TOTAL SYNTHESIS OF 7-Epi-FR 66979 AND 7-Epi-FR 900482

By

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A Dissertation submitted to the

Graduate School-New Brunswick

Rutgers, The State University of New Jersey

In partial fulfillment of the requirements

For the degree of

Doctor of Philosophy

Graduate Program in Chemistry

Written under the direction of

Professor Leslie Jimenez

And approved by

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New Brunswick, New Jersey

May, 2010

ABSTRACT OF THE DISSERTATION

TOTAL SYNTHESIS OF 7-Epi-FR 66979 AND 7-Epi-FR 900482

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Dissertation Director:

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The completion of the total synthesis of 7-Epi-FR 66979 and 7-Epi-FR 900482 is presented in this thesis. The natural product FR 66979 and FR 900482 were isolated by the Fujisawa Pharmaceutical Corporation from Streptomyces sandaensis. They are antibiotics with potent antitumor activity.

The first stage of the total synthesis is to make indole ester. For the preparation of the precursor of the indole ester, the commercial available starting material 3-hydroxymethylphenol was converted to benzyl aldehyde by using the reagents paraformaldehyde and lewis catalyst $SnCl_4$ after the selective protection of hydroxymethyl group. After the phenol had been protected, this benzyl aldehyde precursor was transformed to indole ester by the Hemetsberger-Knittel reaction in 61% yield.

The second stage of the total synthesis is to make fully functionalized pyrroloindole. The indole ester was reduced by DIBAL and then was oxidized to indole aldehyde. The vinylsulfonium salt reacted with this indole aldehyde to form the

tetracyclic oxirane, then subsequently treated by sodium azide in acetone-water to afford pyrroloindole in 74% yield.

The third stage of the total synthesis is to synthesize the core ring system. The fully functionalized pyrroloindole was successfully oxidized by two equivalents of dimethydioxirane (DMDO) in acetone/water to give ring expanded hydroxylamine hemiketal ring system in 57% yield.

The final stage of the total synthesis is to complete the total synthesis. One of the challenging steps is to prepare the hydroxylmethyl group on this core structure. With many studies, the hydrosilylation-oxidation was found to be a good method to make the hydroxymethyl group on this complex molecule. After converting the hydroxymethyl group to urethane and deprotection, 7-Epi-FR 66979 was successfully obtained. With a one step oxidation of 7-Epi-FR 66979, 7-Epi-FR 900482 was prepared. This total synthesis is the shortest and most efficient so far. Epi-FR 66979 is synthesized in 20 steps while epi-FR 900482 required 21 steps.

The attempt of making the beta configuration of the hydroxymethyl group on the 7-position for FR 66979 and FR 900482 is also described in this thesis. The efforts included intramolecular hydrosilylation-oxidation, less hindered intermolecular hydrosilylation-oxidation, catalytic hydroboration-oxidation and Danishefsky's methods of the epoxidation and opening. Both less hindered intermolecular hydrosilylation-oxidation and Danishefsky's methods provided intermediate with beta configuration of hydroxymethyl, but the final product was not obtained. A less hindered intermolecular hydrosilylation-oxidation method will provide the best chance to get the natural product when additional more intermediates are prepared in the future.

ACKNOWLEDGEMENT

In the first place, I wish to express my profound gratitude to my thesis advisor Professor. Leslie Jimenez for her supervision, advice, suggestion, encouragement and support through this research. I also want to thank all people in Professor Leslie Jimenez's group. They give me lot of help from the beginning of research to the end. Many colleagues at the Schering-Plough Research Institute gave me help in my research. I would like to thank Dr. Stephane Bogen for his help, encouragement and discussion. I would also like to thank to Dr. Ronald Doll for his support and encouragement for my part time research. Many thanks in particular to Dr. Jun Qin for his greatly helpful suggestions and discussion. I also benefited from the discussion with colleagues Dr. Xianhai Huang, Dr. Xin Dai, Dr. Guoqin Li, and Dr. Youlong Yu. I would like to thank them. I gratefully thank for Dr. T.M Chan and Dr. Alexei Buevich at the NMR group of structure chemistry at the Schering-Plough Research Institute for analyzing the structure of important intermediates and final target compound of my research.

I gratefully acknowledge the Schering-Plough Research Institute for education assistance program. Without the support in tuition, facilities and chemicals from Schering-Plough, I could not complete the Ph. D thesis.

My deepest gratitude goes to my wife Li Tan and daughter Emily Pan for their unflagging love and support through the time of my research. This dissertation is simply impossible without them.

TABLE OF CONTENTS

LIST OF SYMBOLS AND ABBREVIATIONS

Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
Alloc	(allyloxy)carbonyl
9-BBN	9-borabicyclo[3.3.1]nonane
BF_3	boron trifluoride
Bn	benzyl
Boc	tert-butyloxycarbonyl
BOM	benzyloxymethyl ethers
br s	broad singlet
Bs	benzen
n-Bu_4NF	tetra-n-butylammonium fluoride
n-Bu_4NI	tetra-n-butylammonium iodide
°C	degree Celcius
Cbz	carbobenzyloxy
^{13}C NMR	carbon nuclear magnetic resonance
COSY	correlation spectroscopy
CSA	camphosulphonic acid
δ	chemical shift in ppm
d	doublet
DBU	1, 8-diazabicyclo[5.4.0]undec-7-ene

DCM	dichloromethane
dd	doublet of doublets
DEIPS	diethylisopropylsilyl
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DTBMP	di-tert-butyl-4-methylpyridine
epi	epimeric
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
Et_3SiH	triethylsilane
g	gram
HMBC	heteronuclear multiple bond coherence
^1H NMR	proton nuclear magnetic resonance
HRMS	high resolution mass
HSQC	heteronuclear single quantum coherence

Hz	hertz
IR	infrared radiation
iPrOH	isopropanol
J	coupling constant in hertz
KHDMS	potassium bis(trimethylsilyl)amide
L	liter(s)
LC-MS	liquid chromatography-mass spectrometry
LHDMS	lithium bis(trimethylsilyl)amide
μL	microliters
LDA	lithium diisopropylamide
m	multiplet
M	molarity
m-CPBA	*meta*-chloroperbenzoic acid
μmol	micromole
Me	methyl
MeCN	acetonitrile
MeOH	methanol
mg	milligram
MHz	megahertz
min	minutes
mL	milliliters
mmol	millimole
MOM	methoxymethyl ether

mp	melting point
MPM	methoxybenzyl
MS	mass spectrum
Ms	methylsulfonyl
MTO	methyltrioxorhenium
m/z	mass to charge ratio
N	normal
$NaBH_3CN$	sodium cyanoborohydride
NMO	4-methylmorpholine N-oxide
NOE	nuclear Overhauser effect
NOESY	nuclear overhauser effect spectroscopy
OsO_4	Osmium tetroxide
$Pd(OAc)_2$	palladium(II) acetate
Pf	*N*-9-phenylfluoren-9-yl
PMB	*para*-methoxybenzyl
Ph	phenyl
Ph_3CBF_4	trityl fluoroborate
Ph_3P	triphenylphosphine
$(Ph_3P)_4Pd$	tetra(triphenylphosphine)palladium
PhSH	thiophenol
i-Pr	isopropyl
PSL	pseudomonas stutzeri lipase
Pt(DVDS)	platinum, bis[1,3-bis(2-ethenyl)-1,1,3,3-

	tetramethyldisiloxane]-
q	quartet
RCM	ring-closing metathesis
RT	room temperature
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TBS or TBDMS	*tert*-butyldimethylsilyl
TBDPS	tert-butyldiphenylsilyl
TBHP	tert-butyl hydroperoxide
TFA	trifluoroacetic acid
Tf_2O	trifluoromethanesulfonic (triflic) anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Triton B	benzyl(trimethyl)azanium hydroxide
Troc	2,2,2-trichloroethoxycarbonyl
Ts *or p*-Ts	tosyl, *para*-toluenesulfonyl

LIST OF SCHEMES

LIST OF FIGURES

LIST OF TABLES

Total Synthesis of 7-Epi-FR 66979 and 7-Epi-FR 900482

I. Introduction

1. Isolation and Biological Properties

In 1987 and 1989, a new class of aziridine natural products FR 900482 and FR 66979 (**Figure 1**) similar to the mitomycins in their mechanism of action, were isolated by the Fujisawa Pharmaceutical Corporation from *Streptomyces sandaensis.*[1,2] The structures of FR 900482 and FR 66979, were a mixture of two stereoisomers **A** and **B**, in equilibrium due to their unique hydroxylamine hemiketal functionality.

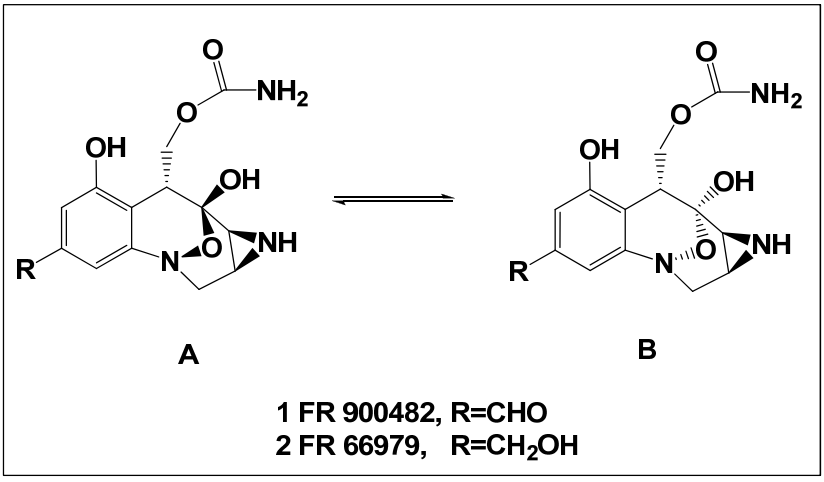


Figure 1. Structure of FR 66979 and FR 900482

They also reported that FR 900482 and FR 66979 are antibiotics with potent antitumor activity[2,3] and are at least as active as mitomycin C (Figure 2) and have less toxicity. The studies found that the FR 900482 and FR 66979 are effective against leukemia P388, melanoma B16, lymphoma EL4, mammary carcinoma FM3A, leukemia

L1210 and baby hamster kidney (BHK-21) cells at low concentration. In the further development of more potent and less toxic agents, FK 973[4] and FK 317[5] (Figure 2), semisynthetic derivatives from FR 900482, were found to be potent antitumor candidates.

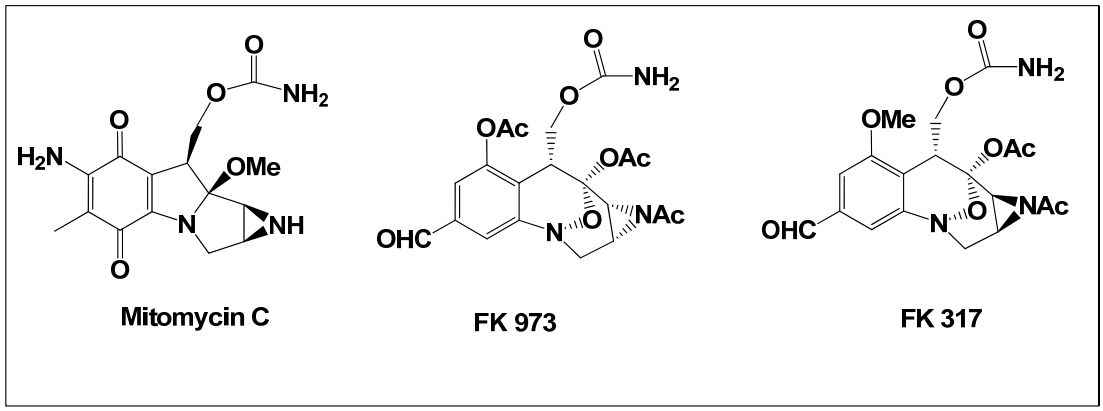
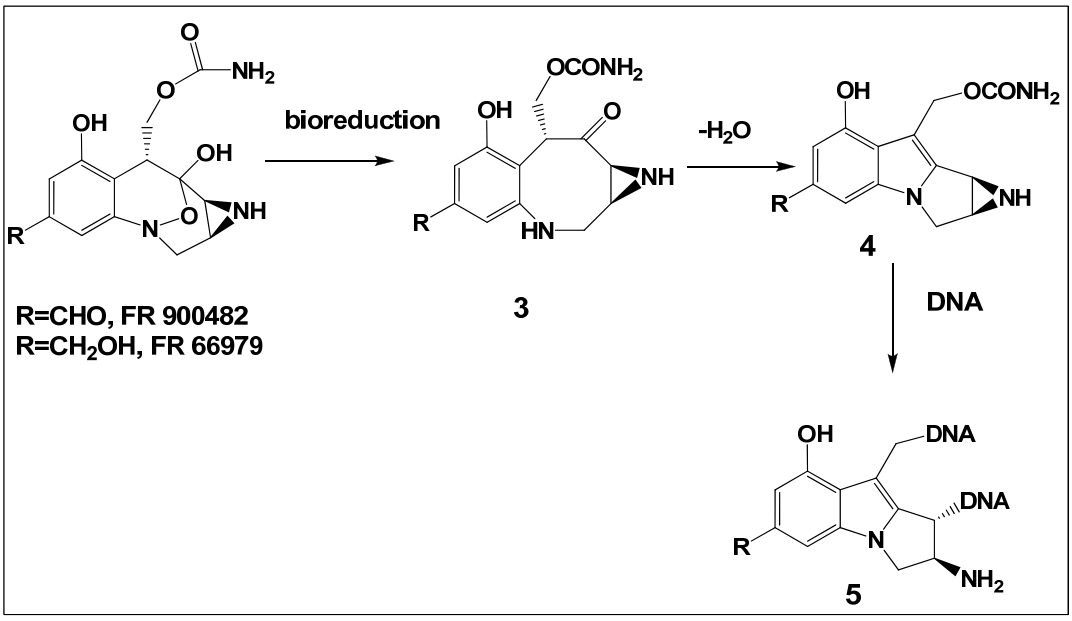


Figure 2. Structures of Mitomycin C, FK 973 and FK 317

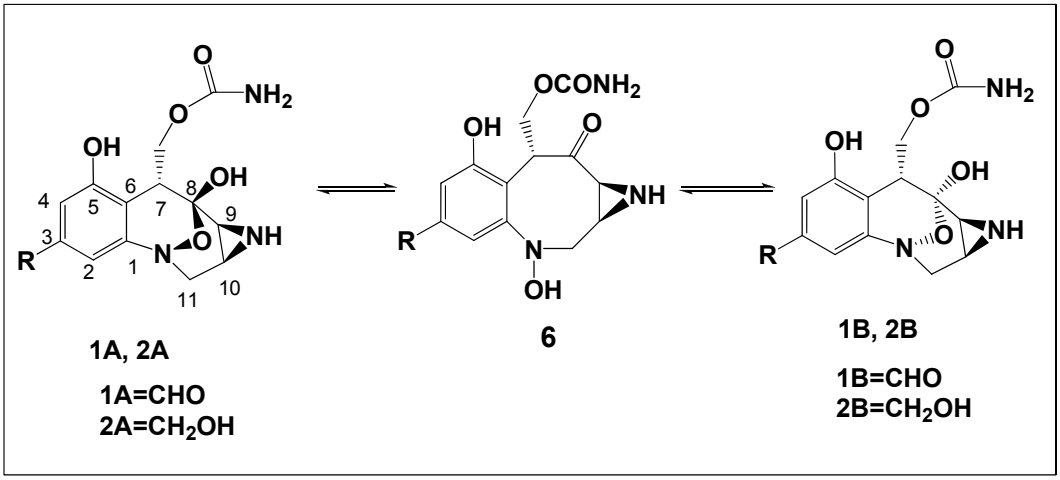
The mode[6]of antitumor action of FR 900482 and FR 66979 shown in **Scheme 1** involves a DNA-cross coupling reaction induced by cytosolic reduction. Thus, FR 900482 and FR 66979 are activated by bioreduction and aromatization to form **4**, which undergoes DNA-cross coupling. The cross-linking disrupts translation and then prevents rapid cellular division related to cancer.



Scheme 1. Mode of antitumor action of FR 900482 and FR 66979

2. Structural Features and Synthetic Challenges

The unique structures and antitumor bioactivities of FR 900482 and FR 66979 have made them interesting targets for total synthesis. FR 900482 and FR 66979 exist as a mixture of stereoisomers, which interconvert through the hydroxylamine ketone (**Scheme 2**). They have four contiguous stereogenic centers at C7, C8, C9 and C10. From current total syntheses, there are two common approaches to the core of the natural products, which are nitroso or amine oxide cyclization to give hemiketal core and the oxidation of pyrroloindole intermediate to form the aminoxyhemiketal derivative. Because FR 900482 and FR 66979 can be made by one simple chemical transformation, the total synthesis of either one can be treated as a formal total synthesis of the other.



Scheme 2. Equilibrium of FR 900482 and FR 66979

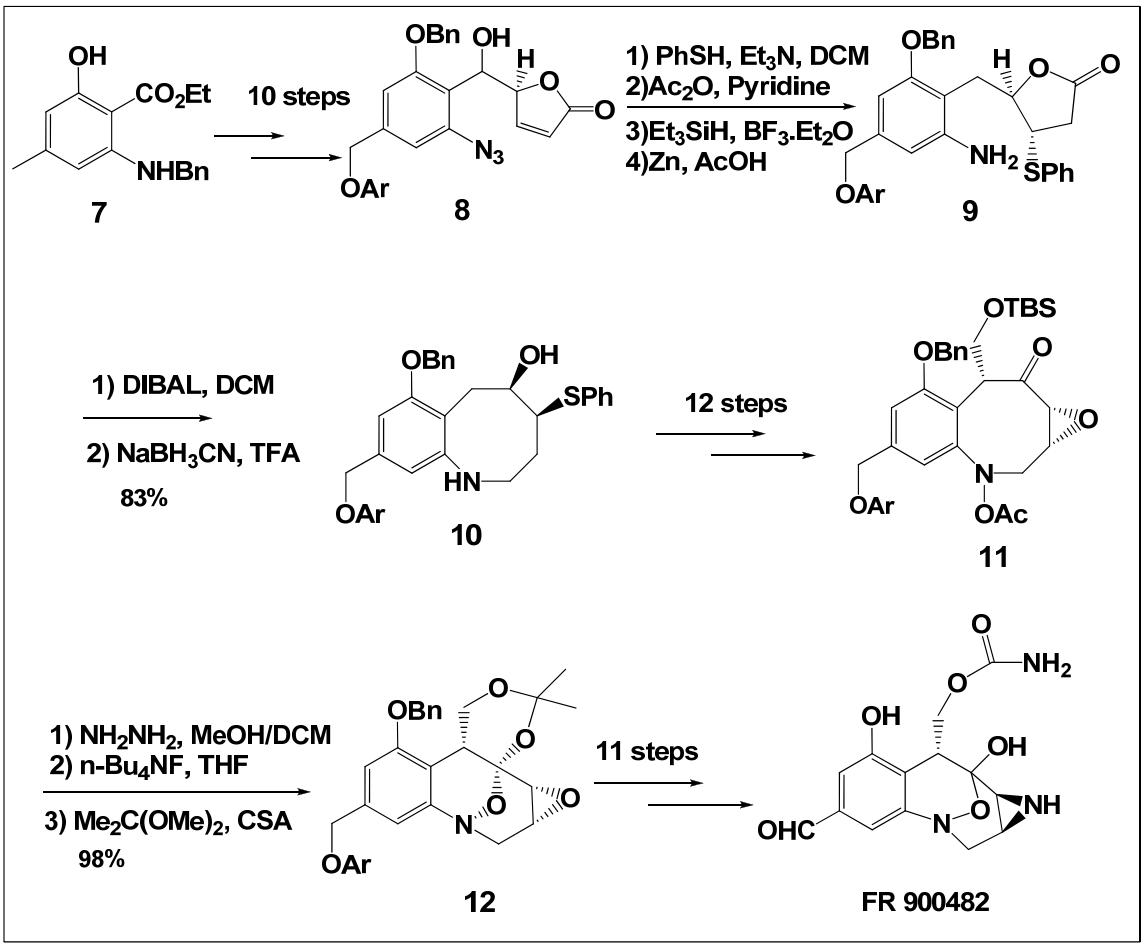
II. Various Strategies for the Total Syntheses of FR 900482 and FR 66979

In 1992, Fukuyama reported the first total synthesis of FR900482[7]. After that, Danishefsky in 1995 finished another racemic total synthesis[8]. In 1997, first enantioselective total synthesis was reported by Terashima[10]. Following that, Williams[11], Fukuyama[12], and Ciufolini[13] also reported enantioselective total syntheses in 2002. Martin[14] and Paleo [15] reported formal total synthesis in 2000 and 2003. In 2008, Trost[16] reported total synthesis of epi 7-Epi-(+)-FR900482.

1. The Fukuyama First Total Synthesis and Enantioselective Total Synthesis

In 1992, the first total synthesis of FR 900482 was reported by Fukuyama[7] (**Scheme 3**). They started with N-benzylamine **7** to form butenolide **8** after 10 steps transformation. The reactive butenolide **8** was protected by thiophenol. The hydroxyl group was removed by acetylation and reduction with triethylsilane. The azido lactone was further reduced with zinc to provide amine lactone **9**. The critical tansformation of lactone **9** to 8-membered amine **10** was achieved by the reduction of the lactone with DIBAL, then followed by reductive amination with sodium cyanoborohydride in 83% yield. After converting **10** to **11** in 12 steps, the key pentacyclic compound **12** was obtained in 98% yield by hydrazinolysis of the actetate, deprotection of TBS ether with n-Bu_4NF, and protection of the diol as an acetonide. The final target was obtained with

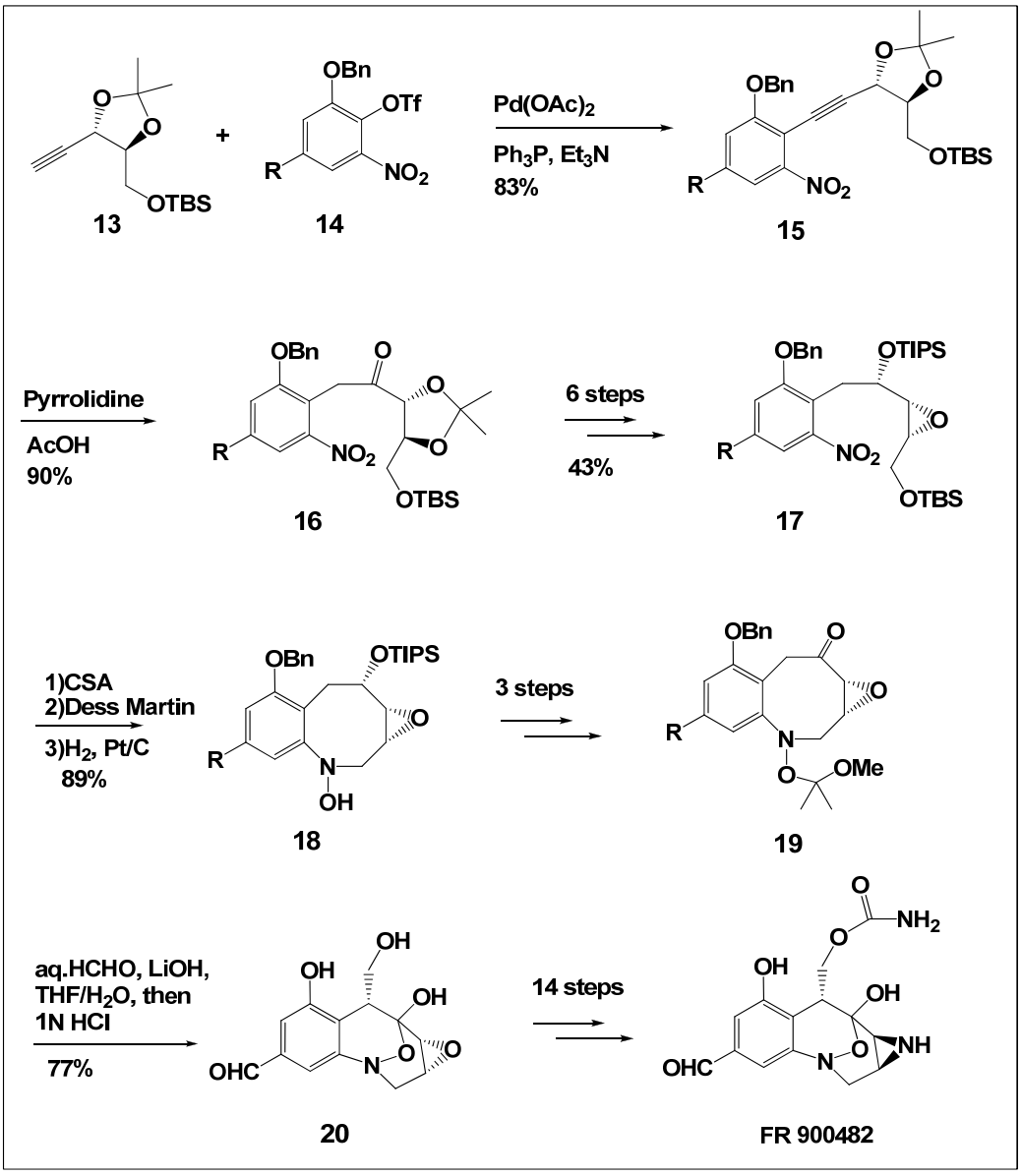
additional 11 steps. In conclusion, FR 900482 was synthesized in 41 steps in overall 0.011% yield.



Scheme 3. Fukuyama first total synthesis

In 2002, Fukuyama developed enantioselective total synthesis which began with a Sonagashira coupling of chiral acetylene **13** and aryl triflate **14** to afford **15** in 83% yield **(Scheme 4)**[11]. Regioselective formation of the ketone **16** was achieved by conjugate addition of second amines to triple bond and hydration. After compound **16** was converted to epoxide **17** by 6 steps, TBS ether was selectively deprotected, the

resulting alcohol was oxidized to aldehyde, then the aryl nitro was hydrogenated over Pt/C (5%) to realize the intramolecular reductive hydroxylamination to form the N-hydroxybenzazocine **18**. With 3 steps, **18** was converted to ketone **19**. The key construction of the hydroxymethyl group and tetra cyclic core ring system was realized by one pot reaction in 77% yield, which **19** was treated with paraformaldehyde and catalytic amount LiOH in aqueous THF, followed by the addition of 1N HCl. The final target was obtained by additional 14 steps transformation in overall 13% yield. The total synthesis was finished in 33 steps in overall 0.7% yield.

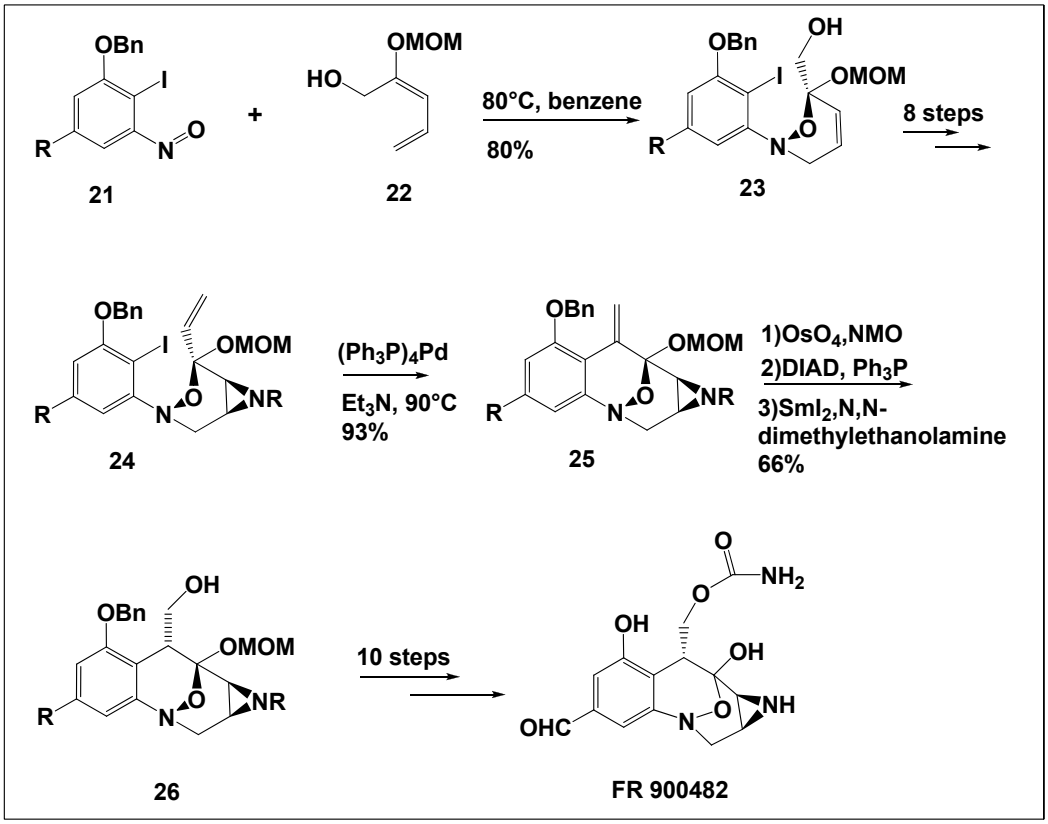


Schem 4. Fukuyama enantioselective total synthesis

2. Danishefsky Cycloaddition Approaches Racemic Total Synthesis

Danishefsky's synthesis featured a Diels-Alder reaction as a key step to prepare the core of natural product (**Scheme 5**)[8]. Diels-Alder reaction between **21** and **22** provided **23** in 80% yield, which was converted to **24** after additional 8 steps reaction.

Compound **24** underwent Heck arylation to provide tetracycle core **25** in 93% yield. The construction of the hydroxymethyl group was more difficulty than they expected. In their early study[9], a long route was developed to complete this task. Then, the compound **26** was obtained by Osmylation, epoxidation and SmI_2 reduction. Finally, they finished the total synthesis in 31 steps.

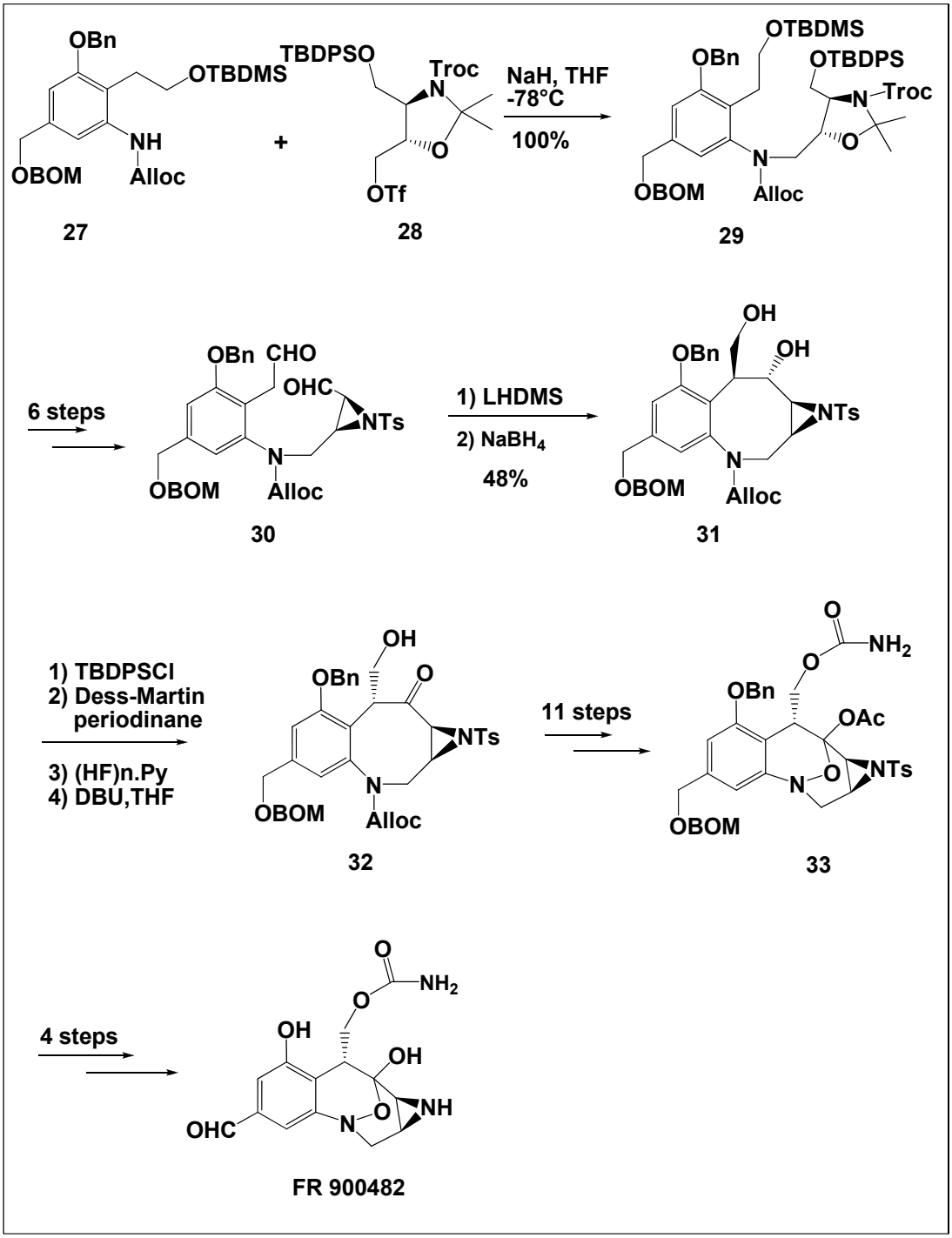


Scheme 5. Danishefsky total synthesis

3. Terashima Total Synthesis-Aldol Cycloaddition

In 1997, Terashima's enantioselective total synthesis (**Scheme 6**)[10] started with L-diethyl tartrate to prepare optically active aliphatic compound **28** in 15 steps. They

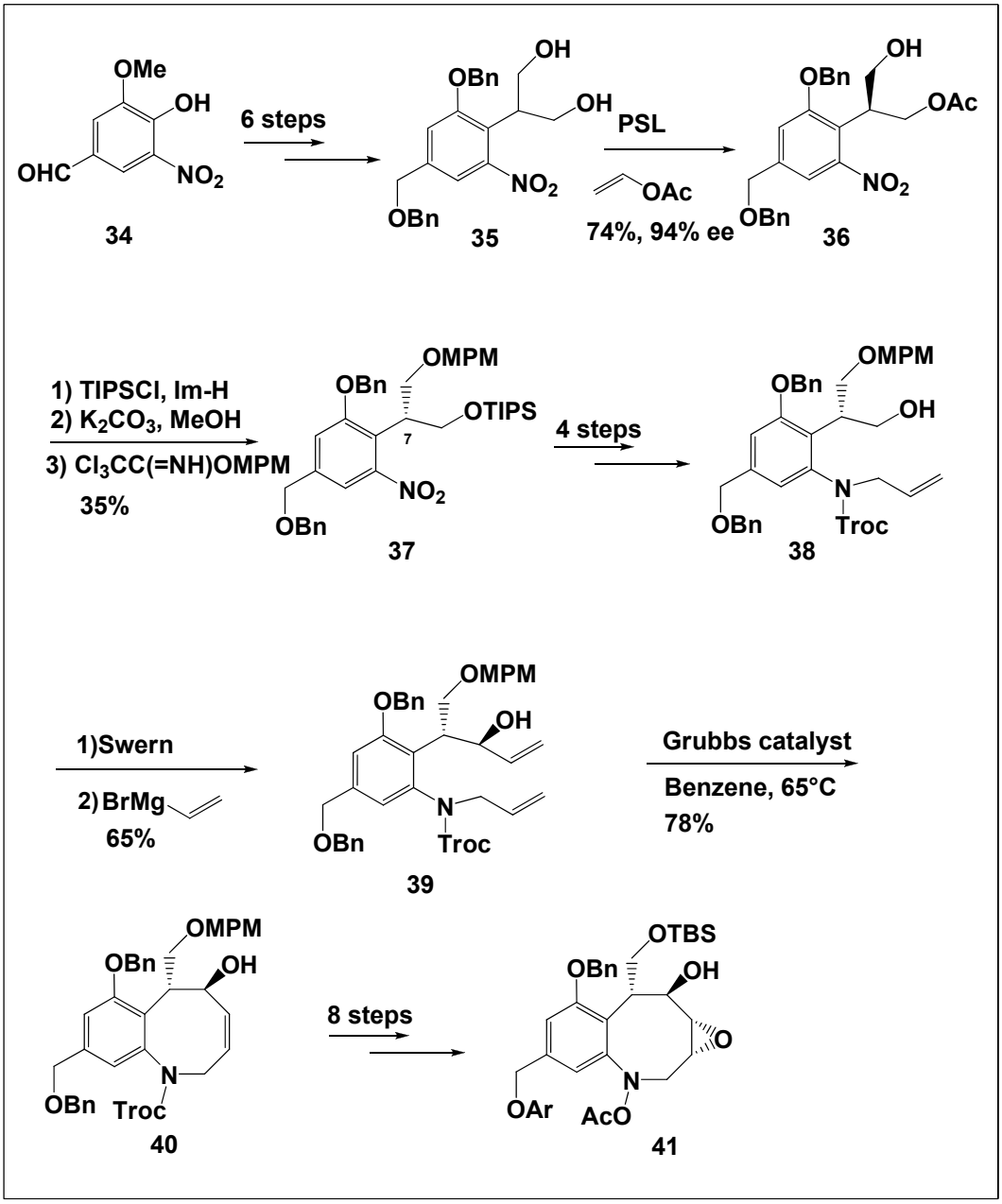
made aromatic compound **27** in 15 steps starting from 5-hydroxyisophthalic acid. Then, the coupling reaction of enantiomerically pure compound **28** with aromatic compound **27** was conducted by treating with sodium hydride in THF to provide compound **29** in a quantitative yield. Dialdehyde **30** was prepared in 6 steps from **29**. The diol **31** was obtained in 48% yield from **30** after intramolecular aldol coupling and reduction. The S configuration of the hydroxymethyl group in compound **31** was converted to R configuration of hydroxymethyl group in compound **32** was achieved by protection, oxidation, deprotection and epimerization with DBU in THF. Compound **32** was converted to the final natural product in additional 15 steps. Overall, this total synthesis was 57 steps with a 0.032% overall yield.



Scheme 6. Terashima total synthesis

4. Ring Closing Metathesis: Martin Formal Total Synthesis

In 1995, Grubbs reported ring-closing metathesis to construct the eight membered tetrahydrobenzazocine intermediate of FR 900482[17]. This was utilized by Martin to complete the formal total synthesis[14] (**Scheme 7**). The racemic diol compound **35** was prepared from **34** in 6 steps. Desymmetrization of the racemic diol **35** by using PSL and vinyl acetate yielded the S configuration hydroxy acetate **36** in 74% yield and 94% ee. . The absolute configuration at C (7) of compound **37** for FR 900482 was obtained by a series of hydroxyl protecting group interchanges. The N-allylamine **38** was prepared in additional 4 steps from **37**. A tandem Swern oxidation, Grignard addition from compound **38** provided the RCM precursor **39**. Subsequent ring closing metathesis of **39** provided benzazocine **40**, which was converted to **41** of Fukuyama's synthesis in additional 8 steps transformation

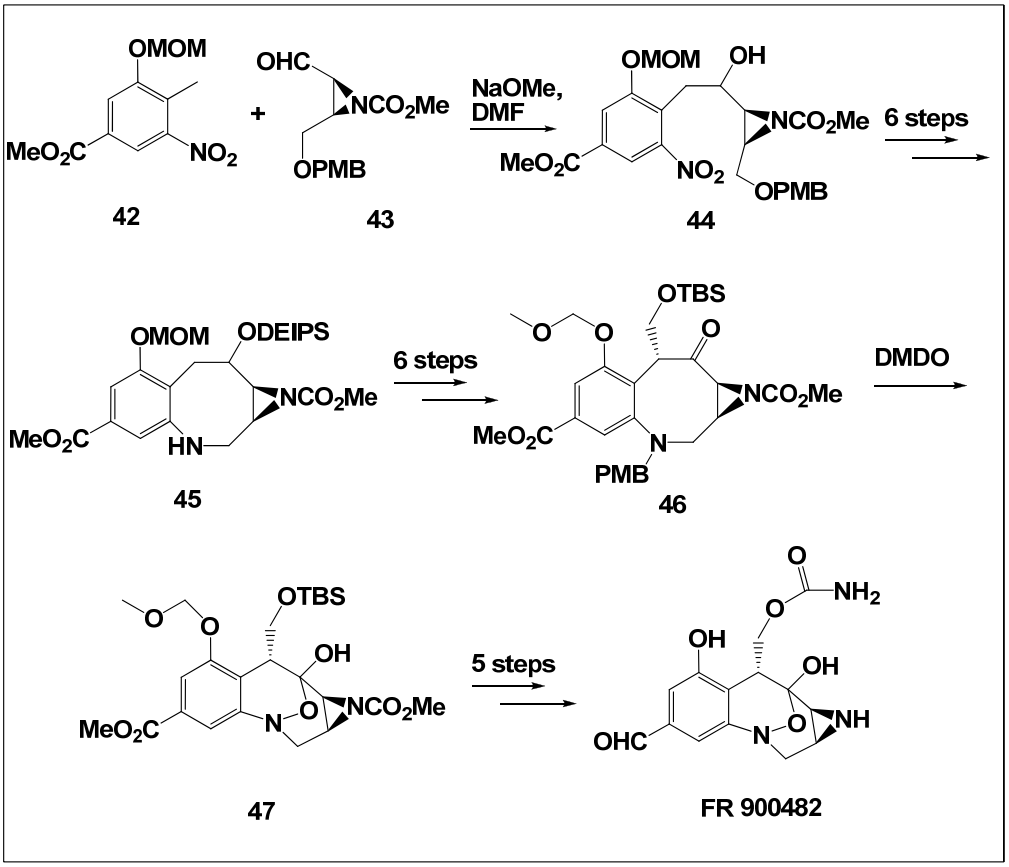


Scheme 7. Martin formal total synthesis

5. Williams Enantioselective Total Synthesis

In 2002, Williams's synthesis[11] featured DMDO oxidation as key step to convert **46** to **47** (**Scheme 8**). Optically active aziridine **43** coupled with trisubstituted

nitrobenzene **42**, followed by 6 additional steps to give eight-membered-ring amine **45**. Ketone **46** was obtained from **45** in 6 steps. A simultaneous oxidative deprotection of eight-membered-ring aminoketone **46** by DMDO formed the core structure of hydroxylamine hemiketal **47**. The synthesis was completed in 33 steps with overall 0.34% yield.

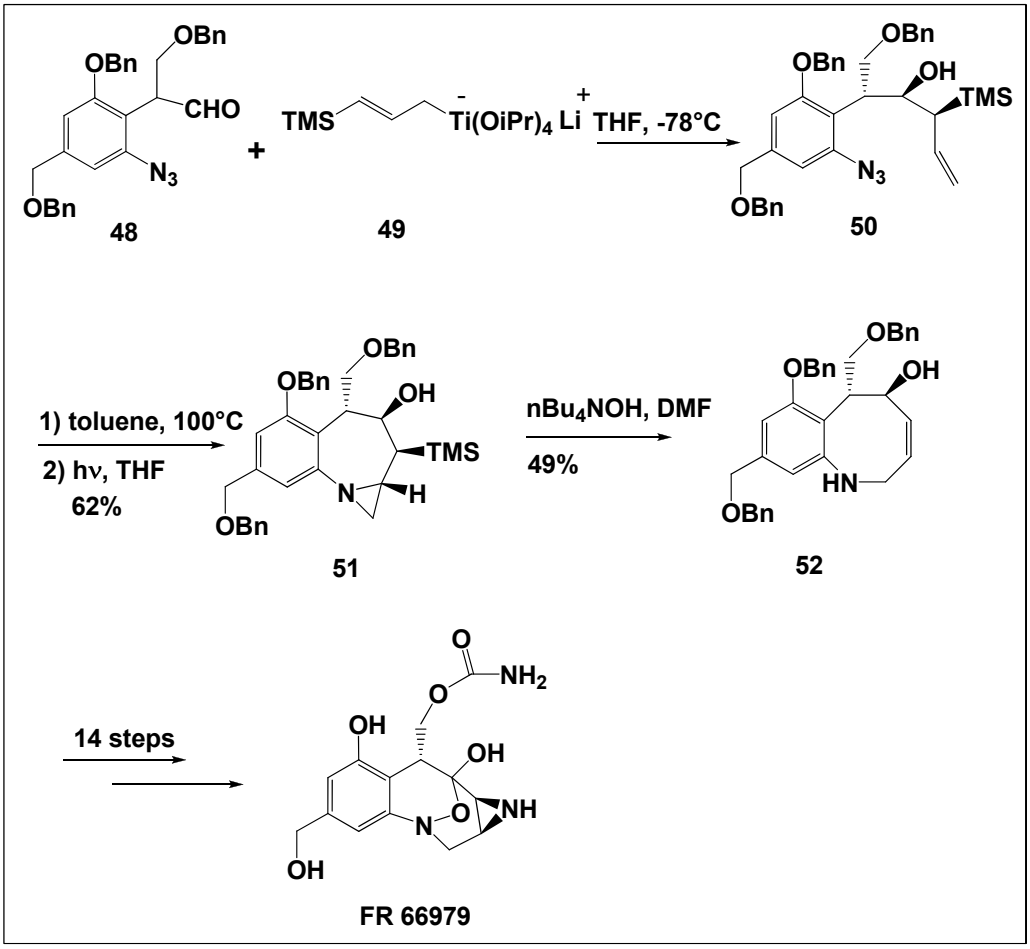


Scheme 8. Williams total synthesis

6. Homo-Brook Fragmentation: Ciufolini Total Synthesi

In 2002, Ciufolini[13] (**Scheme 9**) reported the total synthesis by using the homo-Brook triggered fragmentation. S_E' addition of **49** to aldehyde **48**, which was prepared

from Martin's intermediate 2-(2-nitroaryl)-propanediol in 4 steps[14], provided alcohol **50**. The intramolecular 1,3-dipolar cyclization between azide and double bond in **49**, followed by photolysis afforded **51** in 62% yield. The aziridine **51** underwent a base induced homo-Brook fragmentation to provide **52** in 49% yield. The remaining synthesis is an extension of work performed by Fukuyam, which were N-oxidation and N-acetylation, epoxidation, cyclization, formation of aziridine, and deprotection. Finally, regioselective ammonolysis and concomitantly deprotected the acetyl groups to complete FR 66979. Overall, this total synthesis was completed in 28 steps in 0.23% yield.

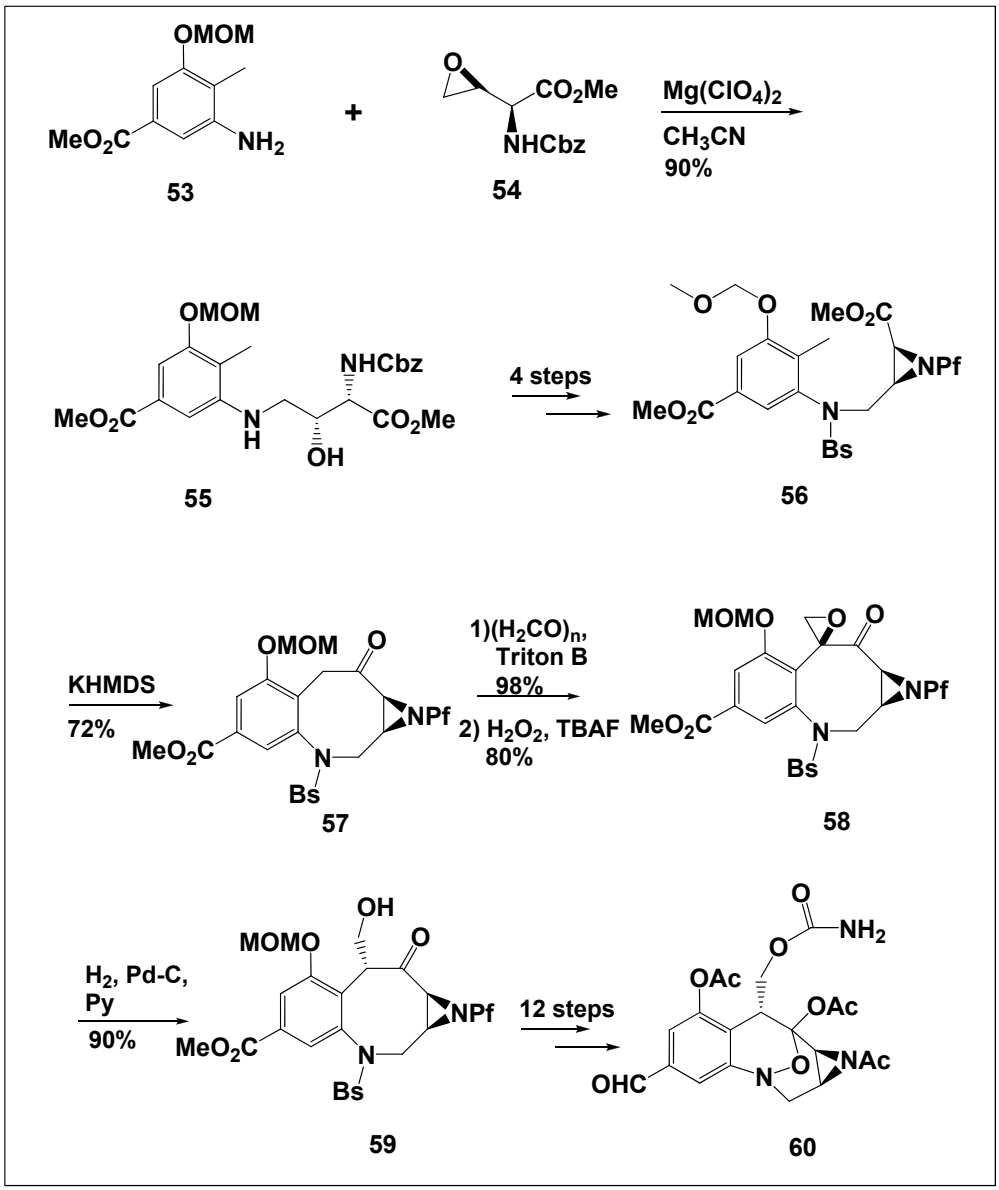


Scheme 9. Ciufolini total synthesis

7. Paleo Formal Total Synthesis

In 2003, Paleo reported another formal total synthesis (**Scheme 10**)[15]. Amino alcohol **55** was prepared by regioselective ring opening of enantio pure epoxide **54** with **53**, while **53** was prepared from 3,5-dinitrop-toluic acid in 3 steps[18] and **54** was prepared from L-methionine methyl ester hydrochloride[19]. Aziridine compound **56** was obtained in 4 steps from **55**. Deprotonation of **56** with KHMDS in THF followed by intramolecular condensation with aziridino methyl ester provided the eight membered

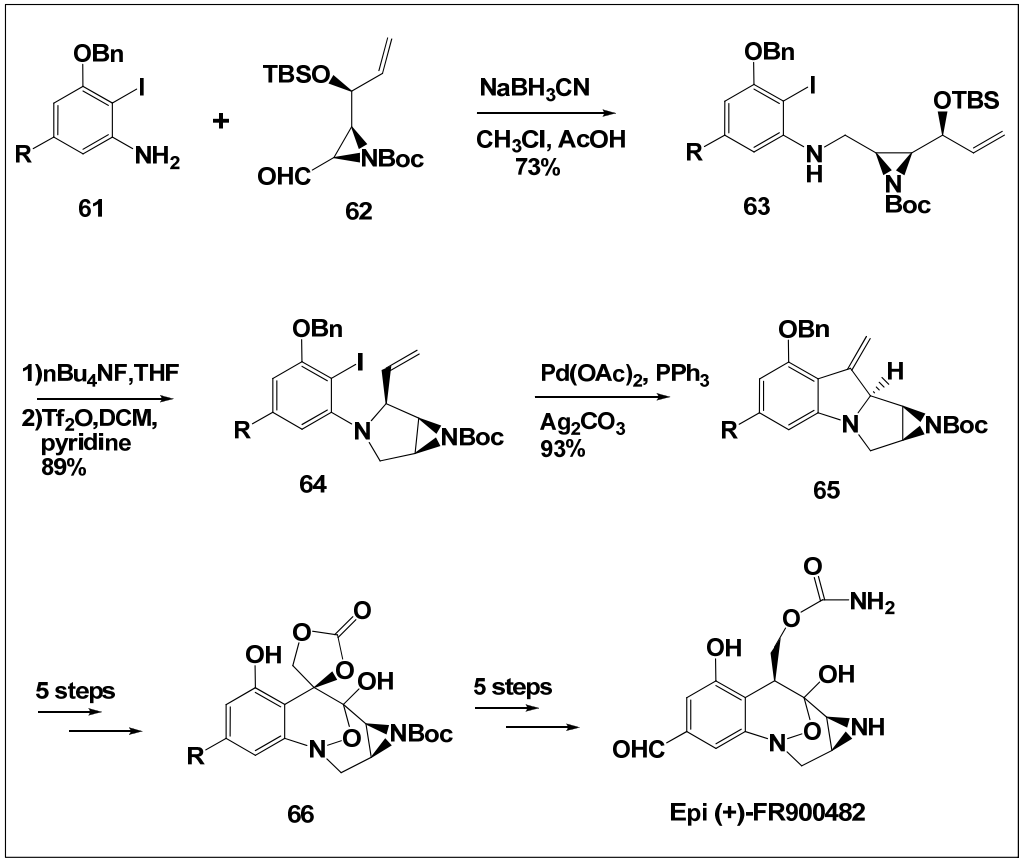
ring **57.** Hydroxymethylation of **57** was achieved by the formation of enone, epoxidation and reduction. A series of steps similar to Fukuyama finished the synthesis of **60** (+) FK-973.



Scheme 10. Paleo formal total synthesis

8. Trost Total Synthesis of epi-(+)-FR 900482

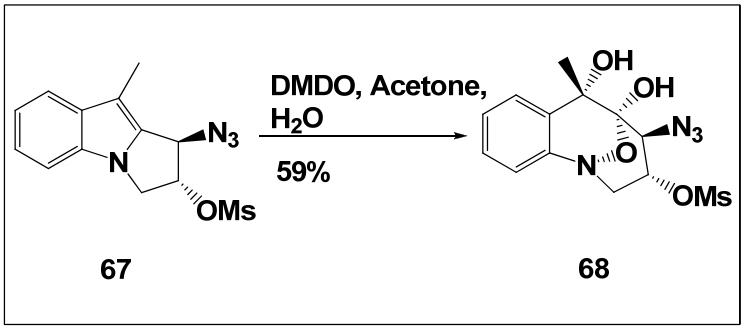
In 2008, Trost reported the total synthesis 7-Epi (+)-FR 900482 (**Scheme11**)[16]. Reductive amination between the aziridine **62** and aniline **61** afforded **63.** Deprotection and activation provided 5-membered ring **64**. Heck reaction of **64** afforded tetracyclic intermediate **65.** Inspired by the pioneering works of Dmitrientko[20] and Ziegler[21], they applied the Polonovski reaction, followed by an oxidative ring expansion to afford hydroxylamine hemiketal **66.** In five additional steps, **66** was converted to epi-(+)-FR900482. Overall, this total synthesis was completed in 25 steps in 1.24% yield.



Scheme 11. Trost epi total synthesis

III. Retrosynthetic Plan

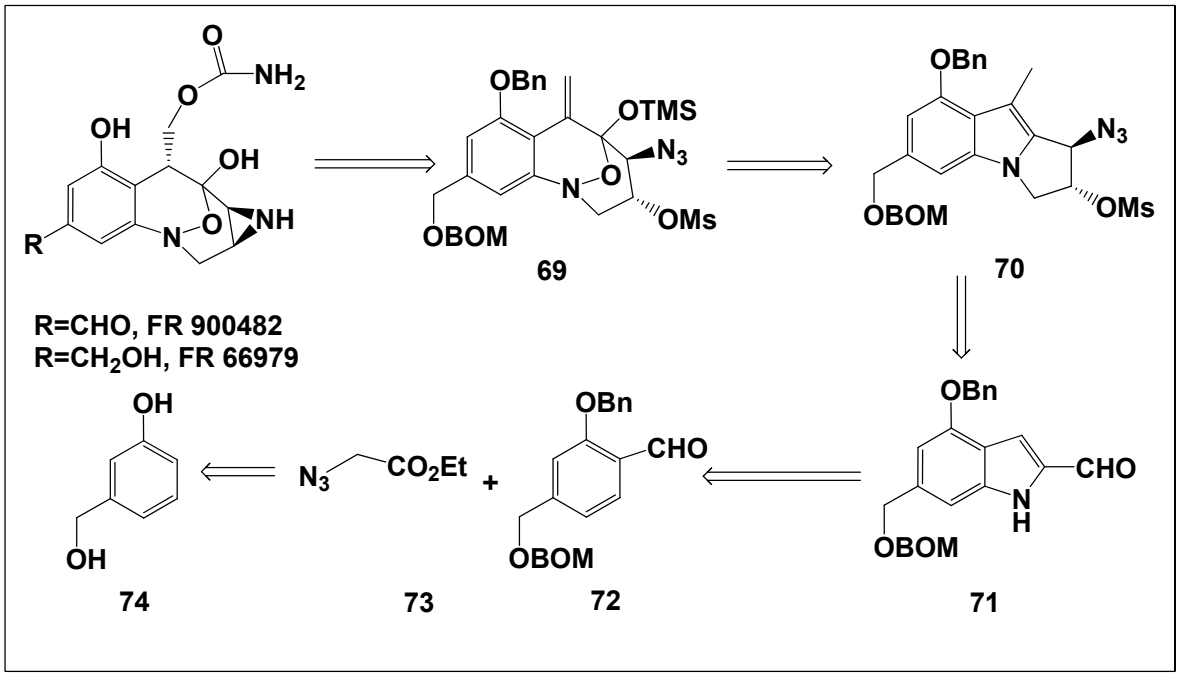
In 2003, our lab reported a new approach to make hydroxylamine hemiketal from pyrroloindole substrate[22]. Because the FR 900482 and FR 66979 generate mitosenses **4** in vivo as the active DNA cross-linking agent, it will provide rapid access to the core structure if they could interconvert. Several groups worked on the oxidation of the pyrroloindole core[20(b), 21(b), 23]. Our lab successfully established that oxidation of pyrroloindole **67** by aqueous dimethyldioxirane afforded tricyclic core **68** in a 59% yield (**Scheme 12**)[21].



Scheme 12. DMDO oxidation

Based on our success to access the core structure, we planned our total synthesis as outlined in **Scheme 13**. The target compound FR 900482 and FR 66979 could obtained from the intermediate **69** by several steps including aziridine formation, hydroxyl methylation, deprotection and oxidation. Compound **69** is accessible from functionalized pyrrolo[1,2-a]indole **70** by DMDO oxidation. Indole **71** can be

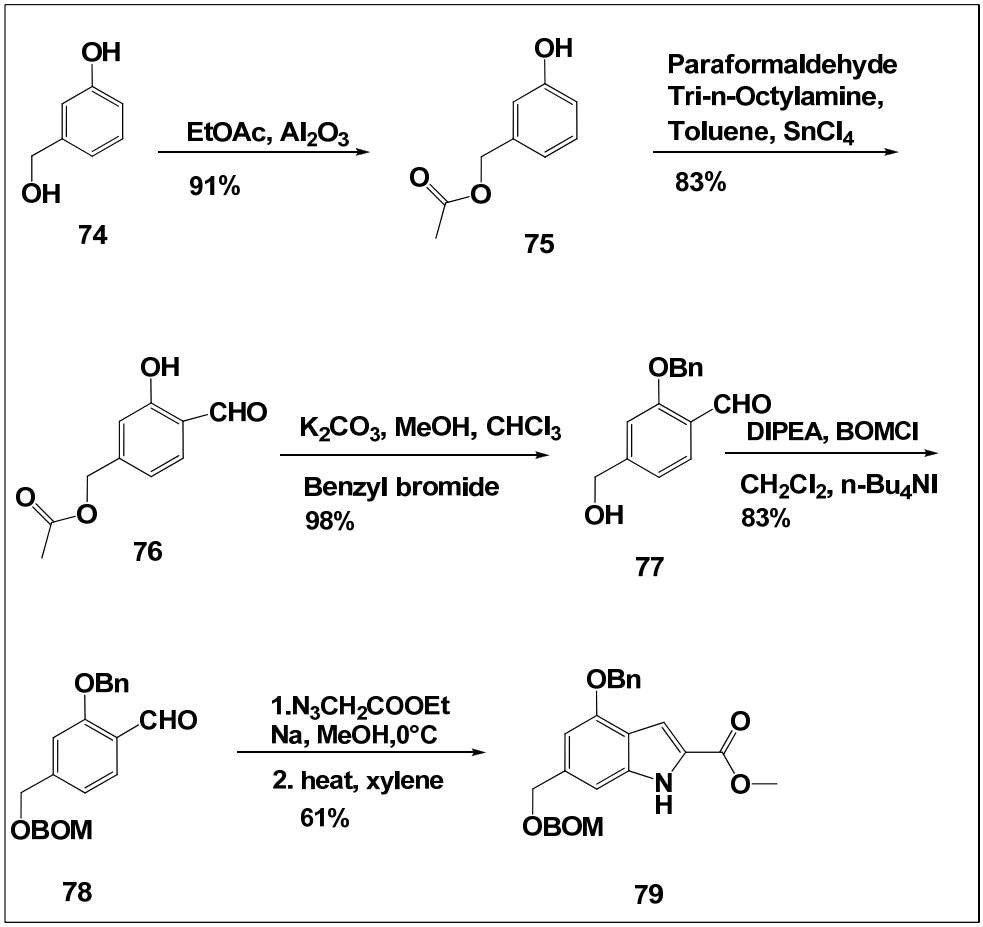
converted to pyrrolo[1,2-a]indoles **70** by reaction with diisopropylvinylsulfonium triflate, followed by the addition of sodium azide. Ethyl azidoacetate **73** reacts with benzaldehyde **72** to give an indole ester, which is reduced to indole aldehyde **71**. Functionalized benzaldehyde **72** is readily available from commercially available 3-hydroxymethylphenol **74**.



