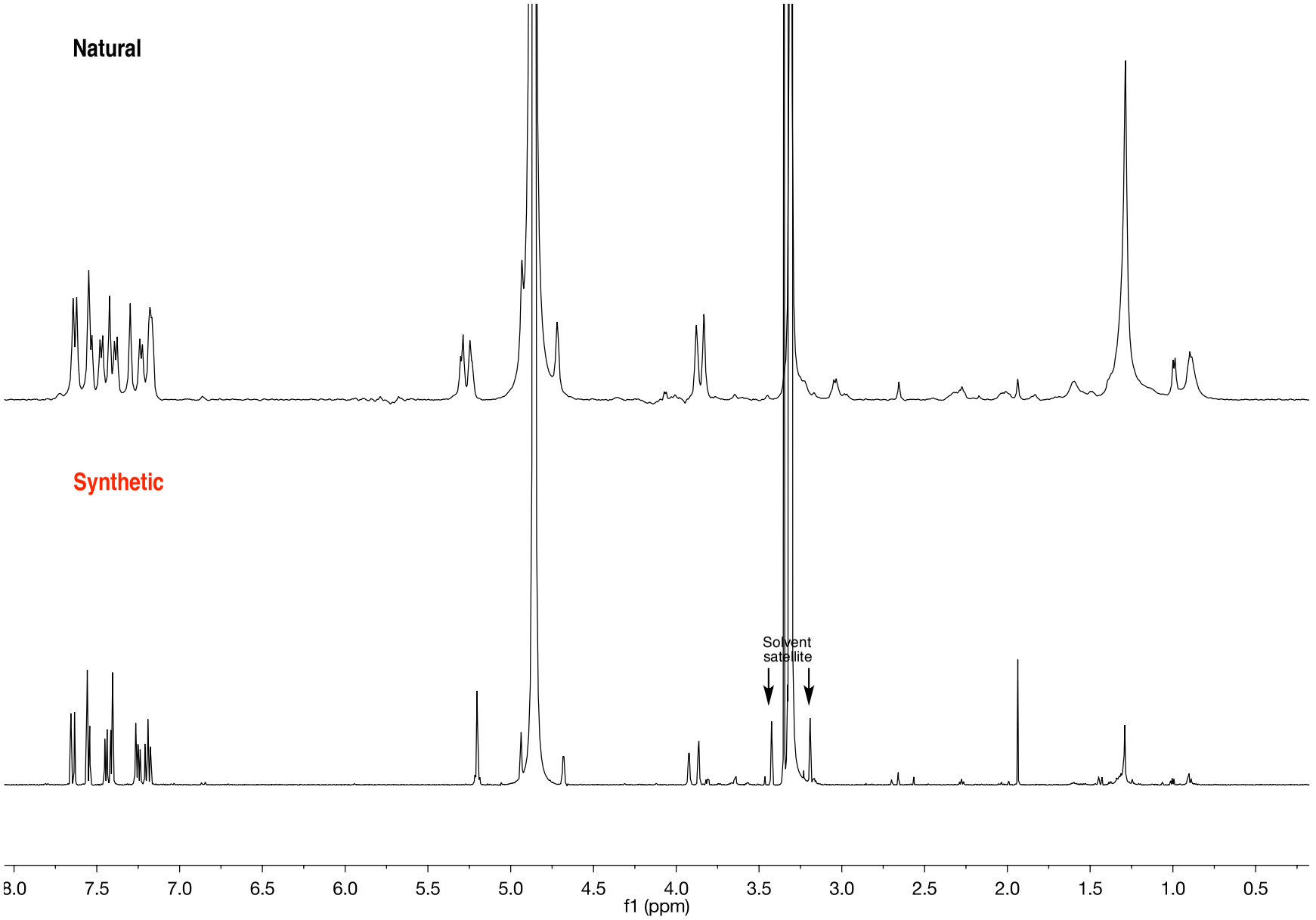
Araiosamine D ^{1}H and ^{13}C spectra comparison:

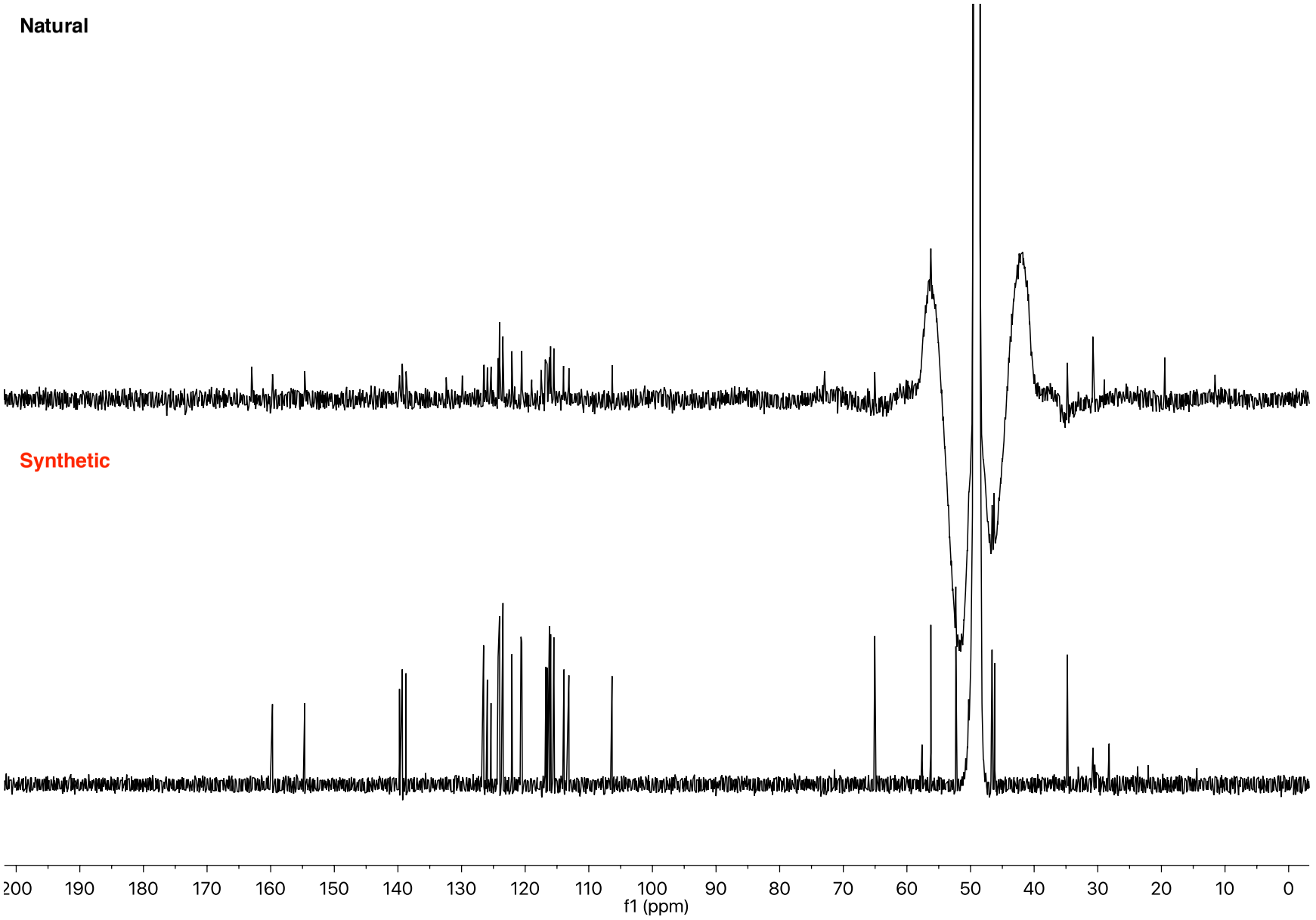


araiosamine D (**4**)

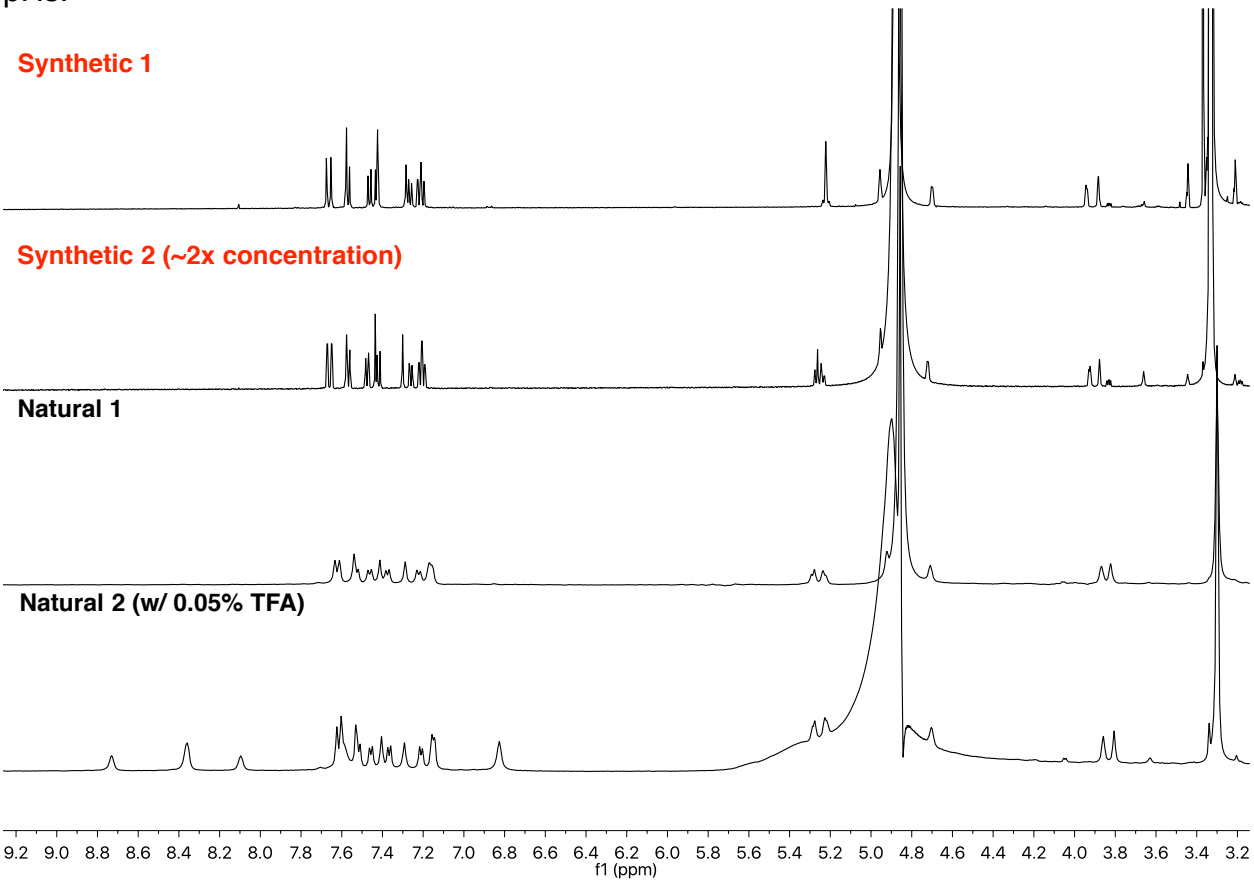
position	**Natural** (600M, MeOD)		**Synthetic** (600M, MeOD)	
	δ_H mult (*J* in Hz)	δ_C	δ_H mult (*J* in Hz)	δ_C
1	4.92 dd (2.3, 1.3)	46.6	4.93 dd (2.1,1.1)	46.6
2	3.82 dd (2.7, 1.3)	34.3	3.86 d (2.5)	34.8
3	4.71 d (3.8)	52.3	4.68 d (3.9)	52.3
4	3.87 dd (3.8, 2.4)	46.3	3.92 dd (4.0, 2.3)	46.2
5	5.23 dd (8.2, 2.4)	65.1	5.17-5.23 m	65.0
6	5.29 d (8.2)	56.3	5.17-5.23 m	56.2
7		154.7		154.6
8				159.7
2’	7.29 s	123.7	7.27 s	124.0
3’		112.9		113.1
4’	7.53 d (8.5)	120.2	7.55 d (8.9)	120.6
5’	7.16 d (8.5)	123.0	7.18 dd (8.4, 1.8)	123.5
6’		116.3		116.6
7’	7.54 s	115.3	7.56 d (1.6)	115.5
8’		138.7		138.7
9’		126.3		126.5
2’’		139.3		139.3
3’’		106.3		106.4
4’’	7.38 d (8.6)	121.6	7.41 d (8.7)	122.1
5’’	7.18 dd (8.4, 1.8)	123.9	7.18 dd (8.6, 1.8)	124.3
6’’		116.7		116.8
7’’	7.63 d (1.8)	115.8	7.65 d (1.8)	116.0
8’’		139.3		139.3
9’’		125.8		126.0

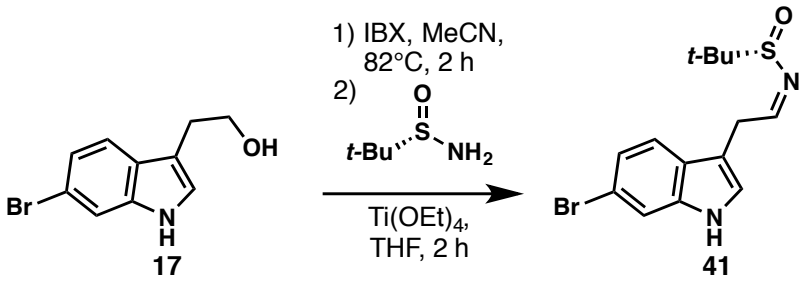
2’’’	7.41 s	126.2	7.40 s	126.4
3’’’		113.6		113.9
4’’’	7.46 d (8.5)	120.2	7.44 d (8.5)	120.5
5’’’	7.23 dd (8.5, 1.6)	123.7	7.24 dd (8.5, 1.8)	124.0
6’’’		116.6		116.7
7’’’	7.61 d (1.6)	115.9	7.63 d (1.7)	116.2
8’’’		139.6		139.8
9’’’		125.3		125.4


Natural
Synthetic
Solvent satellite
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


Natural
Synthetic
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Note: Spectral data of araiosamines showed dependence on pH and concentration. This effect is especially pronounced on small amounts of materials and accounts for differences between chemical shifts of natural and synthetic araiosamines A and D. An example is provided below to illustrate:
Different spectra of synthetic araiosamine D, and natural araiosamine D at different pHs.





Experimental: A round bottom flask equipped with stir bar was charged with 6-bromotryptophol (6.00 g, 25.2 mmol), MeCN (100 mL) and IBX (10.00 g, 41.8 mmol). The mixture was refluxed for 2 hours, filtered through a thin pad of celite and concentrated *in vacuo*. The resulting residue was dissolved in THF (50 mL) and was charged sequentially with (*S*)-2-methylpropane-2-sulfinamide (3.97 g, 32.8 mmol) and titanium (IV) tetraethoxide (14.7 mL, 50.4 mmol). The reaction was stirred for 2 hours and was quenched by the addition of brine (10 mL). The resulting suspsension was filtered through a pad of celite and washed with brine. The combined organic phase was concentrated in vacuo and purified through FCC (20% EtOAc in hexanes) to afford **41** (3.50g, 40.7%).

Physical state: orange solid;

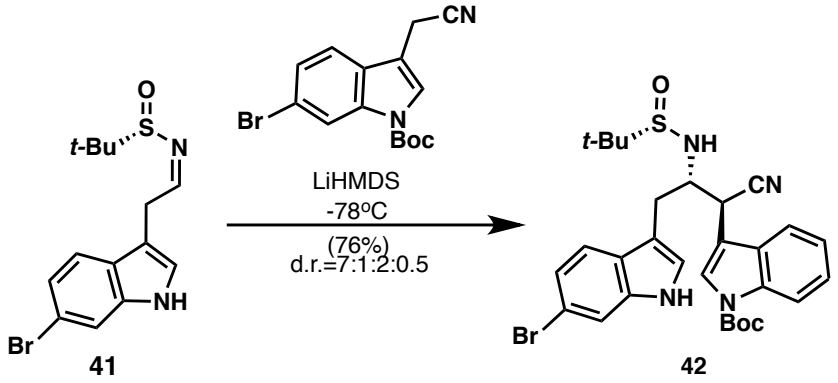
TLC: R_f= 0.23 (10% EtOAc in hexanes);

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.37 (s, 1H), 7.97 (t, *J* = 5.2 Hz, 1H), 7.37 (d, *J* = 1.7 Hz, 1H), 7.27 (s, 1H), 7.12 (s, 0H), 7.07 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.86 (d, *J* = 2.3 Hz, 1H), 3.82 – 3.72 (m, 3H), 1.07 (s, 1H), 1.05 (s, 12H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.45, 137.17, 126.25, 123.43, 123.07, 120.01, 116.04, 114.40, 109.28, 77.37, 77.16, 76.95, 57.02, 32.44, 22.52.

HRMS (m/z): calcd for $C_{14}H_{17}BrN_2OS$ $[M+H]^+$ 341.0318. Found 341.0298.

Compound 42



Experimental: A flame dried round bottom flask under Ar equipped with stir bar was charged with nitrile **19** (4.91 g, 14.7 mmol, 2 equiv.), and THF (160 mL). The solution was cooled to –78 °C when a solution of LiHMDS in THF (15.38 mL, 1.0 M) was added dropwise to the mixture at –78 °C. The reaction was allowed to stir at –78 °C for 1 h and a solution of Ellman imine **41** (2.5 g, 7.4 mmol,1 equiv.) in THF (50 mL) was added dropwise. The resulting mixture was stirred for another 30 mins and was subsequently quenched with sat. NH_4Cl before warming up to room temperature. The aqueous phase was extracted with EtOAc; the combined organic extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The crude was purified by FCC (20%-40% EtOAc in hexanes) to yield a mixture of four diasteromers (3.79 g, 76% yield). Purification of this mixture by FCC (30% EtOAc in hexanes) afforded the desired diastereomer **42** along with an inseparable diastereomer (*syn*) (7:1 mixture, 2.89 g, 58% combined yield).

Physical state: white foam;

TLC: R_f = 0.28 (40% EtOAc in hexanes);

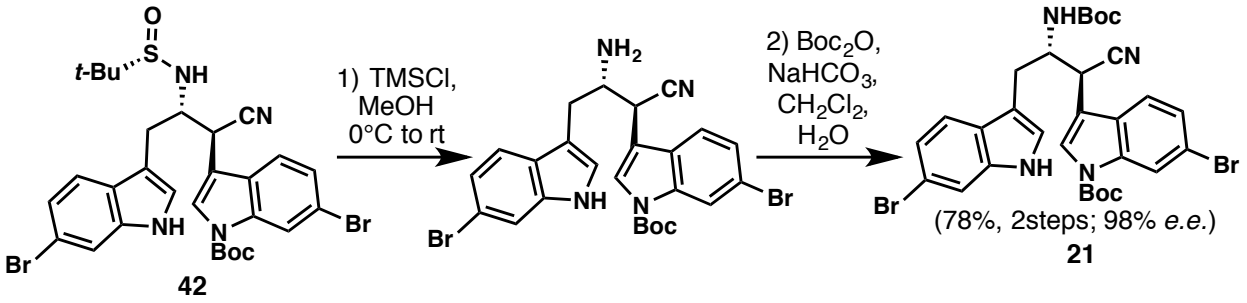
(Isolated as a 7:1 mixture of inseparable diastereomers)

^{1}H NMR (600 MHz, Acetone-d_6) δ 10.28 (s, 1H), 8.54 – 8.33 (m, 1H), 7.94 (d, J = 0.8 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.60 (dd, J = 1.8, 0.5 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.41 (dd, J = 8.5, 1.8 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H), 7.17 (dd, J = 8.5, 1.8 Hz, 1H), 4.79 (dd, J = 4.2, 0.8 Hz, 1H), 4.72 (d, J = 9.3 Hz, 1H), 4.19 (tdd, J = 9.3, 5.1, 4.2 Hz, 1H), 3.38 (ddd, J = 14.5, 5.1, 0.8 Hz, 1H), 3.15 – 3.05 (m, 1H), 1.68 (s, 9H), 1.02 (s, 9H)**;** (major product reported)

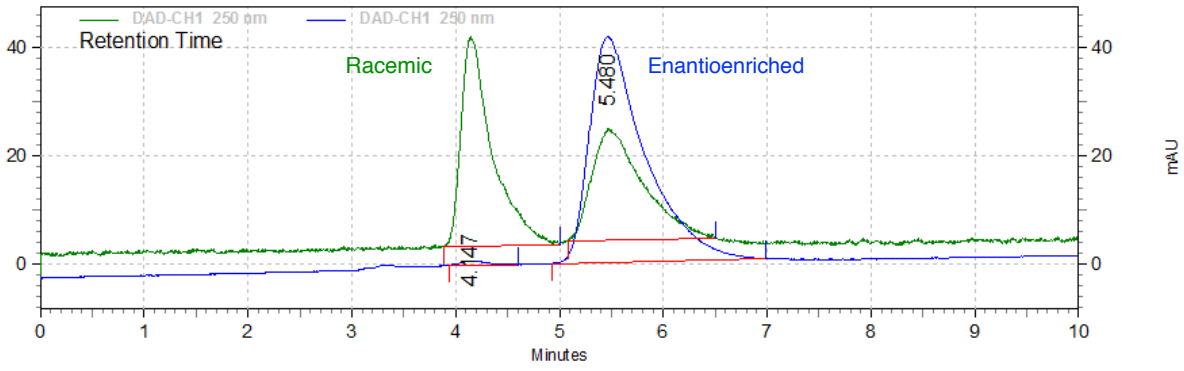
^{13}C NMR (151 MHz, Acetone-d_6) δ 149.64, 138.45, 137.32, 128.95, 128.76, 128.73, 128.60, 128.44, 127.34, 126.69, 126.13, 122.72, 122.16, 120.70, 119.42, 118.96, 118.78, 115.38, 115.20, 112.04, 111.88, 85.53, 60.44, 56.85, 35.43, 30.59, 28.15 (3C), 22.73 (3C); (inseparable mixture of diastereomers)

HRMS (m/z): calcd for $C_{29}H_{33}Br_2N_4O_3S$ $[M+H]^+$ 675.0635 found 675.0680.

