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Hung-Ching Chen for the degree of Master of Chemical Sciences

Title: Optimization of the Synthesis of BNM-III-170 bis-TFA Salt

Project conducted at: Department of Chemistry
University of Pennsylvania
231 S. 34th Street, Philadelphia, PA 19104-6323
Supervisor: Amos B. Smith III
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Abstract approved:

Amos B. Smith III, Principle Investigator

There has been growing interest for small molecule CD4 mimetic compounds due to their capability to inhibit the HIV-1 entry and possibility to eradicate infected cells in livings. Certain experiments also prove that a lead compound, BNM-III-170 **(+)-1**, developed in the laboratory has direct antiviral effect and could sensitize HIV-infected cells toward Antibody-Dependent Cellular Cytotoxicity (ADCC). An efficient and scalable process synthesis for the HIV-1 entry inhibitor BNM-III-170 bis-TFA salt **(+)-1** is described herein for further investigations. The synthesis employs a state-of-the-art dynamic-kinetic resolution (DKR) both to generate the stereogenicity and significantly reduce the number of chromatographic separations throughout the synthesis. By taking advantage of some modifications from the first-generation synthesis, along with the low solubility of late stage intermediate, the scale-up synthesis has been greatly improved from a few hundred milligrams in 6.2% yield over a 15- step sequence. Now to proceed on a 20-gram or larger scale in overall 16 steps and in 9.64% yield, requiring only one chromatographic separation.

Optimization of the Synthesis of BNM-III-170 bis-TFA Salt

by

Hung-Ching Chen

A CAPSTONE REPORT

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Presented on April 22, 2020
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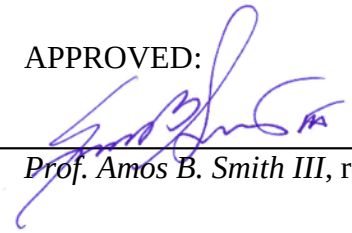
APPROVED:



04/13/2020

Prof. Amos B. Smith III, representing *Organic Synthesis Chemistry*

I understand that my Capstone Report will become part of the permanent collection of the University of Pennsylvania Master of Chemical Sciences Program. My signature below authorizes release of my final report to any reader upon request.

Hung-Ching Chen, Author

Acknowledgments

First, I would like to thank my family for providing endless support and encouragement along the way. Without their help, I could not have been able to travel this far and achieve what I have achieved. I would like to thank Professor Amos B. Smith, III, for giving me the opportunity to join his great group and the large collaboration working on HIV. Special thanks to JunHua Chen who gave me instructions and support for my research. Special thanks to Chris Fritschi who taught me characterization techniques and organic synthesis skills. Thanks also to Ana-Rita Mayol, who instructed and guided me through every aspect of master's study program and helped me succeed. I would like to extend my gratitude to all of the Smith Group members for providing a productive environment and supportive atmosphere while completing my research.

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Introduction

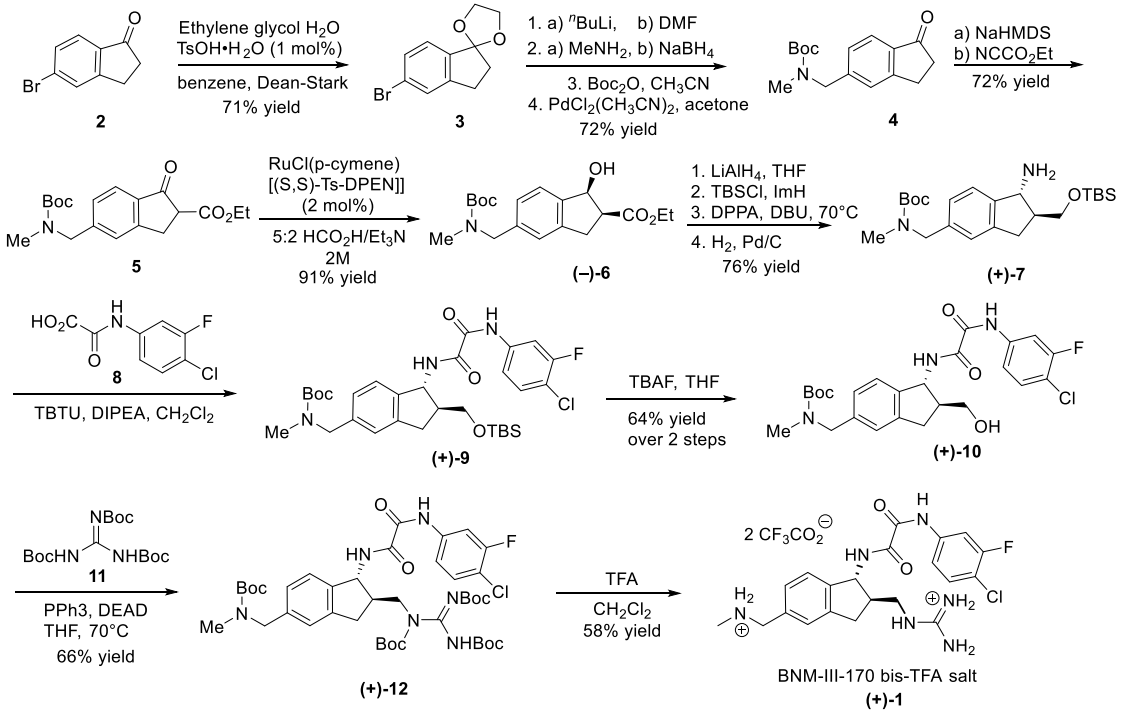
The Human immunodeficiency virus (HIV) is responsible for the acquired immunodeficiency syndrome (AIDS), which has been a global pandemic. Currently, 37.9 million people are living with AIDS, with approximately 1.8 million people new infections reported each year, and with around 32 million people having died from AIDS-related illnesses since the start of the epidemic.[1] Although combination therapy, like antiretroviral or ART has proven to be successful to improve the quality of the lives of the infected patients, a cure for AIDS or a vaccine against HIV-1 remains to be found.

The gp120-gp41 glycoprotein trimer is the only virus-specific protein on the surface of HIV-1 virions and as such is the foremost important target to prevent and interfere with HIV infection. HIV infects the cell through the following sequence of steps: a protein on the HIV Envelope (Env) spike, gp120, binds to CD4, a receptor on helper T cells, which then triggers a conformational change of gp120 so that it can bind with the T cell's coreceptor. Upon binding to the coreceptor, it draws the envelope spike sufficiently close to fuse with the T cell's membrane and pushes the capsid, which contains the genetic information into the cell and thereby infects the cell.[2] Therefore, a compound that could bind to Env tightly with specificity, affinity and breadth should be capable to inactivate or prematurely deactivate Env on the virus and infected cells. In doing so, such compounds could inhibit HIV infection and possibly eradicate the infected cells.

Recently, the Smith group at Penn has reported several syntheses of small molecule CD4-mimetic compounds (CD4mc), including the lead compound, BNM-III-170 as bis-TFA salt **(+)-1**, which binds to the viral Env, gp120 and interferes with HIV-1 entry. Employing structure-based design, along with crystallography and computational analysis, these target compounds are based on compounds identified by high-throughput screening by Debnath *et al*.[3] In 2014, the development of the small molecule CD4mc, (+)-DMJ-I-228 and (+)-DMJ-II-121 displayed antagonist activity in assays and HIV-1 entry inhibition.[4] Then, a new generation of more potent CD4mc, JP-III-048 and BNM-III-170 demonstrated direct anti-viral effect and both improve potency and binding affinity.[5,6] Specifically, the promising bioactivity of BNM-III-170 via synergizing with antibodies has led to the protection of monkeys for up to 6 months from multiple high-dose intrarectal challenges with a simian-human immunodeficiency virus (SHIV).[7] In addition, collaborations have demonstrated that **(+)-1** can also sensitize HIV-infected cells toward Antibody-Dependent Cellular Cytotoxicity (ADCC), the only way to eradicate the virus in livings cells. [8] While CD4mc could help eliminate the virus, it could also bind to the viral shedding to prevent T cells from killing healthy cells. Therefore, small molecule CD4mc is of foremost important in the path to investigate HIV and a promising cure.

The first generation synthesis of the lead small molecule CD4mc, BNM-III-170 as bis-TFA salt **(+)-1** (**Scheme 1**) was capable of producing a few hundred milligrams of **(+)-1** in 6.2% yield and in 15 steps starting from 5-bromoindanone **2**.[5] Protection of the commercially available **2** as the corresponding dioxolane **3**, followed by installation of the (methylamino)-methyl side chain via lithium-halogen exchange, formylation of the resulting aryllithium species, reductive amination and dioxolane solvolysis afford ketone **4**. The β-ketoester **5** was then formed via treatment with sodium bis(trimethylsilyl)amide then carboxylated with ethyl cyanoformate. Next, the stereogenicity in the β-hydroxyester **(–)-6** was established through a dynamic-kinetic resolution (DKR) under transfer hydrogenation condition to achieve excellent enantioselectivity (*er* >99:1).[9] Subsequent LAH reduction, followed by selective protection of the primary alcohol afforded a diol. Azidation via treatment with diphenylphosphoryl azide (DPPA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[10], followed by reduction of the azide employing a palladium catalyzed hydrogenation furnished the primary amine **(+)-7**. A TBTU-mediated amide coupling with oxalyl acid **8** then installed the oxalamide moiety in intermediate **(+)-9**.[11] Following TBS group removal, the primary alcohol **(+)-10** was then subjected to a microwave-assisted Mitsunobu reaction with tri-N-Boc-guanidine **11** to afford the desired guanidine derivative **(+)-12**. Finally, global Boc-removal was achieved in the presence of TFA, and BNM-III-170 **(+)-1** was purified through HPLC as the bis-TFA salt.

Scheme 1. The first generation of Synthesis of (+)-1



Given additional interest in the characteristics and bioactivity profile of the small molecule CD4mc (+)-**1**, a multigram synthesis was required. However, some steps from the first-generation synthesis have certain disadvantages based on their toxicity, high cost, and

difficulties that limit their practical application, when implemented in a process synthesis mode. Take the first step as an example, which has proven to be a sluggish acid-catalyzed ketalization, given to the use of benzene along with the difficulty to achieve full conversion. In addition, the early overall synthesis required 12 chromatographic separations and a HPLC purification of (+)-**1**. Therefore, there was a clear need to develop a robust and efficient synthesis. The further development of a process synthesis that largely reduced the number of chromatography of BNM-III-170 is described herein.

Results and Discussion

The newly developed process synthesis of BNM-III-170 as the TFA salt is illustrated in **Scheme 2**.[12] The first undesirable step, the ketalization was replaced by a cheaper and environmentally more friendly Claisen condensation. Since a mild carbon-carbon bond formation is required in a late stage intermediate, the aryl bromide motif in starting material **2** was retained throughout the first few steps. Toward this end, a Claisen condensation was conducted between 5-bromoindanone **2** and diethyl carbonate, employing sodium hydride as the base. In order to slow down the evolution of hydrogen gas, **2** was slowly added into a suspension of NaH in diethyl carbonate at 0°C before raising the temperature to 70°C, and the stirring retained for 2 hours to achieve complete conversion. Then, the desired sodium salt of **13** and the excess sodium hydride were carefully neutralized with dilute hydrochloric acid (3N) at 0°C. After extraction with ethyl acetate, the resulting β-ketoester **13** was isolated as a mixture of keto and enol tautomers (6:1) and then directly subjected to the dynamic-kinetic resolution (DKR) under transfer hydrogenation to generate the cis stereogenicity between hydroxyl group and the ester group of β-hydroxyester **14**. A positive result indicates that a decreased catalyst loading (0.5 mol%) and the amount of azeotrope (Formic acid: Triethylamine=5:2) did not affect the yield (92%) and enantioselectivity (*er* >99:1).

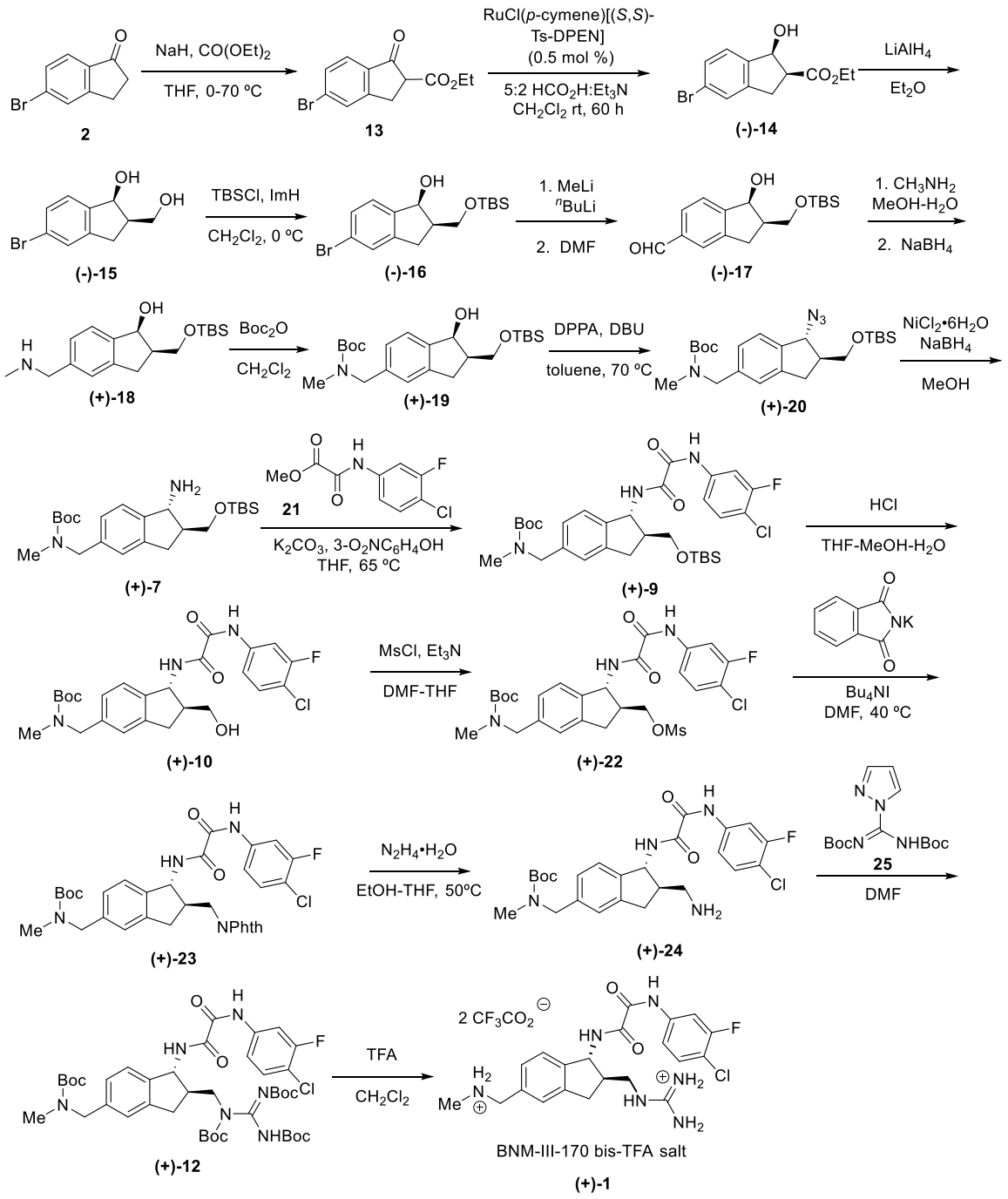
The ester group of **14** was then reduced with $LiAlH_4$, followed by a Fieser & Fieser workup[13], to afford the corresponding diol **15** that was further purified via trituration from a mixture of ethyl acetate and hexanes (v/v 1:20). It was important to use ether as opposed to THF as solvent for the Fieser & Fieser workup to furnish a granular precipitate. Following selective TBS protection of primary alcohol and trituration, bromide **16** was next converted to aldehyde **17** via lithiation-halogen exchange followed by capturing the resulting aryl lithium with DMF.

The Boc-protected (methylamino)-methyl side chain of **18** was then installed via a facile reductive amination, followed by Boc protection of the corresponding secondary amine. The secondary hydroxyl group in **19** was then converted to an azide **20** with inversion of stereochemistry. This reaction was conducted with a lower loading of DPPA and DBU (1.2 equiv. versus 3 equiv. in the first generation synthesis) and in a shorter reaction time (4 hours instead of overnight) than the earlier synthesis. The resulting reaction mixture was then added to water and then extracted with ether. Removal of the solvent gave **20** as a red oil. Without further purification, a highly efficient homogeneous nickel chloride-catalyzed reduction led to amine **(+)-7**. The reduction was completed after 4 hours in the presence of 10 mol% $NiCl_2 \bullet 6H_2O$, compared to the 24 hours with 10 mol% Pd/C employed in the first-generation synthesis.

Aminolysis with a more atom-economical reaction, employing ester **21** instead of the corresponding acid **8** as in the first synthesis, in conjunction with K_2CO_3 and 3-nitrophenol afforded **(+)-9** at 65°C in 48 hours.[14] This result can be explained by the greater electrophilicity of ester **21** and presumably because of the more reactive intermediate ester generated *in situ* by transesterification of **21** with the phenoxide. The excess amount of **33** was then hydrolyzed with aqueous K_2CO_3 and the resulting potassium salt removed via

filtration. Next, removal of the TBS group was achieved via addition of a solution of HCl in 3:1:1 (v/v/v) THF-MeOH-water (pH=1) and stirred overnight. The resulting suspension was then diluted with aqueous $NaHCO_3$ and the precipitated product filtered as a damp solid. Taking advantage of the low solubility of (+)-**10**, purification with an ethereal wash then furnish (+)-**10** as an off white powder.

Scheme 2. New Synthetic Route of BNM-III-170 bis-TFA salt (+)-1



Alcohol **(+)-10** was then converted to mesylate **22** with methane sulfonyl chloride in a 1:4 (v/v) DMF-THF solution, which in turn could be easily purified via filtration as the off white solid in 92% yield. Next, mesylate **22** was converted to the phthalimide **23** via a Gabriel amine synthesis to introduce the nitrogen atom.[15] Following treatment of the hydrazine hydrate (5equiv.) in THF-ethanol (v/v 1:1) at 50°C, the primary amine **24** was obtained. Addition of 5 wt% aqueous Na_2CO_3 then dissolved the phthalhydrazide byproduct, while the desired product **24** nicely precipitated as a pale yellow solid.

By employing commercially available di-Boc-pyrazolecarboximidamide, the guanidine group was next installed successfully by stirring **24** and excess amount of **25** in DMF overnight. Addition of a sacrificial polyamine, ethylenediamine, followed by extraction with 5 wt% aqueous $NaHSO_4$ and ethyl acetate as the solvent readily removed the slight excess of guanidine **25**. After removal of the solvent, the penultimate product **(+)-12** was then purified by the first column throughout the synthesis as an off white solid. Last, dropwise addition of TFA leaded to Boc deprotection, with the TFA salt of **(+)-1** precipitating from trituration of a solution of MeOH-ethyl acetate-hexanes (1:4:4) as a white powder. The overall sequence proceeded in 16 steps and a 9.64% overall yield with only one column compared to the first-generation synthesis which requires 15 steps in 6.2% overall yield with 12 column purifications.

After the contribution to the design and develop of the process synthesis, transitioning it from milligram to decagram scale, 45 grams of BNM-III-170 as TFA salt has been synthesized for animal studies since joining the Smith group. Studies have shown that BNM-III-170 not only has direct antiviral effect, but also hold the promise of a better treatment for HIV than ART (Antiretroviral treatment). Moreover, the process synthesis will clearly aid the investigation on a mechanism to inhibit HIV-1 entry into cells and eventually to the eradication of HIV from infected cells in livings and possibly individuals.

Conclusion

In summary, an effective enantioselective process synthesis of BNM-III-170 as the bis-TFA salt (**1**), employing 16-steps that proceeds in 9.64% overall yield has been achieved **(Scheme 2)**. The scalable process synthesis versus the first-generation synthesis pleasingly obviated a tedious end-game HPLC purification, with flash chromatographic separations avoided in all but one step: that is, a final filtration through a plug of silica. The stereogenicity of the BNM-III-170 bis-TFA salt **(+)-1** was established via a ruthenium-catalyzed transfer hydrogenation by virtue of a DKR, and the aromatic side chain was installed via alkyllithium-mediated formylation, followed by a reductive amination process. The oxalamide moiety was then installed by an aminolysis protocol, and the primary amine necessary for introduction of the guanidine group was attached via a Gabriel amine synthesis. Pleasingly, the overall process has now been demonstrated on a 20-gram scale of starting material **2** to prepare the 6.17 grams of BNM-III-170 bis-trifluoroacetate salt **(+)-1** and 45 grams have been synthesized since joining the laboratory.

Future Work

Although the lead CD4mc, BNM-III-170, could inhibit the HIV-1 entry and sensitize the infected cells to ADCC, there is still possible improvements for the bioactivity. The Smith group, HIV project team, has been working on structural activity relationship (SAR) studies based on the high-throughput screening hits NBD-556 and NBD-557 (**Figure 1.**) identified by Debnath and coworkers.[3] The target has been divided into three regions: aromatic ring in Region I, the oxalamide linker in Region II, and the substituted piperidine ring in Region III. Specifically, analysis of the co-crystal structures and the computational studies show that additional protein ligand interactions with hotspot in the Phe43 cavity, particularly with the highly conserved Asp^{368} residues would greatly enhanced the activity of the CD4mc. Therefore, new CD4mc analogs should be synthesized to investigate its deeper potential to cure HIV.

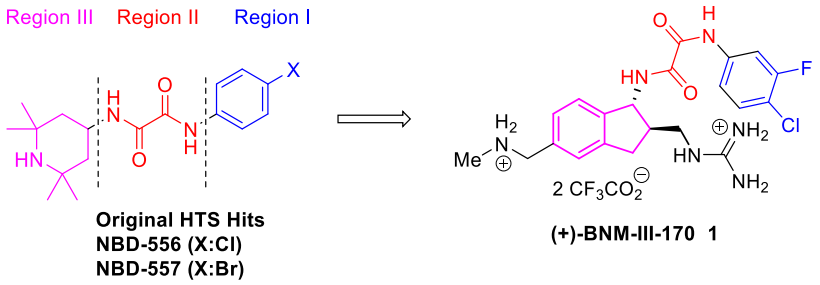


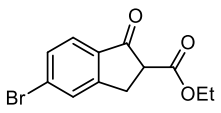
Figure 1. SAR studies from HTS hits and divided regions

More biological studies could be conducted due to the design and development of this efficient process synthesis, since monkey and mice studies need multigrams of compound to proceed. Within our collaborative NIH P01 program, ADCC, X-ray crystallography and computational experiments will list BNM-III-170 as a reference and provide more insights to new compounds.