Scheme 13. Retrosynthetic plan

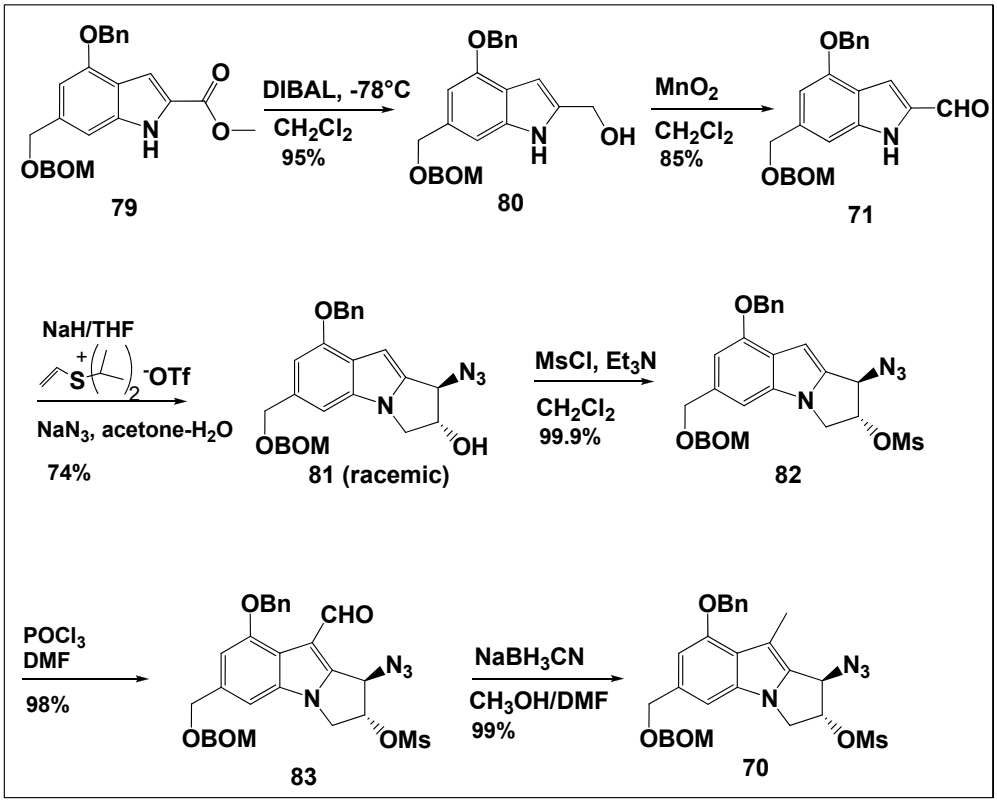
IV. Synthesis of Functionalized Indole-2-Carboxylate

The first stage for this total synthesis is to make the important intermediate indole ester **79** (**Scheme 14**). There are several methods to synthesize functionalized indole. The Hemetsberger-Knittel reaction had been recognized as one of the most important methods for the synthesis of indole-2-carboxylate[24]. Initially we started with commmercial availabe material 3-hydroxymethylphenol **74**. In our early study, compound **74** was treated with chloroform and aqueous sodium hydroxide to prepare ortho phenol aldehyde. This reaction gave low yield and undesired regional by-product. A more efficient way to make aldehyde **76** was to selectively protect hydroxyl methyl group, then react with paraformaldehyde in the presence of a Lewis acid catalyst[25]. The two steps gave a 76% yield. Cleaving the acetate by potassium carbonate and protecting phenol with a benzyl in one pot provided **77** in 98% yield. To streamline the synthesis, the hydroxylmethyl group is protected by the Bom group, which was accomplished with DIPEA, benzyl chloromethyl ether with n-Bu_4NI as catalyst to give **78** in an 83% yield. With **78** in hand, indole **79** was prepared by base-mediated aldol reaction of aryl aldehyde **78** with ethyl azidoacetate, then subsequent thermal cyclization.



Scheme 14. Synthesis of Indole-2-Carboxylate

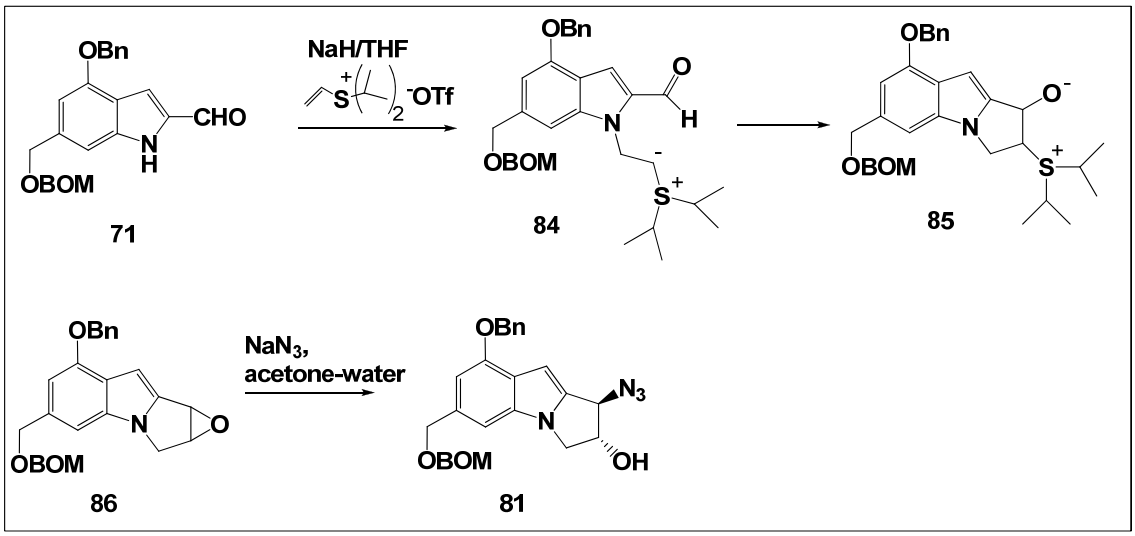
V. Synthesis of Pyrroloindole



Scheme 15. Synthesis of pyrroloindole

The next challenge was to make the ring expansion intermediate **70** (**Scheme 15**). In order to make tricyclic ring intermediate **81**, indole aldehyde **71** should be prepared. It was easily prepared from indole-2-carboxylate **79** by reduction with DIBAL, followed by oxidation with MnO_2 in an overall 81% yield. The synthesis of tricyclic compound **81** was developed in our lab in 1999[26] (**Scheme 16**). The diisopropylvinylsulfonium salt reacted with indole-2-carboxyaldehyde **71** to form the tetracyclic oxirane **86**, then subsequently treatment with sodium azide in acetone-water

afforded **81** in a 74% yield. This conversion gave a racemic product **81** because an achiral vinylsulfonium salt was used.

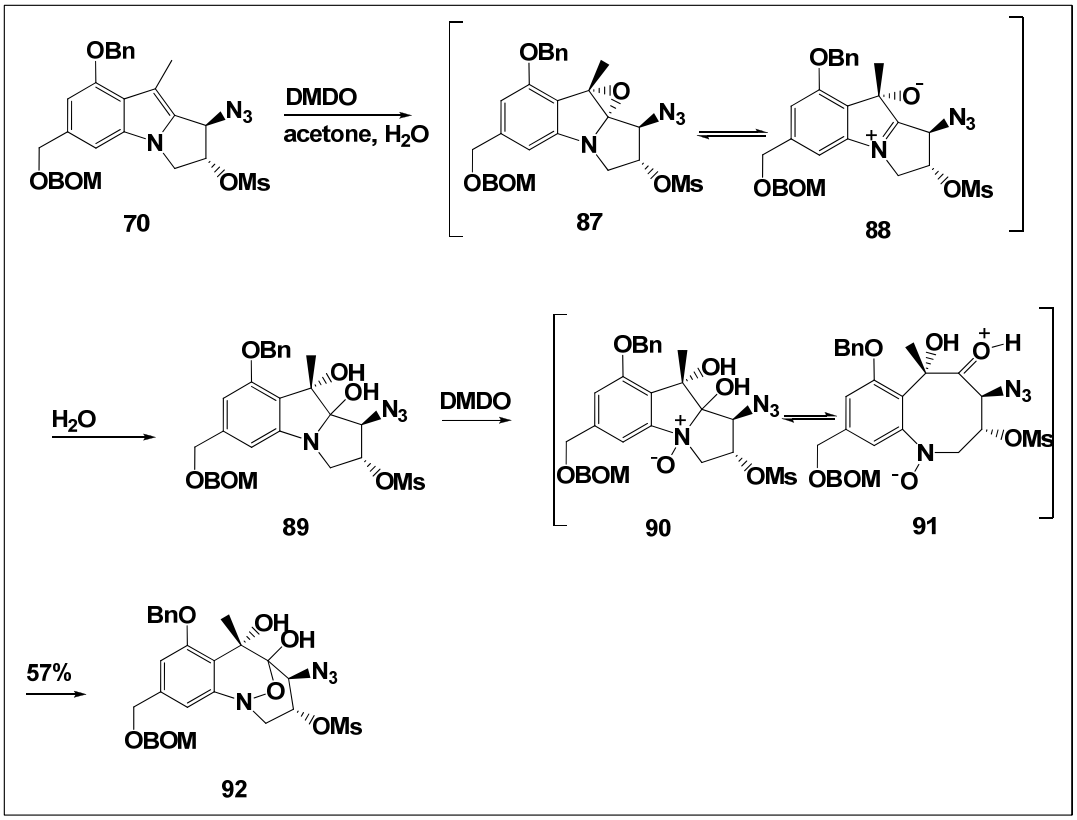


Scheme 16. The formation of pyrroloindole

After the tricyclic product **81** was formed, it was converted into mesylate **82** (**Scheme 15**). The compound **82** was treated with preformed mixture of phosphorus oxychloride and dimethylformamide, followed by water to give **83** in 98% yield. Aldehyde **83** was then reduced by sodium cyanoborohydride in methanol to provide **70** in a 61% yield. It was found that low yield is due to poor solubility of **83** in methanol. After switching the solvent to a mixture of CH_3OH/DMF, the yield was improved to almost quantitative yield.

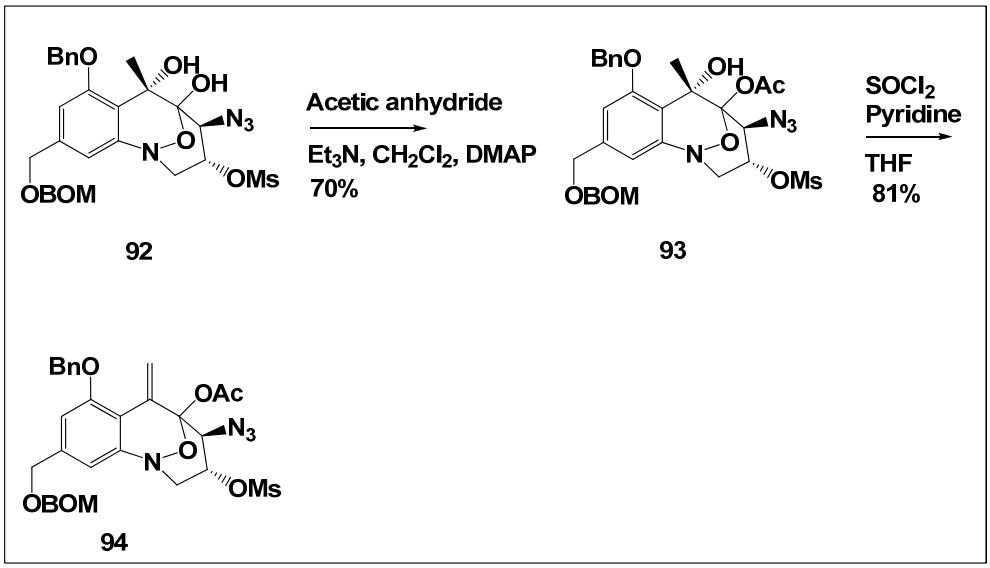
VI Synthesis of Core Ring System

Methodology developed earlier in our lab[22], was applied to the core ring system **92,** which was successfully prepared by dimethyldioxirane (DMDO) oxidation in 57% yield (**Scheme 17**). For this reaction, the first step is presumably to form an epoxide on indole double bond, which has an equilibration with zwitterionic intermediate **88**. Then, water attack the zwitterionic intermediate **88** to form diol **89**. A second equivalent of DMDO oxidized the diol **89** to form the intermediate **91** which eventually lead to the formation of hydroxylamine hemiketal ring system **92**. Hemiketal **92** was a mixture of two diastereomers which was indicated by TLC. The mixture of diastereomers of **92** was not isolated during the study of the next several steps.



Scheme 17. Synthesis of core ring system

Because the hydroxyl hemiketal is not stable, it was necessary to protect this hydroxyl group (**Scheme18**). One easy way to do that was protection by acetate group. The compound **92** was treated with acetic anhydride, Et_3N and DMAP in dichloromethane to give intermediate **93** in 70% yield. The tertiary alcohol didn't react with acetic anhydride, so this condition has a good selectivity. The next step is dehydration of the tertial alcohol of intermediate **93**. The first study on dehydration of compound **93** was tried by Burgess' reagent. This reaction didn't give the desired product, even heated to 55°C and 80°C. The best condition for the dehydration of **93** was found by using thionyl chloride with pyridine in THF[27]. This reaction was conducted at -60°C to -10°C for 1 hour to give product **94** in an 81% yield.

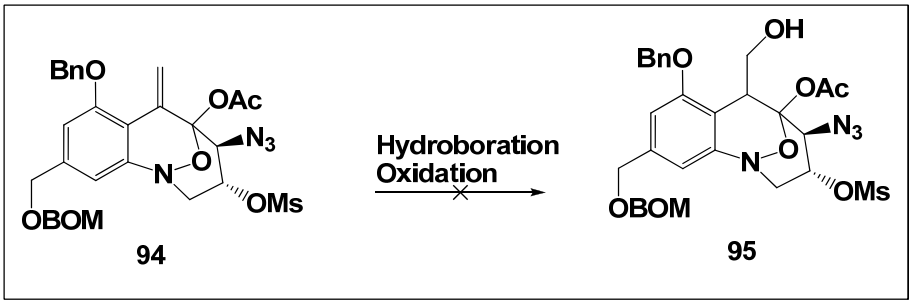


Scheme 18. Protection and dehydration

VII. The Challenge of Making Hydroxymethyl Group

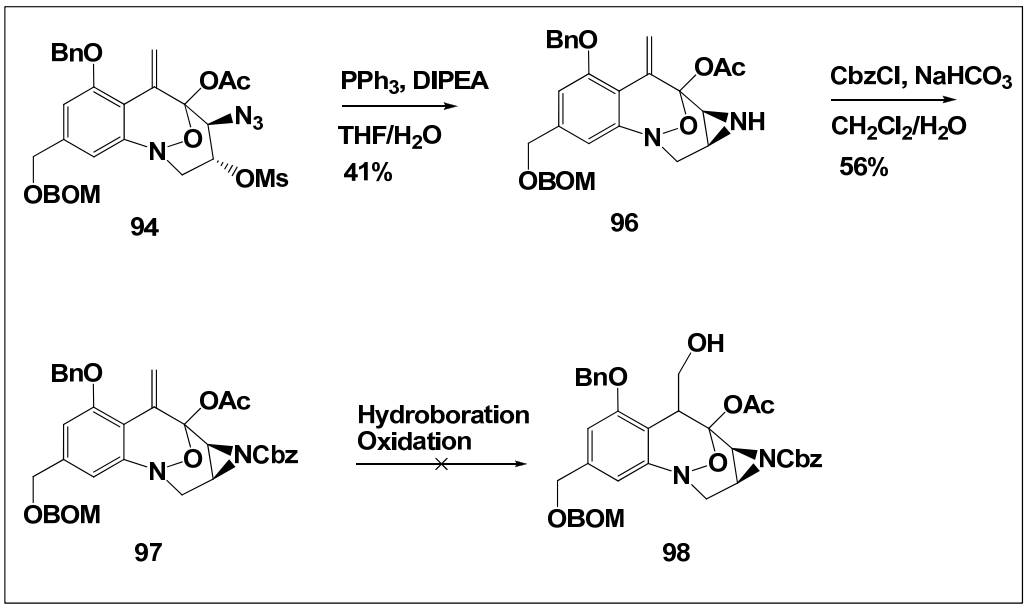
Once the double bond has been formed in the core system, the next key step is to convert this double bond into hydroxymethyl group. As reported by Danishefsky *et al*.,[24] it was more difficult than expected to complete this task.[9]. Because Danishefsky's[8] method required three steps to make hydroxymethyl group alternative methods should be developed to shorten the syntheses.

The hydroboration oxidation was tried first on compound **94** (**Scheme 19**). Borane in THF and $BBr_2.Me_2S$ were tried and followed by standard oxidation with H_2O_2 in aqueous Na_2CO_3. The desired product was not obtained, instead TLC showed decomposed baseline by-product. Another reagent $BHCl_2$ .dioxane , which reported by Brown[28] in 2001 as a superior reagent for the selective hydroboration of terminal alkenes, was also tried. However, this superior reagent still didn't work on the substrate **94**.



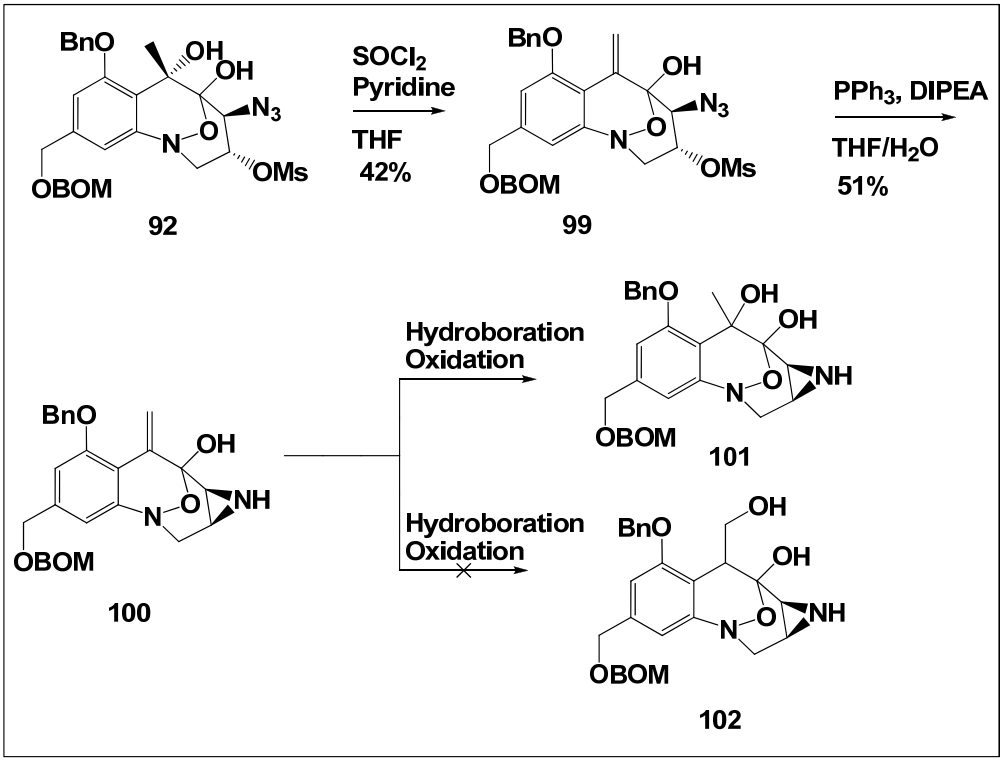
Scheme 19. Hydroboration and oxidation (1)

The failure of the reaction may due to the labile group of azido and mesylate. Based on the results, the azido and mesylate group should be converted to aziridine before the hydroboration oxidation. Compound **94** in THF/water was treated with triphenylphosphine and DIPEA for seventeen hours at room temperature to give intermediate **96** in 41% yield (**Scheme 20**). The aziridine group of **96** is also necessary to be protected by benzyl chloroformate before the hydroboration oxidation. If it is not protected, it will face a selective protection with generated hydroxyl group. This is not a convenient choice. Compound **96** in dilchloromethane/water was treated with benzyl chloroformate and sodium bicarbonate to give product **87** in moderate yield. The hydroboration was conducted by two different reagents BH_3.THF and $BH_3.Me_2S$ in THF at room temperature on substrate **97** (**Scheme 20**). Both conditions didn't give the desired product. It might be due to bulky protecting group, which blocked the approach of borane reagents.



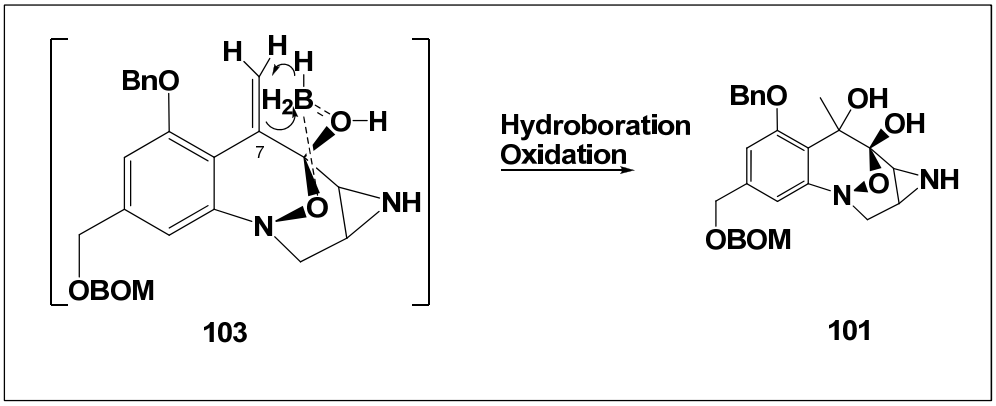
Scheme 20. Hydroboration and oxidation (2)

Followed the results of hydroboration of fully protected intermediate **97**, the next study of hydroboration oxidation should be on the unprotected hemiketal aziridine intermediate. Dehydration of compound **92** by thionyl chloride in THF and pyridine provided compound **99** in 42% yield (**Scheme 21**). Compound **99** was treated with triphenylphosphine and DIPEA in THF/water to give unprotected hemiketal aziridine **100** in 51% yield. The hydroboration and oxidation were conducted on the unprotected hydroxyl hemiketal aziridine **100**. MS and TLC indicated the product generated, but HNMR showed the product was tertial alcohol, no desired product was detected. The results indicated that hydroboration oxidation does work on this unprotected hemiketal aziridine **100**, but did not provide the desired product **102**, instead the the tertiary alcohol **101** was obtained.



Scheme 21. Hydroboration and oxidation (3)

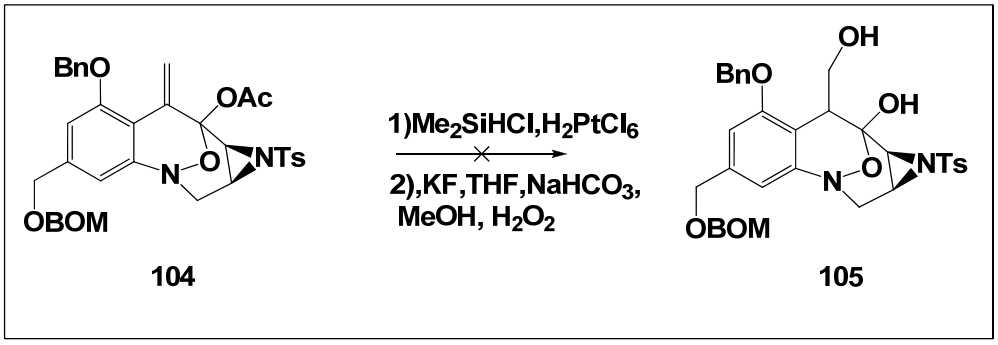
The reason to give Markonikov product may be due to the chelation of borane to two oxygen of hydroxyl hemiketal (**Scheme 22**). Once the borane chelate with two oxygen, it will deliver hydrogen to terminal position and borane attach on 7 position to keep the chelation with two oxygen. After the oxidation, compound **101** was obtained. The reagents of hydroboration used in this reaction were not only BH_3.THF and BH_3.Me_2S, but also 9-BBN, and catecholborane. The 9-BBN and catecholborane did not give any product, which means the bulky reagents can not approach the double bond even with no protecting group on the hydroxyl group.



Scheme 22. The chelation in hydroboration

VIII. Hydrosilylation –Oxidation a Successful Way to Make Hydroxymethyl Group

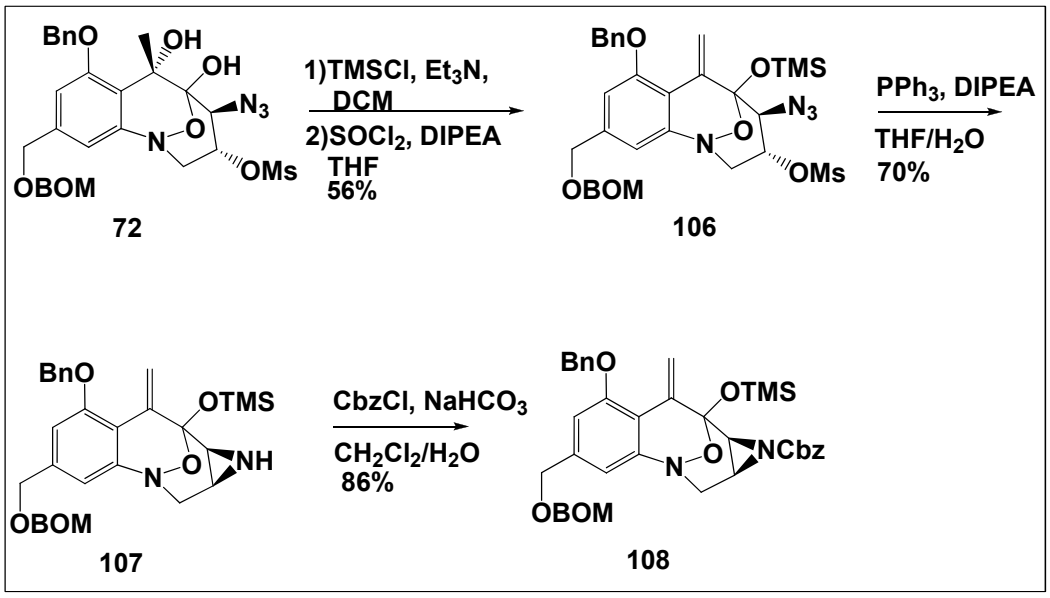
Another alternative way to make the hydroxymethyl group from a double bond can be done by hydrosilylation-oxidation. Since Tamao[29] developed this new methodology for the one-pot anti- Markonikov hydration of olefins to primary alcohols by platinum catalyzed hydrosilylation and then oxidation of resulting alkylsilane, this strategy has been recognized as a powerful method for the synthesis of various alcohols, ketones and hydroxyl ketones from simple available materials in recent years. In 2004, Jens Beckmann[30] reported that the H_2PtCl_6 catalyzed hydrosilylation of the terpenes (+)-a-fenchene, (-)-2-methylene bornane, (+)-camphene and (-)-3-methylene fenchane by using $HSiMe_2Cl$ or $HSiMeCl_2$ proceeded with high regioselectivity and in some cases, with high diastereoselectivity. KF-assisted oxidation of the hydrosilylation products gave predominately endo-terpene alcohol. This method was tried on substrate **104** (**Scheme 22**). The compound **104** was treated with catalytic H_2PtCl_6 and 10 equivalent $HSiMe_2Cl$ in dichloromethane at room temperature, but unfortunately this condition didn't work on this substrate.



Scheme 23. H_2PtCl_6 catalyzed hydrosilylation

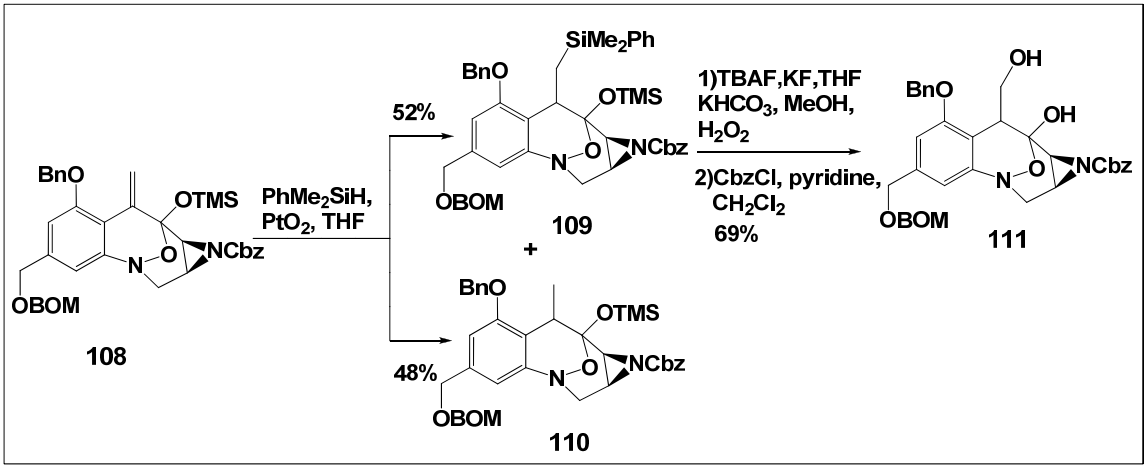
In the early 2002, another potent Adams' catalyst PtO_2 had been reported on hydrosilylation[31]. Charles Mioskowsk reported that although Speier's catalyst ($H_2PtCl_6.6H_2O$) was one of the most efficient, but if the substrates containing aminated functions Speier's catalyst gave only moderate yields and low reproducibility probably as a result of poisoning of the catalyst by the amino function. From their results, PtO_2 catalyst proved to be a highly potent hydrosilylation catalyst compatible with a large range of functionalities including amino functions.

The precursor **108** of hydrosilylation was obtained from TMS protected hemiketal **106** (Scheme 24). The protection group had been switched to TMS on hemiketal was because of the much better yield for next step of forming aziridine. Once the aziridine **107** was obtained, it was treated with benzyl chloroformate to provide fully protected substrate **108** in 86% yield.



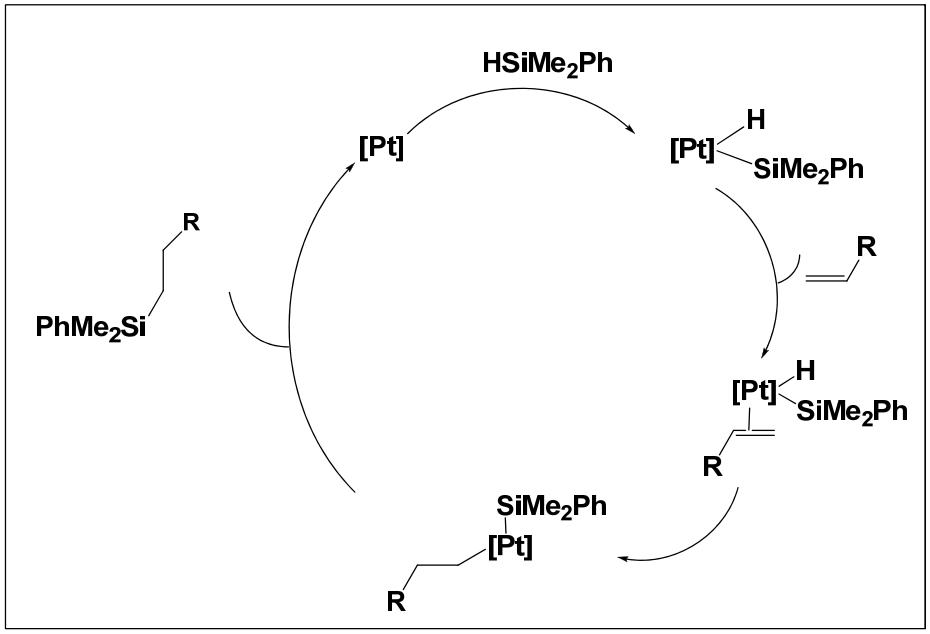
Scheme 24. Preparation of precursor of hydrosilylation

Compound **108** was treated with silane reagents and Adams' catalyst PtO_2 in THF at 55°C for 24 hours (**Scheme 25**). These silane reagents included Cl_3SiH, $ClMe_2SiH$, Ph_2SiH_2, $(EtO)_2MeSiH$ and $ClPh_2SiH$. Only the dimethylphenylsilane was found working on this substrate. This condition gave the silane compound **109** in 52% yield, but also gave double bond saturated by-product **110** in 48% yield. Once the silane compound **109** was treated with TBAF in THF and followed by potassium fluoride, potassium bicarbonate and hydrogen peroxide to give a diol with Cbz cleaved crude product. The crude product was treated with pyridine and one equivalent benzyl chloroformate in dichloromethane at 0°C to provide the desired diol **111** in 69% yield in two steps. Thus, the hydrosilylation-oxidation was successfully applied in the total synthesis of FR 900482 and FR 66979.



Scheme 25. Hydrosilylation with Adams' catalyst PtO_2

The mechanism of catalysis of hydrosilylation as proposed by Chalk and Harrod[32] is shown below (**Scheme 26**). The reaction includes oxidative addition, alkene insertion, and reductive elimination.

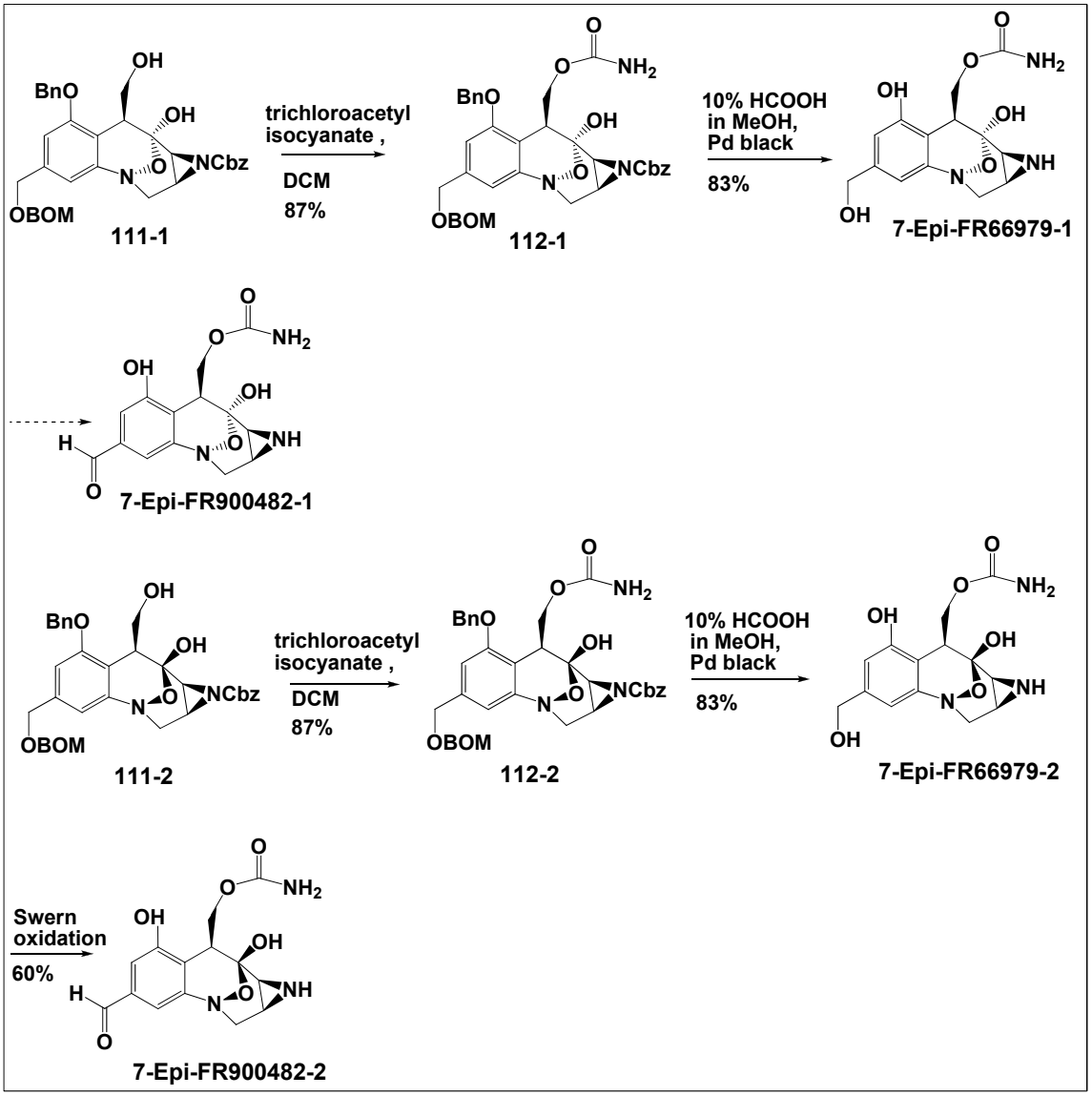


Scheme 26. Hypothesis of mechanism of hydrosilylation

IX. The Completion of 7-Epi-FR 66979 and 7-Epi-FR 900482

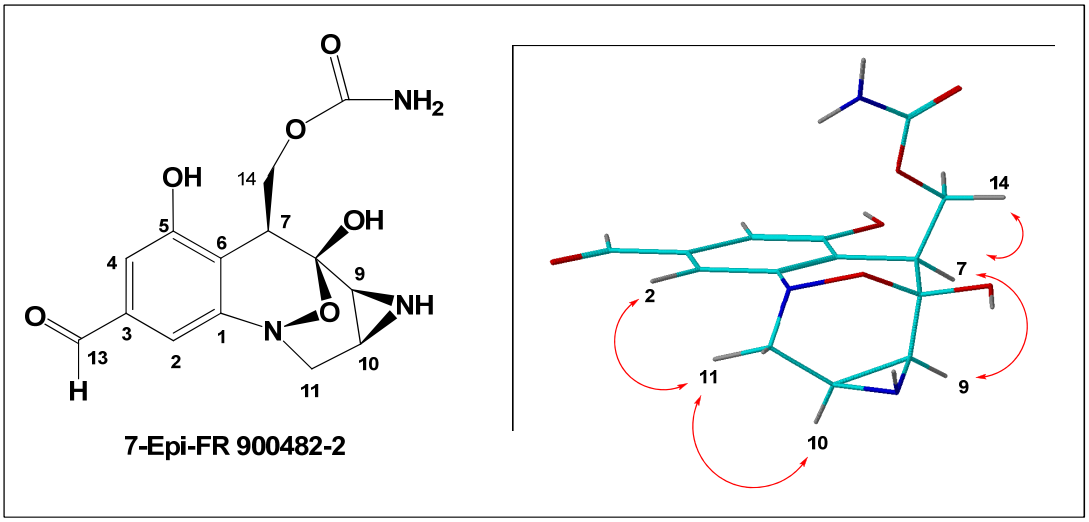
Since the ring expansion gave two diastereomers, the two diastereomers were able to get separation in compound **106** (**Scheme24**). Each diastereomer was carried through the next several steps including the hydrosilylation-oxidation reaction to give minor diastereomer **111-1** and major diastereomer **111-2**. Finally, the racemic diastereomer **111-1** and **111-2** were carried out for next two steps (**Scheme 27**). **111-1** or **111-2** was treated with trichloroacetyl isocyanate, followed by methanol and silica gel worked up to provide the urethane **112-1** and **112-2** in 87% yield[33]. The strategy of global cleavage was tried by hydrogenation under the condition of hydrogen gas, 10% Pd/C in EtOAc. This condition only cleave benzyl and carboxybenzyl group. It does not like the description from Terashima[10], which they claimed 89% yield of cleavage by hydrogenation with 10% Pd/C in EtOAc. The other conditions of catalytic hydrogenation were tried by using10% Pd/C, 20% $Pd(OH)_2$ and Pd black in MeOH or EtOH, from several hours to 24 hours. For these conditions, only benzyl and carboxybenzyl were cleaved in first several hours. After over 10 hours the Bom group was cleaved, but the product was decomposed at same time due to N-O bond connected to hemiketal was reduced. Fortunately, the catalytic transfer hydrogenolysis conducted by using 10% formic acid in methyl alcohol in the presence of a catalytic amount of palladium black[34] at room temperature for 2.5 hours complete the global deprotection in a 83% yield. The structure of deprotection product was confirmed by HNMR and C^{13}-NMR and compared with the structure of FR 66979 published on the Journal of

Antibiotics[1]. The regret is that both of diastereomers give 7-Epi-FR66979. The major isomer 7-Epi-FR66979 was conducted under Swern oxidation condition to give 7-Epi-FR900482-2 in 60% yield. Unfortunately the minor 7-Epi-FR900482-1 was not available because there is no enough amount of the minor 7-Epi-FR66979-1 for oxidation.



Scheme 27. The Completion of 7-Epi-FR 66979 and 7-Epi-FR 900482

The structure of 7-Epi-FR 900482-2 was determined by 2-D NMR. Proton and carbon resonances of 7-Epi-FR 900482-2 were assigned by using COSY, NOESY, HSQC and HMBC experiments. The structure of 7-Epi-FR 900482-2 was established based on HMBC correlations. Relative stereochemistry of the C_7 and C_9, C_{10} carbon centers was determined by strong NOE's between the H_7 and H_9 protons (**Scheme 28**).



Scheme 28. The structure of 7-Epi-FR 900482-2

Proton NMR spectra of 7-Epi-FR 900482-2 were very close to those of previously published for minor isomer of 7-Epi (+)-FR900482 by Trost[16] (**Table 1**). Compared with major isomer of 7-Epi (+)-FR 900482 of Trost by HNMR and C^{13} NMR, there are big difference with 7-Epi-FR 900482-2. Although Trost didn't publish C^{13} NMR of minor, it can be concluded that 7-Epi-FR 900482-2 is racemic minor 7-Epi (+)-FR 900482.

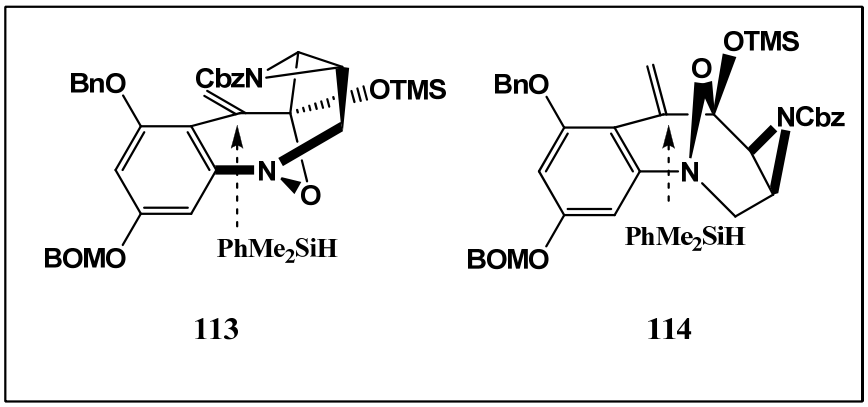
Table 1. Proton NMR Spectra of 7-Epi-FR 900482-2 and Minor Isomer of 7-Epi (+)-FR900482 of Trost

7-Epi-FR 900482-2		7-Epi (+)-FR 900482 (minor isomer of Trost)		
δ(^{1}H), (ppm); J(H,H), (Hz)		δ(^{1}H), (ppm); J(H,H), (Hz)		Δδ(^{1}H), (ppm)
9.66	(s, 1H)	9.77	(s, 1H)	-0.11
7.03	(d, J=1.8, 1H)	6.98	(s, 1H)	0.05
6.92	(d, J=1.8, 1H)	6.88	(s, 1H)	0.04
4.51	(dd, J=5.6, 11.5, 1H)	4.48	(dd, J=5.9, 11.2, 1H)	0.03
4.24	(dd, J=2.9, 11.5, 1H)	4.28	(dd, J=2.5, 11.0, 1H)	-0.04
3.54-3.51	(m, 2H)	3.66-3.53	(m, 2H)	-0.1
3.42	(dd, J=2.9, 5.6, 1H)	3.38	(dd, J=2.0, 5.8, 1H)	0.04
2.33	(m, 2H)	2.23	(m, 2H)	0.1

The assigned structure of 7-Epi-FR 900482-2 was also supported by the experiments of two diastereomers **113** and **114** (**Scheme 29**). The yield from **114** for hydrosilylation is two times higher than from **113**, which means that trans diastereomer **113** is too bulky to react with silane because both face are hindered. The cis diastereomer **114** is less hindered on bottom face and the silane can easily approach from there.

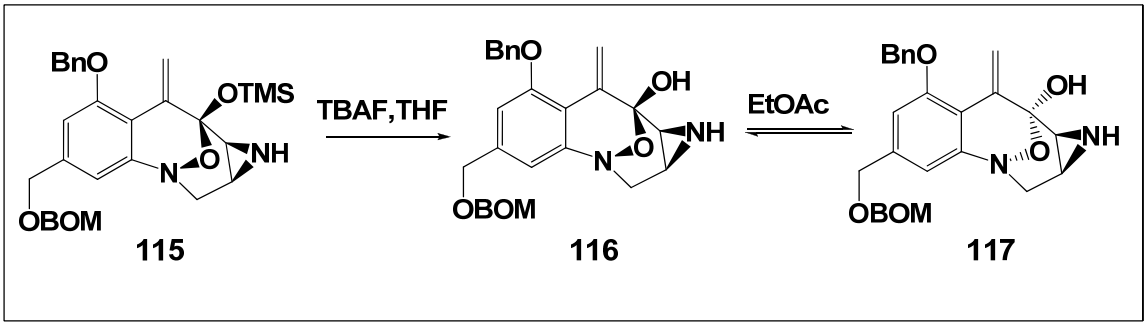
The possible reason for giving epimer can also be explained by the **Scheme 29**. The aziridine group with Cbz on trans isomer **113** blocked the top face. The top face is more hindered than bottom face, so the complex of silane will go bottom phase to approach the double bond. It will give cis silane compound with aziridine by syn addition. When the substrate is cis isomer **114**, the bridge oxygen and TMS on

hydroxyl group blocked the top face, as the same reason, it will give cis silane compound with aziridine. As a final result, the generated hydroxyl methyl group is at same side with aziridine after oxidation.



Scheme 29. The possible approach of $PhMe_2SiH$

Interestingly our 7-Epi-FR 66979 and 7-Epi-FR 900482 only showed one diastereomer from NMR analysis. The tautomerization in hydroxyl hemiketal is not fast than we imaged. One experiment was to put compound **116** in EtOAc solvent after TMS group on compound **115** was cleaved by TBAF (**Scheme 30**). In one to three hours, the TLC only showed one spot of one diastereomer. The TLC showed two spots of two diastereomers after 18hours, but still the major spot is diastereomer **116**, the minor spot is diateromer **117**. The TLC showed that diastereomer **116** didn't change if there is no solvent after 18 hours. Due to the slow tautomerization of hydroxyl hemiketal, it is reasonable that the small amount of final product only show one diastereomer in NMR.

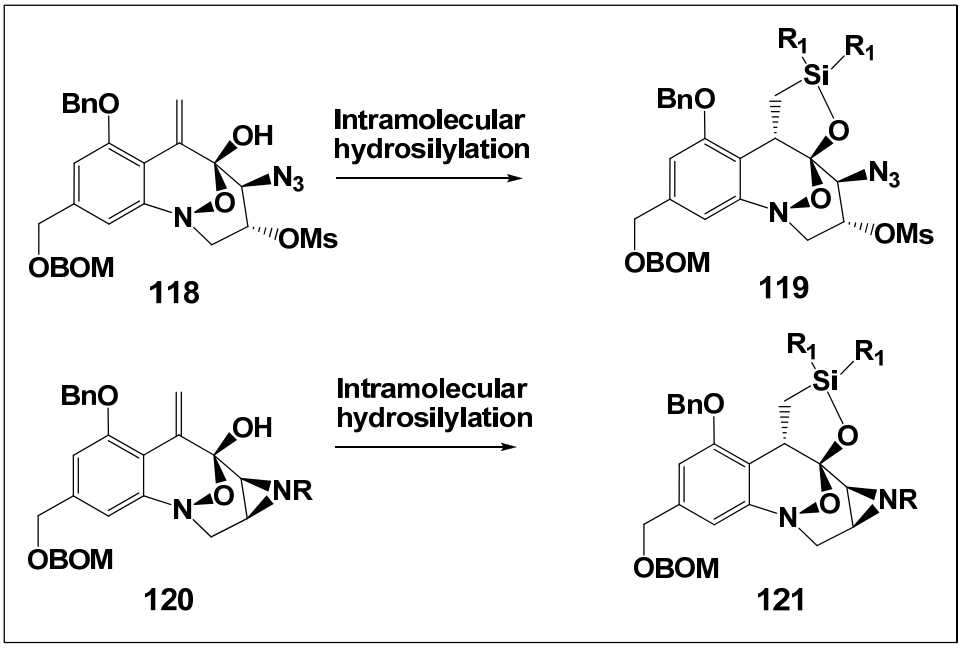


Scheme 30. Tautomerization in hydroxyl hemiketal

X. The Efforts on Approaching Natural Product of FR 66979 and FR 900482

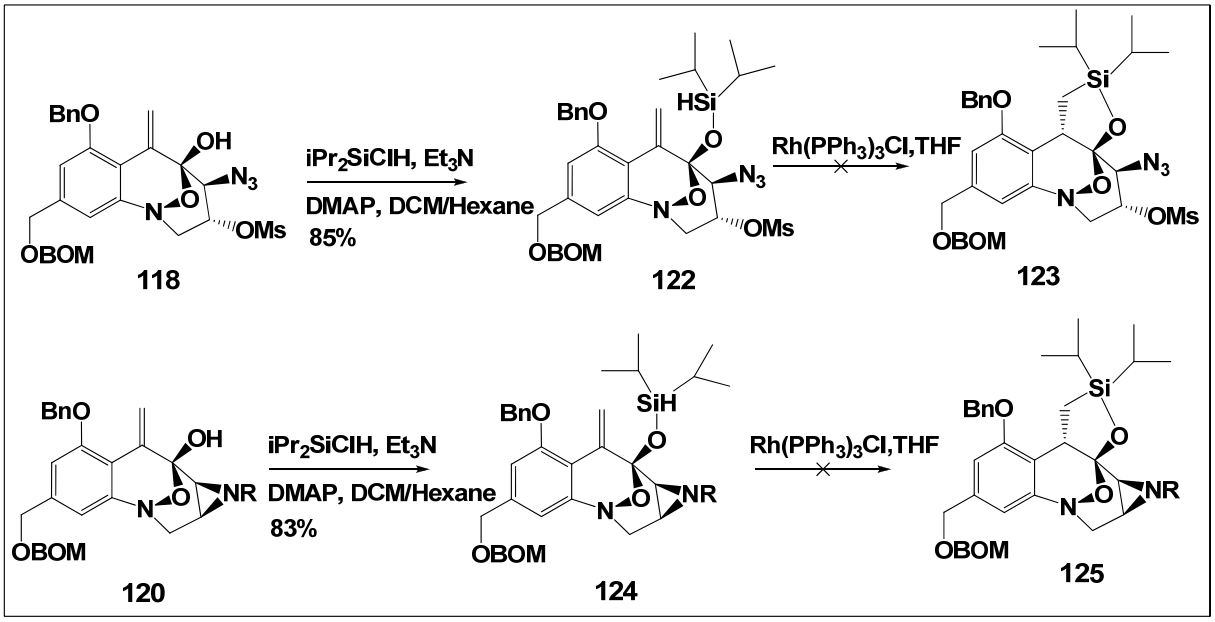
1. Intramolecular hydrosilylation

Because the intramolecular hydrosilylation of allyl and homoallyl alcohols and subsequent oxidative cleavage of the organosilicon intermediates has been found to be widely applicable to the region- and stereo-controlled synthesis of a wide variety of 1,3-diols[35], it could be a good conversion of cis hydroxyl hemiketal **118** and cis hydroxyl aziridine **120** to desired diol of natural product after oxidation since it will undergo syn addition from top face (**Scheme 31**).



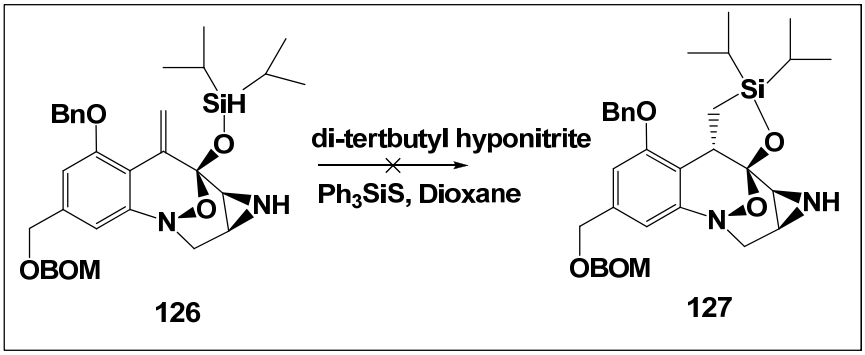
Scheme 31. The strategy of intramolecular hydrosilylation

There is various catalyst were utilized in intramolecular hydrosilylation. In 2000, Robertson published the intramolecular hydrosilylation of diisopropylsilane derivative by using Wilkinson's catalyst $Rh(PPh_3)_3Cl$ in quantitative yield[36]. Both the hemiketal azido **118** and hemiketal aziridine **120** were tried by using $Rh(PPh_3)_3Cl$ catalyzed intramolecular hydrosilylation after the diisopropylsilane **122** and **124** were made (**Scheme 32**). Unfortunately, this condition didn't work on the two substrates. Since the catalyst PtO_2, H_2PtCl_6 and Pt(DVDS) have been used in intermolecular and intramolecular hydrosilylation[32,37], they were applied to the substrate **124** by heating in THF for 17 hours. These conditions still didn't give cyclic product **125**. Not only diisopropylsilane compounds were tested, but also dimethylsilane and diphenylsilane compounds were tested with same condition. No one substrate gives cyclic silane compound.



Scheme 32. $Rh(PPh_3)_3Cl$ catalyzed intramolecular hydrosilylation

Besides the catalytic intramolecular hydrosilylation, there is also radical intramolecular hydrosilylation reported by Roberts to give very good yield and selectivity[38]. The substrate **126** was added into dioxane and followed by catalytic amount of di-tertbutyl hyonitrite and triphenylsilanethiol in two portions (**Scheme 33**). The mixture were heated at 60°C for three hours, HNMR indicated that the double bond didn't change after work-up. Even this reaction was heated to reflux for overnight, HNMR still didn't show the product.

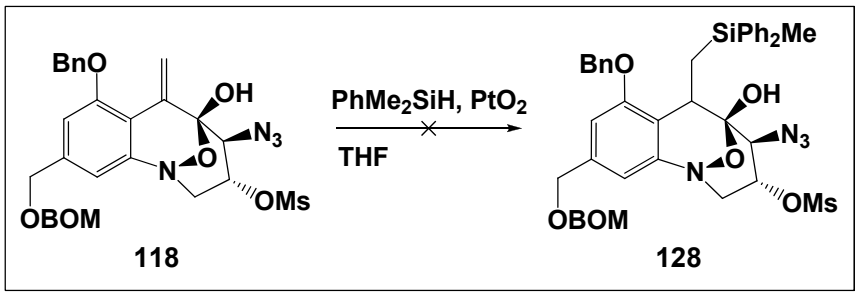


Scheme 33. Radical intramolecular hydrosilylation

2. Less hindered intermolecular hydrosilylation

The intermolecular hydrosilylation oxidation from fully protected intermediates provided 7-Epi-FR 66979 and 7-Epi-FR 900482. For cis diastereomer **118**, its top face is convex face and bottom face is concave face. In theory, the convex face is less hinder than concave face. If there is no protecting group on hydroxyl group of cis diastereomer **118**, Ph_2MeSiH may access from top face to form beta configuration hydroxymethyl group after oxidation which is natural product required. The substrate **118** in THF was treated with $PhMe_2SiH$ and catalytic amount PtO_2 at 50°C for 24 hours,

no product was detected, but starting material disappeared after work-up (**Scheme 34**). The experiment demonstrated that the mesylate and azido group were not stable at this condition. Hydrosilylation didn't work on this substrate.

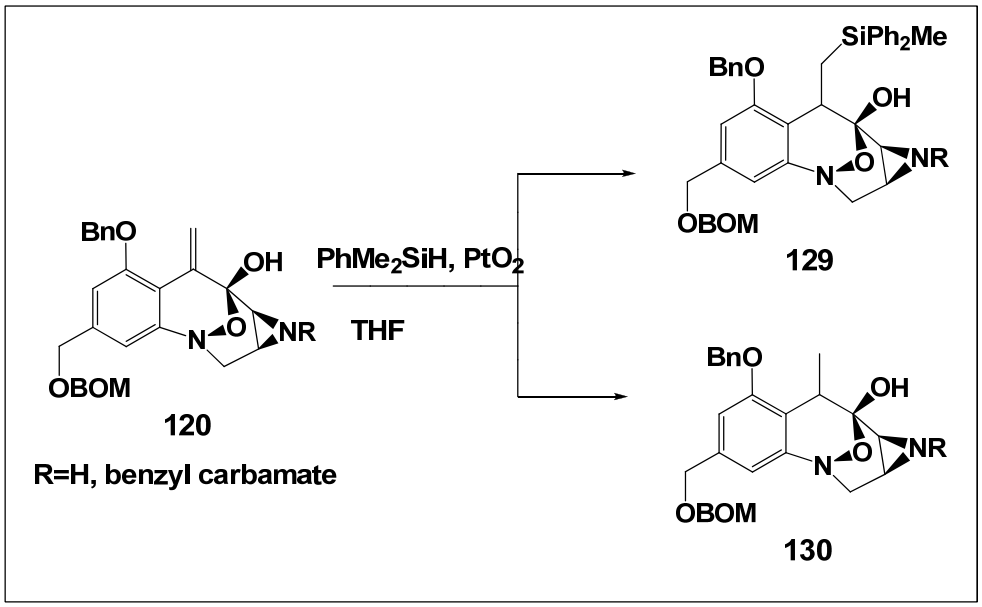


Scheme 34. Less hindered intermolecular hydrosilylation (1)

With the same idea, the unprotected hemiketal aziridine intermediate **120** was tried the hydrosilylation-oxidation (**Scheme 35**). The initial study had been tried in small scale. It did give two diastereomers. However, the yield is very low. The yield for desired product is only about 2%. LC-MS showed the double bond saturated by-product was major product.. It is not clear why the chemoselectivity favored reducuction of double bond. The efforts of changing chemoselectivity have been made by modifying the conditions of the reaction. The first try is to change the reaction temperature. The reaction didn't work at 25°C, 35°C and 40°C. The lowest temperature to make the reaction working is 45°C, but at this temperature it didn't improve yield and change chemoselectivity. At higher temperature 65°C, the reaction also favored the double bond saturated selectivity.

The second try is to change the amount of starting material dimethylphenylsilane. The condition of two equivalents, and six equivalents of

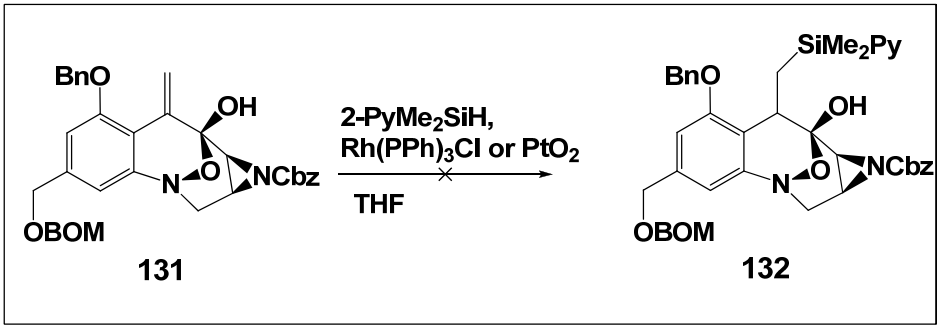
dimethyphenylsilane were used in the reaction. The results showed the more starting material, the faster reaction. Six equivalents of dimethylphenylsilane made the reaction completion in 24 hours. Two equivalent of dimethylphenylsilane made the reaction completion in 48 hours. The ratio of product and by-product didn't change.



Scheme 35. Less hindered intermolecular hydrosilylation (2)

The third try is to change the silane reagent. In the beginning of the study of the hydrosilylation various silane reagents had been screened. Only the dimethylphenylsilane worked on our substrate. However, one of silane reagent didn't try which is dimethylpyridylsilane. It has similar structure with dimethylphenylsilane and was reported by Yoshida[39] to be used on hydrosilylation of alkenes and alkynes in high yield in the presence of a catalytical amount of $RhCl(PPh_3)_3$. Because the 2-$PyMe_2SiH$ was more reactive than 3-$PyMe_2SiH$ and 4-$PyMe_2SiH$ in the rhodium-catalyzed reaction, 2-$PyMe_2SiH$ had been chosen to do the hydrosilylation of substrate

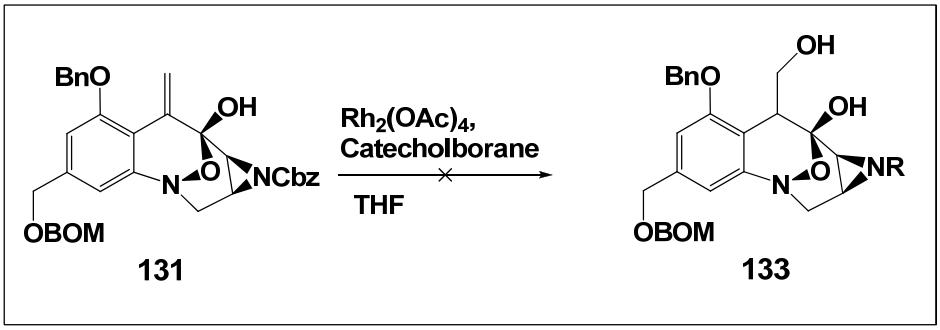
131 (**Scheme 36**). Both the catalyst $RhCl(PPh_3)_3$ and PtO_2 were tested in the hydrosilylation at 45°C and 55°C, but neither product nor double bond saturated by-product were detected from the reaction.



Scheme 36. Less hindered intermolecular hydrosilylation (3)

3. Catalytic hydroboration-oxidation

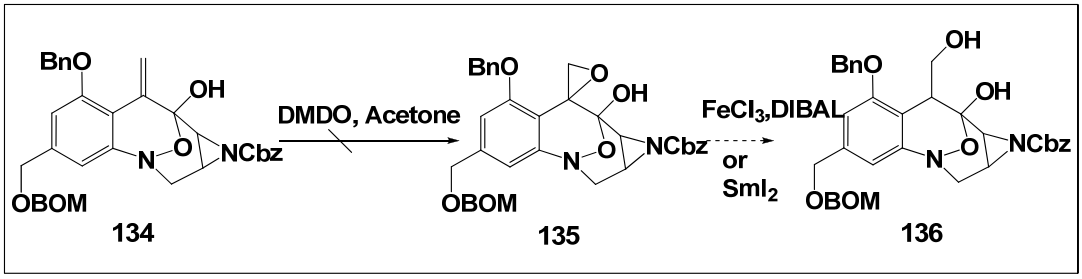
In the early study of hydroboration, many borane reagents were used under normal conditions. No catalytic hydroboration was used in our studies. In the 90s, Evans and Fu reported Rhodium (I) catalyzed hydroboration by using catecholborane[40]. For styrene, they reported that the selectivity favored Markovnikov product. In 1993, Doyle reported that catalyst dirhodium (II) tetraacetate gave the different selectivity of styrene in catalyzed hydroboration[41]. Considered the selectivity, catalyst dirhodium (II) tetraacetate was our choice for the catalytic hydroboration. Compound **131** was treated with dirhodium (II) tetraacetate and catecholborane at room temperature (**Scheme 37**). TLC and LC-MS monitored the reaction, but indicated no reaction with this condition.