Enantioenriched compound 21



Experimental: A flame dried round bottom flask under Ar equipped with a stirrer bar was charged with Mannich product **42** (7:1 diastereomeric mixture) (1.40 g, 2.07 mmol), and MeOH (20 mL). The solution was cooled to 0°C when TMSCl (2 mL, 1,17g, 15.8 mmol) was added dropwise; the reaction was stirred at 0°C for an additional 15mins was quenched with a saturated aqueous solution of Na_2CO_3. The resulting mixture was extracted with EtOAc and the combined organic phase was concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (10mL) and was treated sequentially with saturated aqueous $NaHCO_3$ ($NaHCO_3$) and Boc_2O (600mg, 2.75 mmol). The biphasic mixture was stirred vigorously overnight; the organic phase was then dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by FCC (20% EtOAc in hexanes) afforded enantioenriched **21** (1.1g, 78% yield over 2 steps, 98% *ee*). The absolute configuration of 21 prepared this way was confirmed via X-ray (baran603.cif).



DAD-CH1 250 nm Results

Retention Time	Area	Area %	Height	Height %
4.167	28112	0.83	1579	1.71
5.467	3369526	99.17	91005	98.29
Totals	3397638	100.00	92584	100.00

Figure S3. Chiral HPLC trace of racemic and enantioenriched **21**.

Column: ODH (Chiraclcel)

Dimensions: 0.46cmϕ x 25cm

Eluent: 40% *i*-PrOH in heptanes

Flow rate: 1mL/min

Evaluation of biological activities (Data from Sirenas Marine Discovery)

Part I. Inhibitory Response of Test of Araiosamines Against BT-474 and HCC1954 Cells

[001] BT-474 human mammary gland ductal carcinoma cells were seeded in a white, clear-bottom polystyrene 96-well microculture plate (Greiner® Cellstar® 96-well flat bottom plate, Cat.# 655098) in a total volume of 100 µL/well. After 24 hours of incubation in a humidified incubator at 37 ºC with 5% CO_2 and 95% air, 10 µL of 10X, serially diluted test agents in growth medium were added to each well (8 pt dose response curve, highest final concentration 1 µM of test agent). After 72 hours of culture in a humidified incubator at 37 ºC, in an atmosphere of 5% CO_2 and 95% air, the plated cells and Cell Titer-Glo® (Promega G7571) reagents were brought to room temperature to equilibrate for 30 minutes. 50 µL of Cell Titer-Glo® reagent was added to each well. The plate was shaken for two minutes and then left to equilibrate for ten minutes. Luminescence was read on a Spectramax i3 microplate reader.

[002] Percent inhibition of cell growth was calculated relative to untreated control wells. The IC_{50} value for the test agents was determined using GraphPad Prism by curve-fitting of the data using the following four parameter-logistic equation:

$$Y = \frac{Top - Bottom}{1 + \left(X / IC_{50}\right)^{n}} + Bottom$$

,

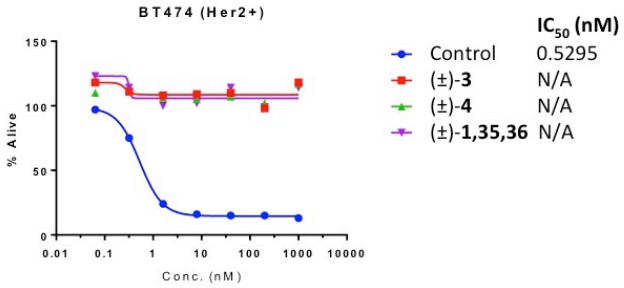
where Top is the maximal % of control absorbance, Bottom is the minimal % of control absorbance at the highest agent concentration, Y is the % of control absorbance, X is the agent concentration, IC_{50} is the concentration of agent that inhibits cell growth by 50% compared to the control cells, and n is the slope of the curve.

[003] Inhibitory response of test compounds against HCC1954 cells was determined using a method analogous to that used for BT-474 cells. IC_{50} values for various test agents in BT-474 and HCC1954 cells are shown in Table 1.

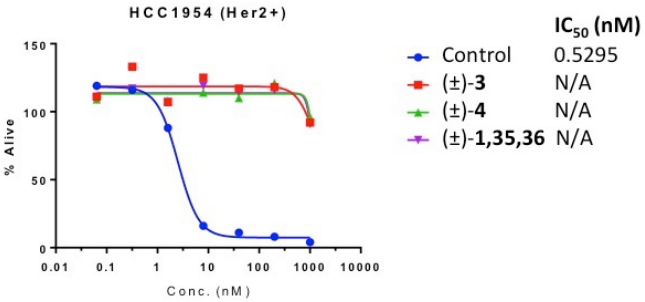
Table 1

Compound No.	BT-474 IC_{50} in nM	HCC1954 IC_{50} in nM
(±)-araiosamine C (**3**)	No IC50, <50% inhibition	No IC50, <50% inhibition
(±)-araiosamine D (**4**)	No IC50, <50% inhibition	No IC50, <50% inhibition
(±)-araiosamine A(tautomeric mixture of **1**, **35**, **36**)	No IC50, <50% inhibition	No IC50, <50% inhibition

Results with BT-474



Results with HCC-1954



Part II. Antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* in the presence/absence of mouse serum or human serum albumin. (Data from Sirenas Marine Discovery)

1.) Test Articles

a.) Investigational agents (fractions; 0.075 mL each) will be provided by Sirenas Marine Discovery in a 96-well plate at a concentration of 2.56 mg/mL dissolved in 100% DMSO.

b.) Ciprofloxacin will serve as the quality control agent.

2.) Organisms

Organism	Phenotype	MMX or ATCC No.	Location
Escherichia coli	Wild type; Parent of tolC	0119	003-2
Escherichia coli	QC; wild type	0102; ATCC 25922	001-3
Staphylococcus aureus	USA 300	2011	198-7

E. coli ATCC 25922 will serve as the quality control strain only for the assay (ciprofloxacin testing only) and will **NOT** be tested against the 27 samples or in the presence of serum or albumin (2).

3.) Test Media

The test medium will be cation-adjusted Mueller-Hinton Broth.

4.) Broth Microdilution Susceptibility Testing

a. *General method:* The method will essentially follow that of CLSI (1). The drug concentration range for the test agents will be 32 – 0.03 µg/mL. Ciprofloxacin will be tested using a drug concentration range of 2 – 0.002 µg/mL.

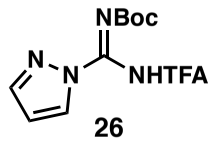
The test agents will arrive in 100% DMSO at a concentration of 2,560 µg/mL. They will be diluted to 1,280 µg/mL with 100% DMSO, which represents 40X the top drug concentration that will be tested. Further dilutions will be made with 100% DMSO (mother plate), and the daughter plates for MIC testing will ultimately contain 185 µL of media, 5 µL of drug from the mother plate, and 10 µL of inoculum.

b. *Testing in the presence of mouse serum*. Each of the isolates will also be tested in the presence of 25% heat-inactivated mouse serum.

c. *Testing in the presence of human serum albumin*. Each of the isolates will also be tested in the presence of 4% human serum albumin (Sigma A1653, >96% by gel electrophoresis).

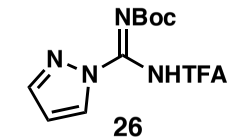
MIC data for araiosamines (in μg/mL)

Compound tested	*staphylococcus aureus* MMX 2011 USA 300 [gram positive]	*Escheria coli* MMX 119 Wild type; parent of tolC [gram negative]
(±)-araiosamine A (**1**) tautomeric mixture	1	2
(±)-araiosamine C (**3**)	1	8
(±)-araiosamine D (**4**)	2	16
axinellamines A	2	2
Ciprofloxacin	>2	0.015



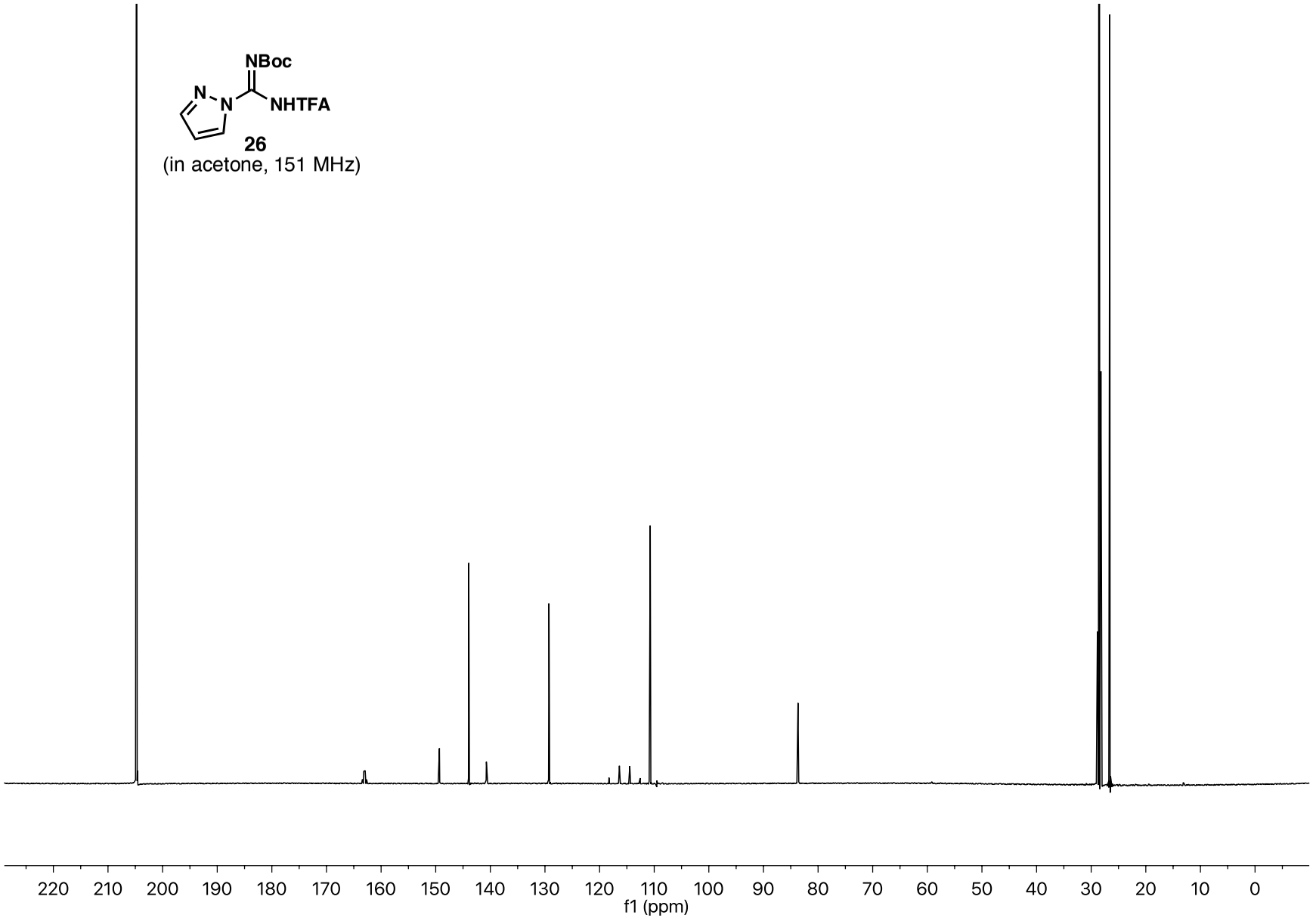
26

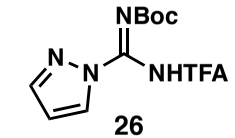
(in acetone, 600 MHz)



26

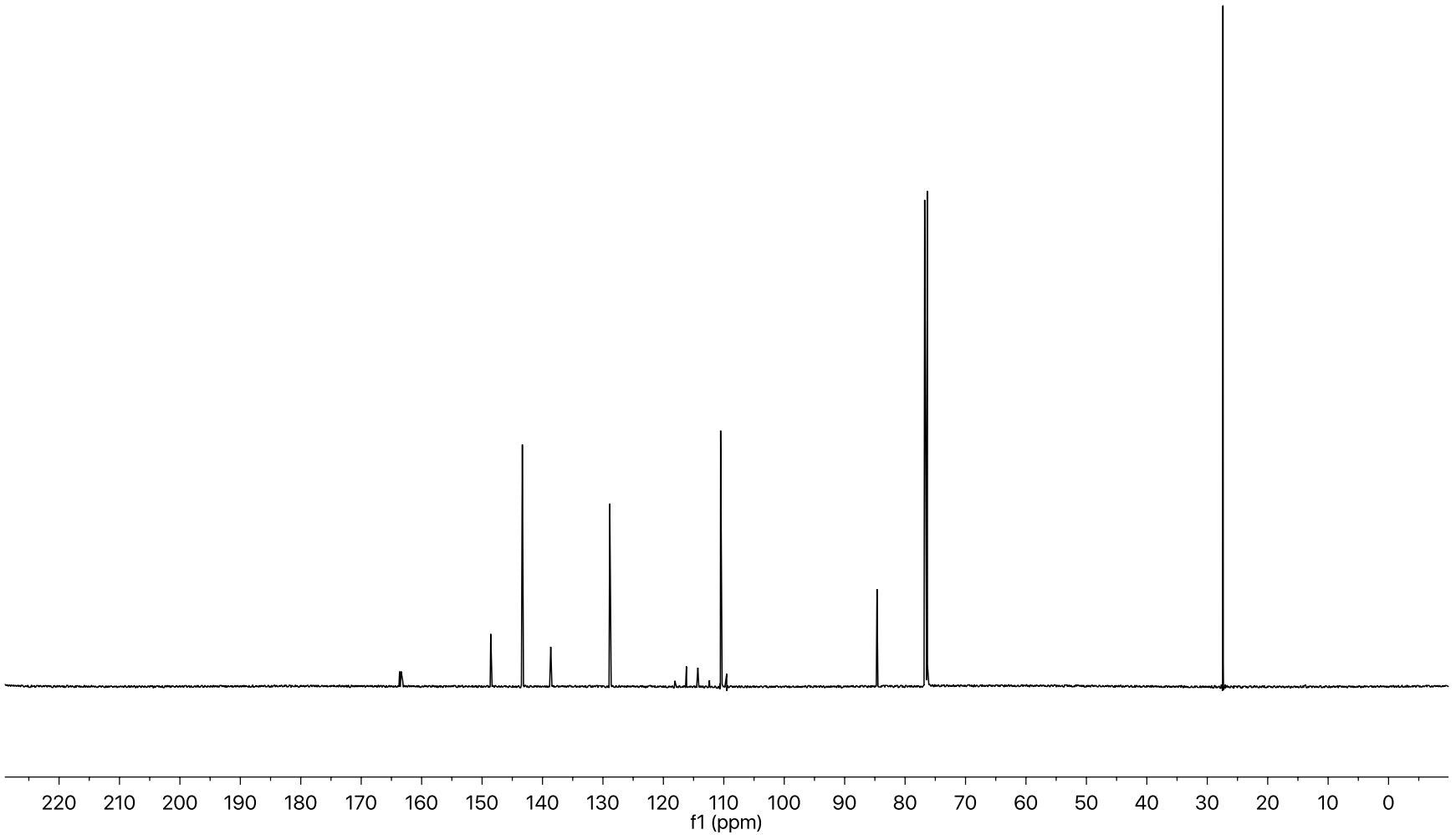
(in $CDCl_3$, 600 MHz)

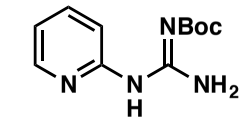

NBoc
NHTFA
N
N
26
(in acetone, 151 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



26

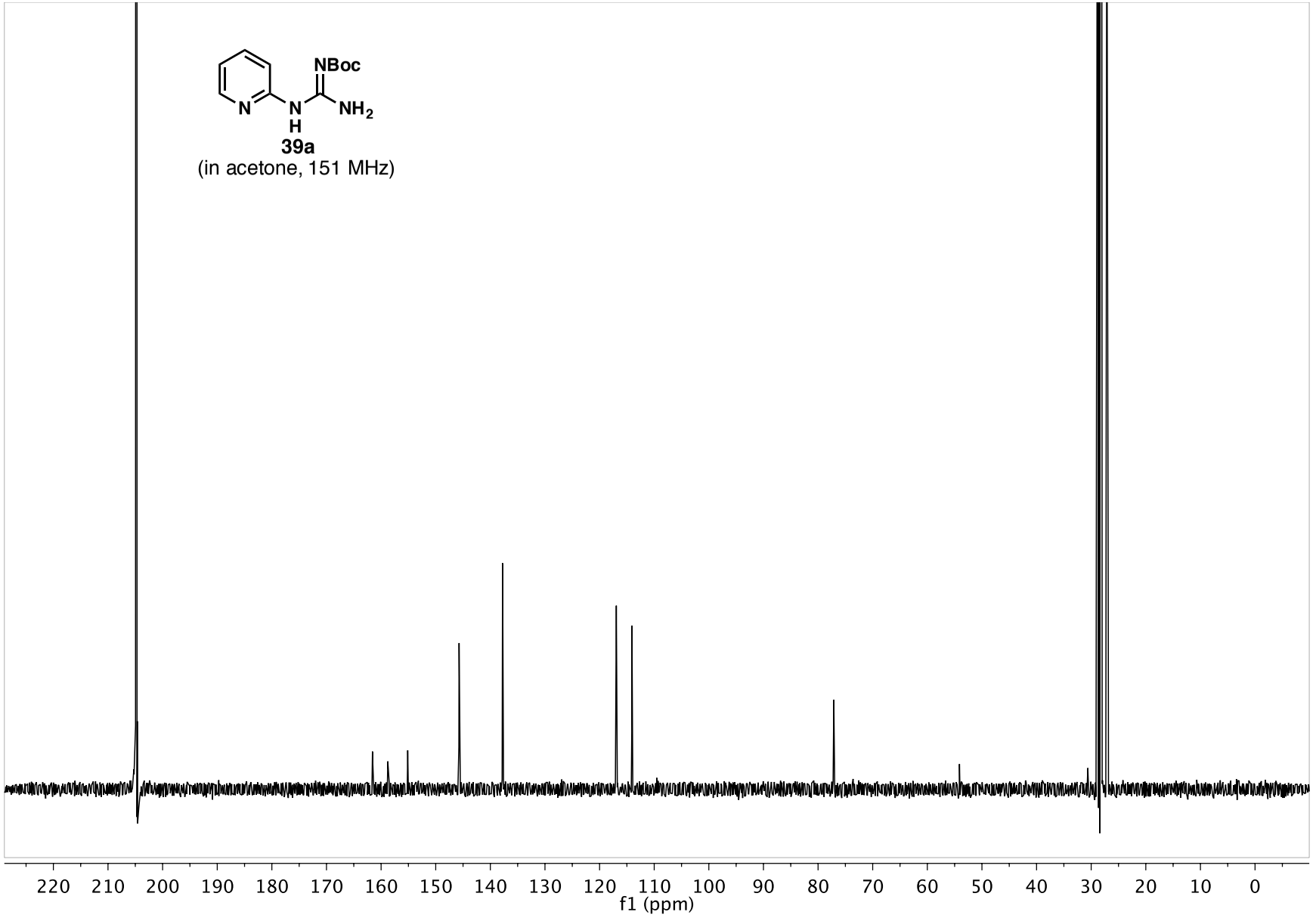
(in $CDCl_3$, 151 MHz)

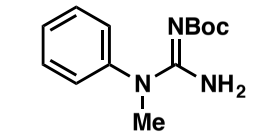




39a

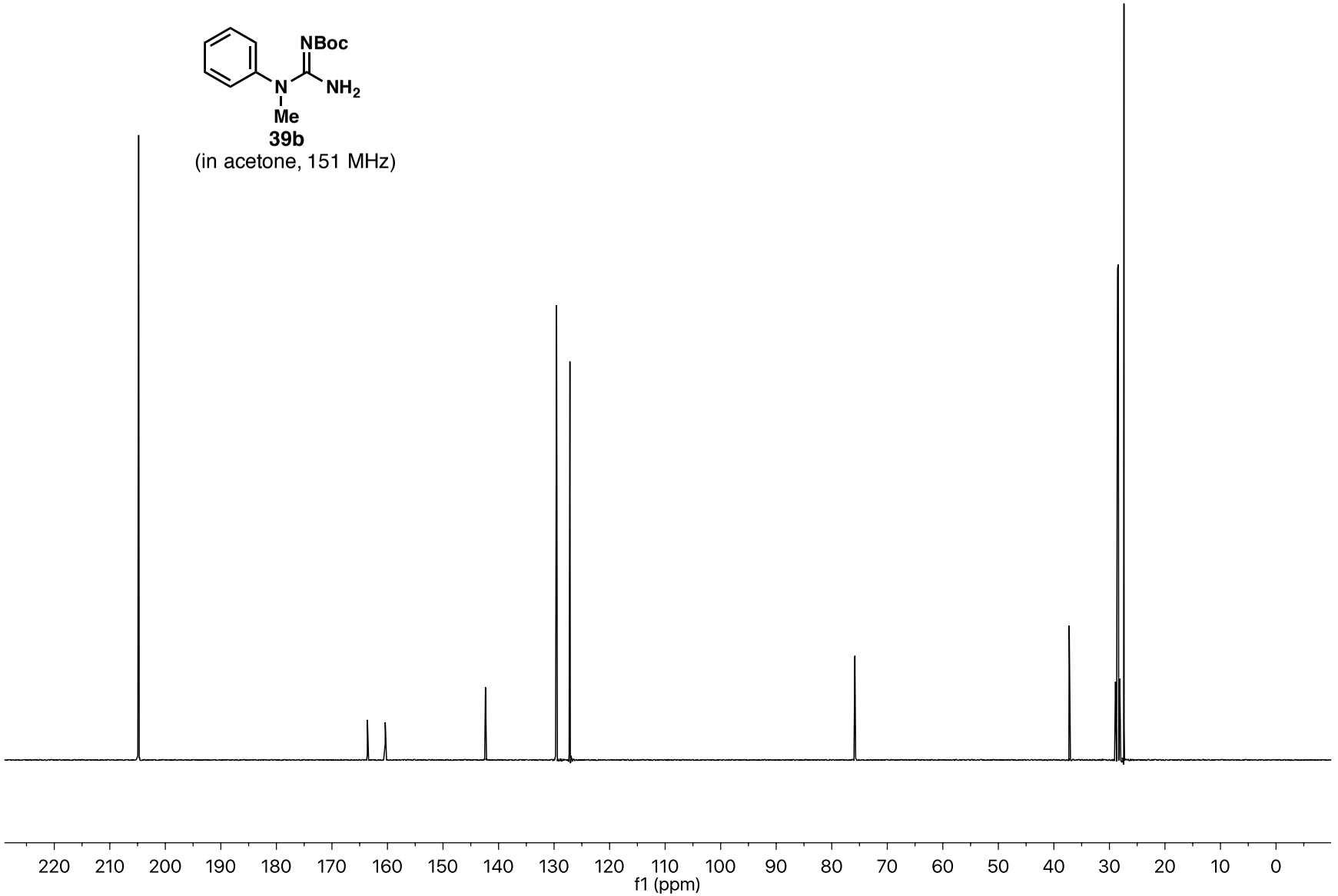
(in acetone, 600 MHz)