Materials and Methods

General Methods: All reactions were conducted in oven-dried glassware under an inert atmosphere of nitrogen or argon, unless otherwise stated. All solvents were reagent or high performance liquid chromatography (HPLC) grade. Anhydrous CH_2Cl_2, THF, Et_2O were obtained from the Pure Solv^{TM} PS-400 system under a nitrogen atmosphere. All reagents were purchased from commercially available sources and used as received. Reactions were magnetically stirred under a nitrogen atmosphere, unless otherwise noted and reactions were monitored by either thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates or analytical liquid chromatography mass spectrometry (LCMS). Yields refer to chromatographically and spectroscopically pure compounds. When the compound is carried crude to the next reaction, the crude product is placed under vacuum pressure until entirely dry from solvent. Optical rotations were measured on a JASCO P-2000 polarimeter. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker Avance III 500 MHz or Avance Neo 400 MHz at 305 K. Data reported as following: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet), coupling constant (Hz), integration. Chemical shifts (δ) are reported in parts per million (ppm) relative to chloroform (δ 7.26), acetone (δ 2.05), methanol (δ 3.31), or dimethyl sulfoxide (δ 2.50) for ^{1}H NMR, and chloroform (δ 77.16), acetone (δ 29.84, 206.26), methanol (δ 49.00), or dimethyl sulfoxide (δ 39.52) for ^{13}C NMR. Infrared spectra were recorded using a JASCO 480-Plus FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded at the University of Pennsylvania Mass Spectroscopy Service Center on either a VG Micromass 70/70H or VG ZAB-E spectrometer. Preparative scale HPLC was performed with a Gilson 333/334 preparative pump system equipped with a 5 mL injection loop, Sunfire C18 OBD column (5 µm packing material, 19 x 100 mm column dimensions) equipped with a UV-Vis dual wavelength (210 and 254 nm) detector and 215 liquid handling module. Solvent systems were comprised of H_2O containing 0.1% trifluoroacetic acid, and acetonitrile containing 0.1% trifluoroacetic acid. SFC purifications and analyses were performed with a JASCO system equipped with a Chiralpak IA column (10 mm x 250 mm), a PU-280-CO_2 plus CO_2 Delivery System, a CO-2060 plus Intelligent Column Thermostat, an HC-2068-01 Heater Controller, a BP-2080 plus Automatic Back Pressure Regulator, an MD-2018 plus Photodiode Array Detector (200 - 648 nm), and PU-2080 plus Intelligent HPLC Pumps. Lyophilization was performed in a Labconco FreeZone 12 Plus lyophilizer (0.28 mbar). The purity of BNM-III-170 was judged by NMR and HPLC (>95%).

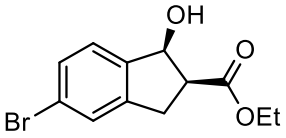
General procedure for process scale synthesis of BNM-III-170 (+)-1



13

Ethyl 5-Bromo-1-oxo-2,3-dihydro-1H-indene-2-carboxylate 13. To a stirring suspension of sodium hydride (7.58 g, 60 % dispersion in oil, 189.5 mmol, 2 equiv.) in THF (200 mL) at 0 ºC was charged with diethyl carbonate (34.4 mL, 284.3 mmol, 3 equiv.). Neat 5-bromo-indanone (20 g, 94.7 mmol) was added to this suspension in ten portions.

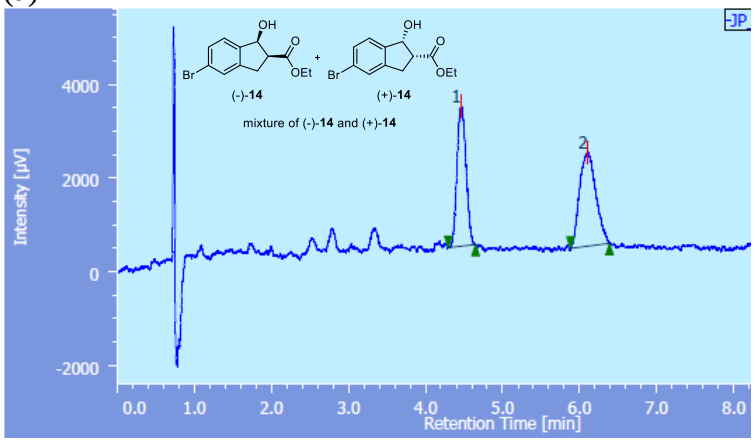
(*caution*: significant H_2 (g) evolution will occur; maintain a strong flow of argon with continuous venting.) The resulting mixture was continued to stir at 0 ºC until gas evolution subsided (40 minutes on this scale). The resulting brown mixture was then slowly brought up to 70 ºC whereupon the reaction mixture turned into a dark cake a few minutes after reflux began. This mixture was aged at 70 ºC for 2 hours. The reaction mixture was then allowed to cool to room temperature and then diluted with EtOAc (150 mL). The resulting mixture was further cooled at 0 ºC, to which aqueous HCl (3 N, 100 mL) was added dropwise, and the solids broke down and dissolved. The organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layers were combined, dried over Na_2SO_4, and filtered through Celite®. The Celite® pad was further washed with EtOAc (200 mL). The filtrate was concentrated in vacuo to give the brown solid that comprised of a mixture of the keto and enol tautomers (6/1, crude). This material was directly used for the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$, mixture of tautomers, keto/enol=1/2) d 10.39 (s, 0.66H), 7.69 (s, 0.33H), 7.66 – 7.57 (m, 0.96H), 7.57 – 7.43 (m, 1.60H), 4.32 (q, *J* = 7.1 Hz, 1.34H), 4.25 (q, *J* = 7.1 Hz, 0.66H), 3.71 (dd, *J* = 8.3, 4.0 Hz, 0.33H), 3.62 – 3.42 (m, 1.65H), 3.35 (dd, *J* = 17.5, 8.3 Hz, 0.33H), 1.37 (t, *J* = 7.1 Hz, 1.98H), 1.31 (t, *J* = 7.1 Hz, 0.97H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of tautomers, keto/enol=2/1) d 198.33, 168.78, 155.26, 145.06, 136.09, 134.31, 131.66, 131.03, 130.31, 130.01, 128.22, 125.95, 123.94, 122.05, 102.92, 62.04, 60.41, 53.44, 32.60, 30.09, 14.59, 14.33; IR (thin film, KBr) 2980, 2359, 1715, 1655, 1420, 1180, 1100 1056 cm^{-1}; HRMS (ESI) calculated for $C_{14}H_{14}BrNO_3Na$ $[M+CH_3CN+Na]^+$ 346.0055, found 346.0069.



(–)-14

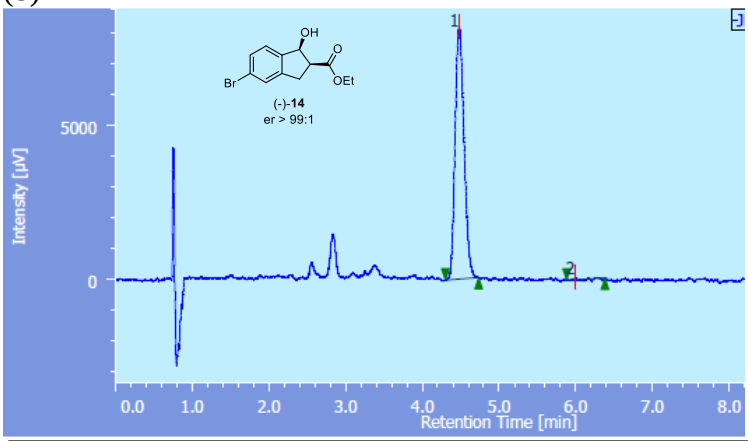
Ethyl (1*S*,2*S*)-5-bromo-1-hydroxy-2,3-dihydro-1H-indene-2-carboxylate (-)-14. To a solution of β-ketoester **13** (26.8 g, 94.7 mmol) in CH_2Cl_2 (28 mL) at ambient temperature was added 5:2 formic acid/triethylamine solution (20 mL), followed by the addition of RuCl(*p*-cymene)[(S,S)-Ts-DPEN] (301 mg, 0.47 mmol, 0.5 mol%) in one portion. The reaction mixture was stirred at room temperature for 64 hours, at which point CO_2 gas evolution had ceased and crude NMR indicated complete consumption of **13**. The reaction was diluted with CH_2Cl_2 (50 mL) and then treated with H_2O (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the product as a brown solid, which was used directly for the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.44 – 7.35 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 1H), 5.32 – 5.22 (m, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.45 - 3.32 (m, 2H), 3.15 – 3.03 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) d 172.68, 144.19, 141.78, 130.35, 128.06, 126.54, 122.98, 75.23, 61.09, 49.59, 32.71, 14.27; IR (thin film, KBr) 3448, 2980, 1735, 1598, 1472, 1442, 1408, 1374 cm^{-1}; HRMS (EI) calculated for $C_{12}H_{13}BrO_3$ $[M]^+$ 284.0048, found 284.0052; Optical rotation crude $[a]_D^{22}$ –5.8 (c = 0.76, CH_2Cl_2), purified $[a]_D^{22}$ –7.7 (c = 2.04, CH_2Cl_2).

(a)



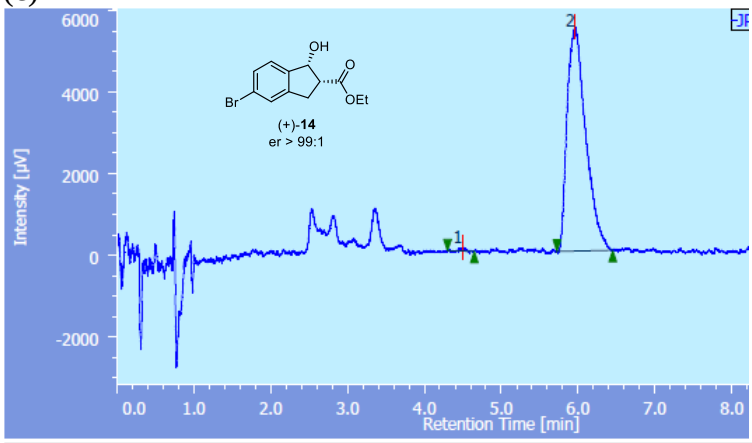
#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor
1	Unknown	10	4.462	24222	2997	45.114	59.985	N/A	6709	5.295	1.104
2	Unknown	10	6.108	29469	1999	54.886	40.015	N/A	3626	N/A	1.110

(b)



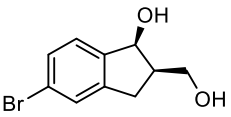
#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor
1	Unknown	10	4.482	66146	8174	99.583	99.006	N/A	6905	12.254	1.178
2	Unknown	10	5.992	277	82	0.417	0.994	N/A	583264	N/A	2.031

(c)



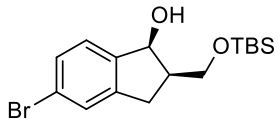
#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor
1	Unknown	10	4.500	393	92	0.425	1.639	N/A	18475	5.070	0.803
2	Unknown	10	5.960	92056	5494	99.575	98.361	N/A	2869	N/A	1.508

Figure 2. Chiral SFC (Supercritical Fluid Chromatography) results to determine the Enantiomeric ratio (*er*) of (-)-**14**. SFC conditions: column: Chiralpak IA; eluent: 10% MeOH in supercritical CO_2; flow rate: 4 mL/min; pressure: 12 MPa; Retention times: (–)-**14**: 4.5 min., (+)-**14**: 6.0 min. **(a)** Racemic material was prepared by mixing (-)-**14** and (+)-**14. (b)** (-)-**14** was synthesized by using 0.5 mol% RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] as a catalyst. **(c)** (+)-**14** was synthesized by using 0.5 mol% RuCl(*p*-cymene)[(*R*,*R*)-Ts-DPEN] as a catalyst.



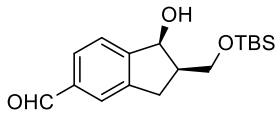
(–)-15

(1*S*,2*R*)-5-Bromo-2-(hydroxymethyl)-2,3-dihydro-1H-inden-1-ol (-)-15. To a solution of **16** (27.0 g, 94.7 mmol) in dry Et_2O (470 mL) at 0 ºC was added lithium aluminum hydride pellets (4.3 g, 113.6 mmol, 1.2 equiv.) in one portion. The reaction mixture was further stirred vigorously at 0 ºC for 4 hours. To the resulting gray mixture, 4.3 mL of water was slowly added, followed by slow addition of 4.3 mL of 15% aqueous NaOH. Additional 12.9 mL of water was added and the reaction mixture was allowed to warm up to room temperature and stirred for 30 minutes. The resulting precipitate was removed via vacuum filtration, and this solid was washed with Et_2O (700 mL). The filtrate was then filtered through Celite, and the Celite pad was further rinsed with Et_2O (300 mL). The filtrate was concentrated in vacuo. The resulting residue was dispersed in EtOAc (20 mL) followed by dilution with Hexanes (400 mL). The resultant brown solid (18.18 g, 79% yield over 3 steps) was collected by Büchner funnel and rinsed with hexanes to give the product as a brown powder. This material was used directly for the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.43 – 7.33 (m, 2H), 7.26 (d, J = 7.5 Hz, 1H), 5.26 (d, J = 6.5 Hz, 1H), 3.99 – 3.81 (m, 2H), 2.98 - 2.81 (m, 2H), 2.76 – 2.65 (m, 1H), 2.51 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) d 145.39, 143.19, 130.22, 128.37, 126.33, 122.86, 62.90, 45.31, 32.75; IR (thin film, KBr) 3397, 2957, 2939, 2884, 2359, 2083, 1652 cm^{-1}; HRMS (EI) calculated for $C_{10}H_{11}BrO_2$ $[M]^+$ 241.9942, found 241.9930; Optical rotation crude $[a]_D^{22}$ –16.6 (c = 1.39, CH_2Cl_2), purified $[a]_D^{22}$ –7.6 (c = 1.14, CH_2Cl_2).



(–)-16

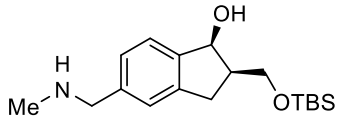
(1*S*,2*R*)-5-Bromo-2-(((*tert*-butyldimethyls-lyl)oxy)methyl)-2,3-dihydro-1H-inden-1-ol (-)-16. To a suspension of diol **15** (18.18 g, 74.8 mmol) in CH_2Cl_2 (150 mL) at 0 ºC was added imidazole (10.18 g, 149.6 mmol, 2.0 equiv.) in one portion and stirred for 10 minutes. To this mixture was added a solution of *tert*-butyldimethylsilyl chloride (11.27 g, 74.8 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) dropwise over 30 minutes. The reaction mixture was stirred at 0 ºC for 30 minutes. The resulting mixture was treated with H_2O (100 mL). The aqueous phase was then extracted with CH_2Cl_2 (2 x 50 mL), the organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The impurities were precipitated by using Et_2O/hexanes mixture (diluted with 30 mL of Et_2O followed by addition of 200 mL of Hexanes). The resulting precipitate was filtered through Celite, and the Celite pad was further rinsed with Hexanes (100 mL). The filtrate was concentrated in vacuo to give the product as a brown oil, which was used directly for the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.38 – 7.32 (m, 2H), 7.29 (d, *J* = 8.5 Hz, 1H), 5.21 (d, *J* = 6.6 Hz, 1H), 3.96 (dd, *J* = 10.3, 4.6 Hz, 1H), 3.86 (dd, *J* = 10.3, 7.1 Hz, 1H), 2.91 (dd, *J* = 16.1, 8.2 Hz, 1H), 2.81 (dd, *J* = 16.1, 6.4 Hz, 1H), 2.74 – 2.62 (m, 1H) 0.85 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) d 144.84, 143.96, 130.03, 127.96, 126.41, 122.26, 76.83, 63.66, 44.97, 33.25, 25.85, 18.16, -5.37, -5.48; IR (thin film, KBr) 3434, 2953, 2928, 2856, 1652, 1599, 1471 cm^{-1}; HRMS (EI) calculated for $C_{16}H_{23}BrOSi$ $[M\text{-}H_2O]^+$ 338.0702, found 338.0701; Optical rotation crude $[a]_D^{22}$ –2.4 (c = 1.30, CH_2Cl_2), purified $[a]_D^{22}$ –4.1 (c = 0.78, CH_2Cl_2).



(–)-17

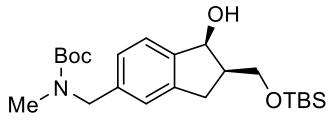
(1*S*,2*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-hydroxy-2,3-dihydro-1H-indene-5-carbaldehyde (-)-17. To a solution of secondary alcohol **16** (25.1 g, 70.2 mmol) in dry THF (200 mL) at –78 ºC, MeLi (3.1 M in diethoxymethane, 27.2 mL, 84.2 mmol, 1.2 equiv.) was added dropwise for 10 minutes and allowed to stir at the same temperature for 10 minutes. *n*-BuLi (2.5 M in hexane, 33.7 mL, 84.2 mmol, 1.2 equiv.) was added dropwise over 10 minutes. The resulting dark solution was stirred at –78 ºC for 10 minutes, to which dry DMF (27.2 mL, 351 mmol, 5.0 equiv.) was added dropwise for 5 minutes. The reaction mixture was allowed to stir at room temperature for 1 hours. The resulting solution was treated with sat. NH_4Cl (100 mL) under ice bath, and then the resulting biphasic mixture stirred vigorously at room temperature for 10 minutes. The volatiles were then evaporated on a rotary evaporator. The residue was extracted with Et_2O (3 x 50 mL), the organic layers combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the product as a brown oil, which was used directly for the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) d 9.95 (s, 1H), 7.76 – 7.68 (m, 2H), 7.55 (d, *J* = 7.6 Hz, 1H), 5.29 (t, J = 6.2 Hz, 1H), 3.95 (dd, *J* = 10.4, 4.7 Hz, 1H), 3.84 (dd, *J* = 10.4, 6.8 Hz, 1H), 3.61 (d, *J* =

6.0 Hz, 1H), 2.98 (dd, *J* = 16.2, 8.1 Hz, 1H), 2.86 (dd, 16.2, 5.6 Hz, 1H), 2.79 – 2.65 (m, 1H), 0.80 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) d 192.43, 151.99, 143.31, 136.88, 129.68, 125.65, 125.32, 77.53, 63.84, 44.90, 33.21, 25.86, 18.16, -5.36, -5.46; IR (thin film, KBr) 3445, 2928, 2856, 1694, 1611, 1582, 1471, 1435 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{24}O_2Si$ $[M-H_2O]^+$ 288.1546, found 288.1562; Optical rotation crude $[a]_D^{23}$ -3.2 (c = 0.75, $CHCl_3$), purified $[a]_D^{22}$ -9.2 (c = 1.20, $CHCl_3$).



(+)-18

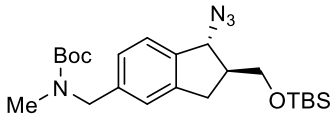
(1*S*,2*R*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-((methylaminuteso)methyl)-2,3-dihydro-1H-inden-1-ol (+)-18. To a solution of the aldehyde **17** (21.5 g, 70.2 mmol) in MeOH (70 mL) was added 40 wt% $MeNH_2$ (18.2 mL, 210.6 mmol, 3.0 equiv.) at 0 ºC. The resulting solution was stirred at 0 ºC for 30 minutes, followed by the addition of $NaBH_4$ (6.64 g, 175.5 mmol, 2.5 equiv.) in portions. The resulting suspension was continued to stir at 0 ºC for 2 hours. The reaction mixture was then treated with sat. $NaHCO_3$ (50 mL) and then H_2O (50 mL). The resulting mixture was allowed to warm to room temperature and extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the secondary amine as an orange oil, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.36 (d, *J* = 7.7 Hz, 1H), 7.19 (s, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 5.21 (d, *J* = 6.4 Hz, 1H), 3.96 – 3.83 (m, 2H), 3.73 (s, 2H), 3.43 (brs, 2H), 2.87 (dd, *J* = 16.0, 8.1 Hz, 1H), 2.80 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.71 – 2.58 (m, 1H), 2.41 (s, 3H), 0.85 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) d 144.13, 142.96, 138.48, 127.11, 124.87, 124.76, 76.44, 63.42, 55.26, 45.45, 35.04, 33.13, 25.78, 18.07, -5.44, -5.52; IR 2928, 2360, 1471, 1360, 1254, 1079 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{31}NO_2Si$ $[M]^+$ 321.2124, found 321.2117; Optical rotation crude $[a]_D^{24}$ +2.0 (c = 0.58, $CHCl_3$), purified $[a]_D^{23}$ +3.1 (c = 0.53, $CHCl_3$).



(+)-**19**

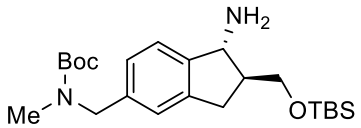
***tert*-Butyl(((1*S*,2*R*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-hydroxy-2,3-dihydro-1H-inden-5-yl)methyl)(methyl)carbamate (+)-19.** To a solution of the amine **18** (22.1 g, 68.7 mmol) was dissolved in CH_2Cl_2 (70 mL) and this solution was cooled at 0 ºC, to which a solution of Boc_2O (13.49 g, 61.8 mmol, 0.9 equiv.) in CH_2Cl_2 (20 mL) was added dropwise for 30 minutes. The reaction mixture was stirred for 1 hours at 0 ºC. The solvent were then evaporated on a rotary evaporator to give crude carbamate **19** as an amber oil, which was used directly for the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.38 (d, *J* = 7.7 Hz, 1H), 7.08 (brs, 2H), 5.26 (dd, *J* = 5.7, 5.2 Hz, 1H), 4.4 (s, 2H), 4.01 – 3.94 (m, 1H), 3.92 – 3.85 (m, 1H), 3.24 (s, 1H), 2.94 – 2.86 (m, 1H), 2.85 – 2.72 (m, 4H), 2.71 – 2.63 (m, 1H), 1.48 (s, 9H), 0.85 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers) d 156.15/ 155.86, 143.93, 142.97,

138.25, 126.45/125.90, 124.81, 124.10/123.45, 79.65, 76.77, 63.62, 52.58/51.92, 45.20, 33.82, 33.25, 28.50, 25.80, 18.09, -5.43, -5.53; IR (thin film, KBr) 3456, 2930, 1808, 1694, 1462, 1392, 1371, 1213, 1120 cm^{-1}; HRMS (ESI) calculated for $C_{23}H_{39}NO_4SiNa$ $[M+Na]^+$ 444.2546, found 444.2550; Optical rotation crude $[a]_D^{22}$ -1.5 (c = 0.99, $CHCl_3$), purified $[a]_D^{24}$ +0.2 (c = 1.07, $CHCl_3$).



(+)-20

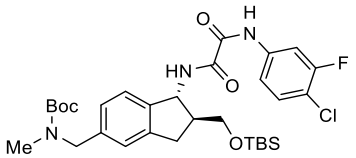
***tert*-butyl (((1*R*,2*S*)-1-azido-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,3-dihydro-1H-inden-5-yl)methyl)(methyl)carbamate (+)-20.** To a solution of the alcohol **19** (29.7 g, 68.7 mmol) in toluene (230 mL) was added diphenylphosphoryl azide (17.7 mL, 82.4 mmol, 1.2 equiv.) dropwise for 10 minutes, followed by dropwise addition of DBU (12.3 mL, 82.4 mmol, 1.20 equiv.) over 30 minutes. During the addition of DBU, the reaction mixture exhibited mild exotherm. The resulting cloudy mixture was warmed to 70 ºC and continued to stir at 70 ºC for 4 hours. The resulting red slurry was allowed to cool to room temperature, and the solvent was evaporated in vacuo. The residue was treated with H_2O (200 mL), and the resulting mixture was extracted with Et_2O (5 x 50 mL). The combined organic layers were then washed with 10 wt% citric acid (50 mL) and then 10 wt% $NaHCO_3$ (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give an red oil, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.31 (d, *J* = 7.6 Hz, 1H), 7.09 (s, 1H), 4.73 (d, *J* = 7.6 Hz, 1H), 4.40 (brs, 2H), 3.78 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.65 (dd, *J* = 10.2, 6.3 Hz, 1H), 3.06 (dd, *J* = 16.0, 8.1 Hz, 1H), 2.86 – 2.76 (m, 3H), 2.71 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.65 – 2.55 (m, 1H), 1.48 (brs, 9H), 0.89 (s, 9H), 0.09 – 0.04 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers) d 156.13/155.75, 142.91, 139.49, 138.90, 126.48/126.08, 124.73, 124.33/123.83, 79.67, 67.32, 63.64, 52.56/51.85, 49.45, 33.97, 33.20, 28.48, 25.92, 18.33, -5.35, -5.37; IR (thin film, KBr) 2929, 2857, 2094, 1698, 1472, 1391, 1366, 1252, 1145 cm^{-1}; HRMS (ESI) calculated for $C_{23}H_{38}N_4O_3SiNa$ $[M+Na]^+$ 469.2611, found 469.2600. Optical rotation crude $[a]_D^{24}$ +1.5 (c = 0.67, $CHCl_3$), purified $[a]_D^{23}$ +18.2 (c = 0.83, $CHCl_3$).