Scheme 37. Catalyzed hydroboration-oxidation

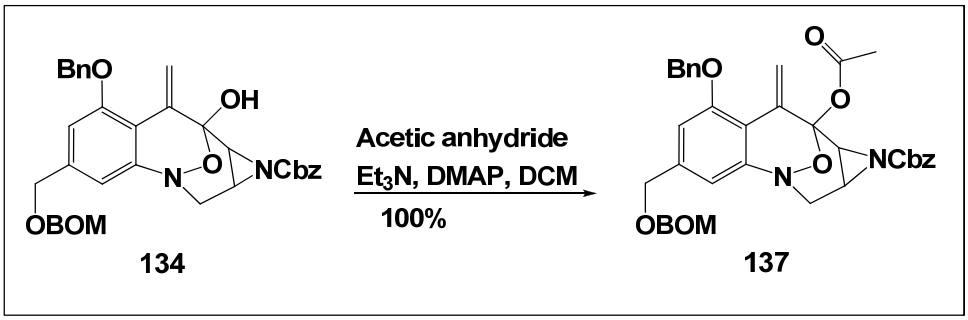
4. **Epoxidation and opening**

Another choice to make β hydroxyl methyl group on this specific substrate is to try the method of Danishefsky[8]. In 1997, Weinreb reported high yield to install hydroxymethyl group on styrene terminal double bond for (-)-pancracine and (-)-coccinine total synthesis by DMDO epoxidation and $FeCl_3$ opening[42]. Our key hemiketal intermediate come from ring expansion of DMDO oxidation. When the functional group on the core intermediates had been transfered to protected intermediate **134**, DMDO oxidation may directly give epoxide on double bond. Because there is no protecting group on hydroxyl hemiketal, it may favor to form β epoxide configuration. The desired β hydroxyl methyl group may be obtained after it is opened by $FeCl_3$ or SmI_2. The compound **134** was treated with DMDO at -20°C and monitored by TLC and MS (Scheme **38**). The MS indicated the molecular weight of epoxide product **135** in 20 minutes, but TLC showed that the major spot was the decomposed base line product. After one hour, the reaction mixture was concentrated to remove solvent and purified by preparative thin-layer chromatography plate, but no product **135** was obtained.



Scheme 38. Epoxidation by DMDO

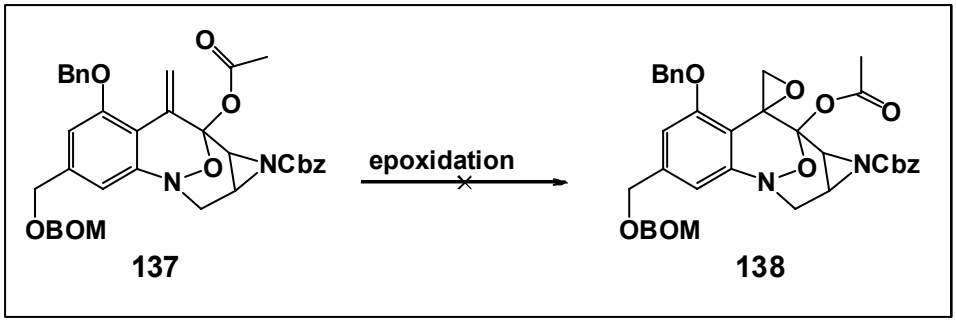
To consider the compound stability for epoxidation and opening, it's better to protect the hydroxyl group of hemiketal. The protecting group better be small, easily form and deprotectable. The acetate is a good candidate. The compound **134** was treated with acetic anhydride, Et_3N and catalytic DMAP in dichloromethane for 48 hours to provide compound **137** in 100% yield (**Scheme 39**).



Scheme 39. Protection of 134

With the fully protected compound **137** in hand, various epoxidation conditions had been explored (**Scheme 40**). DMDO was still unsuccessful to the protected **137**. m-CPBA was tested on this substrate, but it didn't give desired product. Seung Bum Park reported that m-CPBA epoxidation of styrene provided desired product in high yield in the presence of DTBMP (Di-tert-butyl-4-methylpyridine) as a proton sponge[43].

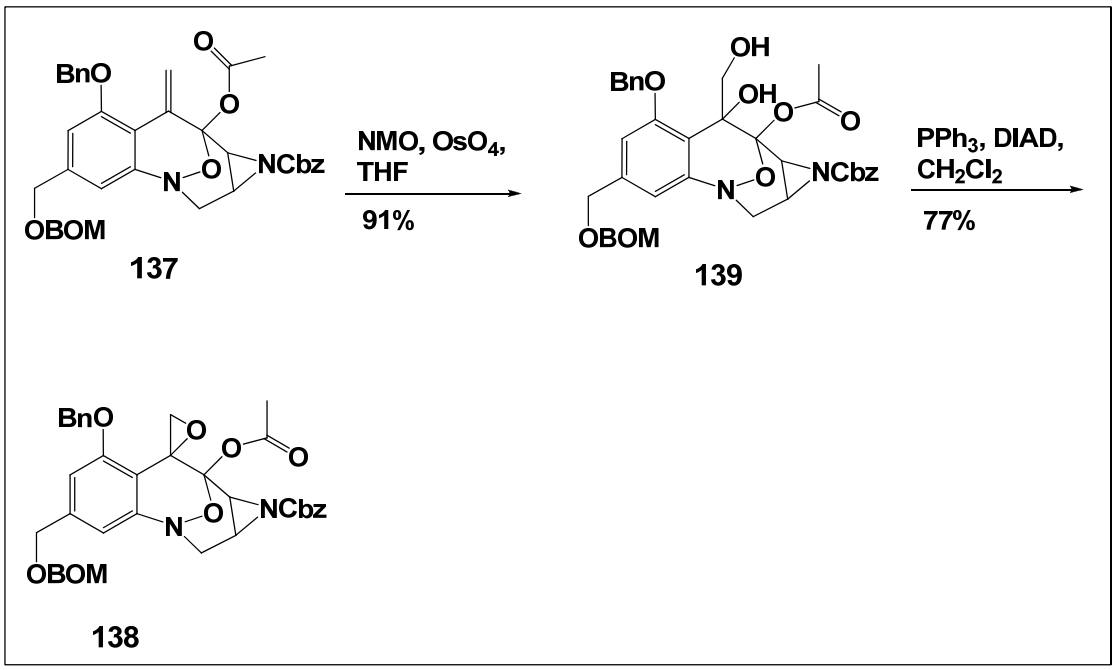
The compound **137** was treated with m-CPBA, DTBMP in dichloromethane for 5 hour, LC-MS indicated no desired product. Sharpless reported another efficient method for epoxidation of olefins including styrene in high yield by using aqueous H_2O_2 and catalytic MTO (methyltrioxorhenium)/pyridine[44]. Shortly afterward Herrmann reported pyrazole as a superior additive to pyridine because pyrazole is not affected under the reaction conditions while pyridine is oxidized to pyridine N-oxide during epoxidation[45]. Based on these information, Compound **137** was treated with aqueous H_2O_2, catalytic MTO/pyrazole in dichloromethane. No product was detected by MS, even after 3 days. In the formal total synthesis of (+)-FR 900482 by Paleo, they reported the epoxidation of enone by H_2O_2 with TBAF or TBHP (tert-butyl hydroperoxide) with Triton B[15]. Both conditions had been tried on compound **137**, but neither one work.



Scheme 40. Direct epoxidation

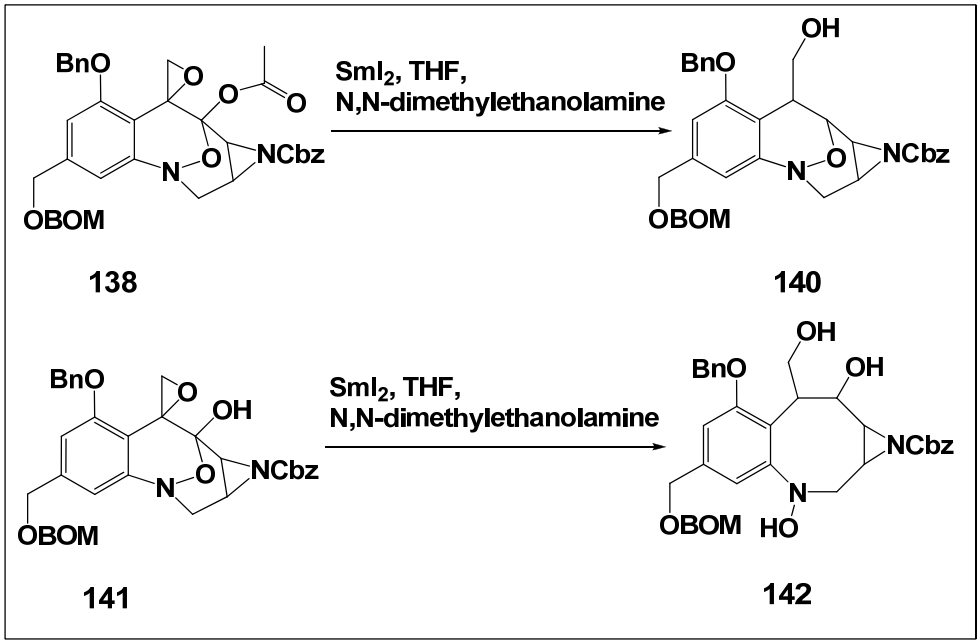
Since no conditions found for direct epoxidation of substrate **137**, the two steps condition of Danishefsky[8] will be the choice. Osmylation of compound **137** provided a 4:3:2 mixture of diols **139** in 91% yield, which treated with diisopropyl azodicarboxylate and triphenylphosphine to gave a 7:1 mixture of compound **138** in 77% yield. Because the opening of epoxide of two diastereomer will give same

stereochemistry of hydroxyl compound by SmI_2 according Danishefsky's report[8], the mixture of **138** and mixture of **139** were not isolated.



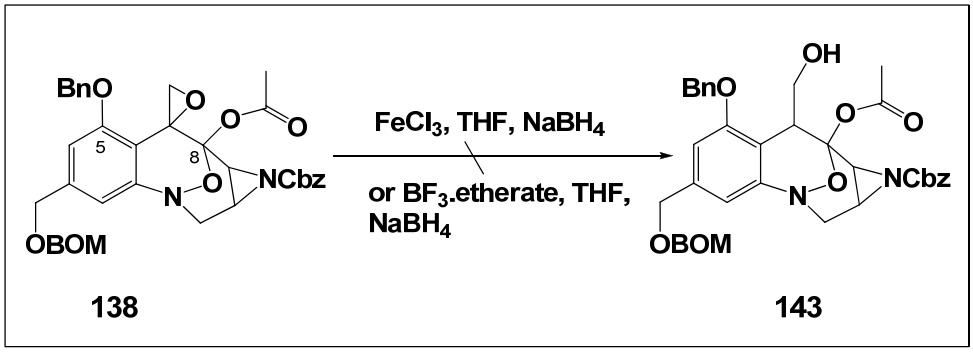
Scheme 41. Danishefsky's condition for epoxidation

Compound **138** was treated with SmI_2 , N.N-dimethylethanolamine in THF at -78°C. The LC-MS indicated that the epoxide was opened, but the acetate group had been cleaved (**Scheme 42**). Unprotected hemiketal epoxide **141** was then studied under same condition. Mass spectra indicated that the epoxide was opened, but hemiketal was reduced.



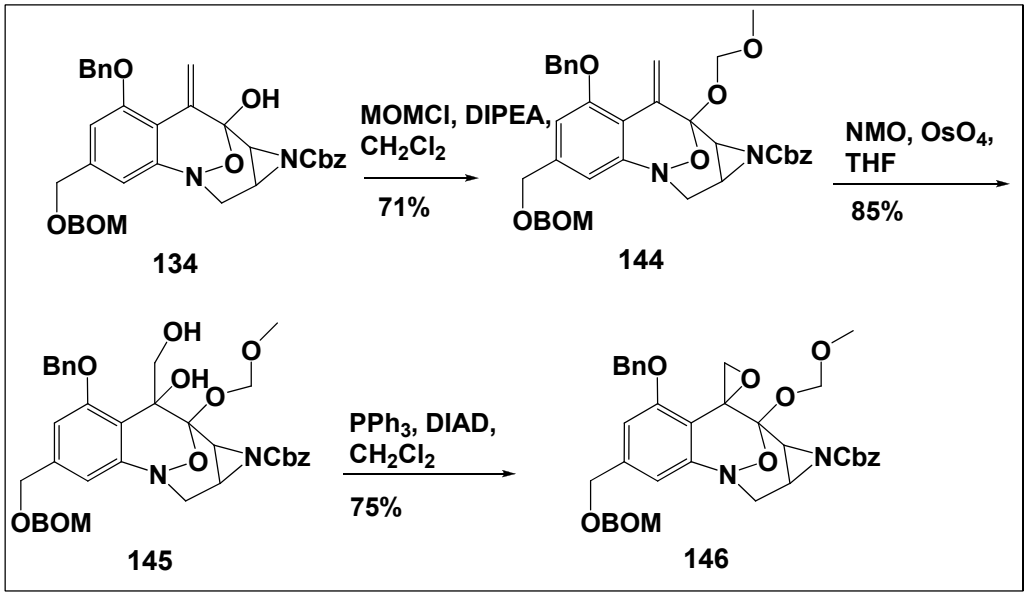
Scheme 42. Epoxide opening by SmI_2

Since single electronic reduction could not provide the desired product, the compound **138** was conducted under the condition of the lewis acid mediated epoxide opening (**Scheme 43**). Unfortunately, lewis acid $FeCl_3$ or BF_3.etherate failed to open the epoxide. For similar substrate of **138**, Danishefsky reported that the lewis acid $FeCl_3$ mediated epoxide opening didn't work if the protecting group on hemiketal is MOM[8]. They said it may be due to the consequence of labile ether functions at C_5 and C_8. It may be the similar reason for the failure of **138** with the labile C_5 ether and C_8 acetate functions.



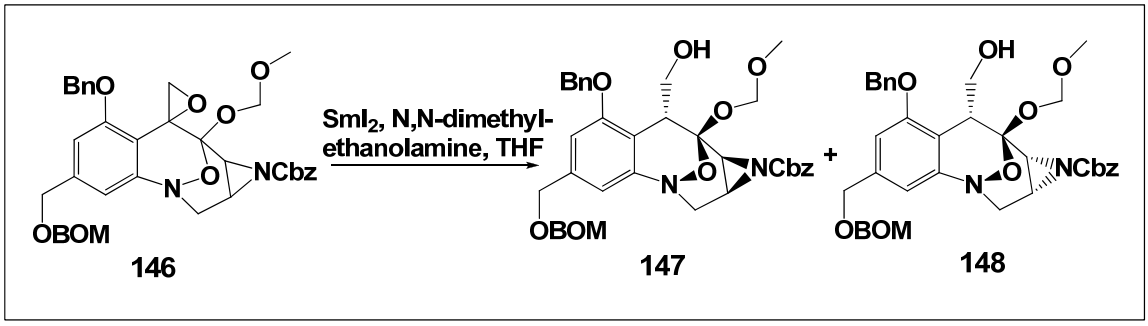
Scheme 43. Lewis acid mediated expoxide opening

With these results, the MOM group on hemiketal is essential for this substrate. The compound **134** was treated with methyl chloromethyl ether and DIPEA in dichloromethane at room temperature to provide MOM protected intermediate **144** in 71% yield (**Scheme 44**). The mixture of diastereomer (3:1) diol **145** was obtained by osmylation of compound **144** in 85% yield. Diol **145** was then converted to epoxide mixture of diastereomer (3:1) **146** through routine transformations.



Scheme 44. Synthesis of MOM protected intermediate

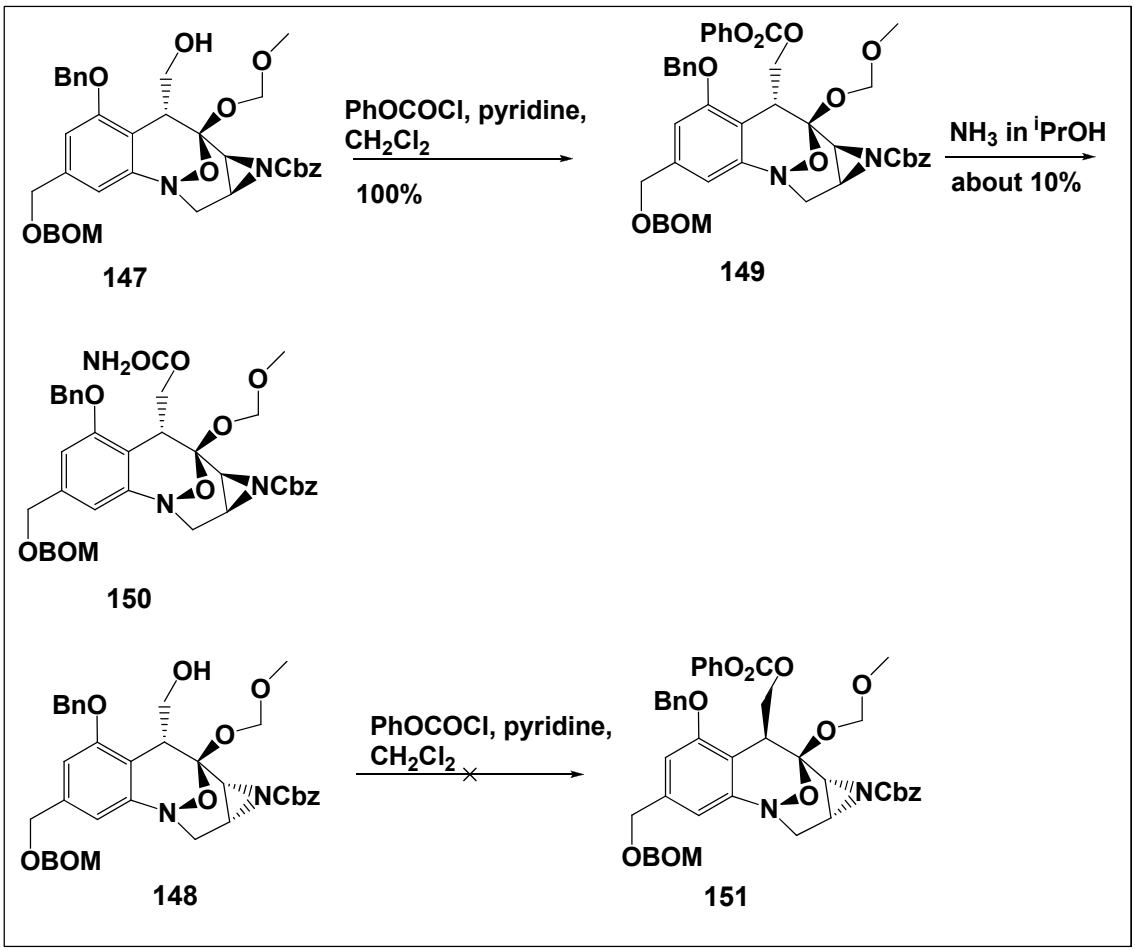
The epoxide intermediate **146** was treated with samarium diiodide and N,N-dimethylethanolamine in THF at -78°C to provided two mixture of diastereomer hydroxymethyl intermediate **147** (major) and **148** (minor) in 60% yield (**Scheme 45**). This reaction should be handled carefully since it will generate the elimination product **144** if the reagent SmI_2 was added too fast. From the previous study we know that **146** was a mixture of two diastereomers which major diastereomer was cis configuration hemiketal with aziridine and minor diastereomer was trans configuration hemiketal with aziridine. From Danishefsky's SmI_2 expoxide opening reaction we know that hydroxymethyl group was trans configuration with hemiketal. Based on these informations, the structure of **147** and **148** could be assumed as drawed in **Scheme 45**.



Scheme 45. Epoxide opening by reduction of SmI_2

With successful installation of hydroxymethyl group at C_7 stereogenic center, our next goal was to form urethane on hydroxymethyl group. The final product FR 66979 may be obtained after deprotection if the urethane was successfully installed. Compound **147** was treated with large excess of trichloroacetyl isocyanate in dichloromethane. This reaction gave low yield after overnight reaction. Compound **148** didn't work at the same condition, even after heating the reaction for overnight. The alternative route was to form phenyl carbonate, followed by the addition of NH_3 in isopropanol (**Scheme 46**). Quantitative yield was obtained when **147** was reacted with phenyl chloroformate, pyridine in dichloromethane. The yield of urethane was about 10% even after a long reaction period, detected by LC-MS. Compound **148** had no reactivity for the formation of phenyl carbonate, even with harsh condition. The results supported the assumed structures that **147** was cis configuration of hydroxymethyl group with MOM protected hemiketal and **148** was trans configuration of hydroxymethyl group with MOM protected hemiketal. Because in **148** the trans-aziridine blocked the bottom face and the top face has the MOM group, this prevented the reaction of **148** with trichloroacetyl isocyanate and phenyl chloroformate. Although

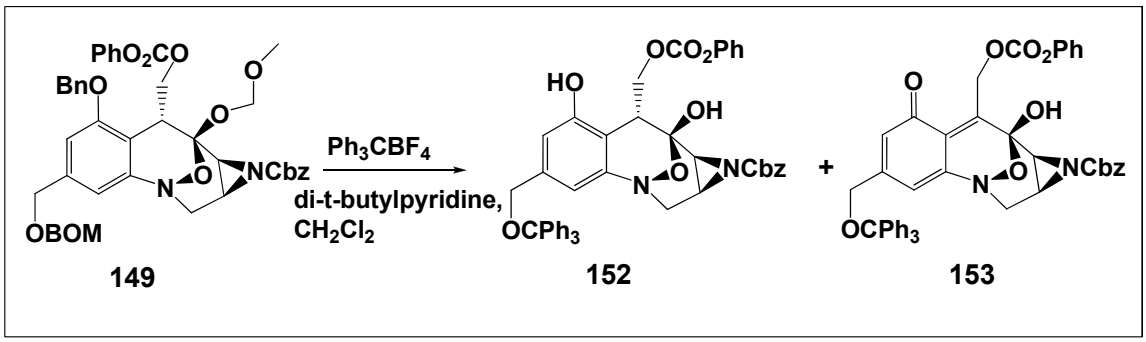
the phenyl carbonate trans **149** was easily prepared, urethane **150** was generated in low yield due to the large groups at the C_5, C_7 and C_8 positions. To avoid this problem, deprotection of MOM should be the next step after the formation of phenyl carbonate.



Scheme 46. Formation of phenyl carbonate and urethane

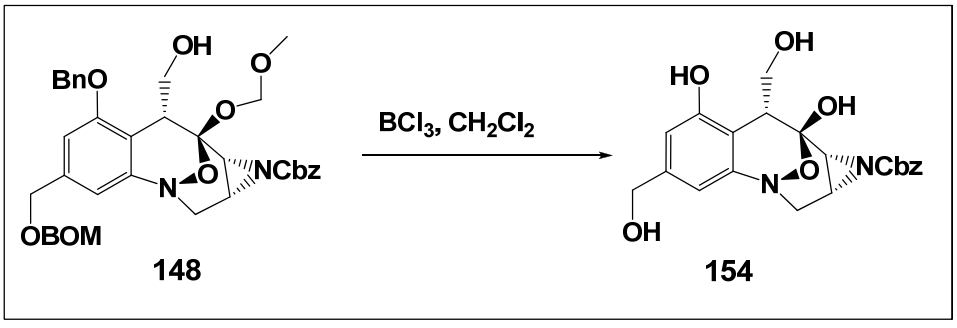
By using the deprotection condition of Danishefsky, phenyl carbonate **149** was treated with two equivalents of Ph_3CBF_4, and one equivalent of di-tert-butylpyridine at room temperature and monitored by LC-MS (**Scheme 47**). The reaction didn't occur in two hours. After additional one equivalent of Ph_3CBF_4 was added and stirred for one hour, LC-MS indicated **152** and **153** were generated. 0.1mg of **152** and 0.2mg of **153**

were obtained from 0.5mg of starting material **149** after work-up and purification. Their structures can not be confirmed by HNMR with this low scale reaction.



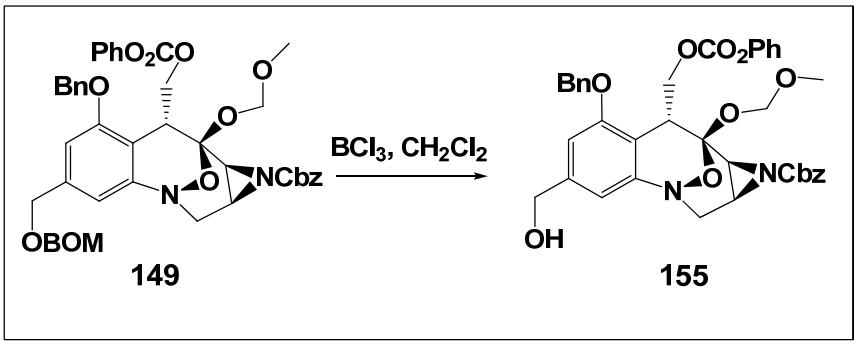
Scheme 47. Deprotection of MOM by Ph_3CBF_4

Tays[46] reported the deprotection of MOM with high yield by 1.0M BCl_3 in dichloromethane at -40°C. This condition was applied to **148** (**Scheme 48**). 0.7mg of cis **148** was treated with BCl_3 in dichloromethane at -40°C to -10°C for one hour LC-MS indicated **154** was generated with 70% yield. Not only did this condition cleave the MOM group, but it also cleaved BOM and benzyl groups.



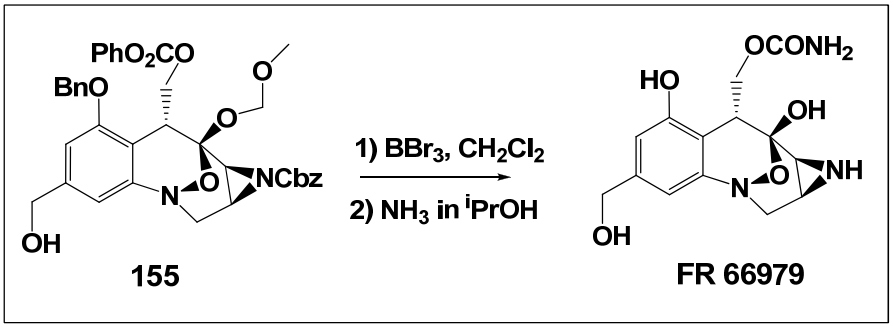
Scheme 48. Deprotection of MOM by BCl_3 (1)

The trans phenyl carbonate **149** was reacted in a similar way (**Scheme 49**). Unfortunately the reaction didn't provide desired product even with longer reaction time and room temperature, but only cleaved the BOM group. This may be due to that the phenyl carbonate was a large group which made steric hinder near the MOM group.



Scheme 49. Deprotection of MOM by BCl_3 (2)

Finally the trans phenyl carbonate **155** was cleaved by stronger lewis acid BBr_3 at -40°C to -10°C in two hours. MS indicated that the MOM, benzyl, and benzyl carbamate groups were cleaved at same time (**Scheme 50**). But the LC-MS also showed many by-product peaks. Due to low scale reaction, the product was not isolated after work-up. The crude product was treated with 2M NH_3 in iPrOH to give final product FR 66979 which was indicated by MS. The crude HNMR also showed the peaks of product. The pure product had not been obtained after the purification by preparative thin-layer chromatography plate, so the final product had not been confirmed by NMR.

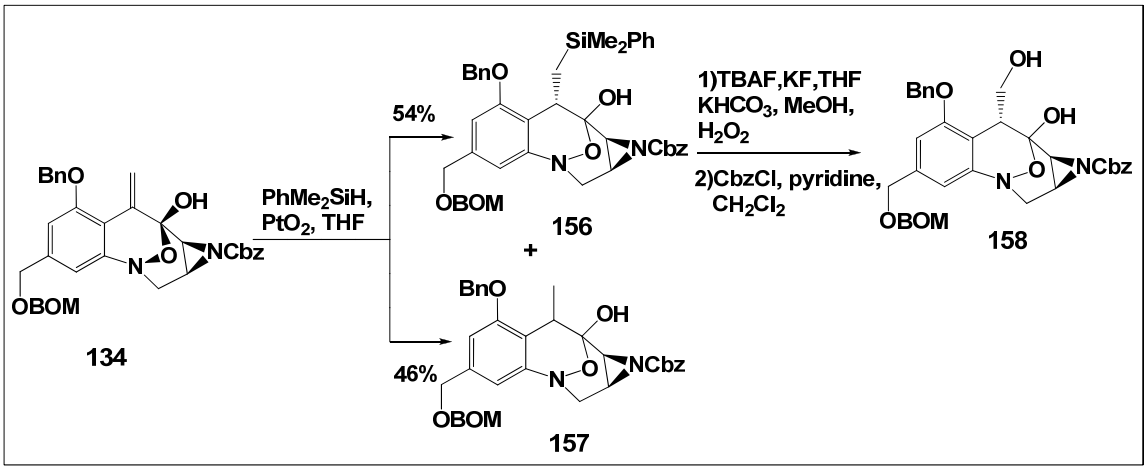


Scheme 50. Deprotection of MOM by BBr_3

5. Second time to work out the hydrosilylation oxidation

Although the methodology of making the hydroxylmethy group by epoxidation and opening worked on Danishefsky's intermediate **25** and our intermediate **134**, Danishefsky's synthesis required 10 steps to get final product after installed the hydroxylmethy group. By using this methodology in our total synthesis had trouble cleaving the protecting group. We felt it is still worth developing the conditions for the hydrosilylation oxidation in our substrate. Further study on the hydrosilylation oxidation of the less hindered substrate was conducted on the substrate **134 (Scheme 51)**. It was found that if the concentration was low, 3.2μM/mL, the reaction of hydrosilylation with 10% PtO_2 provided an acceptable yield of product (54%) and the double bond saturated by-product was dramatically decreased. After oxidation, the reaction gave two diastereomers. The HNMR of each diastereomer was different with the same intermediate of two diastereomers of epi-FR66979. Because the structure of **158** has four diastereomers and two diasteromers from fully protected intermediate already gave two epimers, the remaining should give natural product. The finalization of the total synthesis with this intermediate was not finished since we didn't get enough

of this intermediate. It is the great hope for the future if we prepare more the precursor **134** of hydrosilylation the natural product will be obtained with short steps from this unique method of hydrosilylation and oxidation.



Scheme 51. Hydrosilylation and oxidation in very dilute solution

XI. Conclusions

This total synthesis started from 3-hydroxymethylphenol in six steps by Hemetsberger-Knittel indole synthesis to make Methyl 4-(benzyloxy)-6-((benzyloxymethoxy)methyl)-1H-indole-2-carboxylate **69** in overall 34.7% yield. In additional six steps, the indole **69** was converted to racemic tricyclic pyrroloindole **60** in overall 49% yield which involved the method to make pyrroloindole by using vinylsulfonium salt developed early in our lab.

The DMDO ring expansion oxidation was successfully applied in the total synthesis. The pyrroloindole **60** was oxidized to hemiketal core **82** by DMDO in 57% yield. The installation of hydroxymethyl group is a challenge. Hydroboration only worked on unprotected hydroxyhemiketal, but gave the wrong regional isomer. Intermolecular hydrosilylation-oxidation successfully afforded the hydroxylmethyl compound **100** in 35% yield. After the conversion of two diastereomers **101** and **103** to urethane **102** and **104,** the global deprotection by catalytic transfer hydrogenation gave epi-FR66979 in 83% Yield. The Swern oxidation of epi-FR66979 provided epi-FR900482 in 60% yield. Overall the total synthesis was completed in 21 steps to provide epi-FR66979 in 1.06% yield and in 22 steps to provide epi-FR900482 in 0.64% yield.

The effort to install the beta hydroxylmethyl group involved intramolecular hydrosilylation-oxidation, but it was not successful. Further efforts involved the epoxidation and opening by samarium diiodide reduction. The hydroxymethyl group had been successfully installed. Final product was not obtained due to the deprotection

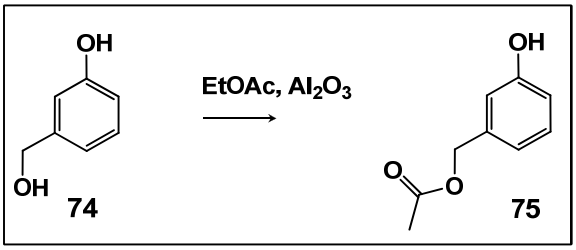
issues. Another effort to work out hydrosilylation oxidation on less hindered hydroxylamine hemiketal intermediate was successful. Hydrosilylation oxidation with unprotected hydroxyl hemiketal substrate **134** in very dilute solution provide modest of yield of desired product. It will provide natural product with few steps if more intermediate **134** is prepared in the future.

XII. Experiment

General: All melting points were determined by MEL-TEMP® Laboratory Devices, USA melting point apparatus. Nuclear magnetic resonance (NMR) spectra were acquired using a Bruker Avance 500 Digital NMR (500 MHz) spectrometer and Varian 600 MHz spectrometers. NMR chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane (TMS) or relative to the residual proton signal of $CHCl_3$ (7.24 ppm) or the carbon signal of $^{13}CDCl_3$ (77.0 ppm). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), and doublet of doublets (dd). Infrared (IR) spectral measurements were carried out with a Thermo Nicolet/Avatar 360 FT IR spectrometer. Low resolution mass (MS) spectra are taken with Waters Micromass ZQ MM1mass spectrometer, and high resolution mass (HRMS) spectra were obtained on a Thermo Electron High Resolution Orbitrap mass spectrometer.

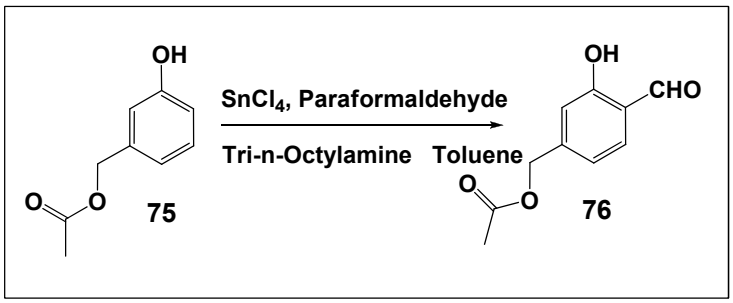
All reactions involving air or moisture sensitive reagents were conducted under nitrogen atmosphere with dry solvents. Unless otherwise noted, reagents were obtained from commercially available sources and use without further purification. The anhydrous solvents tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), toluene, dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF) were obtained from Aldrich and Acros and used as received.

Reaction monitored by thin-layer chromatography (TLC) using ANALTECH TLC Plates (Scored 10 x 20 cm, 250 microns). Flash column chromatography was performed on Biotage Flash Horizon purification system and Analogix IntelliFlash 310 purification system by using 8g ~ 300g silica gel pre- packed columns. Preparative thin-layer chromatography purifications were carried out on ANALTECH Pre. TLC Plates (20 x 20 cm, 1000 microns).

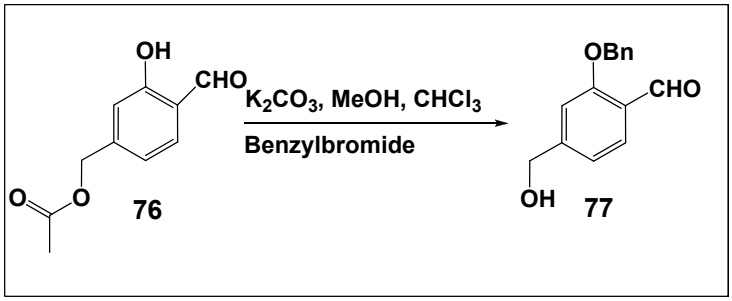


3-Hydroxybenzyl acetate (75). To 3-hydroxymethylbenzyl alcohol (**74**) (29.00g,0.24mmol) in ethyl acetate/hexanes(320mL/640mL) was added 250.00g of Al_2O_3. The resulting mixture was heated at reflux for two days which TLC indicated about half of starting material reacted. Continued to reflux the reaction for another two days, which TLC showed the reaction almost completed. The reaction mixture was cooled to room temperature, filtered to remove Al_2O_3. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (Ethyl acetate/hexane 2:3) to give **75 (**36.00g, Yield 91%) as a white solid. mp 48-49°C. IR: 3400.0, 2918.8, 1713.1, 1455.9, 1261.4, 750.2 cm^{-11}; HNMR (500 MHz, $CDCl_3$) δ 7.24 (t, J=7.88 Hz, 1H), 6.92 (d, J=7.57 Hz, 1H), 6.84 (s, 1H), 6.79 (d, J=8.20 Hz, 1H), 5.06 (s, 2H), 4.88 (s, 1H), 2.11 (s, 3 H); ^{13}C NMR (125 MHz,

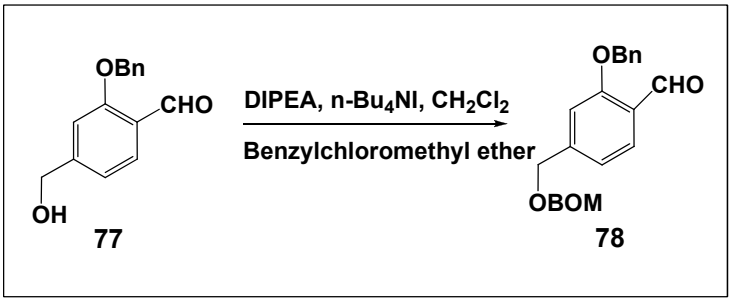
CDCl3) 171.4, 155.9, 130.3, 120.9, 115.6, 115.4, 66.3, 21.4; EIMS calcd for $C_9H_{10}O_3$ (M)166.18, found 166.16



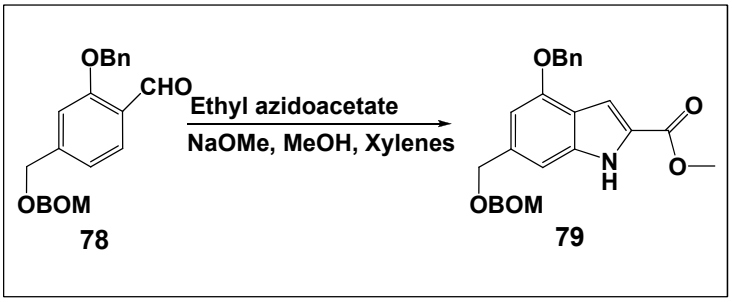
4-Formyl-3-hydroxybenzyl acetate (76). To a solution of 3-hydroxybenzyl acetate (**75**) (15.60g, 93.87mmol) in toluene (500mL) was added $SnCl_4$ (1.2mL, 10.3mmol) and tri-n-octylamine (16.4mL, 37.5mmol) at room temperature. The resulting mixture was stirred at room temperature for 20min, then paraformaldehyde (8.45g, 0.28mol) was added and the mixture was heated at 95°C for 16 hours. The reaction mixture was cooled to room temperature, poured into ice water, then acidified to PH=1 with 1N HCl. Extracted with EtOAc. The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/CH_2Cl_2 1:24) to give **76(**15.1g, Yield 83%) as a white solid. mp 42~43°C. IR: 3401.2, 2921.0, 1745.5, 1663.2, 1222.8, 1046.4, 804.7, 748.6 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 11.06 (s, 1H), 9.88 (s, 1H), 7.55 (d, J=8.51 Hz, 1H), 6.97 (d, J=6.6 Hz, 1H), 6.96 (s, 1H), 5.12 (s, 2H), 2.15 (s, 3 H); ^{13}C NMR (125 MHz, CDCl3) 196.5, 162.2, 146.3, 134.4, 120.5, 119.0, 116.5, 65.5, 21.3; HRMS calcd for $C_{10}H_{11}O_4$ (M+H) 195.0657, found 195.0666



2-(Benzyloxy)-4-(hydroxymethyl)benzaldehyde (77). K_2CO_3 (46.97g, 0.25mol) was added into a solution of MeOH (300mL) and $CHCl_3$ (600mL) and heated at reflux for 20 minutes, followed by 4-formyl-3-hydroxybenzyl acetate (**76**) (11.0g, 56.6mmol). Benzyl bromide (6.9mL, 57.7mmol) was added after 5min and the reaction mixture was heated at reflux for 24 hours. The solution was poured into an ice water and extracted with ether (2x500mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Ethyl acetate/hexane 3:7) to give **77 (**13.10g, Yield 98%) as a pale yellow oil. IR: 3582.7, 3406.2, 2918.2, 1678.4, 1426.8, 1256.2, 1156.6, 810 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 10.51 (s, 1H), 7.83 (d, J=7.88 Hz, 1H), 7.46-7.34 (m, 5H), 7.13 (s, 1H), 6.99 (d, J=7.88, 1H), 5.20 (s, 2H), 4.75 (s, 2 H); ^{13}C NMR (125 MHz, CDCl3) 189.9, 161.8, 150.1, 136.4, 129.2, 129.1, 128.7, 127.8, 124.7, 119.2, 111.1, 70.9, 65.1; HRMS calcd for $C_{15}H_{15}O_3$ (M+H) 243.0994, found 243.0998

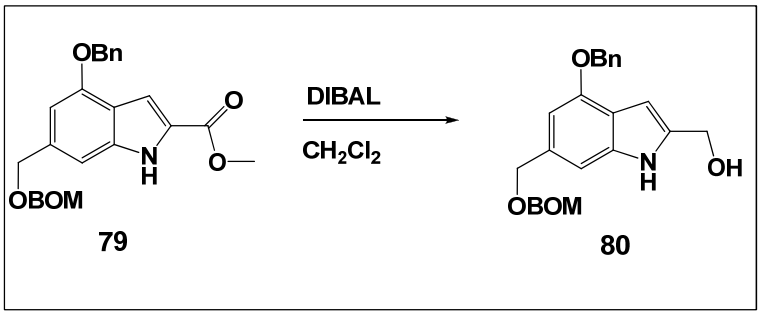


2-(Benzyloxy)-4-((benzyloxymethoxy)methyl)benzaldehyde (78). To 2-(Benzyloxy)-4-(hydroxymethyl)benzaldehyde (**77**) (15.20g, 62.74mmol) in methylene chloride (600mL) was added n-Bu_4NI, (2.32g, 6.27mmol), DIPEA (43.7mL, 251mmol), followed by benzyl chloromethyl ether (26.2mL, 188mmol) at 0°C. The resulting mixture was stirred at room temperature for 17 hours. The originally pale yellow reaction mixture was turned to orange solution. It was washed with saturated sodium bicarbonate and brine. The separated organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Ethyl acetate/hexane 1:4) to give **78 (**18.81g, Yield 83%) as a pale yellow oil. IR: 3484.3, 3031.8, 2881.1, 1682.5, 1429.0, 1257.7, 1049.2, 812.5, 736.6cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 10.52 (s, 1H), 7.84 (d, J=7.88 Hz, 1H), 7.46-7.28 (m, 10H), 7.08 (s, 1H), 6.00 (d, J=7.88, 1H), 5.18 (s, 2H), 4.86 (s, 2 H), 4,68 (s, 2H), 4.65 (s, 2H); ^{13}C NMR (125 MHz, CDCl3) 189.8, 161.6, 147.2, 138.0, 136.4, 129.7, 129.1, 129.1, 129.0, 128.9, 128.7, 128.3, 128.3, 128.2, 127.9, 127.8, 124.8, 120.2, 112.0, 94.7, 70.9, 70.2, 69.3; HRMS calcd for $C_{23}H_{23}O_4$ (M+H) 363.1588, found 363.1585



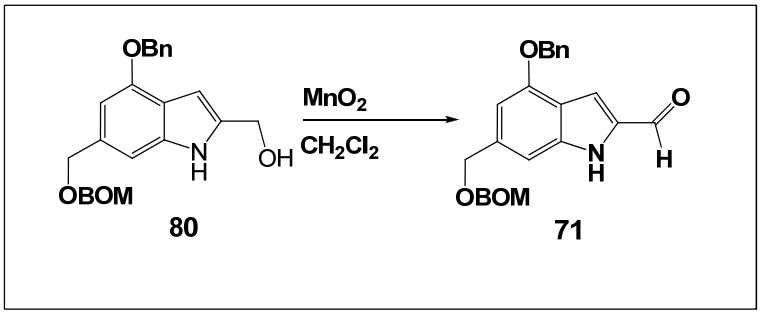
Methyl 4-(benzyloxy)-6-((benzyloxymethoxy)methyl)-1H-indole-2-carboxylate (79). To a solution of 2-(Benzyloxy)-4-((benzyloxymethoxy)methyl)benzaldehyde (**78**) (16.20g, 44.70mmol) and ethyl azidoacetate (31.99g, 223mmol) in anhydrous methanol (250mL) was added sodium methoxide in methanol (50mL, 268mmol) dropwise at -30°C ~ -40°C. The reaction was warmed up to 3°C and stirred at this temperature for 18 hours which TLC indicated the reaction completed. Ice water and saturated ammonium chloride solution were added and the mixture was extracted with ether. The organic layer was washed with brine. It was dried over anhydrous $MgSO_4$. Dry xylene (30mL) was added into the solution and concentrated under reduced pressure to give a clear oil. The oil was quickly added over refluxing anhyrdous xylenes. The resulting solution was heated to 142°C for 3hrs under N_2. TLC showed the reaction completed. The xylenes were removed in the rotary evaporator. The residue was crystallized by CH2Cl2/Hexane (1/2). The filtrate was purified by flash column chromatography (EtOAc/CH_2Cl_2 1:19) to give **79** (11.76g, Yield 61%) as a pale yellow solid. mp 114.2~114.5°C. IR: 3327.6, 2913.5, 1689.4, 1438.8, 1275.4, 1133.7, 814.1, 745.1, 697.8 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.49 (d, J=6.94 Hz, 2H), 7.41 (d, J=7.25 Hz, 2H), 7.39-7.28 (m, 6H), 7.26 (s, 1H), 6.02 (s, 1H), 6.60 (s, 1H), 5.19 (s, 2H), 4.86 (s, 2 H),

4.72 (s, 2H), 4.66 (s, 2H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) 162.7, 154.2,138.5, 138.3, 137.4, 137.2, 129.0, 128.9, 128.4, 128.2, 127.8, 126.6, 119.3, 107.2, 104.9, 101.8, 94.3, 70.5, 70.3, 70.0, 52.4; HRMS calcd for $C_{26}H_{26}NO_5$ (M+H) 432.1811, found 432.1799.

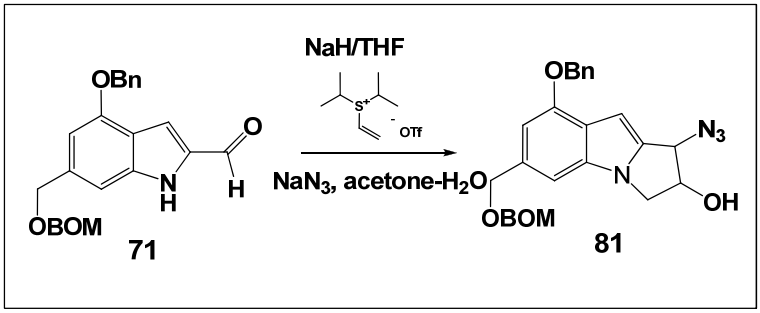


(4-(Benzyloxy)-6-((benzyloxymethoxy)methyl)-1H-indol-2-yl)methanol (80). To a solution of Methyl 4-(benzyloxy)-6-((benzyloxymethoxy)methyl)-1H-indole-2-carboxylate (**79**) (6.99g, 16.2mmol) in anhydrous methylene chloride (330mL) was added slowly DIBAL (48.6mL, 48.6mmol) at -78°C. After 3 hours reacted at -78°C, the mixture was quenched by addition of 100mL 1N HCl at same temperature. The solid was filtered. The filtrate was extracted with methylene chloride and washed with saturated sodium bicarbonate solution and brine. The organic layer was dried by anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Ethyl acetate/hexane 3:2) to give **80** (6.25g, yield 95%) as a pale yellow solid. mp 82.8-83.1°C. IR: 3422.0, 3030.5, 2878.6, 1621.6, 1453.3, 1264.4, 1164.5, 820.6, 736.5, 697.6 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.54 (d, J=7.57 Hz, 1H), 7.47-7.33 (m, 8H), 7.01 (s, 1H), 6.66 (s, 1H), 6.60(s, 1H), 5.25 (s, 2H), 4.89 (s, 2 H), 4.82 (s, 2H), 4.76 (s, 2H), 4.72 (s, 2H); ^{13}C NMR (125

MHz, CDCl3) 152.9, 138.4, 138.1, 137.9, 137.0, 133.3, 128.9, 128.8, 128.6, 128.5, 128.4, 128.2, 128.1, 127.8, 127.6, 127.5, 119.2, 105.0, 102.2, 98.6, 94.0, 70.8, 70.4, 70.0, 59.1; HRMS calcd for $C_{25}H_{26}NO_4$ (M+H) 404.18618, found 404.18478.



4-(Benzyloxy)-6-((benzyloxymethoxy)methyl)-1H-indol-2-carbaldehyde (71). To a solution of (4-(Benzyloxy)-6-((benzyloxymethoxy)methyl)-1H-indol-2-yl)methanol (**80**) (10.66g, 26.4mmol) in anhydrous methylene chloride (250mL) was added slowly MnO_2 (35.7g, 0.40mol) at room temperature. The reaction was heated at reflux for 40 minutes. TLC indicated the reaction completed. Filtered it through celite and washed by hot CH_2Cl_2 (200mL). The filtrate was concentrated to dryness to give **71** (9.0g, yield 85%) as a pale yellow solid. mp 117.5-117.8 °C. IR: 3293.1, 2937.57, 2880.4, 1658.6, 1572.8, 1270.4, 1147.8, 808.6, 755.5. 694.2cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 9.34 (s, 1H), 7.53 (d, J=6.94 Hz, 2H), 7.47-7.42 (m, 3H), 7.41-7.37 (m, 5H), 7.36-7.32 (m, 1H), 7.07 (s, 1H), 6.63 (s, 1H), 5.23 (s, 2H), 4.90 (s, 2 H), 4.76 (s, 2H), 4.70 (s, 2H); ^{13}C NMR (125 MHz, CDCl3) 182.0, 154.8, 139.8, 139.5, 138.2, 137.1, 135.6, 129.0, 128.9, 128.5, 128.3, 128.2, 127.9, 119.5, 113.4, 105.0, 101.7, 94.4, 70.4, 70.4, 70.1; HRMS calcd for $C_{25}H_{24}NO_4$ (M+H) 402.1705, found 402.1696.



1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-ol (81). To a solution of 4-(Benzyloxy)-6-((benzyloxymethoxy)methyl)-1H-indol-2-carbaldehyde (**71**) (9.0g, 22.4mmol) in THF (300mL) was added NaH under N_2 at 0°C. After 20min, diisopropylvinylsulfonium triflate (13.4g, 44.8mmol) in 20mL THF was added slowly. Then the reaction mixture was stirred at room temperature for 14 hours. NaN_3 in 108mL of acetone/H_2O (1/1) was added and stirred for another 20 hours. H_2O (300mL) was added and the aqueous solution was extracted with CH_2Cl_2 (2x200mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/CH_2Cl_2 2:23) to give **81** (7.84g, Yield 74%) as a pale yellow solid. mp 95.4-95.7°C. IR: 3407.5, 2880.4, 2095.8, 1568.67, 1446.1, 1245.9, 1045.6, 739.2, 698.3 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.55-7.50 (m, 2H), 7.46 -7.31(m, 8H), 6.93 (s, 1H), 6.71 (s, 1H), 6.65 (s, 1H), 5.24 (s, 2H), 4.81 (s, 2 H), 4.81 (d, J=2.52 Hz, 1H), 4.76 (s, 2H), 4.69 (s, 2H), 4.37 – 4.30(m, 1H), 3.95-3.89 (m, 1H), 2.50 (d, J=4.73 Hz, 1H). ^{13}C NMR (125 MHz, CDCl3) 153.2, 138.3 137.7, 136.4, 134.7, 133.5, 128.9, 128.4, 128.3, 128.2, 127.8, 123.0, 103.8, 102.2,

95.0, 94.1, 80.6, 70.7, 70.4, 70.0, 65.2, 51.1; HRMS calcd for $C_{27}H_{27}N_4O_4$ (M+H) 471.2032, found 471.2003.

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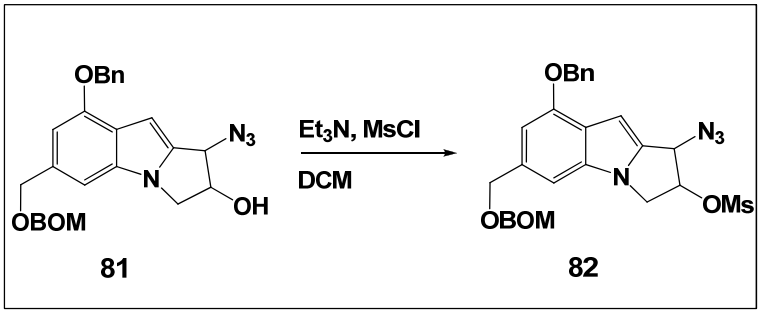
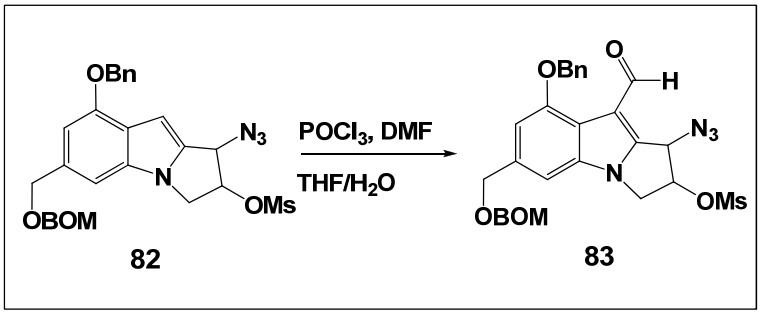


1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-yl methanesulfonate (82). To a solution of 1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-ol (**81**) (7.84g, 16.7mmol) in CH_2Cl_2 (190mL) was added Et_3N (9.3mL, 66.6mmol) and MsCl (2.6mL, 33.4mmol) dropwise at 0°C. The reaction was stirred at 0°C for 2 hours which TLC indicated the reaction completed. Diluted it with ether and washed it with water. Aqueous layer was extracted with ether (2x200mL). Combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Ethyl acetate/hexane 2:3) to give **82** (9.15g, Yield 99.9%) as a pale yellow solid. mp 87.9-88.2 °C. IR: 3435.0, 2872.2, 2099.9, 1621.8, 1572.8, 1442.0, 1364.4, 1241.8, 1168.2, 1045.6, 739.2, 694.2 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.52-7.27 (m, 10H), 6.92 (s, 1H), 6.73 (s, 1H), 6.64 (s, 1H), 5.52-5.47 (m, 1H), 5.21(s, 2H), 5.16 (d, J=2.20Hz, 1H), 4.86 (s, 2H), 4.73 (s, 2H), 4.66 (s, 2H), 4.53 (dd, J=5.13Hz, J=12.45Hz, 1H), 4.27 (dd, J=2.20Hz, J= 12.45Hz, 1H), 3.11 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) 162.4, 157.0, 147.1, 139.3,

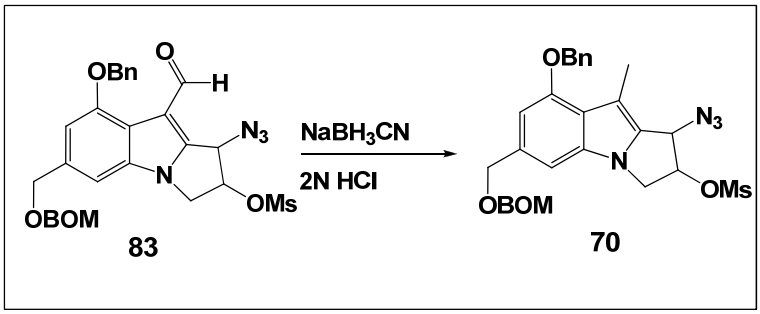
136.9, 135.5, 129.1, 129.1, 128.9, 128.8, 128.5, 128.2, 127.5, 113.4, 111.3, 106.4, 94.6, 93.2, 70.5, 70.1, 69.7, 69.4, 62.9, 54.0, 41.9, 40.3, 36.6; HRMS calcd for $C_{28}H_{29}N_4O_6S$ (M+H) found 549.1812 w/error 1.7845ppm.



82 83

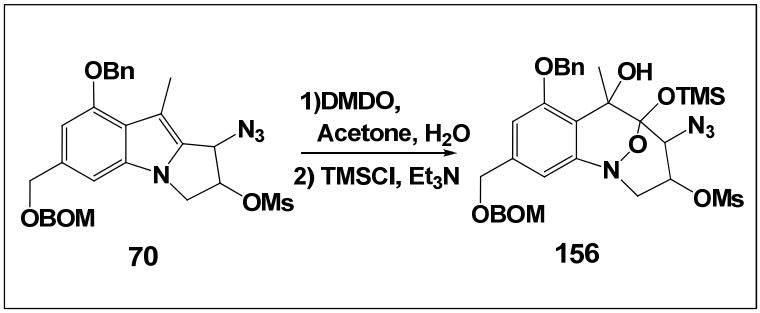
1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-9-formyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-yl methanesulfonate (83). Phophorus oxychloride (12.5mL, 133.6mmol) was added dropwise into anhydrous DMF (81mL) at 0°C under N_2. After the mixture was stirred for 45 minutes, 1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-yl methanesulfonate (**82**) (9.16g, 16.7mmol) in anhydrous THF (420mL) was added slowly at 0°C. The solution was stirred at room temperature for 20 hours. Then water (95mL) was added and stirred for 4 hours at room temperature. The aqueous layer was extracted with CH_2Cl_2 (3x200mL). The combined organic layer was dried over anhydrous $MgSO_4$. Filtered and concentrated to dryness. Purified it by flash column chromatography (Ethyl acetate/hexane 1:1) to give **83** (9.44 g, Yield 98%) as a yellow solid. mp 98.5-98.7°C. IR: 2928.7, 2114.9, 1656.7, 1541.6, 1366.4, 1172.8, 1048.2, 743.3, 694.2 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 10.48 (s, 1H), 7.52-7.32 (m, 10H), 7.01 (s, 1H), 6.87 (s, 1H), 5.62 (s, 1H), 5.19(s, 2H), 5.51(d, J=4.41Hz, 1H), 5.27 (s,

2H), 4.90 (s, 2H), 4.78 (s, 2 H), 4.70 (s, 2H), 4.53 (dd, J=4.73Hz, J=12.93Hz, 1H), 4.40 (d, J=12.93Hz), 3.14 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) 187.9, 154.3, 141.5, 136.8, 136.0, 134.3, 129.2, 128.9, 128.7, 128.3, 128.2, 128.0, 113.8, 104.8, 104.0, 94.5, 84.7, 70.9, 70.2, 70.1, 62.9, 50.7, 39.2; HRMS calcd for $C_{29}H_{29}N_4O_7S$ (M+H) 577.1757, found 577.1746.



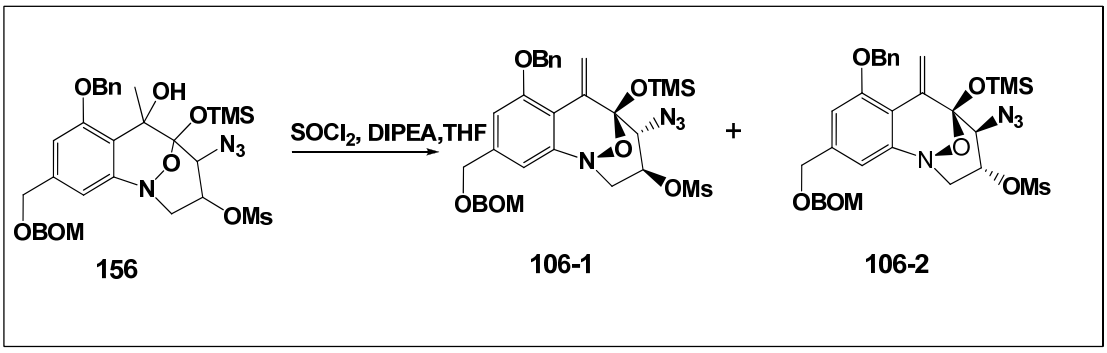
1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-9-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-yl methanesulfonate (70). 1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-9-formyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-yl methanesulfonate (**83**) (9.63g, 16.7mmol) in 300mL of MeOH and 70mL of DMF was added $NaBH_3CN$ (4.21g, 66.8mmol) at 0°C. At the same time, 2.0N HCl in ether was added dropwise with indicator of Methyl-orange (a few crystals) to keep solution was acidic condition. The reaction mixture was stirred at room temperature for 3 hours, TLC indicated the reaction completed. The mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with CH_2Cl_2 (2x200mL). Organic layer was dried over anhydrous $MgSO_4$ and filtered, concentrated down. Purified it by flash column chromatography (Ethyl acetate/hexane 2:3) to give **70** (9.30 g, Yield 99%) as a white solid mp 95.3- 95.5 °C. IR: 2929.8, 2103.2, 1565.2, 1364.7,

1176.1, 1044.3, 738.1, 697.6 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) □7.57-7.34 (m, 10H), 6.90 (s, 1H), 6.64 (s, 1H), 5.56-5.52 (m, 1H), 5.23(s, 2H), 5.21(s, 1H), 4.91 (s, 2H), 4.78 (s, 2H), 4.73 (s, 2H), 4.53 (dd, J=5.04Hz, J=11.98Hz, 1H), 4.28 (dd, J=1.89Hz, J=11.98Hz, 1H), 3.15 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) 155.1, 138.4, 137.7, 134.8, 134.3, 132.2, 128.9, 128.9, 128.7, 128.3, 128.2, 128.1, 127.7, 108.5, 103.4, 101.7, 94.2, 85.3, 70.6, 70.4, 70.0, 62.3, 49.4, 39.1. HRMS calcd for $C_{29}H_{31}N_4O_6S$ (M+H) 563.1939, found 563.1964.



1-azido-8-(benzyloxy)-6-(benzyloxymethoxymethyl)-9-hydroxy-9a-trimethylsilyloxy-4,9a-epoxy-9-methyl-2,3-dihydro-2-(methanesulfonyloxy)-1H-pyrrolo[1,2-a]-indole (156). To a solution of 1-azido-8-(benzyloxy)-6-((benzyloxymethoxy)methyl)-9-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-2-yl methanesulfonate (**70**) (150mg, 0.27mmol) in acetone (2mL) was added DMDO(16mL, 0.80mmol) and water (0.2mL) at 0°C. The reaction mixture was stirred at 0°C for 3 hours, which TLC showed the reaction almost completed. The mixture was concentrated under reduced pressure and diluted it with EtOAc. Washed with brine. Dried it over anhydrous Na_2SO_4. Filtered and concentrated to dryness to give 141mg of crude product.