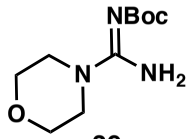

NBoc
N
N
H
NH2
39a
(in acetone, 151 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



39b

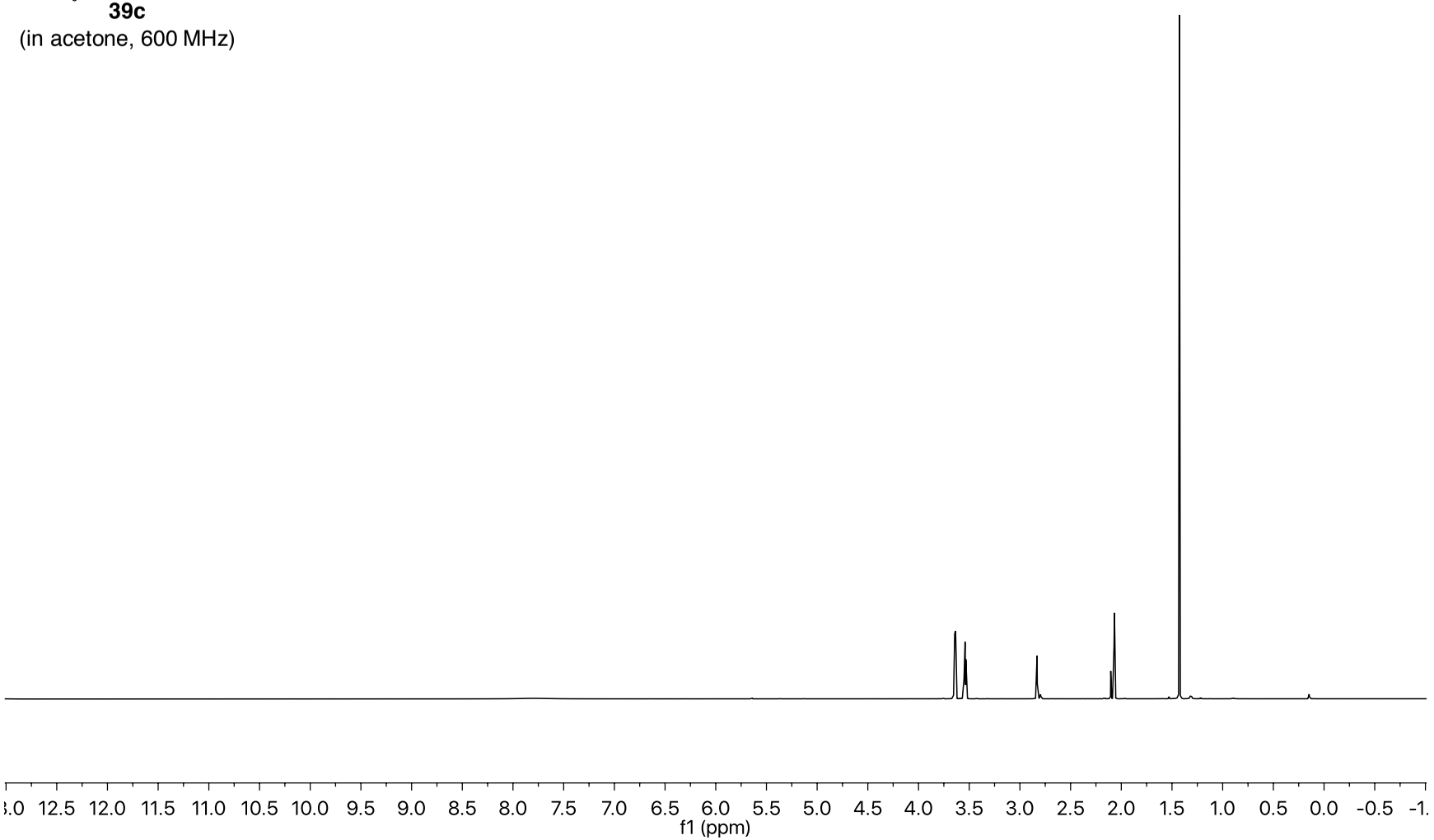
(in acetone, 151 MHz)

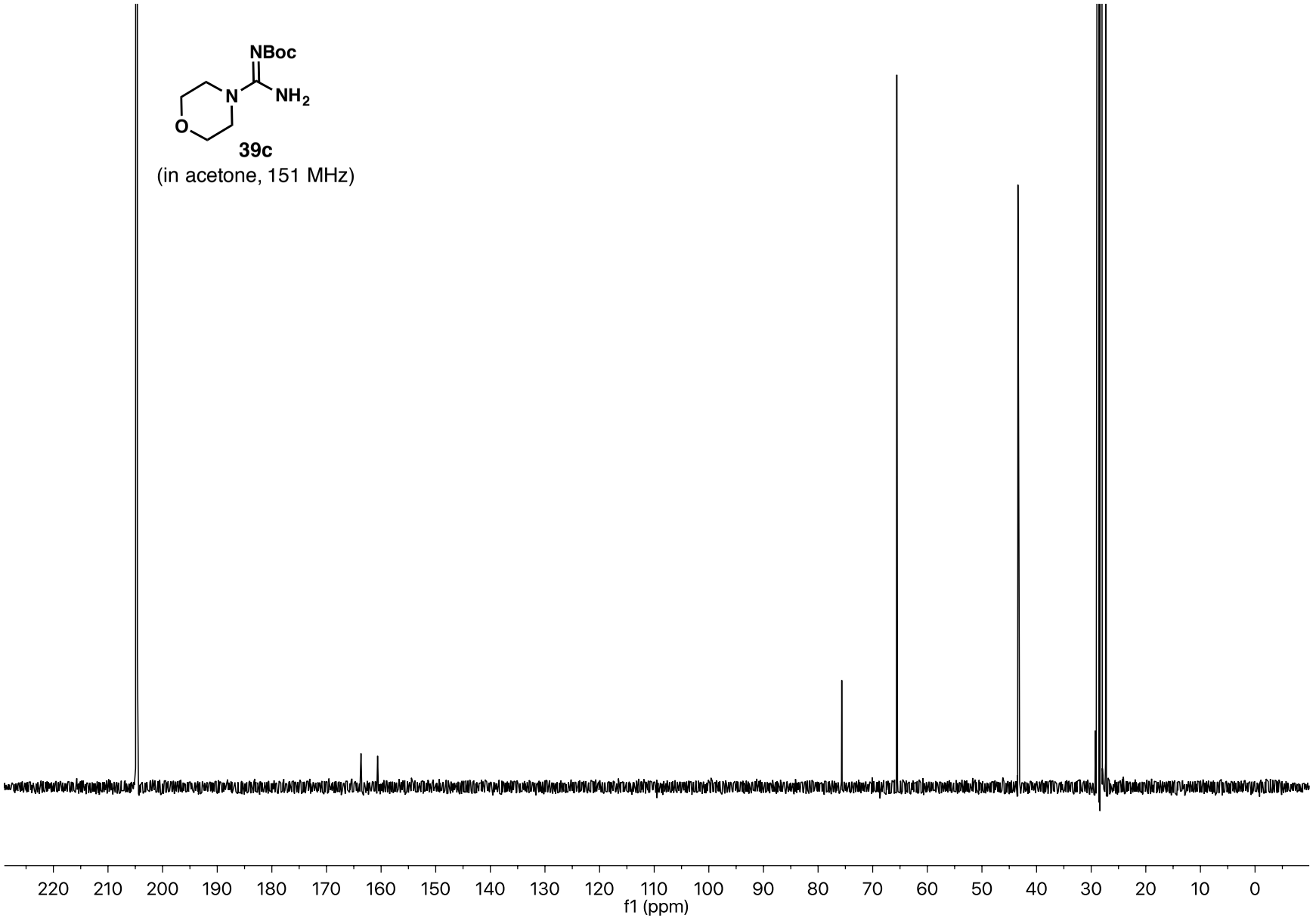

NBoc
N
NH2
Me
39b
(in acetone, 151 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

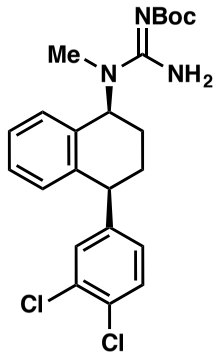


39c

(in acetone, 600 MHz)

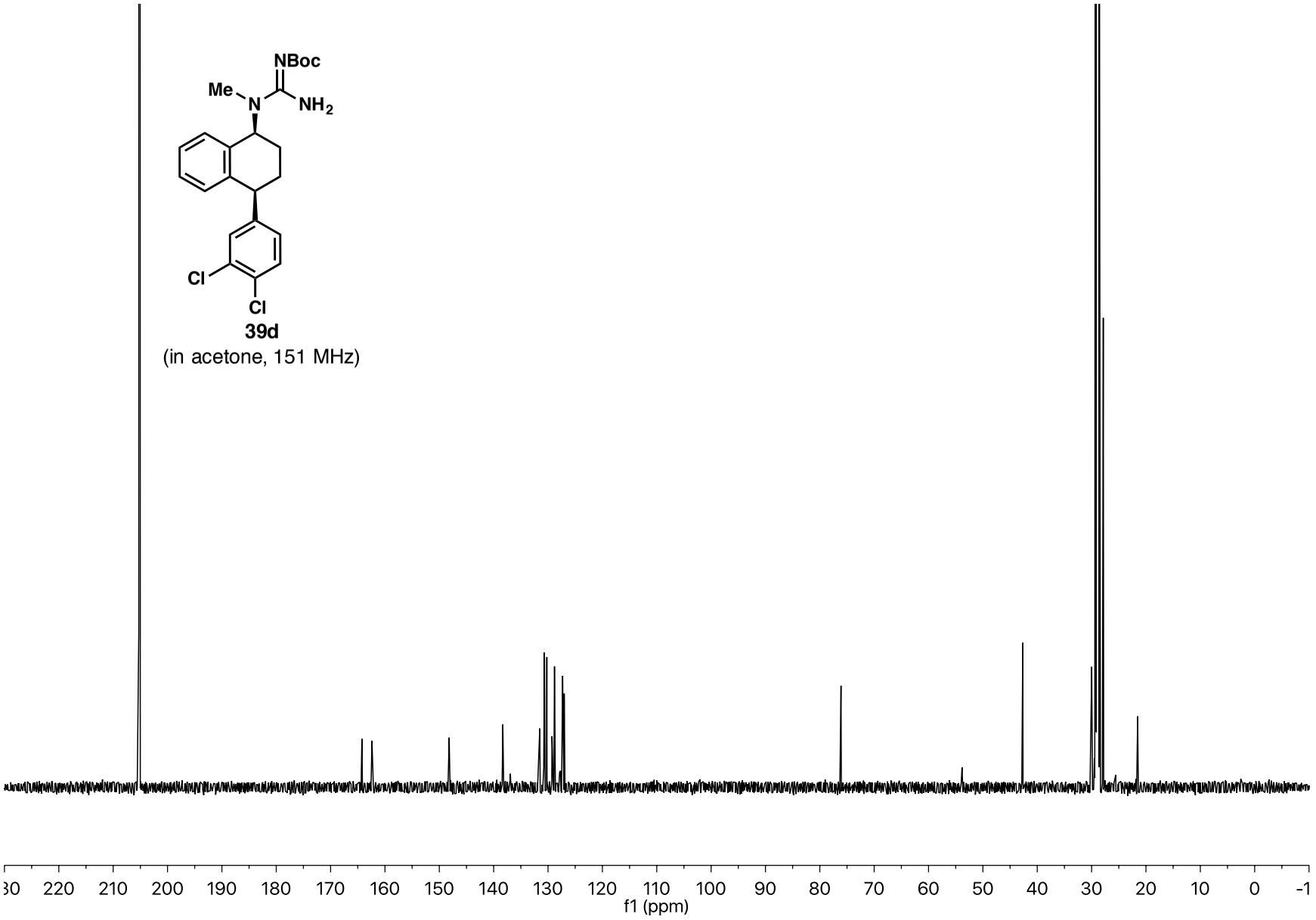


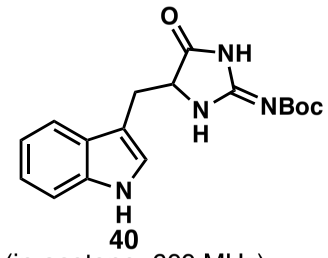

NBoc
N
NH2
O
39c
(in acetone, 151 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



39d

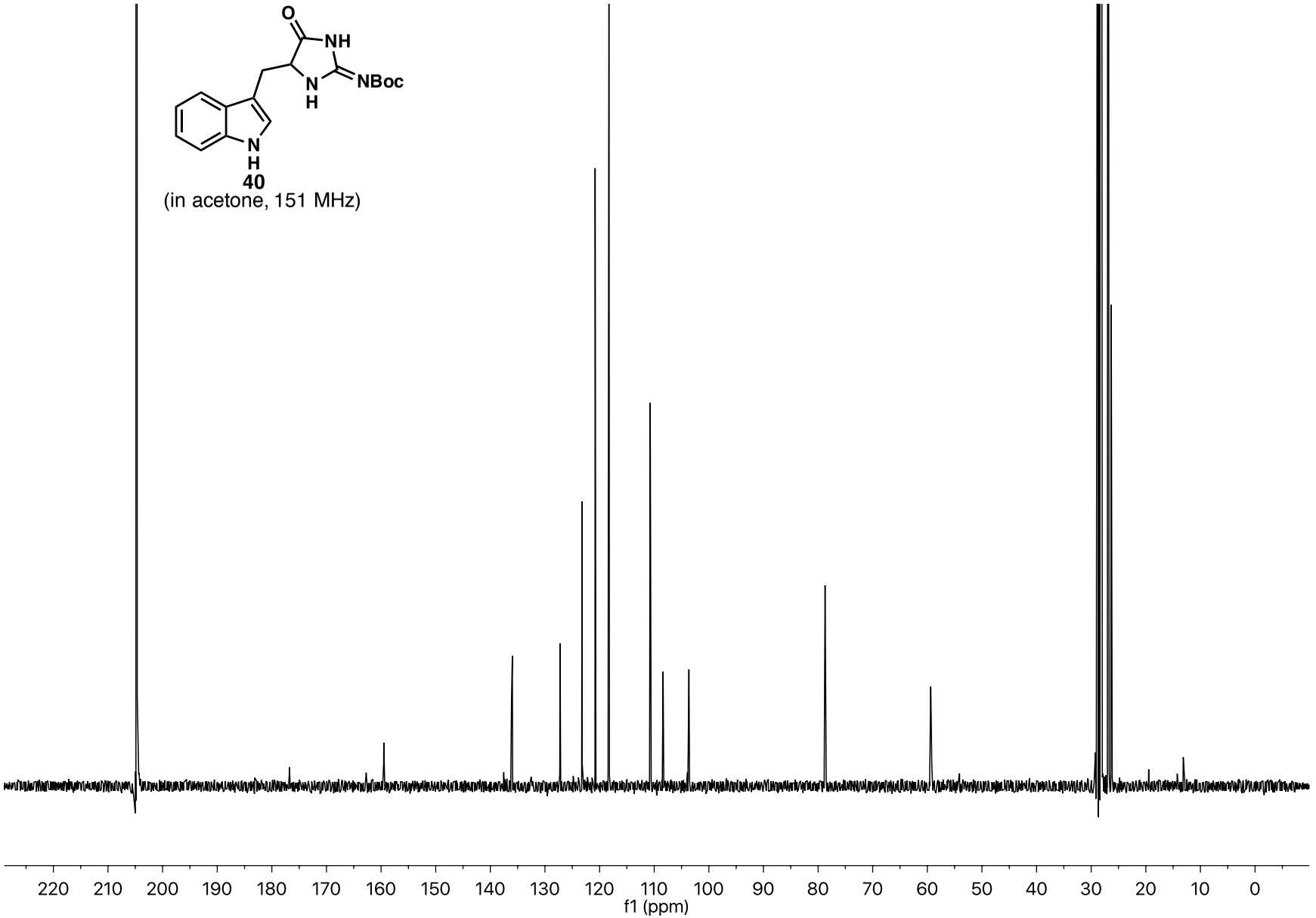
(in acetone, 600 MHz)

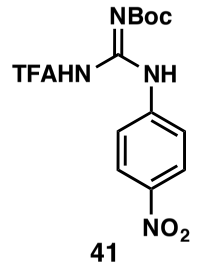

NBoc
Me
N
NH2
Cl
Cl
39d
(in acetone, 151 MHz)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



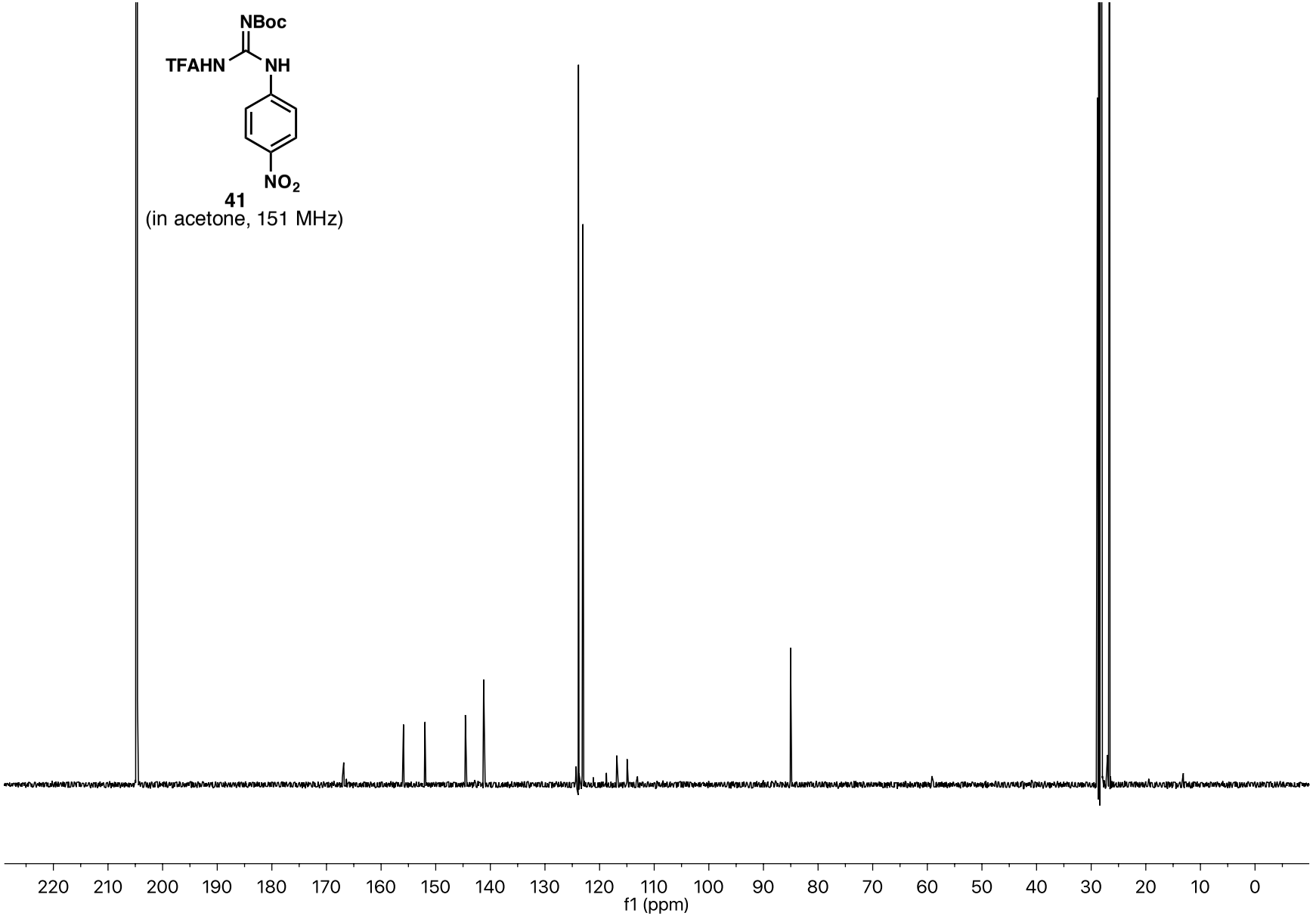
40

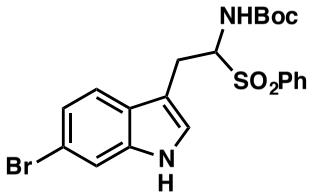
(in acetone, 600 MHz)


O
NH
N
H
NBoc
N
H
40
(in acetone, 151 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