(+)-7

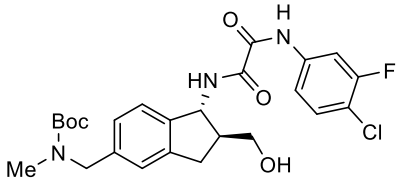
***tert*-Butyl(((1*R*,2*S*)-1-amino-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,3-dihydro-1H-inden-5-yl)methyl)(methyl)carbamate 11.** To a solution of the azide **20** (30.7 g, 68.7 mmol) was dissolved in MeOH (230 mL). To the resulting solution was added $NiCl_2$•$6H_2O$ (1.63 g, 6.87 mmol, 0.1 equiv.). After $NiCl_2$•$6H_2O$ was completely dissolved, the resulting solution cooled to 0 ºC and was treated with $NaBH_4$ (7.80 g, 206.1 mmol, 3 equiv.) in portions such that the reaction mixture maintained mild gas evolution. After the addition was complete, the reaction mixture was stirred at 0 ºC until the gas evolution had ceased. The resulting brown solution was then allowed to warm to room temperature and further

stirred for 4 hours until the reaction mixture became a green suspension. The solvent was evaporated in vacuo. The residue was diluted with CH_2Cl_2 (50 mL) and H_2O (50 mL), and then treated with aqueous NH_4OH (50 mL, 30 wt%) with stirring. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (2 x 50 mL). The organic layers were combined and filtered through a fritted funnel. The aqueous layer of the filtrate was removed, the organic layer dried over Na_2SO_4, filtered, and concentrated in vacuo to give crude **7** as an brown oil, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.35 (d, *J* = 7.6 Hz, 1H), 7.03 (brs, 2H), 4.37 (brs, 2H), 4.25 (d, *J* = 7.6 Hz, 1H), 3.97 (brs, 2H), 3.88 – 3.81 (m, 1H), 3.80 – 3.72 (m, 1H), 2.98 (dd, *J* = 15.9, 8.1 Hz, 1H), 2.82 – 2.73 (m, 3H), 2.65 (dd, *J* = 15.9, 8.3 Hz, 1H), 2.40 – 2.30 (m, 1H), 1.46 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers) d 156.22/155.95, 143.38/143.12, 142.76, 137.98, 126.31/126.03, 124.11, 123.65, 79.75, 64.69, 59.25, 52.61, 52.23, 33.97, 33.38, 28.57, 26.02, 18.37, -5.24, -5.30; IR (thin film, KBr) 3387, 2360, 1686, 1391, 1250 cm^{-1}; HRMS (ESI) calculated for $C_{23}H_{41}N_2O_3Si$ $[M+H]^+$ 421.2886, found 421.2880; Optical rotation crude $[a]_D^{22}$ -3.3 (c = 0.79, $CHCl_3$), purified $[a]_D^{24}$ +10.0 (c = 0.78, $CHCl_3$).



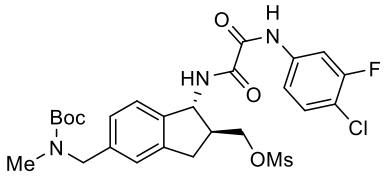
(+)-9

***tert*-butyl(((1*R*,2*S*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-(2-((4-chloro-3-fluorophenyl)amino)-2-oxoacetamido)-2,3-dihydro-1H-inden-5-yl)methyl)(methyl)carbamate (+)-9.** A mixture of amine **7** (28.9 g, 68.7 mmol), ester **21** (19.2 g, 78.3 mmol, 1.14 equiv.), 3-nitrophenol (1.91 g, 13.74 mmol, 0.2 equiv.), and K_2CO_3 (1.90 g, 13.74 mmol, 0.2 equiv.) in THF (100 mL) was stirred at 65 ºC for 48 h. The resulting suspension was allowed to cool to room temperature and then treated with 10 wt% K_2CO_3 (50 mL). The resulting mixture was further stirred at room temperature for 6 hours, and then diluted with EtOAc (50 mL). The insoluble material was removed via vacuum filtration, and the solid was rinsed with EtOAc (2x100 mL). After the filtrates were combined, the organic layer was separated and washed with 10 wt% K_2CO_3 (50 mL). The aqueous layers were combined and extracted with EtOAc (50 mL). The organic layers were combined and washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give crude amide **9** as a brown oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) d 9.45 (s, 1H), 7.82 – 7.63 (m, 2H), 7.36 (t, *J* = 8.3 Hz, 1H), 7.31 – 7.23 (m, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.13 – 7.00 (m, 2H), 5.34 (dd, *J* = 8.4, 8.2 Hz, 1H), 4.40 (s, 2H), 3.80 (d, 5.4 Hz, 2H), 3.07 (dd, *J* = 16.1, 8.3 Hz, 1H), 2.91 – 2.72 (m, 4H), 2.62 – 2.43 (m, 1H), 1.48 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 159.37, 158.25 (d, J_{CF} = 248.4 Hz), 157.74, 156.28/155.90, 142.93, 140.65, 138.78, 136.45 (d, J_{CF} = 9.8 Hz), 130.96, 126.64/126.21, 124.27, 123.84, 117.24 (d, J_{CF} = 18.0 Hz), 116.1 (d, J_{CF} = 3.6 Hz), 108.6 (d, J_{CF} = 26.0 Hz), 79.87, 63.95, 57.05, 52.62/51.98, 51.06, 34.07, 33.58, 28.60, 25.96, 18.38, -5.30, -5.31; IR (thin film, KBr) 3284, 2929, 2857, 1667, 1595, 1516, 1428 cm^{-1}; HRMS (ESI) calculated for $C_{31}H_{44}ClFN_3O_5Si$ $[M+H]^+$ 620.2723, found 620.2729; Optical rotation crude $[a]_D^{22}$ +65.8 (c = 2.47, CH_2Cl_2), purified $[a]_D^{24}$ +60.4 (c = 0.59, CH_2Cl_2).



(+)-10

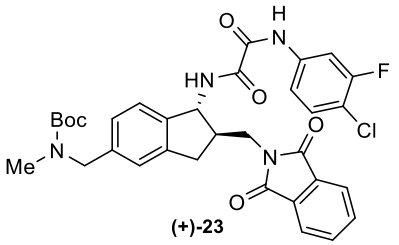
***tert*-Butyl(((1*R*,2*S*)-1-(2-((4-chloro-3-fluorophenyl)amino)-2-oxoacetamido)-2-(hydroxymethyl)-2,3-dihydro-1H-inden-5-yl)methyl)(methyl)carbamate (+)-10.** Crude amide **9** (42.6 g, 68.7 mmol) was dissolved in THF (210 mL), and the resulting solution was diluted with MeOH (70 mL) and H_2O (70 mL), to which conc. HCl (2.5 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight. The resulting thick slurry was then treated with sat. $NaHCO_3$ (50 mL) followed by H_2O (200 mL). The insoluble material was collected via vacuum filtration, washed with H_2O (5x50 mL) and then diethyl ether (5 x 50 mL), followed by drying under vacuum to constant weight to give amide **10** as an off-white powder (13.2 g, 26.2 mmol, 35% yield from diol **17**). ^{1}H NMR (400 MHz, DMSO-d_6) d 11.06 (s, 1 H), 9.31 (d, J = 8.8 Hz, 1 H), 7.96 (dd, J = 11.8, 2.0 Hz, 1 H), 7.74 (dd, J = 8.8, 1.2 Hz, 1 H), 7.58 (t, J = 8.7 Hz, 1 H), 7.11 (d, J = 7.6 Hz, 1 H), 7.07 (s, 1 H), 7.02 (d, J = 7.6 Hz, 1 H), 5.21 (t, J = 7.7 Hz, 1 H), 4.70 (t, J = 4.8 Hz, 1 H), 4.33 (s, 2 H), 3.61 – 3.45 (m, 2 H), 3.10 – 2.96 (m, 1 H), 2.78 – 2.65 (m, 5 H), 1.41 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6, mixture of rotamers) d 159.80, 159.04, 156.83 (d, J_{CF} = 244.0 Hz), 155.22/154.77, 142.67, 142.00, 138.35 (d, J_{CF} = 10.0 Hz), 137.61, 130.59, 125.65, 123.87, 123.60, 117.36 (d, J_{CF} = 3.0 Hz), 114.35 (d, J_{CF} = 17.6 Hz), 108.51 (d, J_{CF} = 25.7 Hz), 78.81, 61.86, 55.91, 51.72/51.04, 48.47, 33.71, 33.38, 28.10; IR (thin film, KBr) 3268, 1699, 1663, 1516, 1140 cm^{-1}; HRMS (ESI) calculated for $C_{25}H_{29}ClFN_3O_5Na$ $[M+Na]^+$ 528.1677, found 528.1684; Optical rotation crude $[a]_D^{22}$ +66.6 (c = 0.42, acetone), purified $[a]_D^{24}$ +65.2 (c = 0.51, acetone).



(+)-22

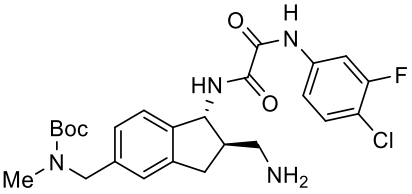
((1*R*,2*S*)-5-(((*tert*-Butoxycarbonyl)(methyl)amino)methyl)-1-(2-((4-chloro-3-fluorophenyl)amino)-2-oxoacetamido)-2,3-dihydro-1H-inden-2-yl)methyl methanesulfonate (+)-22. Primary alcohol **10** (13.2 g, 26.2 mmol) was added to DMF (25 mL). The resulting mixture was stirred at room temperature until most of the solid was dissolved. The resulting suspension was diluted with THF (100 mL), and the resulting mixture was cooled to 0 ºC, to which triethylamine (7.3 mL, 52.4 mmol, 2 equiv.) was added in one portion, followed by dropwise addition of methanesulfonyl chloride (4.1 mL, 52.4 mmol, 2 equiv.). The reaction mixture was further stirred at 0 ºC for 2 hours, and then allowed to warm to room temperature. The resulting suspension was treated with H_2O (250 mL). The resulting precipitate was collected via vacuum filtration. The solid was then washed with H_2O (5 x 50 mL) followed by Et_2O (5 x 50 mL), dried under vacuum to constant weight to give mesylate **22** as an off-white solid (14.1 g, 24.1 mmol, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) d 11.07 (s, 1H), 9.44 (d, J = 8.9 Hz, 1H), 7.97 (dd, J = 11.8,

2.1 Hz, 1H), 7.76 (dd, J = 8.9, 1.2 Hz, 1H), 7.58 (t, J = 8.7 Hz, 1H), 7.17 – 7.09 (m, 2H), 7.07 (d, J = 7.7 Hz, 1H), 5.30 (dd, J = 8.6, 8.5 Hz, 1H), 4.41 (d, J = 5.6 Hz, 2H), 4.35 (s, 2H), 3.21 (s, 3H), 3.16 – 3.06 (m, 1H), 3.05 – 2.93 (m, 1H), 2.84 – 2.71 (m, 4H), 2.50 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, mixture of rotamers) d 159.91, 158.81, 156.83 (d, J_{CF} = 244.0 Hz), 155.22/154.74, 141.47, 141.12, 138.34 (d, J_{CF} = 10.0 Hz), 137.93, 130.59, 125.93, 123.72, 123.60, 117.36 (d, J_{CF} = 3.1 Hz), 114.37 (d, J_{CF} = 17.6 Hz), 108.50 (d, J_{CF} = 25.7 Hz), 78.83, 71.01, 55.77, 51.68/51.00, 45.28, 36.58, 33.71, 32.93, 28.09; IR (thin film, KBr) 3282, 3262, 2905, 1696, 1663, 1591, 1518, 1412, 1359 cm^{-1}; HRMS (ESI) calculated for $C_{26}H_{31}ClFN_3O_7SNa$ $[M+Na]^+$ 606.1453, found 606.1476; Optical rotation crude $[a]_D^{22}$ +52.1 (c = 1.08, acetone), purified $[a]_D^{24}$ +47.3 (c = 1.12, acetone).



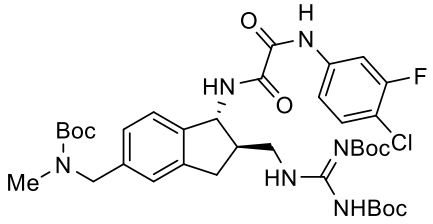
(+)-23

***tert*-Butyl(((1*R*,2*R*)-1-(2-((4-chloro-3-fluorophenyl)amino)-2-oxoacetamido)-2-((1,3-dioxoisoindolin-2-yl)methyl)-2,3-dihydro-1H-inden-5-yl)methyl)(methyl)carbamate (+)-23.** A mixture of mesylate **22** (14.1 g, 24.1 mmol), potassium phthalimide (6.87 g, 37.1 mmol, 1.54 equiv.), and tetrabutylammonium iodide (0.89 g, 2.41 mmol, 0.1 equiv.) in DMF (80 mL) was stirred at 35 ºC for 3 days. The reaction mixture was allowed to cool to room temperature and treated with H_2O (300 mL) dropwise with vigorous stirring, and the resulting precipitate collected via vacuum filtration. The solid was washed with H_2O (5 x 50 mL) and then Et_2O (5 x 50 mL). The ethereal phase of the filtrate was separated, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was treated with Et_2O (20 mL), and the insoluble material was collected via vacuum filtration. The combined solids were dried under vacuum to constant weight to give the phthalimide **23** as a pale yellow powder (15.0 g, 23.62 mmol, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) d 10.89 (s, 1H), 9.38 (d, 8.5 Hz, 1H), 7.90 – 7.78 (m, 3H), 7.77 – 7.70 (m, 2H), 7.65 (d, J = 8.8 Hz, 1H), 7.55 (t, J = 8.5 Hz, 1H), 7.13 – 6.98 (m, 3H), 5.18 (dd, J = 7.6, 7.5 Hz, 1H), 4.32 (s, 2H), 3.90 – 3.72 (m, 2H), 3.18 – 2.94 (m, 2H), 2.80 – 2.63 (m, 4H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6, mixture of rotamers) d 167.91, 159.49, 158.55, 156.75 (d, J_{CF} = 244.1 Hz), 155.17/154.71, 141.79, 141.30, 138.23 (d, J_{CF} = 10.1 Hz), 137.77, 134.20, 131.54, 130.47, 125.78, 123.77, 123.43, 123.00, 117.31, 114.25 (d, J_{CF} = 17.6 Hz), 108.41 (d, J_{CF} = 25.9 Hz), 78.78, 57.74, 51.67/50.98, 44.87, 34.38, 33.67, 28.07; IR (thin film, KBr) 3266, 2975, 2383, 2348, 1769, 1707, 1661, 1594, 1517 cm^{-1}; HRMS (ESI) calculated for $C_{33}H_{32}ClFN_4O_6Na$ $[M+Na]^+$ 657.1892, found 657.1864; Optical rotation crude $[a]_D^{22}$ +52.9 (c = 0.50, acetone), purified $[a]_D^{24}$ +54.0 (c = 0.55, acetone).



(+)-24

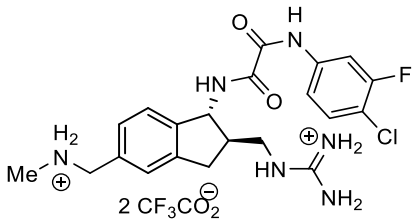
***tert*-Butyl(((1*R*,2*R*)-2-(aminomethyl)-1-(2-((4-chloro-3-fluorophenyl)amino)-2-oxoacetamido)-2,3-dihydro-1H-inden-5-yl)methyl)(methyl)carbamate (+)-24.** Phthalimide **23** (15.0 g, 23.62 mmol) was added to THF (180 mL), and the resulting mixture was warmed to 50 ºC. The resultant solution was charged with EtOH (180 mL). The resulting suspension was stirred at 50 ºC until a homogeneous solution had formed, to which hydrazine monohydrate (5.73 mL, 118.1 mmol, 5.0 equiv.) was added dropwise, and the reaction mixture was continued to stir at 50 ºC for 24 hours. The resulting thick slurry was allowed to cool to room temperature and then concentrated in vacuo, and the residue was treated with 5 wt% Na_2CO_3 (200 mL). The insoluble material was collected via vacuum filtration, washed with 5 wt% $NaHCO_3$ (100 mL), H_2O (100 mL), and then Et_2O (5 x 50 mL). The resulting damp solid was allowed to dry in air followed by drying under vacuum to constant weight to give amine **24** as a pale yellow solid (9.42 g, 18.66 mmol, 79%). ^{1}H NMR (400 MHz, MeOH-d_4) d 7.86 (dd, J = 11.4, 2.3 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.45 (t, J = 8.4 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.19 – 7.10 (m, 2H), 5.27 (d, J = 7.5 Hz, 1H), 4.43 (s, 2H), 3.36 – 3.31 (m, 1H), 3.29 – 3.16 (m, 2H), 2.86 -2.65 (m, 5H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, MeOH-d_4, mixture of rotamers) d 162.16, 159.49, 159.14 (d, J_{CF} = 245.7 Hz), 157.54, 142.81, 140.96, 140.05, 139.04 (d, J_{CF} = 9.8 Hz), 131.73, 127.83/127.69, 125.30, 124.96/124.77, 118.09 (d, J_{CF} = 3.6 Hz), 117.26 (d, J_{CF} = 17.9 Hz), 109.76 (d, J_{CF} = 26.3 Hz), 81.33, 59.28, 53.36/52.64, 47.90, 43.39, 35.69, 34.41, 28.70; IR (thin film, KBr) 3279, 2902, 2386, 1703, 1662, 1595, 1514, 1429 cm^{-1}; HRMS (ESI) calculated for $C_{25}H_{31}ClFN_4O_4$ $[M+H]^+$ 505.2018, found 505.2017; Optical rotation crude $[a]_D^{23}$ +26.7 (c = 0.85, CH_3OH), purified $[a]_D^{23}$ +11.9 (c = 0.85, CH_3OH).



(+)-12

The *tri*-Boc-BNM-III-170 (+)-12. To a slurry of amine **24** (9.42 g, 18.66 mmol) in DMF (40 mL) was added *N*,*N'*-Di-Boc-1H-pyrazole-1-caboxamidine **25** (6.37 g, 20.53 mmol, 1.1 equiv.) in one portion. The reaction mixture was stirred at room temperature for 24 hours, and the resulting solution then treated with ethylenediamine (3 mL). The resulting mixture was further stirred at room temperature overnight, and then was diluted with ethyl acetate (100 mL). The resulting solution was treated with 5 wt% $NaHSO_4$ (200 mL). The organic layer was separated. The aqueous filtrate was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with H_2O (200 mL) and then brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in minimal volume of CH_2Cl_2 (20 mL), and resulting solution was passed through a plug of silica gel (Hexanes/EtOAc 10/1 to 1/1) to give **12** as a pale yellow solid (7.67 g, 10.26 mmol, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) d 11.47 (s, 1H), 9.44 (s, 1H), 8.65 – 8.44 (m, 1H), 7.83 (d, J = 9.3 Hz, 1H), 7.74 (dd, J = 10.5, 1.3 Hz, 1H), 7.36 (t, J = 8.3 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.14 – 7.03 (m, 3H), 5.28 (t, J = 8.6 Hz, 1H), 4.38 (s, 2H), 3.87 – 3.74 (m, 1H), 3.73 – 3.61 (m, 1H), 3.16 (dd, J = 15.3, 7.5 Hz, 1H), 2.87 – 2.58 (m, 5H), 1.56 –

1.33 (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of rotamers) d 163.57, 159.82, 158.16 (d, J_{CF} = 248.3 Hz), 157.48, 156.39, 156.24/155.86, 153.31, 141.78, 140.24, 138.97, 136.55 (d, J_{CF} = 9.8 Hz), 130.87, 126.84/126.37, 124.29, 123.79, 117.07 (d, J_{CF} = 17.8 Hz), 116.00 (d, J_{CF} = 3.5 Hz), 108.43 (d, J_{CF} = 26.1 Hz), 83.25, 79.86, 79.50, 58.77, 52.53/51.89, 47.99, 43.69, 34.71, 34.04, 28.56, 28.38, 28.02; IR (thin film, KBr) 3285, 2979, 2927, 1722, 1668, 1642, 1515, 1413, 1137 cm^{-1}; HRMS (ESI) calculated for $C_{36}H_{49}ClFN_6O_8$ $[M+H]^+$ 747.3284, found 747.3290; Optical rotation crude $[a]_D^{24}$ +30.7 (c = 1.32, $CHCl_3$), purified $[a]_D^{24}$ +33.0 (c = 1.29, $CHCl_3$).



(+)-(*R*,*R*)-BNM-III-170 **1**

1-((1*R*,2*R*)-2-(((amino(iminio)methyl)amino)methyl)-1-(2-((4-chloro-3-fluorophenyl)amino)-2-oxoacetamido)-2,3-dihydro-1H-inden-5-yl)-*N*-methylmethanaminium 2,2,2-trifluoroacetate 1. To a solution of **12** (7.67 g, 10.26 mmol) in CH_2Cl_2 (102 mL) at 0 ºC was added a solution of trifluoroacetic acid (31.4 mL, 410.4 mmol, 40 equiv.) in CH_2Cl_2 (30 mL) dropwise over 30 minutes. The reaction mixture was allowed to warm to room temperature and then further stirred at room temperature for 14 hours, by which point LC-MS indicated full deprotection. The solvent and excess acid were then removed in vacuo. The residue was dissolved in methanol (50 mL) and then diluted with EtOAc (200 mL). The resulting solution was treated hexanes (200 mL), and the resulting precipitate collected via vacuum filtration. The solid was washed with Hexanes/EtOAc (1:1 v/v, 300 mL) and was further dried under vacuum to constant weight to give the bistrifluoroacetate salt **1** as a white powder (6.17 g, 9.14 mmol, 89% yield). ^{1}H NMR (500 MHz, DMSO-d_6) d 11.07 (s, 1 H), 9.47 (d, *J* = 8.9 Hz, 1 H), 8.81 (s, 2 H), 7.98 (dd, *J* = 11.8 Hz, 2.2 Hz, 1 H), 7.82 – 7.69 (m, 2 H), 7.60 (t, *J* = 8.7 Hz, 1 H), 7.35 (s, 1 H), 7.30 (d, *J* = 7.8 Hz, 1 H), 7.21 (d, *J* = 7.8 Hz, 1H), 5.18 (t, *J* = 8.7 Hz, 1 H), 4.10 (s, 2 H), 3.47 – 3.34 (m, 2 H), 3.13 (dd, *J* = 15.7, 8.0 Hz, 1 H), 2.93 – 2.78 (m, 1 H), 2.68 (dd, *J* = 15.5, 9.2 Hz, 1H), 2.55 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) d 160.25, 159.53 (q, J_{CF} = 32.2 Hz, TFA), 158.96, 157.46, 157.01 (d, J_{CF} = 244.1 Hz), 143.54, 141.97, 138.48 (d, J_{CF} = 9.9 Hz), 131.70, 130.71, 128.58, 126.32, 124.01, 117.50 (d, J_{CF} = 2.7 Hz), 117.13 (q, J_{CF} = 297.7 Hz, TFA), 114.57 (d, J_{CF} = 17.8 Hz), 108.66 (d, J_{CF} = 25.7 Hz), 57.14, 51.37, 45.56, 43.13, 34.02, 32.11; IR (thin film, KBr) 3277, 2359, 1664, 1521, 1205, 1145 cm^{-1}; HRMS (ESI) calculated for $C_{21}H_{25}ClFN_6O_2$ $[M+H]^+$ 447.1712, found 447.1707. Optical rotation $[a]_D^{24}$ +37.3 (c = 1.00, CH_3OH).