To above crude product in anhydrous CH_2Cl_2 (2mL) was added Et_3N (0.11mL, 0.81mmol), TMSCl (0.069mL, 0.41mmol) and DMAP (3.2mg, 0.027mmol). The mixture was stirred at 0°C for 3 hours. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, and brine. It was dried over anhydrous Na_2SO_4, then filtered and concentrated down. Purified it by flash column chromatography (Ethyl acetate/hexane 2:3) to give **156** (74 mg, Yield 40%) as a pale yellow oil. IR: 2913.5, 2114.4, 1427.9, 1358.9, 1253.6, 1177.3, 1053.8, 745.1 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ7.51-7.32 (m, 10H), 6.87 and 6.75 (s, 1H), 6.61 and 6.43 (s, 1H), 5.14 (s, 2H), 4.89 and 4.86(s, 2H), 4.79-4.72 (m, 1H), 4.68 and 4.66 (s, 2H), 4.61 and 4.60 (s, 2H), 4.49(dd, J=8.19Hz, J=13.56Hz, 0.6H), 4.45 (d, J= 10.7Hz, 0.4H), 4.33 (s, 0.6H), 3.86 (d, J= 10.4Hz, 0.4H), 3.76-3.78 (m, 0.4H), 3.51-3.46 (m, 0.6H), 3.11 and 3.04 (s, 3H), 1.64 and 1.60 (s, 3H), 0.322 and 0.20(s, 9H). ^{13}C NMR (125 MHz, CDCl3) 157.6, 148.2, 140.2, 138.1, 135.7, 129.4, 129.2, 129.1, 128.9, 128.7, 128.4, 128.3, 128.2, 118.3, 111.0, 107.1, 107.0, 100.8, 94.7, 94.6, 76.4, 74.0, 71.5, 70.2, 69.3, 61.3, 60.1, 38.7, 30.1, 24.1, 22.4, 2.4, 2.2. HRMS calcd for $C_{32}H_{41}N_4O_9SS_i$(M+H) found 685.2358 w/error 0.0492ppm.



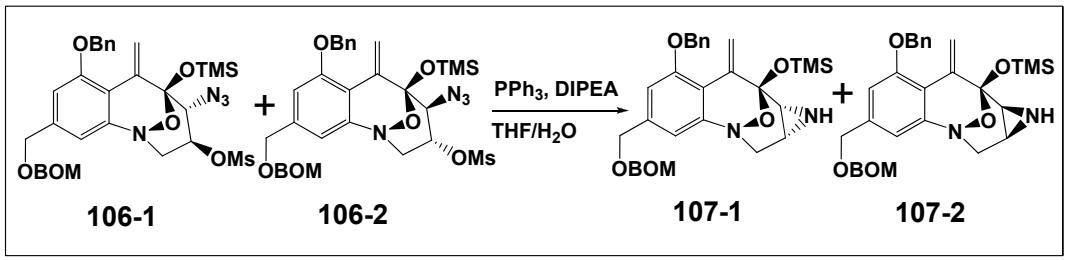
1-azido-8-(benzyloxy)-6-(benzyloxymethoxymethyl)-9-methylene-9a-trimethylsilyloxy-4,9a-epoxy-9-methyl-2,3-dihydro-2-(methanesulfonyloxy)-1H-pyrrolo[1,2-a]-indole (106). To a solution of 1-azido-8-(benzyloxy)-6-(benzyloxymethoxymethyl)-9-hydroxy-9a-trimethylsilyloxy-4,9a-epoxy-9-methyl-2,3-dihydro-2-(methanesulfonyloxy)-1H-pyrrolo[1,2-a]-indole (**156**) (300mg, 0.43mmol) in THF (3mL) was added DIPEA (0.28mL, 1.72mmol), followed by $SOCl_2$ (0.064mL, 0.88mmol) in THF (1mL) at -60°C. The mixture was stirred at -60°C ~ -10°C for 1 hour. Mass spectrum indicated the reaction completed. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The reaction mixture was diluted with EtOAc and washed with water, 1N aqueous HCl and brine. It was dried over anhydrous Na_2SO_4. Filtered and concentrated to dryness. Purified it by flash column chromatography (Ethyl acetate/hexane 2:3) to give racemic **106-1** (149mg) and racemic **106-2** (80mg,Yield 80%) as a yellow oil. IR: 3031.7, 2937.3, 2115.3, 1608.4, 1567.4, 1343.6, 1051.1, 879.9, 738.5, 698.5 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) **106-1:** δ7.50-7.31 (m, 10H), 6.87 (s, 1H), 6.86 (s, 1H), 6.62 (s, 1H), 5.81 (s, 1H), 5.22-5.12 (m, 2H), 4.73 (s, 1H), 4.86(s, 2H), 4.67 (s, 2H), 4.61(s, 2H), 4.26-4.17 (m, 1H), 3.86 (d, J= 10.4Hz, 1H), 3.79-3.66 (m, 1H), 3.04 (s, 3H), 0.20 (s, 9H). ^{13}C NMR (125 MHz, CDCl3) **106-1:** 159.6, 158.4, 145.7, 139.7, 136.5, 134.1, 129.1, 128.9, 128.7, 128.4, 128.3, 127.4, 120.6, 113.2, 109.0, 101.9, 94.6, 73.5, 71.4, 70.4, 70.1, 69.2, 65.8, 59.7, 38.7, 2.2.

HRMS calcd for $C_{32}H_{39}N_4O_8SS_i$(M+H) found 667.22579 w/error 1.83ppm.

^1H NMR (500 MHz, $CDCl_3$) **106-2:** δ7.49 (s, 1H), 7.54-7.33 (m, 8H), 7.08 (s, 1H), 6.81 (s, 1H), 6.73 (s, 1H), 5.77 (s, 1H), 5.19 (s, 2H), 4.83 (s, 2H), 4.77-4.75 (m,

1H), 4.66 (s, 2H), 4.58 (s, 2H), 4.03 (d, J=3.15Hz, 1H), 3.89 and 3.87 (d, J=3.47Hz, 1H), 3.46 and 3.43 (s, 1H), 2.42 (s, 3H), 0.22 (s, 9H). ^{13}C NMR (125 MHz, CDCl3) **106-2:** 158.1, 148.0, 139.6, 139.1, 138.1, 136.7, 129.1, 128.9, 128.7, 128.5, 128.3, 128.2, 128.0, 118.0, 114.1, 113.1, 108.9, 98.7, 94.4, 74.6, 71.2, 70.4, 70.1, 69.2, 64.3, 62.5, 52.6, 45.3, 38.4, 30.3, 29.4, 2.1.

HRMS calcd for $C_{32}H_{39}N_4O_8SS_i$(M+H) found 667.2270 w/error 1.7984ppm.



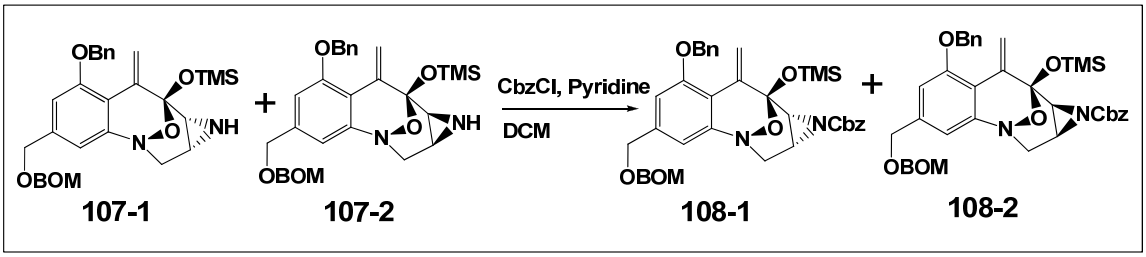
Racemic 107-1 and Racemic 107-2. To a solution of compound **106-1 or 106-2** (130mg, 0.20mmol) in THF/water (2.0mL/0.2mL) was added DIPEA (0.089mL, 0.54mmol) and PPh_3 (82mg, 0.31mmo). The reaction mixture was stirred at room temperature for 24 hours. The mixture was diluted with dichloromethane and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, then filtered and concentrated down. It was purified by flash column chromatography (Ethyl acetate/hexane 3:2) to give **107.** (84mg, Yield 70%) as a yellow oil. IR: 2917.1, 1725.8, 1438.8, 1275.4, 1111.9, 1050.2, 752.3 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) **107-1:** δ7.49-7.27 (m, 10H), 6.65 (s, 1H), 6.48 (s, 1H), 6.43 (s, 1H), 5.72 (s, 1H), 5.11 (s, 2H), 4.81 (s, 2H), 4.63(s, 2H), 4.57 (s, 2H), 3.91 (d, J= 13.9Hz, 1H), 3.71-3.55 (m, 2H), 2.75 (d, J=6.6Hz, 1H), 2.37 (d, J=5.86Hz, 1H), 0.23 (s, 9H). ^{13}C NMR (125 MHz, CDCl3) **107-1:** 158.4, 138.4, 138.2, 137.0, 133.1, 132.6, 132.5, 132.4, 129.0, 128.9, 128.6, 128.3,

115.4, 115.2, 113.0, 111.2, 106.5, 94.3, 74.1, 71.1, 69.9, 69.4, 65.3, 62.5, 52.9, 40.0, 30.3, 30.1, 27.1, 2.5.

HRMS calcd for $C_{31}H_{37}N_2O_5S_i$(M+H) found 545.24717 w/error -1.30ppm.

^{1}H NMR (500 MHz, $CDCl_3$) **107-2:** δ7.50-7.28 (m, 10H), 6.74 (s, 1H), 6.54 (s, 1H), 6.49 (s, 1H), 5.83 (s, 1H), 5.18-5.08 (m, 2H), 4.83 (s, 2H), 4.64 (s, 2H), 4.59 (s, 2H), 3.79 (d, J=14.64Hz, 1H), 3.62-3.53 (m, 1H), 2.22 (s, 2H), 0.18 (s, 9H). ^{13}C NMR (125 MHz, CDCl3) **107-2:** 158.7, 139.1, 136.7, 129.1, 129.0, 128.9, 128.6, 128.3, 128.2, 115.4, 112.4,107.1, 94.5, 71.3, 70.1, 69.4, 55.2, 2.3.

HRMS calcd for $C_{31}H_{37}N_2O_5S_i$(M+H) found 545.2466 w/error 0.0835ppm.



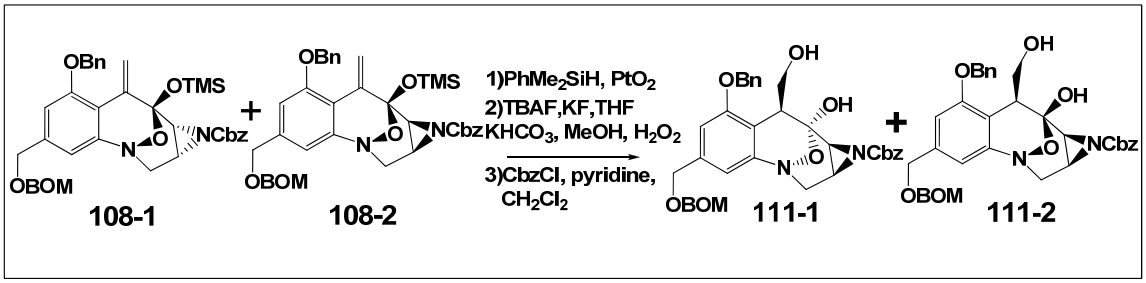
Racemic 108-1 and Racemic 108-2. To a solution of compound **107-1 or 107-2** (30mg, 0.055mmol) in dichloromethane (1.0mL) at 0°C was added benzyl chloroformate (9.4mL, 0.066mmol) slowly. The mixture was stirred at 0°C for 1hrs, MS showed the reaction almost completed. The mixture was diluted with ethyl acetate and washed with saturated aqueous NH_4Cl and brine. The organic layer was dried over anhydrous Na_2SO_4, then filtered and concentrated down. It was purified by flash column chromatography (Ethyl acetate/hexane 3:7) to give **108.** (32mg, Yield 86%). IR: 2952.9, 1728.0, 1572.8, 1433.9, 1276.4, 1167.1, 1052.6, 845.0, 698.1 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) **108-1:** δ7.44-7.19 (m, 15H), 6.64 (s, 1H), 6.54 (s, 1H), 6.41 (s, 1H),

5.77 (s, 1H), 5.09 (s, 2H), 5.09-5.01 (m, 2H), 4.81 (s, 2H), 4.62(s, 2H), 4.55 (s, 2H), 3.86 (d, J=1.56Hz, 1H), 3.73 (d, J=14.85, 1H), 3.19 (d, J=6.25Hz, 1H), 2.81 (dd, J=2.34Hz, J=7.03Hz, 1H), 0.20 (s, 9H). ^{13}C NMR (125 MHz, CDCl3) **108-1:** 138.6, 138.3, 137.1, 131.0, 130.5, 130.3, 130.1, 130.0, 129.0, 128.9, 128.5, 128.4, 128.2, 127.9, 114.0, 113.7, 111.6, 107.2, 94.4, 71.2, 70.2, 69.6, 68.2, 52.2, 45.8, 33.6, 2.4.

HRMS calcd for $C_{39}H_{43}N_2O_7S_i$(M+H) found 679.28395 w/error -0.88ppm.

^{1}H NMR (500 MHz, $CDCl_3$) **108-2:** δ7.50-7.29 (m, 15H), 6.71 (s, 1H), 6.47 (s, 1H), 6.46 (s, 1H), 5.91 (s, 1H), 5.25-5.03 (m, 4H), 4.83 (s, 2H), 4.70 (s, 1H), 4.63 (s, 2H), 4.57 (s, 2H), 3.83 (d, J=14.64Hz, 1H), 3.56 (dd, J=6.59Hz, J=15.38Hz, 1H), 2.84-2.78 (m, 1H), 2.71 (d, J=6.59Hz, 1H), 0.17 (s, 9H). ^{13}C NMR (125 MHz, CDCl3) **108-2:** 162.7**,** 158.5, 147.3, 139.2, 137.5, 136.7, 136.2, 132.6, 132.5,129.1, 129.0, 128.9, 128.7, 128.6, 128.3, 128.2, 127.4, 115.6, 107.0, 94.5, 93.1, 71.3, 70.2, 70.1, 69.4, 68.5, 54.4, 40.1, 35.6, 2.4.

HRMS calcd for $C_{39}H_{43}N_2O_7S_i$(M+H) found 679.2829 w/error -0.5091mmu.



Racemic 111-1 and Racemic 111-2. To a solution of compound **108-1 or 108-2** (30mg, 0.044mmol) in THF (0.4mL) at room temperature was added dimethylphenylsilane (0.014mL, 0.088mmol) and PtO_2 (0.20mg, 0.0009mmol). The

mixture was heated at 55°C for 24 hours, MS showed the reaction almost completed. It was filtered and concentrated to dryness to give a crude product.

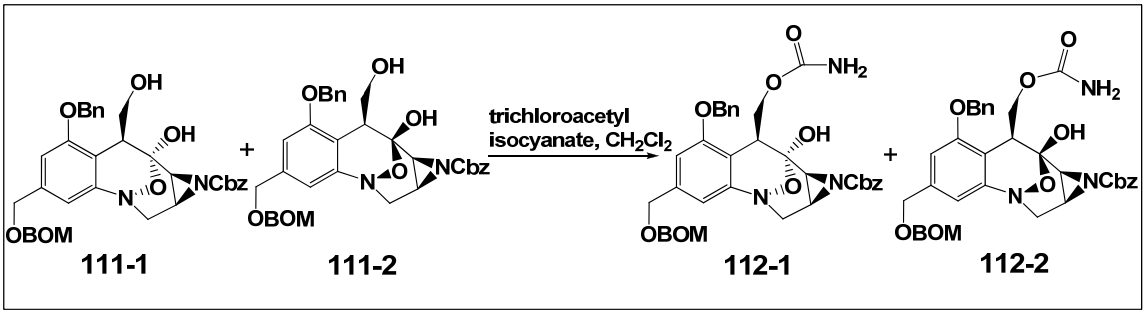
To above crude product in anhydrous THF (1.2mL) was added TBAF (0.13mL, 0.13mmol). The mixture was stirred at room temperature for 1 hours, then KF (5.1mg, 0.088mmol) and KHCO3 (13mg, 0.13mmol) were added, followed by MeOH (1.2mL), and H_2O_2 (0.091mL, 0.88mmol). The mixture was stirred at 58°C for 2hrs. After cooled down, the mixture was diluted with EtOAc (5mL) and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4, then filtered and concentrated to dryness to give 13mg of a diol with Cbz cleaved crude product.

To above crude product in anhydrous 1mL of DCM was added pyridine (0.011mL, 0.13mmol) at 0°C, followed by benzyl chloroformate (7.5mg, 0.044mmol) in 0.5 mL of DCM dropwise. MS showed the reaction completed after 30min. It was concentrated down and purified by preparative thin-layer chromatography plate(Ethyl acetate/hexane 1:1) to give **111** (9.6mg, Yield 35%). ^{1}H NMR (500 MHz, $CDCl_3$) **111-1:** δ7.49-7.31 (m, 15H), 6.69 (s, 1H), 6.46 (s, 1H), 5.19 (s, 2H), 5.18-5.08 (m, 2H), 4.85 (s, 2H), 4.68 (s, 1H), 4.65 (s, 2H), 4.59 (s, 2H), 4.08-4.01 (m, 1H), 3.99-3.91 (m, 1H), 3.85 (dd, J=2.21Hz, 15.13Hz, 1H), 3.57 (dd, J=6.62Hz, 15.13Hz, 1H), 3.48 (dd, J=2.52Hz, J=8.20Hz, 1H), 3.00-2.92 (m, 1H), 2.88-2.82 (m, 1H), 2.78 and 2.77(s, 1H).. ^{13}C NMR (125 MHz, CDCl3) **111-1:** 162.4**,** 157.0, 147.1, 139.3, 138.1, 136.9, 135.5, 129.1, 128.9, 128.8, 128.7,128.5, 128.2, 128.0, 127.5,113.4, 111.3, 106.4, 94.6, 93.2, 70.5, 70.1, 69.7, 69.4, 62.9, 54.0, 41.9, 40.3, 36.6, 30.1.

HRMS calcd for $C_{36}H_{37}N_2O_8$ (M+H) found 625.25499 w/error -2.86 ppm

^{1}H NMR (500 MHz, $CDCl_3$) **111-2:** δ7.46-7.27 (m, 15H), 6.66 (s, 1H), 6.43 (s, 1H), 5.16 (s, 2H), 5.17-5.06 (m, 2H), 4.82 (s, 2H), 4.73 (s, 1H), 4.62 (s, 2H), 4.56 (s, 2H), 4.06-3.99 (m, 1H), 3.96-3.89 (m, 1H), 3.81 (dd, J=2.20Hz, 14.65Hz, 1H), 3.54 (dd, J=5.86Hz, 14.65Hz, 1H), 3.46 (dd, J=2.93Hz, J=8.06Hz, 1H), 3.01-2.94 (m, 1H), 2.85-2.79 (m, 1H), 2.76 and 2.74(s, 1H). ^{13}C NMR (125 MHz, CDCl3) **111-2:** 162.4**,** 157.0, 147.1, 139.3, 138.1, 136.9, 135.5, 129.2, 129.1, 128.9, 128.8, 128.5, 128.2, 127.5,113.4, 111.3, 106.4, 94.6, 93.2, 70.5, 70.1, 69.7, 69.4, 62.9, 54.0, 41.9, 40.3, 36.5.

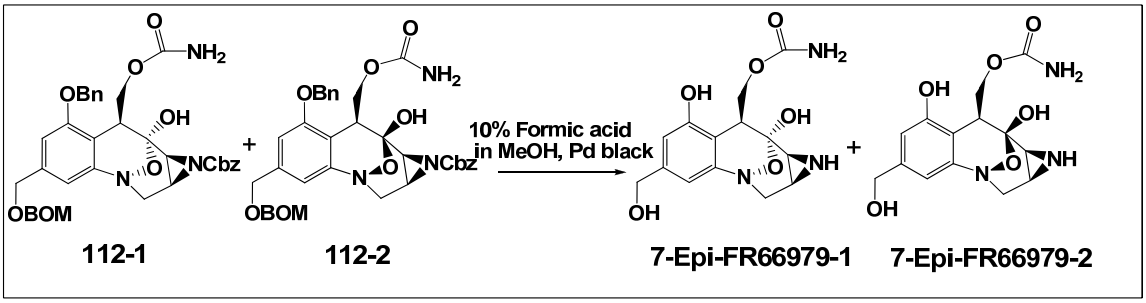
HRMS calcd for $C_{36}H_{37}N_2O_8$ (M+H) found 625.2534 w/error -1.7372 ppm



Racemic 112-1 and 112-2. To a solution of compound **111-1 or 111-2** (5.6mg, 0.009mmol) in CH_2Cl_2 (0.5mL) was added trichloroacetyl isocyanate (0.0021mL, 0.018mmol). The mixture was stirred at 0°C for 10 minutes. The reaction was quenched by MeOH (5 drops) and concentrated down. The residue was dissolved in methanol (2mL) and treated with silica gel (70mg). After 5hours of stirring, the mixture was filtered and washed with ethyl acetate. It was concentrated down and purified by preparative thin-layer chromatography plate (MeOH/ CH_2Cl_2 1:9) to give **112** (5.2mg, Yield 87%). ^{1}H NMR (500 MHz, $CDCl_3$) **112-1:** δ7.47-7.31 (m, 15H), 7.01 (s,1H), 6.71 (s, 1H), 6.49 (s, 1H), 5.17 (s, 2H), 5.15-5.03 (m, 2H), 4.87 (s, 2H), 4.67 (s, 2H),

4.61 (s, 2H), 4.60-4.54 (m, 1H), 3.84 (d, J=16.71Hz, 1H), 3.77 (t, J=6.31Hz, 1H), 3.57 (dd, J=6.31Hz, J=14.82Hz, 1H), 3.41 (d, J=4.73Hz, 1H), 2.82-2.77 (m, 1H), 2.71 and 2.70 (s, 1H), 2.30 (s, 1H), 1.91-1.86 (m, 2H). ^{13}C NMR (125 MHz, CDCl3) **112-1:** 162.5**,** 157.6, 157.0, 147.6, 139.5, 138.1, 136.8, 135.7, 129.1, 128.9, 129.0, 128.9,128.8, 128.6, 128.2, 127.8, 125.9, 111.4, 106.2, 94.7, 91.7, 70.7, 70.1, 69.7, 69.2, 68.4, 62.9, 54.4, 40.1, 39.8, 35.9, 34.6, 30.7, 30.1, 26.0.

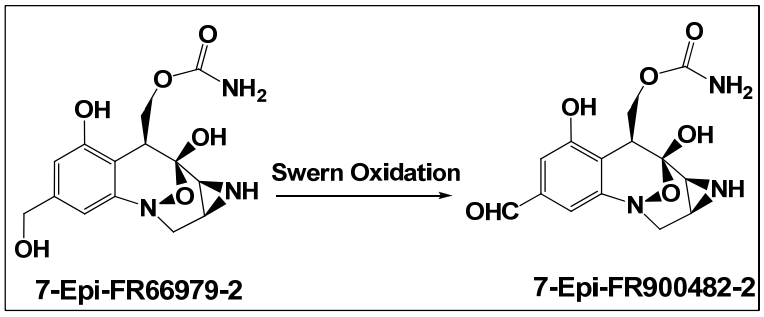
^{1}H NMR (500 MHz, $CDCl_3$) **112-2:** δ7.45-7.29 (m, 15H), 6.68 (s, 1H), 6.46 (s, 1H), 5.14 (s, 2H), 5.12-5.00 (m, 2H), 4.85 (s, 2H), 4.64 (s, 2H), 4.58 (s, 2H), 4.57-4.50 (m, 1H), 3.82 (d, J=13.18Hz, 1H), 3.75 (t, J=6.59Hz, 1H), 3.55 (dd, J=6.59Hz, J=15.38Hz, 1H), 3.39 (d, J=2.93Hz, 1H), 2.79-2.73 (m, 1H), 2.69 and 2.67 (s, 1H), 2.27 (s, 1H), 1.88-1.82 (m, 1H). ^{13}C NMR (125 MHz, CDCl3) **112-2**: 161.8, 157.2, 146.7, 146.0, 141.1, 138.0, 136.1, 135.6, 129.3, 129.0, 128.9, 128.7, 128.3, 128.2, 127.9, 111.4, 108.8, 106.5, 95.7, 94.8, 71.0, 70.2, 69.5, 69.2, 66.6, 54.6, 36.8, 35.4, 33.1. HRMS calcd for $C_{36}H_{37}N_2O_8$ (M+H) found w/error -1.7372 ppm



Racemic 7-Epi-FR66979-1 and 7-Epi-FR66979-2. To a solution of compound **112-1 or 112-2** (5.2mg, 0.0078mmol) in 10% formic acid/MeOH (0.5mL) was added Pd black (1.0mg). The mixture was stirred at RT for 2.5 hours. MS and TLC indicated

the reaction completed. Filtered and concentrated down. Purified it by preparative thin-layer chromatography plate (MeOH/ CH_2Cl_2 1:4) to give **7-Epi-FR66979** (2.1 mg, Yield 83%). ^{1}H NMR (500 MHz, D_2O) **7-Epi-FR66979-1:** δ6.59 (s, 1H), 6.38 (s, 1H), 4.46 (dd, J=5.68Hz, J=11.35Hz, 1H), 4.43 (s, 2H), 4.23 (dd, J=2.84Hz, J=11.35Hz, 1H), 3.50 (s, 2H), 3.37 (s, 1H), 3.23 (s, 1H), 2.35 (s, 1H). ^{13}C NMR (125 MHz, CDCl3) **7-Epi-FR66979-1:** 147.4, 142.1, 112.9, 110.0, 109.6, 63.6, 63.0, 55.3, 39.5, 28.7. MS (ESI) m/z 324 ($[M + H]^+$).

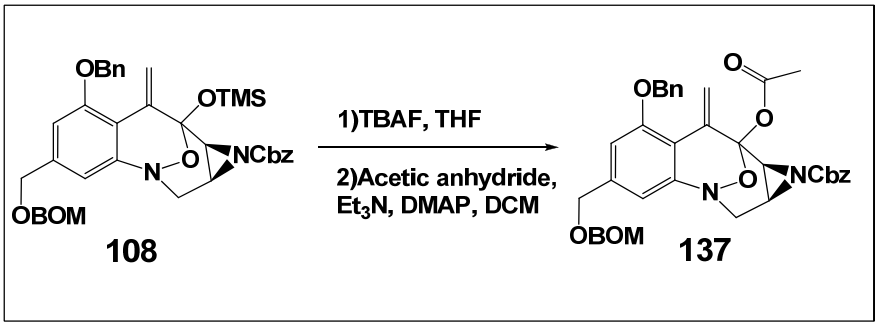
^{1}H NMR (500 MHz, D_2O) **7-Epi-FR66979-2:** 6.61 (s, 1H), 6.40 (s, 1H), 4.46 (dd, J=5.68Hz, J=11.35Hz, 1H), 4.43 (s, 2H), 4.26 (dd, J=2.84Hz, J=11.35Hz, 1H), 3.60-3.57 (br s, 2H), 3.41-3.38 (m, 1H), 2.63-2.56 (m, 2H). ^{13}C NMR (125 MHz, D_2O) **7-Epi-FR66979-2:** 159.7, 155.9, 146.4, 142.3, 112.2, 110.0, 109.8, 63.5, 62.7, 54.1, 39.5, 33.5, 29.9. MS (ESI) m/z 324 ($[M + H]^+$).



Racemic 7-Epi-FR900482-2. DMSO (3uL) in anhydrous CH_2Cl_2 (0.1mL) was added dropwise to a stirred solution of oxalyl chloride (1.7uL) in anhydrous CH_2Cl_2 (0.1mL) at -78°C. After 2min, a solution of **7-Epi-FR66979-2** (2.5mg, 0.0077mmol) in 0.2mL of DCM/DMSO (1:1) was added dropwise and stirring was continued for 20min. After the addition of Et_3N (13uL, 0.092mmol, 12eq.), the mixture was gradually

warmed up to room temperature and further stirred for 20min. The reaction mixture was concentrated down. Purified it by preparative thin-layer chromatography plate(MeOH/ CH_2Cl_2 1:4) to give **7-Epi-FR900482-2** (1.5mg, yield 60%) as a white solid. ^{1}H NMR (600 MHz, D_2O) δ9.66 (s, 1H), 7.03 (s, 1H), 6.92 (s, 1H), 4.51 (dd, J=5.6Hz, J=11.5Hz, 1H), 4.24 (dd, J=2.9Hz, J=11.5Hz, 1H), (s, 2H), 3.51-3.54 (m, 2H), 3.42 (dd, J=2.9Hz, J=5.6Hz, 1H), 2.33 (bs, 2H). ^{13}C NMR (150 MHz, D_2O) 195.5, 159.5, 156.3, 147.3, 136.5, 120.6, 113.5, 110.5, 92.8, 62.2, 55.1, 39.9, 32.0, 28.2.

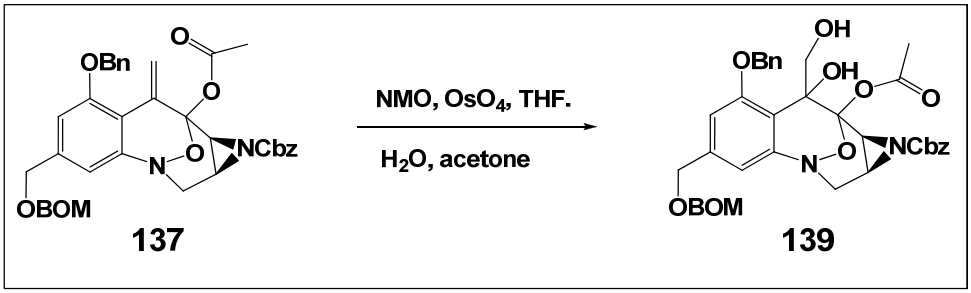
HRMS m/z found 322.1030 ($[M + H]^+$). with error -1.228ppm



Compound 137. To compound **108** (79mg, 0.116mmol) in 5mL of THF was added TBAF (0.17mL, 0.17mmol) at 0°C. The mixture was stirred at room temperature for 1 hour. LC-MS showed the reaction completed. The reaction mixture was diluted with EtOAc and washed with aqueous saturated NH_4Cl and brine. Organic layer was dried over anhydrous $MgSO_4$. Filtered and concentrated to dryness to give 79mg of crude product (89% purity)

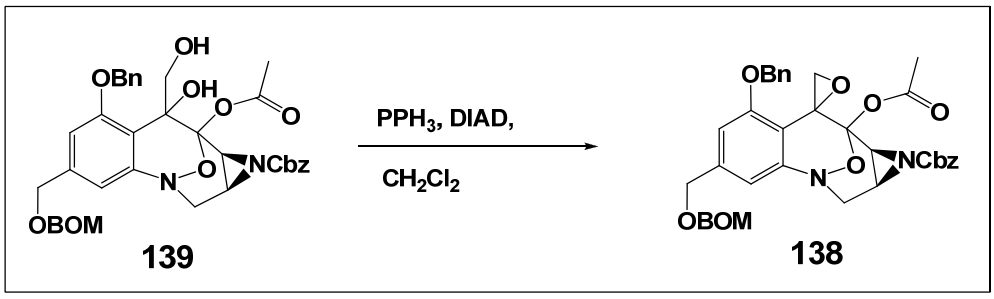
To above crude product in 1mL of dichloromethane was added Et_3N (0.15mL, 1.06mmol) then followed by acetic anhydride (0.060mL, 0.63mmol) and DMAP (5.0mg, 0.041mmol) at room temperature. The reaction mixture was stirred at room

temperature for 48 hours, LC-MS showed the reaction completed. The mixture was diluted with EtOAc and washed with aqueous 0.5M HCl and brine. The organic layer was dried over anhydrous Na_2SO_4. Filtered and concentrated down. Purified by column with 7~40% EtOAc in hexane to give compound **137** (68.1mg, yield 100%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ7.50-7.32 (m, 14H), 7.28-7.24 (m,1H), 6.79 and 6.71 (s, 1H), 6.66 and 6.63 (s, 1H), 6.54 and 6.48 (s, 1H), 5.73 and 5.57 (s, 1H), 5.25-5.08 (m, 3H), 4.88 and 4.87 (s, 2H), 4.69 and 4.68 (s, 2H), 4.63 and 4.62 (s, 2H), 4.18 (q, J=7.25Hz, 1H), 4.04 (t, J=14.82Hz, 1H), 3.81 (d, J=14.82Hz, 0.3H), 3.64 (dd, J=6.31Hz, J=14.82Hz, 0.7H), 3.50 (d, J=6.62Hz, 0.3H), 3.22 (d, J=6.62Hz, 0.7H), 3.00 (d, J=6.62Hz, 0.3H), 2.96 (t, J=6.31Hz, 0.7H), 2.25 and 2.17 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) 167.7, 163.3, 162.2, 158.7, 148.3, 147.0, 142.8, 139.8, 137.0, 136.6, 135.8, 133.5, 129.1, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 117.3, 115.4, 113.1, 112.1, 111.9, 111.4, 107.5, 107.2, 96.7, 95.4, 94.6, 94.5, 71.4, 71.3, 70.1, 69.5, 69.4, 69.2, 68.4, 54.8, 53.9, 51.6, 43.7, 43.6, 38.6, 35.2, 34.2, 22.2, 14.6.

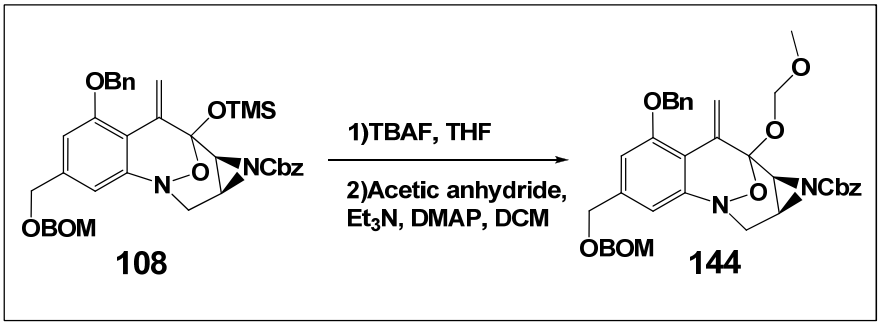


Compound 139. To compound **137** (48mg, 0.074mmol) in 2mL of THF, 0.6mL of acetone, and 0.6mL of water was added 4-methylmorpholine N-oxide (45mg, 0.37mmol) and OsO_4 (92μL, 0.015mmol) at room temperature. The mixture was stirred

at room temperature for 48 hour. LC-MS showed the reaction completed. The reaction quenched by the addition of aqueous $Na_2S_2O_3$ and extracted with EtOAc (2x10mL). The combined organic layer was washed with water and brine. Organic layer was dried over anhydrous $MgSO_4$. Filtered and concentrated down. It was purified by preparative thin-layer chromatography plate (EtOAc/hexane 4:1) to give **139** (46mg, Yield 91%) as a yellow oil. IR: , ^{1}H NMR (500 MHz, $CDCl_3$) δ7.53-7.34 (m, 15H), 6.78 and 6.70 and 6.64 (s, 1H), 6.51 and 6.44 (s, 1H), 5.28-5.23 (m, 1H), 5.21-5.16 (m, 1.5H), 5.15-5.10 (m, 1.5H), 5.03 (t, J=11.98Hz, 1H), 4.90 and 4.88 (s, 1H), 4.87 and 4.84 and 4.83 (s, 1H), 4.81 and 4.79 and 4.78 and 4.75 (s, 1H), 4.69 and 4.68 (s, 2H), 4.63 and 4.61 and 4.60 (s, 2H), 4.18 (q, J=7.25Hz, 2H), 3.91-3.85 (m, 1H), 3.56 (d, J=6.62Hz, 0.3H), 3.43 (s, 0.5H), 3.39 (d, J=6.62Hz, 0.3H), 3.07 and 3.08 (s, 0.4H), 3.04 (t, J=5.99Hz, 0.5H), 2.98 (t, J=6.31Hz, 0.5H), 2.91 (dd, J=2.21Hz, J=6.62Hz, 0.5H), 2.03 and 1.99 and 1.92 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) 158.0, 148.5, 141.3, 140.4, 138.1, 136.5, 136.3, 135.8, 135.7, 129.4, 129.2, 129.0, 128.9, 128.8, 128.7, 128.3, 128.2, 128.1, 112.0, 112.0, 111.8, 111.2, 106.8, 106.2, 94.9, 94.8, 94.7, 94.6, 94.4, 92.3, 73.0, 71.9, 71.8, 71.5, 71.3, 70.2, 69.4, 69.3, 69.2, 66.9, 65.6, 65.2, 60.8, 54.6, 52.4, 51.3, 42.1, 37.6, 37.0, 36.3, 36.1, 33.4, 21.5, 21.4, 21.2, 14.6.

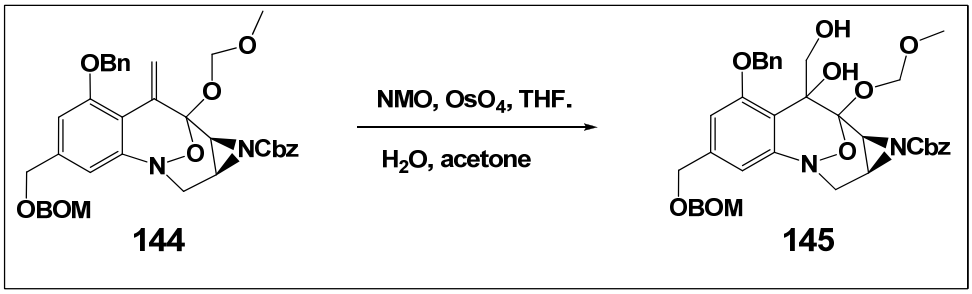


Compound 138. To compound **139** (42mg, 0.062mmol) in 3mL of dichloromethane was added triphenylphosphine (32mg, 0.12mmol) and DIAD (27μL, 0.015mmol) at room temperature under a N_2 atmosphere. The reaction vessel was sealed and stirred in the dark at room temperature for 61 hours. LC-MS showed the reaction almost completed. The reaction mixture was concentrated to remove solvent. The residue was purified by preparative thin-layer chromatography plate (EtOAc/hexane 1:1) to give **138** (32mg, Yield 77%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ7.57-7.34 (m, 15H), 6.73 and 6.70 and 6.67 (s,1H), 6.60 and 6.56 and 6.46 (s, 1H), 5.17-5.05 (m, 3H), 4.89 and 4.87 (s, 2H), 4.75 and 4.73 (s, 1H), 4.70 and 4.68 (s, 2H), 4.65 and 4.64 (s, 1H), 4.62 (s, 1H), 3.91 (d, J=6.31Hz, 0.5H), 3.88 (d, J=6.62Hz, 0.5H), 3.75-3.73 (m, 0.5H), 3.70 (d, J=5.68Hz, 0.5H), 3.18-3.12 (m, 1H), 2.71 (t, J=5.99Hz, 0.5H), 2.04 and 2.03 and 1.97 (s, 3H). ^{13}C NMR (125 MHz, CDCl3) 170.9, 162.7, 159.0, 148.5, 141.3, 140.2, 138.1, 136.3, 135.8, 135.7, 129.4, 129.2, 129.0, 128.9, 128.8, 128.7, 128.3, 128.2, 128.1, 112.0, 111.8, 107.0, 106.9, 106.1, 94.9, 94.8, 94.6, 94.4, 92.3, 73.0, 71.9, 71.8, 71.5, 71.3, 70.2, 70.1, 69.4, 69.3, 69.2, 69.1, 65.6, 65.2, 60.8, 54.6, 52.4, 51.3, 42.1, 37.6, 37.0, 36.3, 36.1, 33.4, 21.5, 21.4, 14.6.



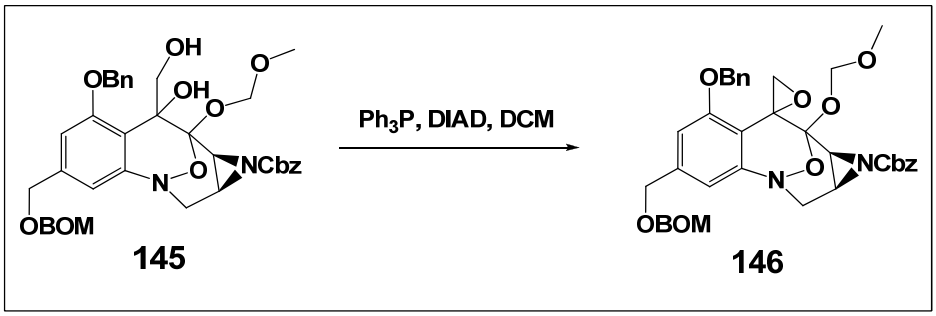
Compound 144. To compound **108** (37mg, 0.054mmol) in 2mL of THF was added TBAF (0.081mL, 0.081mmol) at 0°C. The mixture was stirred at room temperature for 1 hour. LC-MS showed the reaction completed. The reaction mixture was diluted with EtOAc and washed with aqueous saturated NH_4Cl and brine. Organic layer was dried over anhydrous $MgSO_4$. Filtered and concentrated to dryness to give 41mg of crude product (87% purity)

To above crude product in 1mL of dichloromethane was added DIPEA (0.072mL, 0.43mmol) then followed by methyl chloromethyl ether (0.060mL, 0.63mmol) at room temperature. The reaction mixture was stirred at room temperature for 7 days, LC-MS showed the reaction completed. The mixture was poured into brine and extracted with CH_2Cl_2 x 2.. The organic layer was dried over anhydrous Na_2SO_4. Filtered and concentrated down. Purified by column with 10~40% EtOAc in hexane to give compound **144** (25mg, yield 70%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ7.47-7.27 (m, 15H), 6.73 and 6.72 (s, 1H), 6.68 and 6.65 (s, 1H), 6.49 and 6.47 (s, 1H), 6.02 and 5.92 (s, 1H), 5.21-5.08 (m, 4H), 5.05 and 5.04 (s, 1H), 4.83 (s, 2H), 4.64 (s, 2H), 4.58 and 4.57 (s, 2H), 4.12 (q, J=7.03Hz, 0.5H), 3.96-3.89 (m, 1H), 3.56 (d, J=5.47Hz, 0.5H), 3.53 (d, J=6.25Hz, 0.5H), 3.51 (s, 0.5H), 3.47 (s, 2H), 2.86-2.76 (m, 2H), 2.05 (s, 1H). ^{13}C NMR (125 MHz, CDCl3) 161.9, 158.4, 146.8, 139.0, 136.1, 135.5, 135.1, 134.4, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.8, 127.6, 116.3, 111.9, 106.7, 94.4, 94.1, 92.0, 70.9, 69.7, 68.9, 68.5, 56.6, 53.2, 38.4, 34.3, 20.4, 14.2.



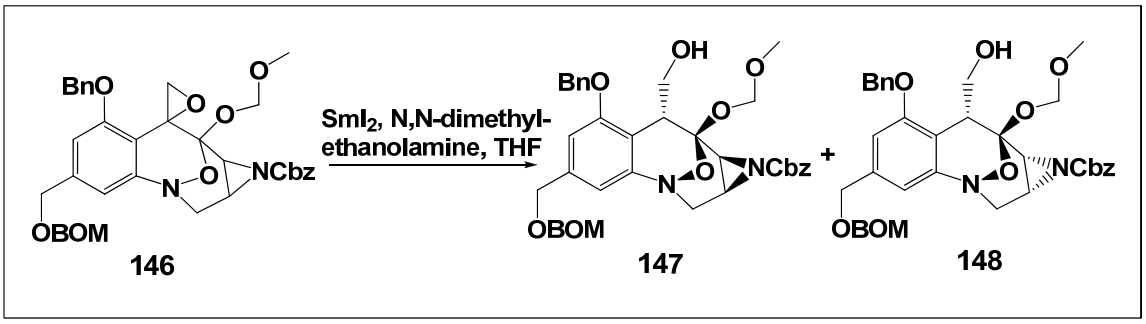
Compound 145. To compound **144** (20mg, 0.031mmol) in 1mL of THF, 0.3mL of acetone, and 0.3mL of water was added 4-methylmorpholine N-oxide (37mg, 0.31mmol) and OsO_4 (79μL, 0.012mmol) at room temperature. The mixture was stirred at room temperature for 48 hour. LC-MS showed the reaction completed. The reaction quenched by the addition of aqueous $Na_2S_2O_3$ and extracted with EtOAc (2x10mL). The combined organic layer was washed with water and brine. Organic layer was dried over anhydrous $MgSO_4$. Filtered and concentrated down. It was purified by preparative thin-layer chromatography plate (EtOAc/hexane 4:1) to give **145** (18mg, Yield 85%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ7.52-7.27 (m, 15H), 6.75 and 6.72 (s, 1H), 6.51 and 6.44 (s, 1H), 5.36 and 5.34 (s, 1H), 5.25 and 5.23 (s, 1H), 5.21-5.18 (s,1H), 5.14 (s, 2H), 5.09 and 5.06 (s, 1H), 4.89 and 4.83 (s, 2H), 4.63 and 4.62 (s, 2H), 4.58 and 4.56 (s, 2H), 4.41 (dd, J=5.47Hz, J=12.50Hz, 1H), 4.18 (t, J=9.38Hz, 1H), 4.11 (d, J=7.04Hz, 1H), 3.86(d, J=2.35Hz, 0.5H), 3.82 (d, J=1.56Hz, 0.5H), 3.63 (d, J=6.25Hz, 0.5H), 3.59 (d, J=6.25Hz, 0.5H), 3.43 and 3.41 (s, 3H), 3.37 (d, J=6.25Hz, 1H), 3.33 (s, 1H), 2.85 (t, J=7.04Hz, 1H), 2.20 (dd, J=5.47Hz, J=9.38Hz, 1H). ^{13}C NMR (125 MHz, CDCl3) 161.9, 158.0, 149.6, 149.3, 148.8, 148.3, 141.89, 140.3, 137.6, 135.8, 135.2, 128.8, 128.6, 128.5, 128.2, 127.9, 127.8, 115.6, 112.7,

107.8, 95.0, 94.2, 92.2, 72.3, 71.8, 69.7, 68.9, 68.8, 68.7, 63.8, 60.4, 56.7, 53.9, 34.9, 31.2, 21.1, 14.2.



Compound 146. To compound **145** (18mg, 0.026mmol) in 1mL of dichloromethane was added triphenylphosphine (10mg, 0.039mmol) and DIAD (8μL, 0.040mmol) at room temperature under a N_2 atmosphere. The reaction vessel was sealed and stirred in the dark at room temperature for 61 hours. LC-MS showed the reaction almost completed. The reaction mixture was concentrated to remove solvent. The residue was purified by preparative thin-layer chromatography plate (EtOAc/hexane 1:1) to give **146** (8mg, Yield 75%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ7.55-7.29 (m, 15H), 6.71 and 6.68 (s, 1H), 6.54 and 6.51 and 6.44 (s, 1H), 5.47 (d, J=5.68Hz, 0.5H), 5.26-5.23 (m, 1H), 5.21-5.20 (s, 2H), 5.15 and 5.14 (s, 0.5H), 5.14 (d, J=2.21Hz, 0.3H), 5.07-5.04 (m, 0.7H), 5.03-4.98 (m, 0.5H), 4.86 and 4.84 (s, 2H), 4.67 and 4.65 (s, 1H), 4.63 (d, J=2.52Hz, 1H), 4.60 and 4.57 (s, 2H), 4.42-4.36 (m, 0.7H), 4.35-4.30 (m, 0.5H), 4.15 (q, J=6.94Hz, 0.3H), 3.84 (d, J=2.52Hz, 0.3H), 3.83 (d, J=2.52Hz, 0.3H), 3.75 (d, J=6.94Hz, 0.5H), 3.73 (d, J=6.62Hz, 0.2H), 3.70 (d, J=6.31Hz, 0.3H), 3.57 and 3.48 and 3.45 (s, 3H), 3.17-3.11 (m, 0.7H), 2.91-2.86 (m, 0.8H), 2.77 (d, J=6.62Hz, 0.2H), 2.07 (s, 0.3H). ^{13}C NMR (125 MHz, CDCl3) 162.2,

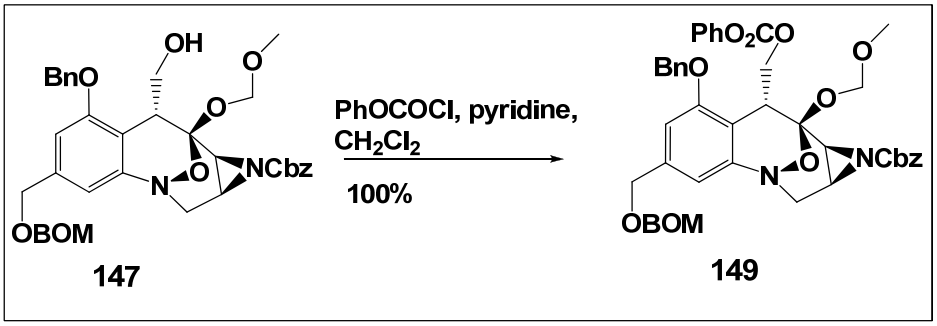
158.4, 148.4, 141.2, 141.1, 138.0, 136.8, 135.6, 129.1, 129.9, 128.9, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 127.6, 113.7, 112.4, 111.1, 110.8, 107.9, 107.6, 96.0, 94.7, 94.6, 94.5, 93.2, 92.5, 92.0, 71.6, 71.2, 70.9, 70.1, 69.9, 69.2, 69.0, 65.4, 57.4, 56.8, 56.5, 55.6, 54.4, 54.0, 53.9, 48.1, 42.0, 36.9, 35.9, 35.8, 35.1, 22.4.



Compound 147 and 148. To compound **146** (4mg, 0.006mmol) in 0.5mL of THF at -78°C was added N,N-dimethylethanolamine (9μL, 0.09mmol) , then followed by SmI_2 (0.12mL, 0.012mmol) dropwise under a N_2 atmosphere. The reaction mixture was stirred at -78°C for 30 minutes. LC-MS indicated that product generated, but also had dehydration by-product. The reaction was quenched by aqueous 1M HCl and extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. Filtered and concentrated down. The residue was purified by preparative thin-layer chromatography plate (EtOAc/hexane 1:1) to give **147** (1.4mg) and **148** (1mg) (total Yield 60%) as a yellow film. **147**: ^{1}H NMR (500 MHz, $CDCl_3$) δ7.54-7.29 (m, 15H), 6.78 and 6.67 (s, 1H), 6.54 and 6.45 (s, 1H), 5.28-5.20 (m, 2H), 5.13-5.06 (m, 2H), 5.05-4.98 (m, 2H), 4.90 (d, J=7.57Hz, 1H), 4.86 (s, 2H), 4.66 (s, 2H), 4.59 (s, 2H), 4.21 (dd, J=5.36Hz, J=12.61Hz, 1H), 4.18-4.13 (m, 1H), 3.91 (dd, J=2.52Hz, J=14.82Hz, 1H), 3.83 and 3.80 (s, 1H), 3.55 (d, J=6.31Hz, 1H), 3.53 (s, 3H),

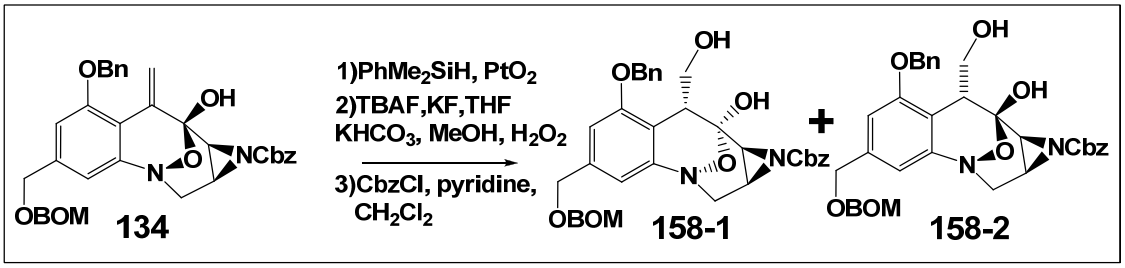
3.46-3.39 (m, 2H), 2.82 (dd, J=2.21Hz, J=6.94Hz, 1H). ^{13}C NMR (125 MHz, CDCl3) 157.2, 137.3, 129.4, 129.3, 129.2, 129.1, 94.5, 91.8, 71.5, 70.0, 69.7, 68.9, 62.3, 56.7, 52.2, 47.9, 42.0, 34.6, 33.3, 30.1.

148: ^{1}H NMR (500 MHz, $CDCl_3$) δ7.45-7.21 (m, 15H), 6.62 (s, 1H), 6.53 (s, 1H), 5.07-4.99 (m, 2H), 4.96 (d, J=3.91Hz, 2H), 4.75 (s, 2H), 4.62 (d, J=10.16Hz, 1H), 4.56 (s, 3H), 4.52 (s, 4H), 3.89 (d, J=10.94Hz, 1H), 3.67 (s, 2H), 3.30-3.23 (m, 1H), 3.21 (s, 3H), 2.56 (d, J=14.07Hz, 1H). ^{13}C NMR (125 MHz, CDCl3) 154.8, 152.6, 148.4, 131.2, 129.0, 128.9, 128.8, 128.4, 128.3, 128.2, 127.9, 127.7, 127.4, 97.2, 95.8, 94.5, 73.3, 72.2, 70.9, 70.6, 70.1, 69.4, 67.8, 67.5, 56.3, 55.8, 55.6, 51.1, 39.3, 38.1, 37.9, 30.1.



Compound 149. To compound **147** (1mg, 0.0015mmol) in 0.1mL of dichloromethane at -78°C was added pyridine (0.5μL, 0.006mmol) , then followed by phenyl chloroformate (0.38μL, 0.003mmol) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for three hours. LC-MS indicated that the reaction completed. The reaction mixture was diluted by EtOAc, then washed with aqueous 1M HCl and brine. The organic layer was dried over anhydrous $MgSO_4$. Filtered and concentrated to dryness to give **149** (1.2mg, Yield 100%) as a yellow film. **147**: ^{1}H NMR (500 MHz, $CDCl_3$) δ7.41-7.06 (m, 20H), 6.48 (s, 1H), 6.33 (s, 1H), 5.25

(d, J=7.03Hz, 1H), 4.99-4.97 (m, 3H), 4.95 (s, 1H), 4.77 (d, J=7.03Hz, 2H), 4.74 (s, 2H), 4.55 (s, 2H), 4.47 (s, 2H), 4.05 (q, J=7.82Hz, 1H), 3.85 (d, J=2.35Hz, 0.5H), 3.80 (d, J=5.47Hz, 0.5H), 3.78 (s, 1H), 3.63 (d, J=6.25Hz, 1H), 3.49 (s, 3H), 2.78 (dd, J=1.56Hz, J=6.25Hz, 1H). ^{13}C NMR (125 MHz, CDCl3) 152.5, 151.4, 143.3, 136.9, 136.6, 130.0, 129.8, 129.1, 129.0, 128.9, 128.8, 128.7, 128.3, 128.2, 127.8, 126.7, 121.5, 121.3, 96.4, 94.4, 92.0, 74.8, 70.9, 70.0, 69.6, 69.2, 68.9, 66.3, 66.2, 62.0, 61.9, 46.6, 30.1.



Racemic 158-1 and Racemic 158-2. To a solution of compound **134** (5mg, 0.0082mmol) in toluene (2.1mL) at room temperature was added dimethylphenylsilane (7.7mg, 0.049mmol) and PtO_2 (0.36mg, 0.0016mmol). The mixture was heated at 55°C for 24 hours, MS showed the reaction almost completed. It was filtered and concentrated to dryness to give a crude product.

To above crude product in anhydrous THF (0.2mL) was added TBAF (0.013mL, 0.013mmol). The mixture was stirred at room temperature for 1 hours, then KF (1.5mg, 0.026mmol) and KHCO3 (6.5mg, 0.065mmol) were added, followed by MeOH (0.1mL), and H_2O_2 (0.010mL, 0.086mmol). The mixture was stirred at 58°C for 2hrs. After cooled down, the mixture was diluted with EtOAc (2mL) and washed with water

and brine. The organic layer was dried over anhydrous Na_2SO_4, then filtered and concentrated to dryness to give 4mg of a diol with Cbz cleaved crude product.

To above crude product in anhydrous 1mL of DCM was added pyridine (1mg, 0.013mmol) at 0°C, followed by benzyl chloroformate (0.7mg, 0.0043mmol) in 0.1 mL of DCM dropwise. MS showed the reaction completed after 30min. It was concentrated down and purified by preparative thin-layer chromatography plate(Ethyl acetate/hexane 1:1) to give **158-1** (0.5mg) and **158-2** (1.1mg) overall yield of 32%. ^{1}H NMR (500 MHz, $CDCl_3$) **158-1:** δ7.68-7.22 (m, 15H), 6.54 (s, 1H), 6.31 (s, 1H), 5.02 (s, 2H), 4.76 (s, 2H), 4.57 (s, 2H), 4.50 (s, 2H), 4.18-4.10 (m, 1H), 4.08-4.02 (m, 1H), 3.88-3.82 (m, 1H), 3.77-3.71 (m, 1H), 3.63-3.57(m, 1H), 3.24-3.14 (m, 1H), 2.81-2.76 (m, 1H), 2.57-2.52 (m, 1H). MS (ESI) m/z 625 ($[M + H]^+$).

^{1}H NMR (500 MHz, $CDCl_3$) **158-2:** δ7.39-7.20 (m, 15H), 6.65 (s, 1H), 6.36 (s, 1H), 5.11 (s, 2H), 5.08-4.98 (m, 2H), 4.77 (s, 2H), 4.56 (s, 2H), 4.50 (s, 2H), 4.42 (s, 1H), 3.85-3.68 (m, 2H), 3.63 (s, 1H), 3.54 (d, J=6.25Hz, 1H), 3.51 (d, J=6.25Hz, 1H), 2.94-2.91 (m, 1H), 2.78 and 2.76(s, 1H). ^{13}C NMR (125 MHz, CDCl3). MS (ESI) m/z 625 ($[M + H]^+$).