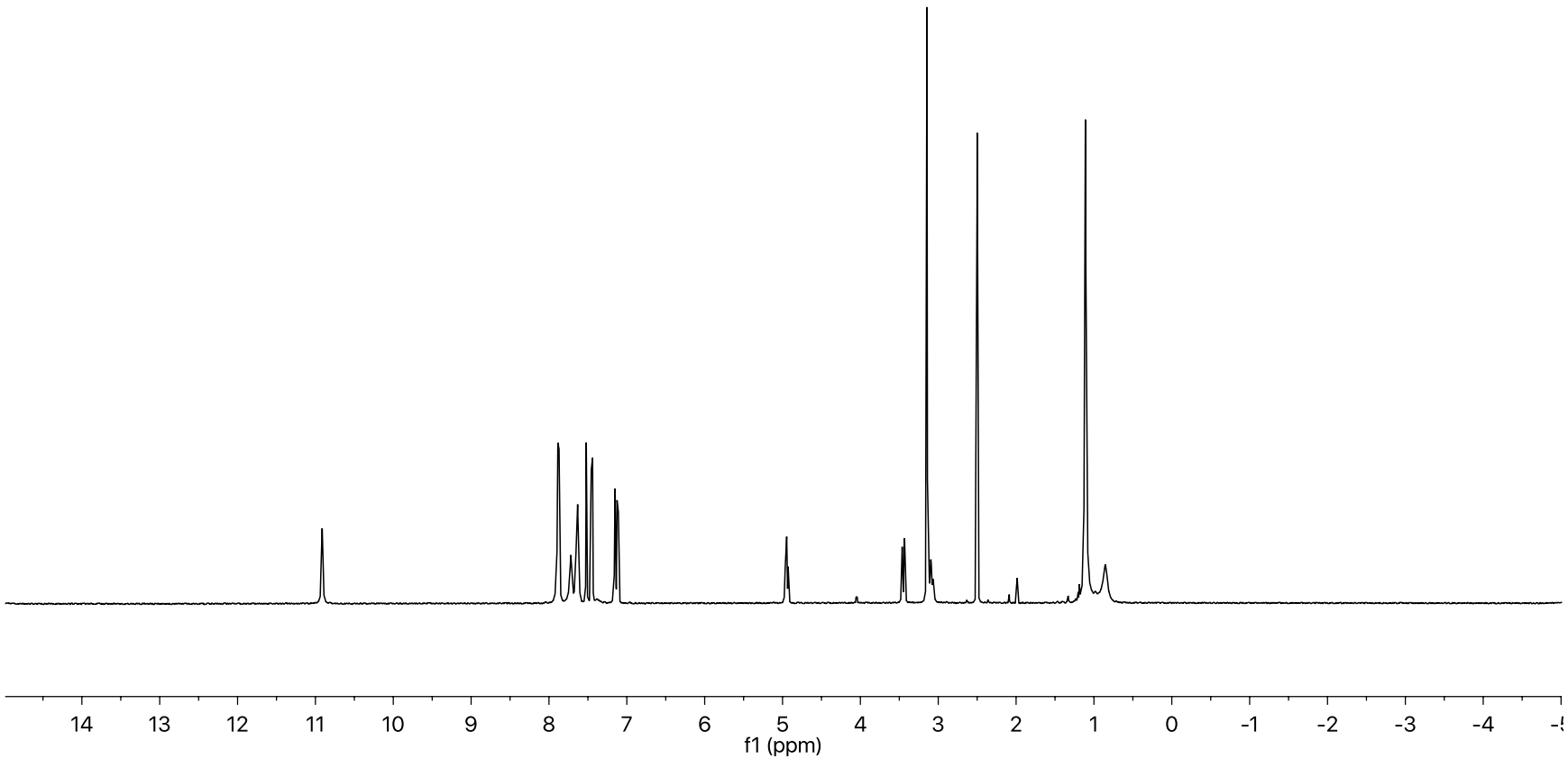


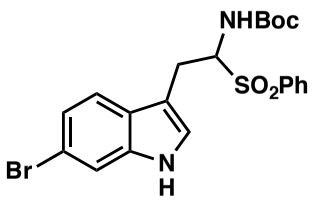
41
(in acetone, 600 MHz)


NBoc
TFAHN
NH
NO2
41
(in acetone, 151 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

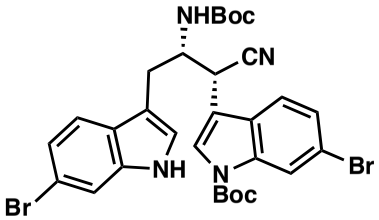


18
(in DMSO-d6, 500 MHz, 60°C)

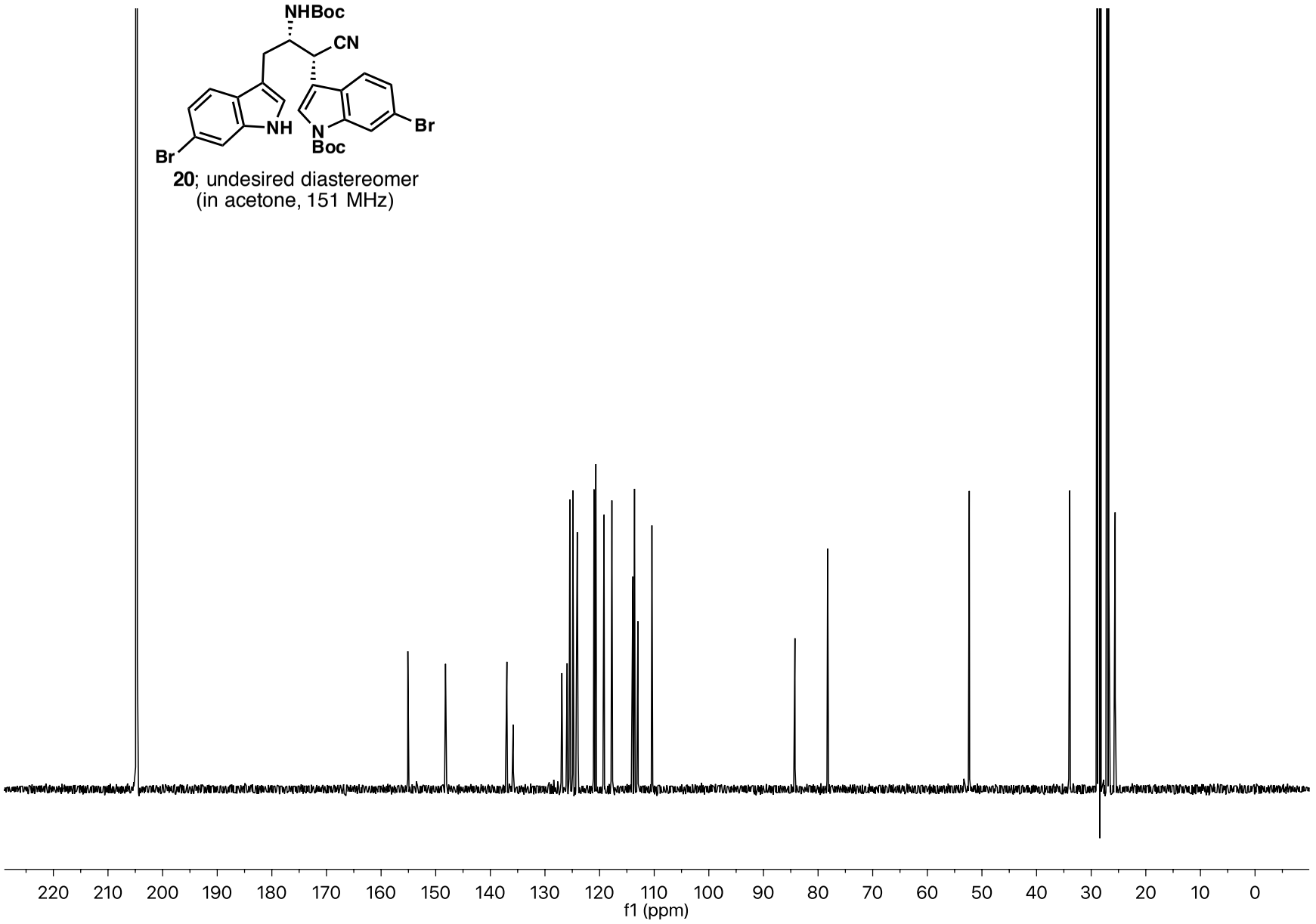




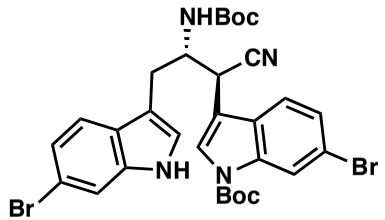
18
(in DMSO-d6, 151 MHz, 60°C)



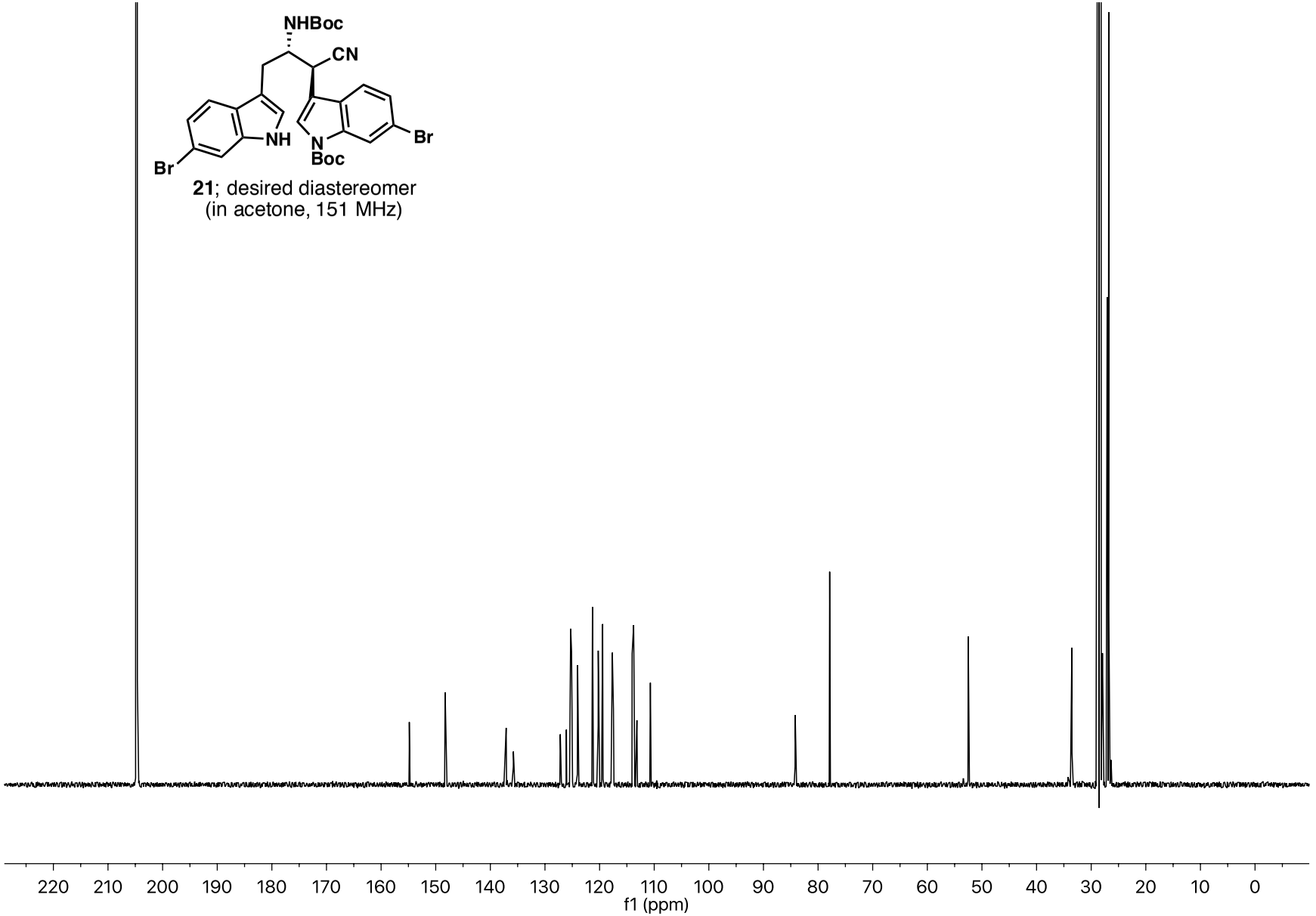
20; undesired diastereomer
(in acetone, 600 MHz)



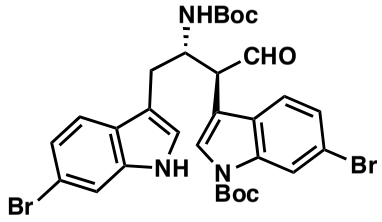
20; undesired diastereomer
(in acetone, 151 MHz)



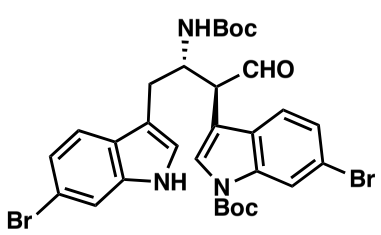
21; desired diastereomer
(in acetone, 600 MHz)



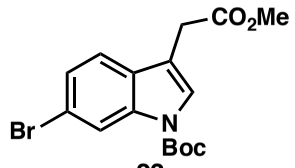
21; desired diastereomer
(in acetone, 151 MHz)



22
(in acetone, 600 MHz)

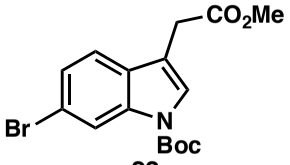


22
(in acetone, 151 MHz)



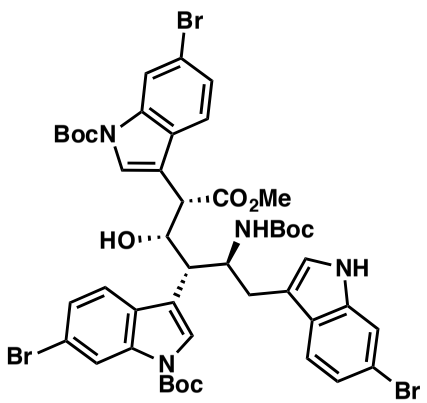
23

(in acetone, 600 MHz)

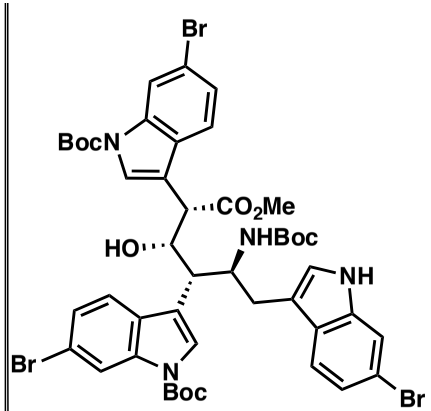


23

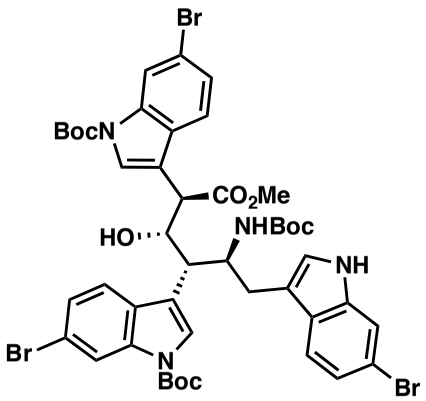
(in acetone, 151 MHz)



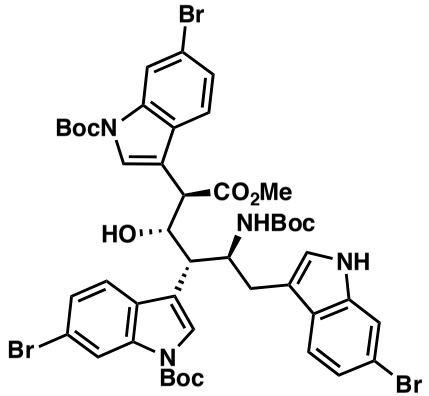
24; desired diastereomer
(in acetone, 600 MHz)



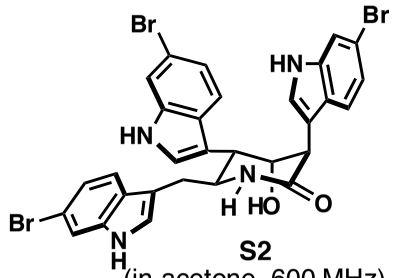
24; desired diastereomer
(in acetone, 151 MHz)



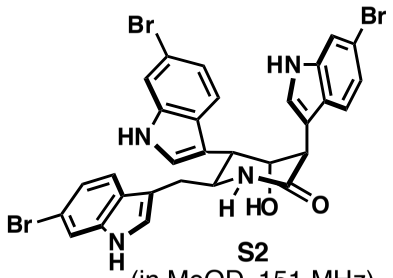
SI; undesired diastereomer
(in acetone, 600 MHz)



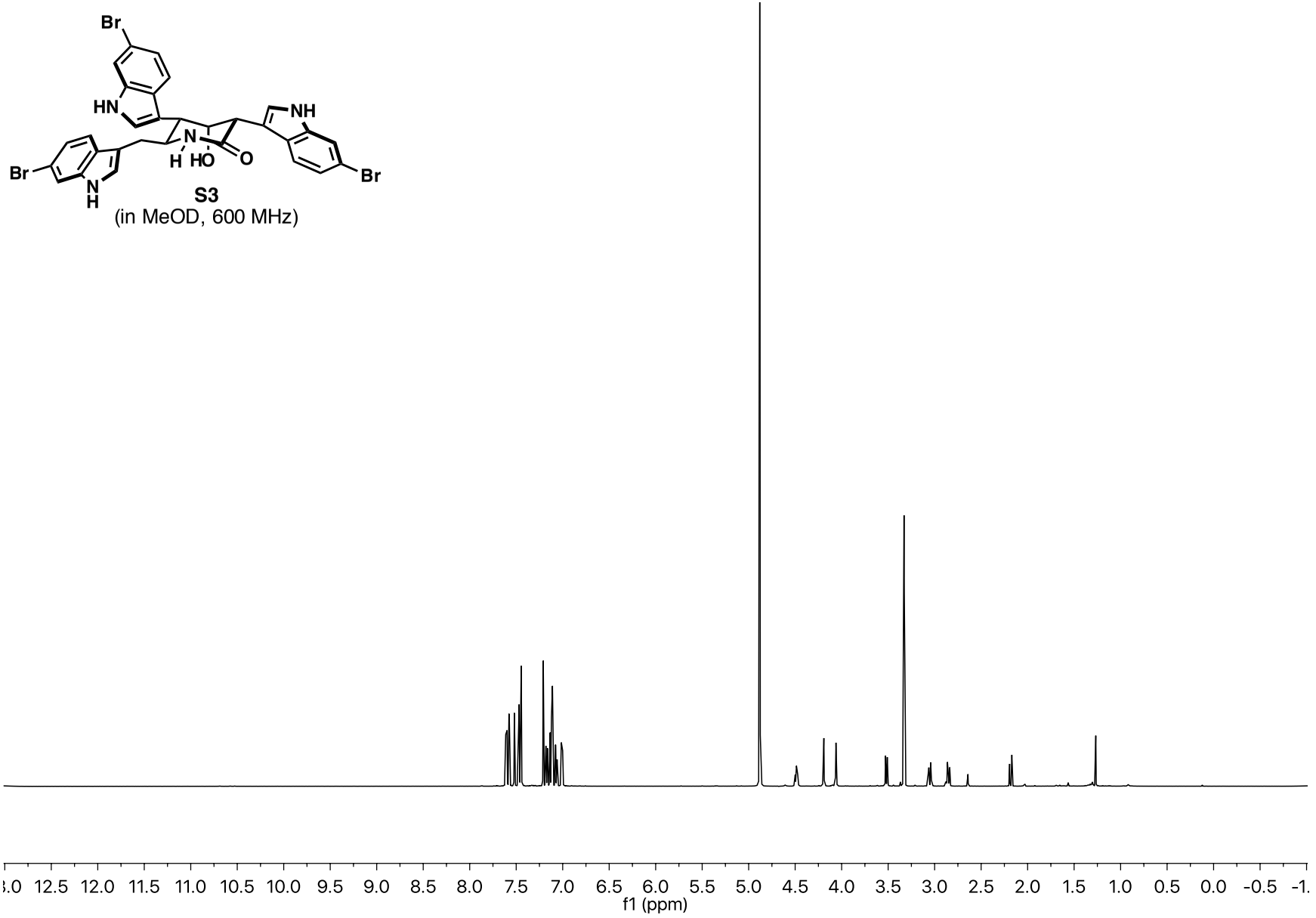
SI; undesired diastereomer
(in acetone, 151 MHz)

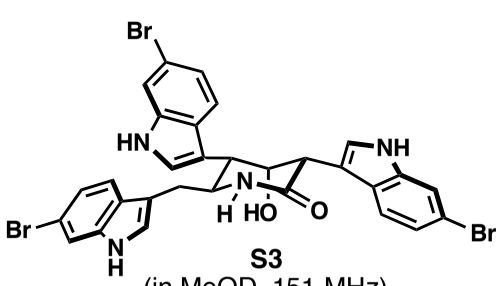


S2
(in acetone, 600 MHz)

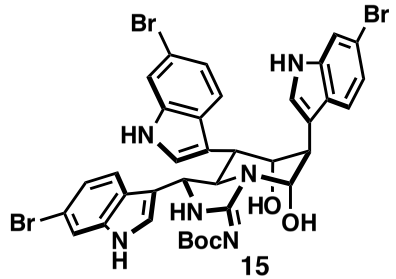


S2
(in MeOD, 151 MHz)


Br
HN
NH
N
H HO
O
Br
Br
N
H
S3
(in MeOD, 600 MHz)
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