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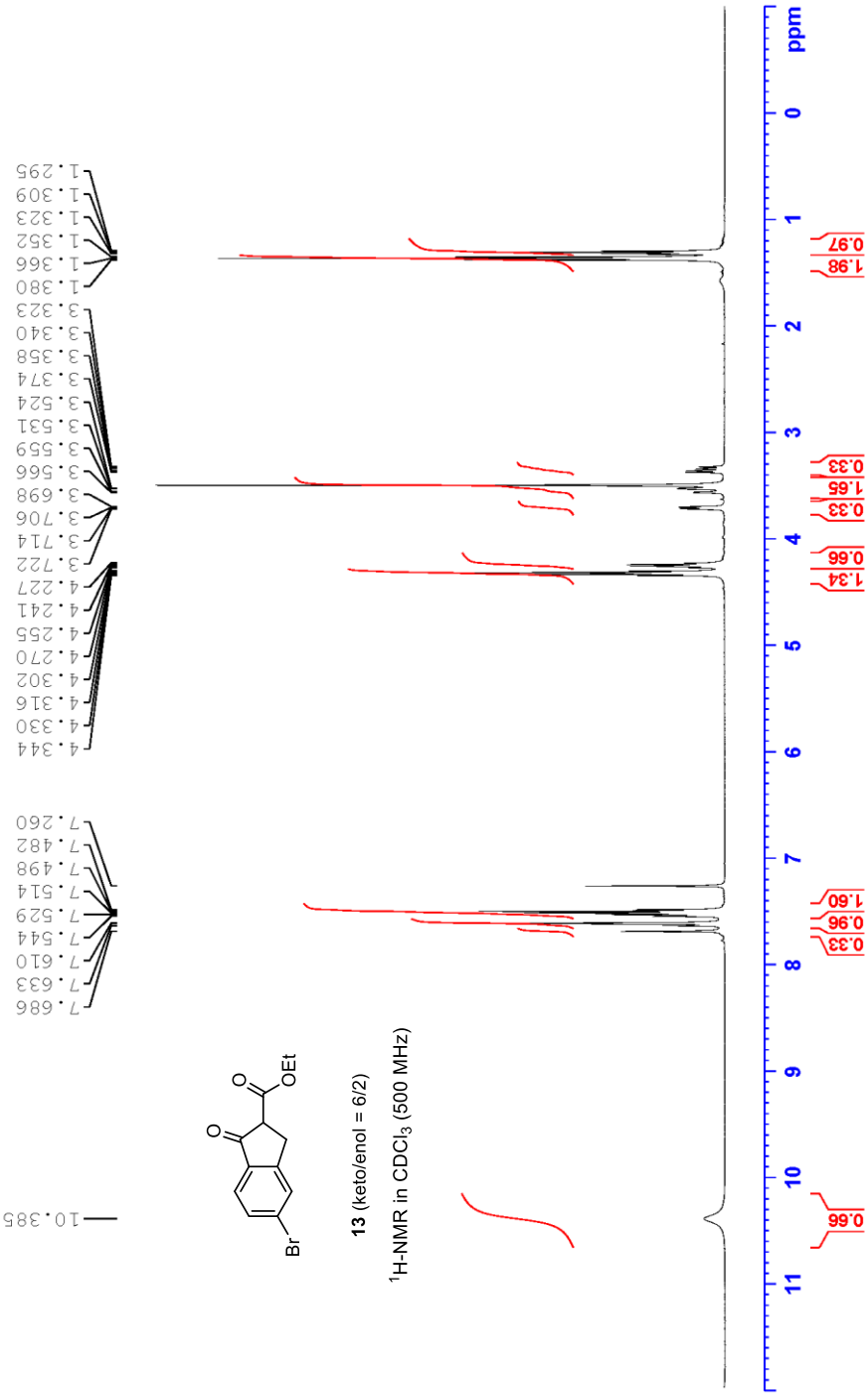
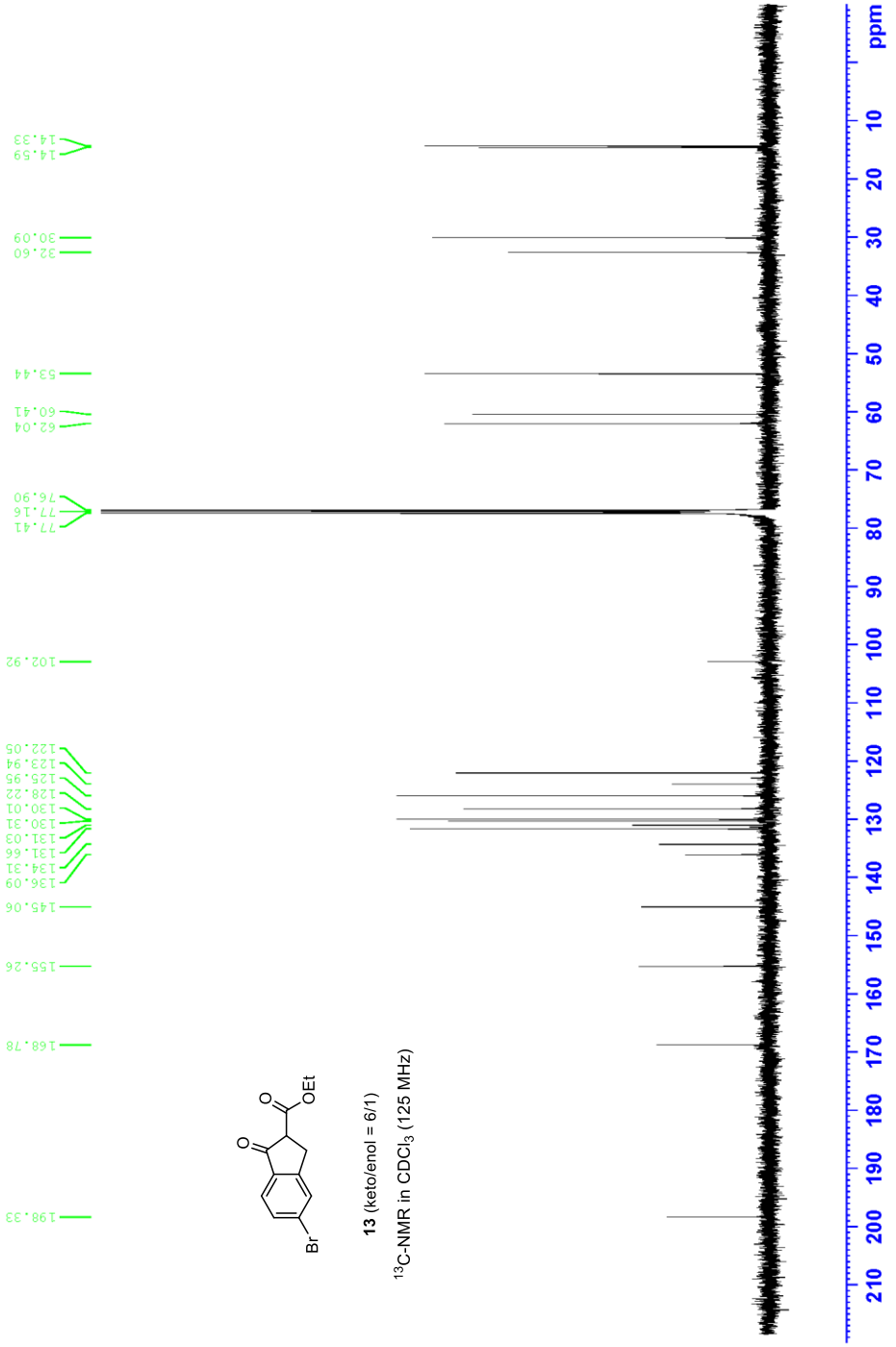
Appendices