XIII Reference

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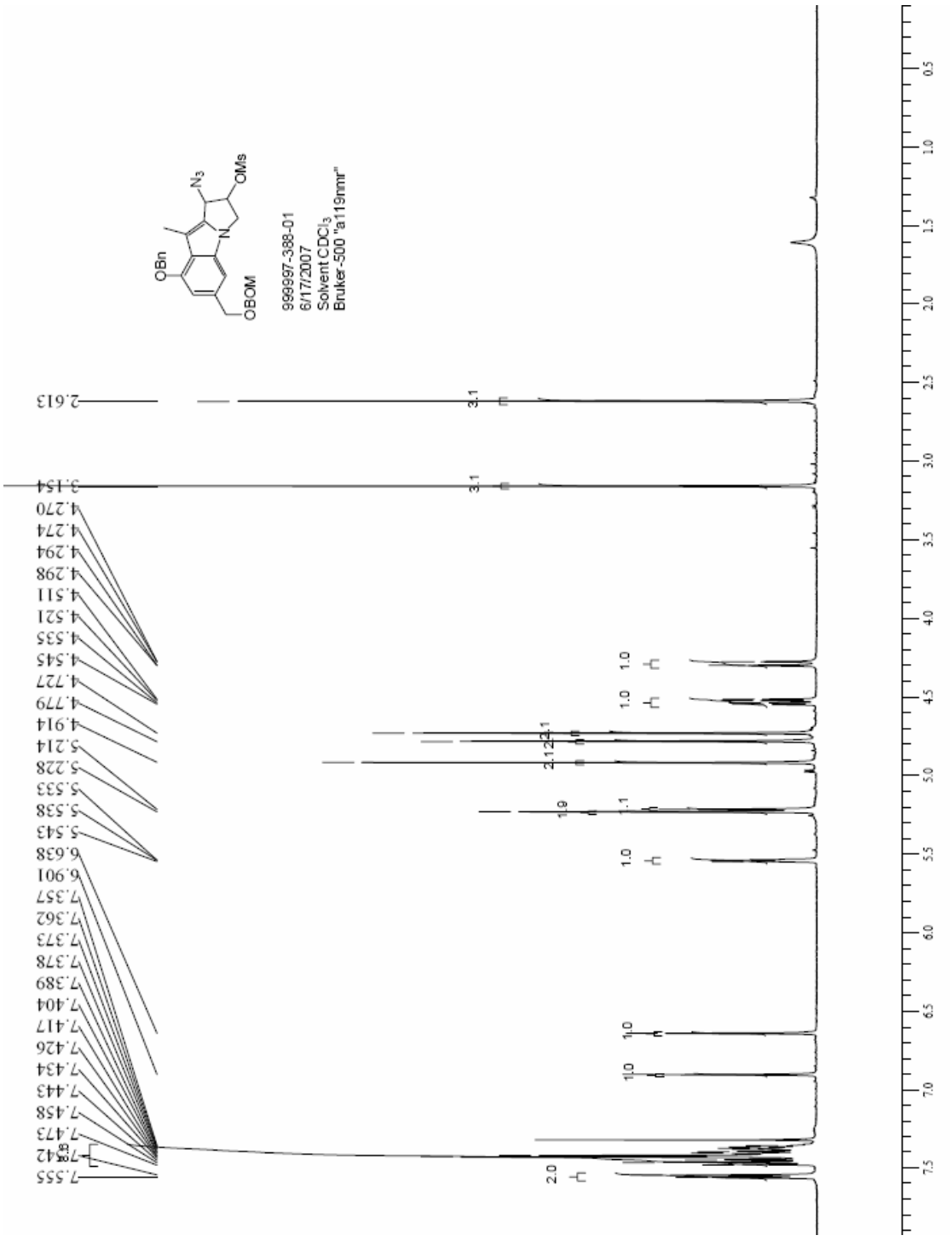
M. Spectra

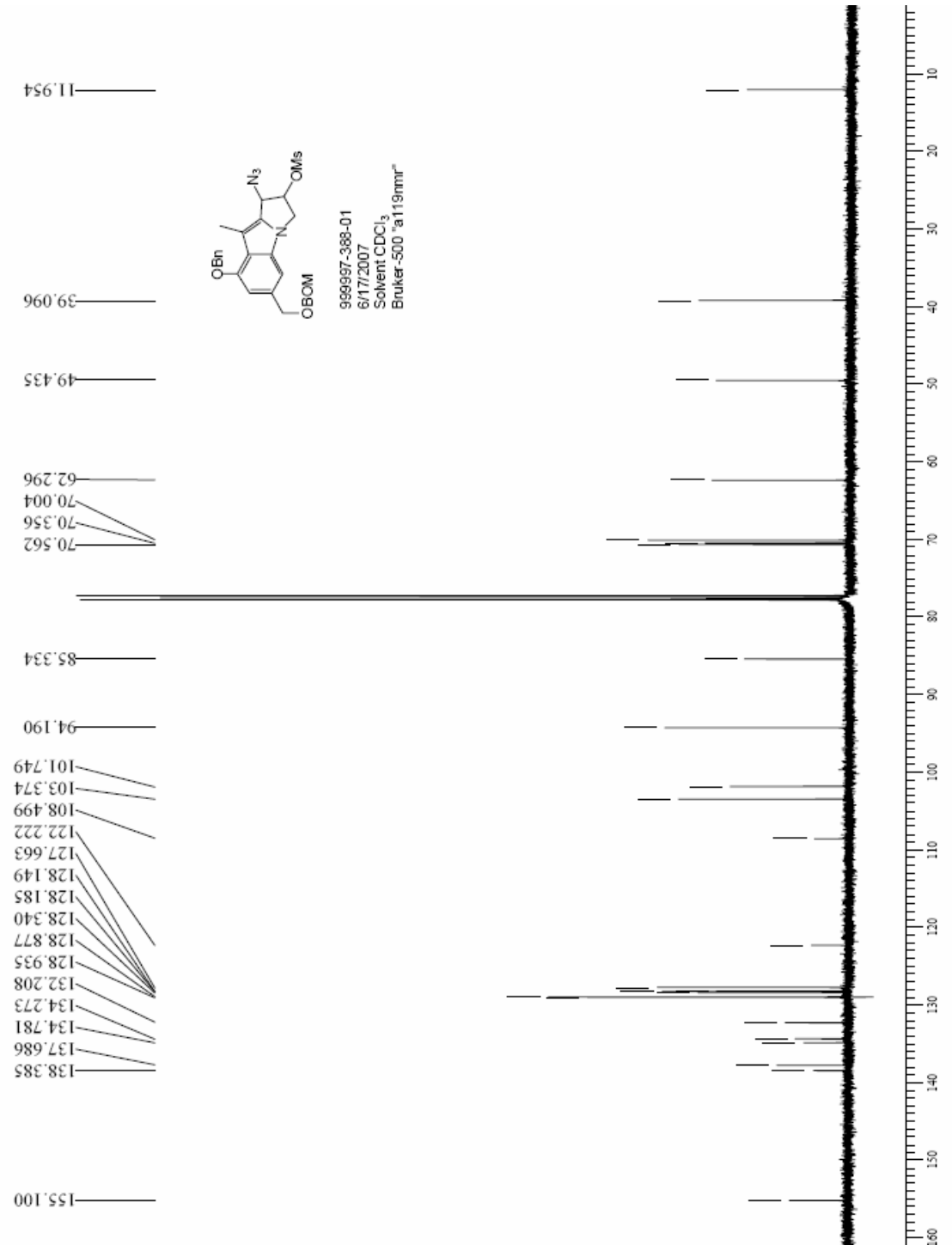
Compound #	Page# (^{1}HNMR)	Page# (^{13}CNMR)	Compound #	Page# (^{1}HNMR)	Page# (^{13}CNMR)
70	102	103	106-2	126	127
71	104	105	107-1	128	129
75	106	107	107-2	130	131
76	108	109	108-1	132	133
77	109	111	108-2	134	135
78	112	113	111-1	136	137
79	114	115	111-2	138	139
80	116	117	112-1	140	141
81	118	119	112-2	142	143
82	120	121	137	144	145
83	122	123	139	146	147
106-1	124	125	144	148	149

Compound #	Page# (^{1}HNMR)	Page# (^{13}CNMR)	Compound #	Page# (^{1}HNMR)	Page# (^{13}CNMR)
145	150	151	7- Epi-FR 66979-1	162	163
146	152	153	7-Epi-FR 66979-2	164	165
147	154	155	7-Epi-FR 900482-2	166	167
148	156	157	158-1	168	
149	158	159	158-2	169	
156	160	161			

Compound **70** HNMR



Compound **70** C^{13}NMR



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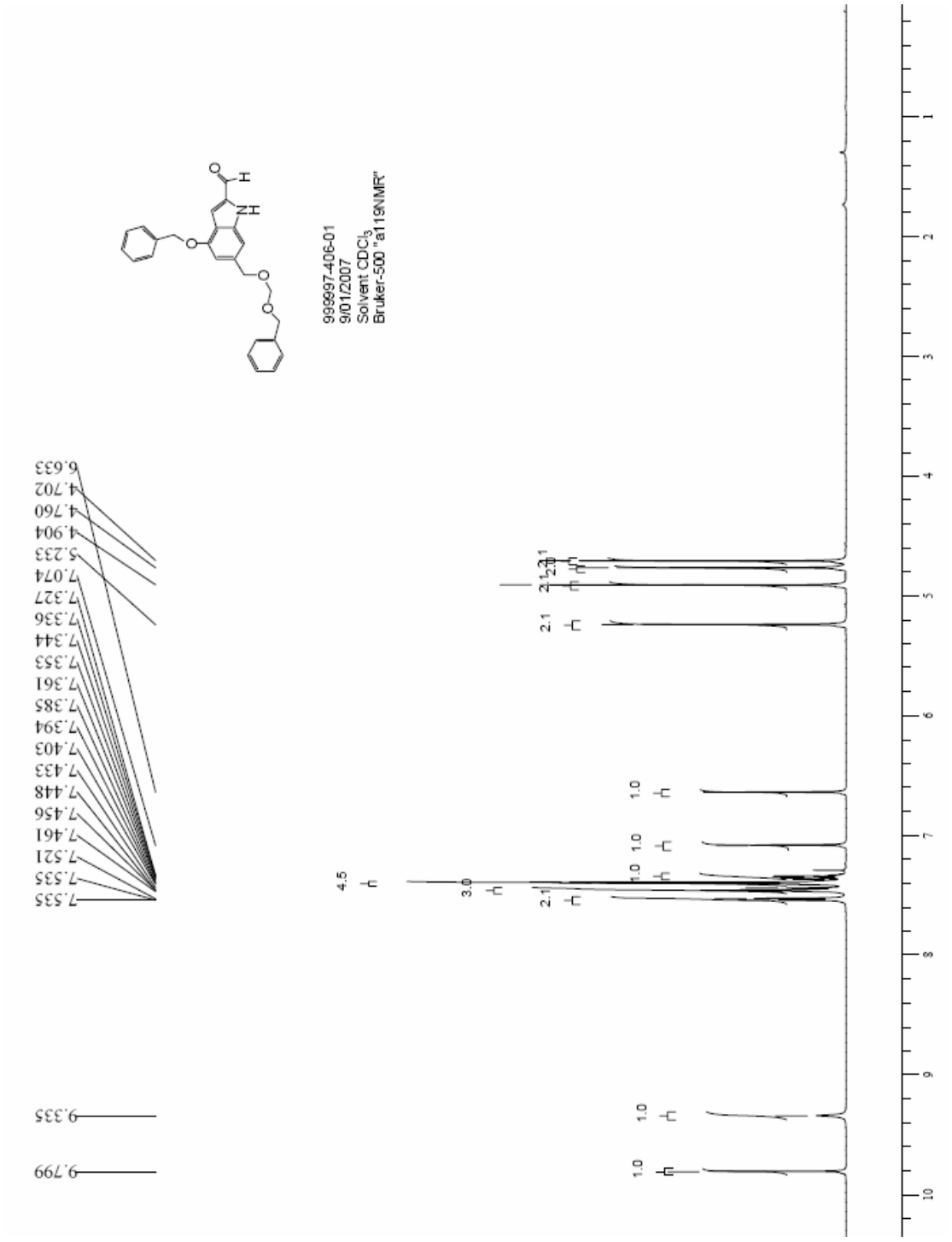

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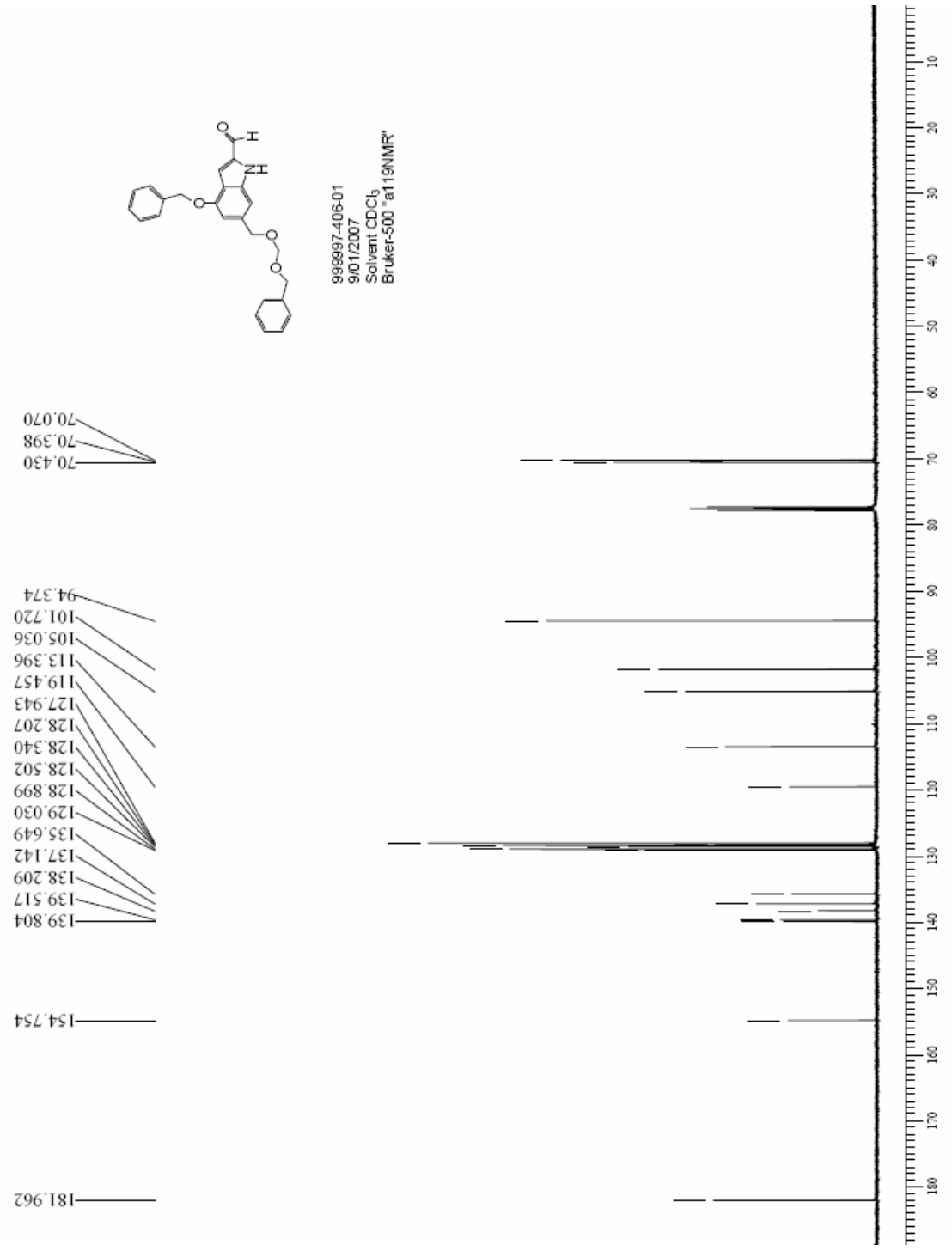

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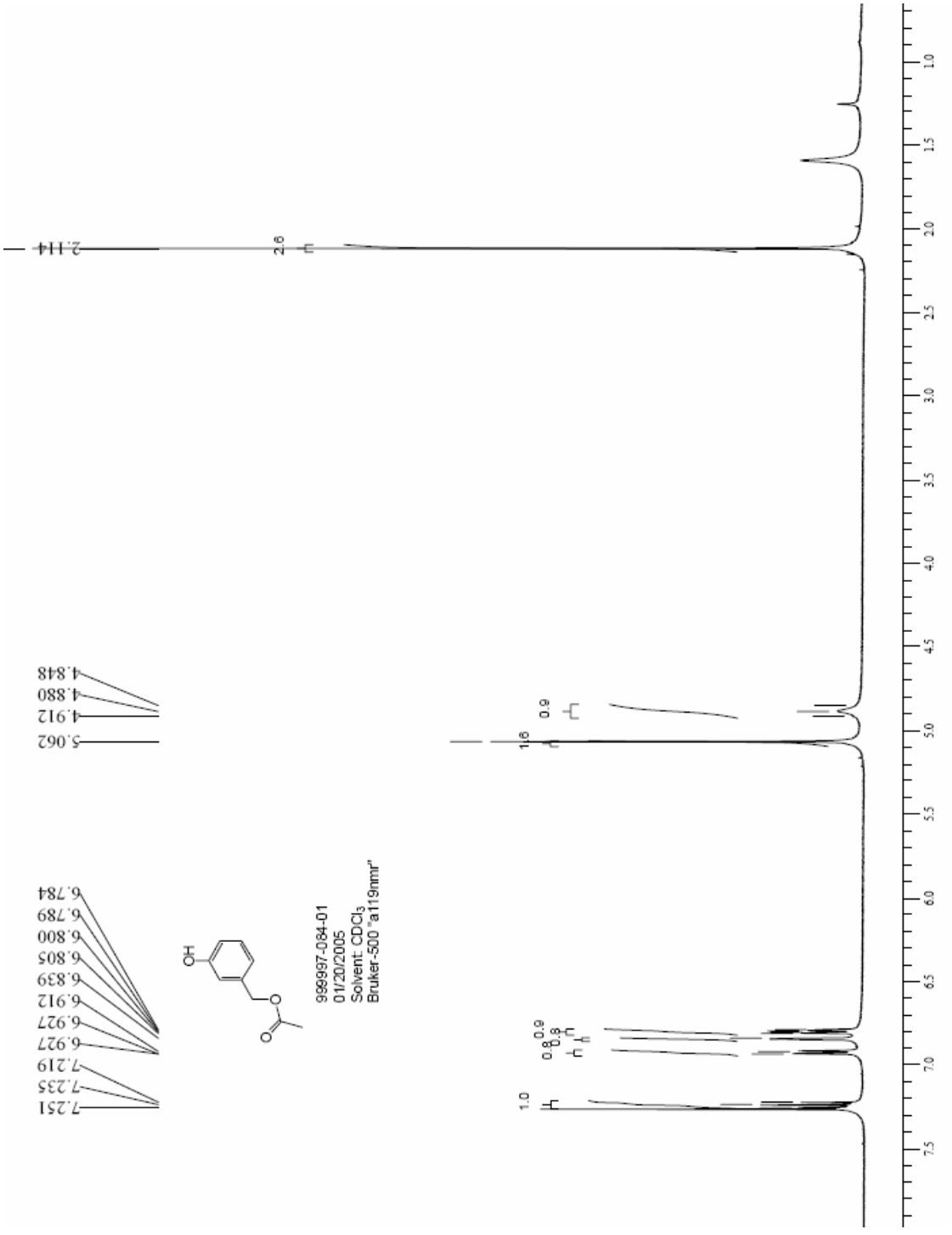
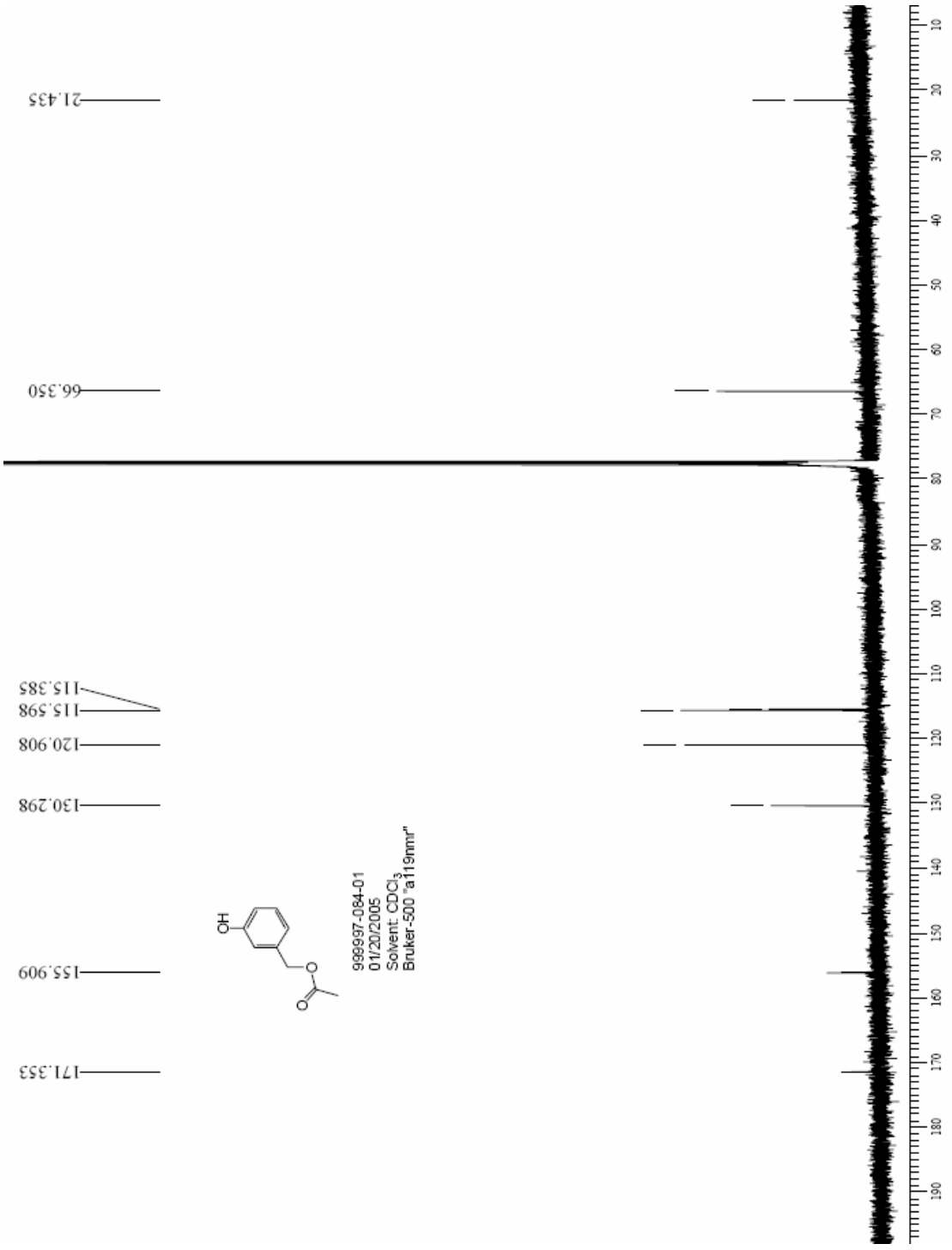


Compound **75** C^{13}NMR



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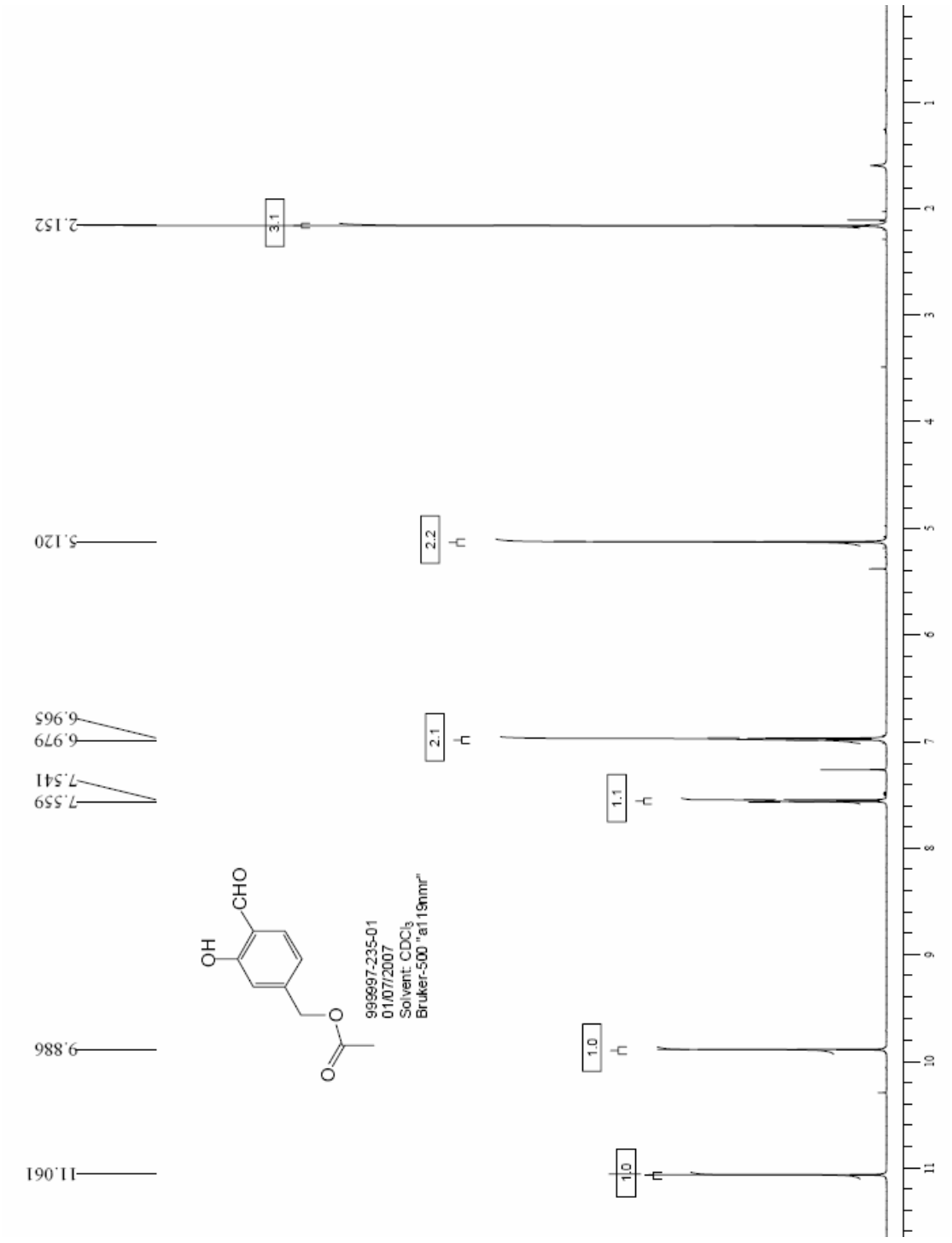

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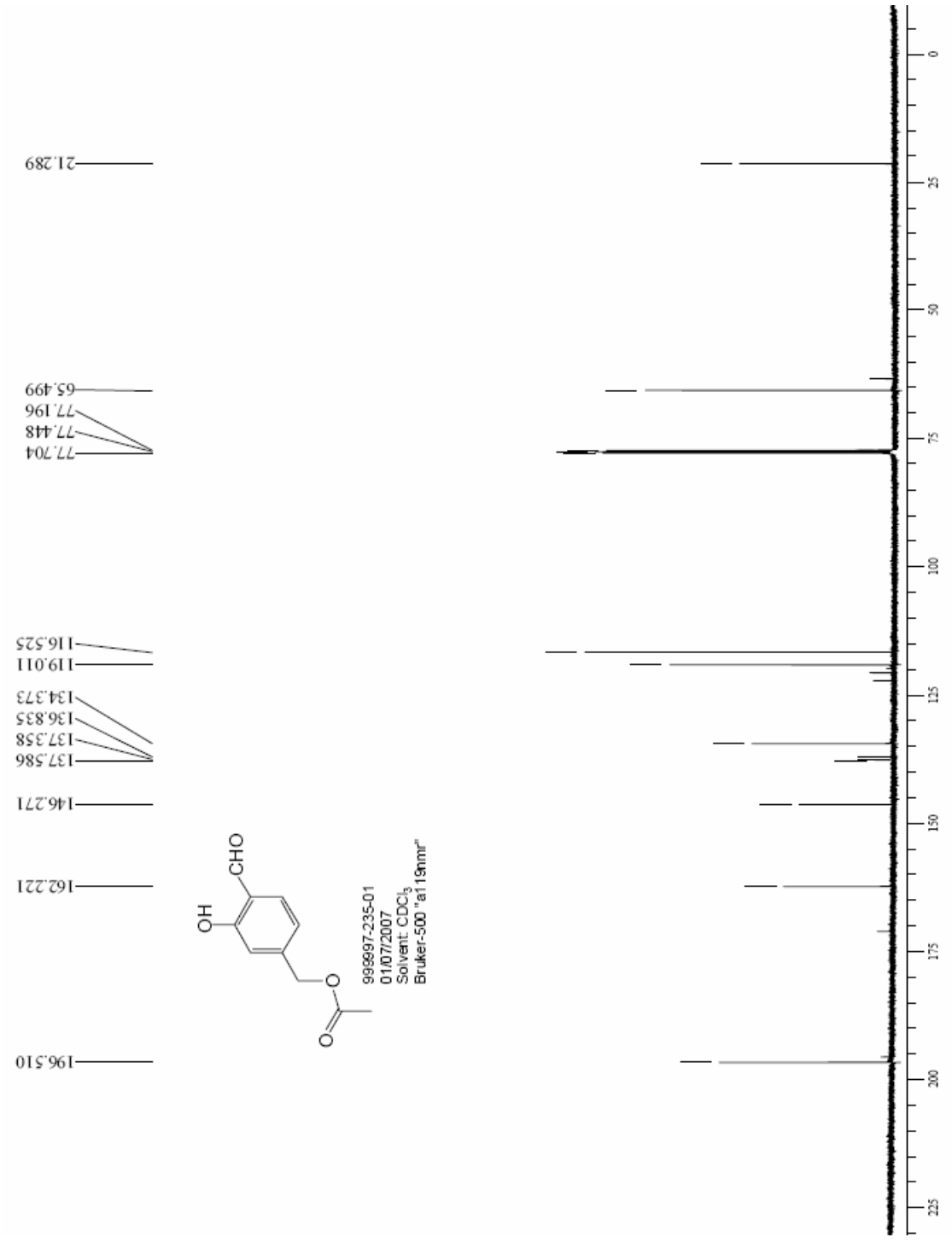

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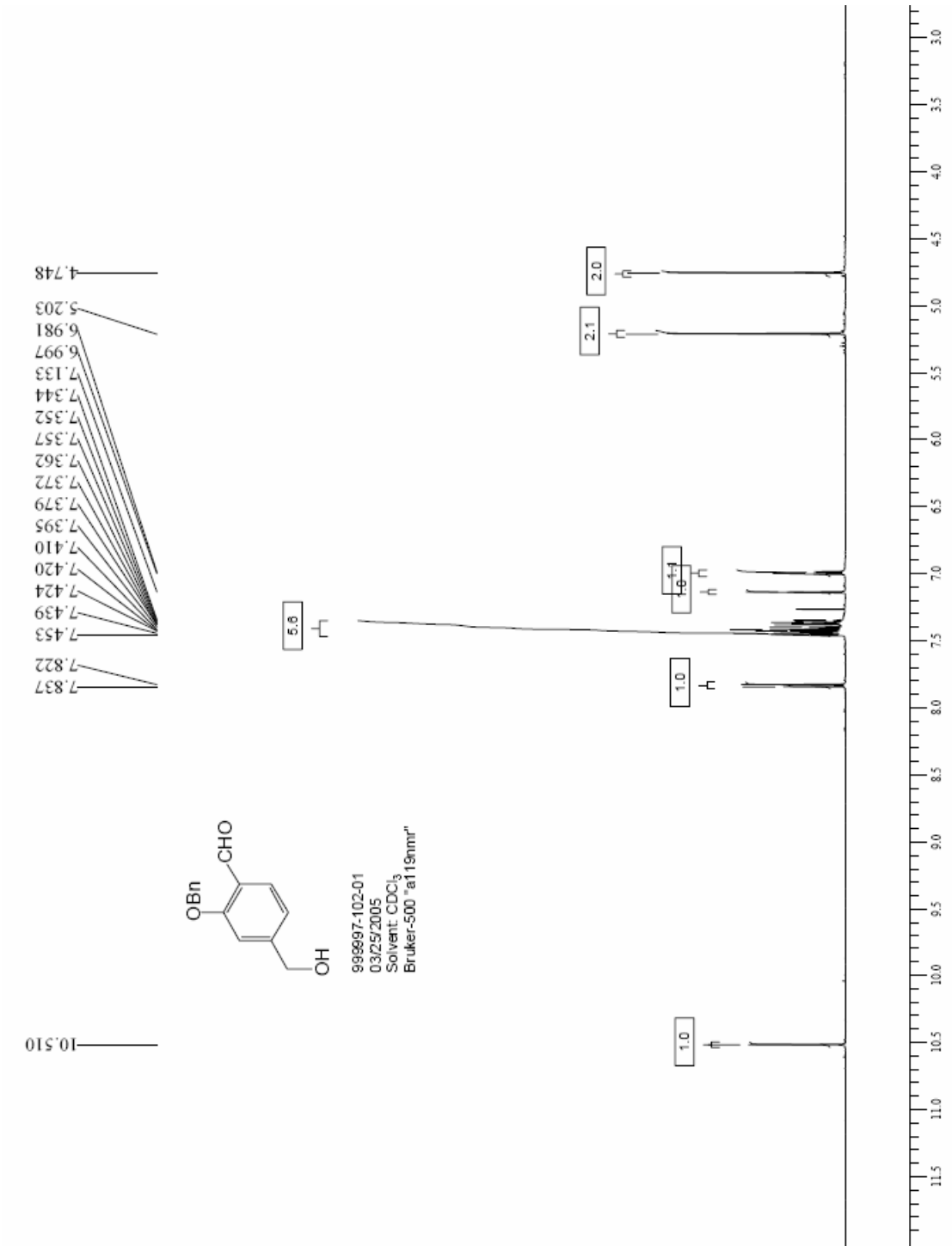

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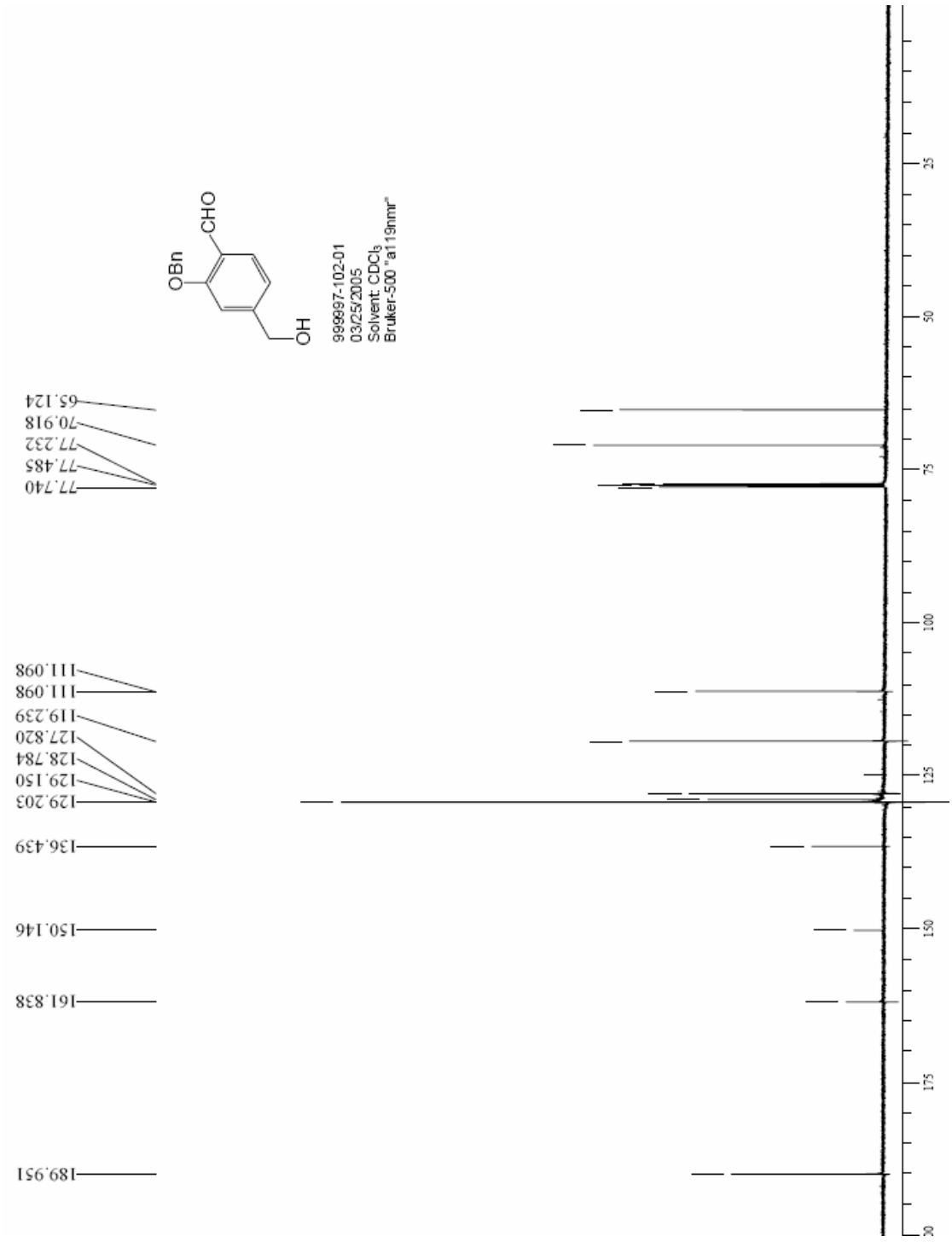

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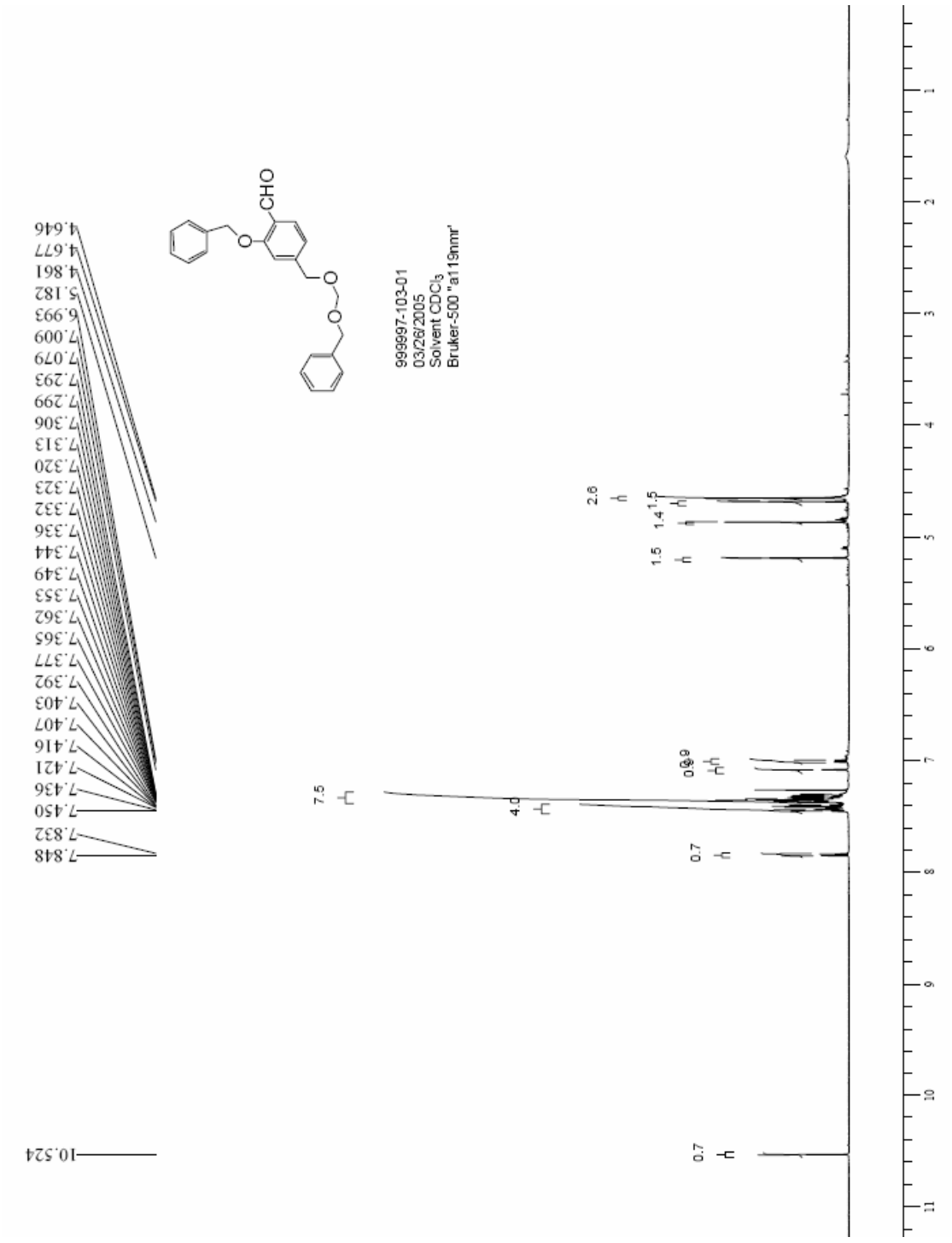

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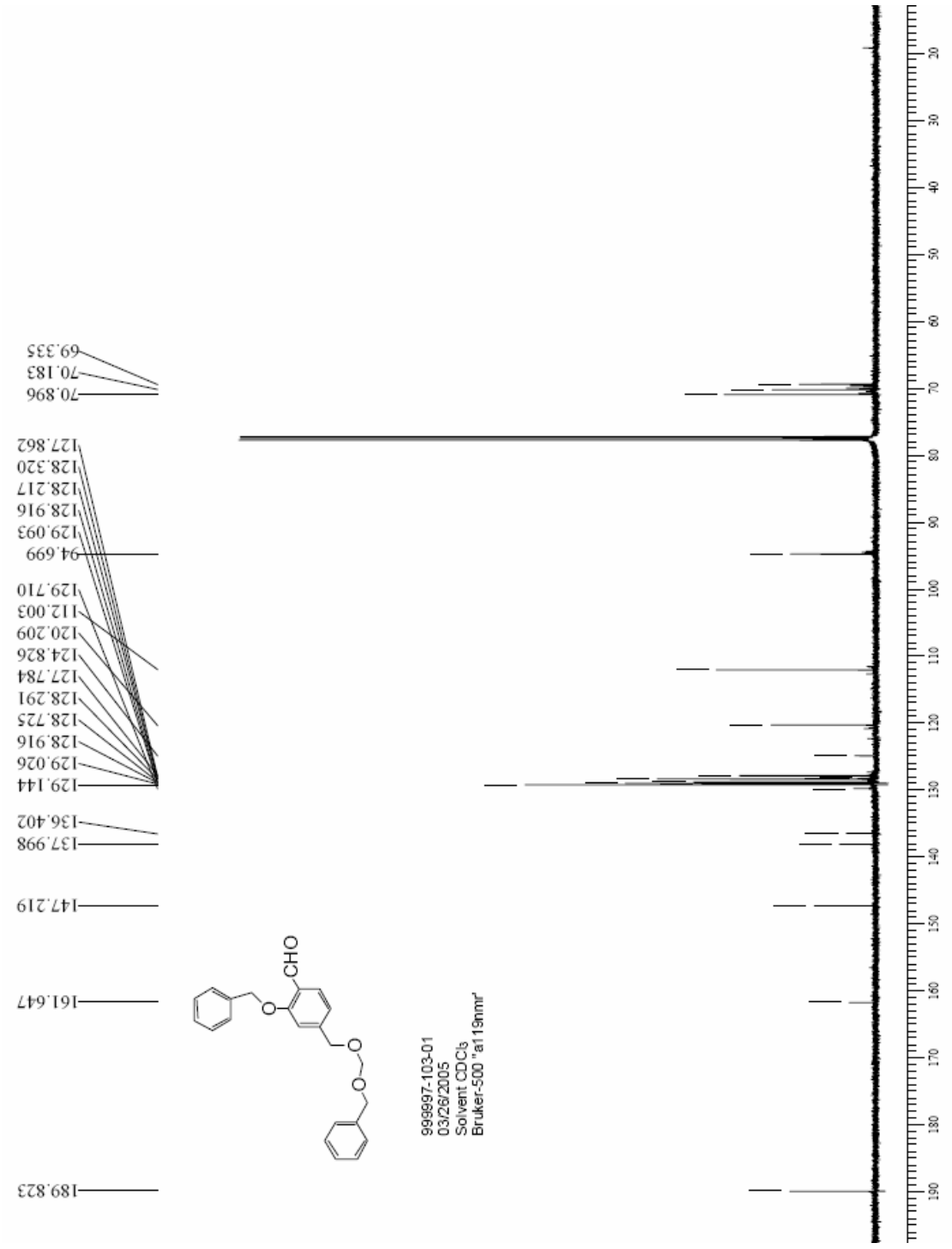

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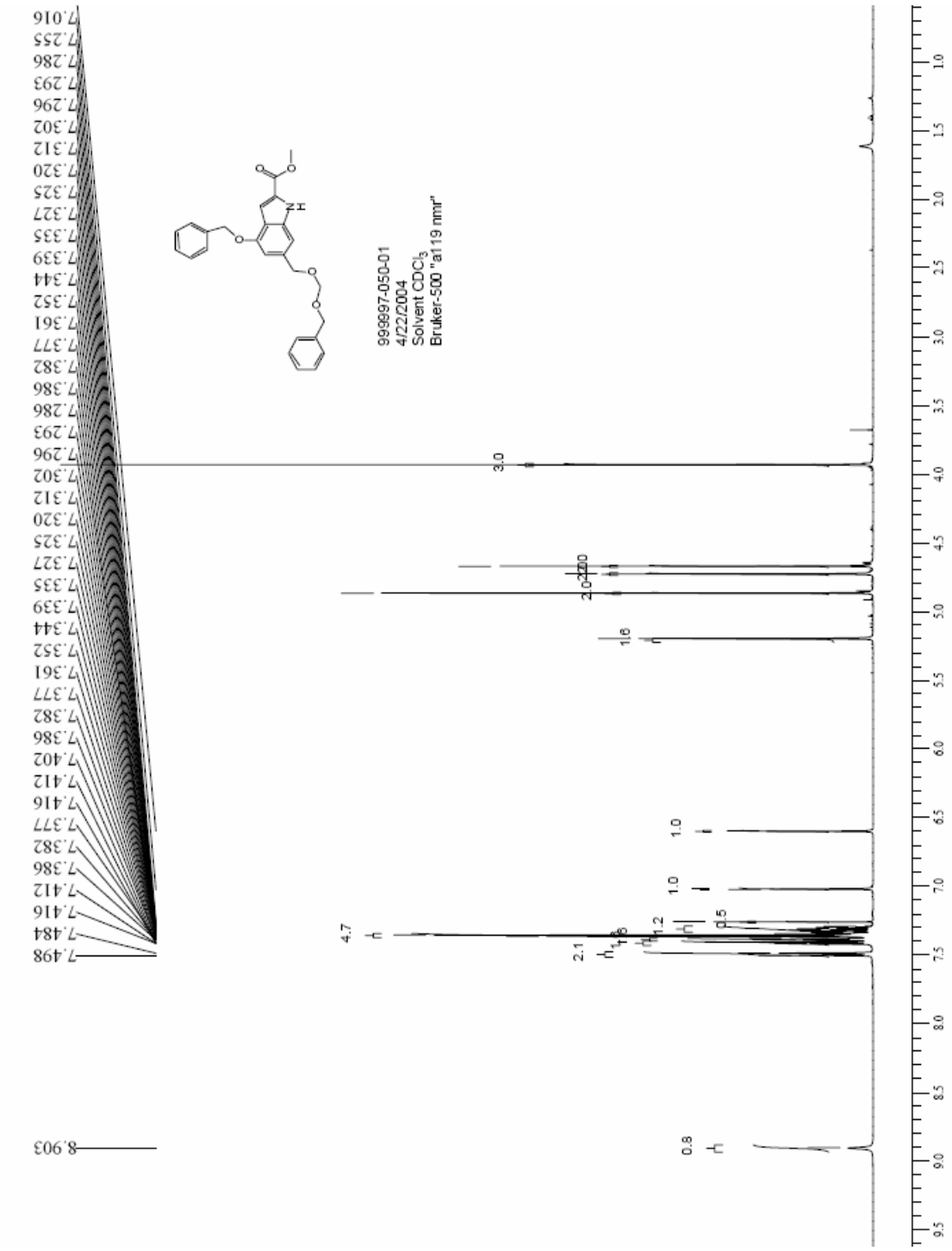

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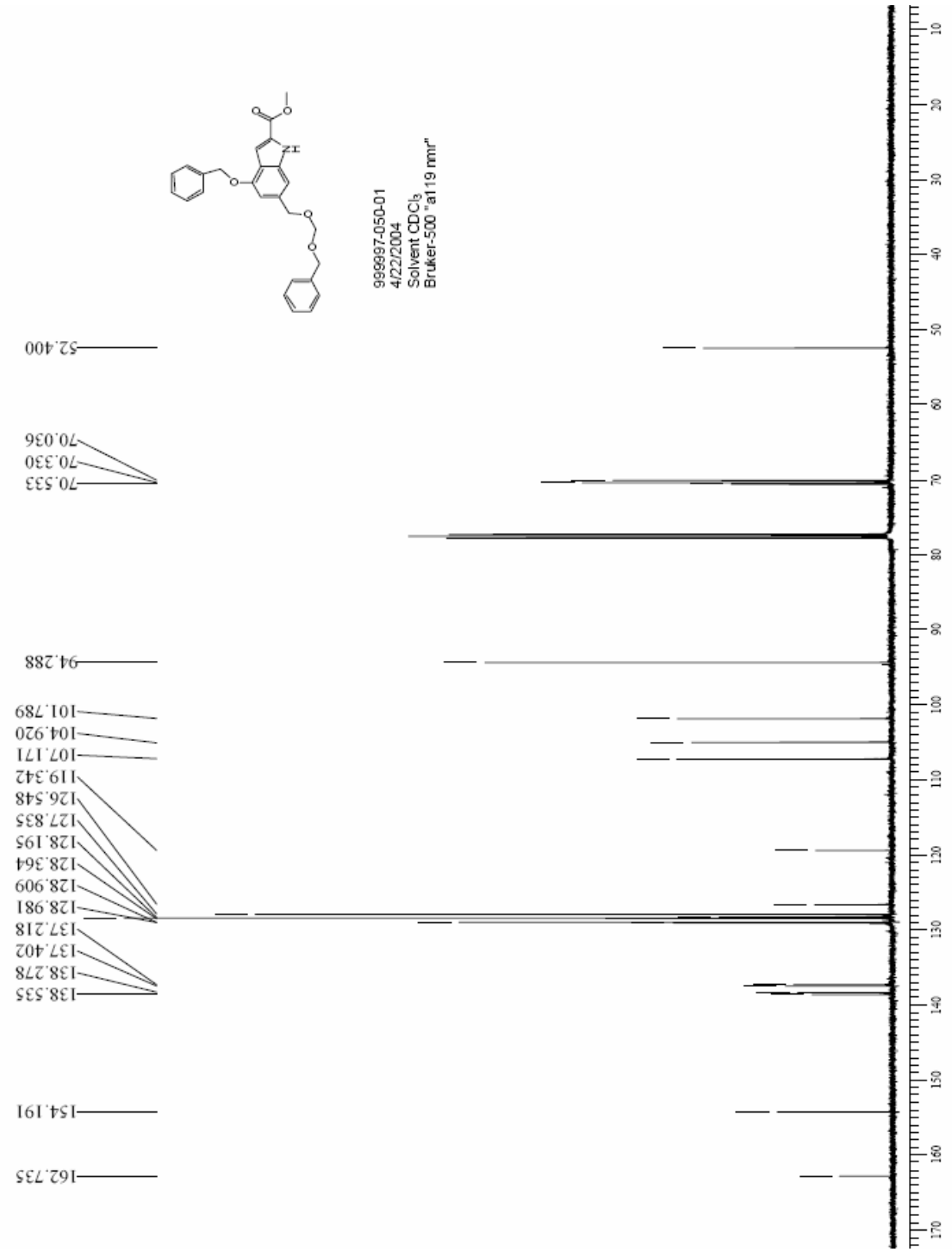

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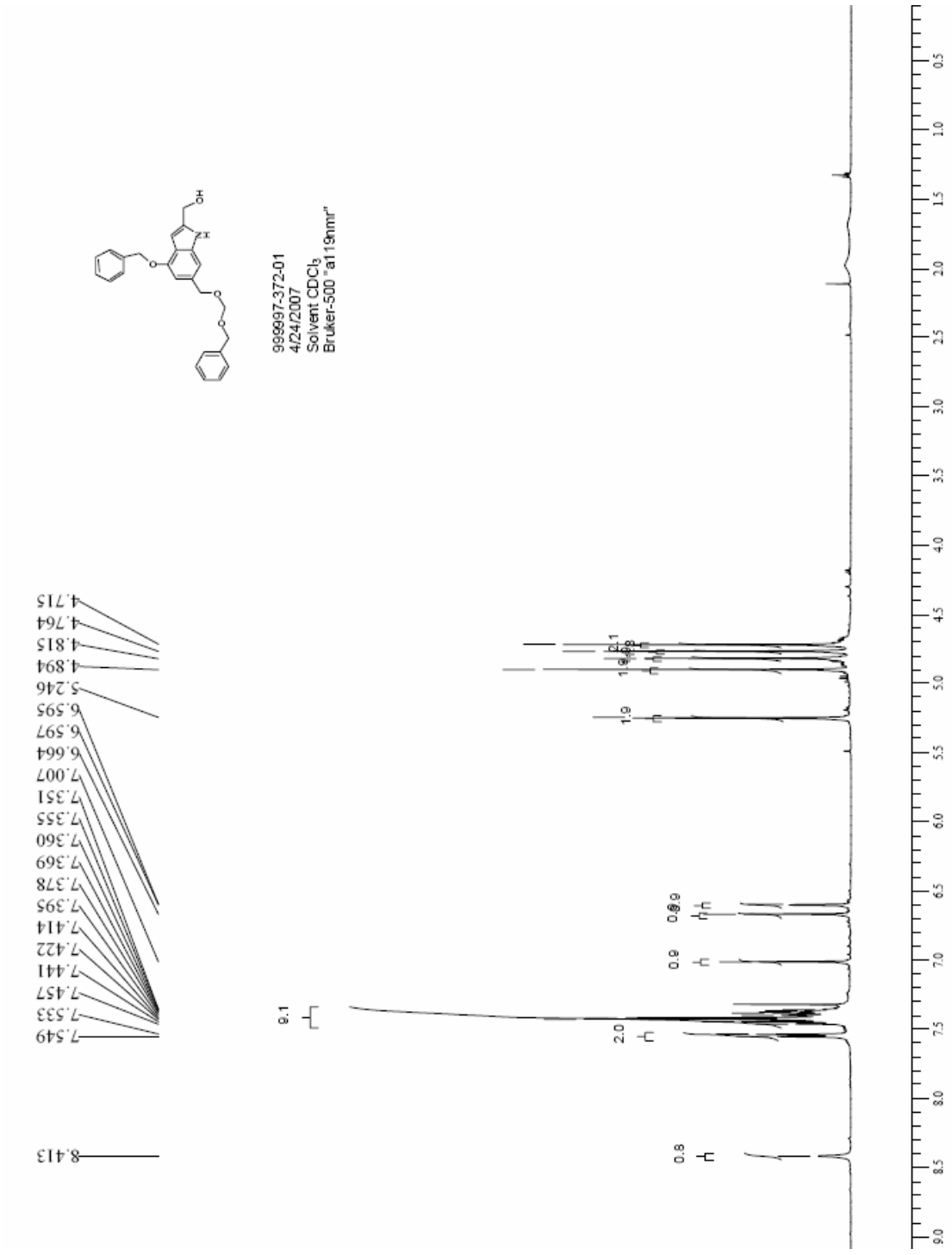
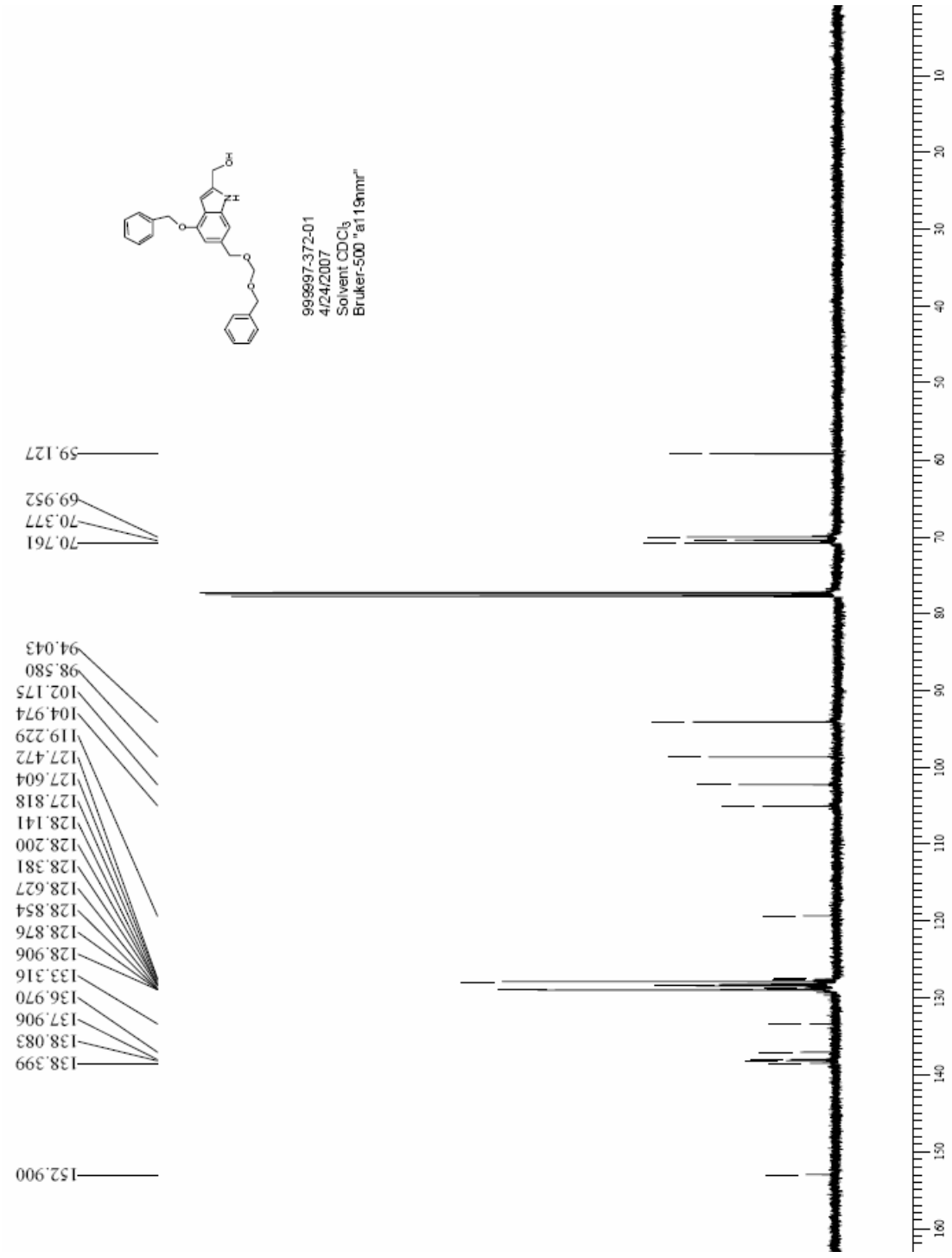


Compound **80** C^{13}NMR



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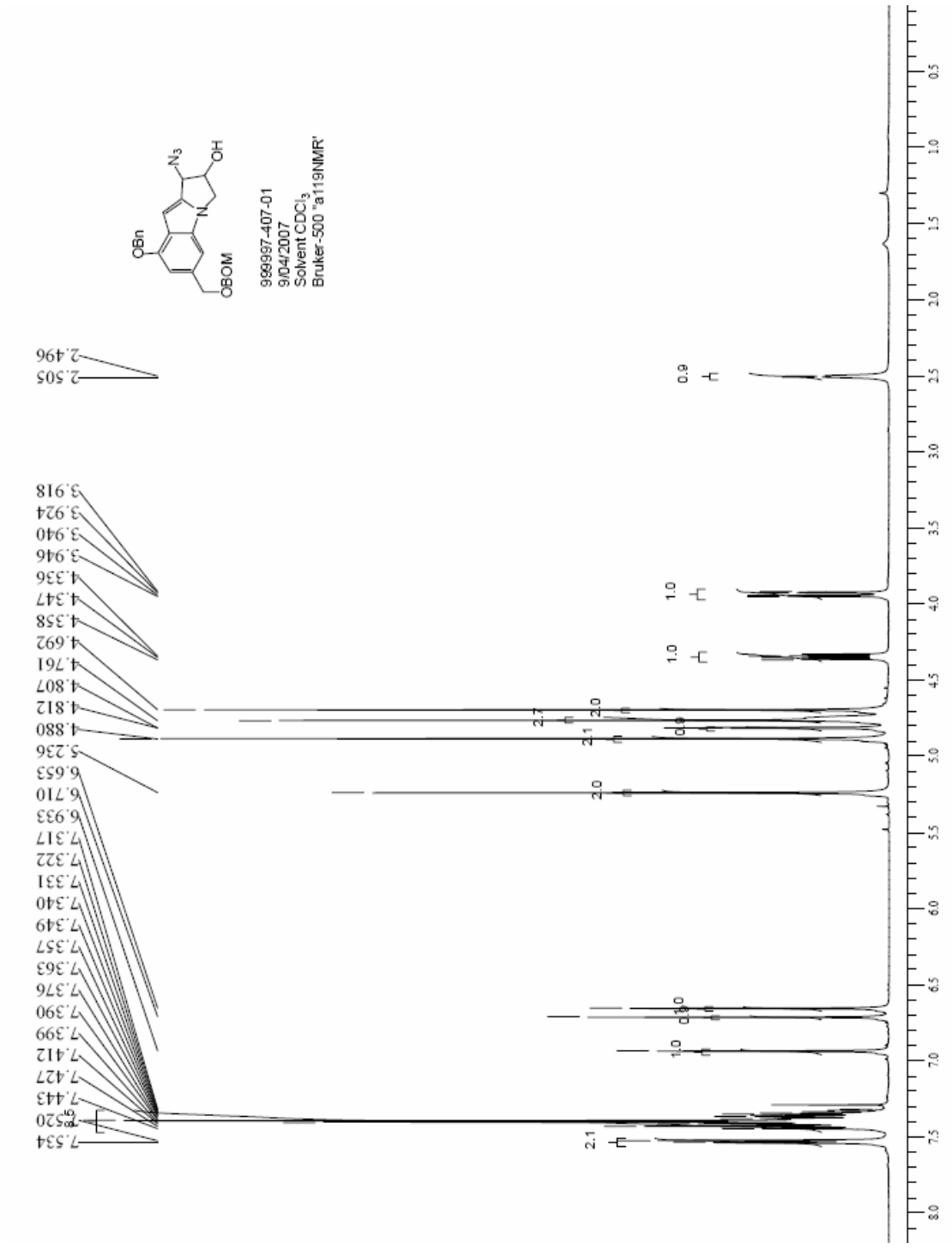
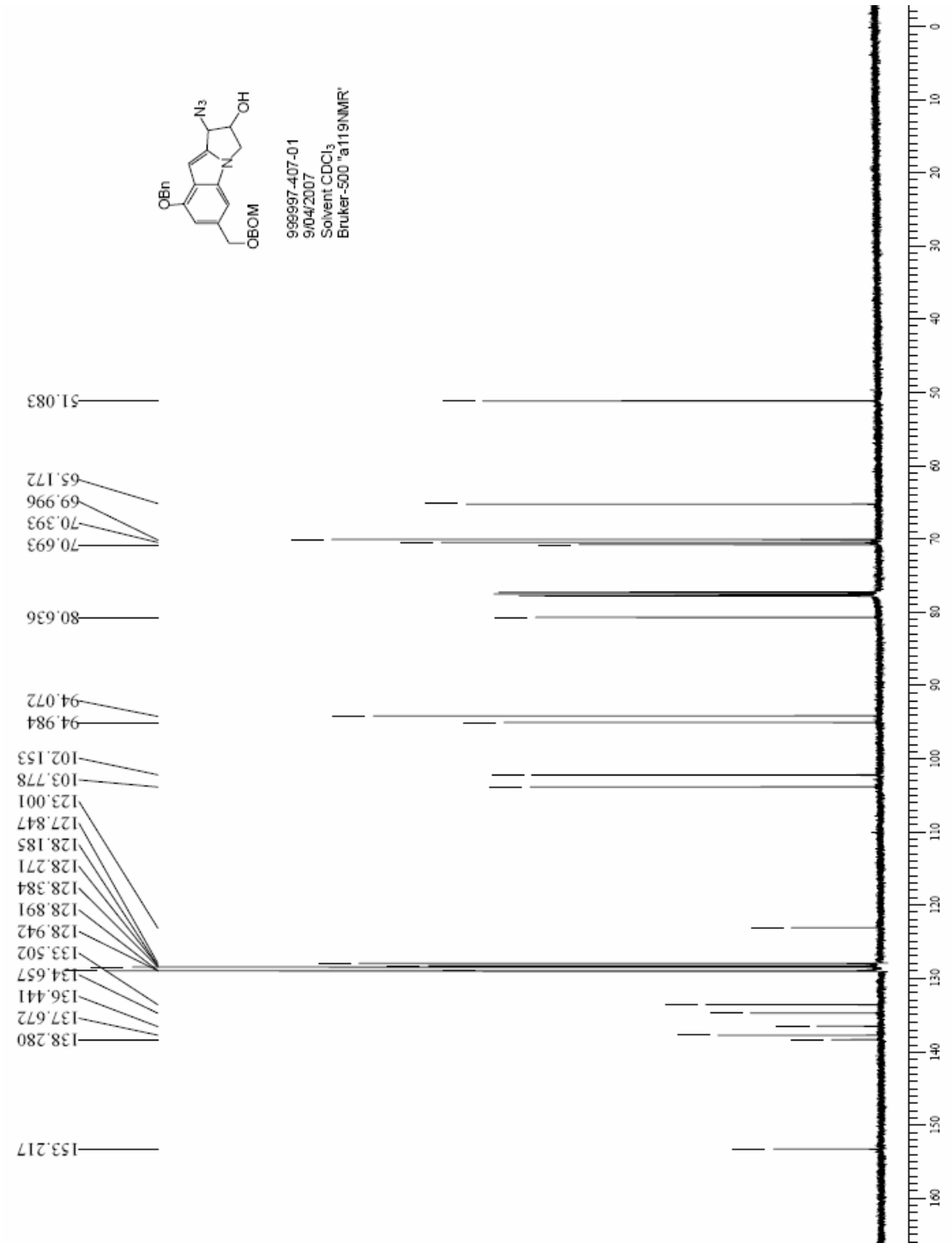