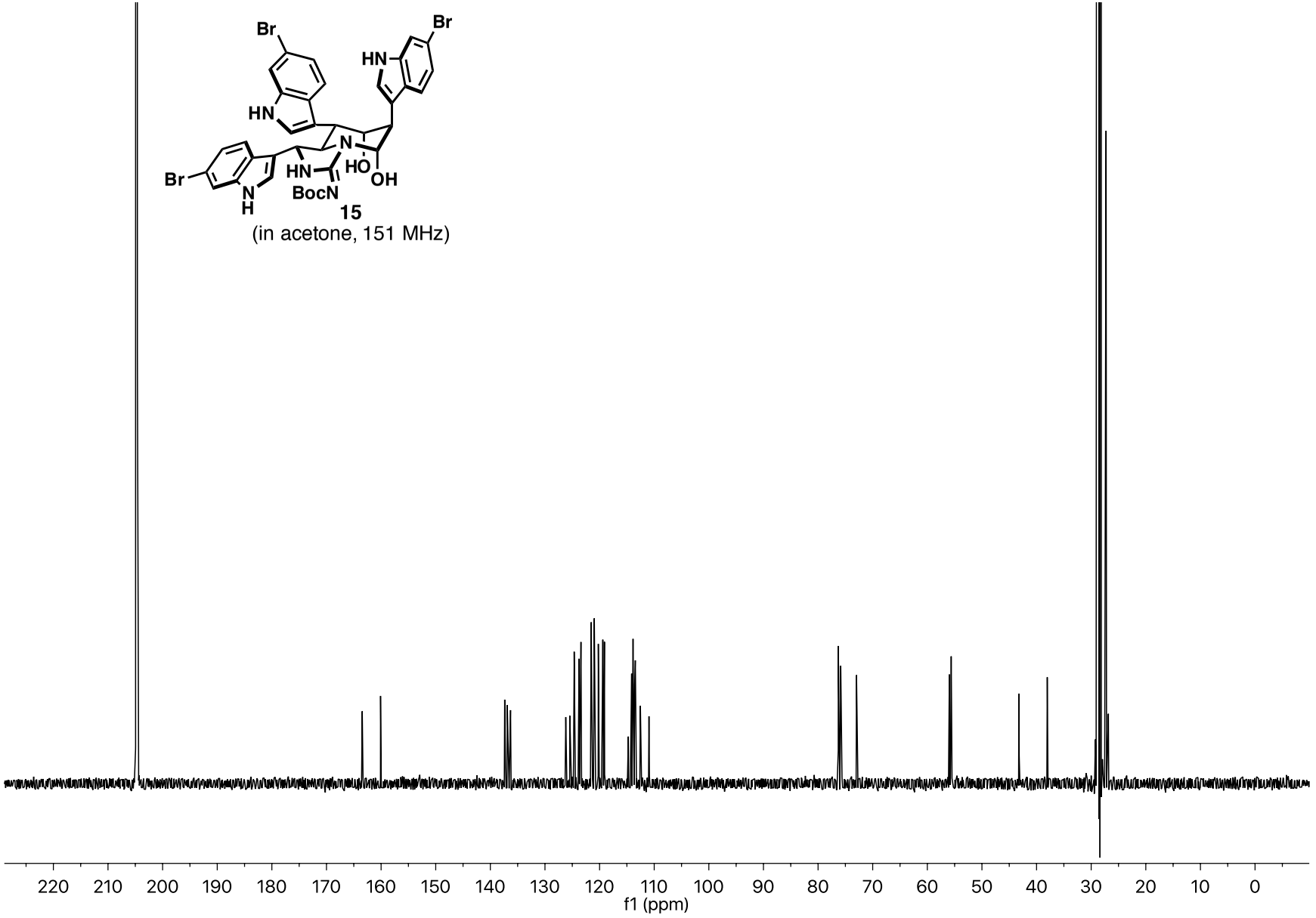


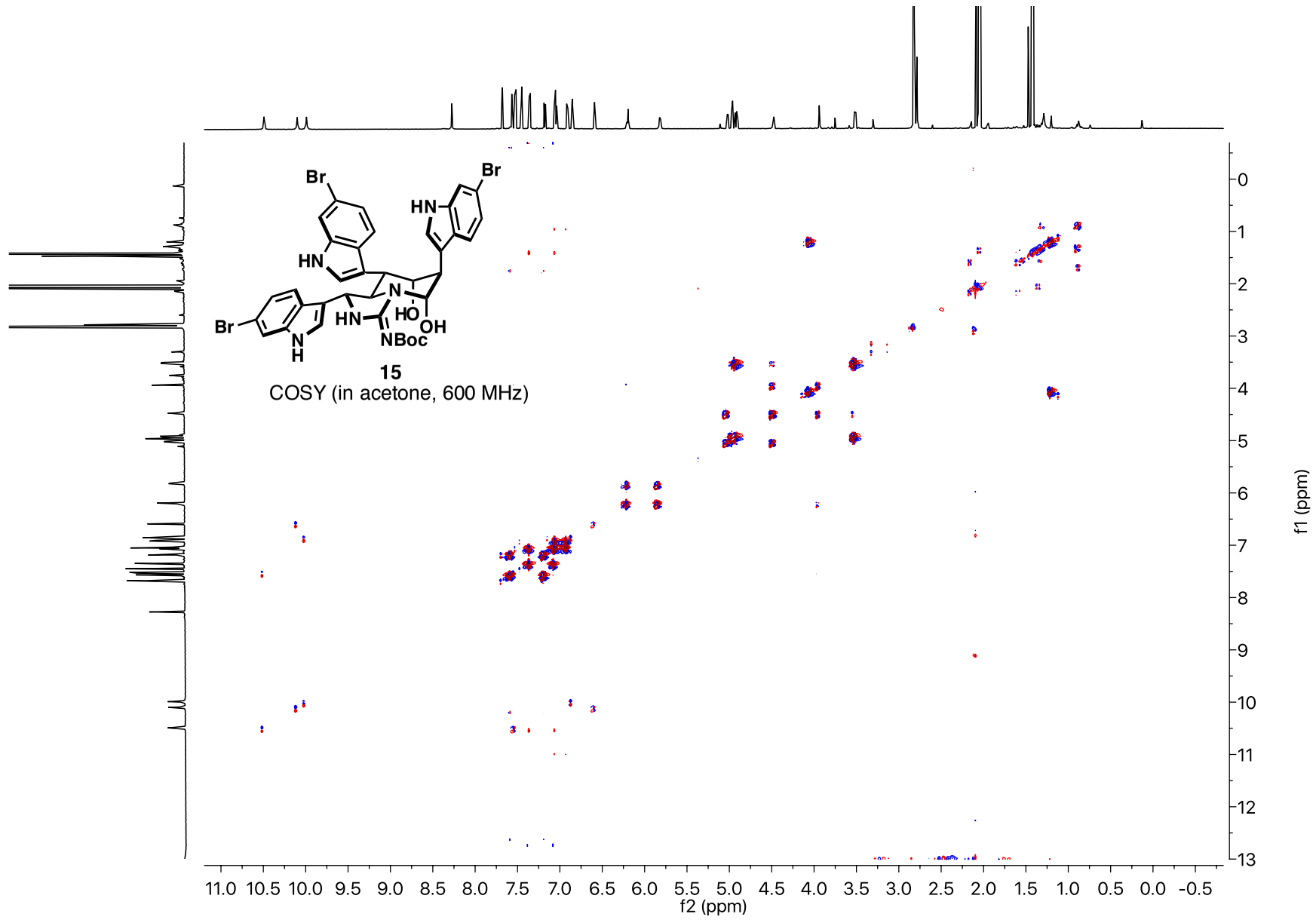
S3
(in MeOD, 151 MHz)

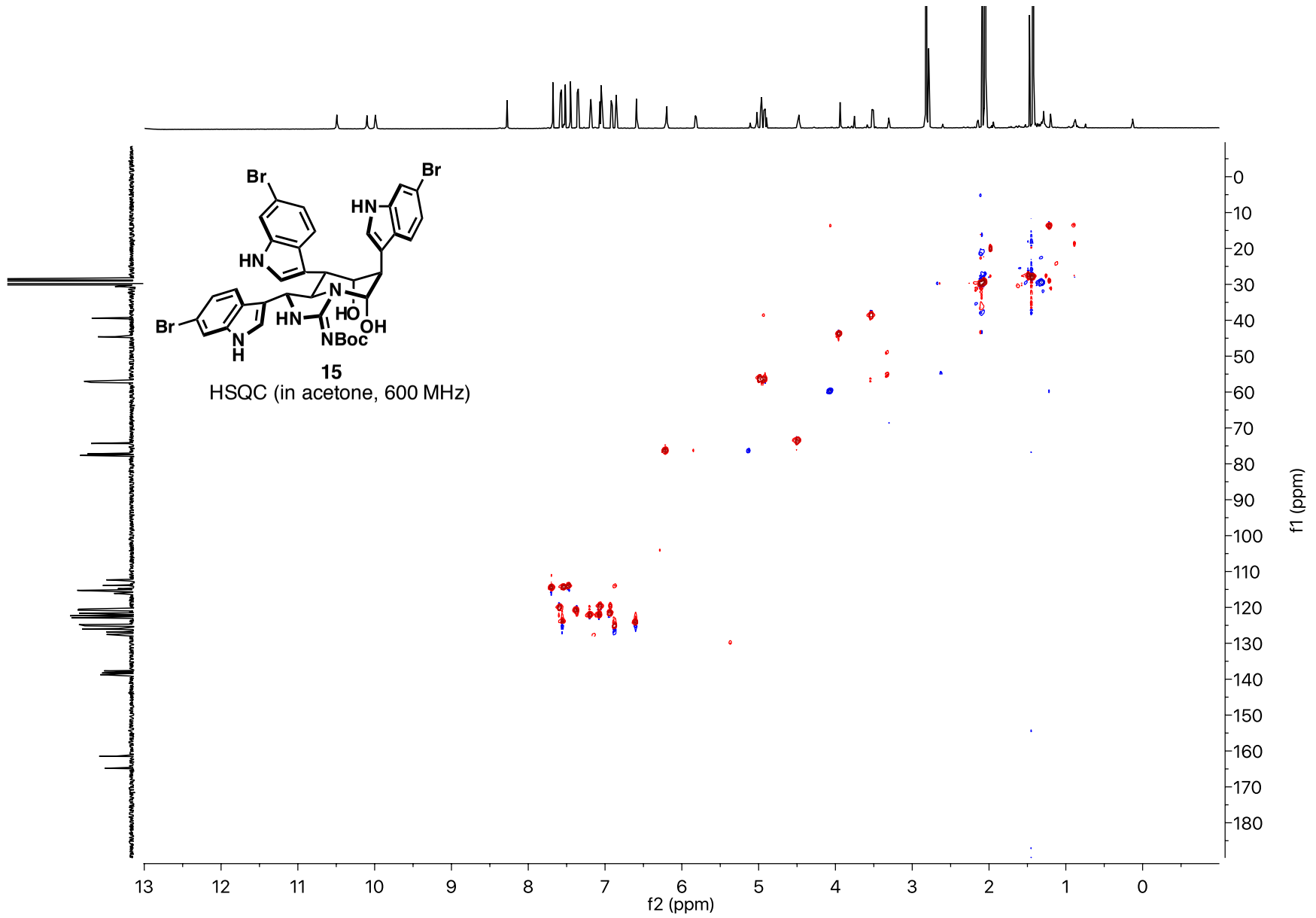


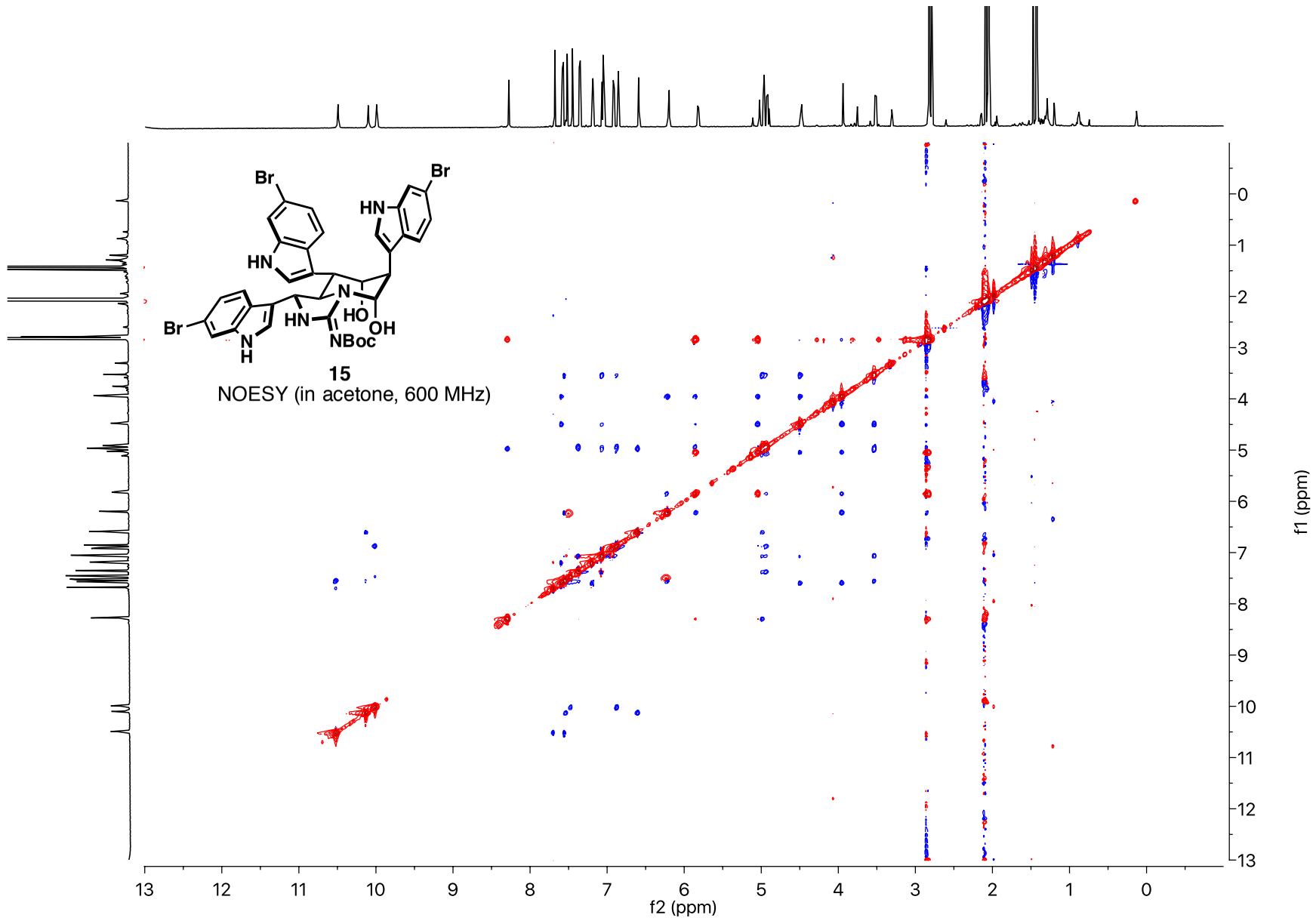
15

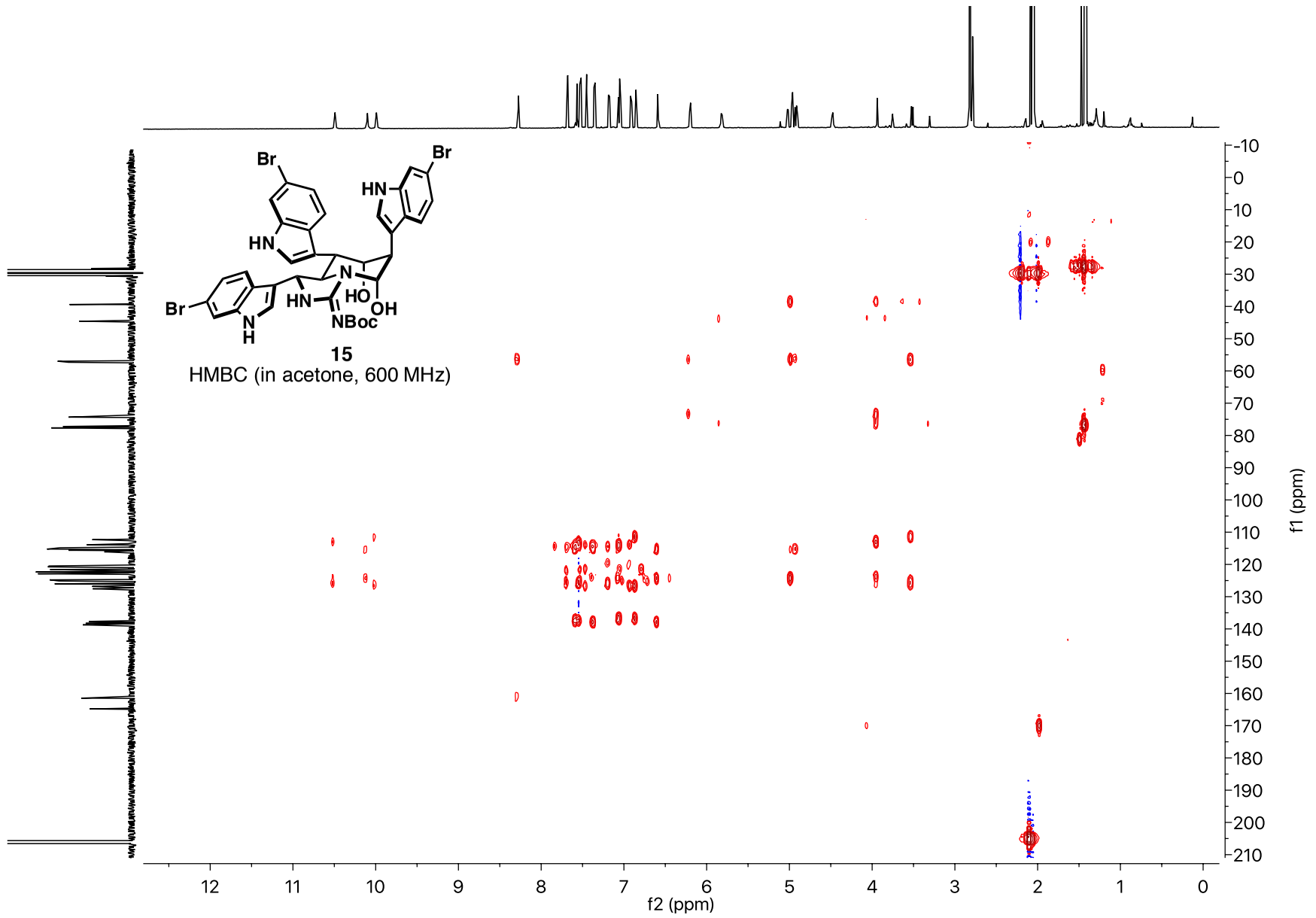
(in acetone, 600 MHz)

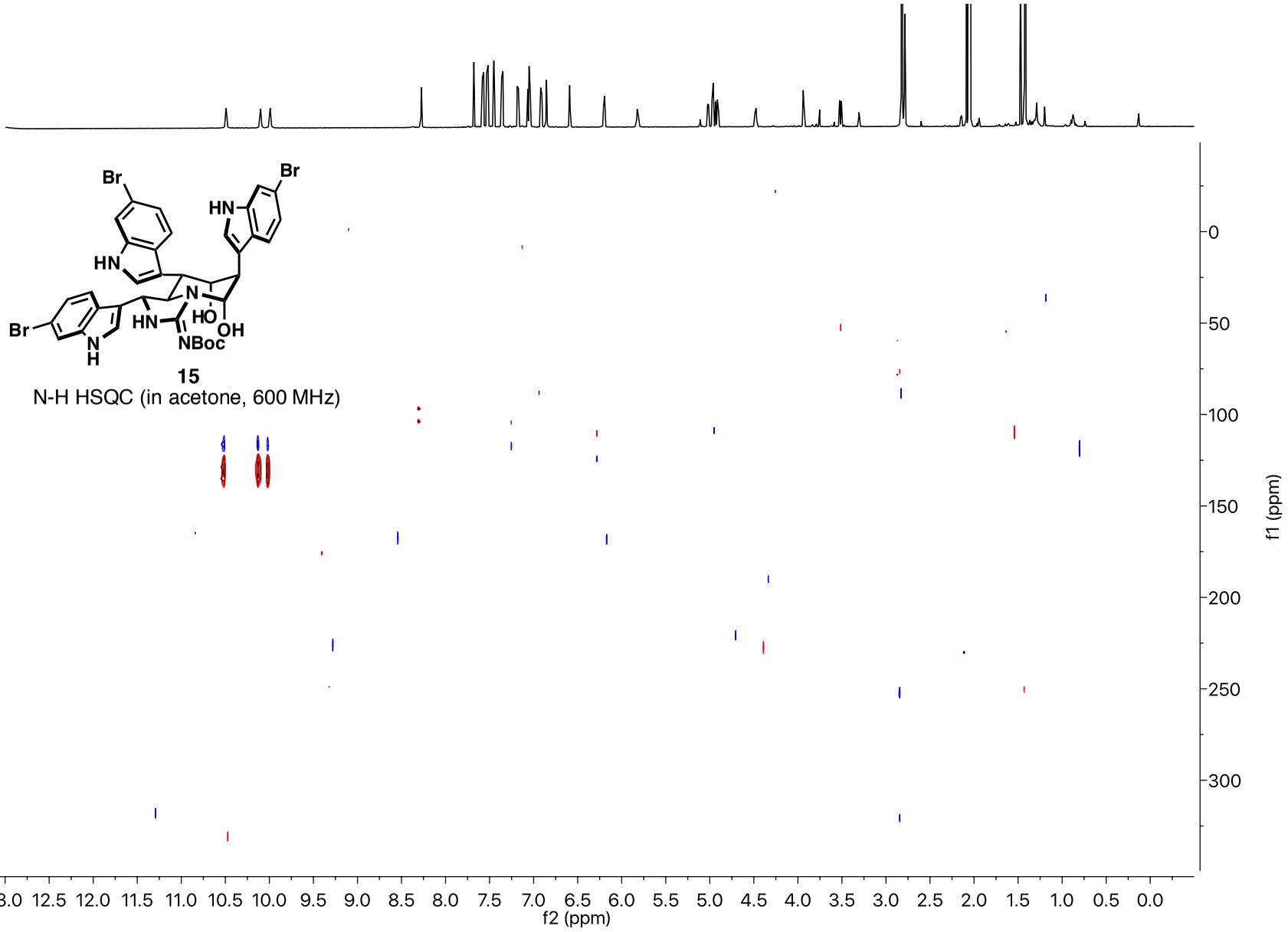

Br
HN
Br
HN
N
HO
OH
HN
BocN
Br
N
H
15
(in acetone, 151 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