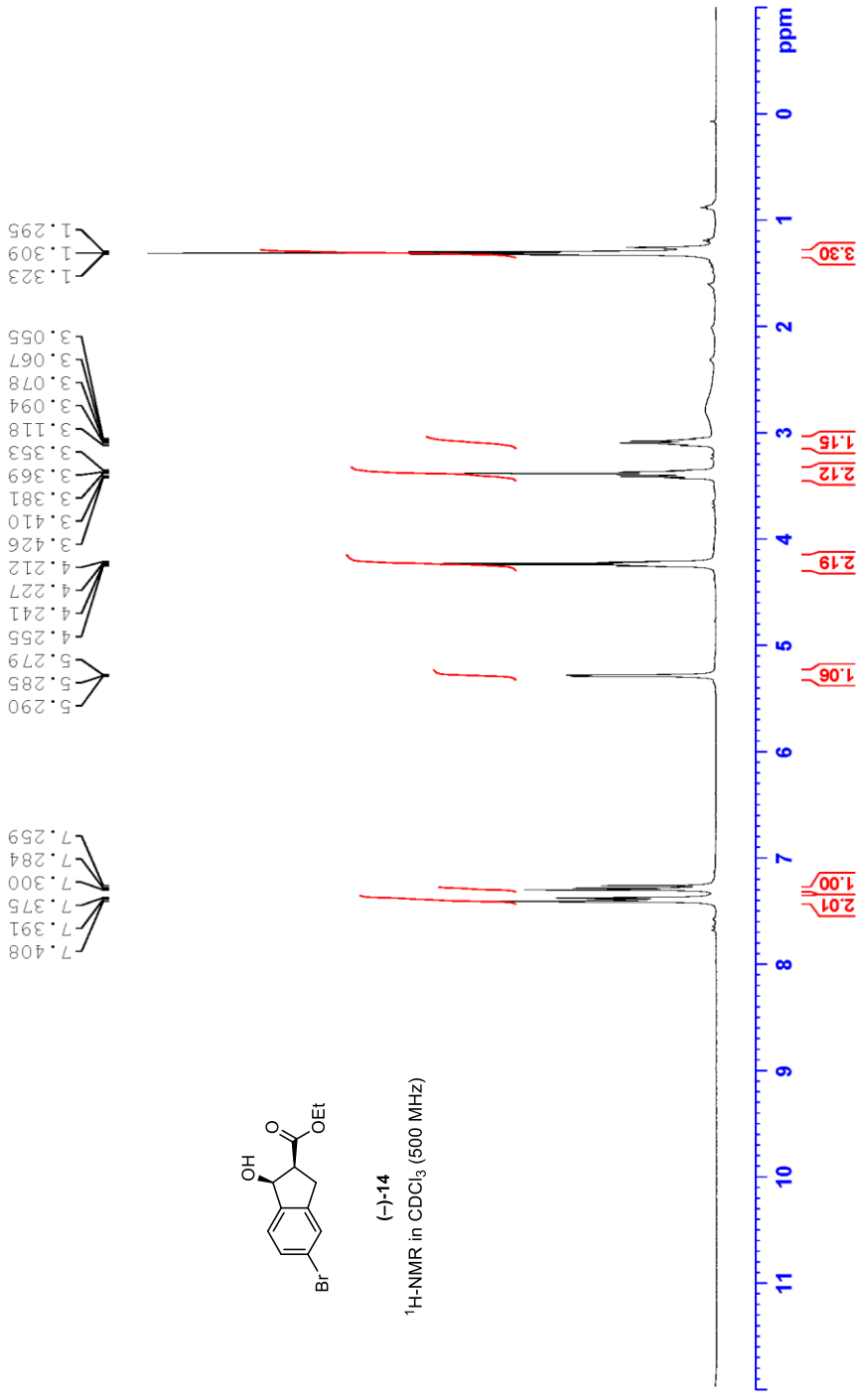
Appendix 1. ^{1}H NMR of **13**



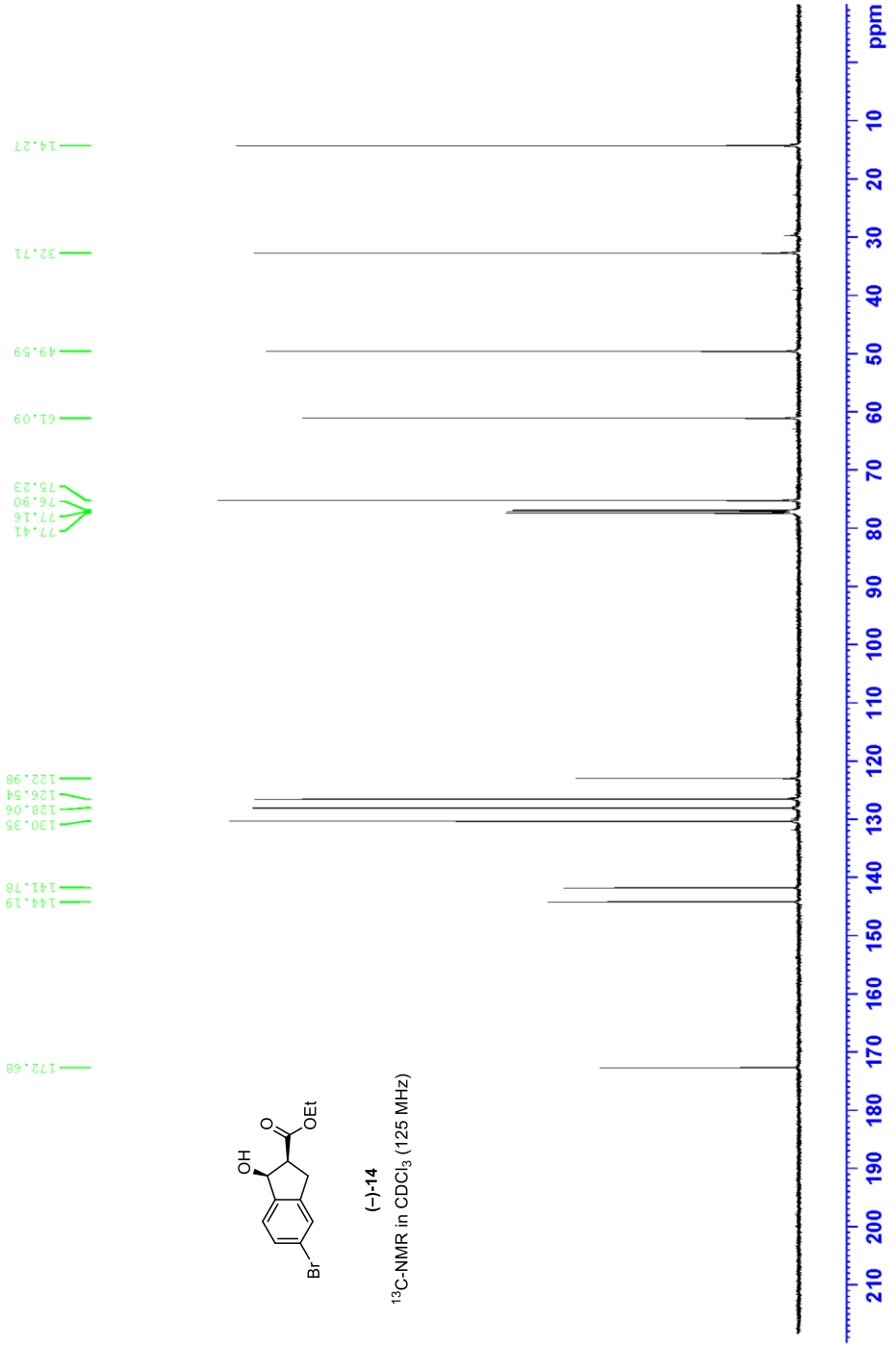
Appendix 2. ^{13}C NMR of **13**



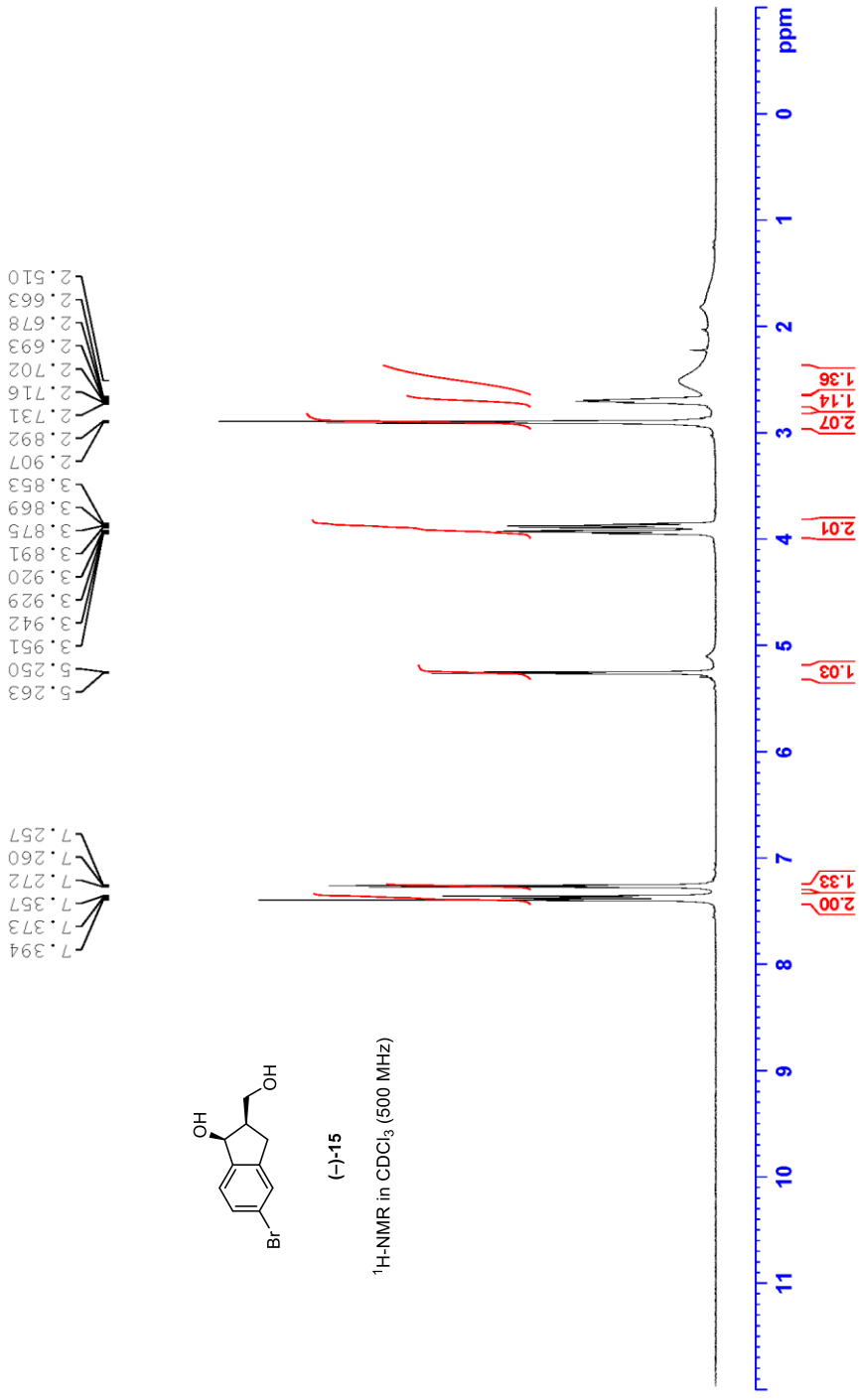
Appendix 3. ^{1}H NMR of **(-)-14**



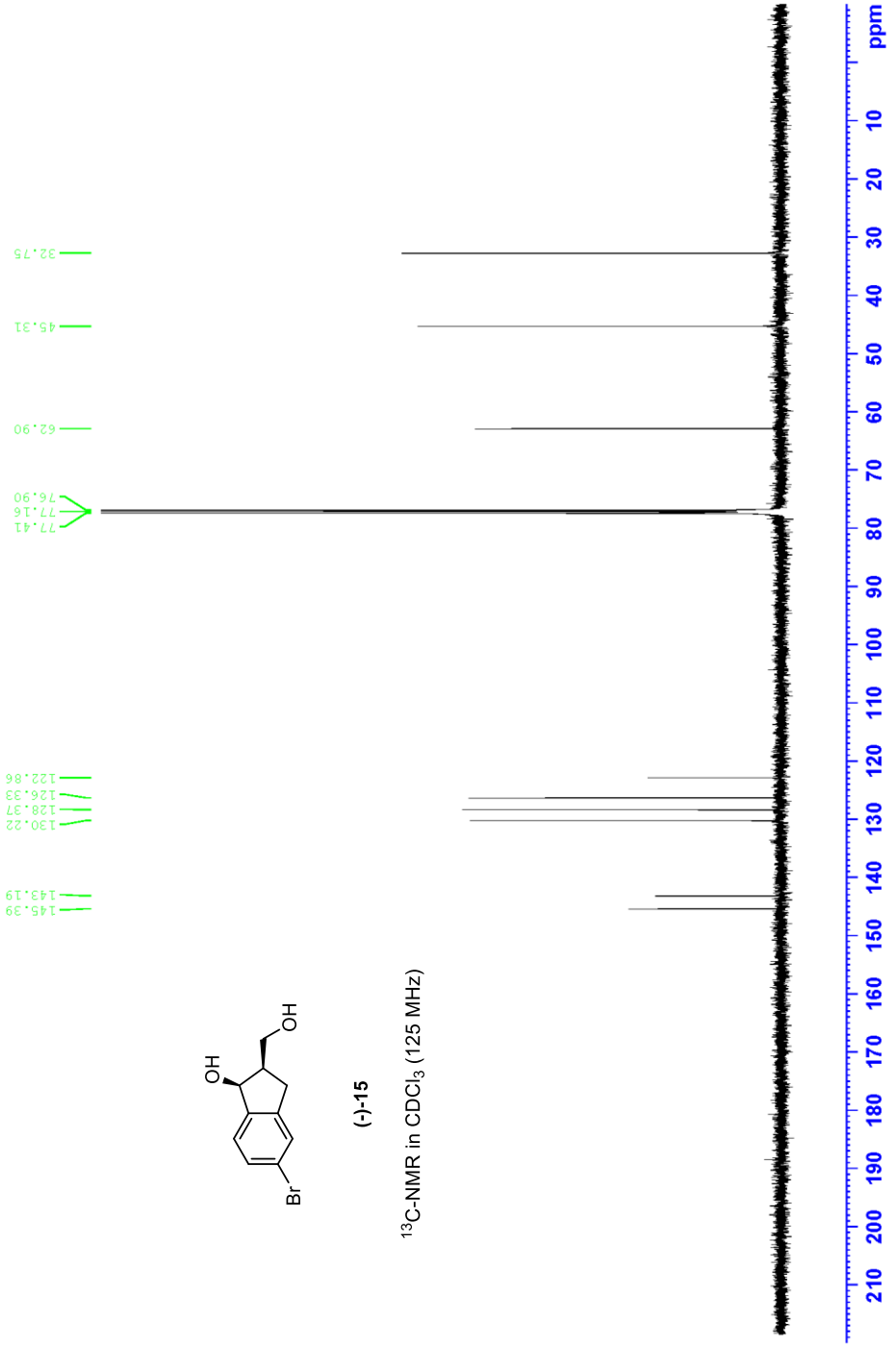
Appendix 4. ^{13}C NMR of **(-)-14**



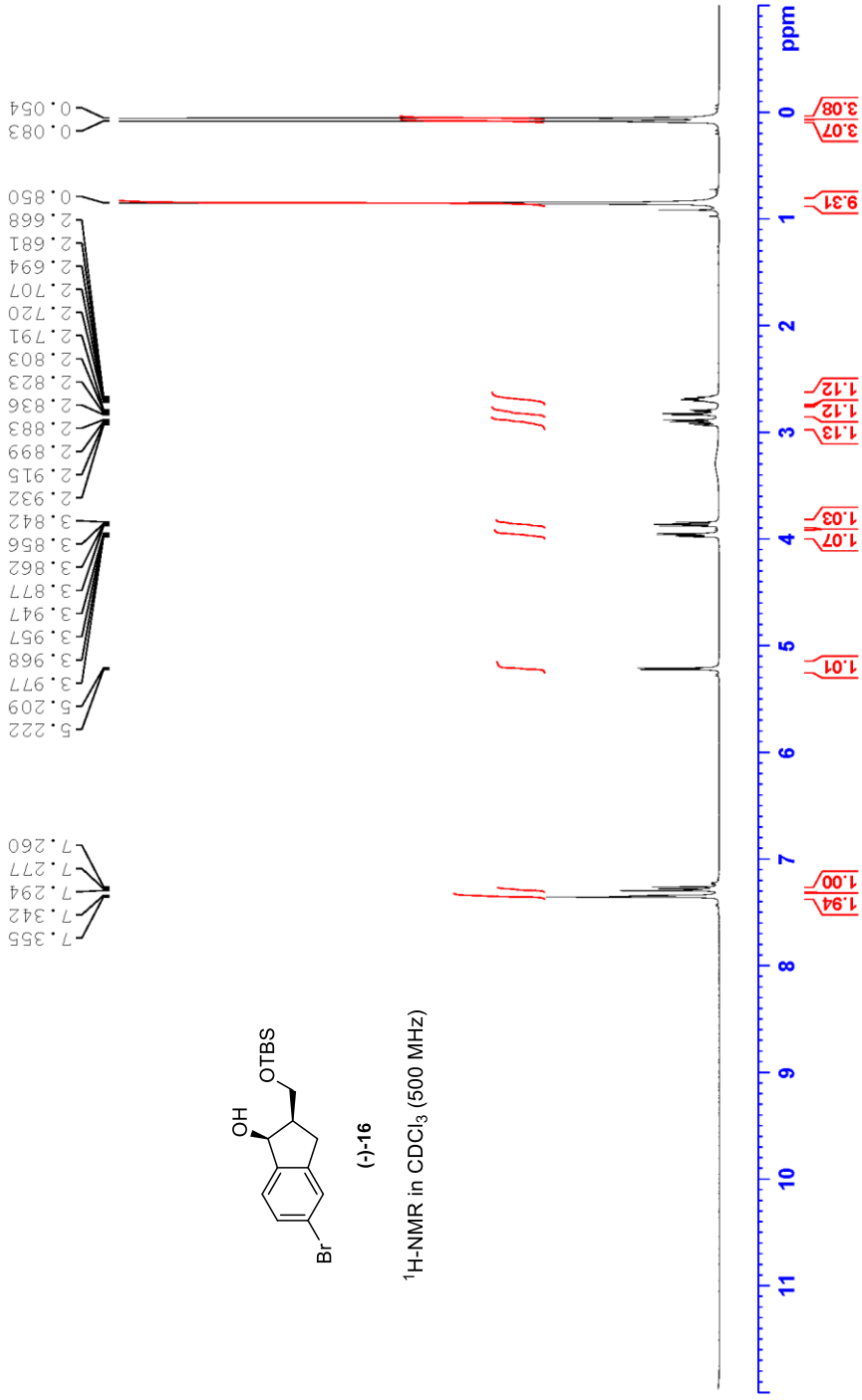
Appendix 5. ^{1}H NMR of **(-)-15**



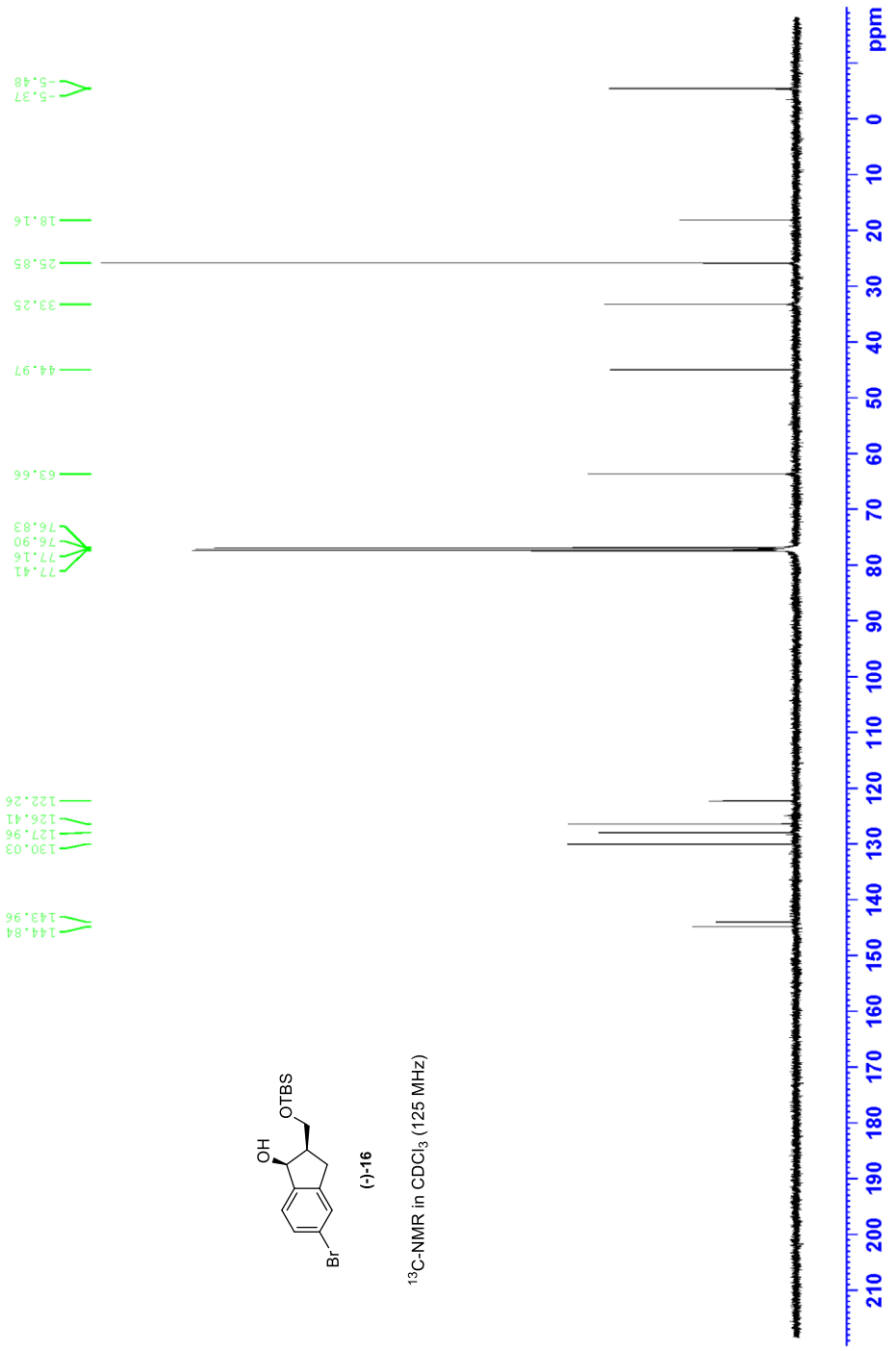
Appendix 6. ^{13}C NMR of **(-)-15**



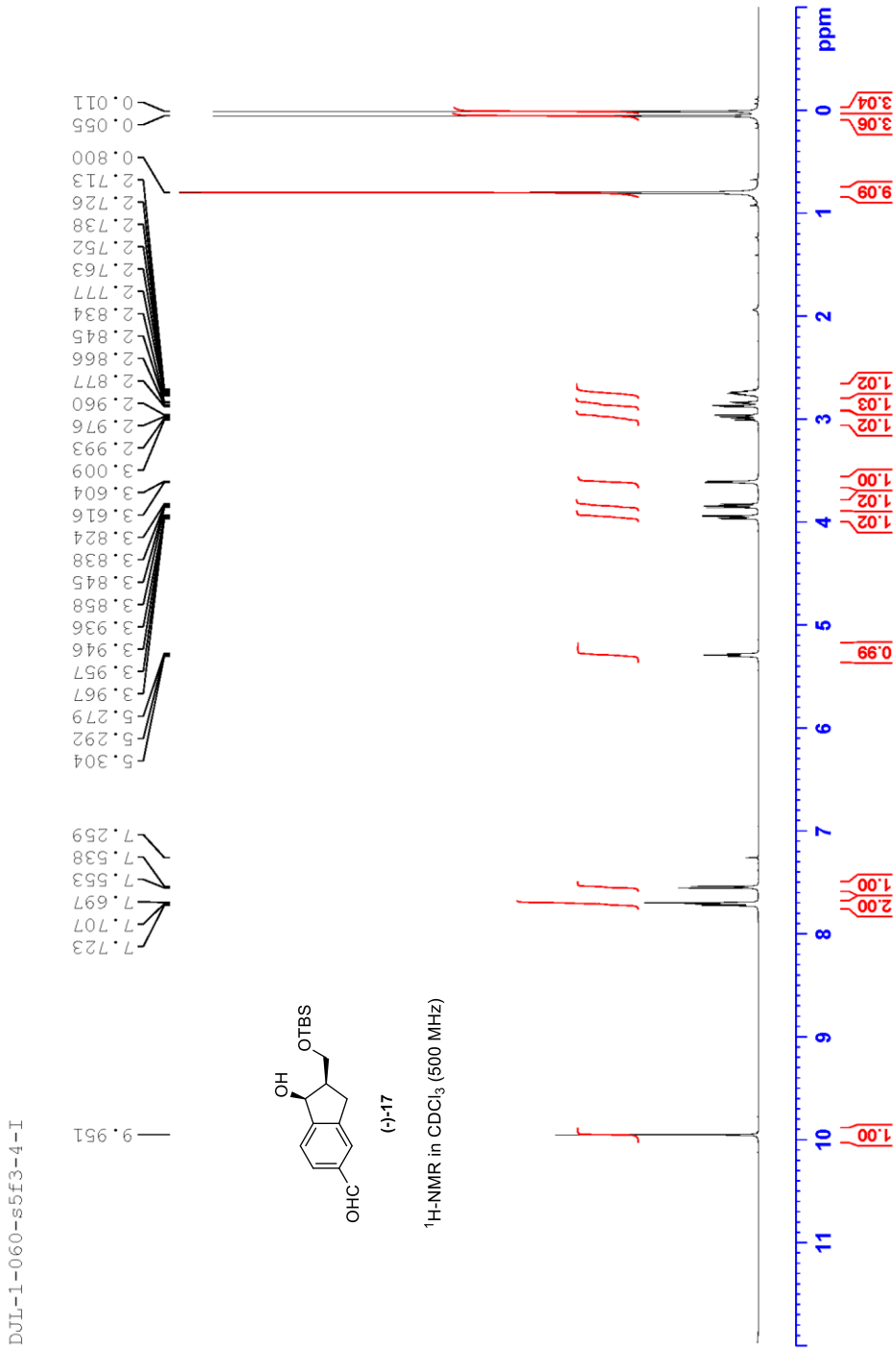
Appendix 7. ^{1}H NMR of **(-)-16**



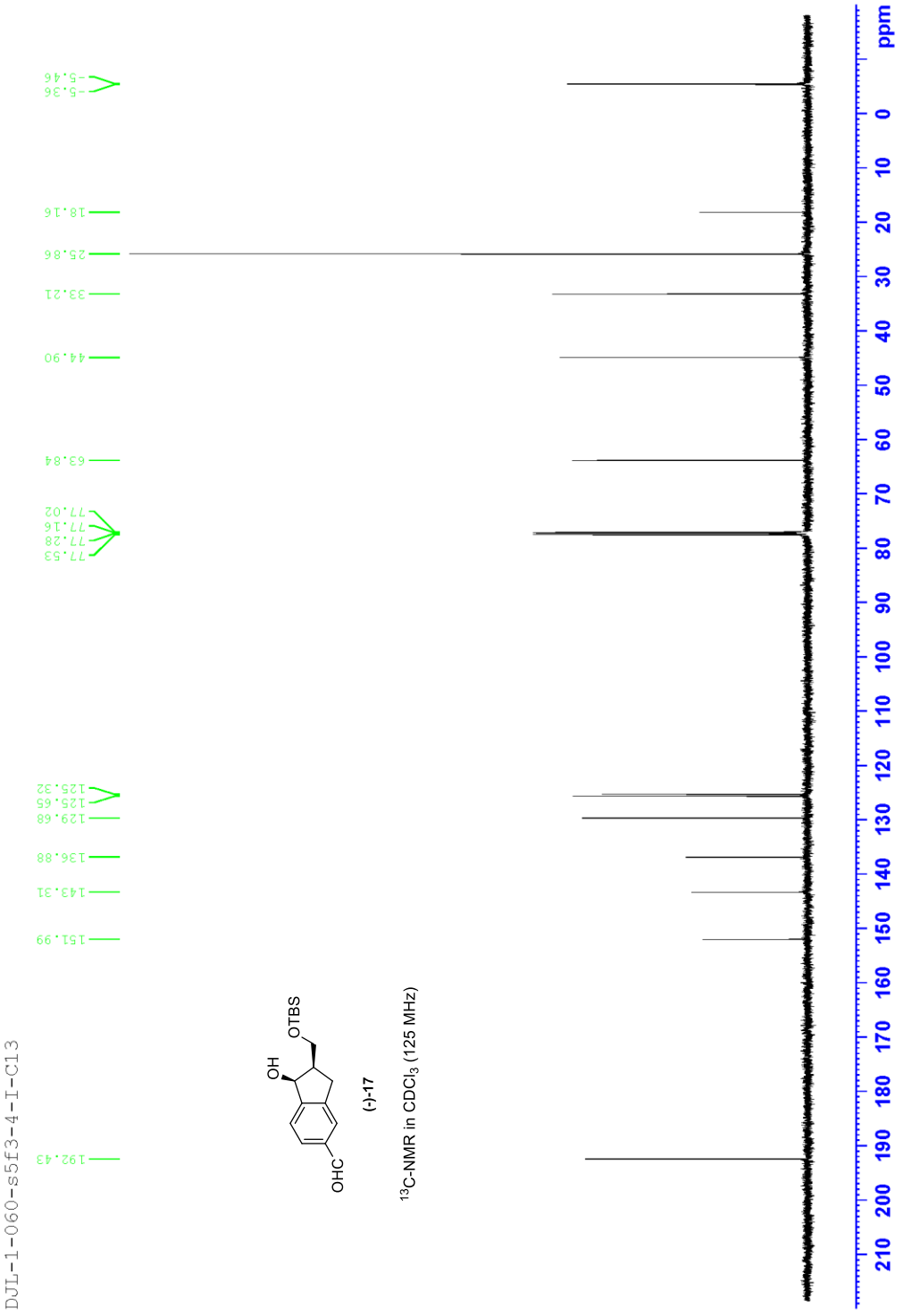