Compound **81** C^{13}NMR



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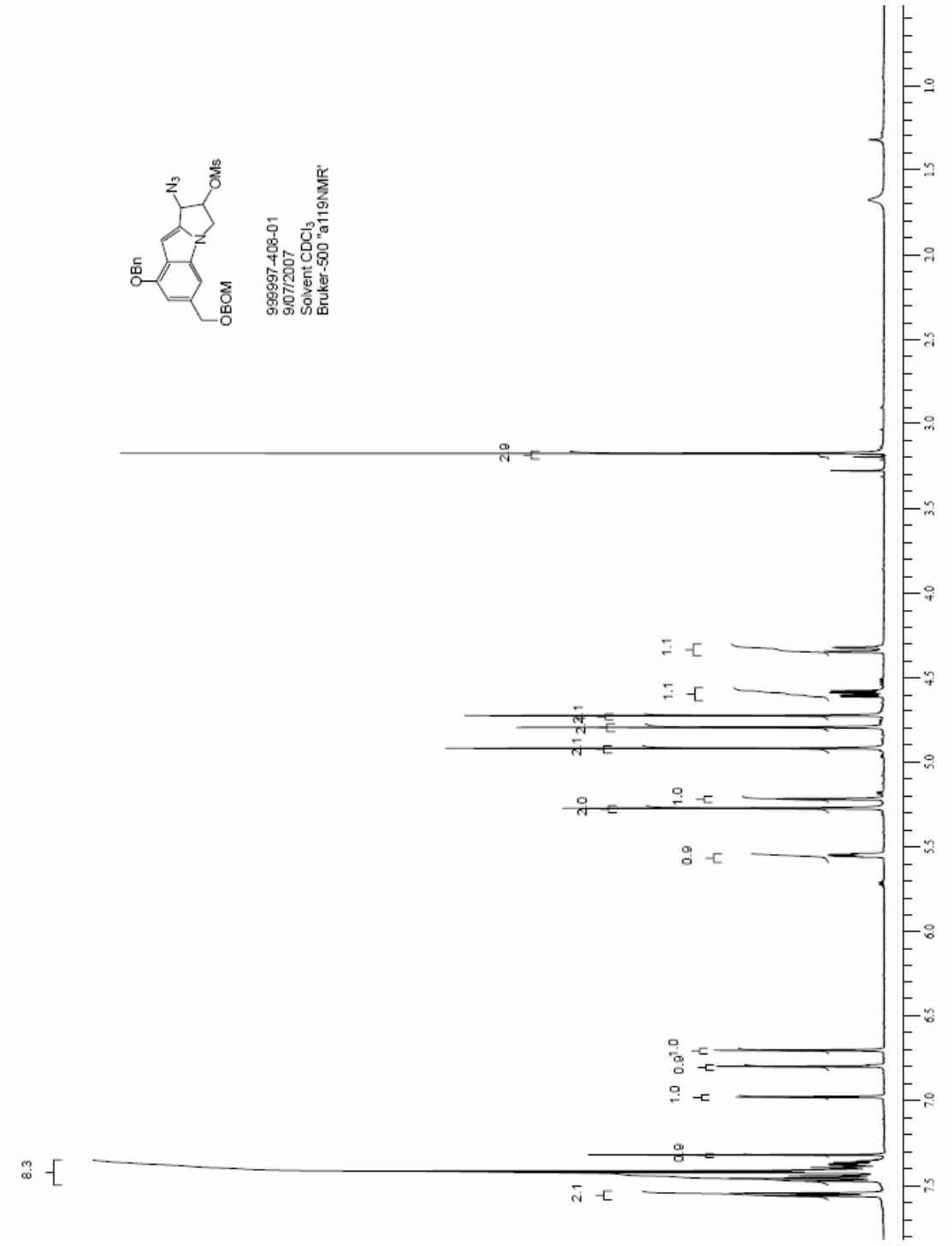

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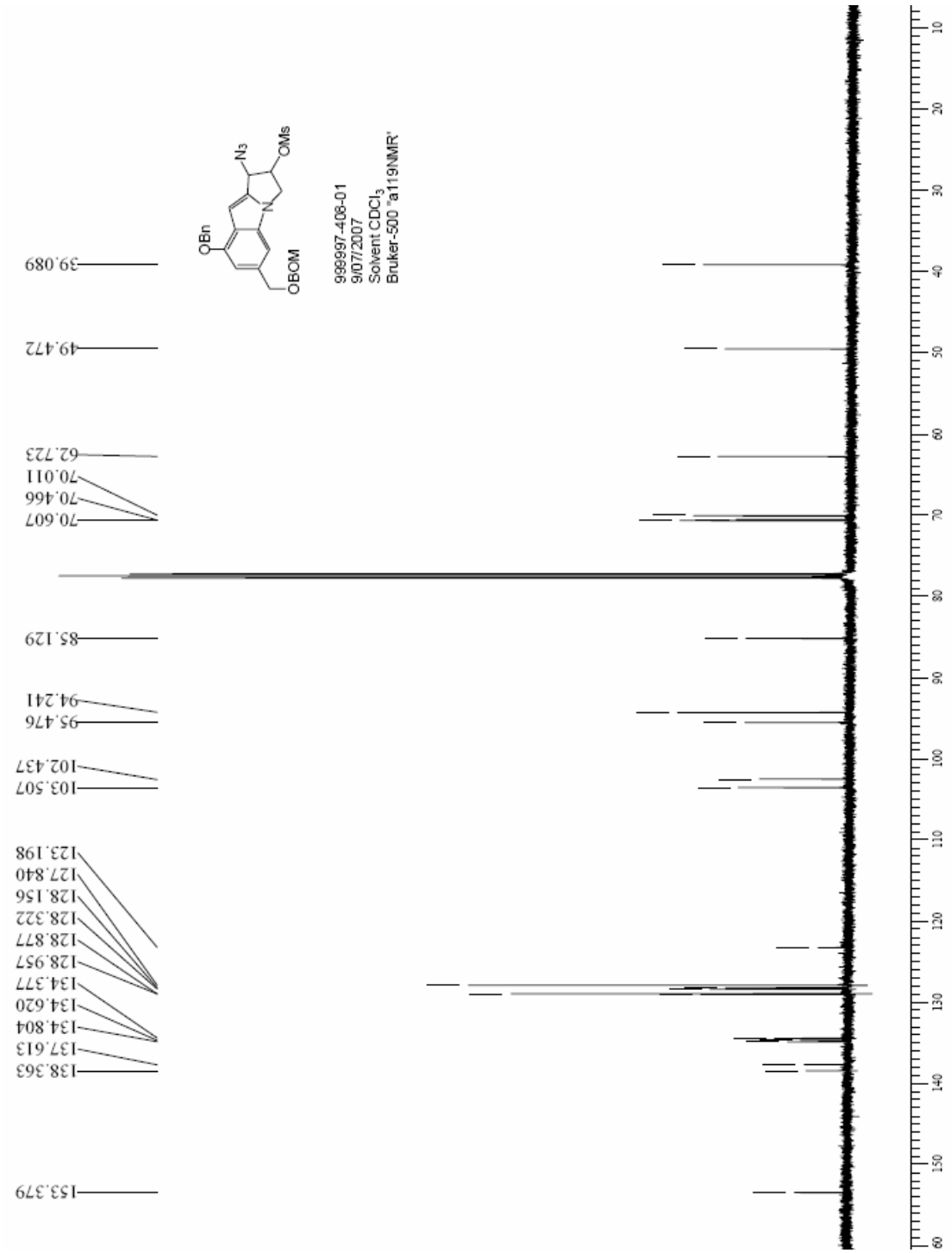

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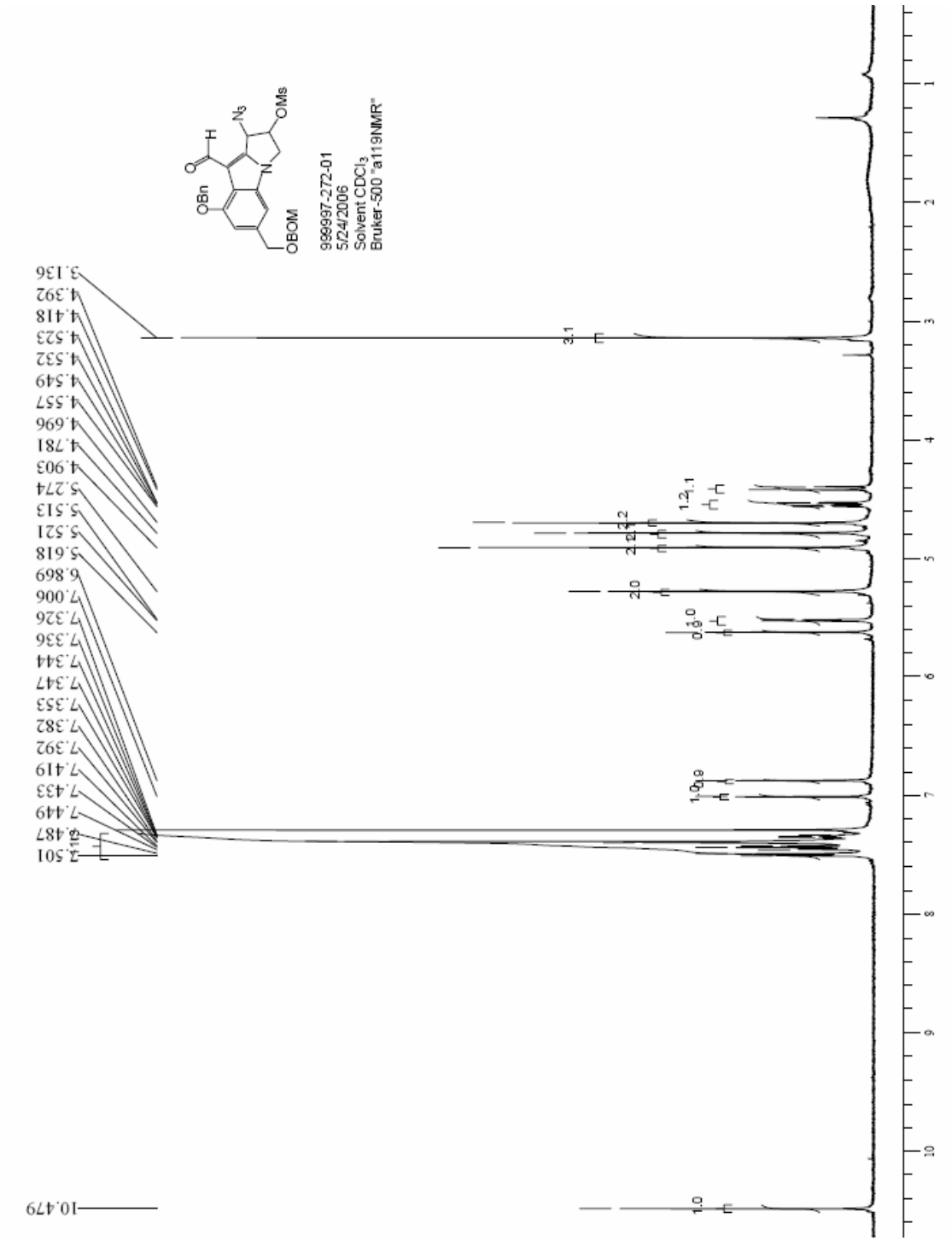

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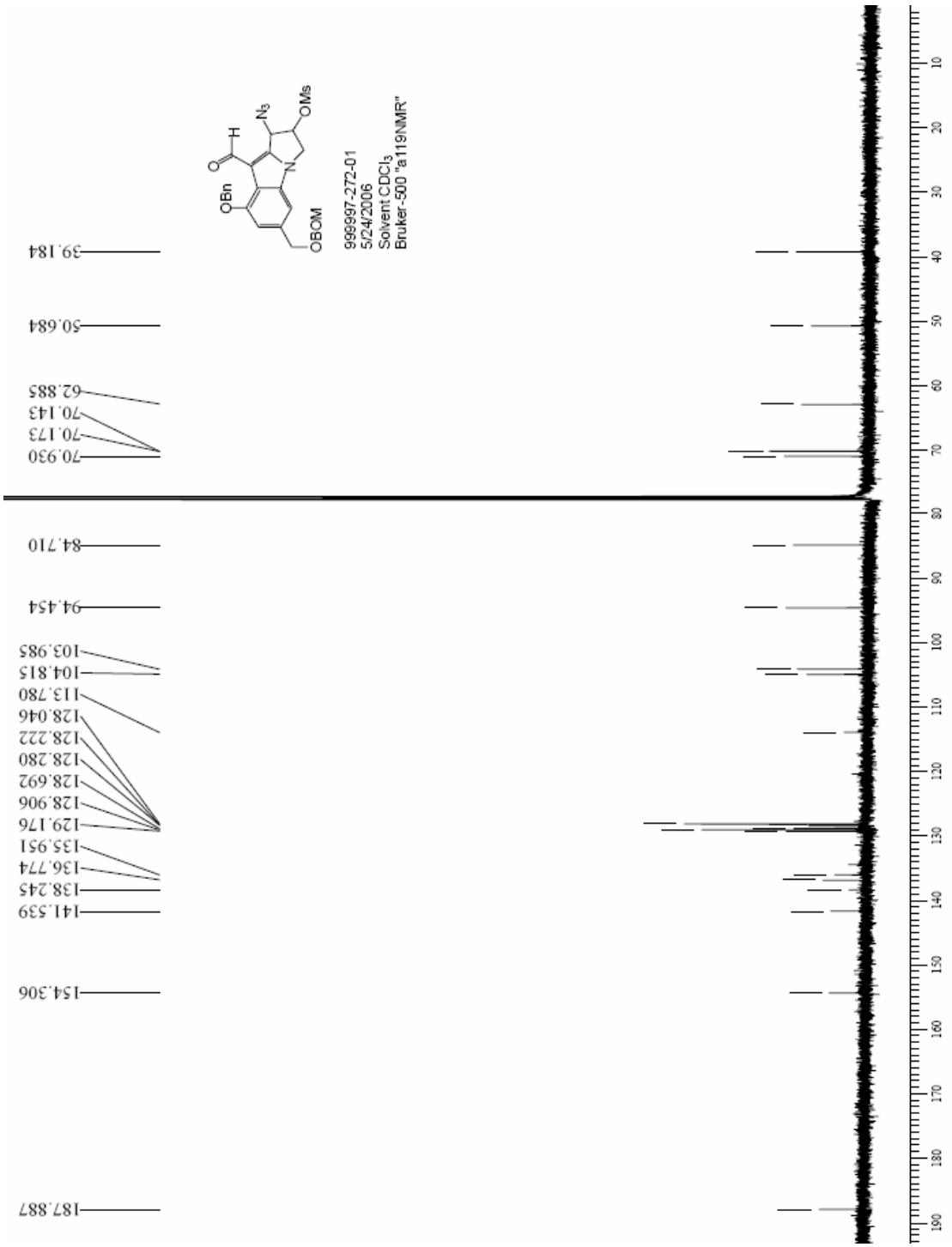

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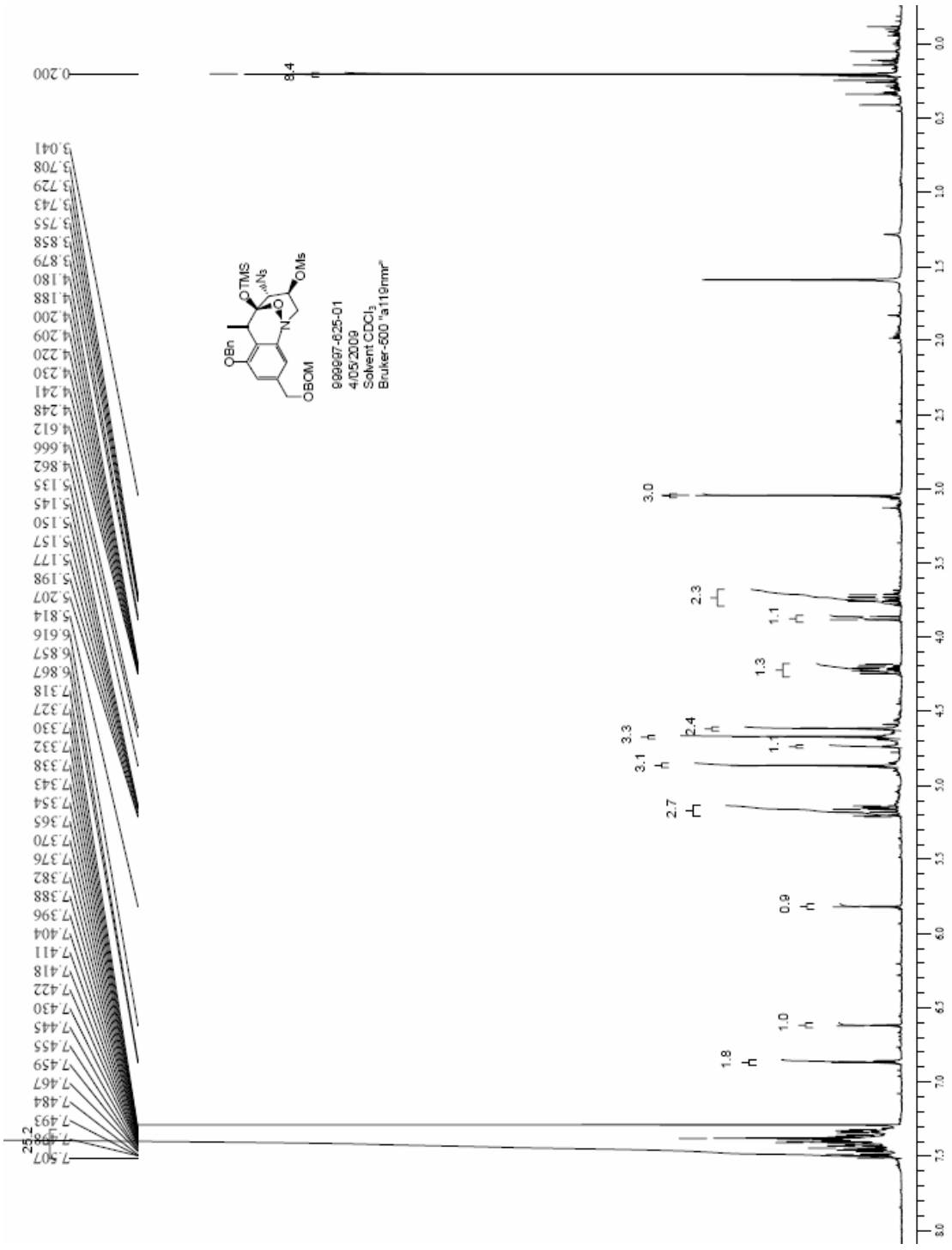
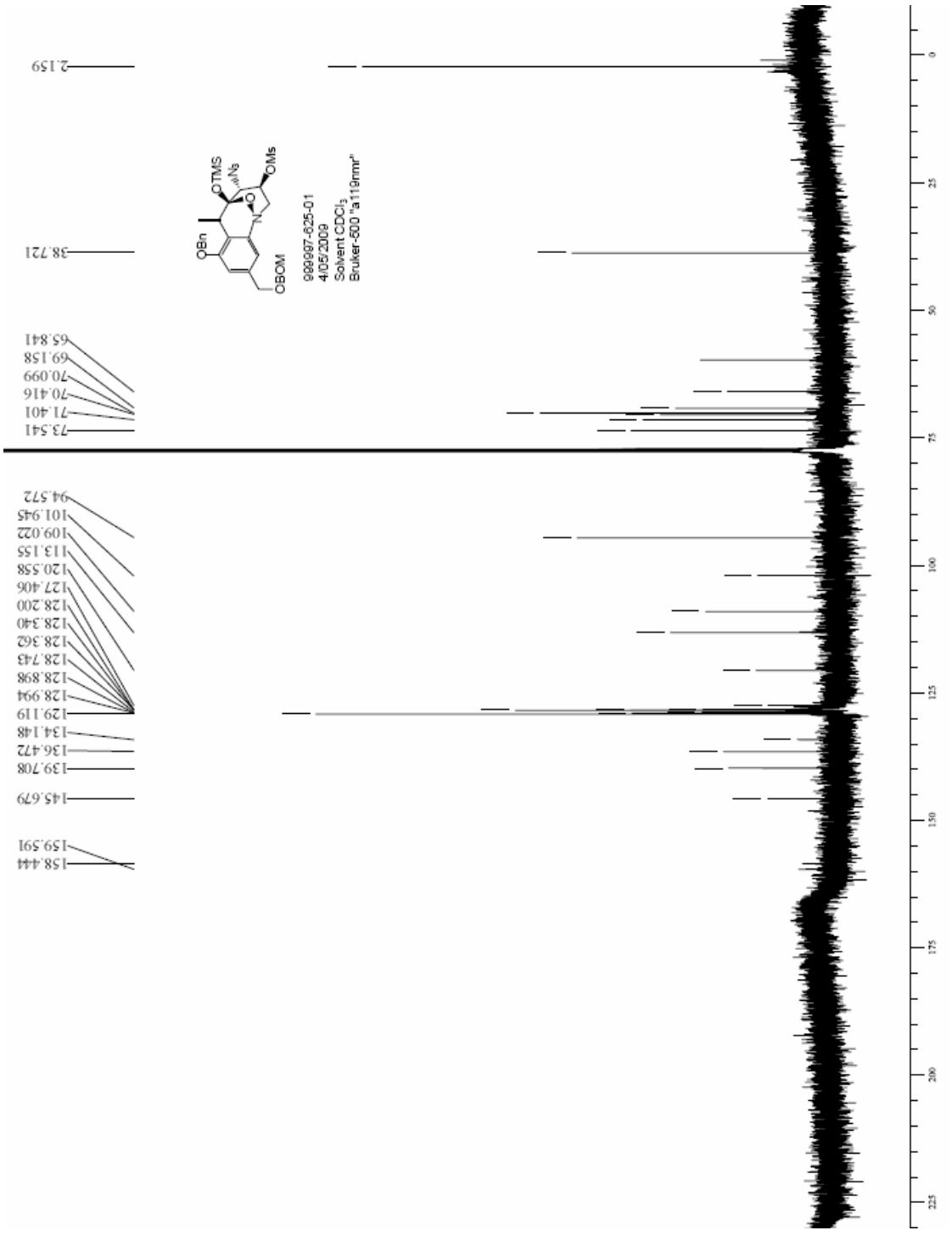


Compound **106-1** C^{13}NMR



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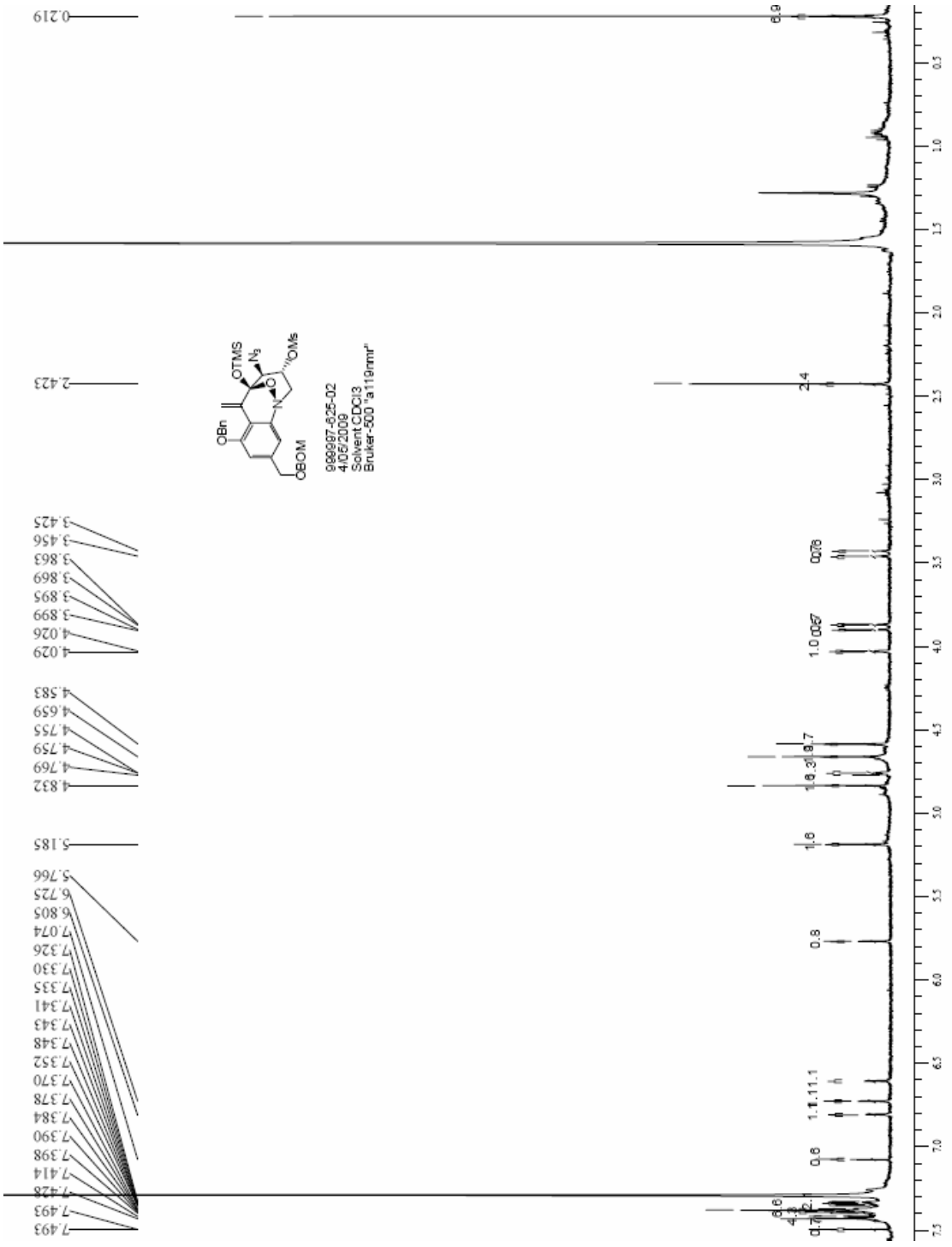

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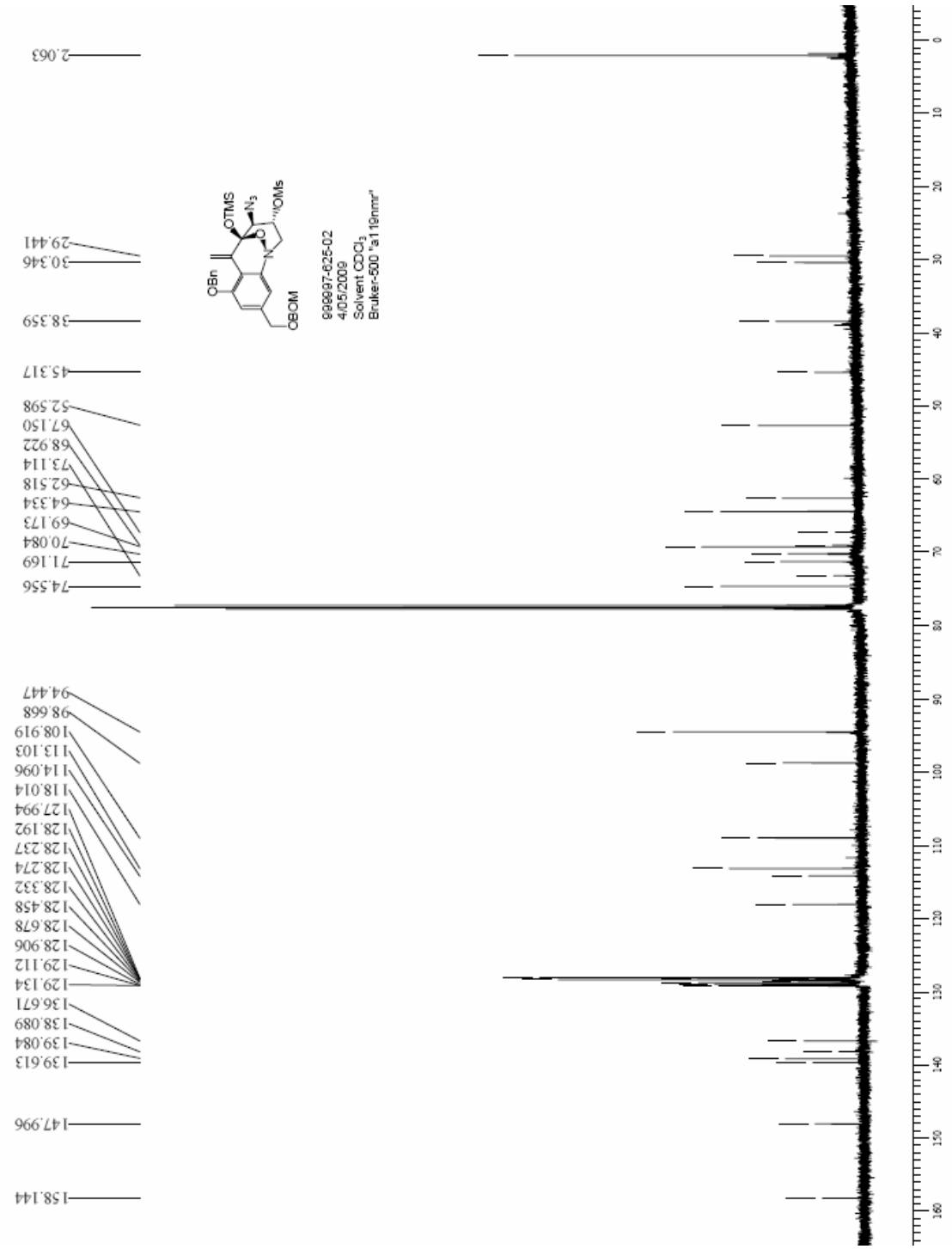

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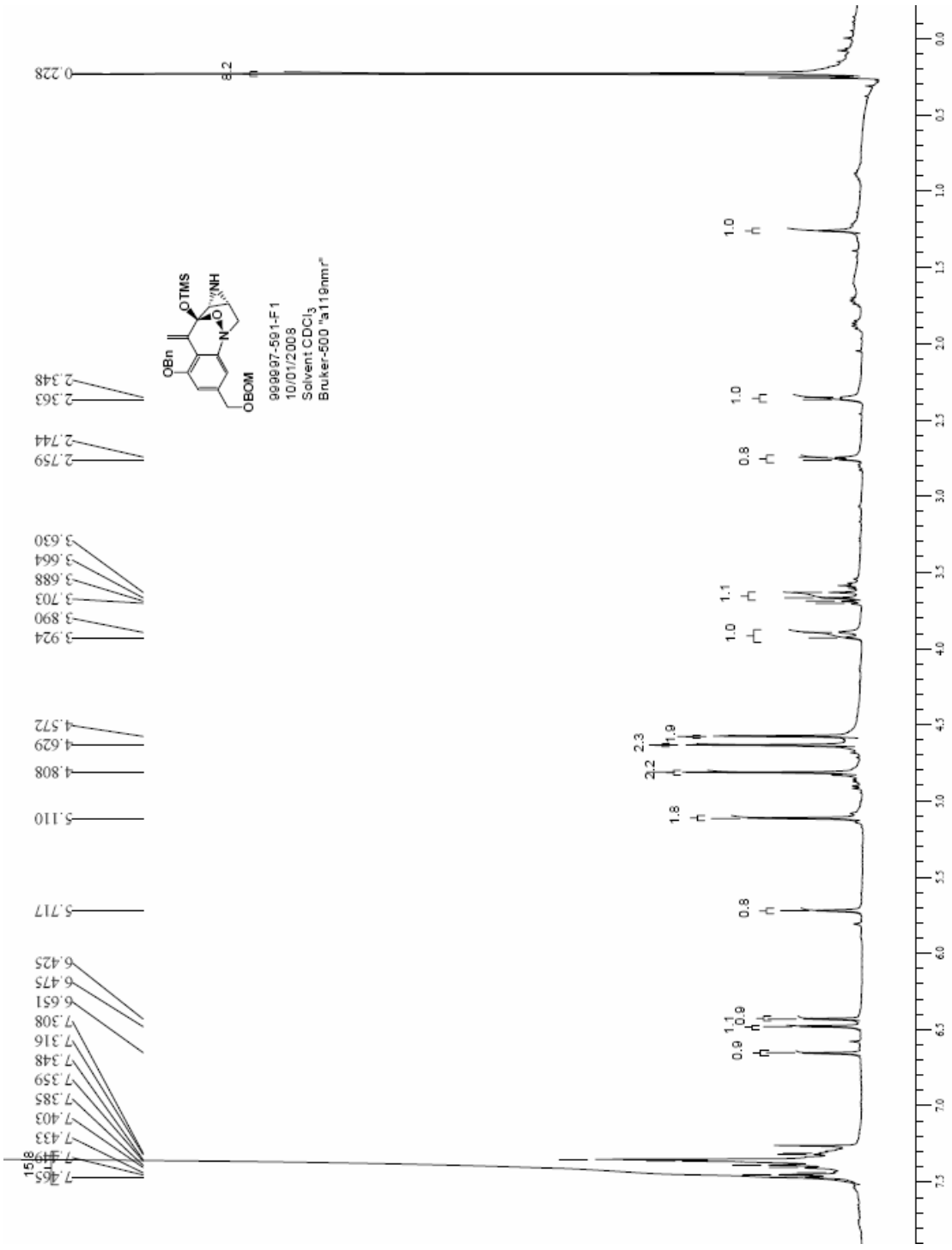

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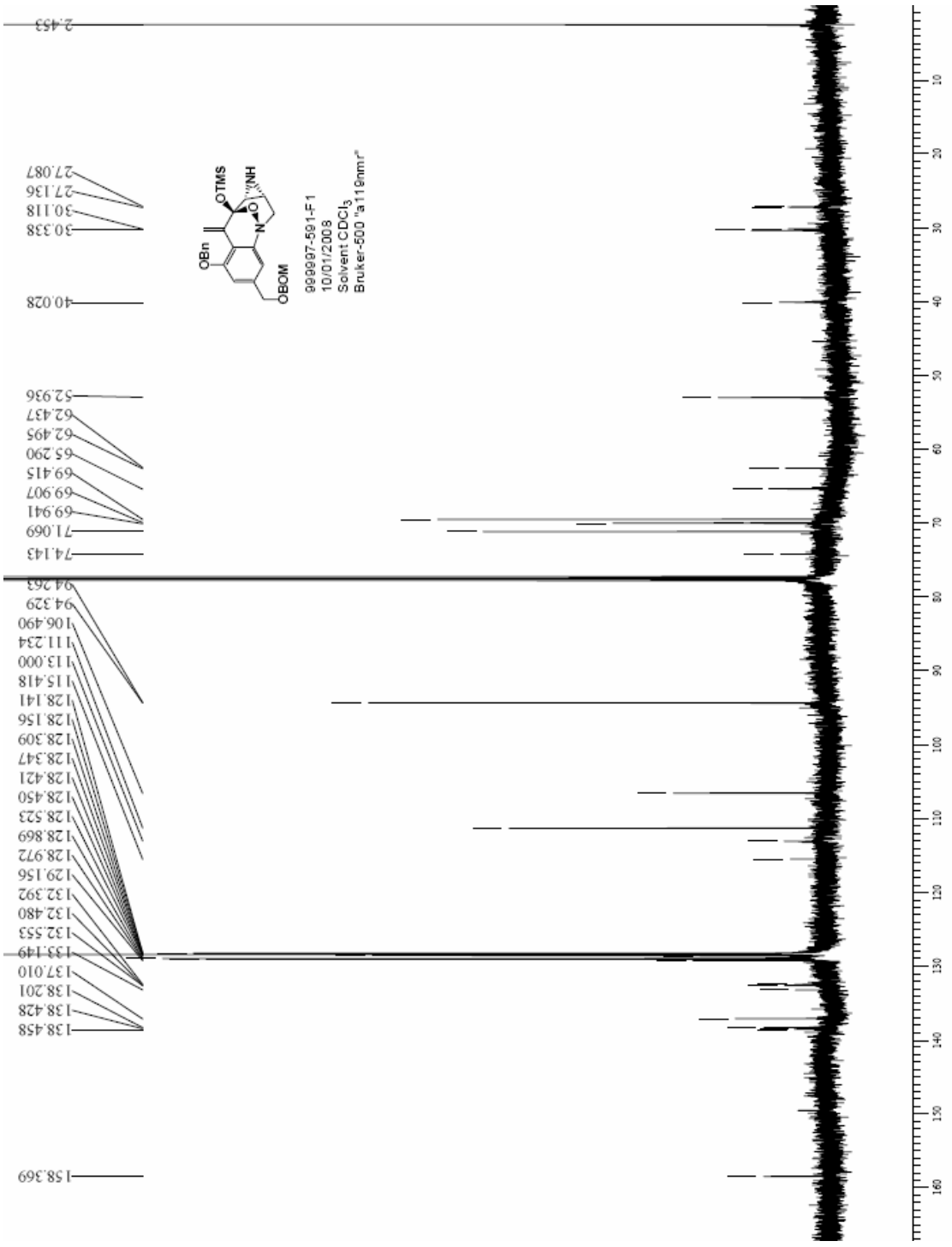

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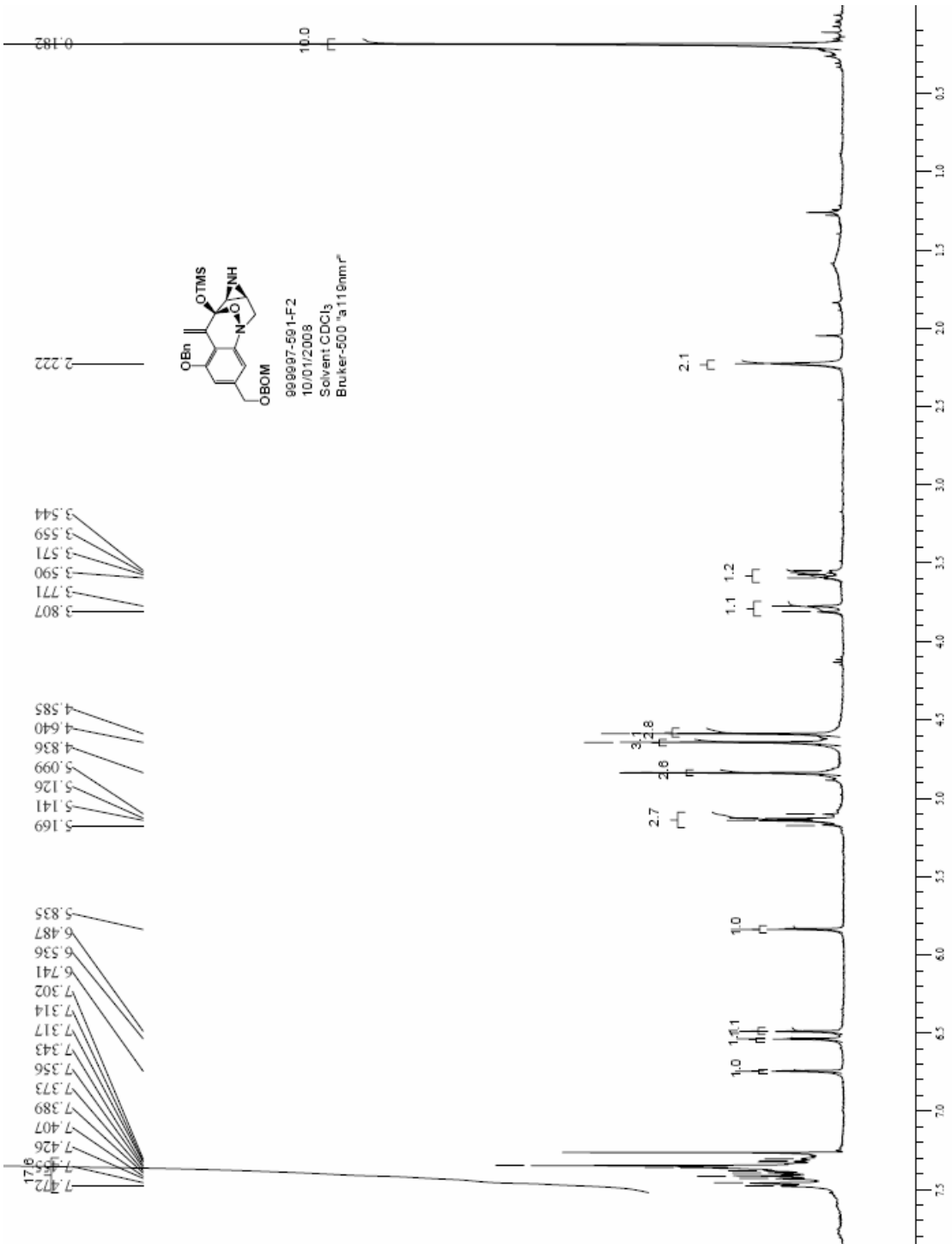

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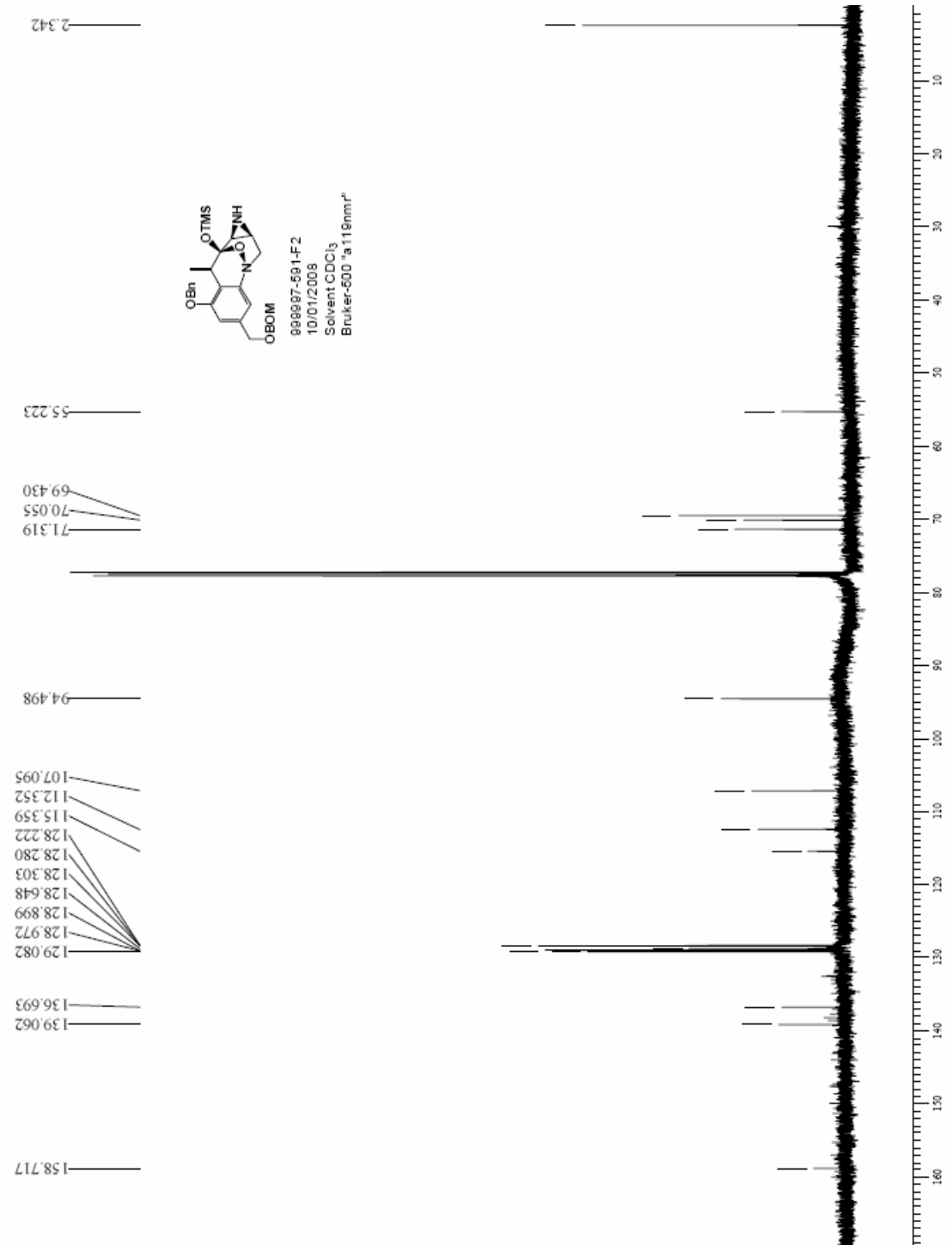

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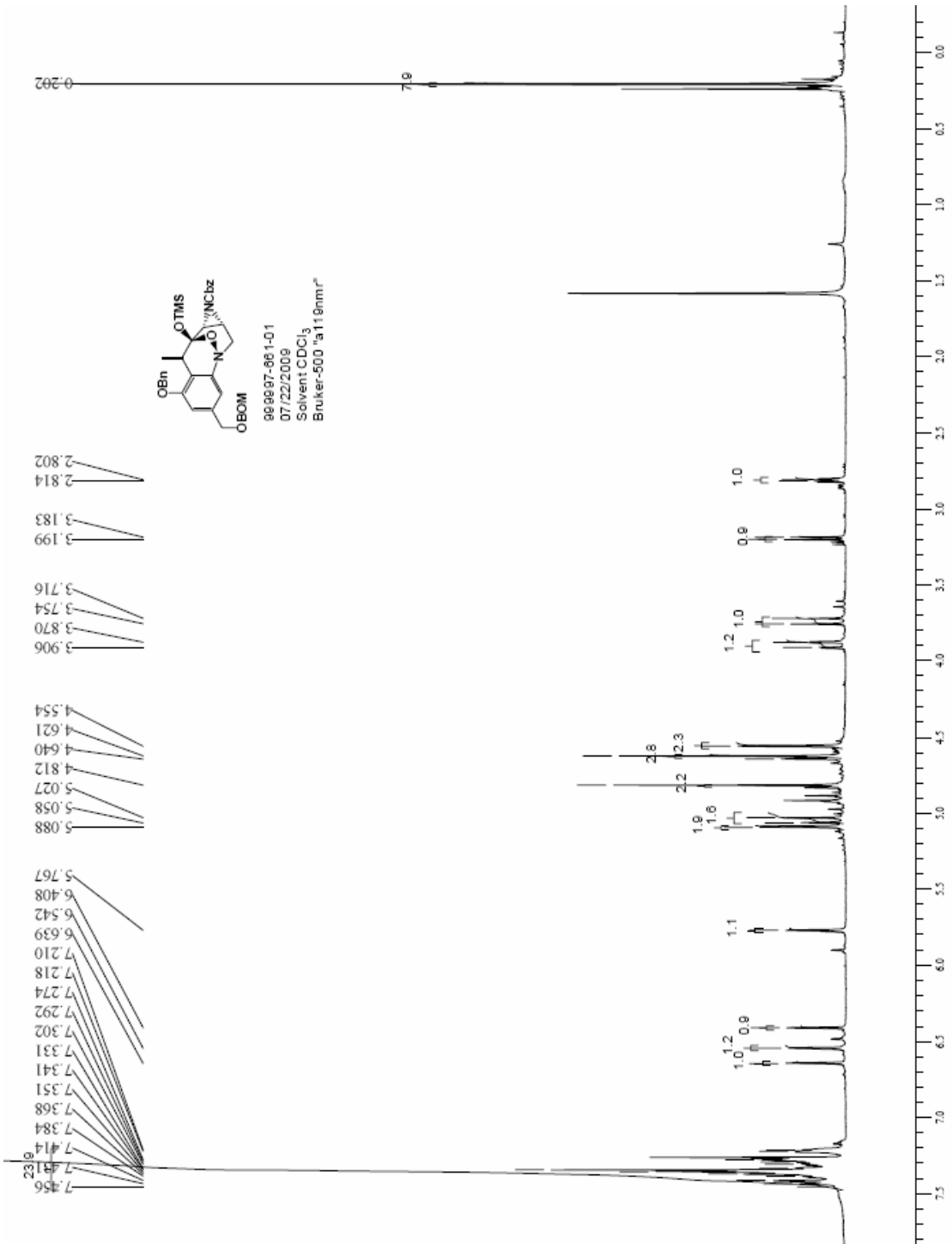

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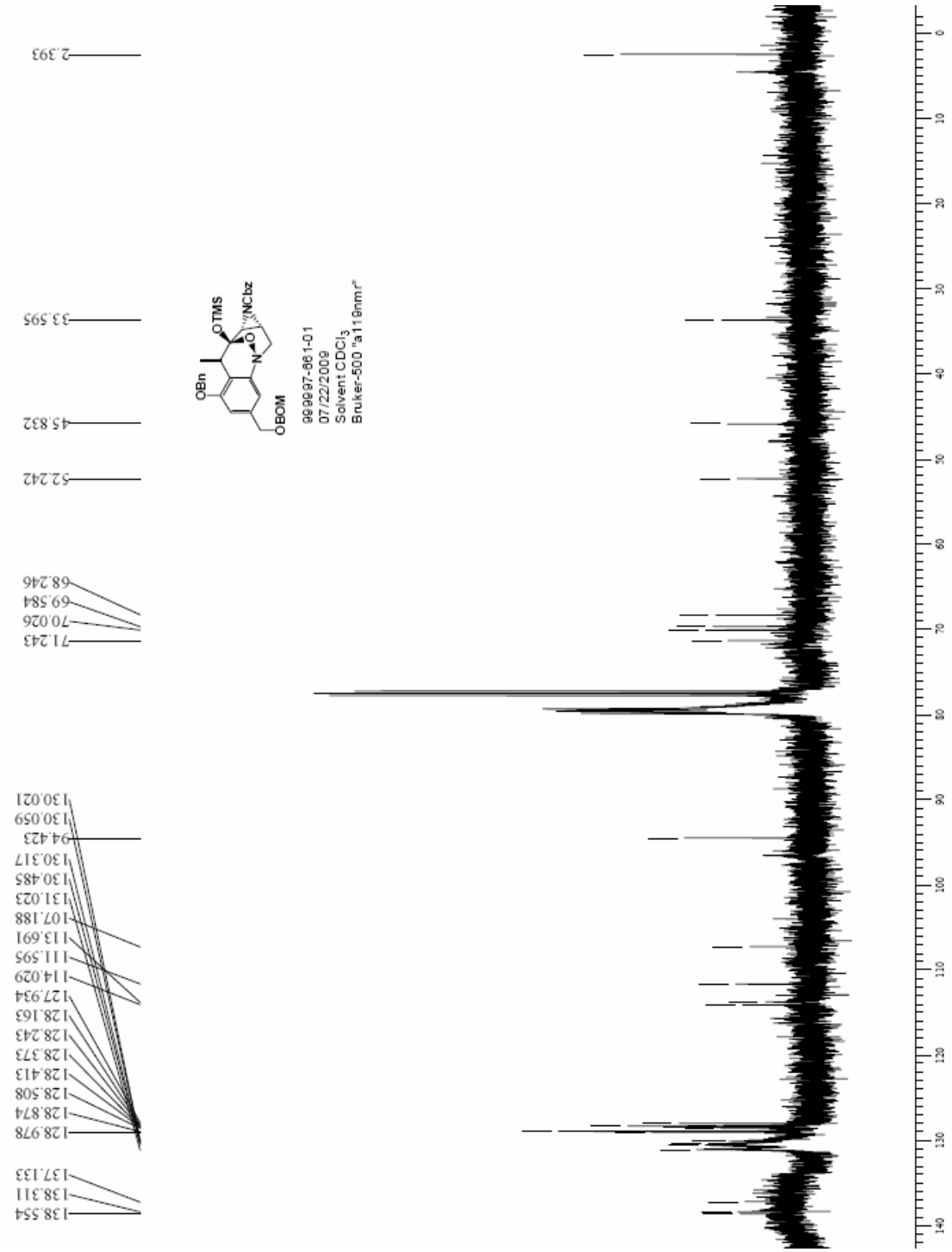

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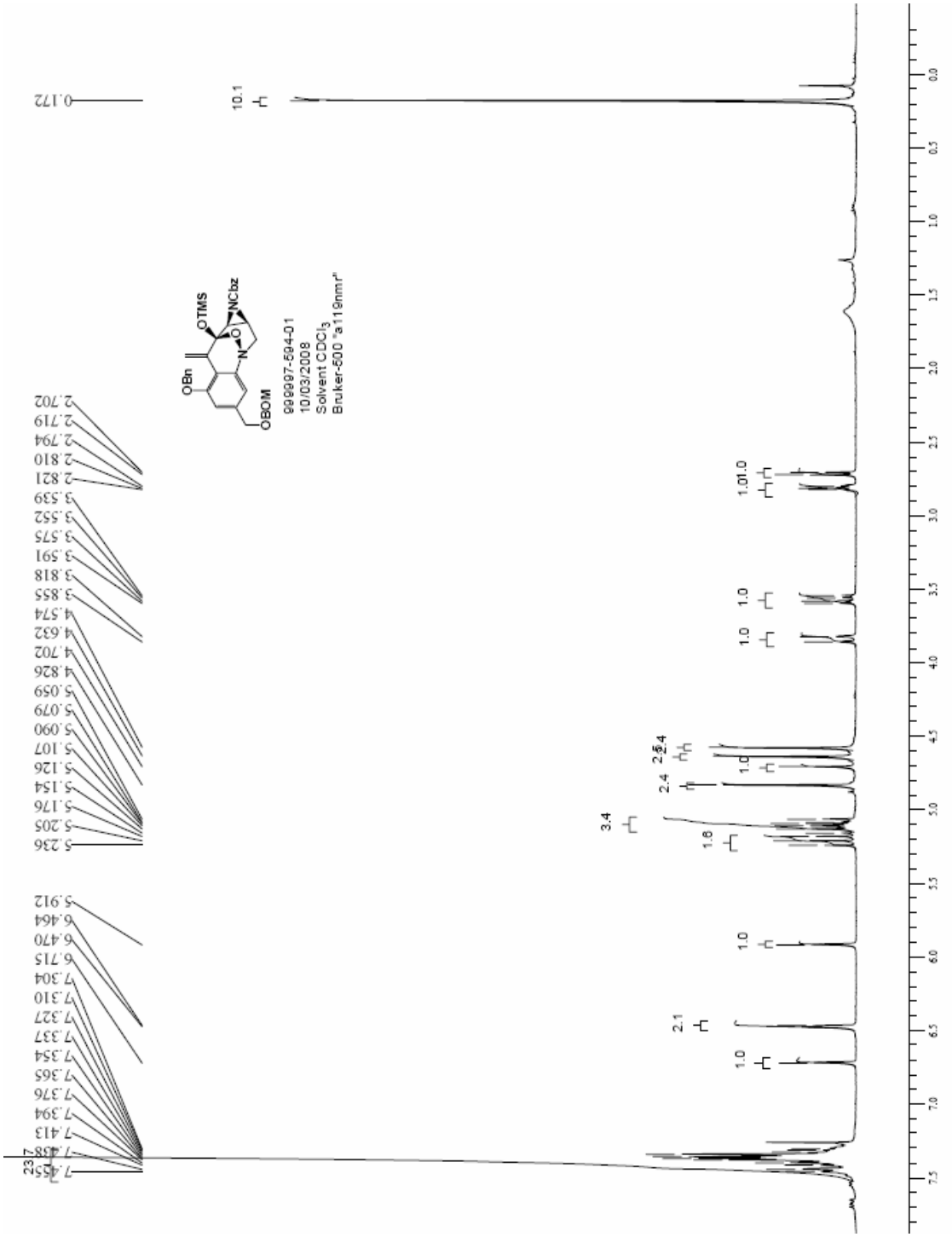

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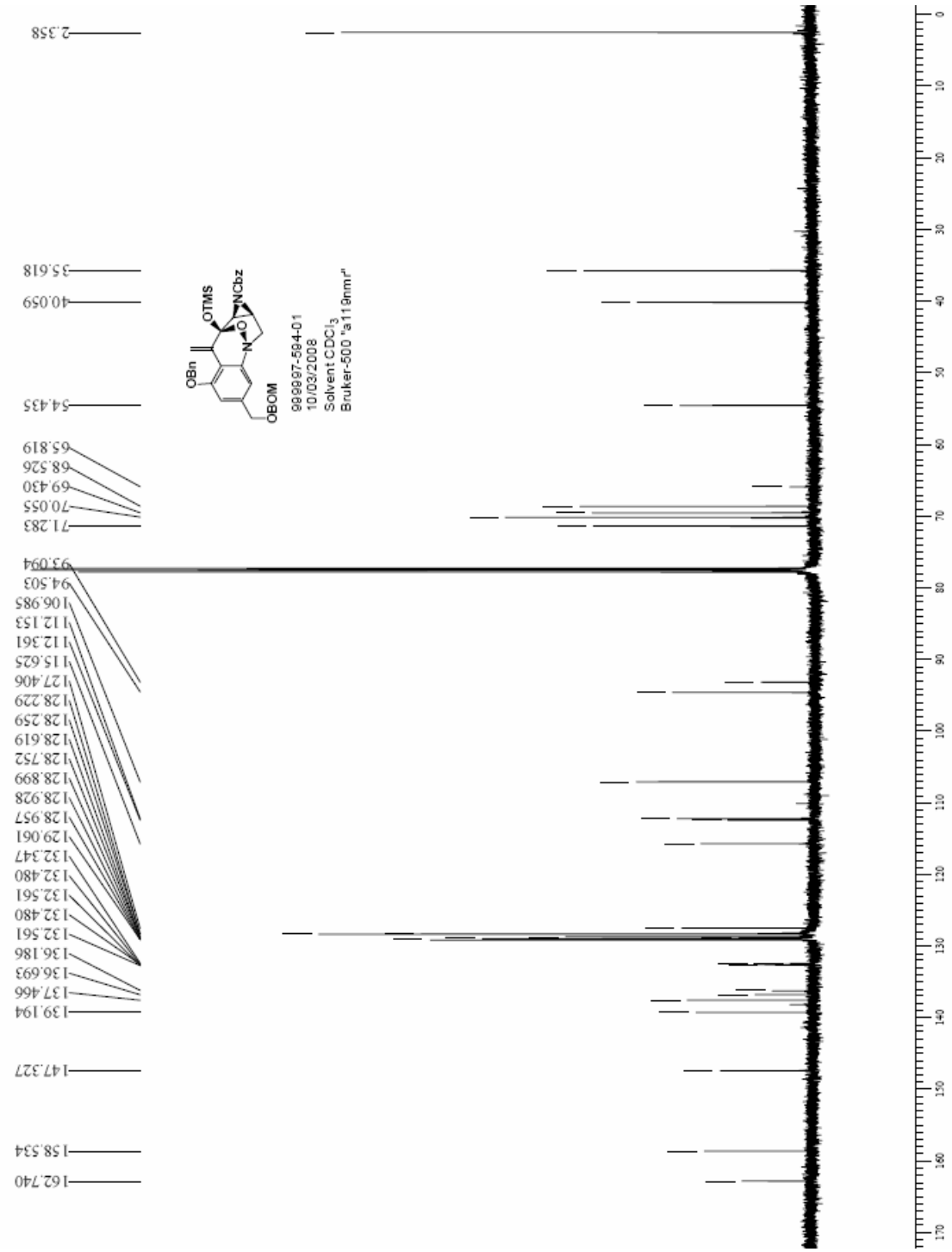

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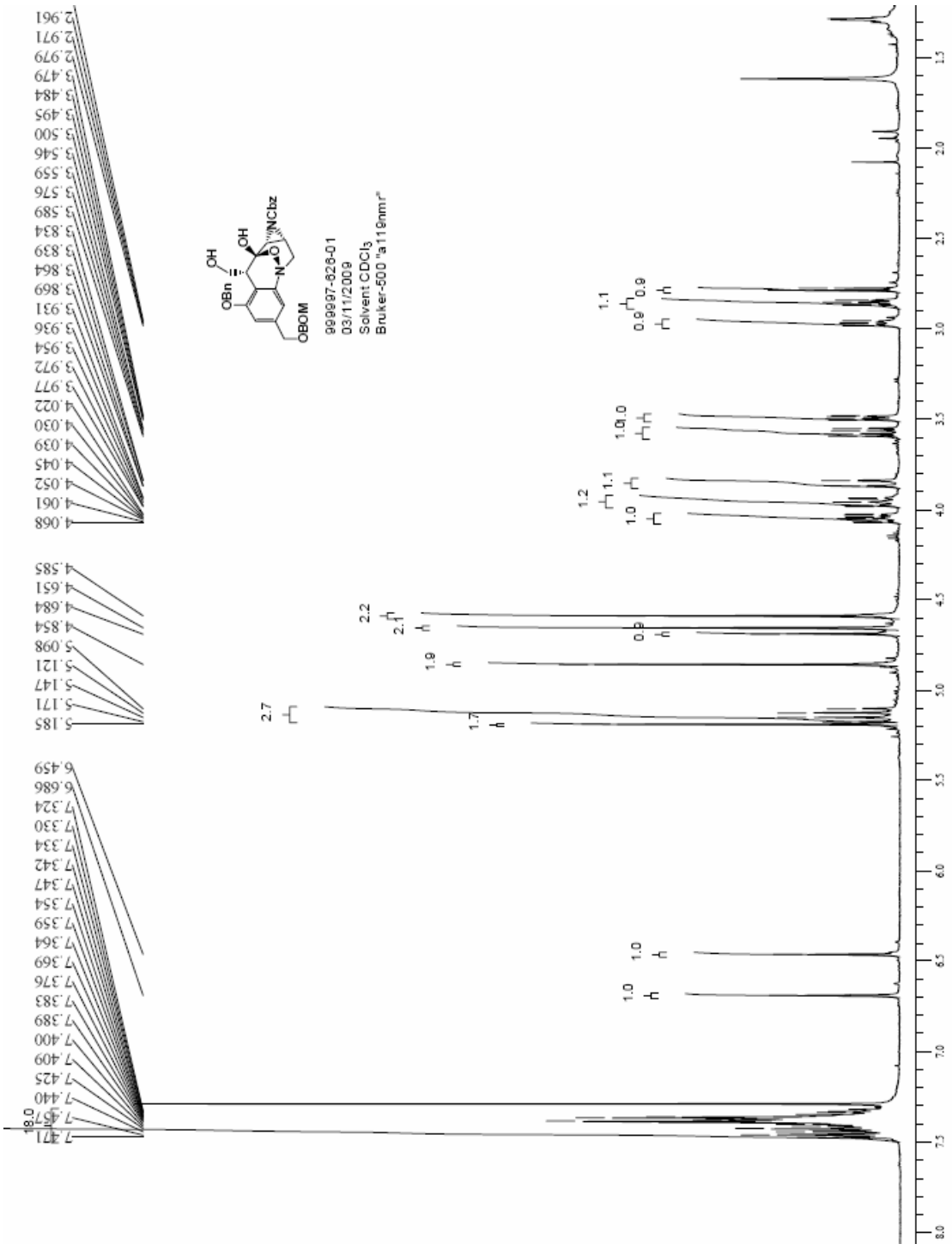
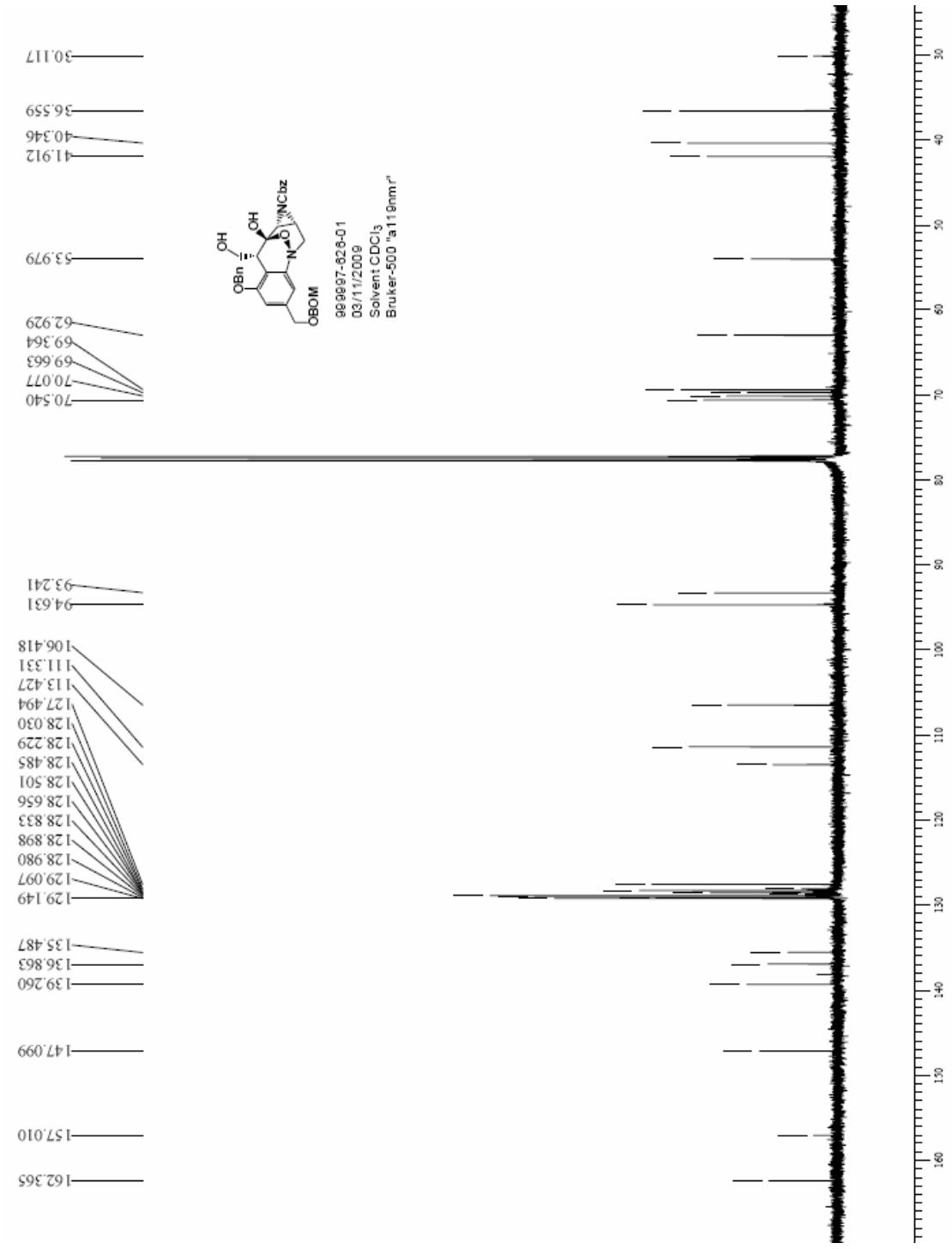