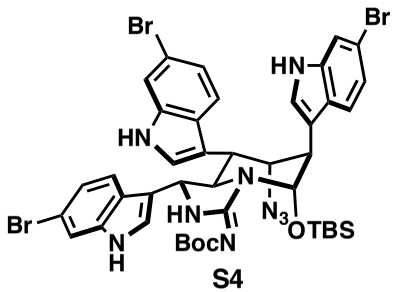

Br
HN
Br
HN
N
HO
OH
HN
NBoc
Br
N
H
15
COSY (in acetone, 600 MHz)
f2 (ppm)
f1 (ppm)


Br
HN
Br
HN
N
HO
OH
HN
NBoc
Br
N
H
15
HSQC (in acetone, 600 MHz)
f2 (ppm)
f1 (ppm)


Br
HN
Br
HN
N
HO
OH
HN
NBoc
Br
N
H
15
NOESY (in acetone, 600 MHz)
f2 (ppm)
f1 (ppm)

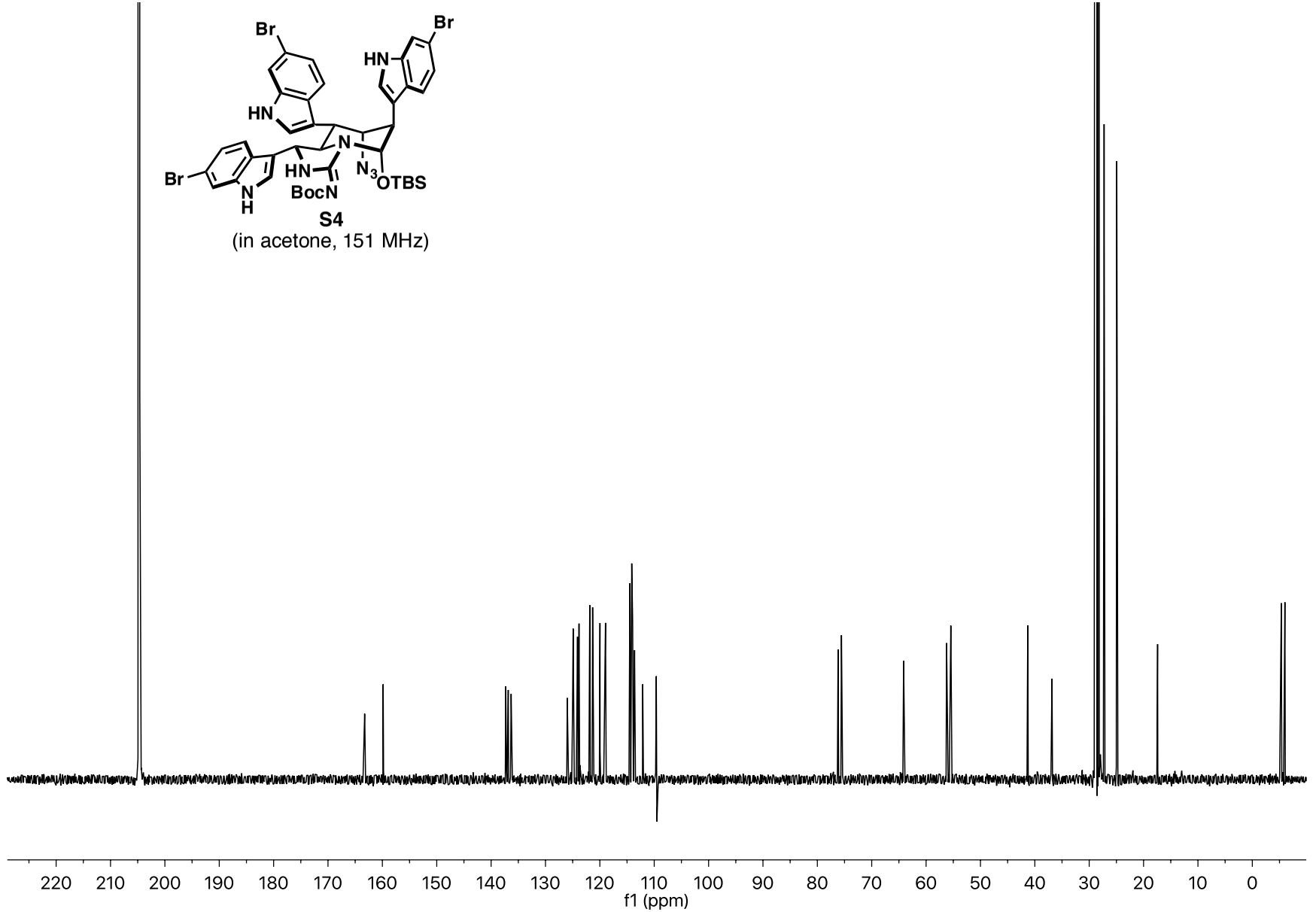

Br
HN
Br
HN
N
HO
OH
HN
NBoc
Br
N
H
15
HMBC (in acetone, 600 MHz)
f2 (ppm)
f1 (ppm)

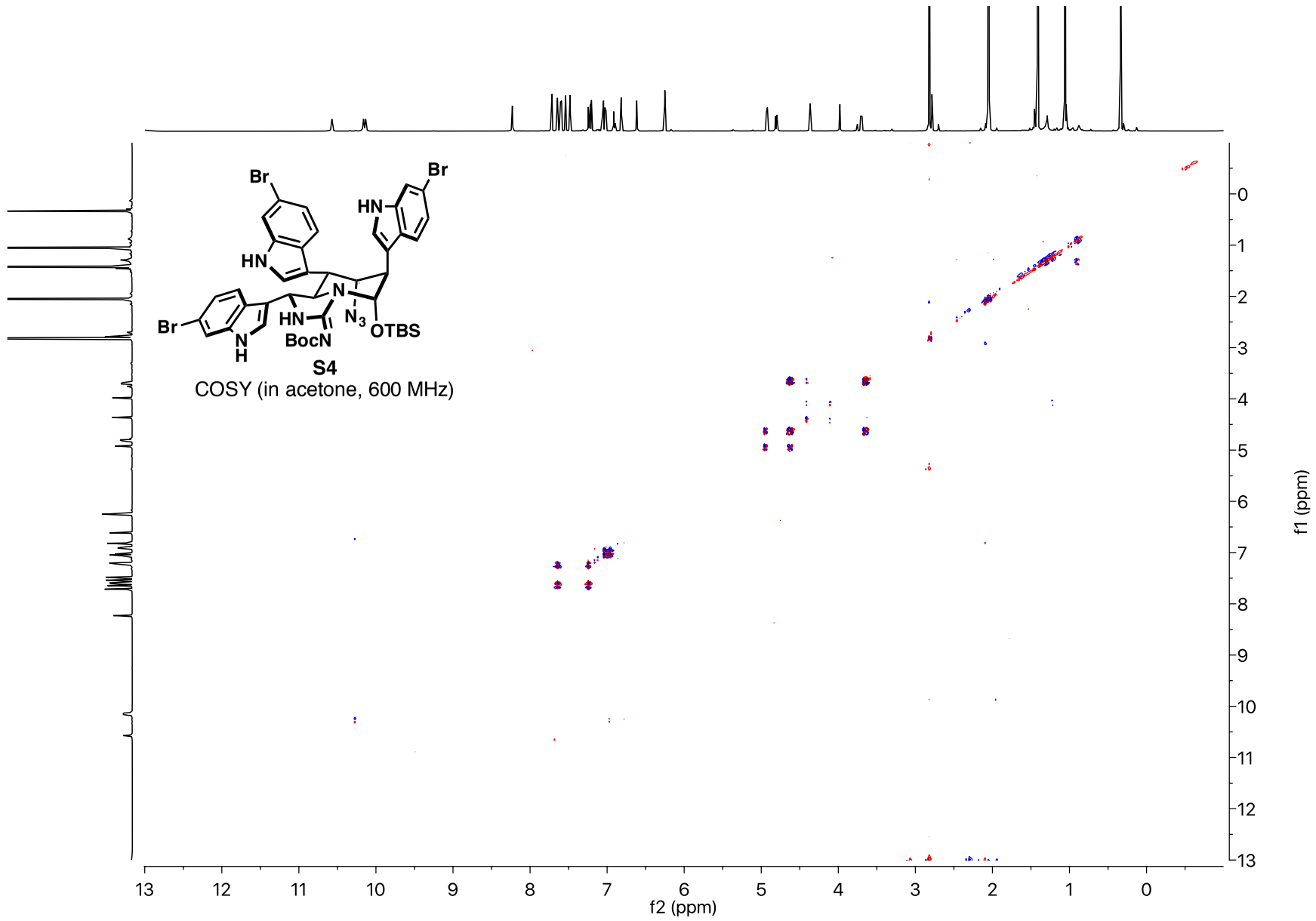

Br
HN
Br
HN
N
HN
HO
OH
Br
N
H
NBoc
15
N-H HSQC (in acetone, 600 MHz)
0
50
100
150
200
250
300
f1 (ppm)
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)

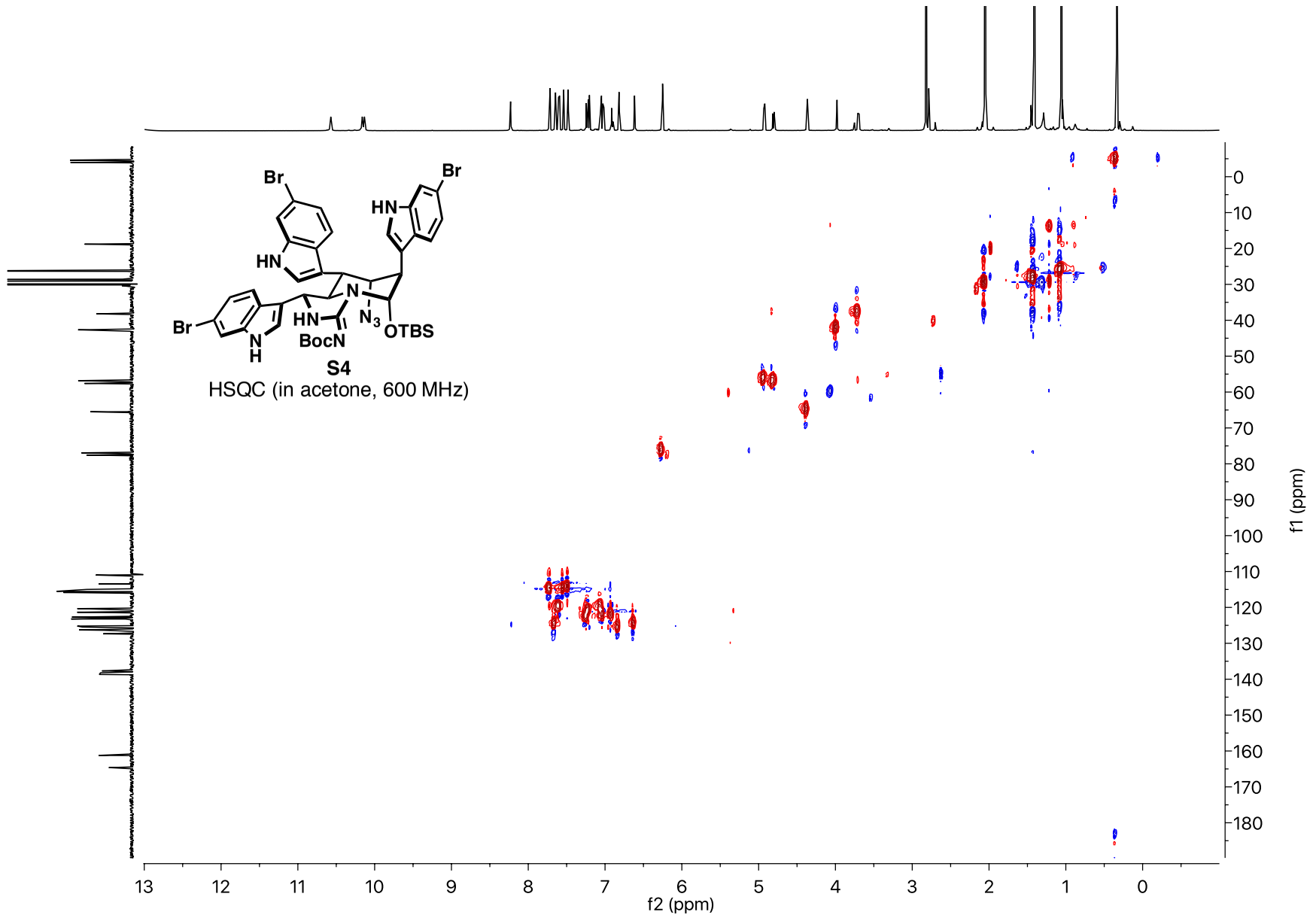


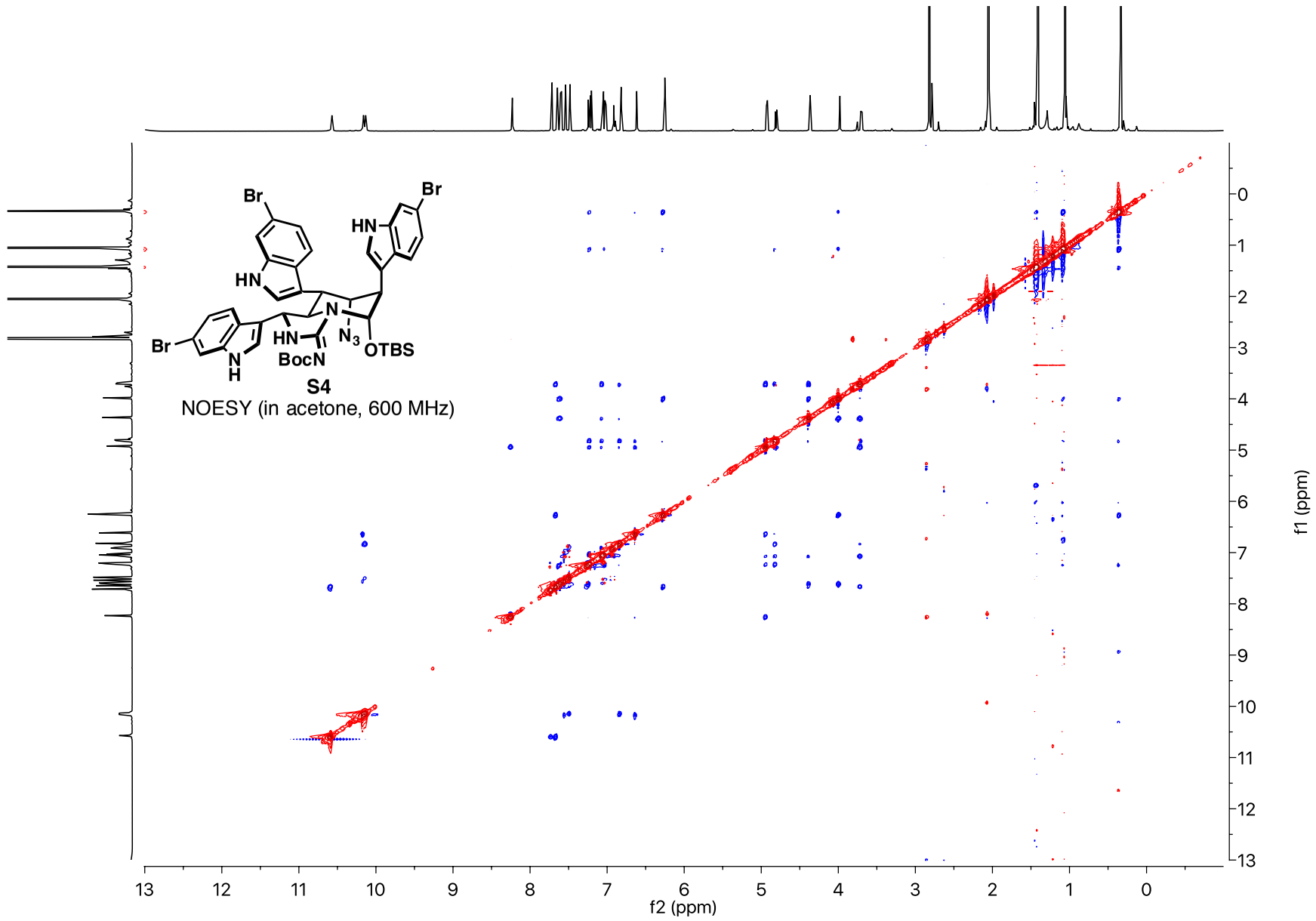
S4

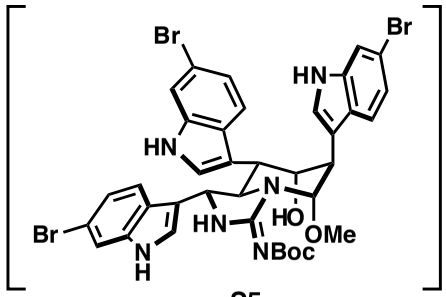
(in acetone, 600 MHz)


Br
HN
Br
HN
N
Br
HN
BocN
N3
OTBS
N
H
S4
(in acetone, 151 MHz)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

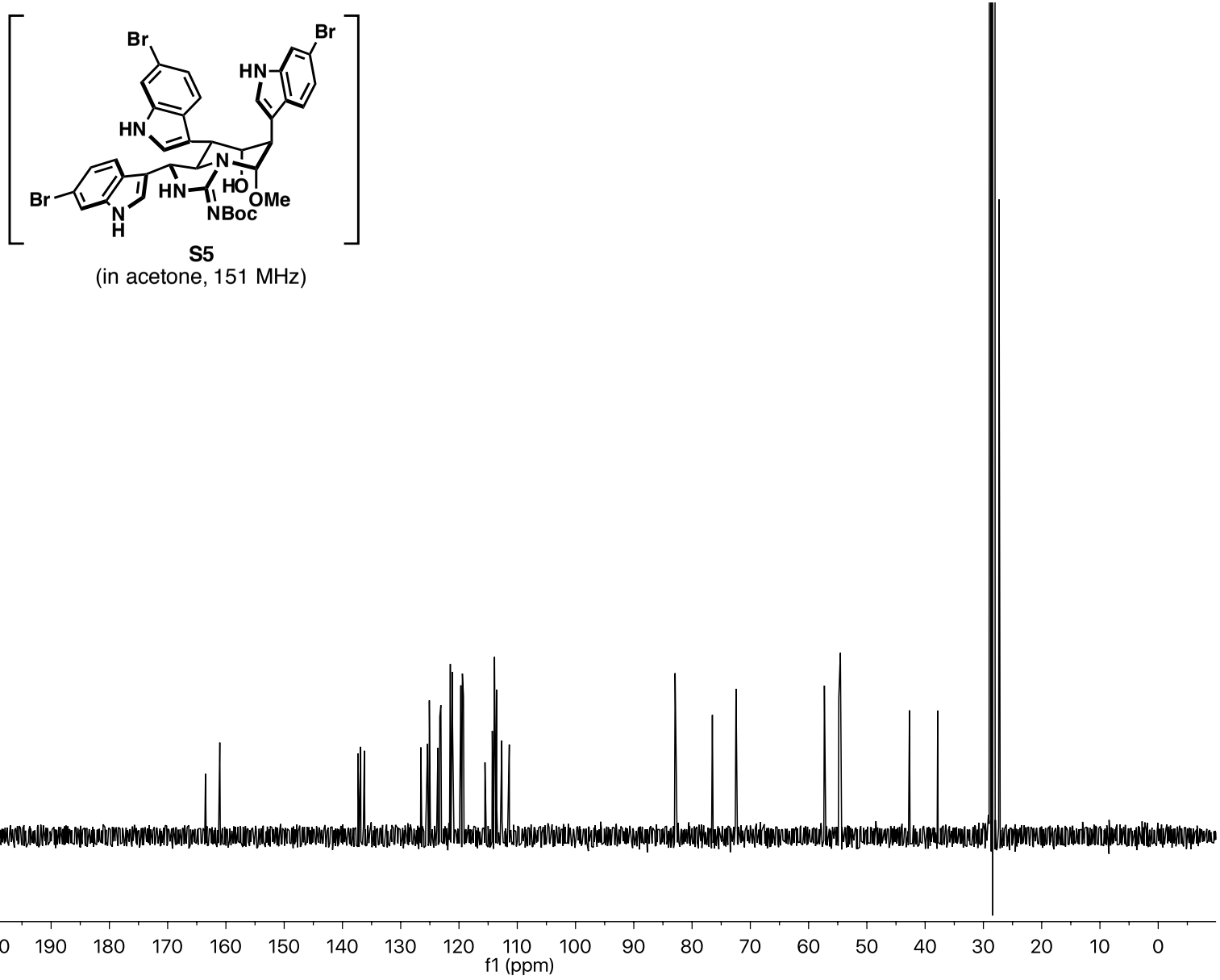

Br
HN
Br
HN
N
Br
N
H
HN
BocN
N3
OTBS
S4
COSY (in acetone, 600 MHz)
f2 (ppm)
f1 (ppm)


Br
HN
Br
HN
N
N3
HN
BocN
OTBS
Br
N
H
S4
HSQC (in acetone, 600 MHz)
f2 (ppm)
f1 (ppm)

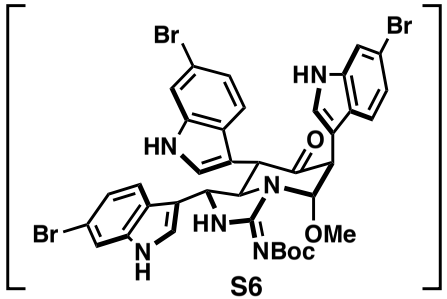

Br
HN
Br
HN
N
Br
HN
BocN
N3
OTBS
N
H
S4
NOESY (in acetone, 600 MHz)
f2 (ppm)
f1 (ppm)