Appendix 8. ^{13}C NMR of **(-)-16**



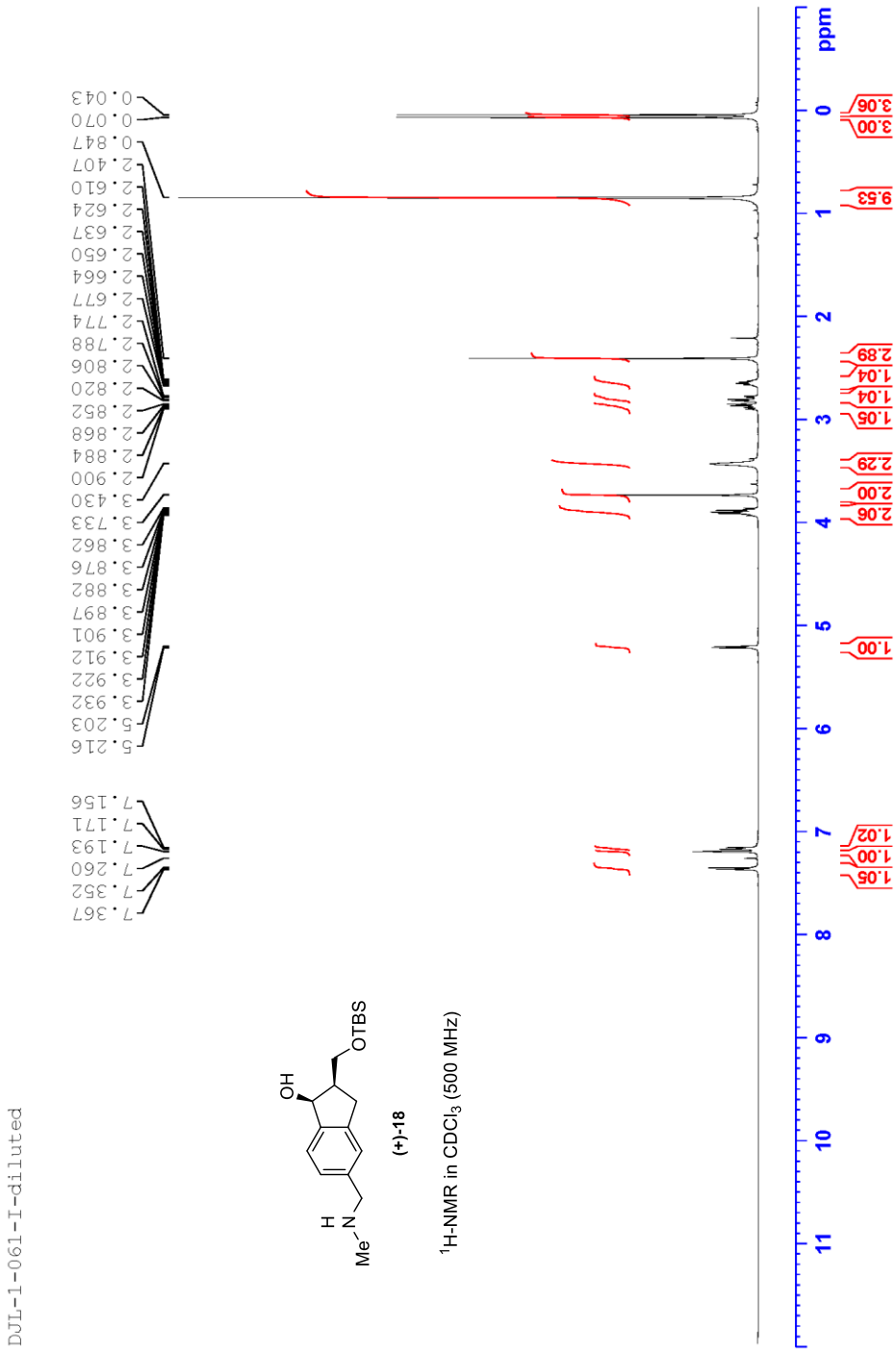
Appendix 9. ^{1}H NMR of **(-)-17**



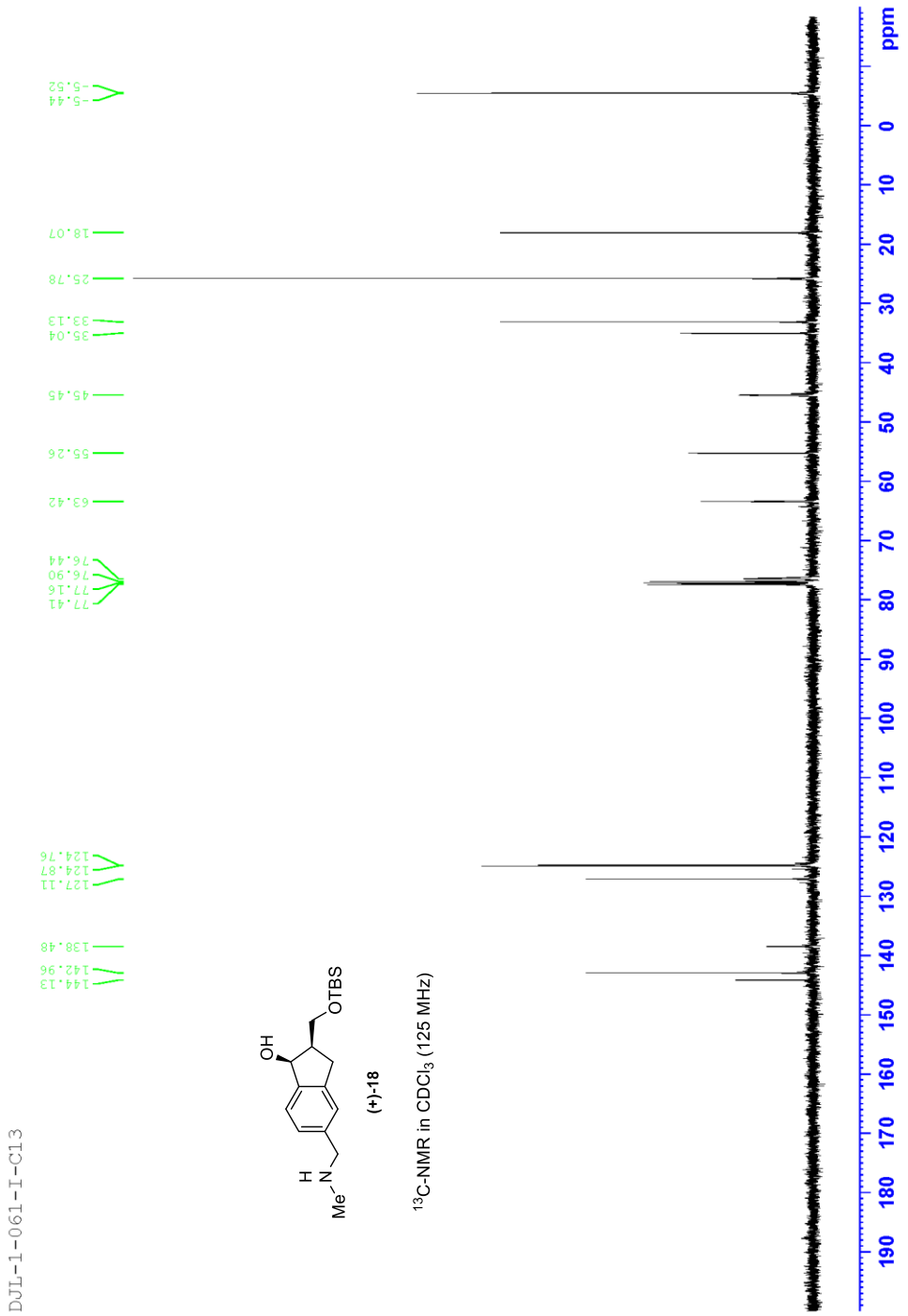
Appendix 10. ^{13}C NMR of **(-)-17**



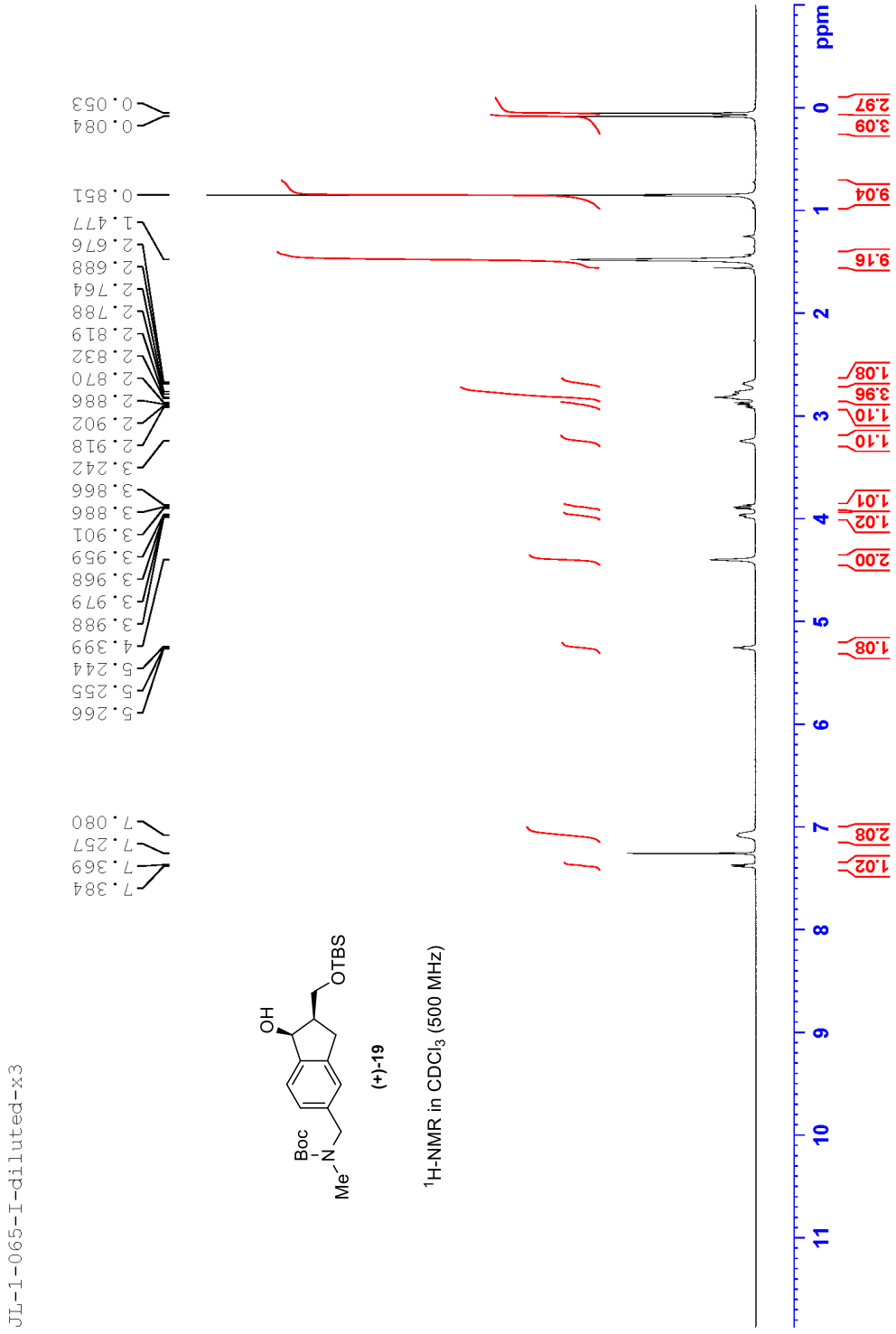
Appendix 11. ^{1}H NMR of **(+)-18**



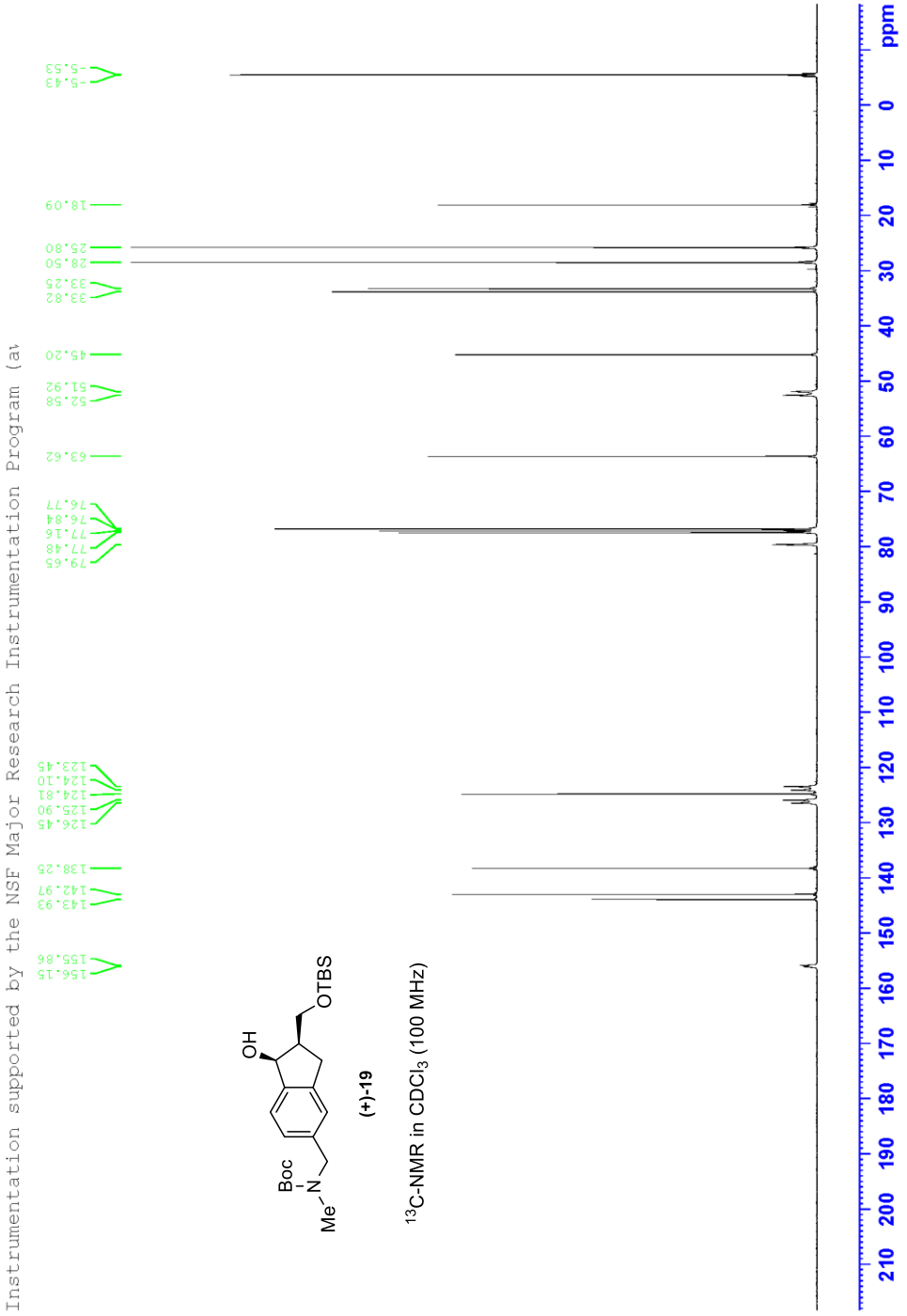
Appendix 12. ^{13}C NMR of **(+)-18**



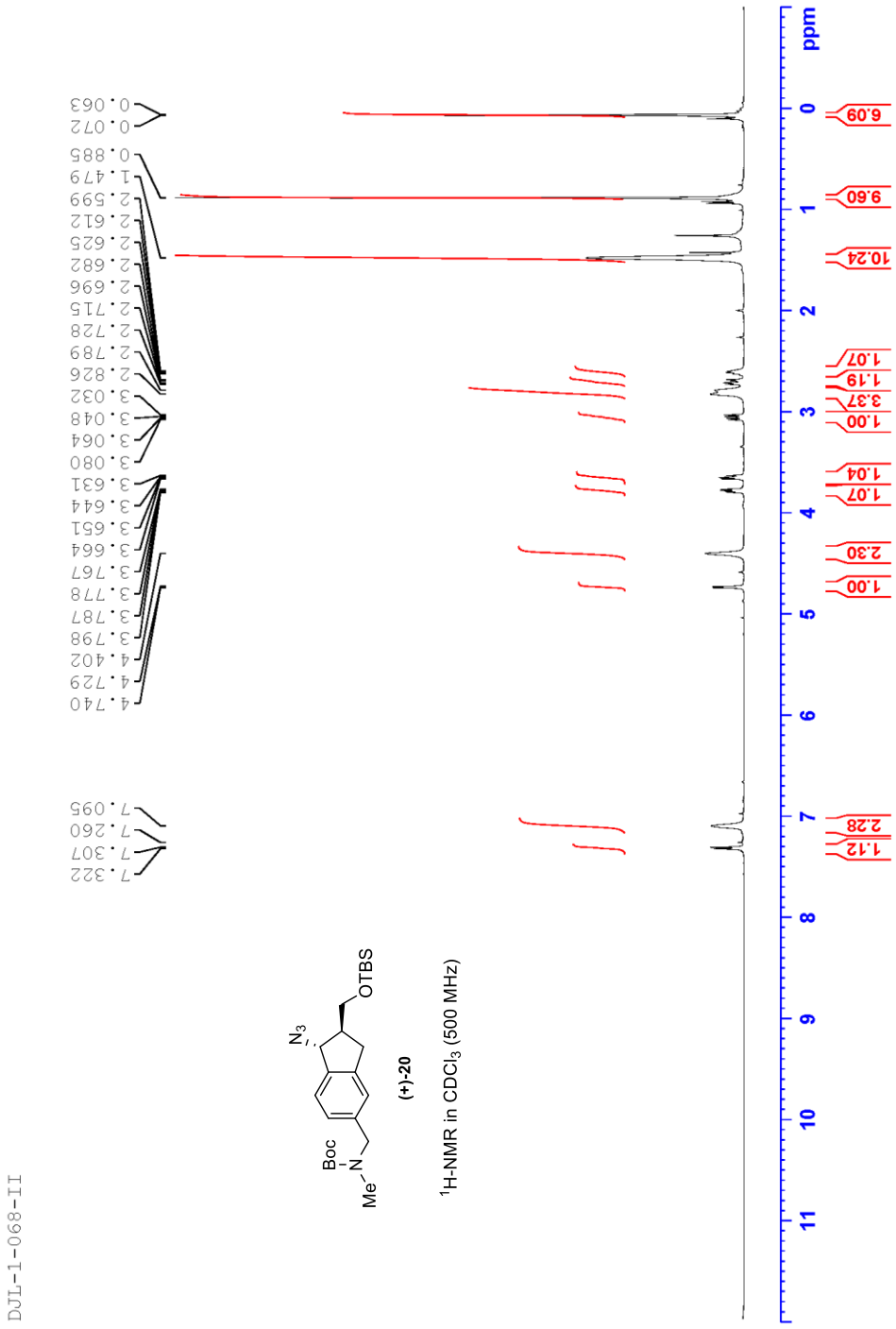
Appendix 13. ^{1}H NMR of **(+)-19**



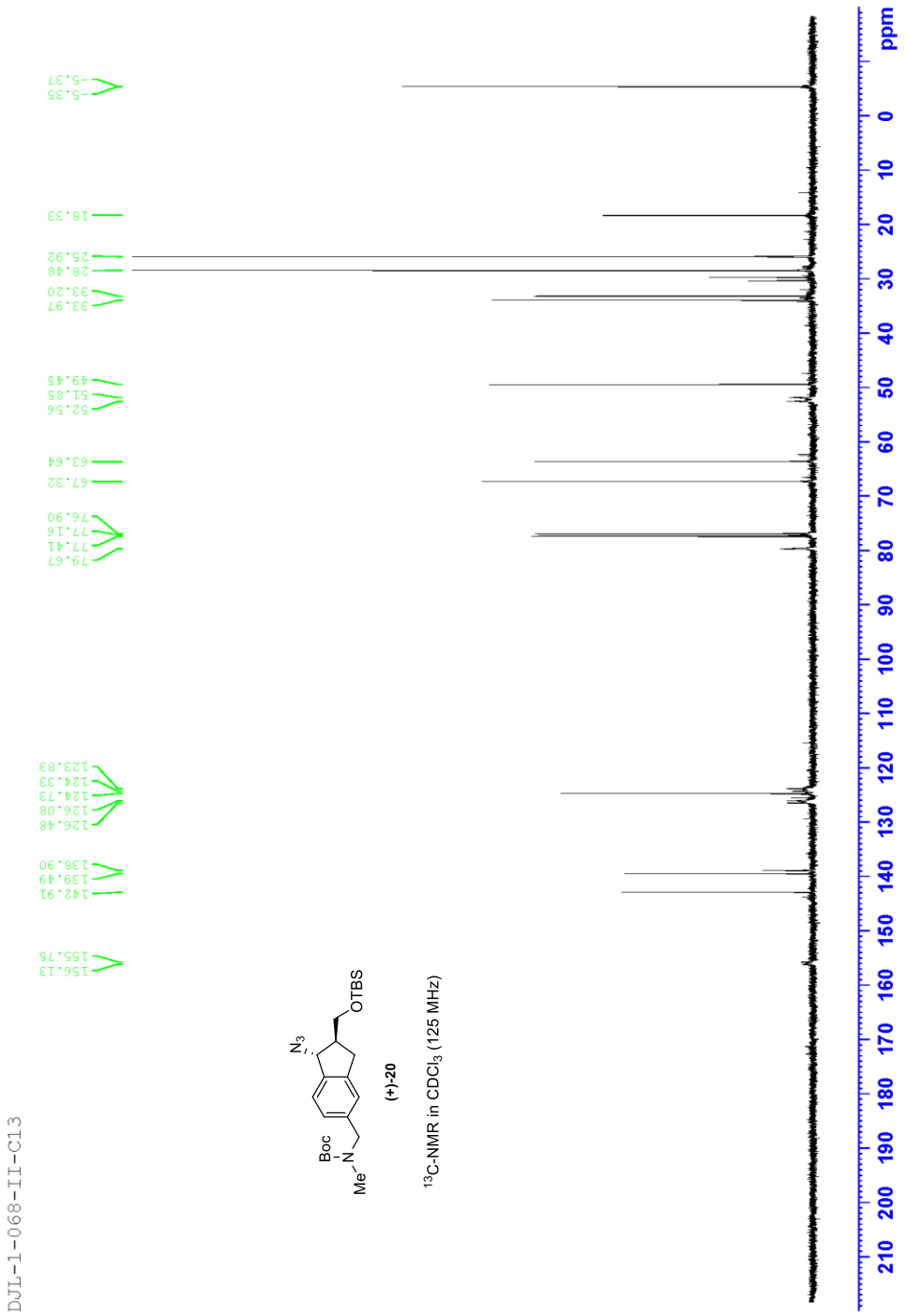
Appendix 14. ^{13}C NMR of **(+)-19**



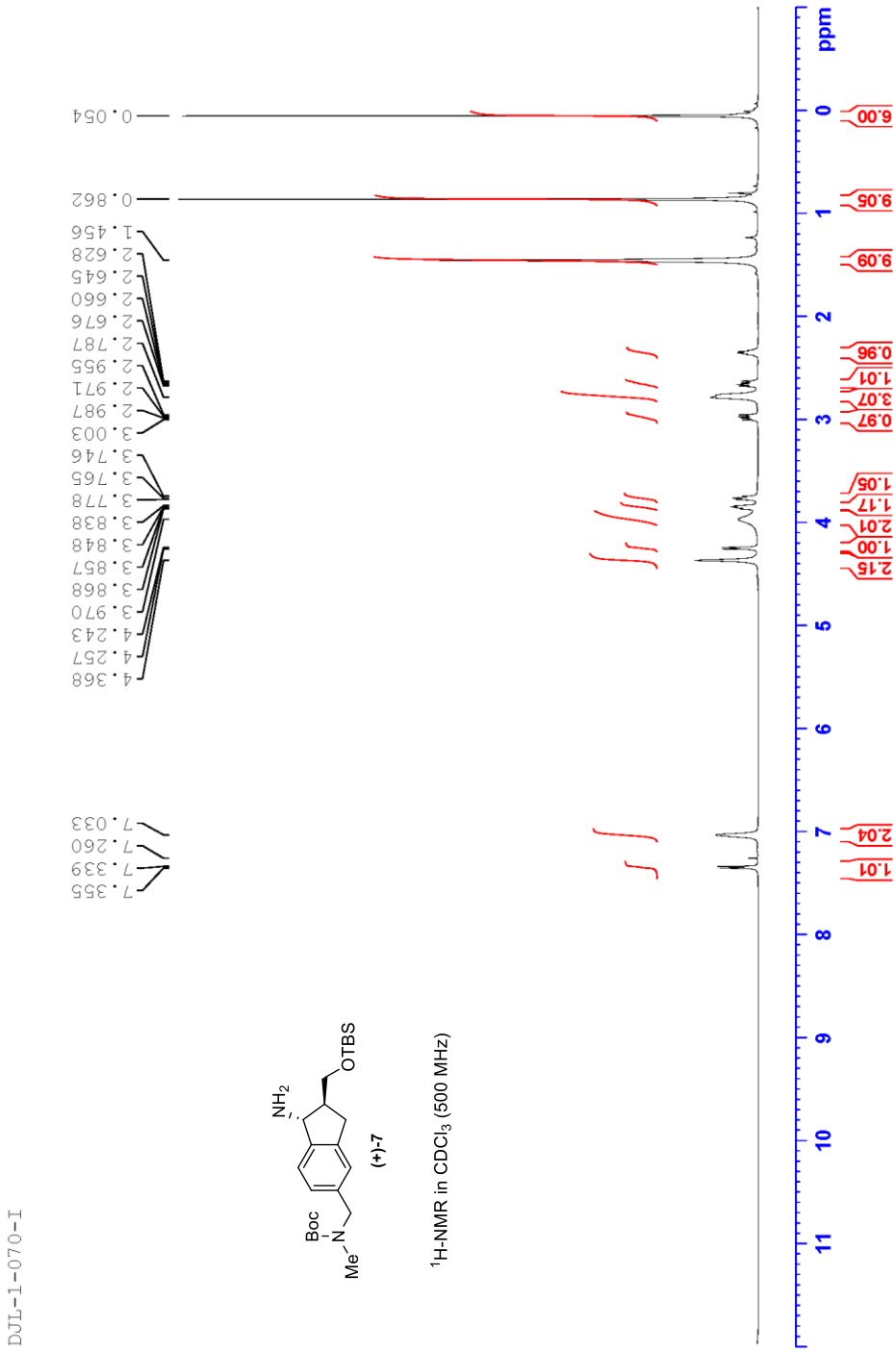
Appendix 15. ^{1}H NMR of **(+)-20**