Compound **111-1** C^{13}NMR



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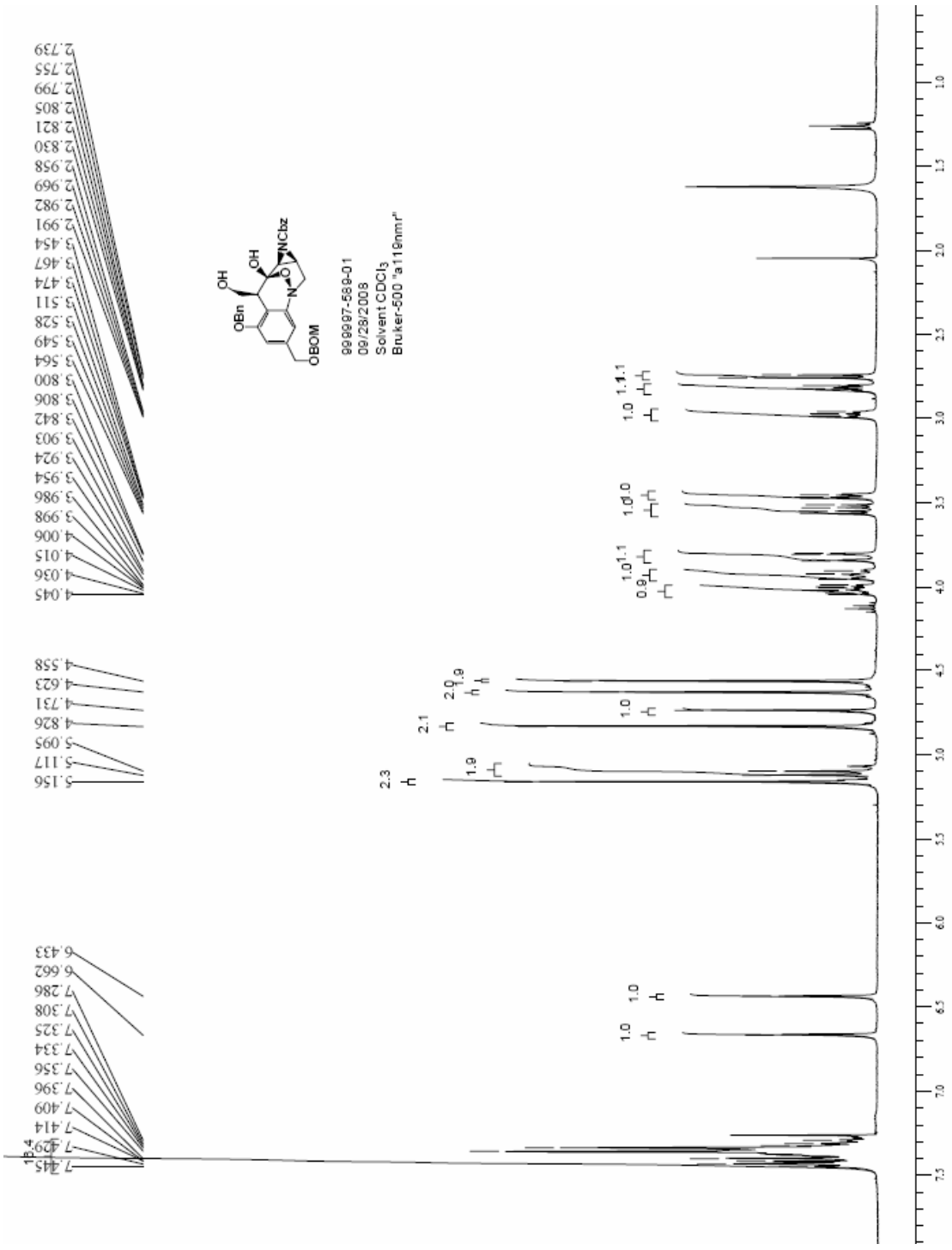
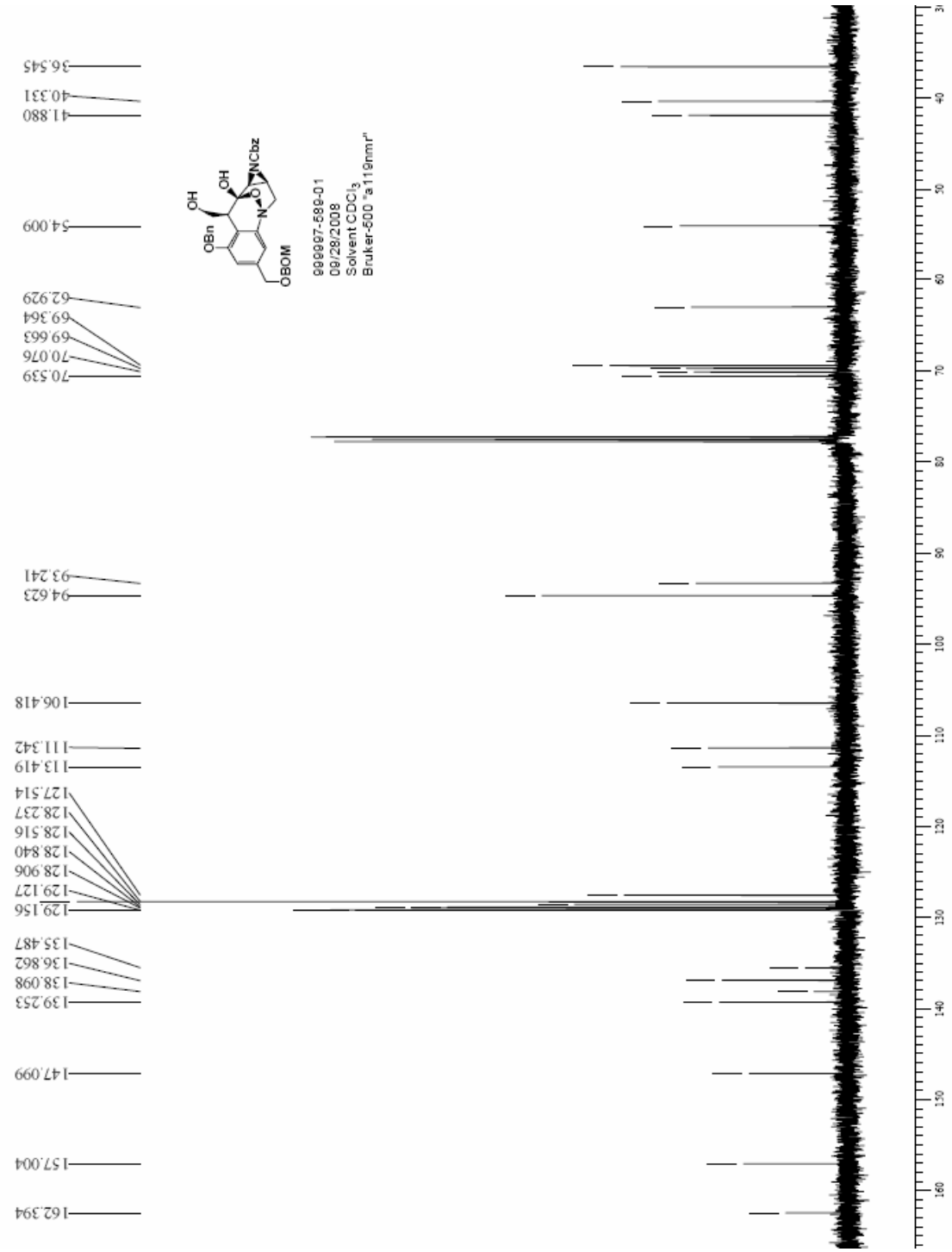
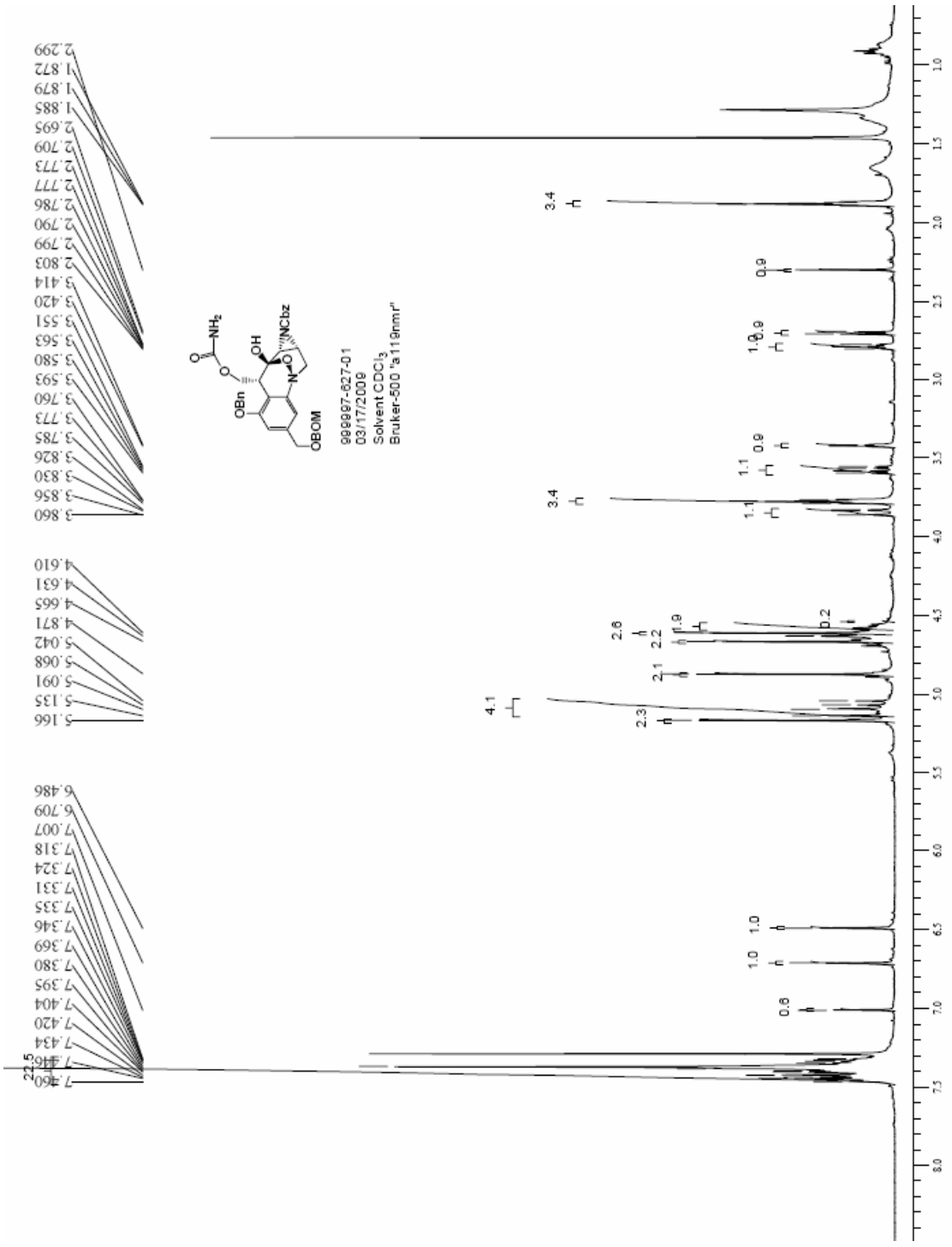


Compound **111-2** C^{13}NMR



Compound **112-1** HNMR



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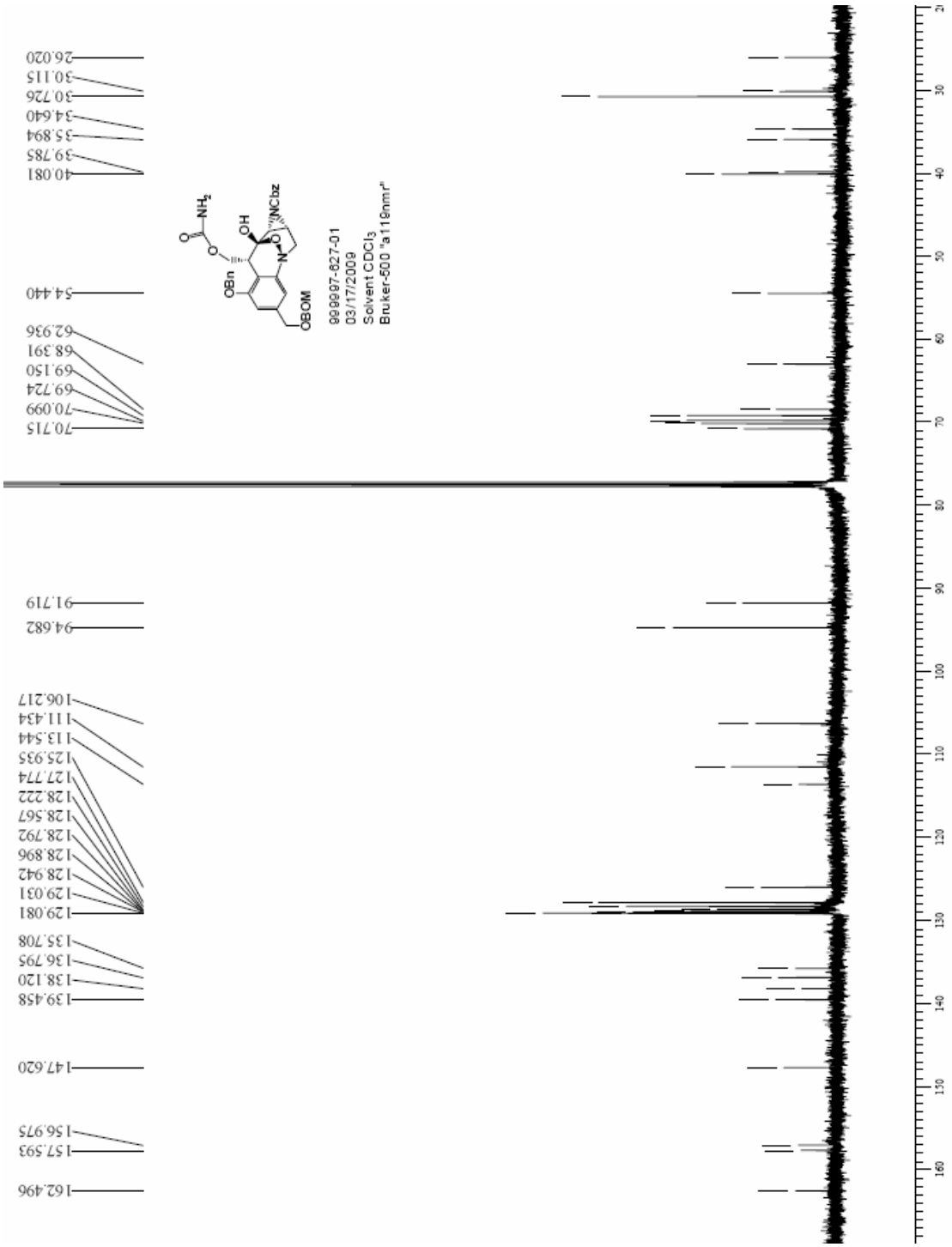

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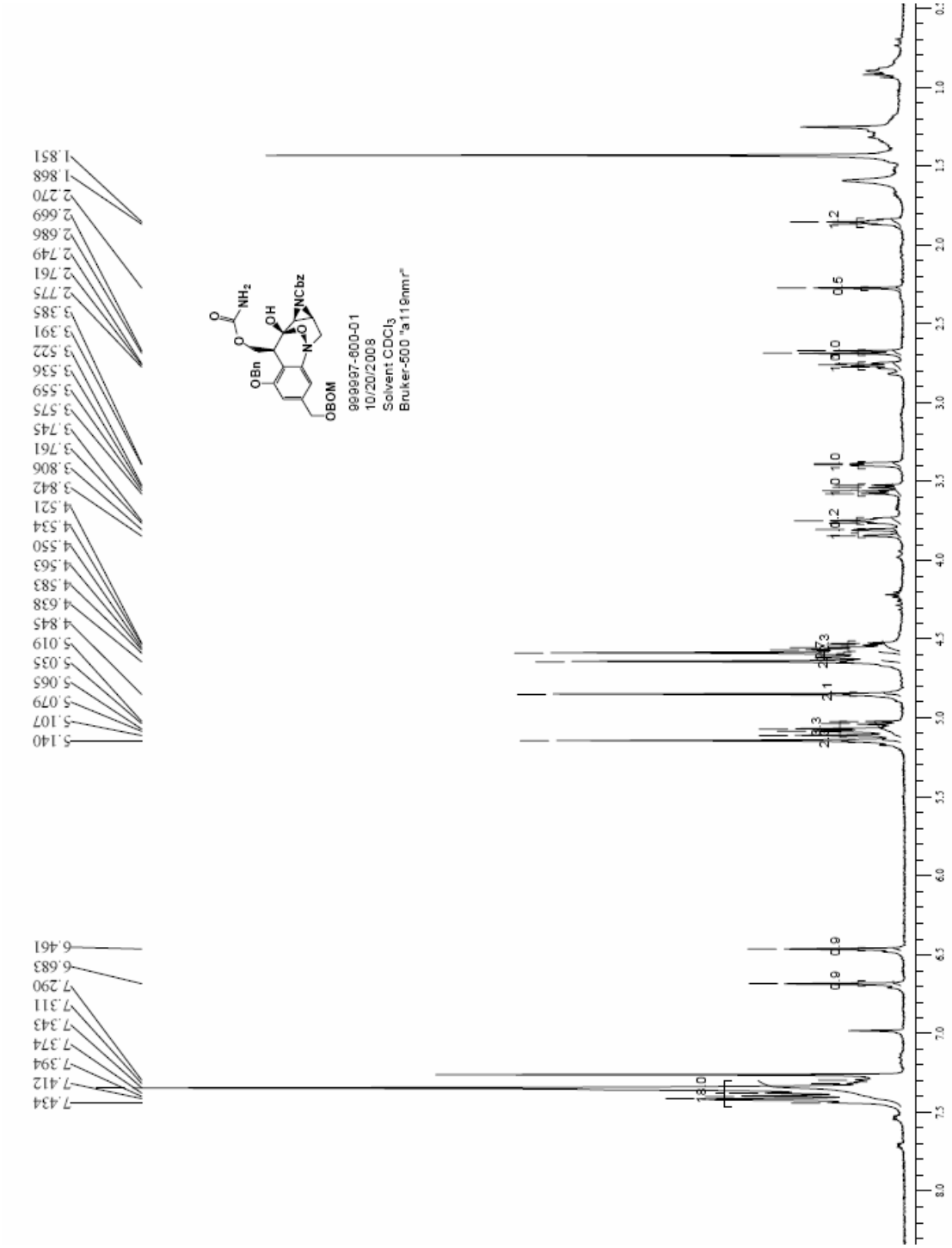

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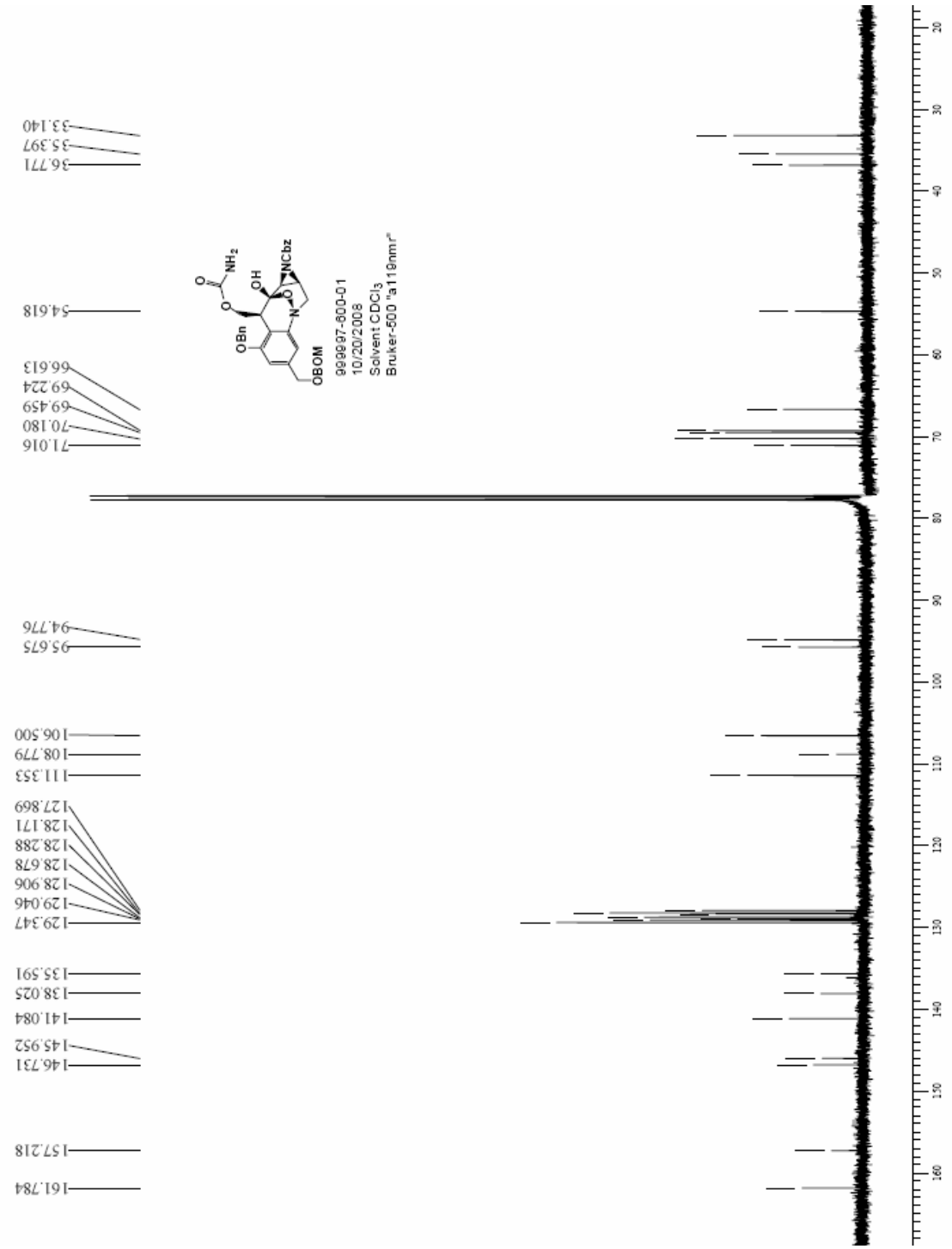

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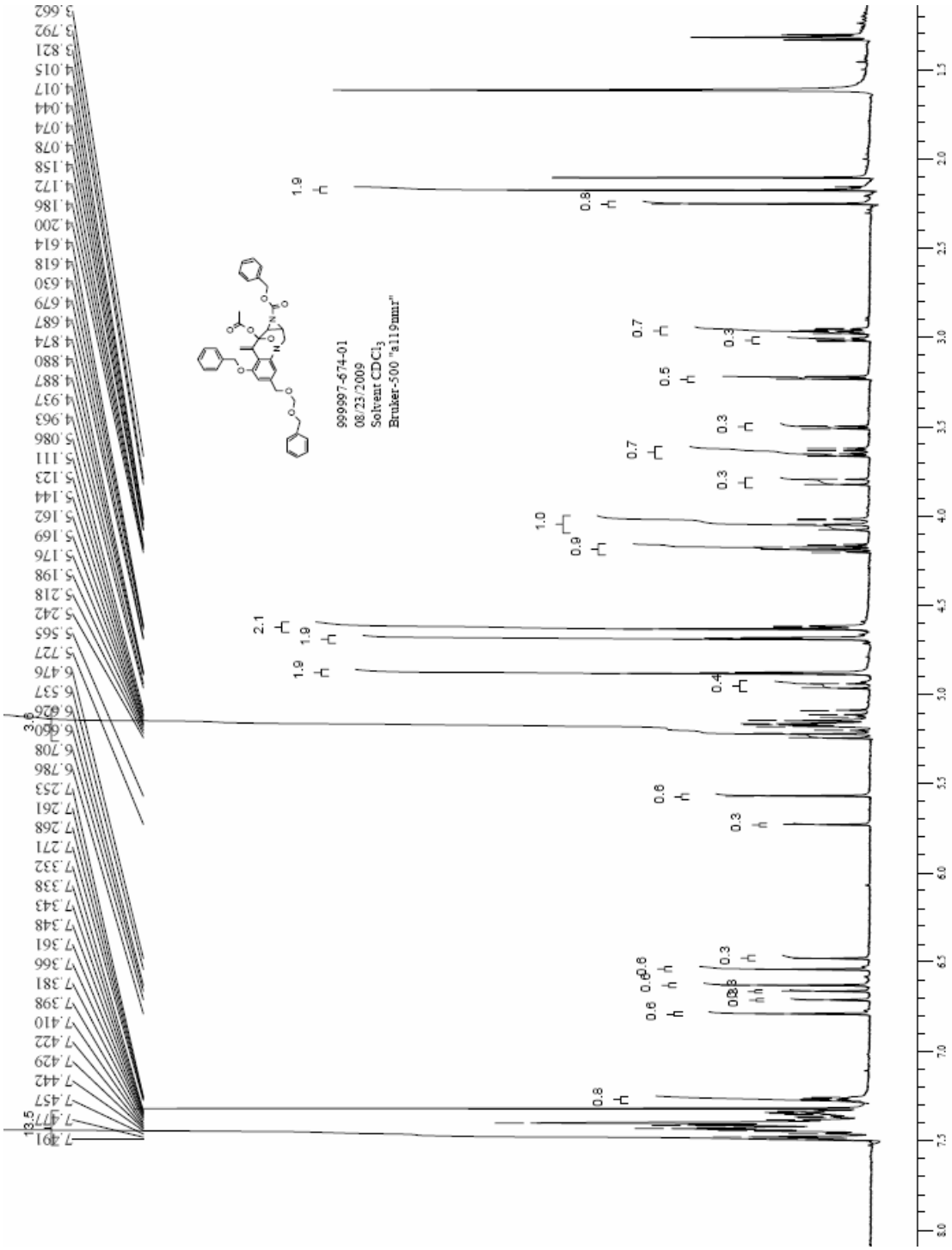

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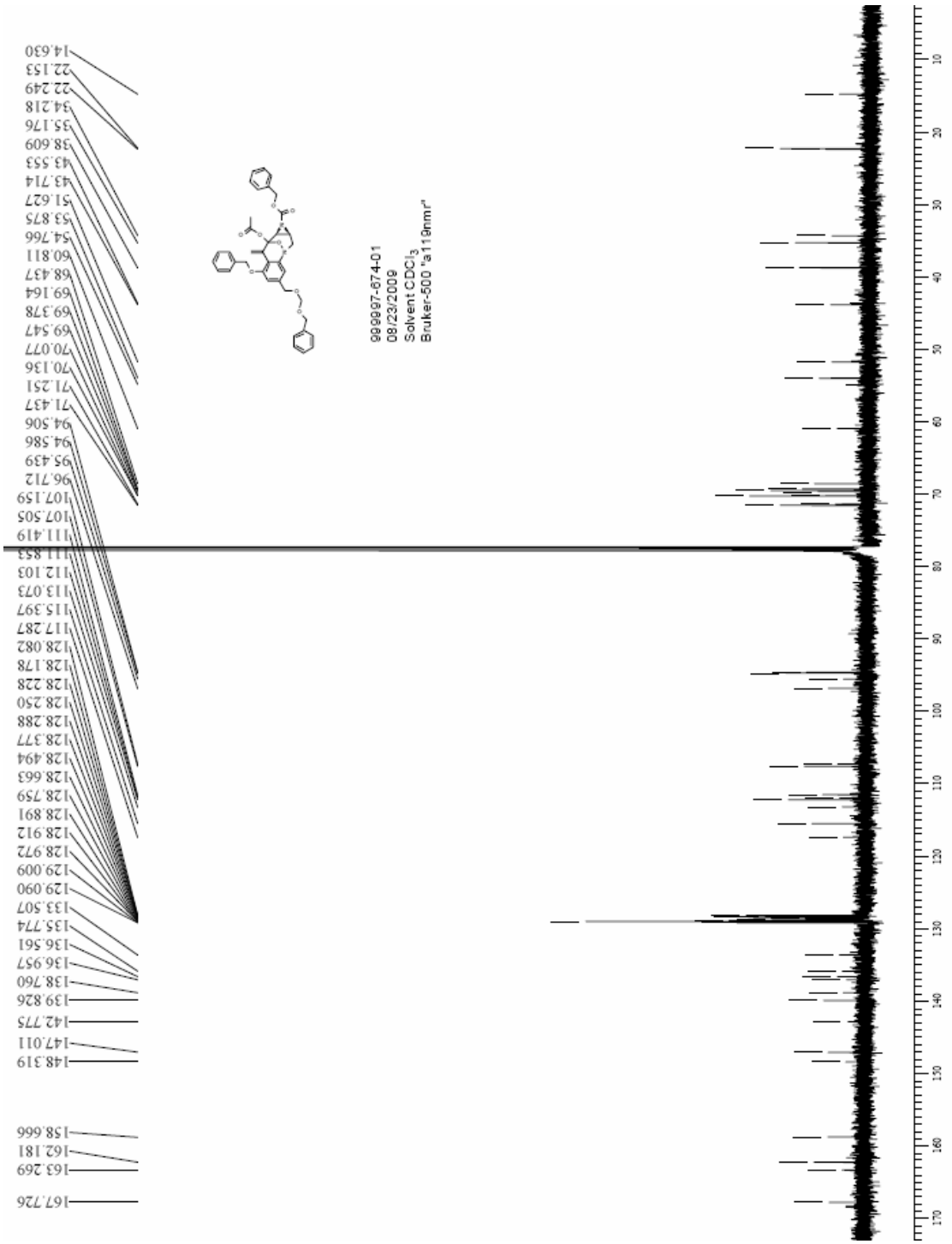

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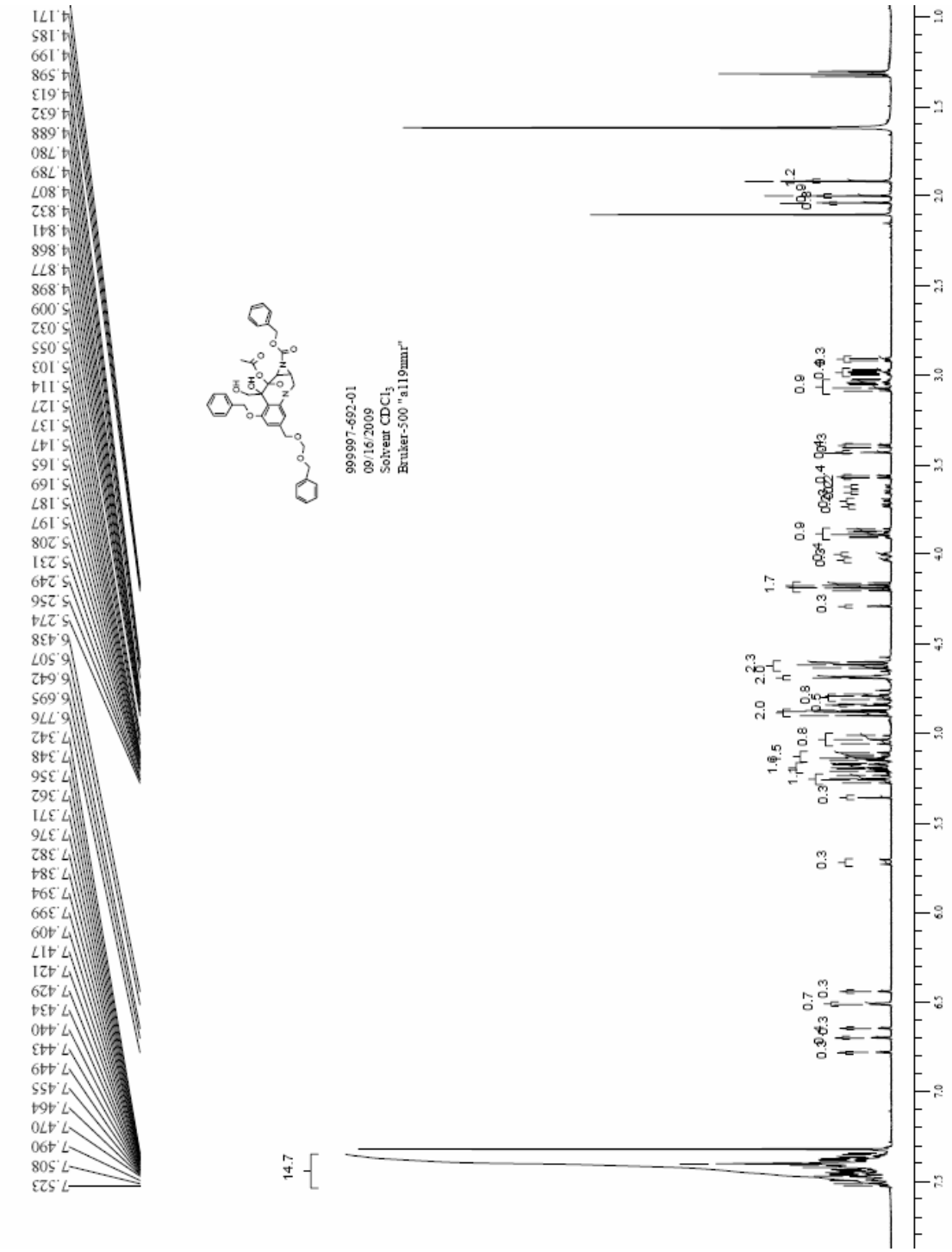

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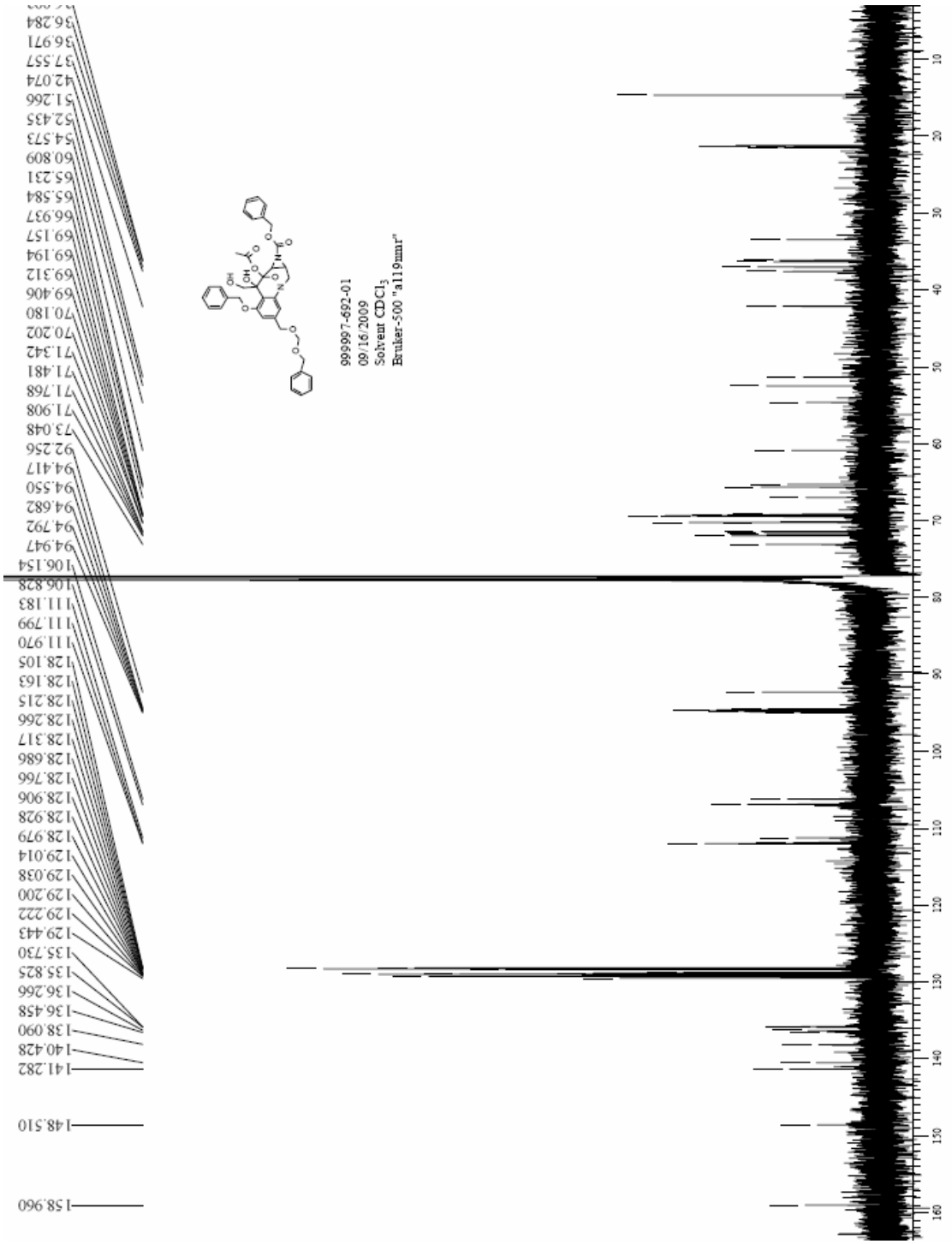

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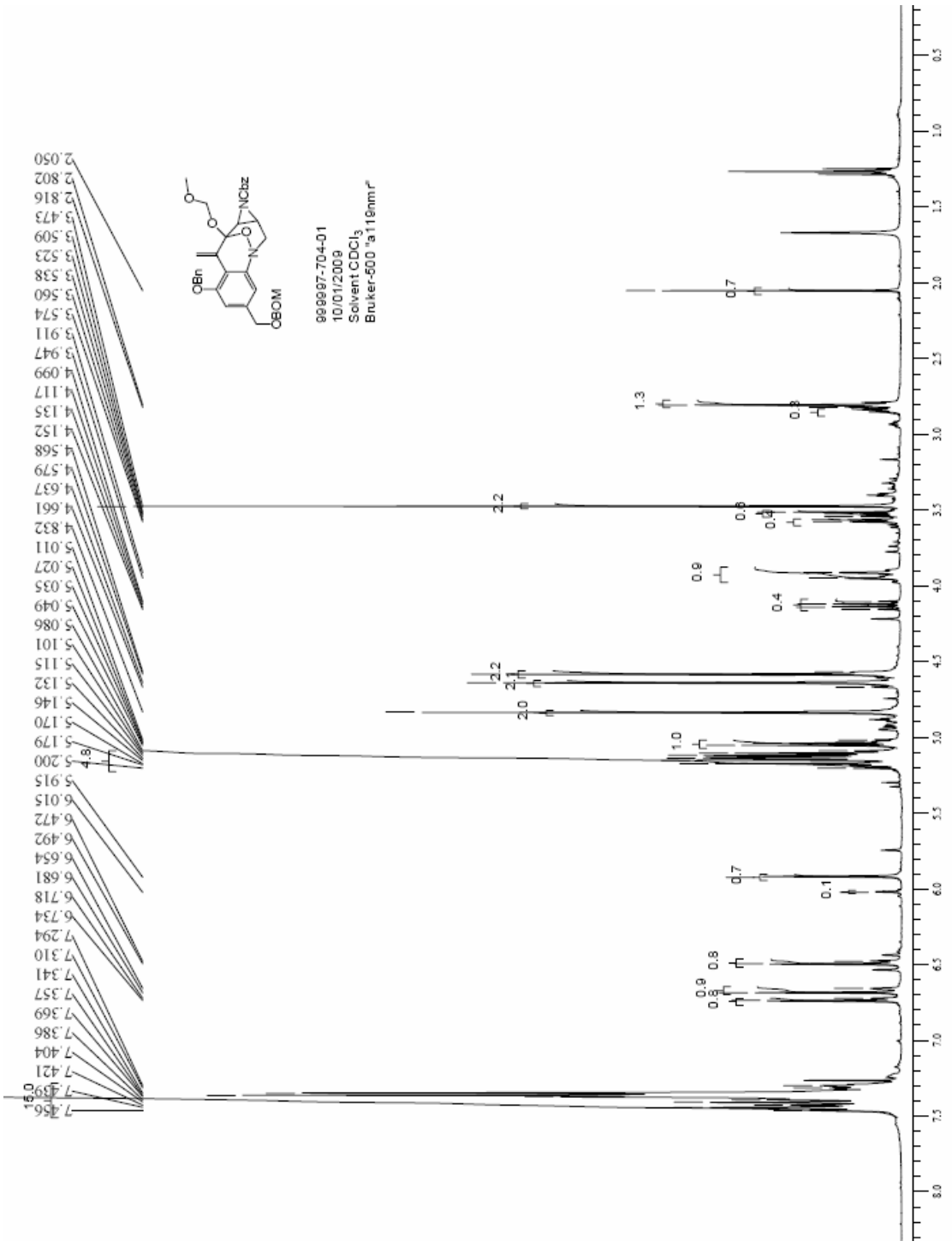
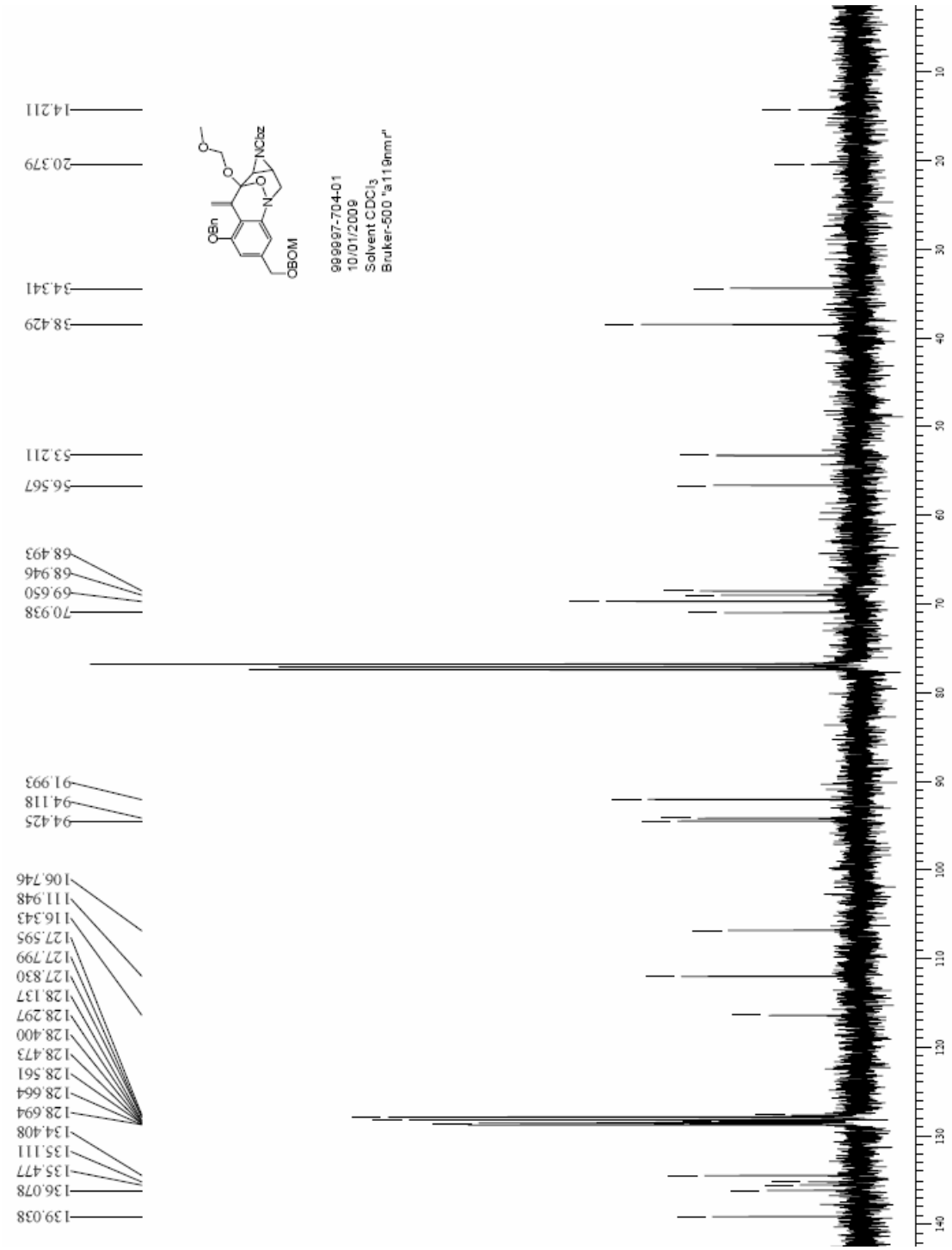


Compound **144** C^{13}NMR



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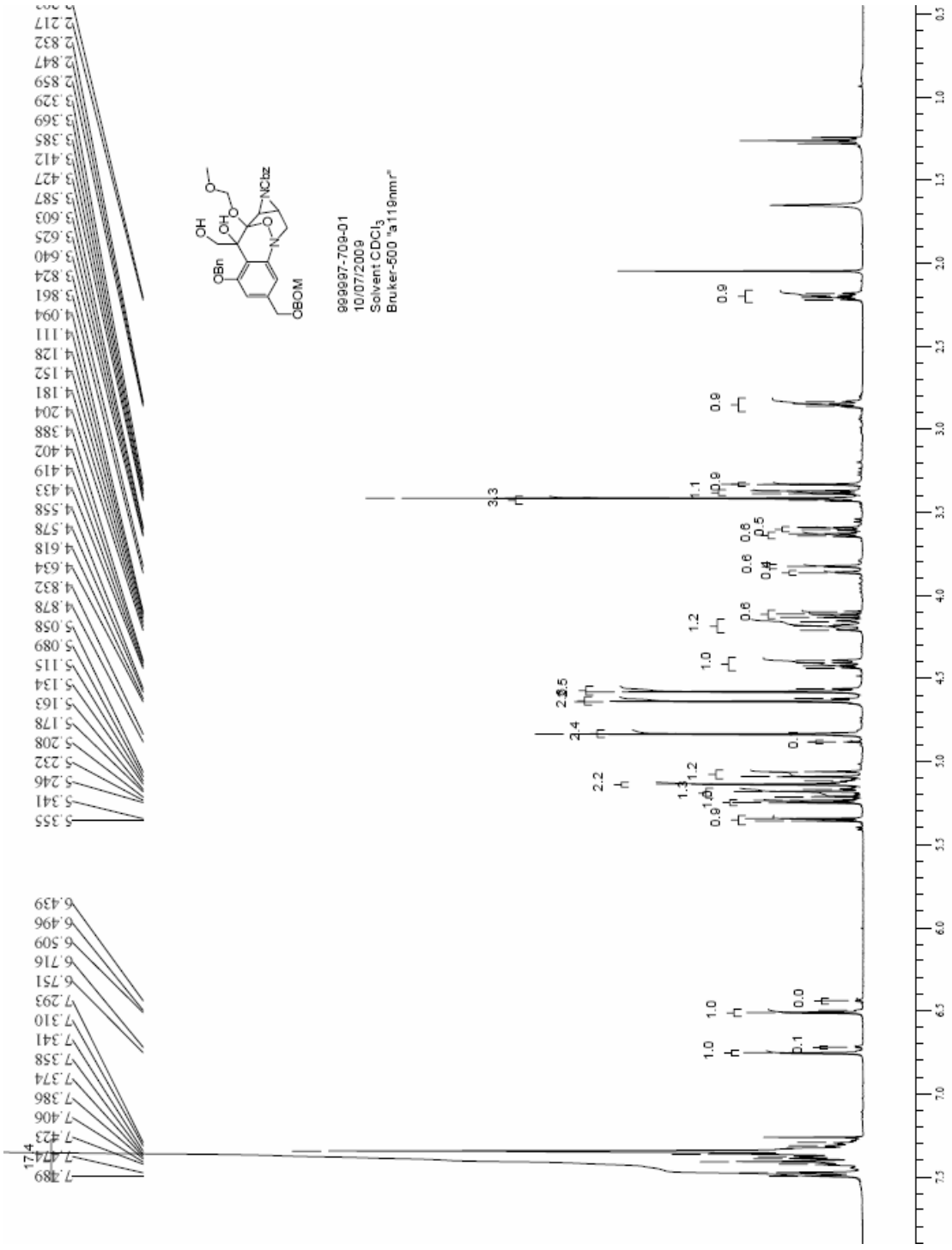

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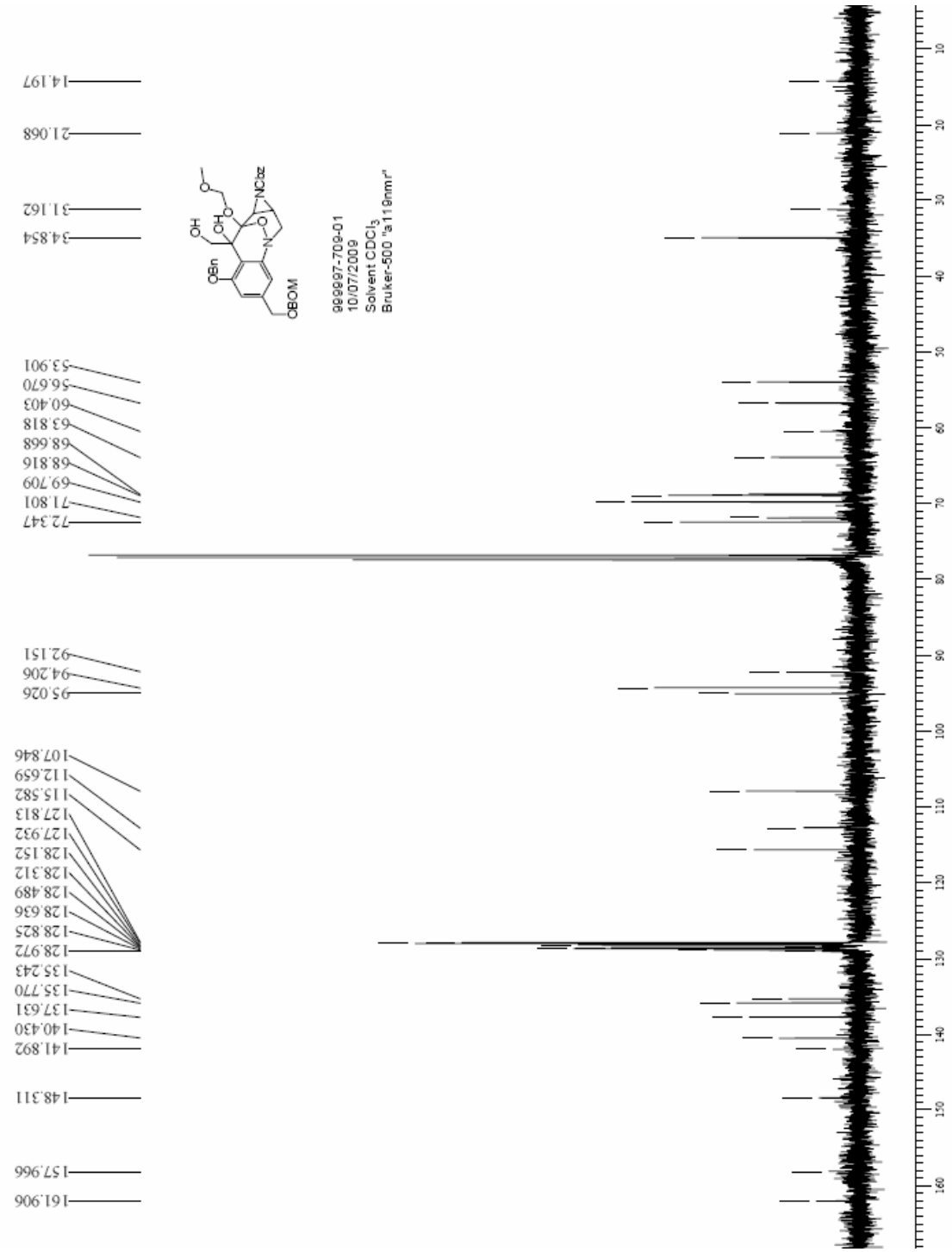

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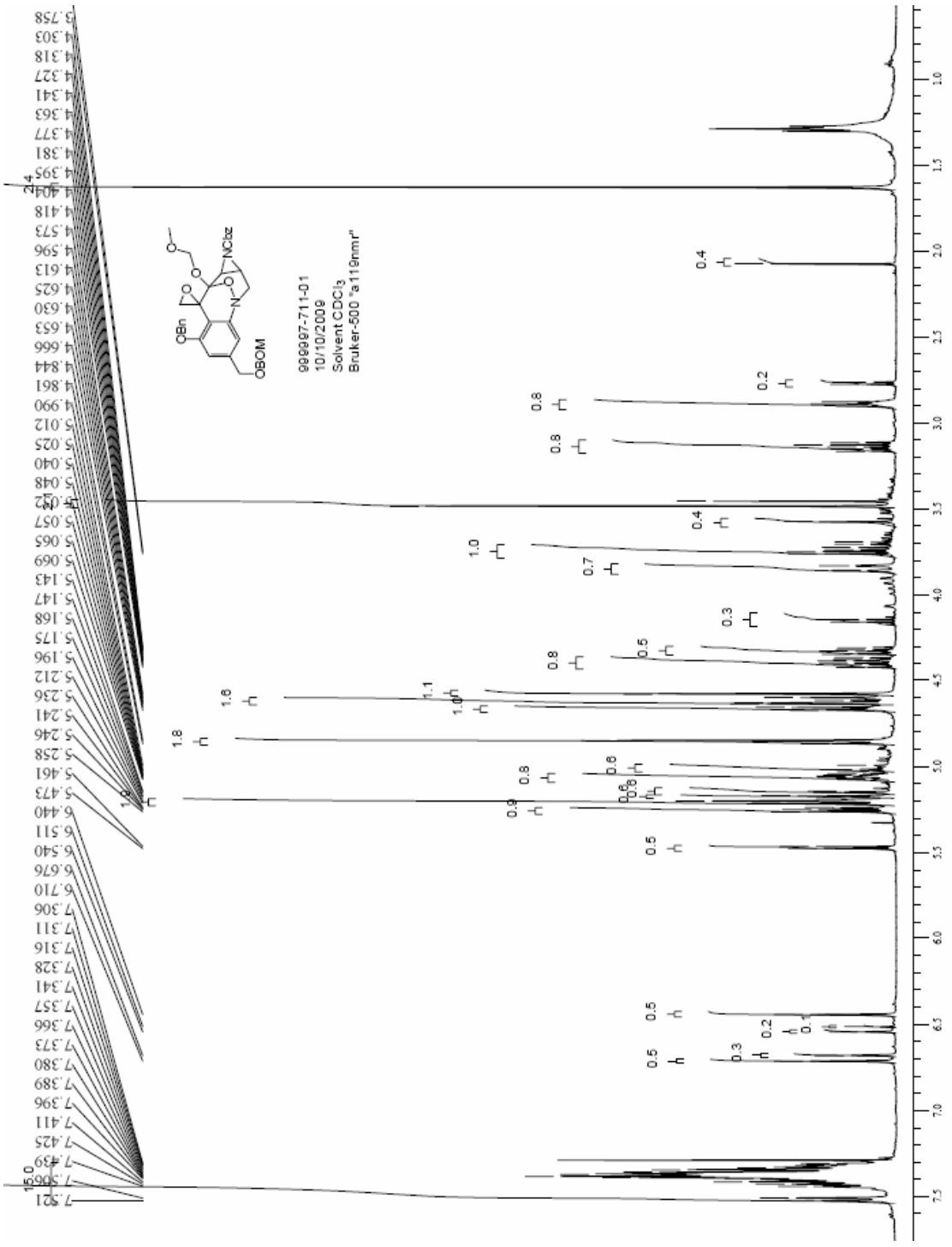

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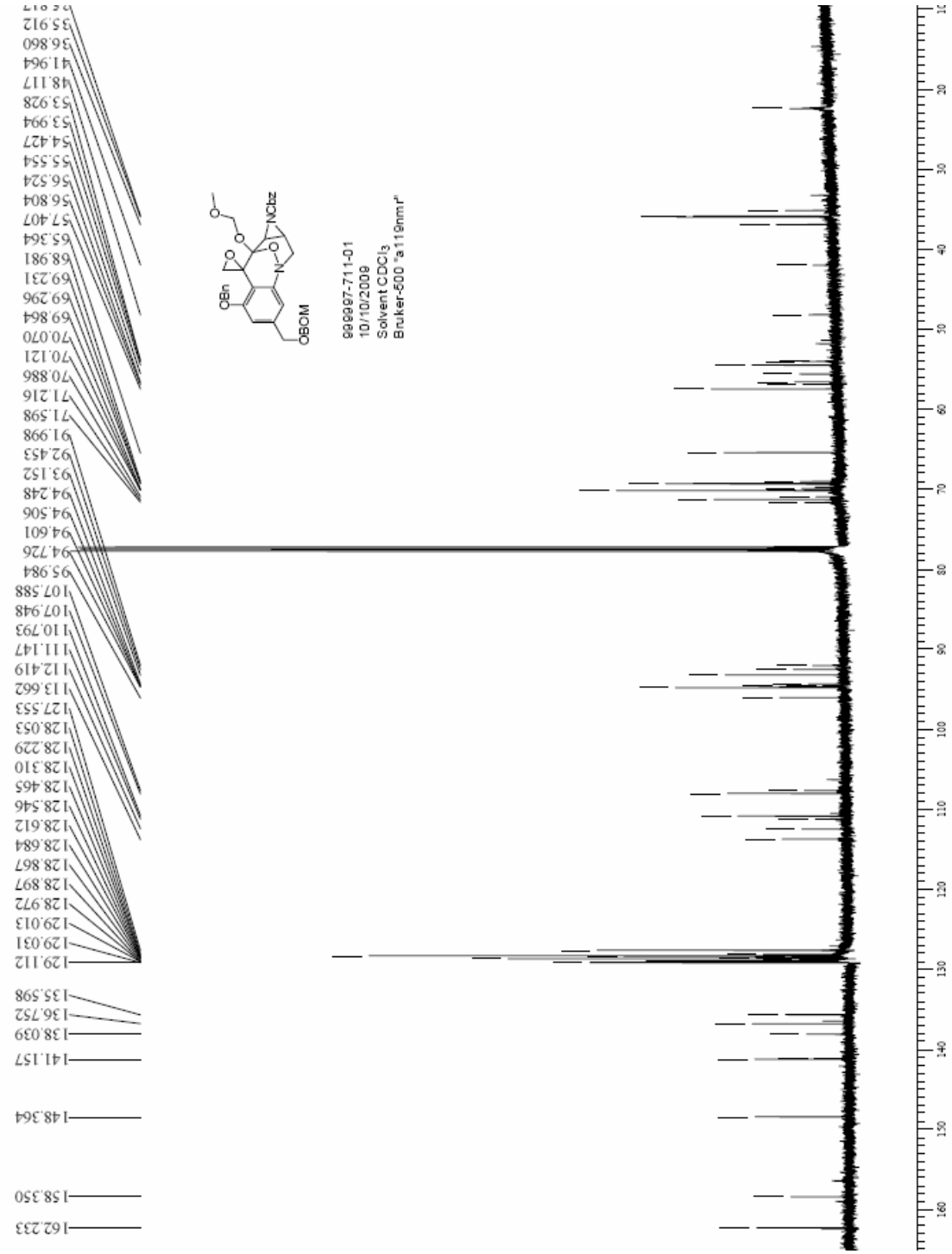