S5
(in acetone, 600 MHz)

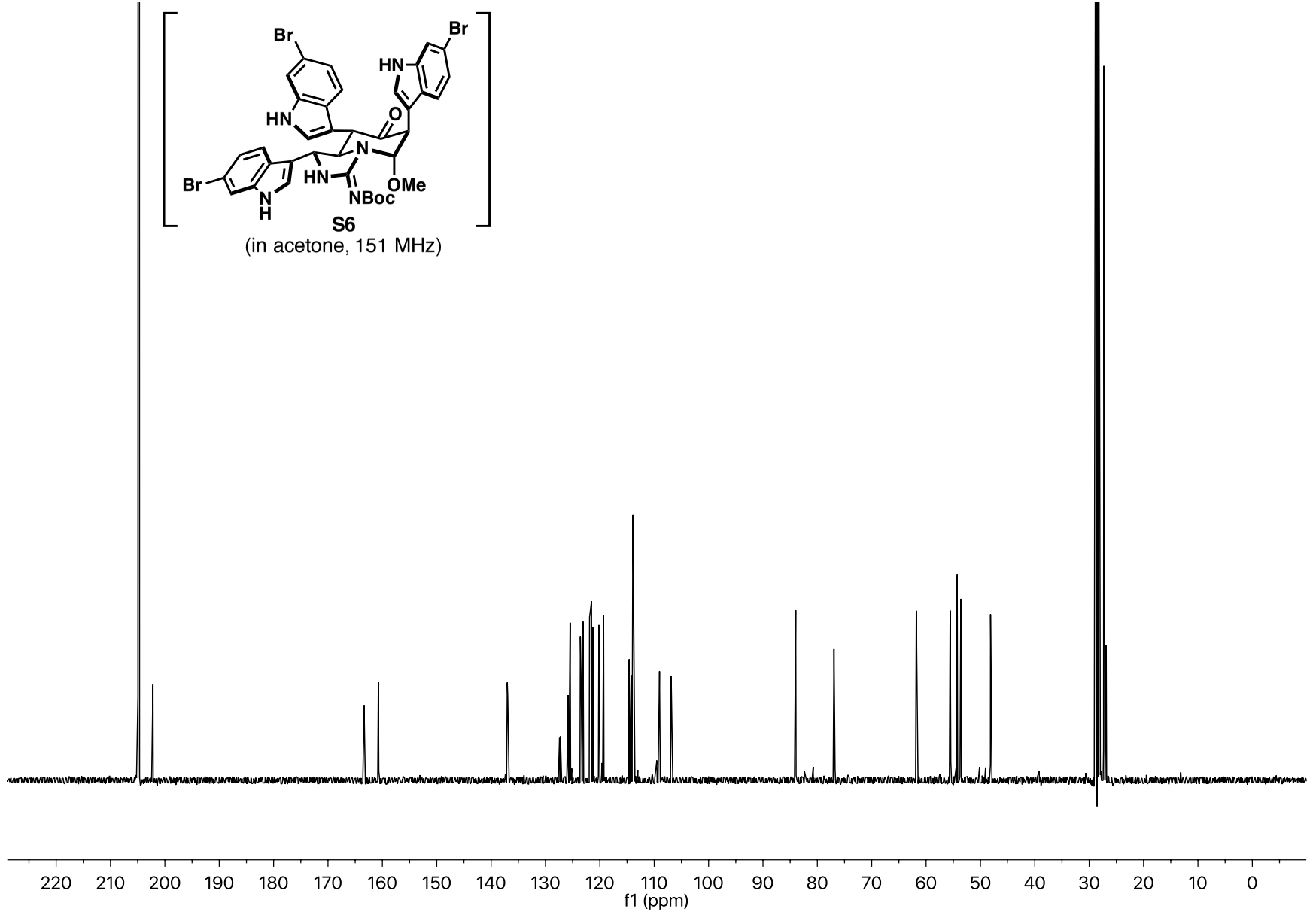


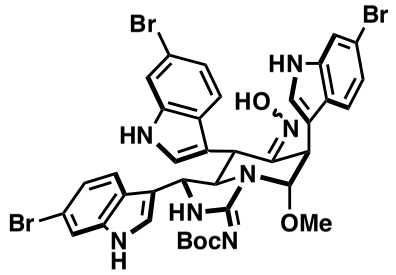
S5
(in acetone, 151 MHz)



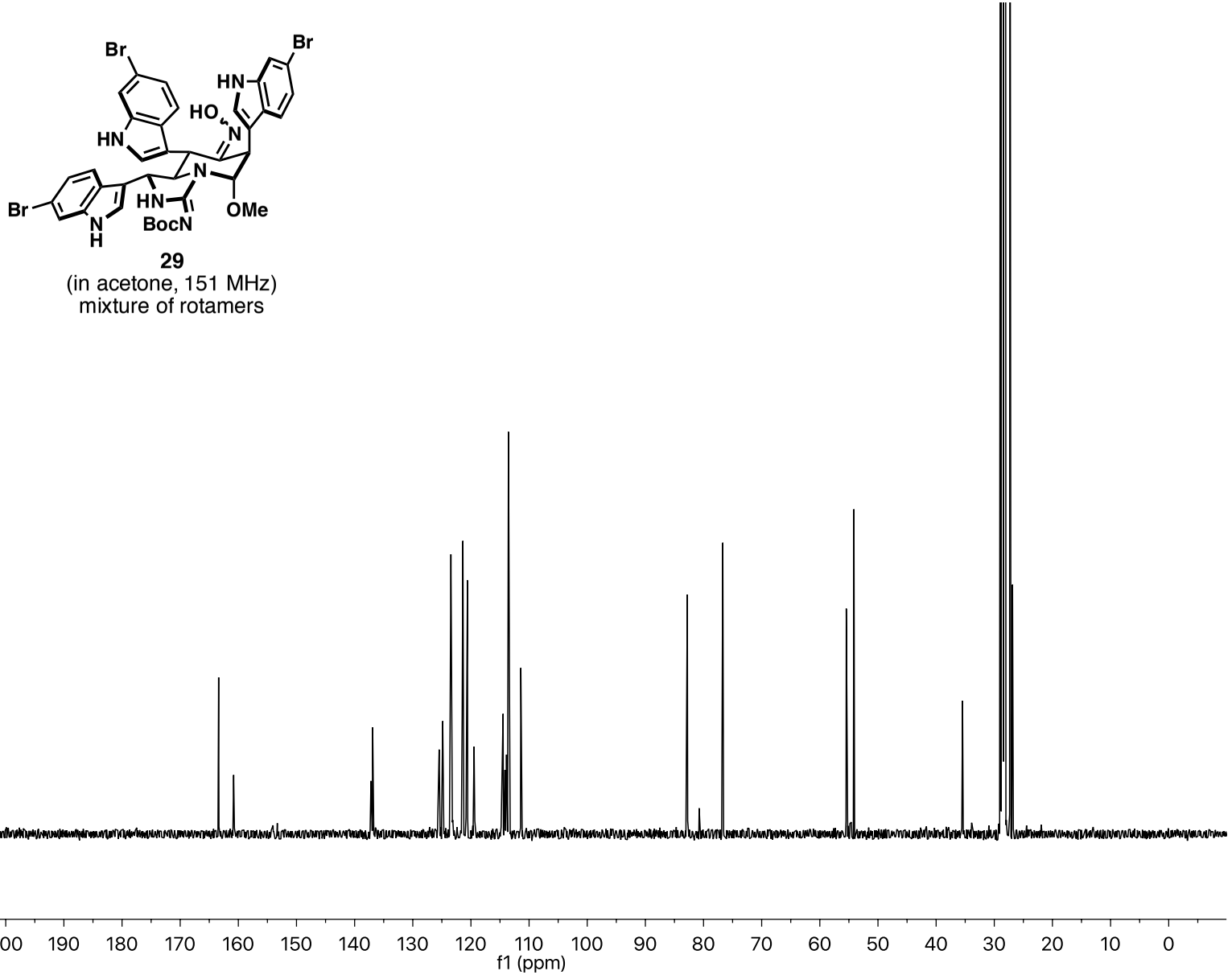
S6

(in acetone, 600 MHz)

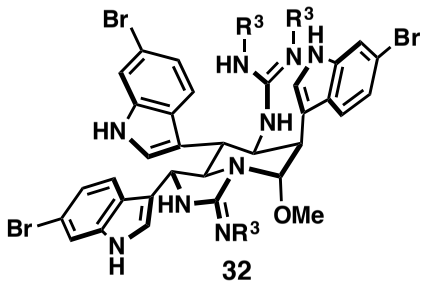

Br
Br
HN
HN
O
N
Br
HN
NBoc
OMe
N
H
S6
(in acetone, 151 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



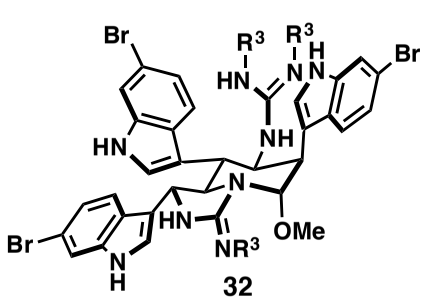
29
(in acetone, 600 MHz)
mixture of rotamers



29
(in acetone, 151 MHz)
mixture of rotamers

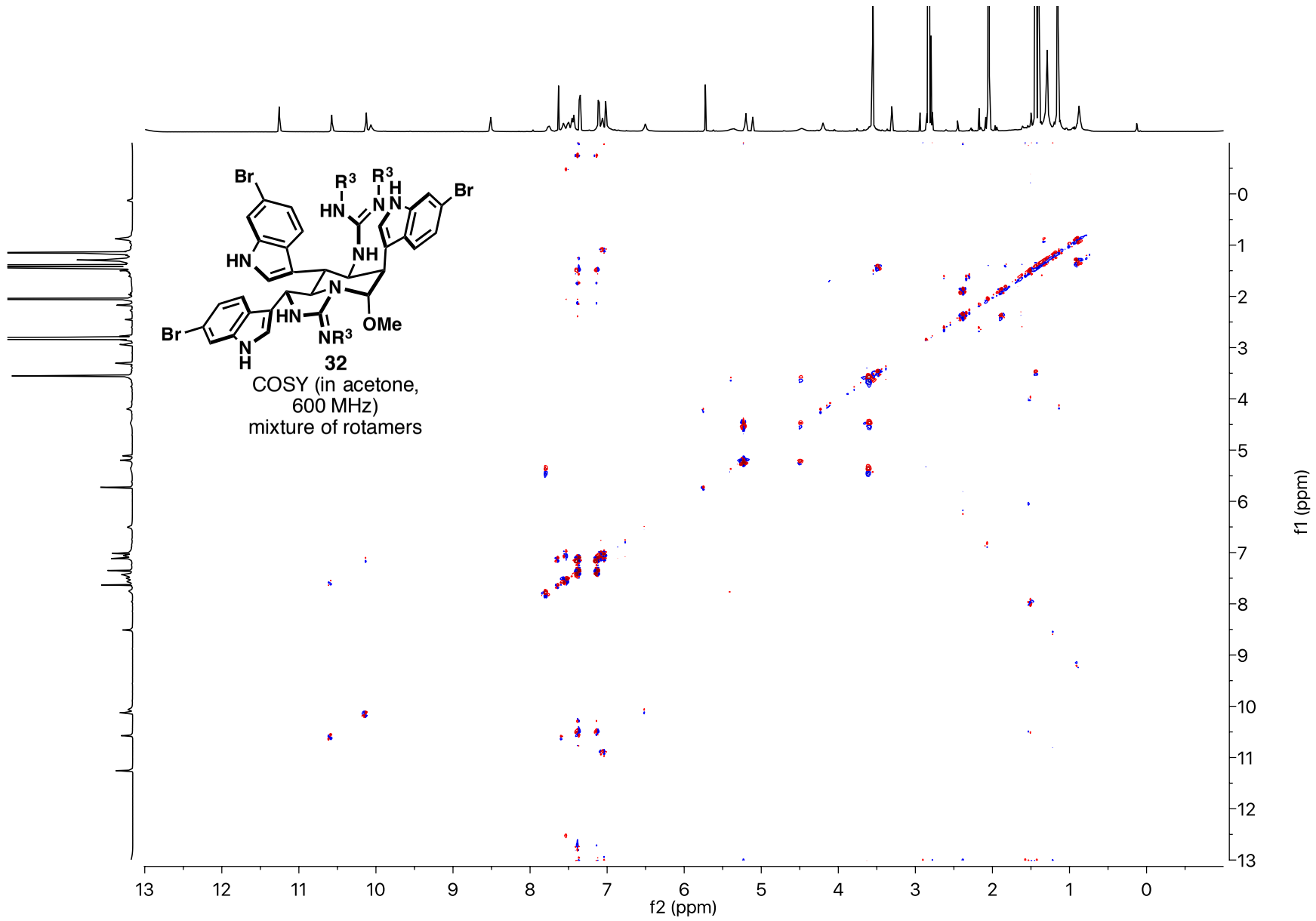


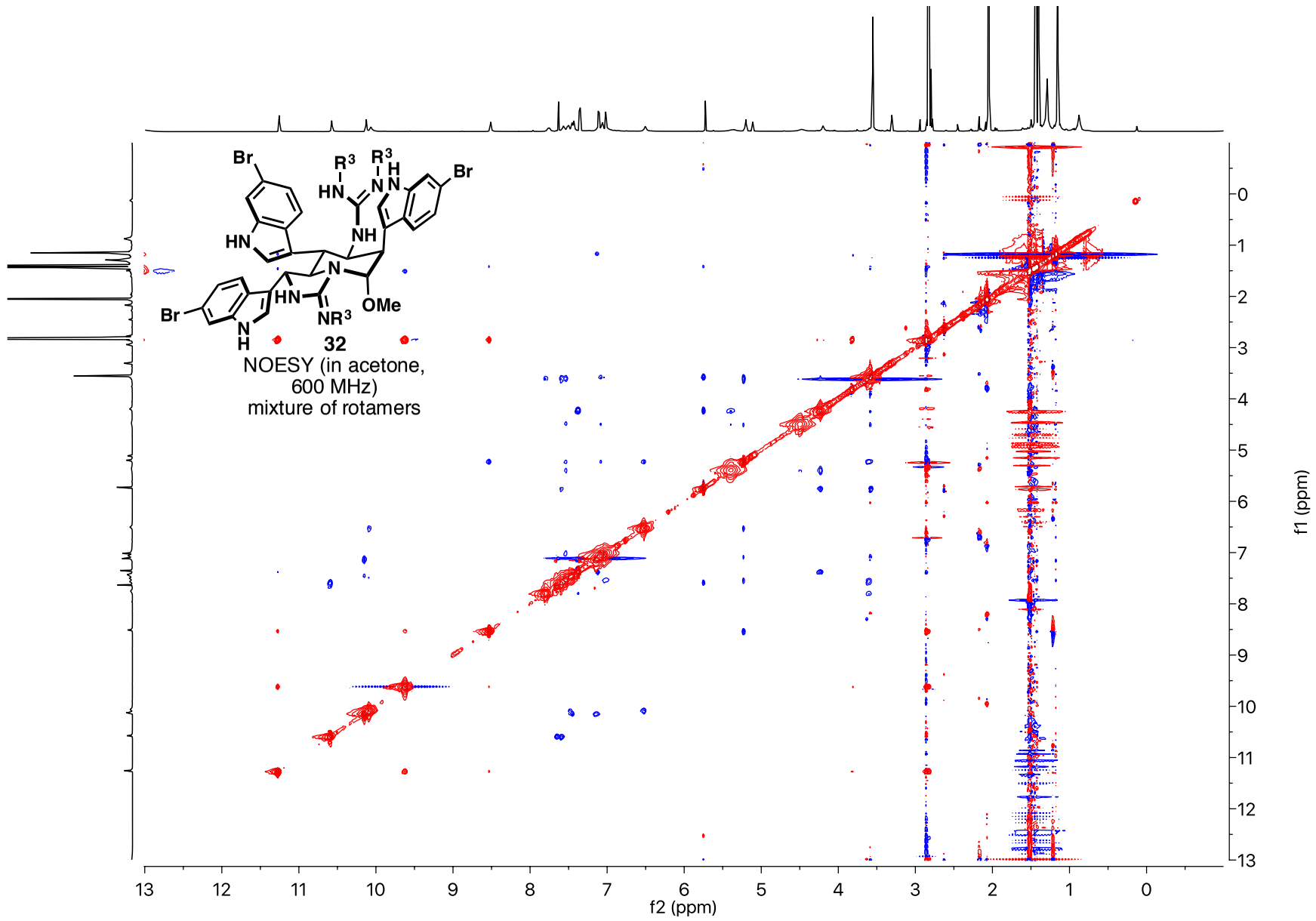
32
(in acetone, 600 MHz)
mixture of rotamers

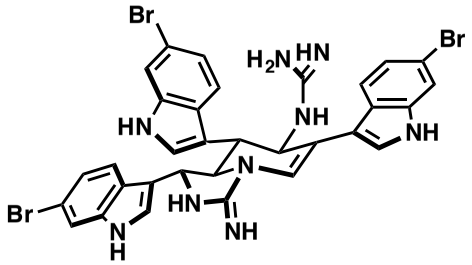


32

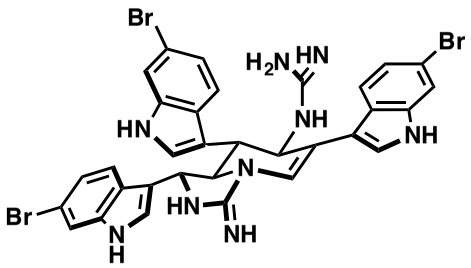
(in acetone, 151 MHz)
mixture of rotamers


Br
R3
R3
H
N
HN
N
N
Br
HN
NH
N
HN
OMe
Br
NR3
N
H
32
COSY (in acetone,
600 MHz)
mixture of rotamers
f2 (ppm)
f1 (ppm)

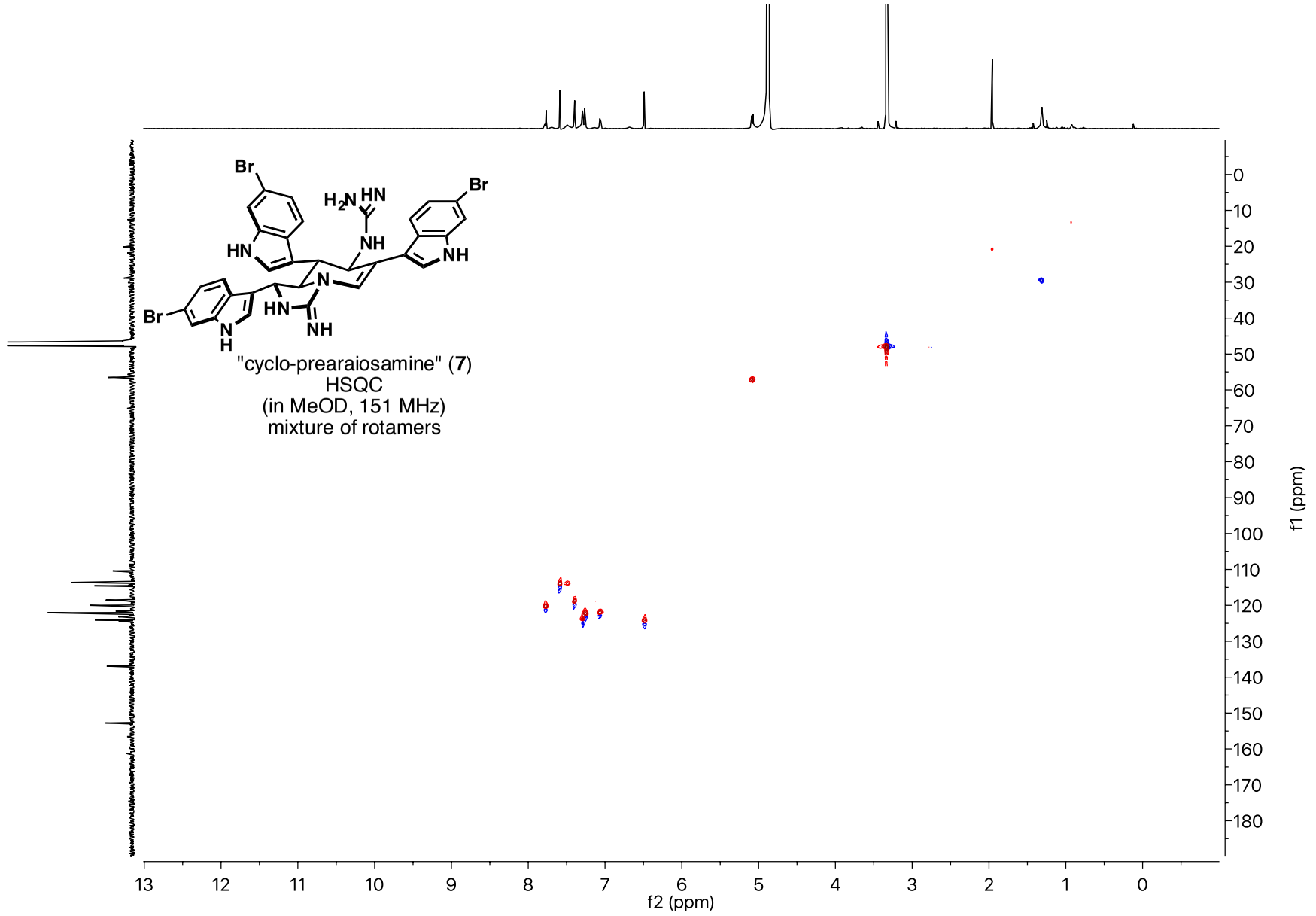

Br
R3
R3
H
N
HN
N
Br
HN
NH
N
HN
OMe
Br
NR3
N
H
32
NOESY (in acetone,
600 MHz)
mixture of rotamers
f2 (ppm)
f1 (ppm)