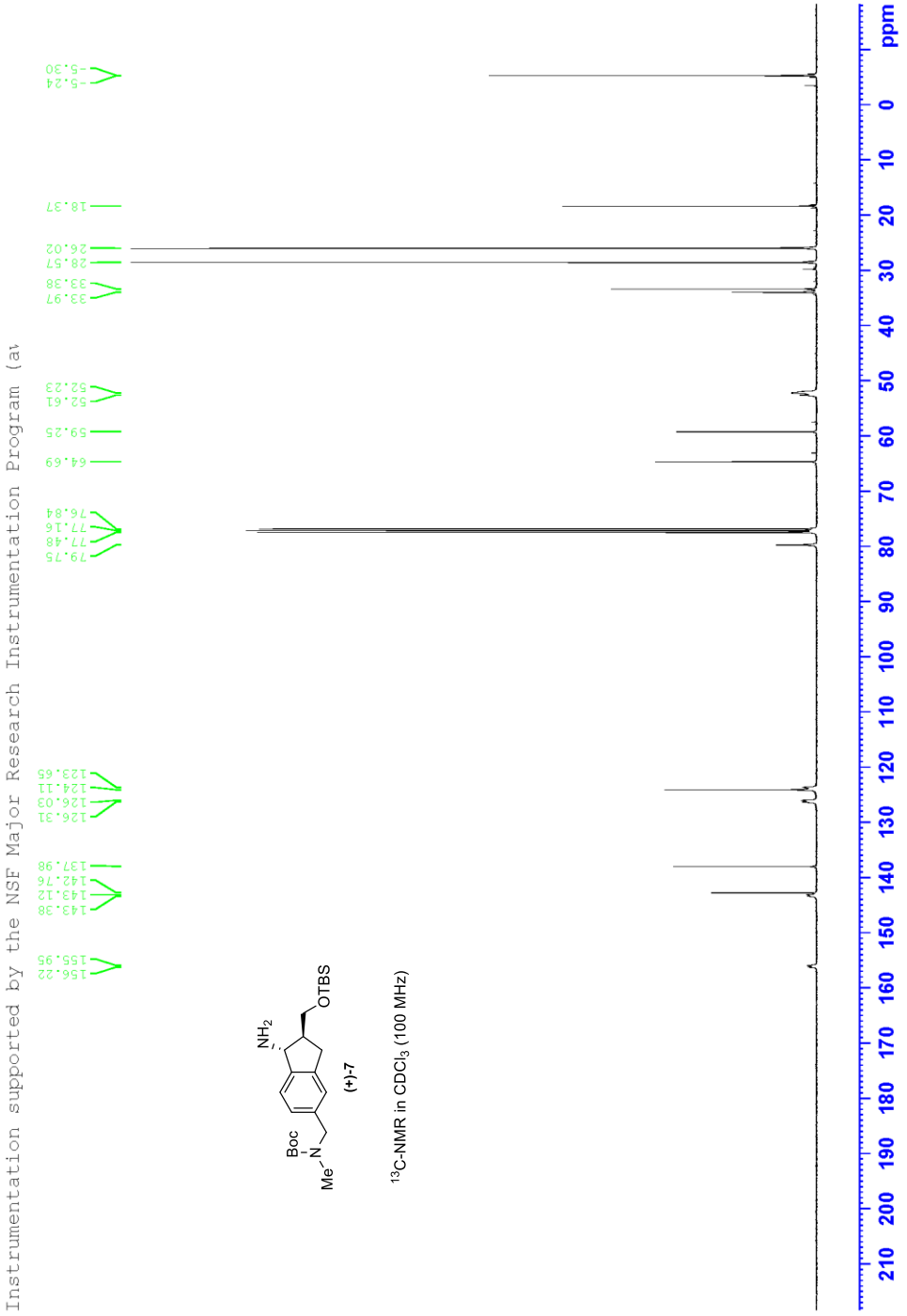
Appendix 16. ^{13}C NMR of **(+)-20**



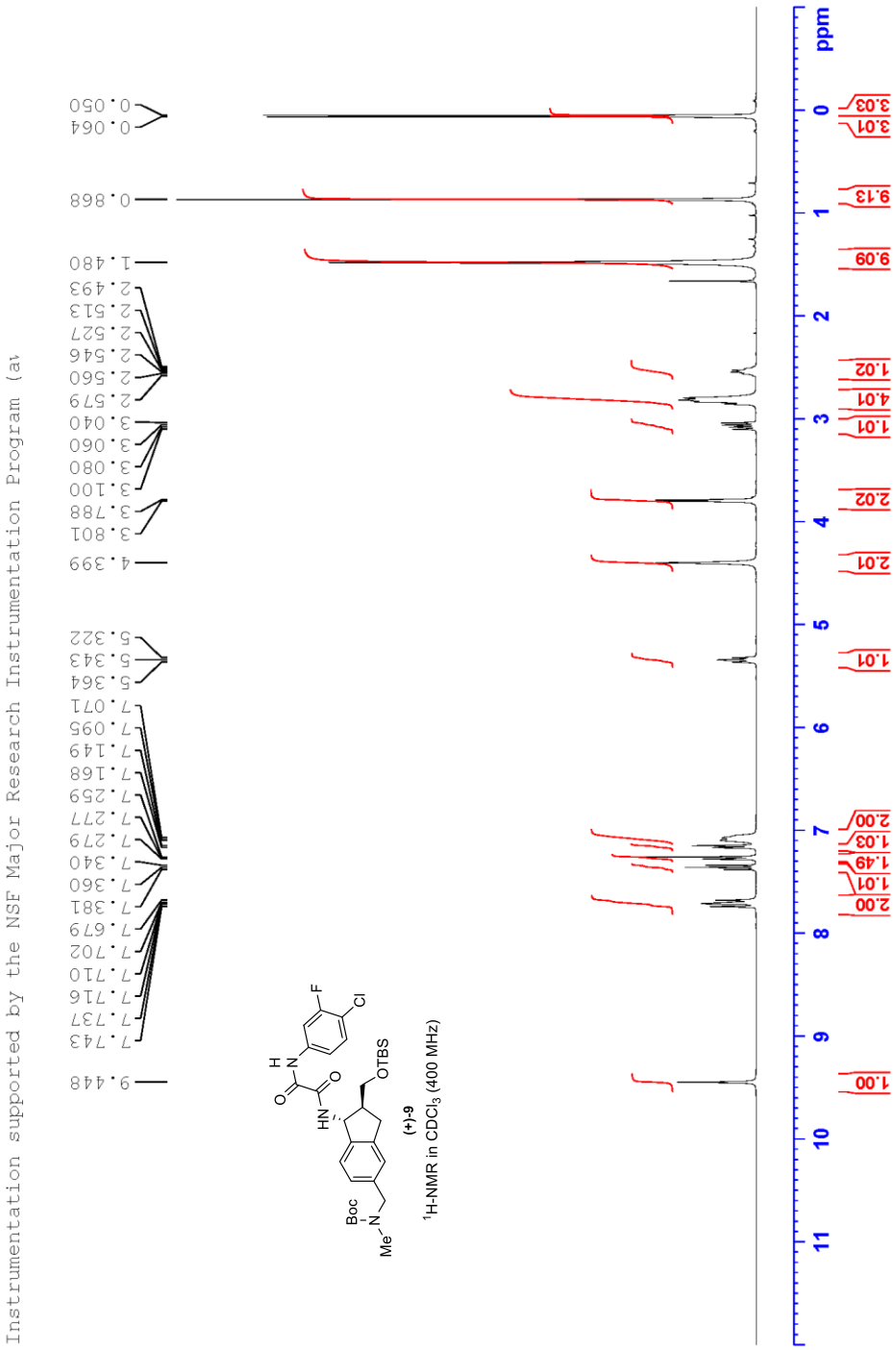
Appendix 17. ^{1}H NMR of **(+)-7**



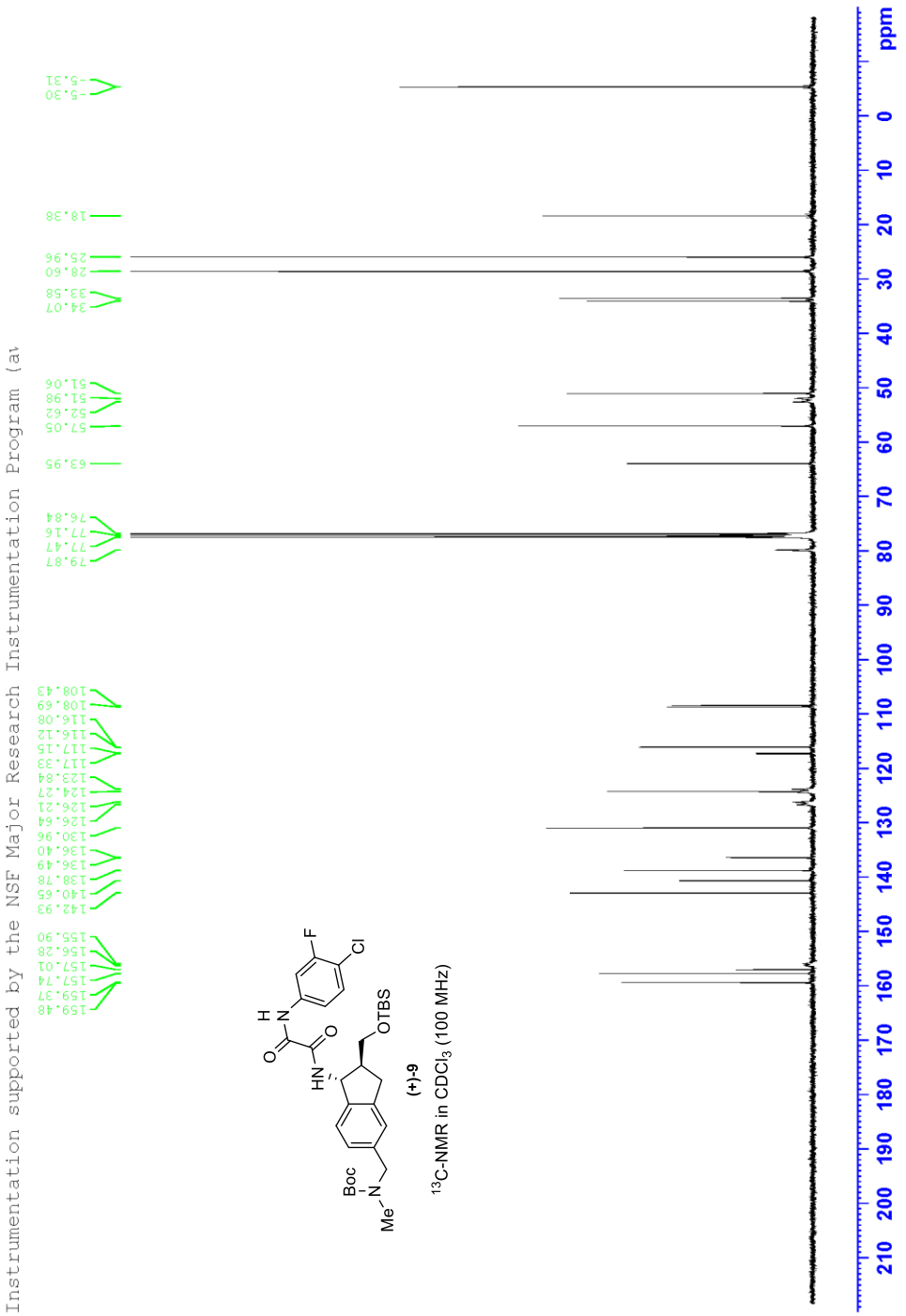
Appendix 18. ^{13}C NMR of **(+)-7**



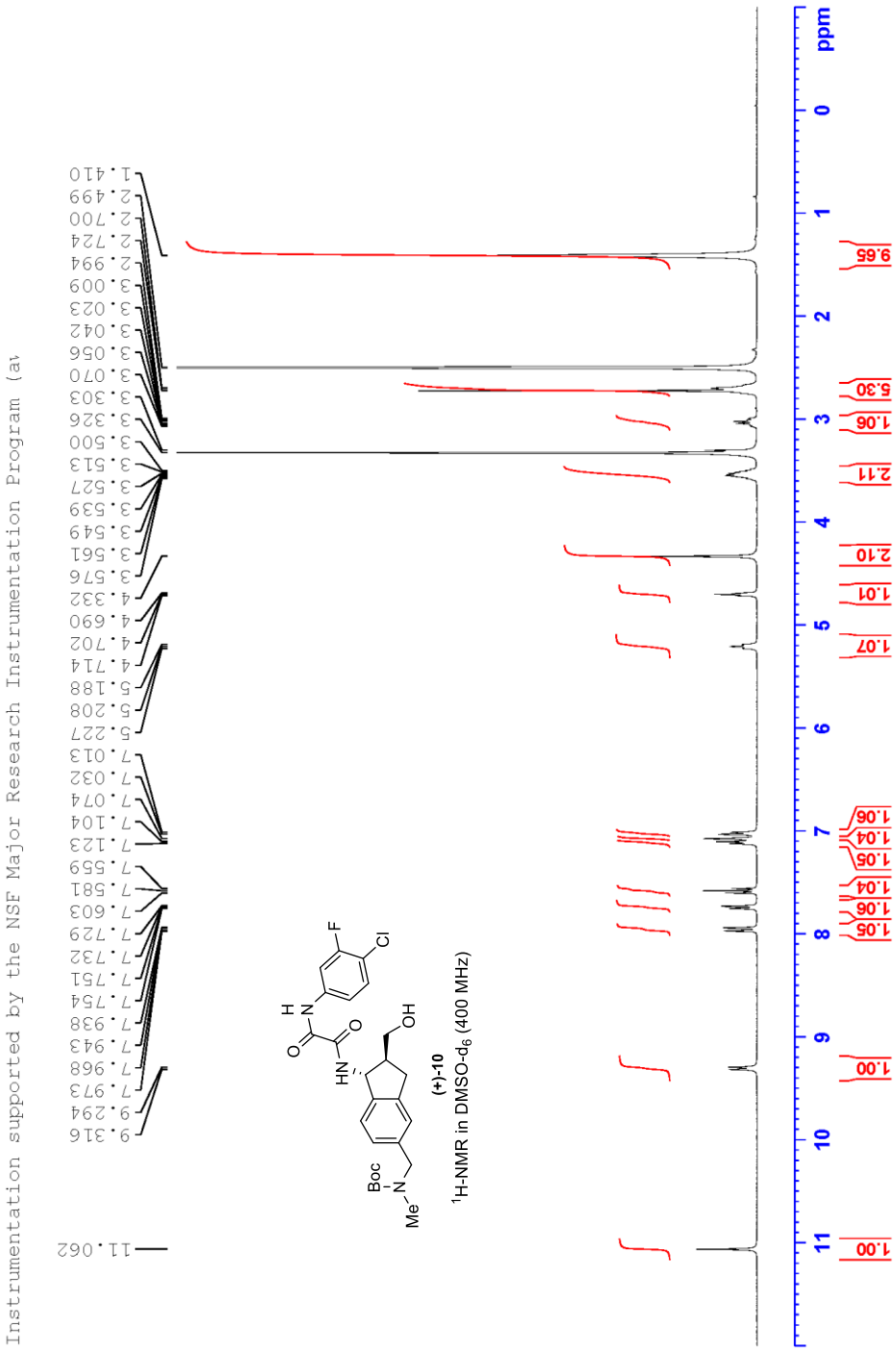
Appendix 19. ^{1}H NMR of **(+)-9**



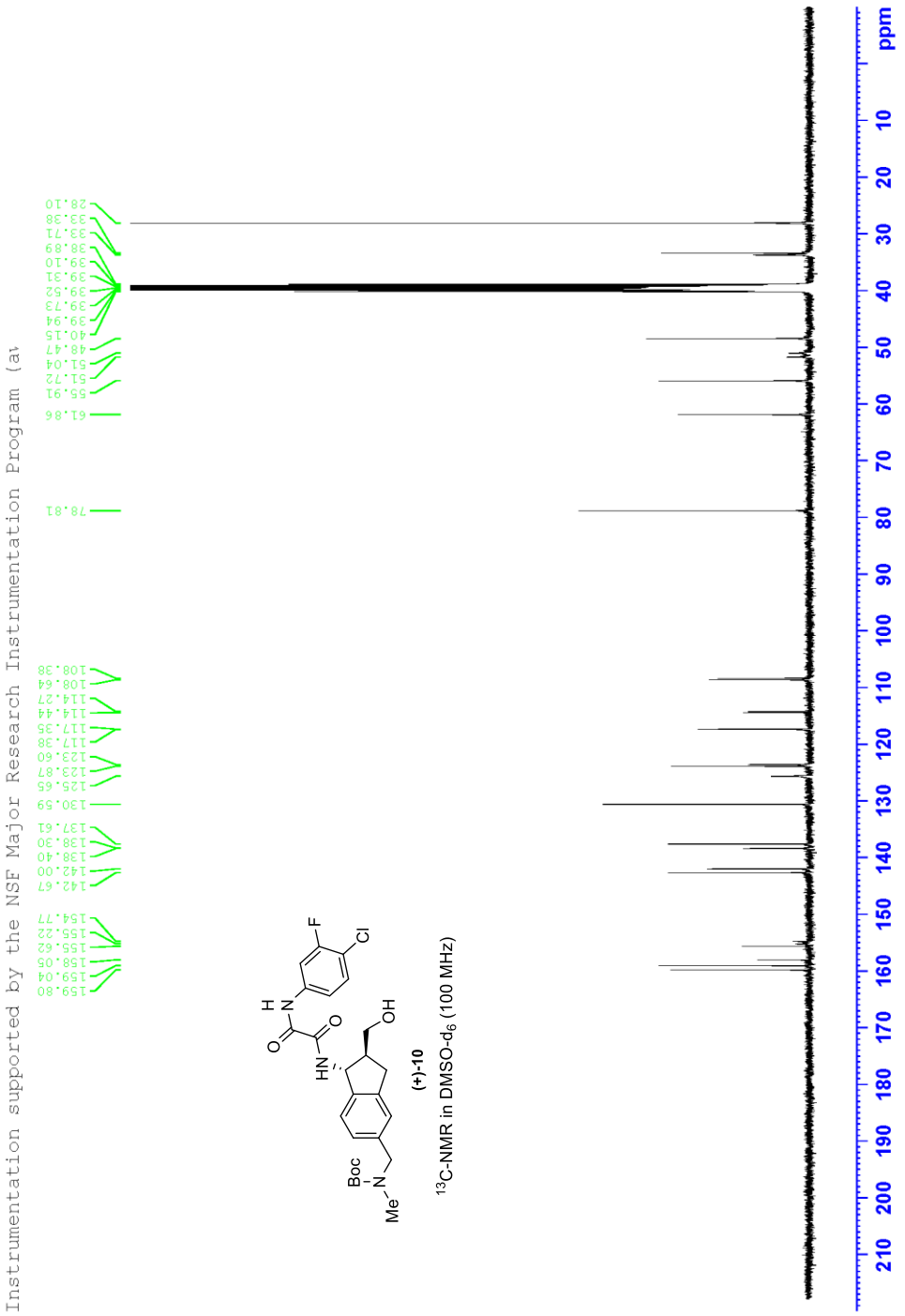
Appendix 20. ^{13}C NMR of **(+)-9**



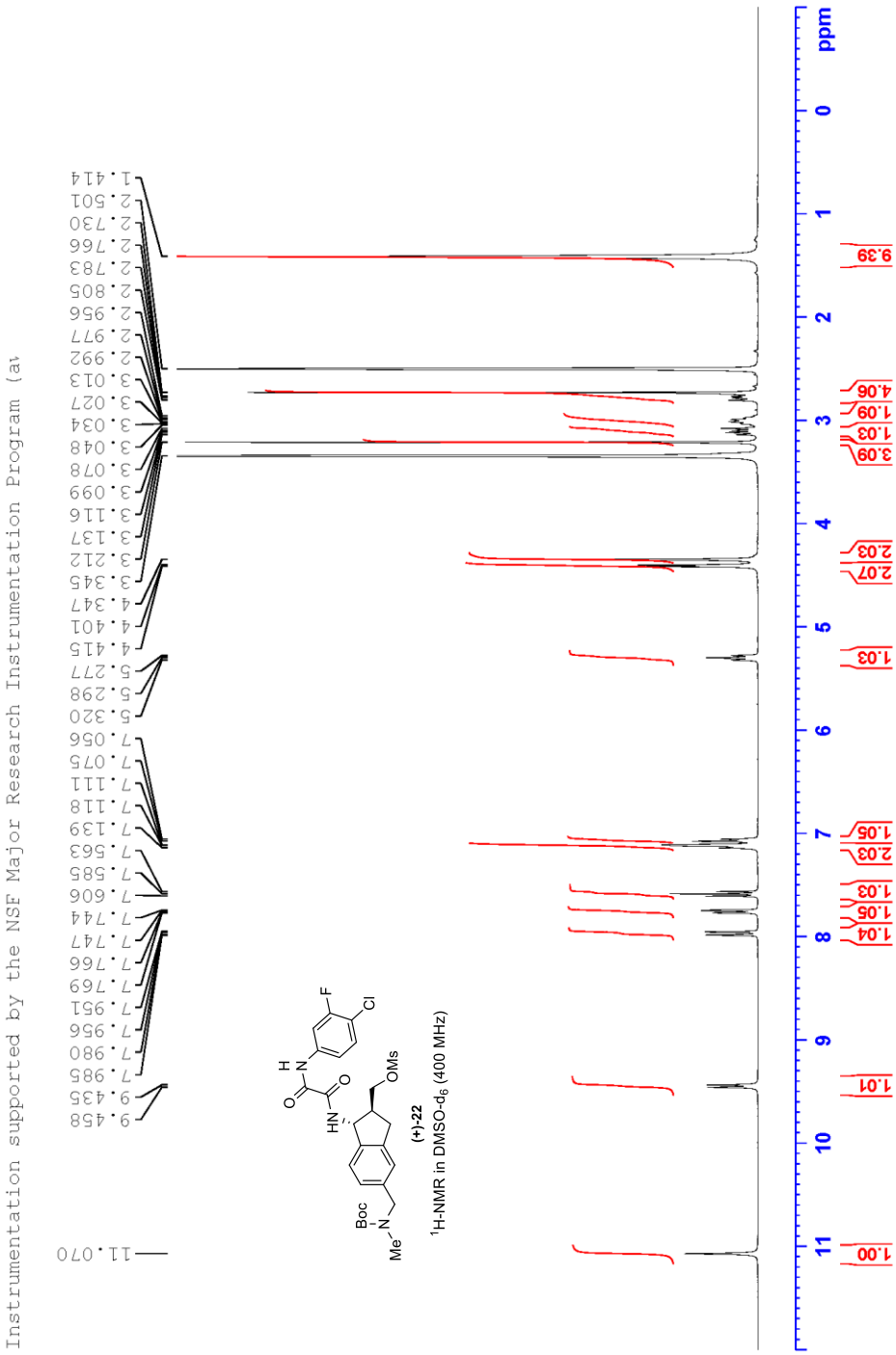
Appendix 21. ^{1}H NMR of **(+)-10**



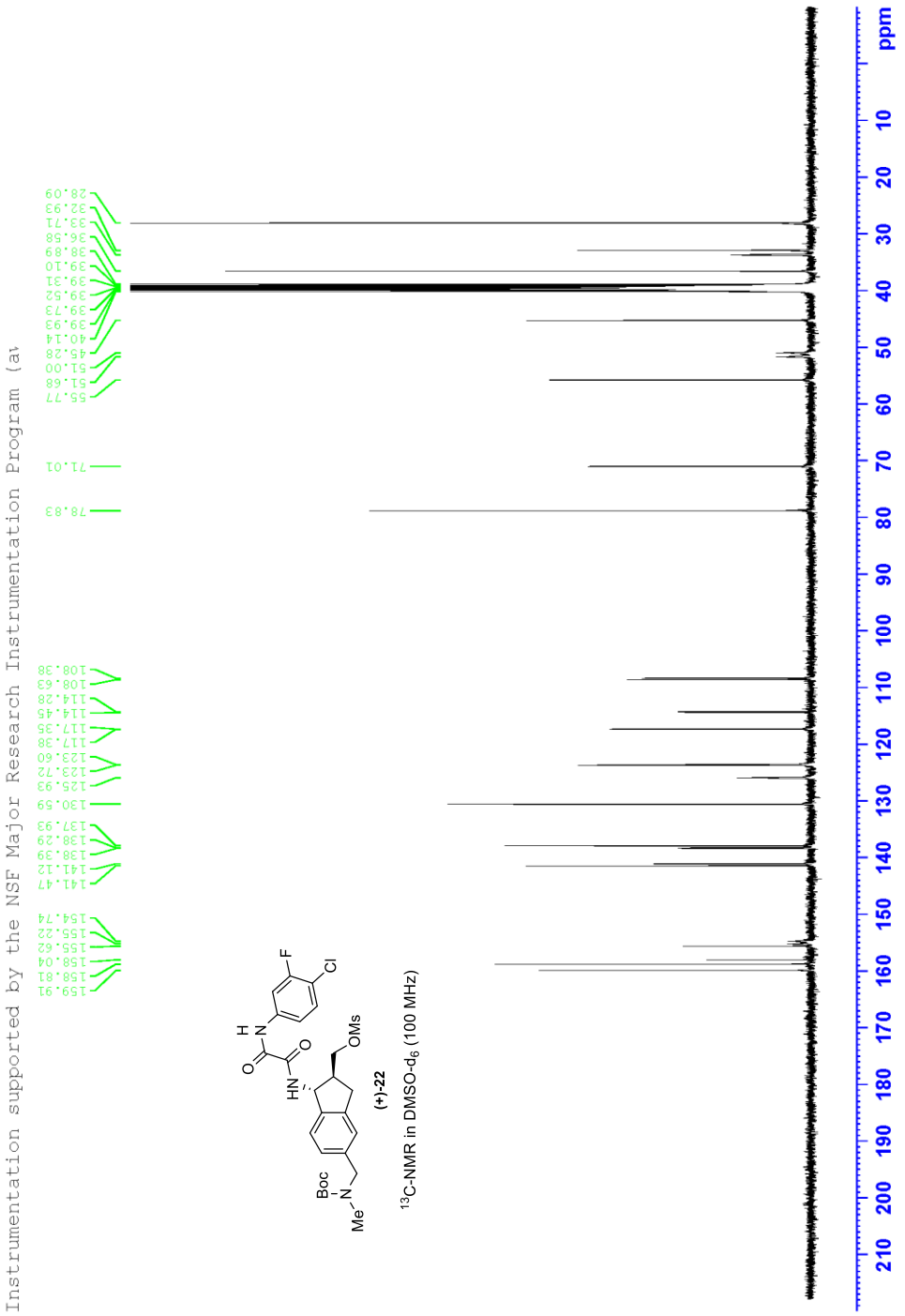
Appendix 22. ^{13}C NMR of **(+)-10**



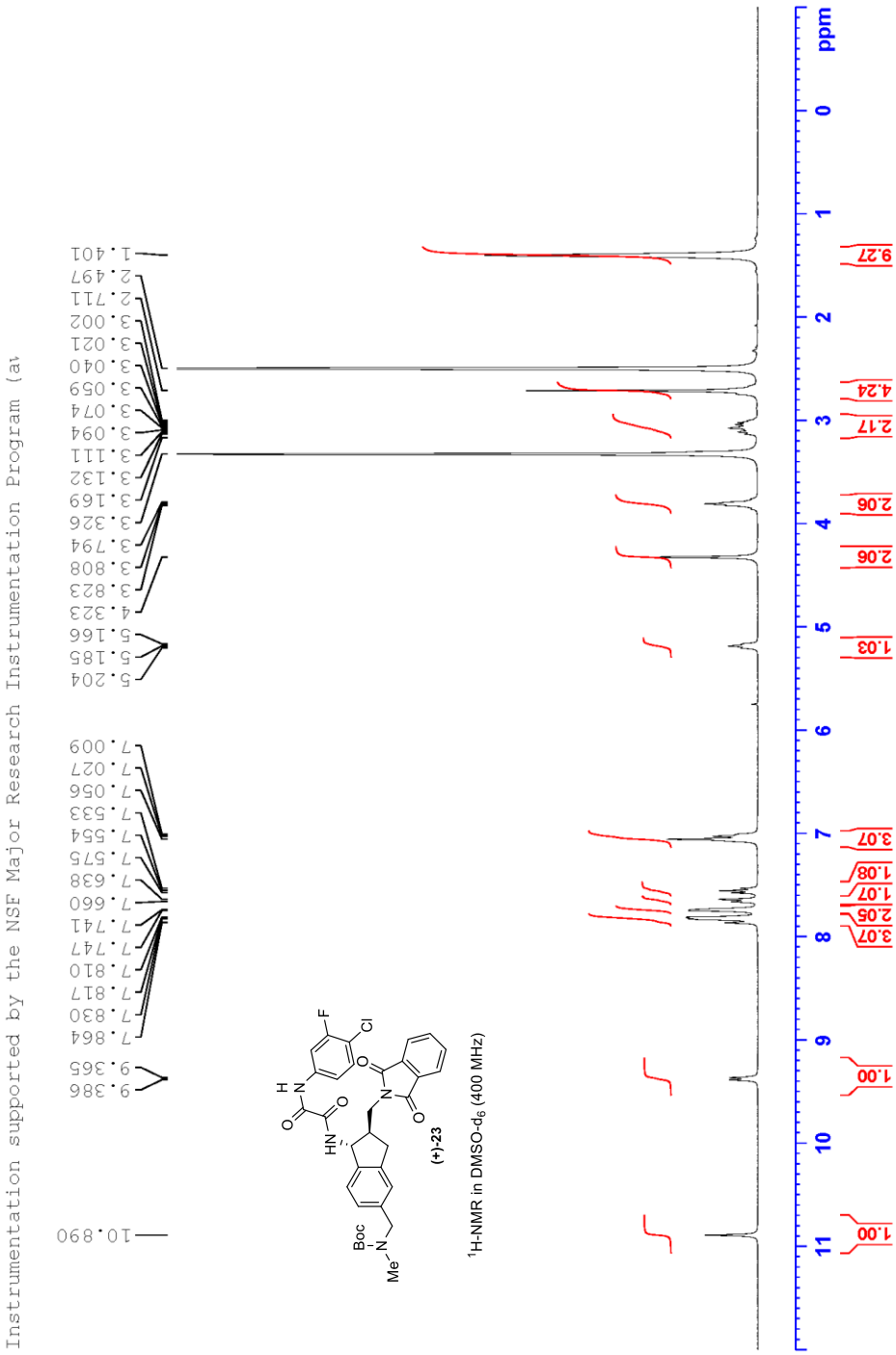
Appendix 23. ^{1}H NMR of **(+)-22**