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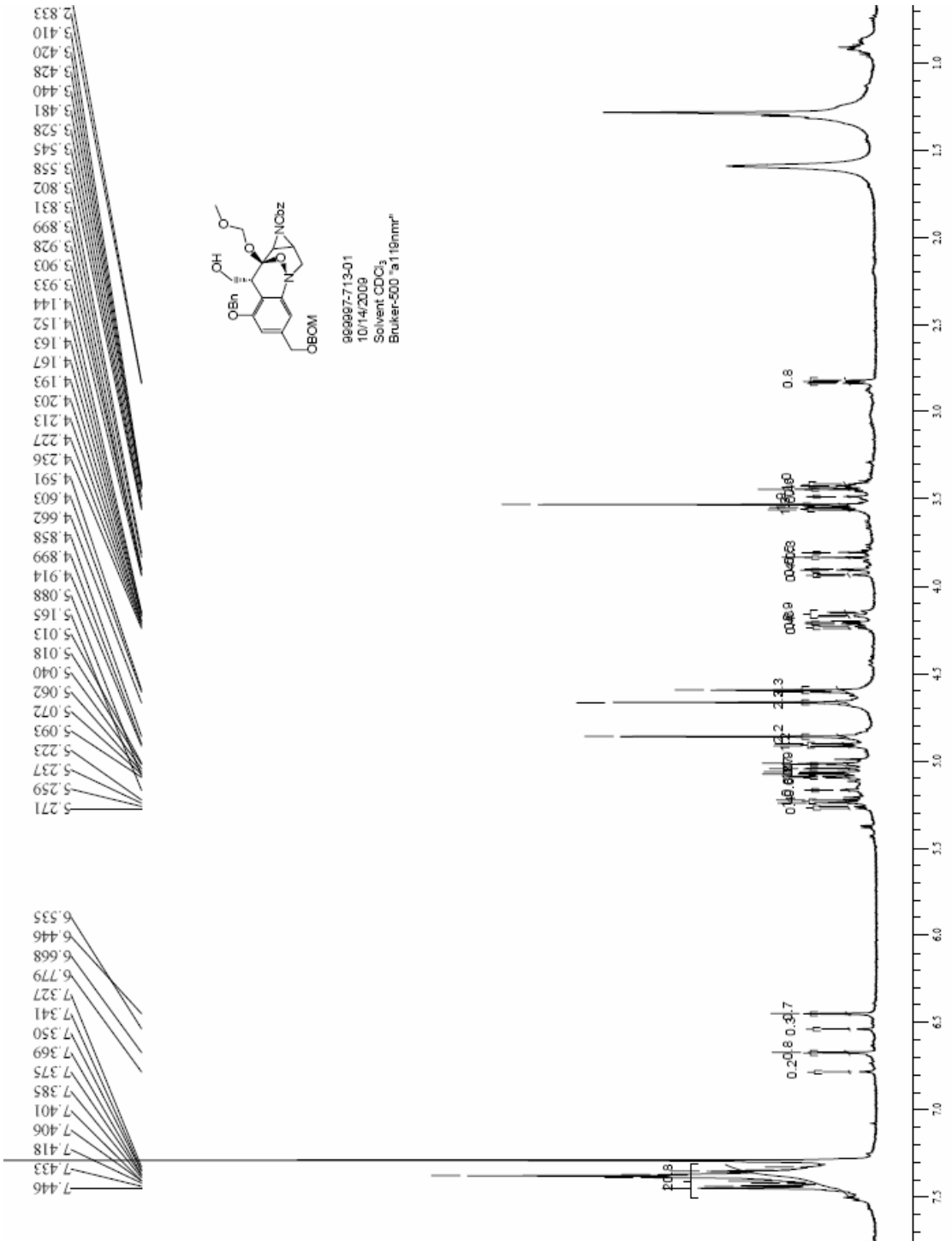

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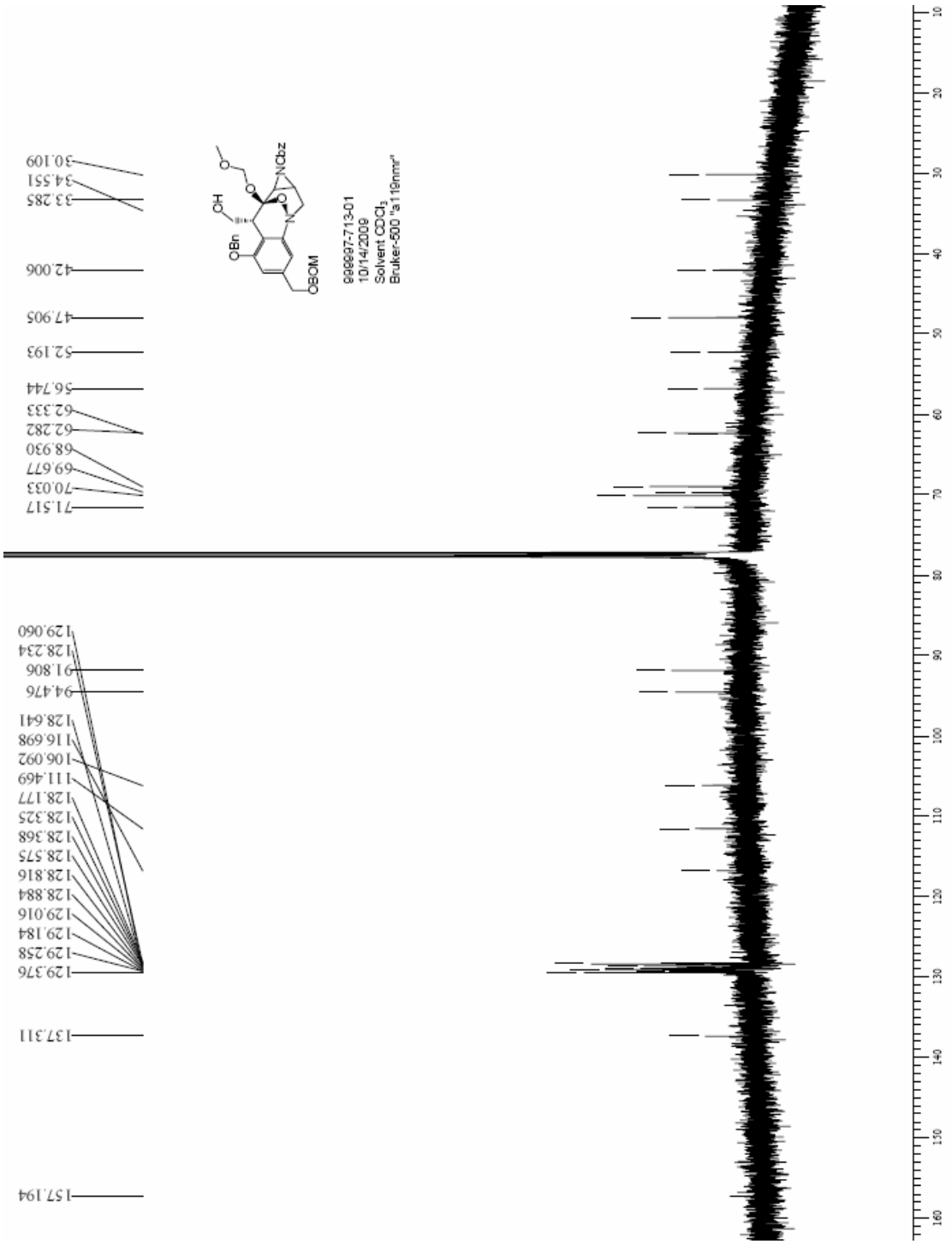

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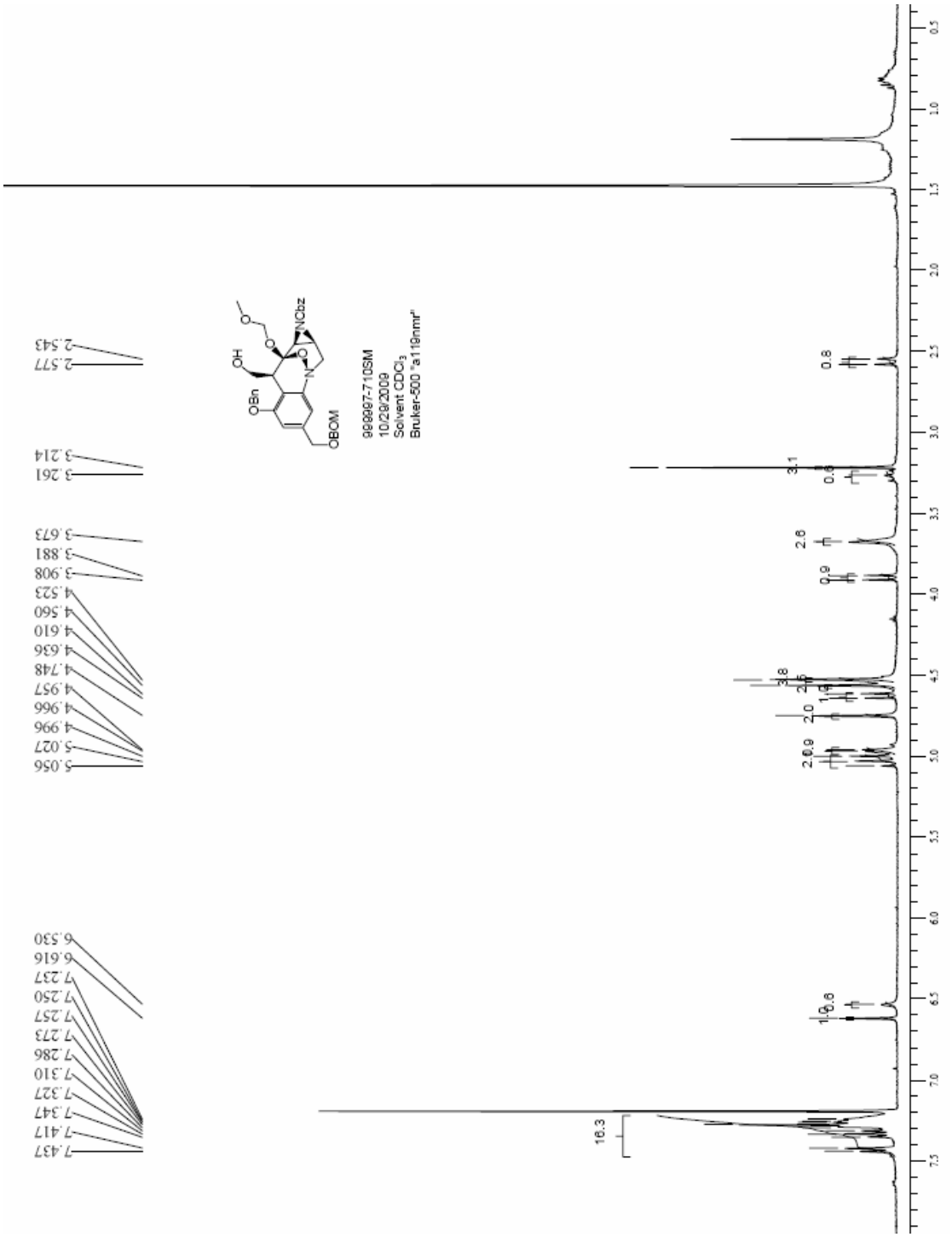

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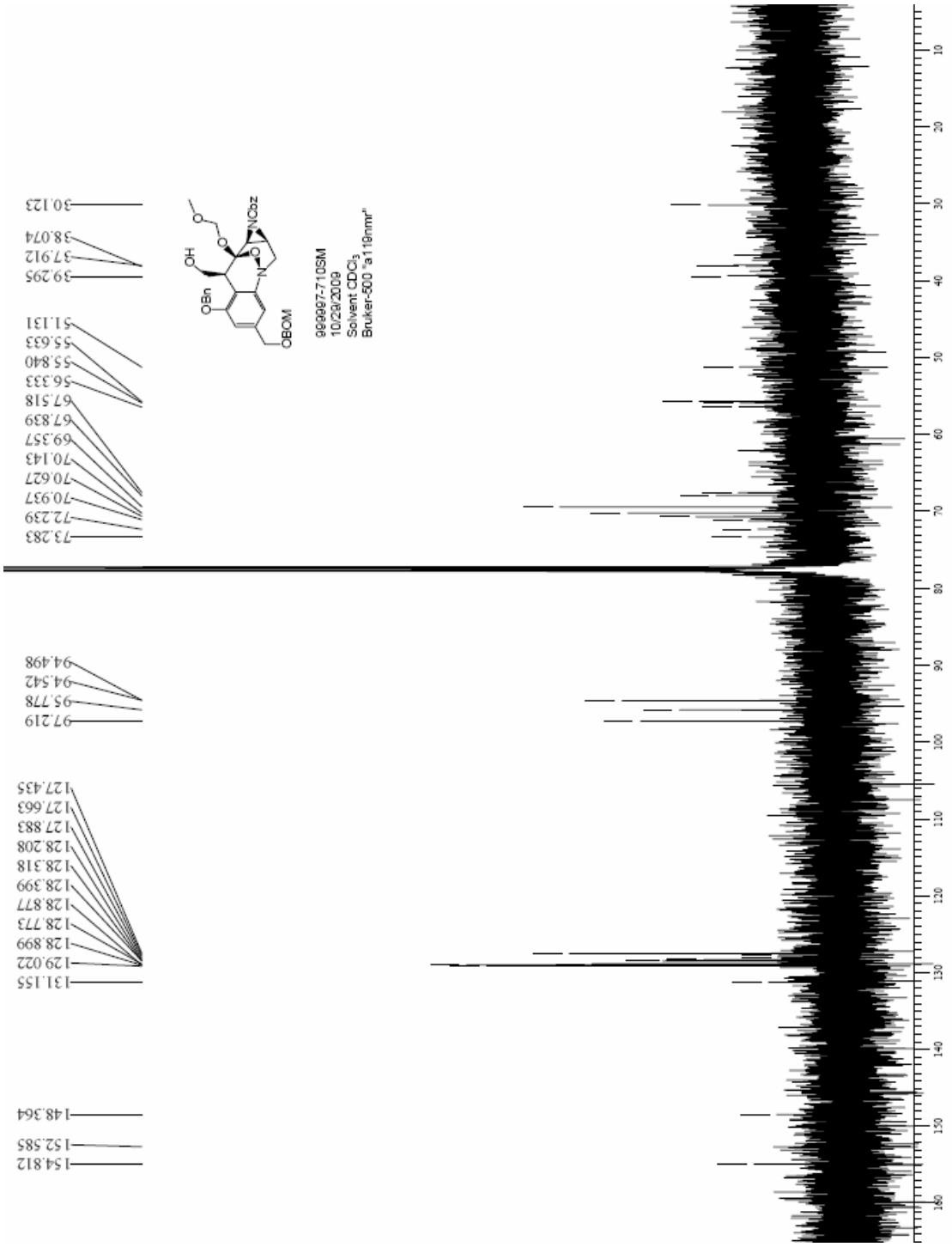

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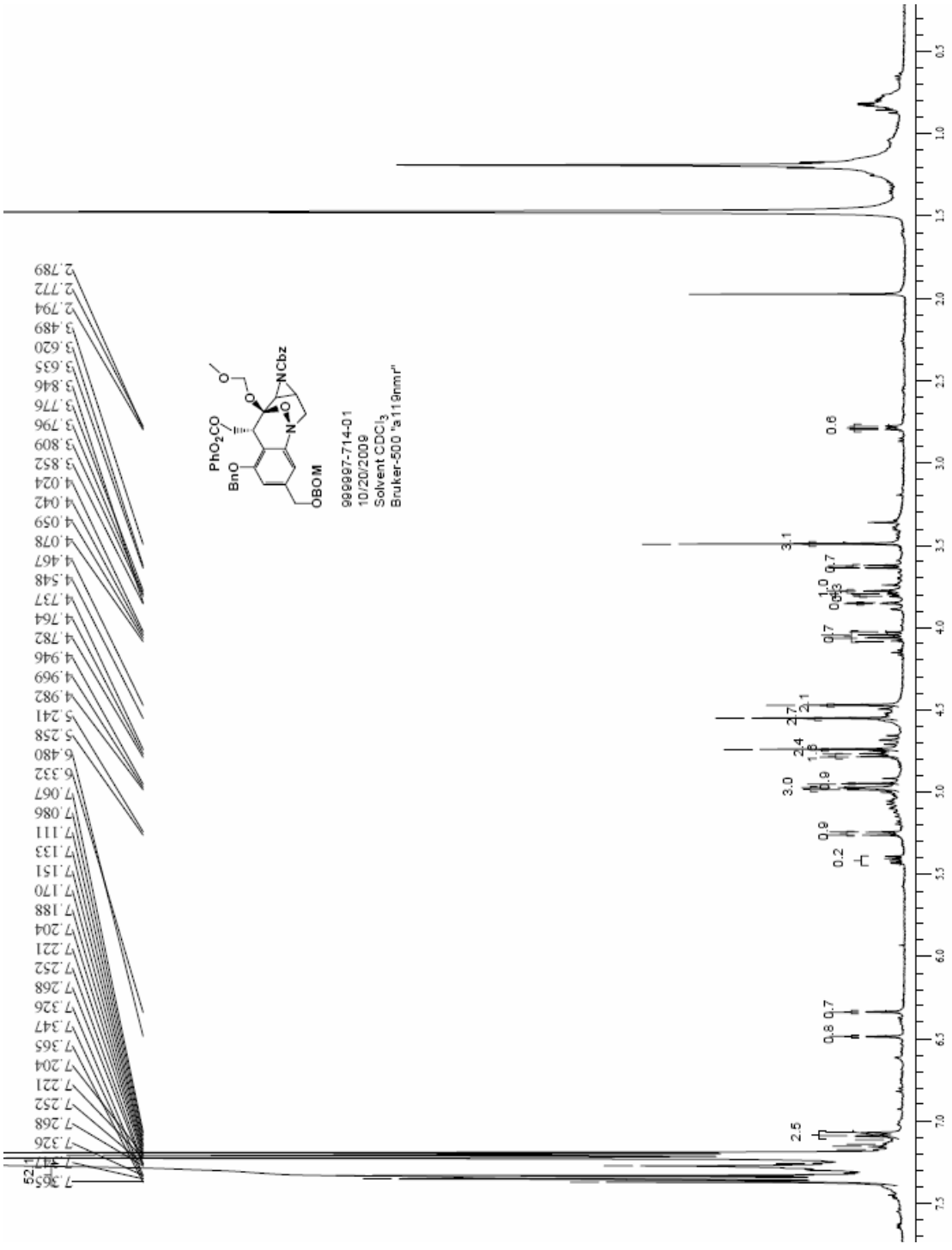

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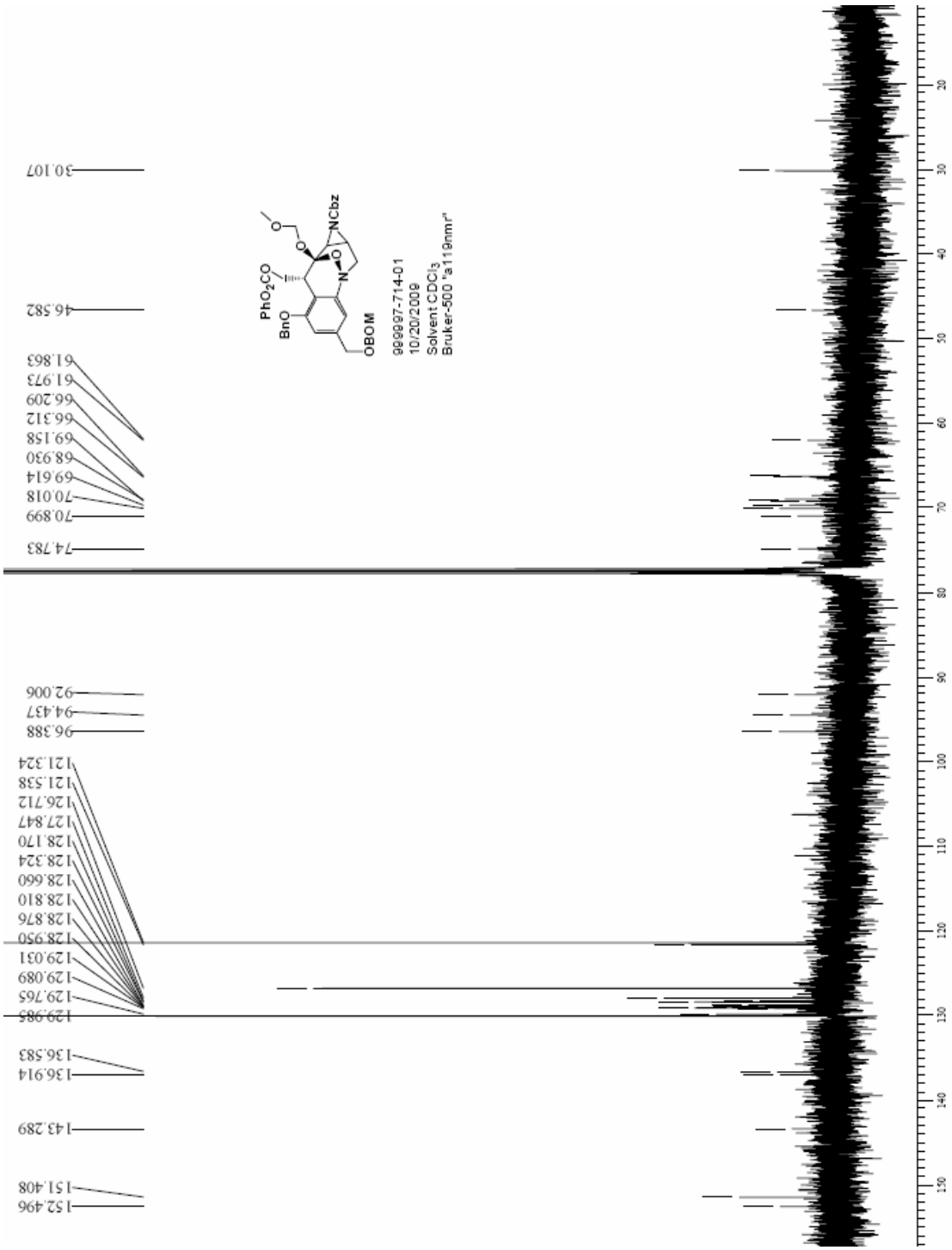

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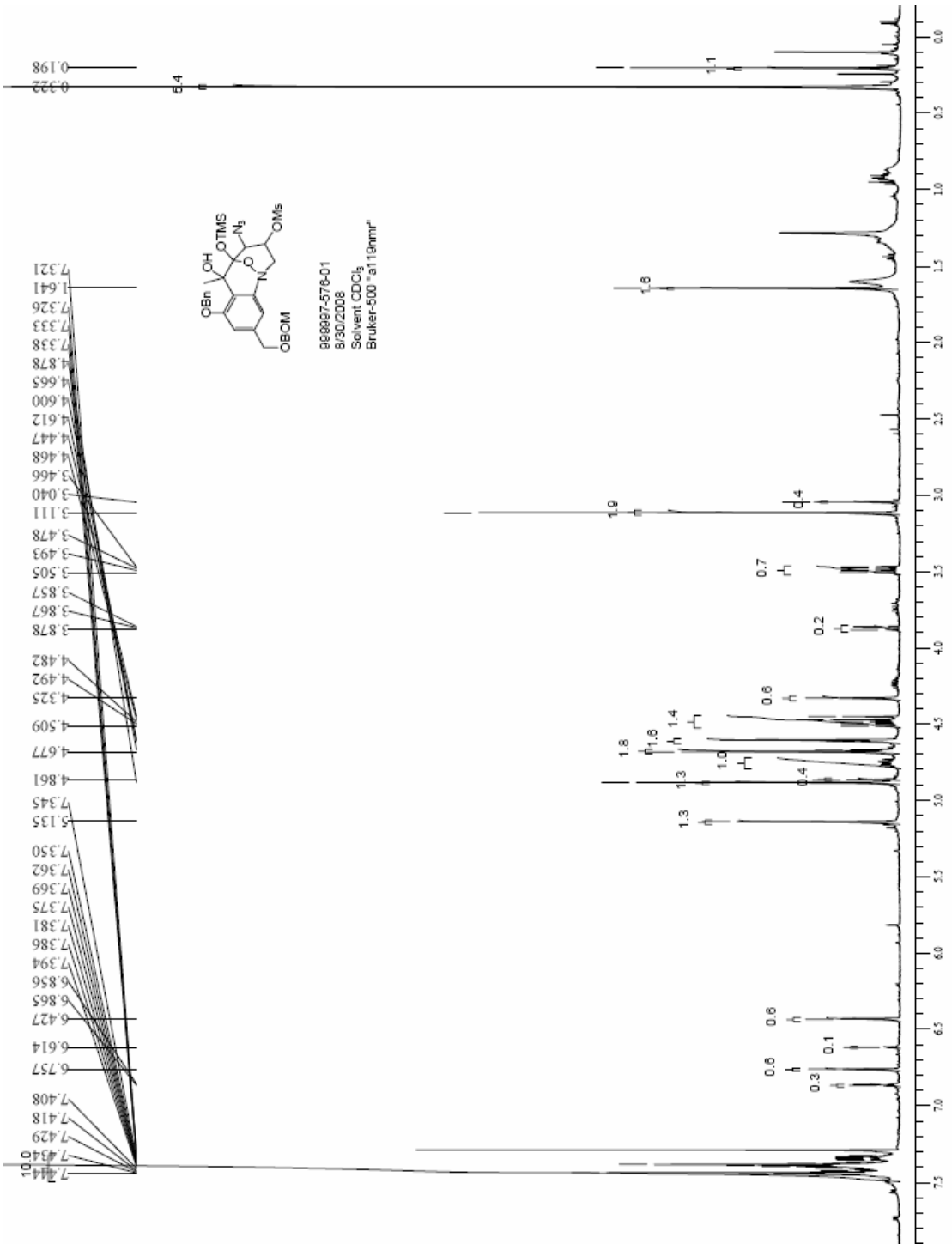

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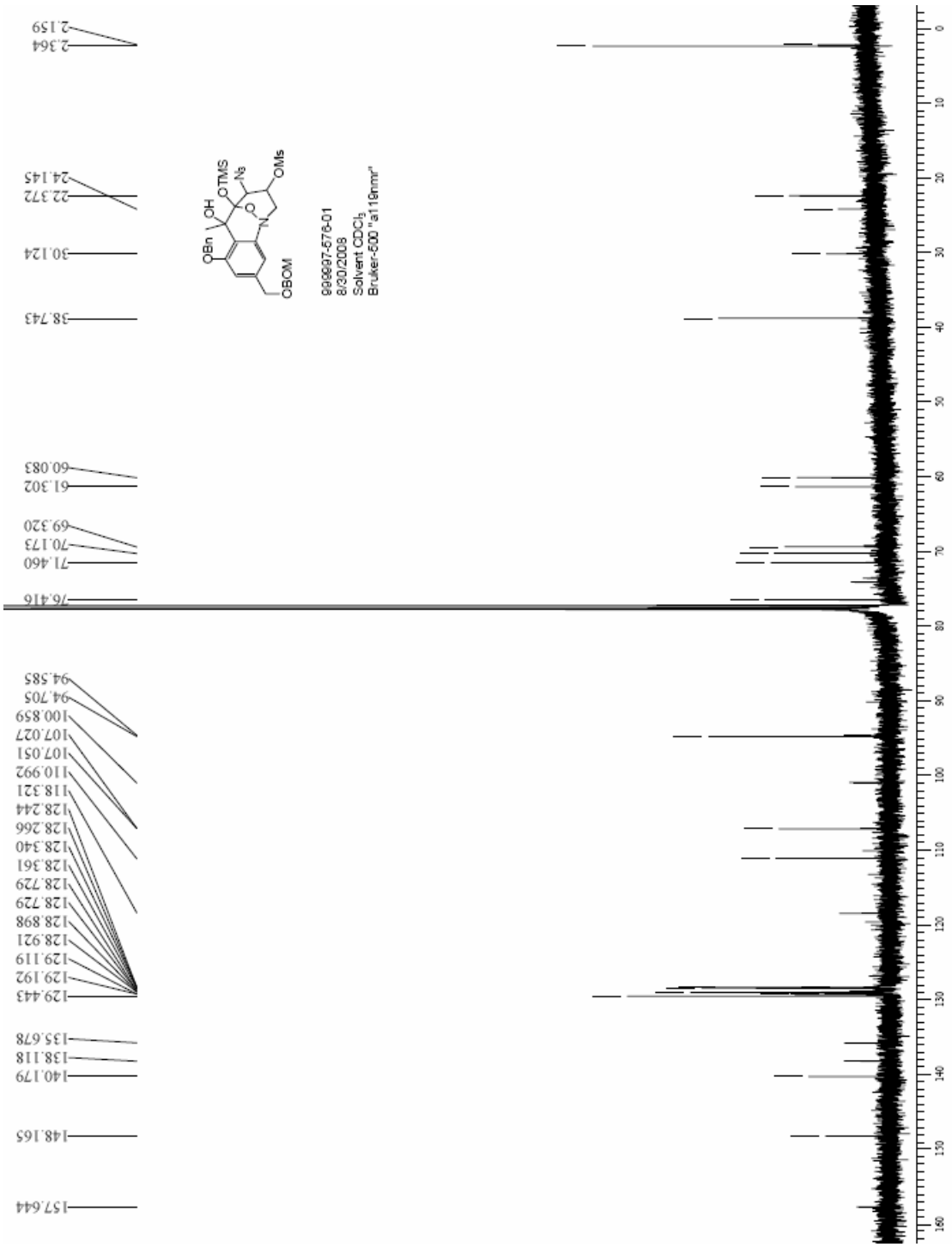
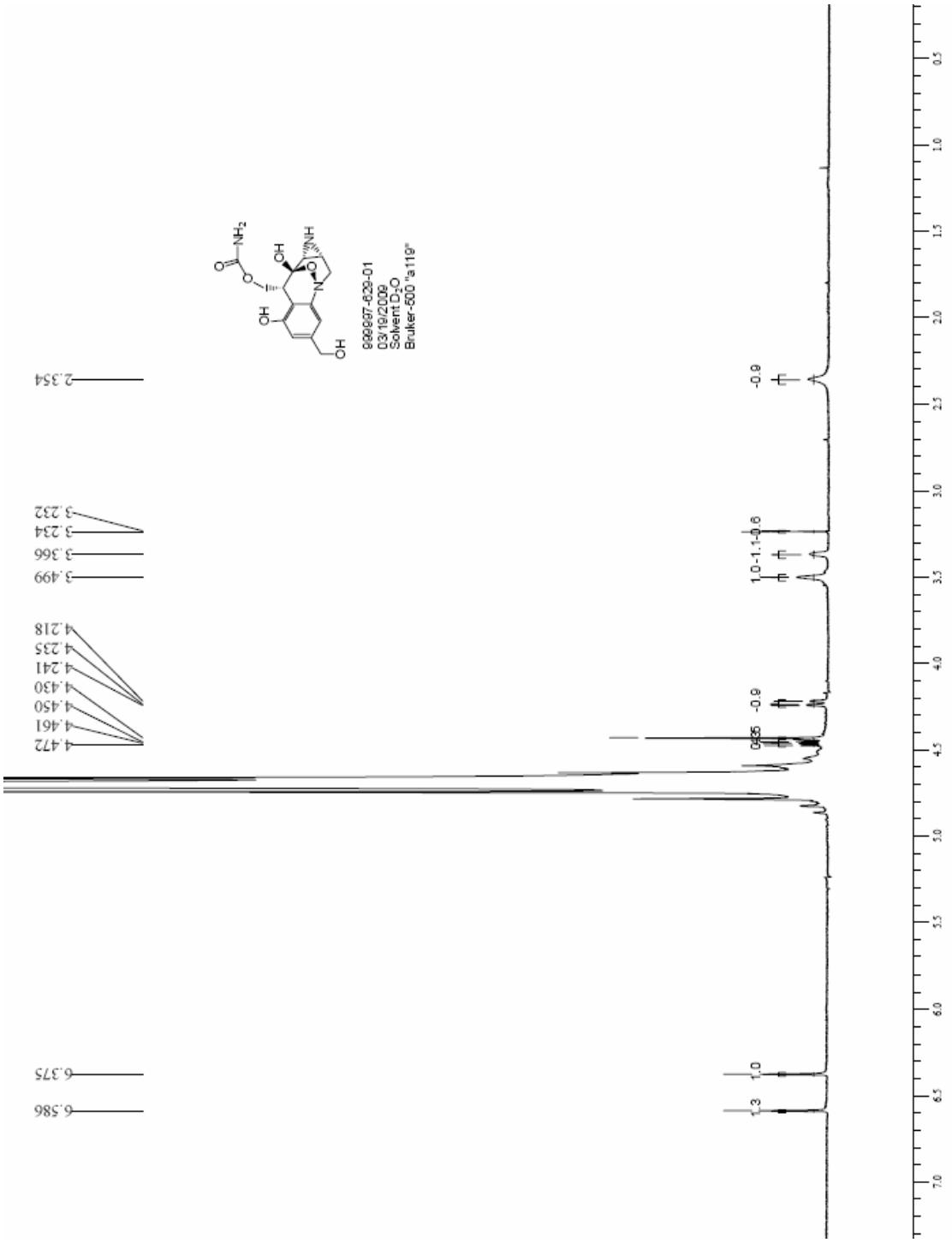


7-Epi-FR66979-1 HNMR



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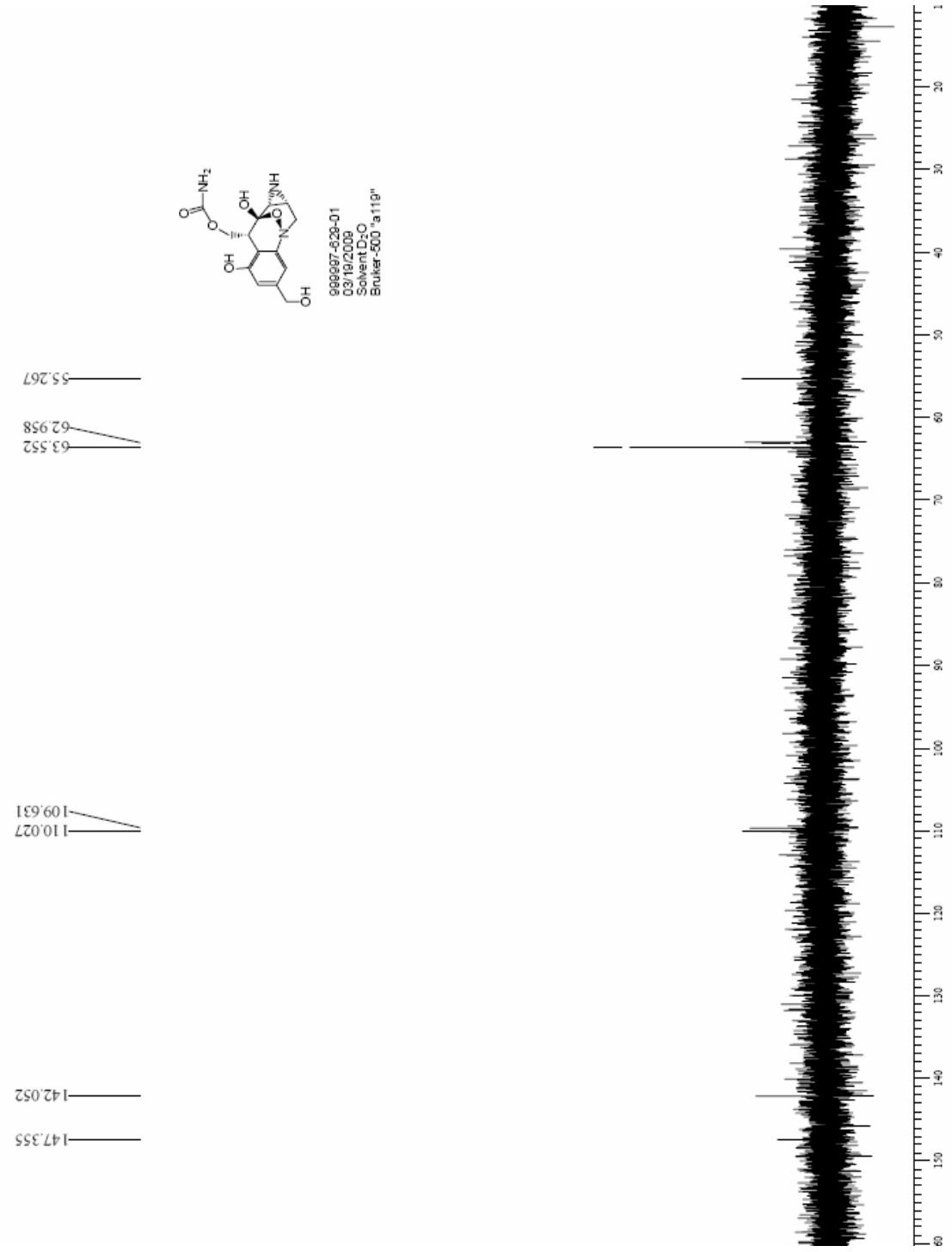

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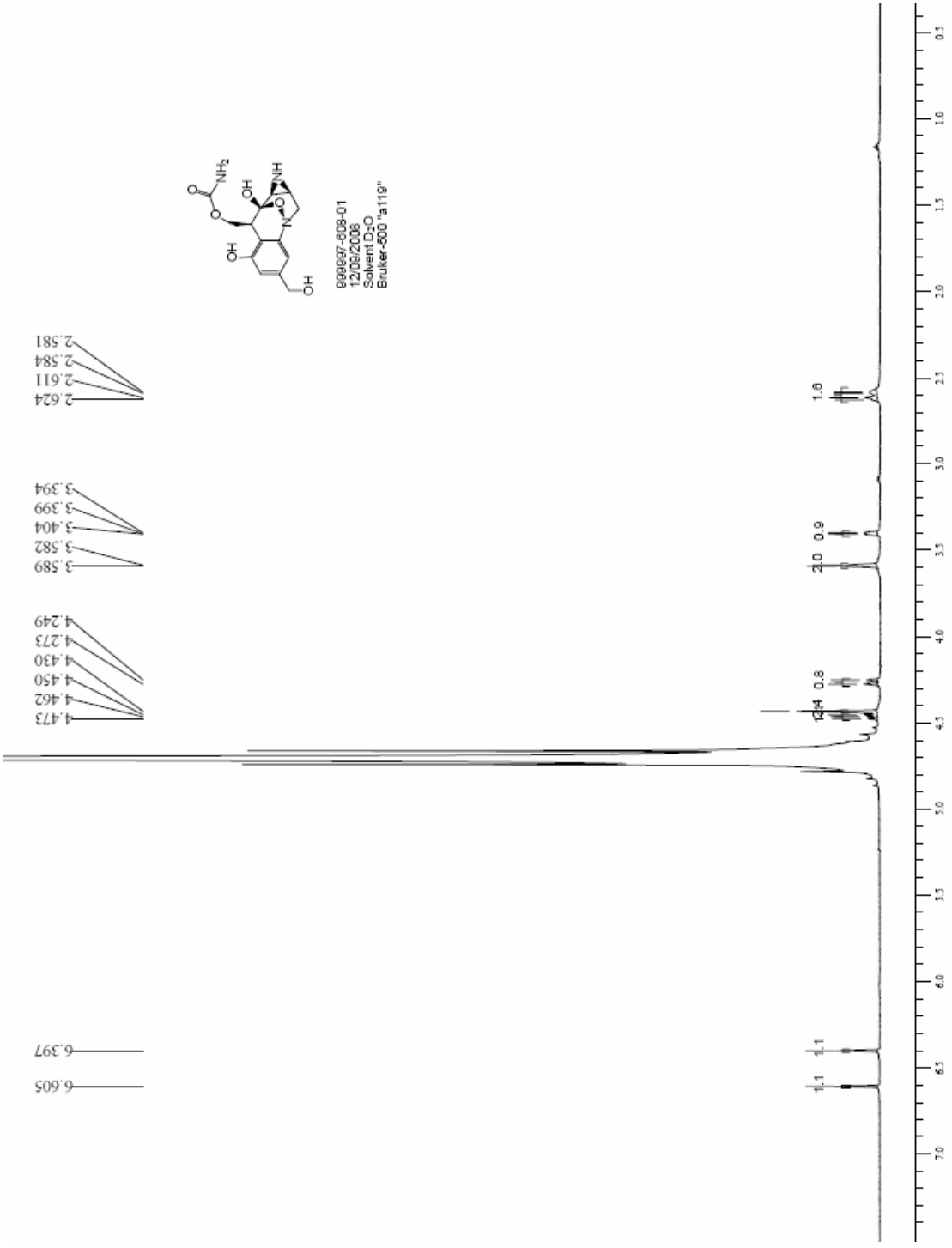
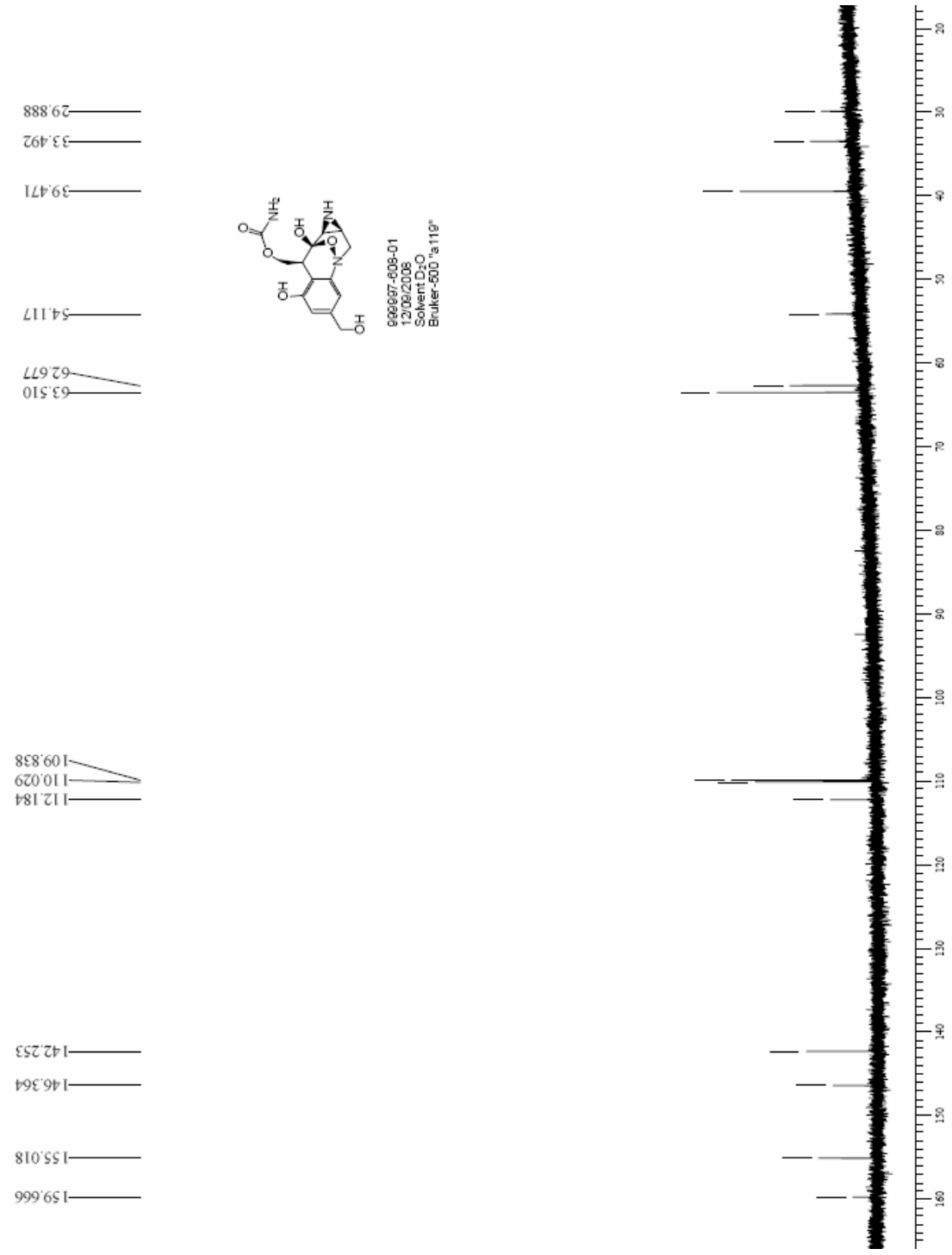
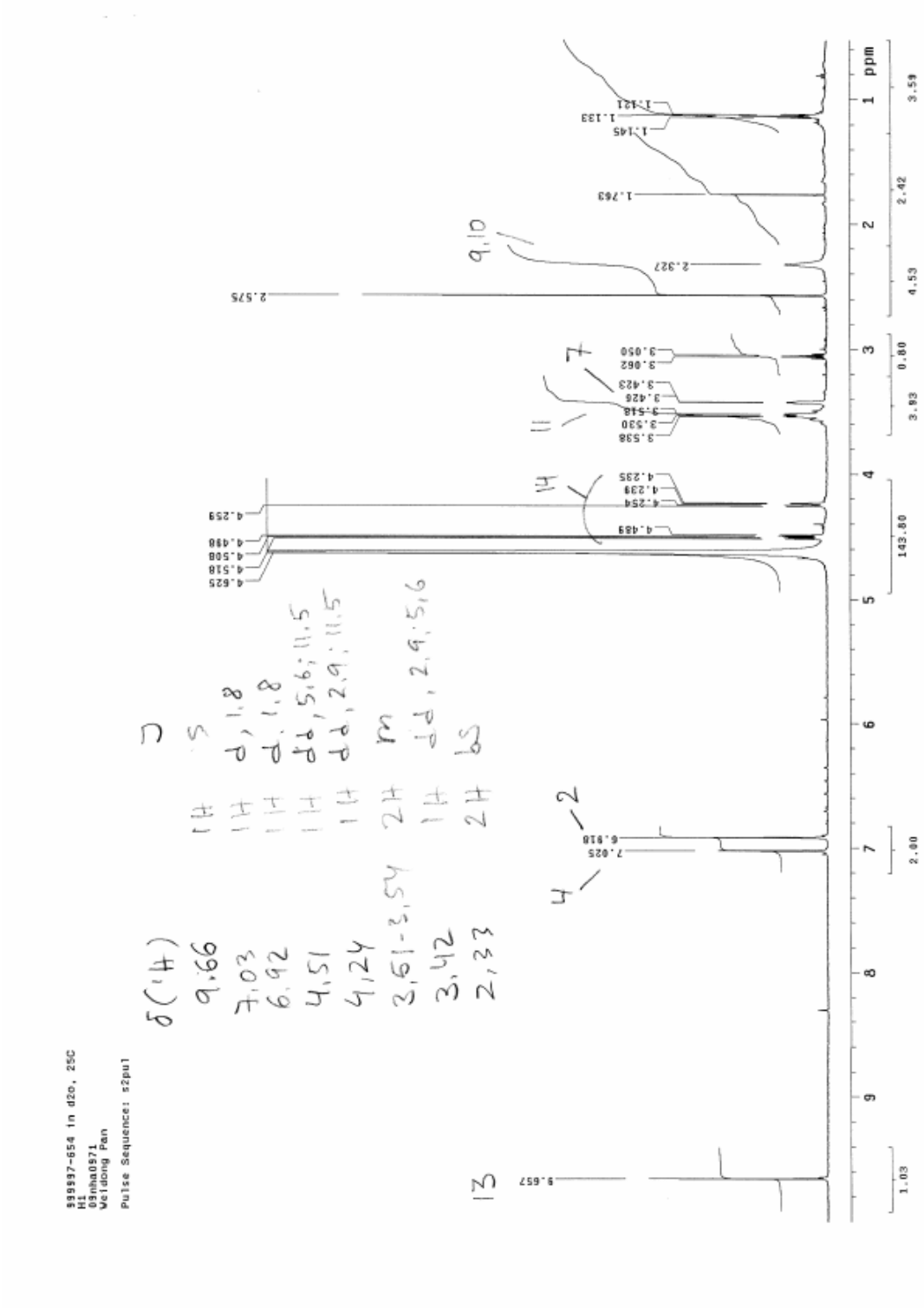


7-Epi-FR66979-2 C^{13}NMR



7-Epi-FR900482-2 HNMR



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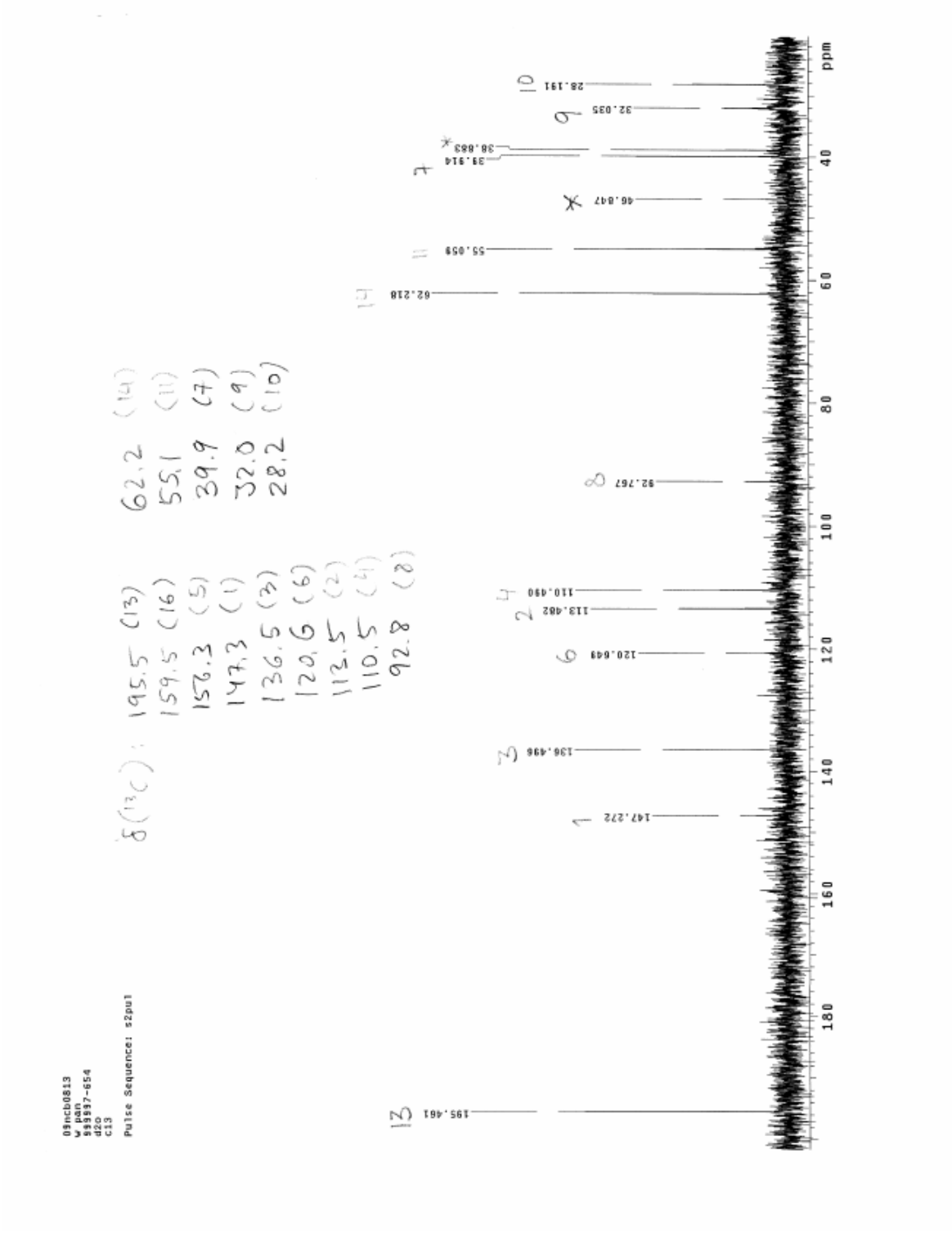

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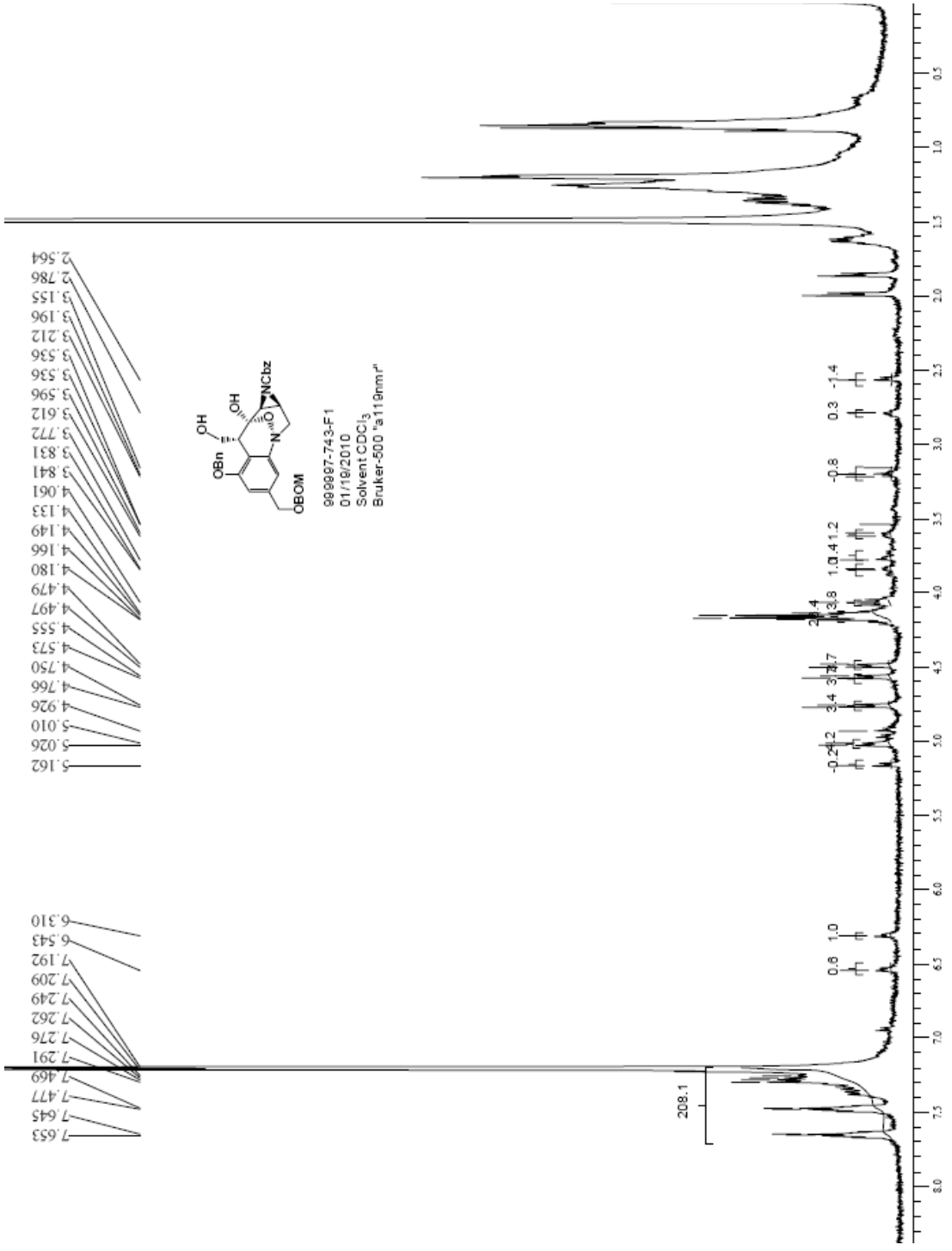

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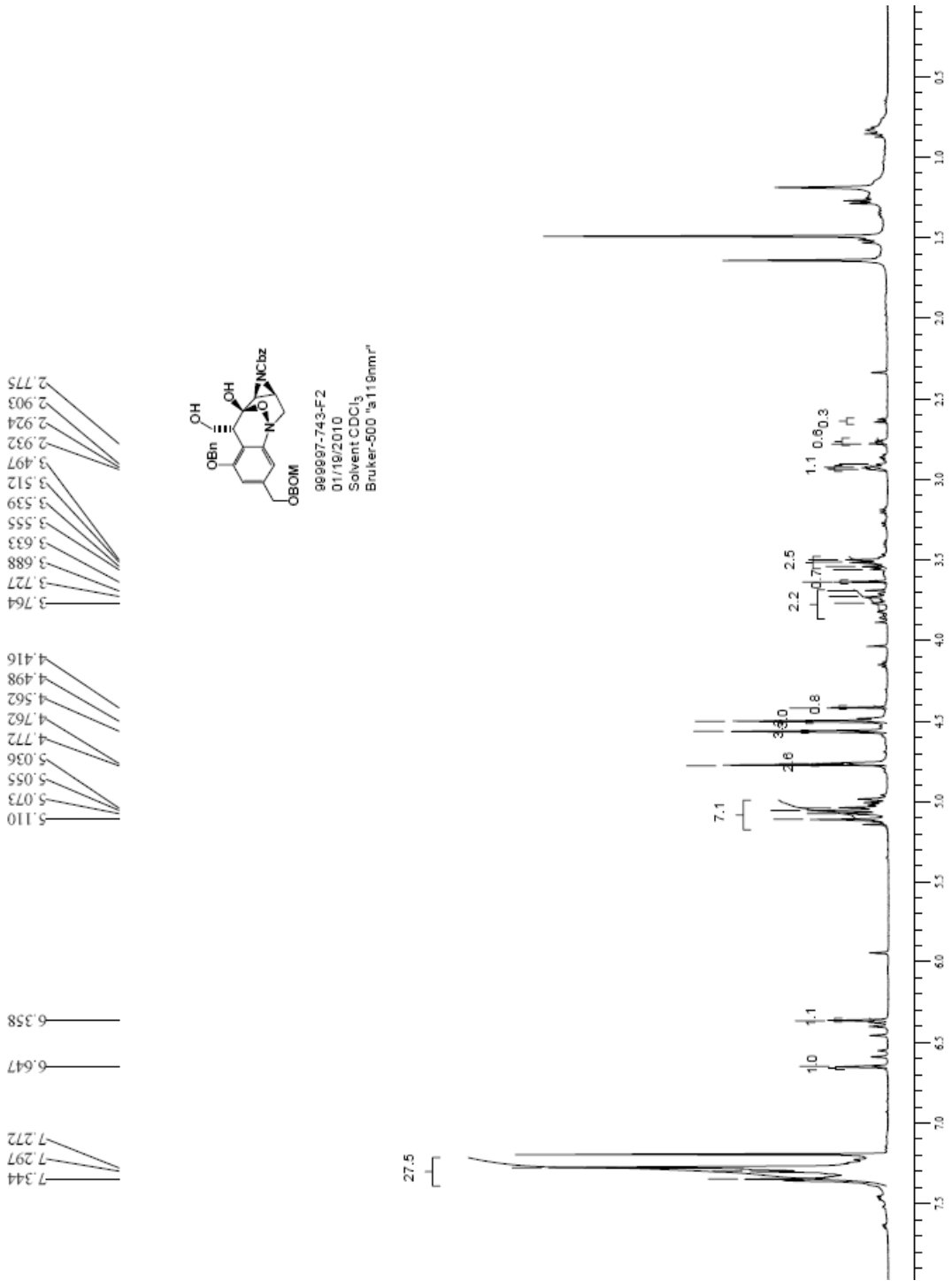

Curriculum Vitae

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EDUCATION

2003-2010 Ph.D. in Chemistry, Rutgers, the State University of New Jersey
1998-2000 M.S. in Chemistry, Rutgers, the State University of New Jersey
1990-1993 M.S. in Chemistry, Sichuan University, P. R. China.
1983-1987 B.S. in Chemistry, Sichuan Normal College, P. R. China

PROFESSIONAL EXPERIENCE

2009-2010 Scientist I in Chemical Research, Merck Research Laboratory, Kenilworth, NJ
2000-2009 Assistant Scientist ~Scientist I in Chemical Research, Schering-Plough Research Institute, Kenilworth, NJ
1998-2000 Research Assistant in Department of Chemistry, Rutgers University, New Brunswick, NJ
1993-1998 Research Associate in Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, China
1990-1993 Research Assistant in Department of Chemistry, Sichuan University, China

PUBLICATIONS, PATENTS and PRESENTATIONS

- Toward the Back-Up of Boceprevir (SCH 503034): Discovery of New Extended P4-Capped Ketoamide Inhibitors of Hepatitis C Virus NS3 Serine Protease with Improved Potency and Pharmacokinetic Profiles. Bogen, Stephane L.; Pan, Weidong; Ruan, Sumei; Nair, Latha G.; Arasappan, Ashok; Bennett, Frank; Chen, Kevin X.; Jao, Edwin; Venkatraman, Srikanth; Vibulbhan, Bancha; Liu, Rong; Cheng, Kuo-Chi; Guo, Zhuyan; Tong, Xiao; Saksena, Anil K.; Girijavallabhan, Viyyoor; Njoroge, F. George. *J.Med.Chem.* **2009**, 52(12), 3679-3688.
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- Design and SAR of P1-P3 ketoamide derived macrocyclic inhibitors of HCV protease. Venkatraman, Srikanth; Velazquez, Francisco; Pan, Weidong; et. al.. Abstracts of Papers, *234th ACS National Meeting*, Boston, MA, United States, August 19-23, **2007**.
- Discovery of Novel P4 capped sulfonamide derived inhibitors of HCV NS3 protease**.** Venkatraman, Srikanth; Wu, Wanli; Pan, Weidong; et. al. Abstracts of Papers, *234th ACS National Meeting, Boston*, MA, United States, August 19-23, **2007**.
- Discovery of new P4 (esters, acids, ketones) extended ketoamide inhibitors of the HCV NS3 serine protease with improved potency and PK profile. Bogen, Stephane L.; Pan, Weidong; et. al. Abstracts of Papers, *234th ACS National Meeting*, Boston, MA, United States, August 19-23, **2007**.
- Discovery of (1*R*,5*S*)-*N*-[3-Amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(*S*)-[[[(1,1- dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(*S*)-carboxamide (SCH 503034), a Selective, Potent, Orally Bioavailable Hepatitis C Virus NS3 Protease Inhibitor: A Potential Therapeutic Agent for the Treatment of Hepatitis C Infection. Srikanth Venkatraman; Pan, Weidong; et. al. *J.Med.Chem*, **2006**, 49, 6074-6086
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W. Wu, W. Yang, J. Pichardo, N. Butkiewicz, B. Malcolm, R. Liu, S. Agarwal, A. Hart, S. Kong, K.-C. Cheng, X. Cui, Y. Hsieh, L. Wang, L. Broske, D. Prelusky, W. Korfmacher, R. White, S. Bogdanowich-Knipp, P. Bradley, A. Prongay, Z. Guo, V. Madison, A. K. Saksena, V. Girijavallabhan, J. Piwinski, A. Ganguly and B. Baroudy, *230th ACS National Meeting, Washington, D. C.,* **2005**, Medi Oral presentation # 252.

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