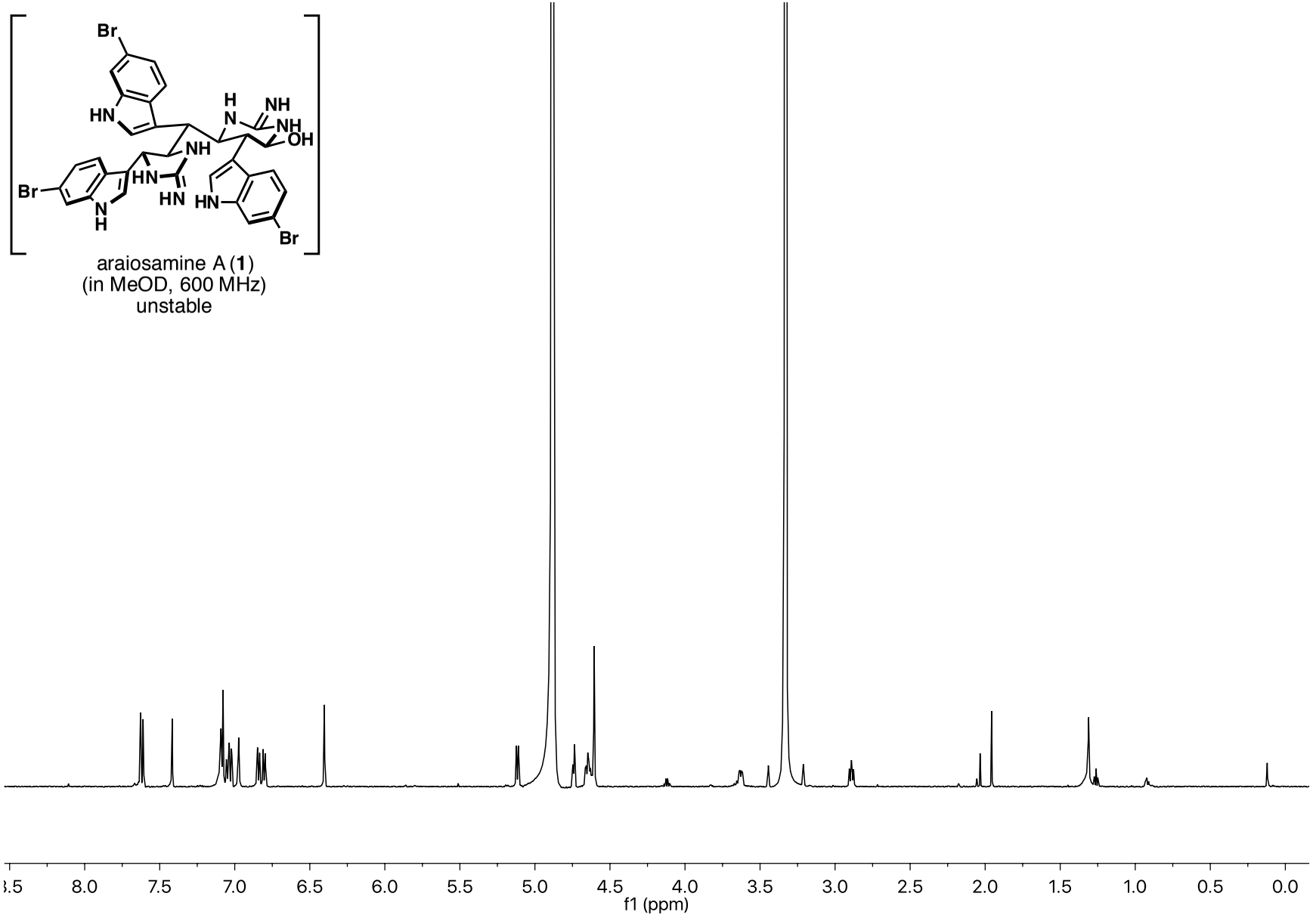


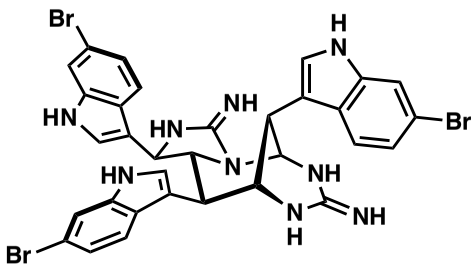
"cyclo-prearaiosamine" (**7**)
(in MeOD, 600 MHz)
mixture of rotamers



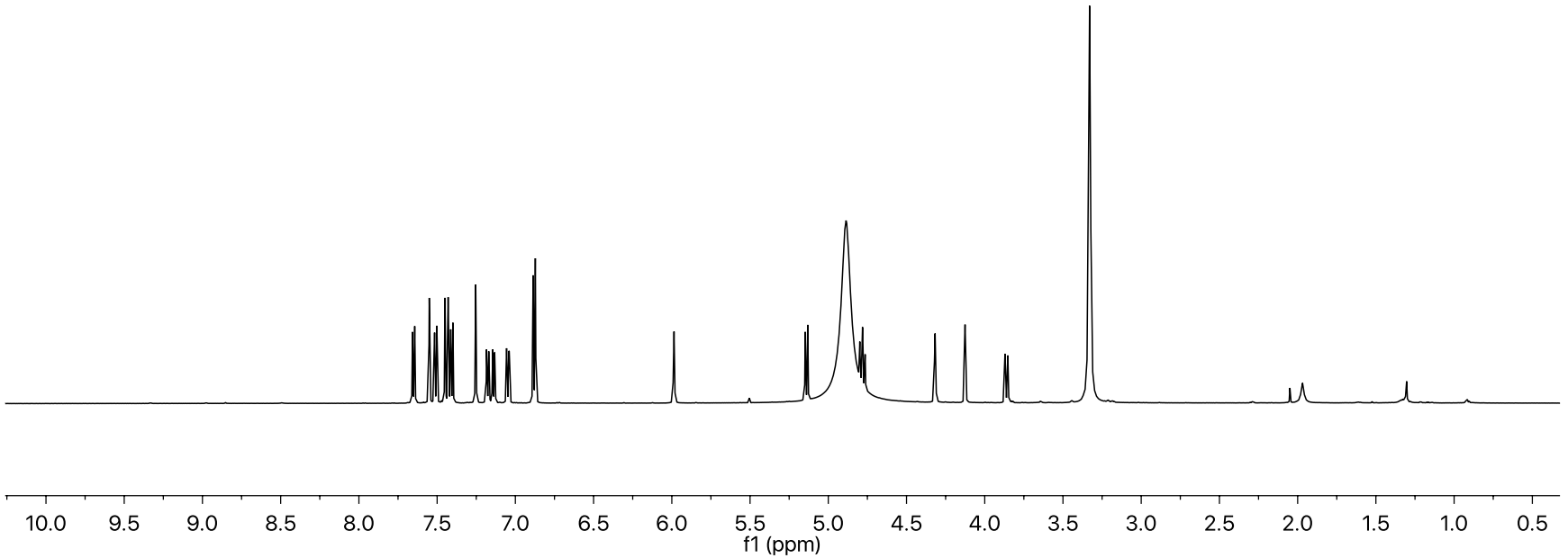
"cyclo-prearaiosamine" (**7**)
(in MeOD, 151 MHz)
mixture of rotamers

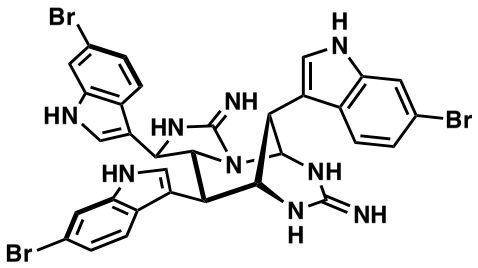

"cyclo-prearaiosamine" (7)
HSQC
(in MeOD, 151 MHz)
mixture of rotamers
f2 (ppm)
f1 (ppm)


Br
HN
H
N
NH
NH
OH
NH
HN
HN
HN
Br
N
H
HN
Br
araiosamine A (1)
(in MeOD, 600 MHz)
unstable
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

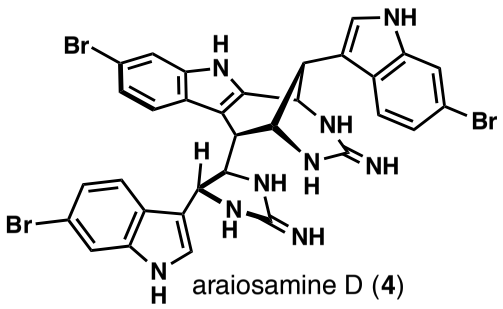


araiosamine C (**3**)
(in MeOD, 600 MHz)

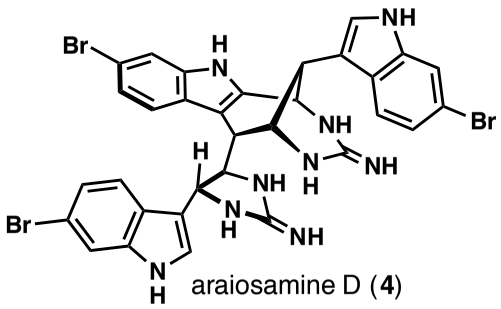




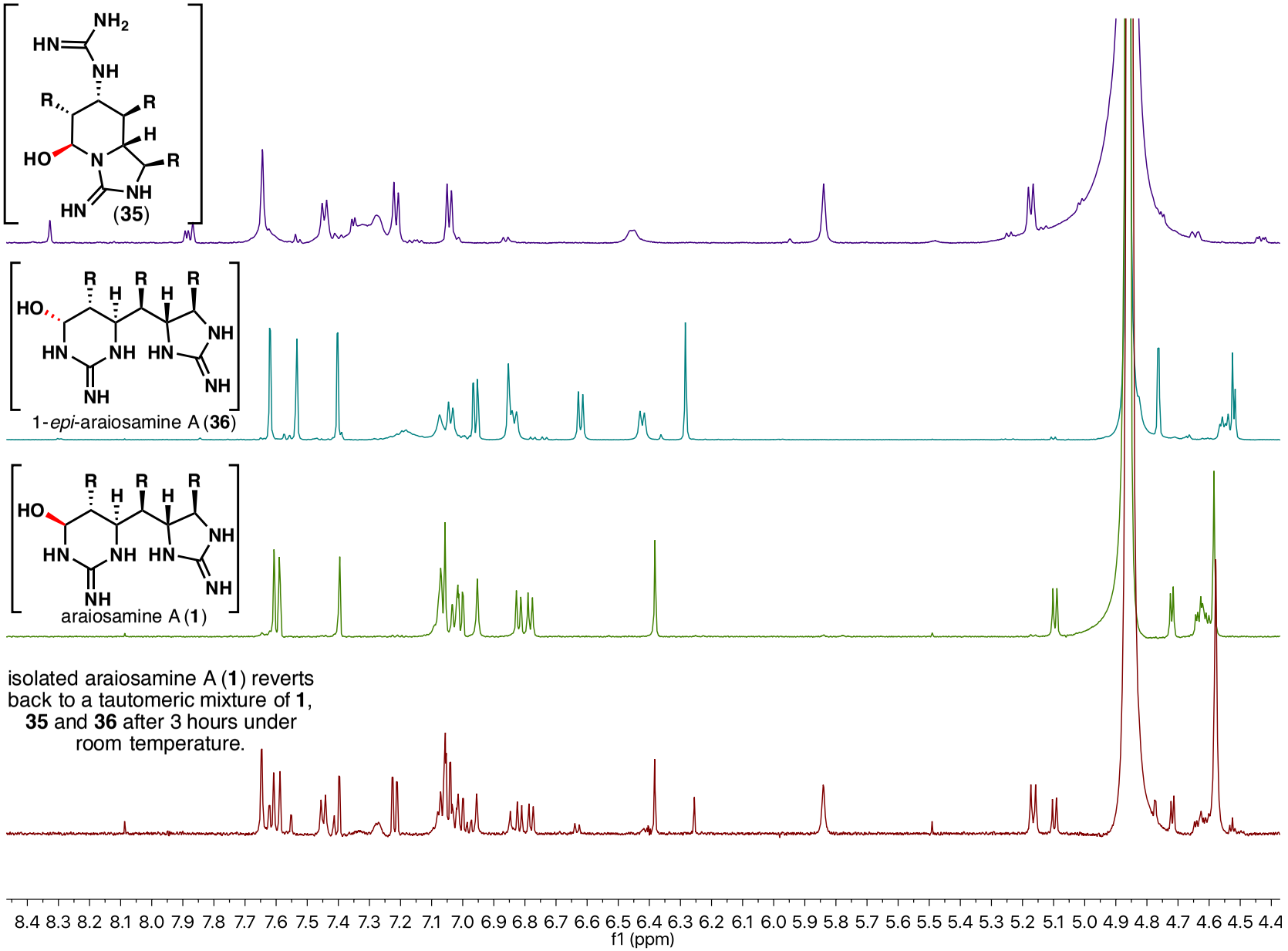
araiosamine C (**3**)
(in MeOD, 151 MHz)

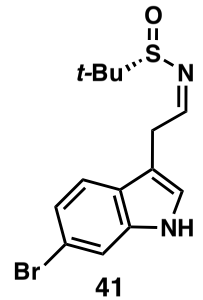


araiosamine D (**4**)
(in MeOD, 600 MHz)



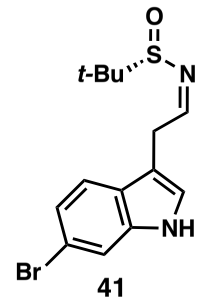
araiosamine D (**4**)
(in MeOD, 151 MHz)


(35)
1-epi-araiosamine A (36)
araiosamine A (1)
isolated araiosamine A (1) reverts back to a tautomeric mixture of 1, 35 and 36 after 3 hours under room temperature.
8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 6.1 6.0 5.9 5.8 5.7 5.6 5.5 5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4
f1 (ppm)



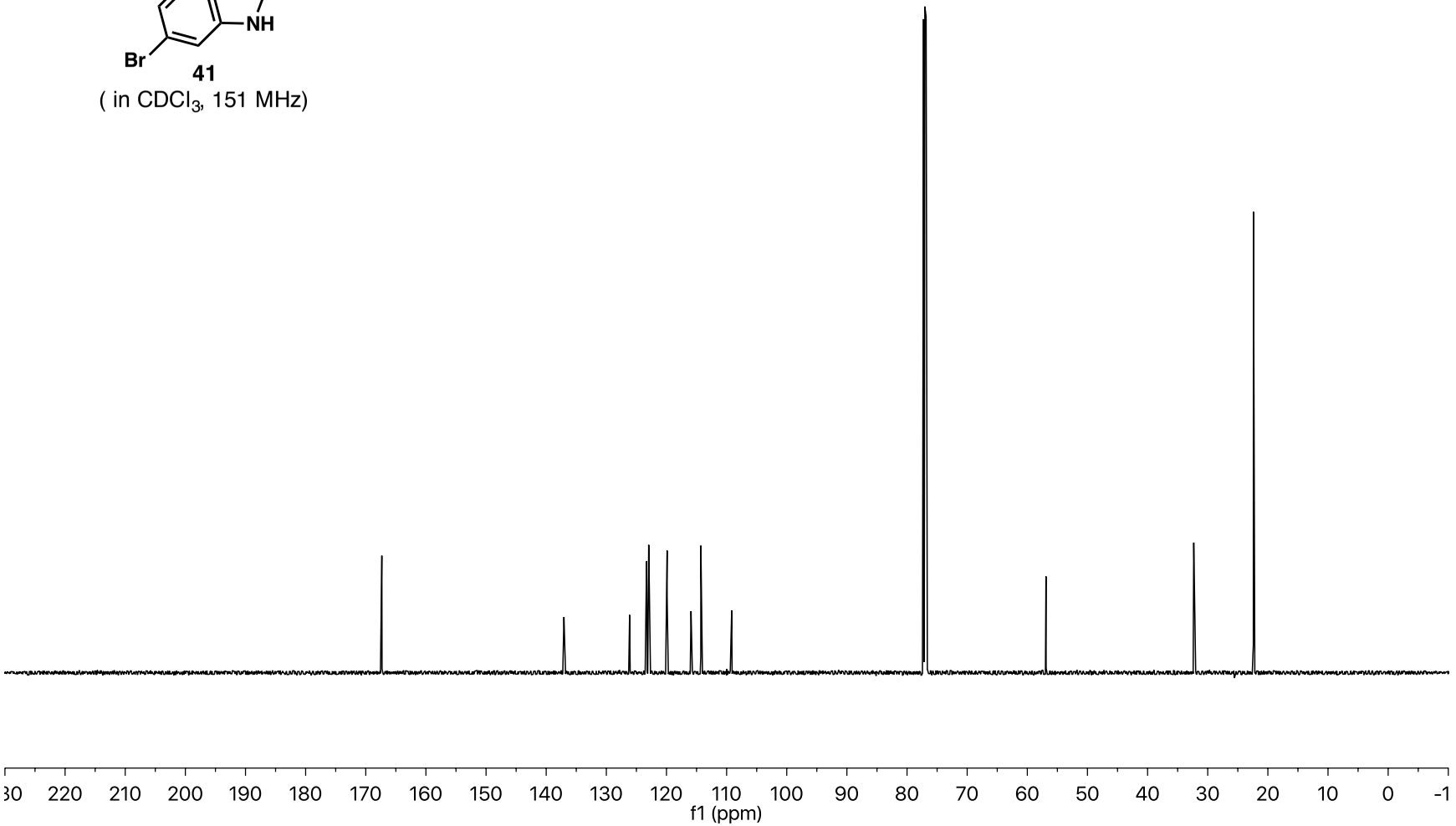
41

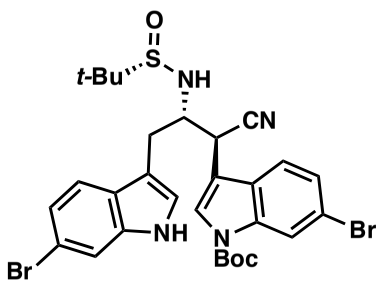
(in $CDCl_3$, 600 MHz)



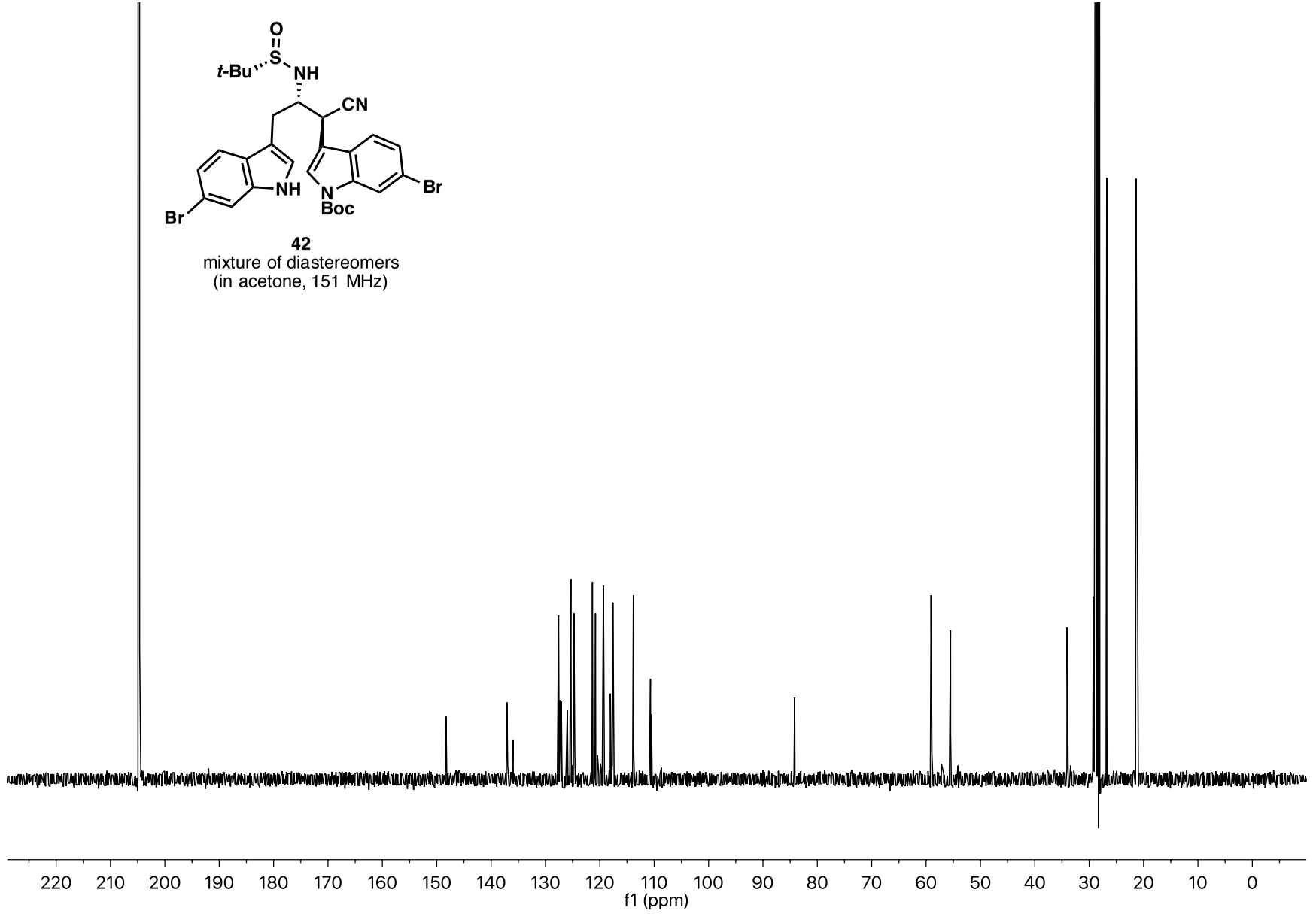
41

(in $CDCl_3$, 151 MHz)





42
mixture of diastereomers
(in acetone, 600 MHz)



42
mixture of diastereomers
(in acetone, 151 MHz)

References

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