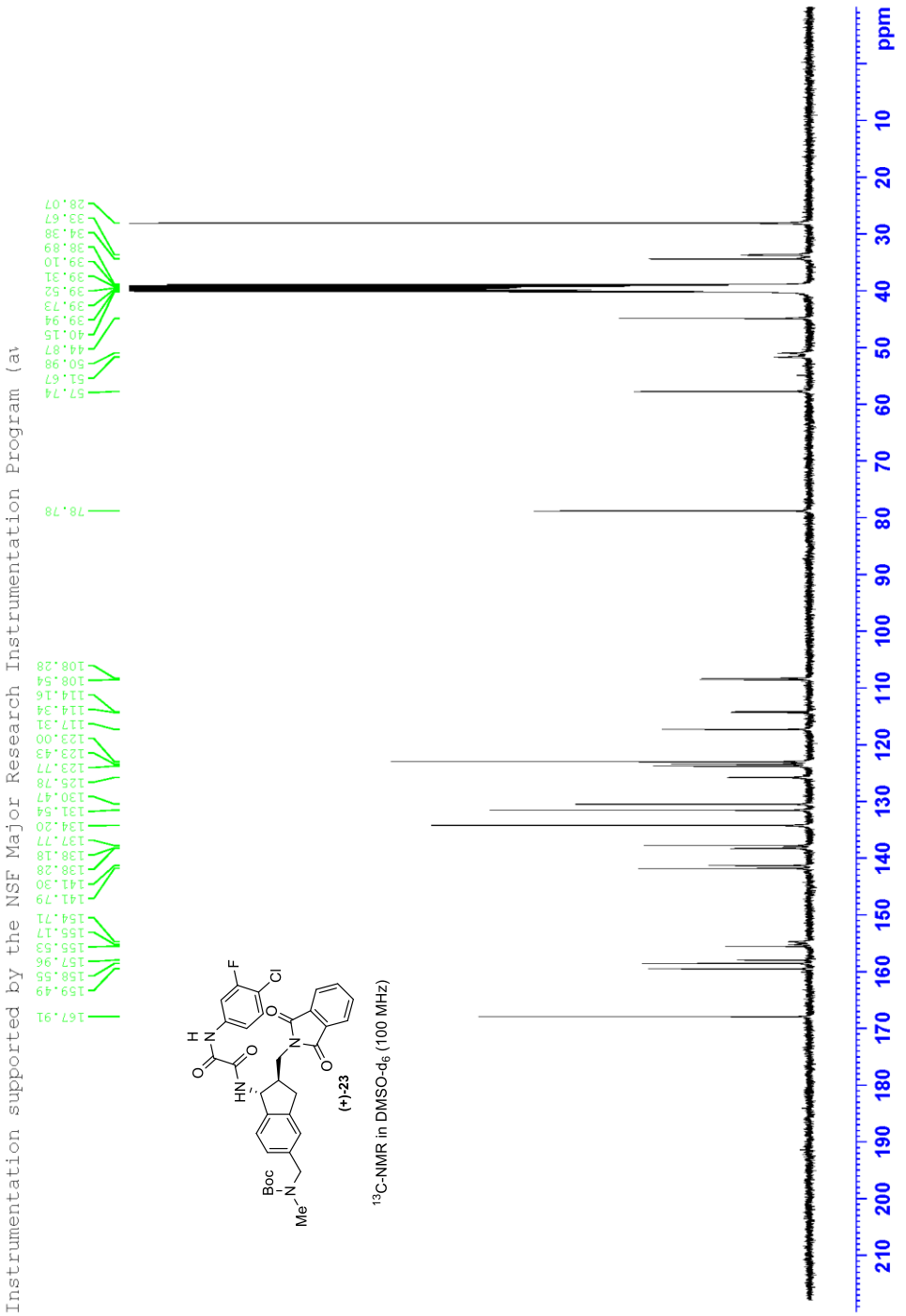
Appendix 24. ^{13}C NMR of **(+)-22**



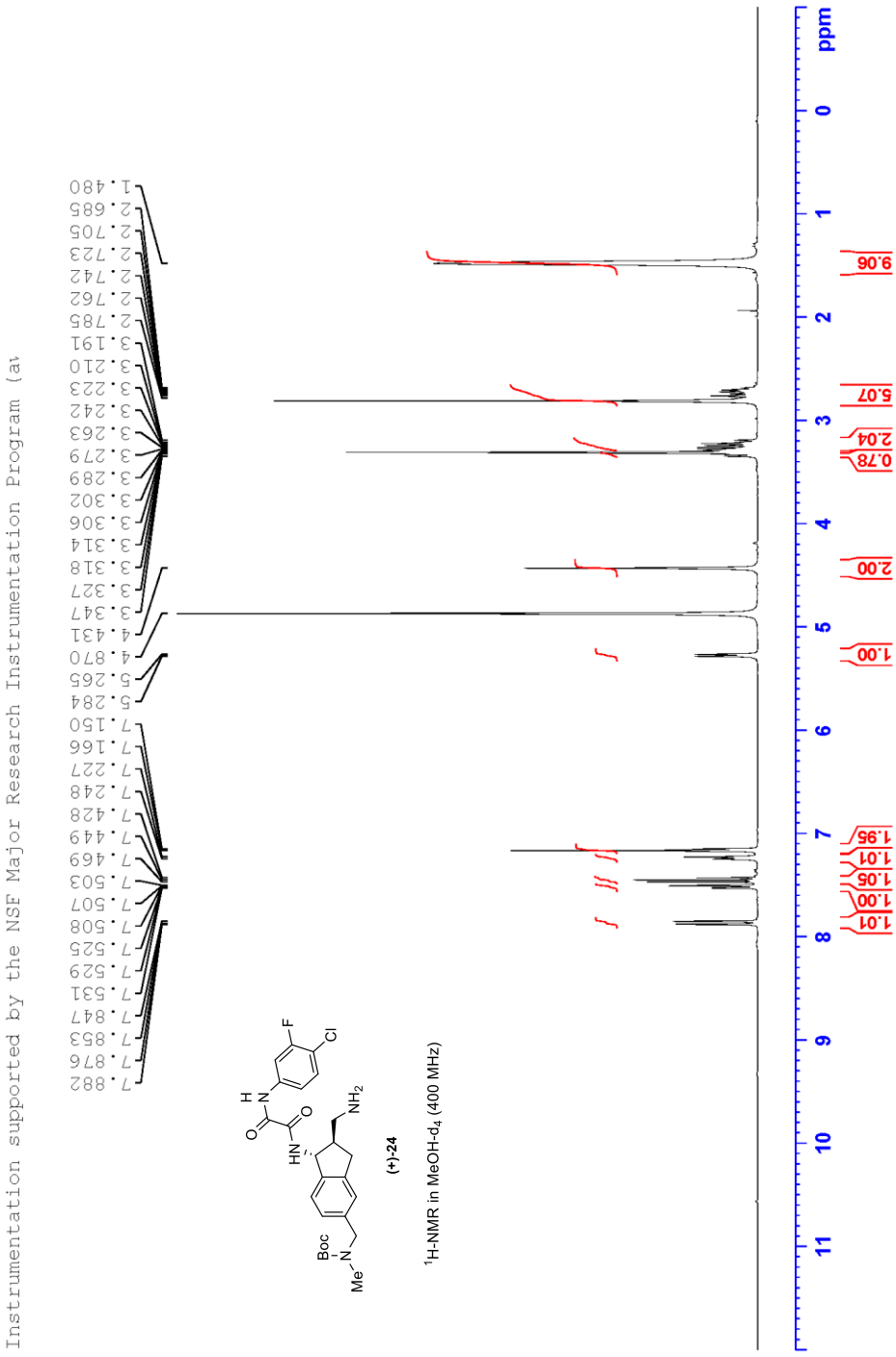
Appendix 25. ^{1}H NMR of **(+)-23**



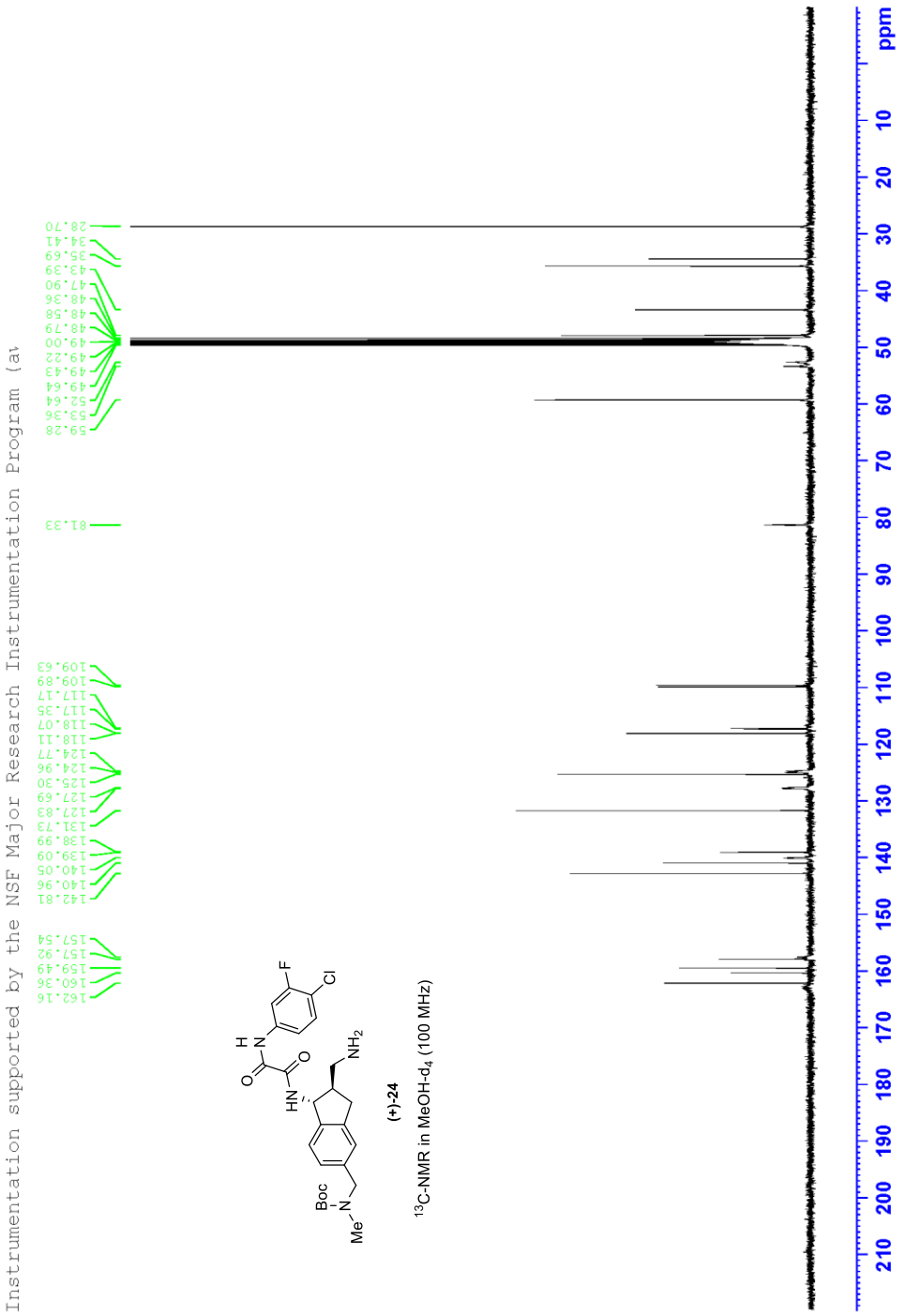
Appendix 26. ^{13}C NMR of **(+)-23**



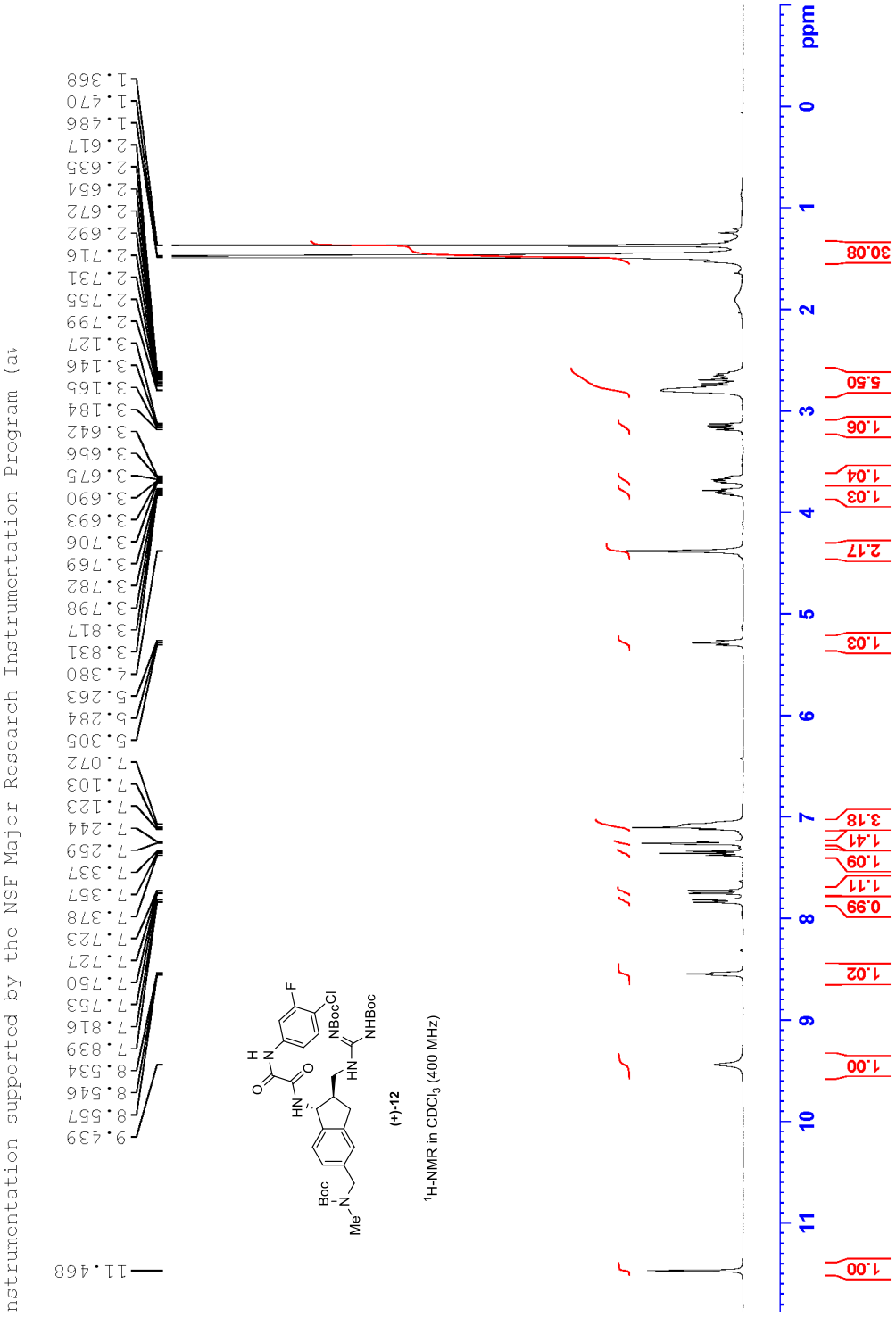
Appendix 27. ^{1}H NMR of **(+)-24**



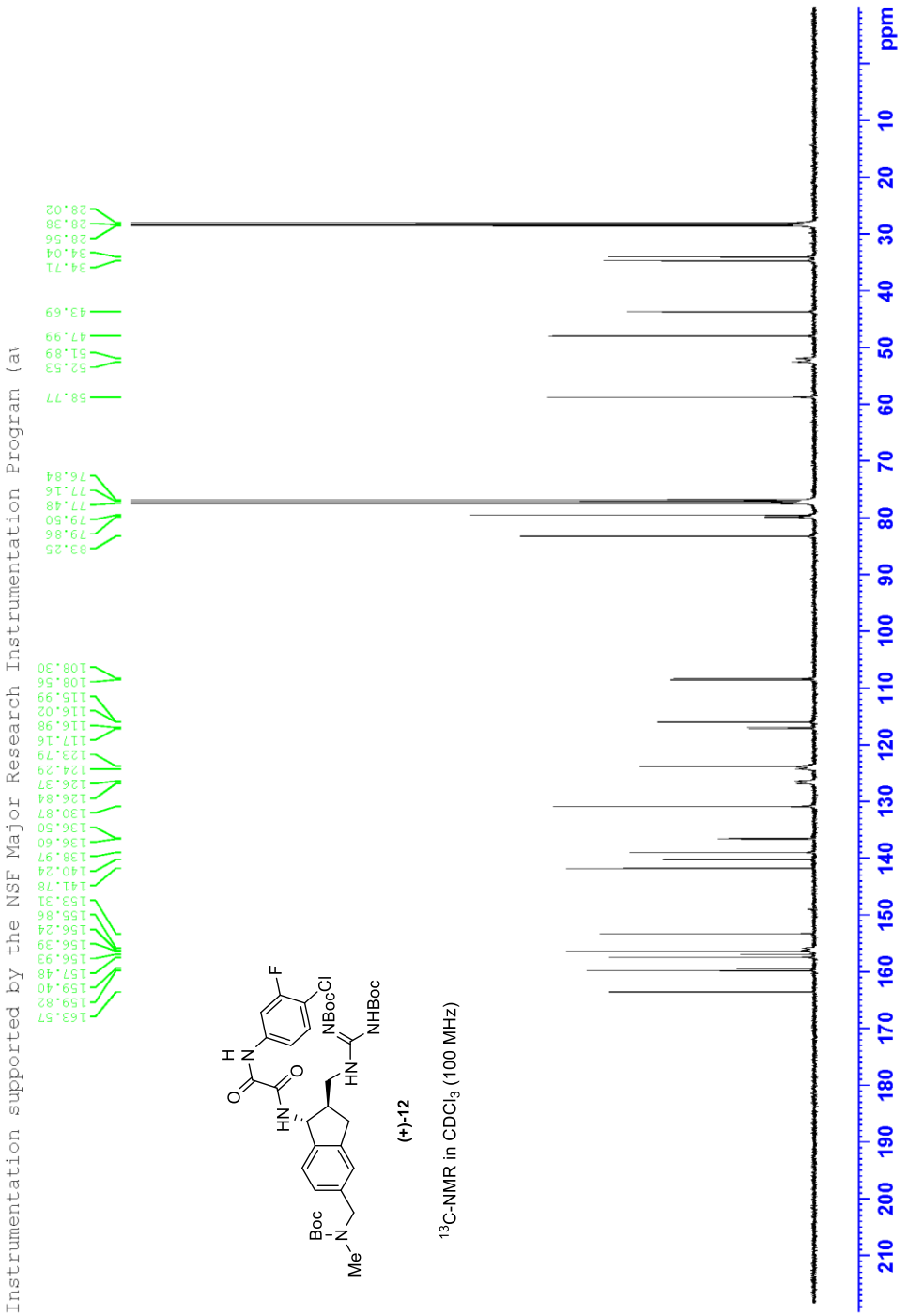
Appendix 28. ^{13}C NMR of **(+)-24**



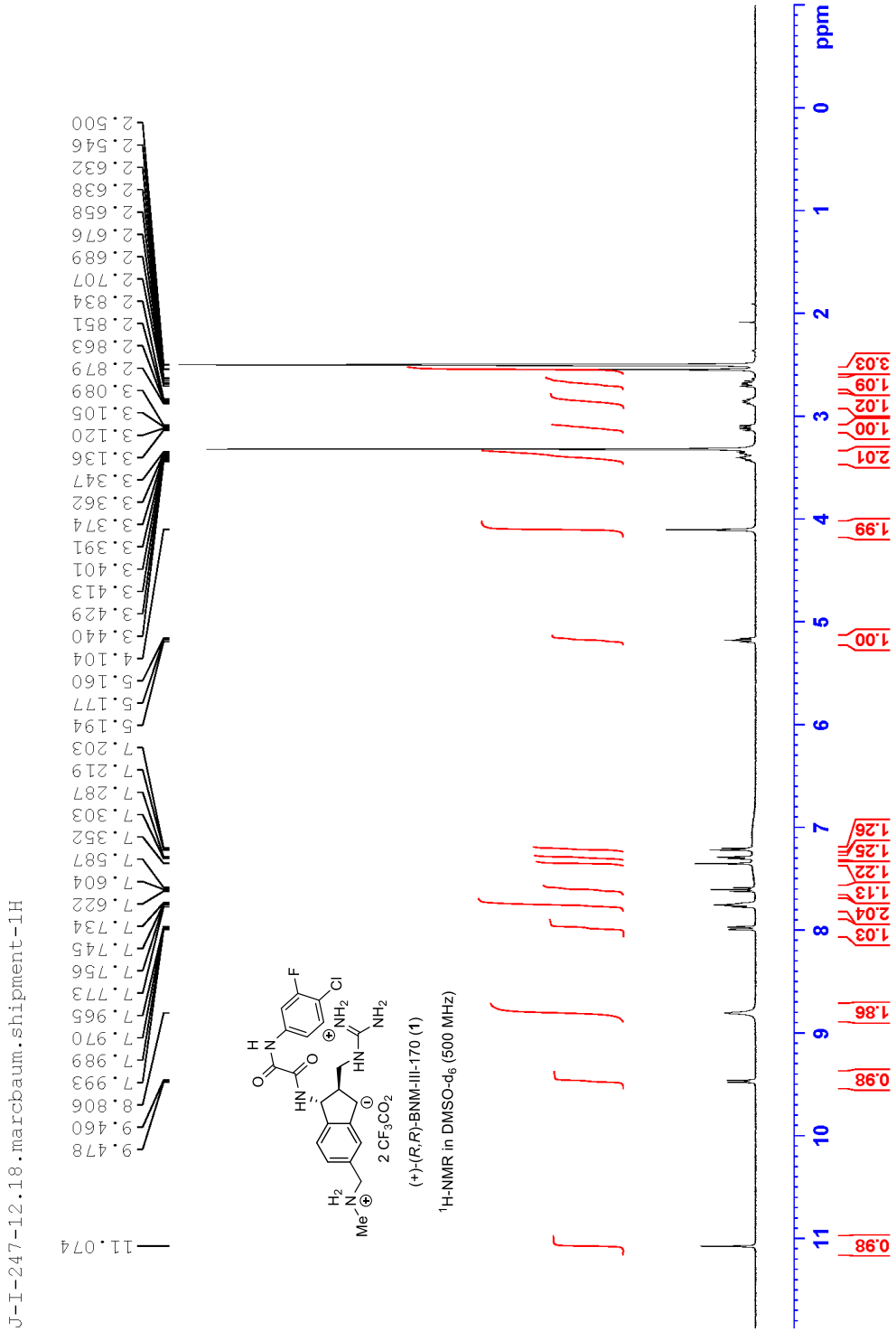
Appendix 29. ^{1}H NMR of **(+)-12**



Appendix 30. ^{13}C NMR of **(+)-12**



Appendix 27. ^{1}H NMR of **1**



Appendix 28. ^{13}C NMR of **1**