UNIVERSITY OF CALIFORNIA,
IRVINE

Development of Transition Metal-Catalyzed Reactions for the Synthesis and Biological Evaluation of Enantioenriched Diarylalkanes and Homopropargylic Sultams

DISSERTATION

Submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Charlotte A. Osborne

Dissertation Committee:
Professor Elizabeth R. Jarvo, Chair
Professor Jennifer A. Prescher
Professor Kenneth J. Shea

2015

DEDICATION

For my family

for their unwavering love and support

TABLE OF CONTENTS

Page

LIST OF FIGURES

LIST OF SCHEMES

Page

LIST OF TABLES

ACKNOWLEDGEMENTS

I am grateful for funding from the NIH National Cancer Institute for a Ruth L. Kirschstein NRSA Predoctoral Fellowship, and to the Chao Family Comprehensive Cancer Center for a seed grant to support my research.

To Liz Jarvo, thank you for being my research advisor and mentor during graduate school. I have learned so much while being in your lab. I am grateful for the opportunity to have worked on different yet exciting projects from the rest of the group, including biological experiments and silver chemistry.

To Jenn Prescher, thank you for being my mentor since day one. I have valued our conversations about classes, research, and career goals. I sincerely appreciate your support and guidance. Thank you for hooding me and being a member of my dissertation committee.

To Ken Shea, thank you for your support and career advice. Whether we were discussing research projects or proposal ideas, you have always encouraged me to go with my gut, and your guidance has been very helpful. I appreciate you being a member of my dissertation committee.

To Andy Borovik, thank you for being a friendly face since the beginning. I very much enjoyed auditing your class and having random conversations whenever we ran into each other in the hallway. Thank you for your support.

I would like to acknowledge Naomi Morrissette and Xiaolin Zi for being excellent collaborators on several projects. I am thankful to have had the opportunity to learn from your expertise while working with you and your lab members.

Thank you to the countless other mentors from whom I have learned valuable lessons (both for science and for life), including: Professors Andrew Duncan, Sarah Kirk, and Chuck Williamson (Willamette University), Dr. Malcolm Low (Oregon Health & Science University),

Mrs. Eleanor Ritter and Mrs. Beth Deal (School of Science & Technology), and Ms. Meredith VandenBerg (Meadow Park Middle School).

I wish to thank all current and former members of the Jarvo group with whom I have had the pleasure of working, especially Buck Taylor, Ben Kohn, and the Jarvo "posse": Hanna Wisniewska, Iva Yonova, and Elizabeth Swift. I will always remember our Jarvo lab game nights! Thank you also to Lucas Erickson, Luke Hanna, Mikhail Konev, Ruben Martinez, Thom Endean, Dave Dawson, George Johnson, Emily Tollefson, and Erika Lucas for the many bizarre yet amusing conversations that have taken place in lab.

I am indebted to my fantastic coauthors, without whom, publishing would have been a very stressful experience – thank you to Iva Yonova, George Johnson, Thom Endean, Emily Tollefson, and Dave Dawson. A special thank you goes out to past and present members of Team Silver: Hanna Wisniewska, Ben Kohn, and Thom Endean, and particularly to Hanna and Thom for being such enjoyable baymates during graduate school.

I would also like to acknowledge the current and former members of the Prescher and Borovik laboratories. Thank you for always making me feel welcome, whether I was rotating with the group or stopping by to borrow a chemical.

I especially wish to thank my parents, who have been there to support me every step of the way. Mom and Dad, thank you for your wisdom, encouragement, and love. "One bag at a time, one day at a time…" I am exceptionally proud to be your daughter.

And finally, thank you to my fiancé, Michael – you are an incredible human being. Your love, support, and patience during graduate school have made it a thousand times easier for me to succeed, and I could not have done it without you. My absolute favorite part of each day has been coming home to you. I am so lucky to have you in my life.

CURRICULUM VITAE
CHARLOTTE A. OSBORNE

1102 Natural Sciences II
Irvine, CA 92697

(949) 824-9402
osbornec@uci.edu

EDUCATION

2011–2015	Ph.D. in Organic Chemistry, University of California, Irvine, Irvine, CA
2007–2011	B.A. Honors in Chemistry, *magna cum laude*, Willamette University, Salem, OR

RESEARCH EXPERIENCE

2011–2015	NIH NRSA Predoctoral Fellow (UC Irvine) *Development of Transition Metal-Catalyzed Reactions for the Synthesis and Biological Evaluation of Enantioenriched Diarylalkanes and Homopropargylic Sultams* Advisor: Prof. Elizabeth R. Jarvo
Summer 2011	Chemistry Summer Graduate Student Fellow (UC Irvine) *Synthesis of Luciferin Derivatives for In Vivo Bioluminescence Imaging* Advisor: Prof. Jennifer A. Prescher
Summer 2010	Research Internships in Science & Engineering (UC Santa Barbara) *Synthesis of Cyclobutanediol Monomers as BPA Replacements* Advisor: Prof. Craig J. Hawker
2009–2011	Science Collaborative Research Program (SCRP) & Senior Chemistry Thesis Research Assistant (Willamette University) *Progress Toward the Synthesis of Anti-Depressant (+)-SCH 50911* Advisor: Prof. Andrew P. Duncan

PUBLICATIONS

"Silver-Catalyzed Enantioselective Propargylation Reactions of *N*-Sulfonylketimines." **Osborne, C. A.**; Endean, T. B. D.; Jarvo, E. R. *Org. Lett.* **2015**, *17*, 5340.

"Aromatic Sulfide Compounds and Methods and Use Thereof." Yonova, I. M.; **Osborne, C. A.**; Morrissette, N. S.; Jarvo, E. R. **2015**, U. S. Patent Appl. No. 14/666,088.

"Stereospecific Cross-Coupling Reactions of Aryl-Substituted Tetrahydrofurans, Tetrahydropyrans, and Lactones." Tollefson, E. J.; Dawson, D. D.; **Osborne, C. A.**; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 14951.

"Diaryl and Heteroaryl Sulfides: Synthesis via Sulfenyl Chlorides and Evaluation as Selective Anti-Breast-Cancer Agents." Yonova, I. M.; **Osborne, C. A.**; Morrissette, N. S.; Jarvo, E. R. *J. Org. Chem.* **2014**, *79*, 1947.

"Stereospecific Nickel-Catalyzed Cross-Coupling Reactions of Alkyl Grignard Reagents and Identification of Selective Anti-Breast-Cancer Agents." Yonova, I. M.; Johnson, A. G.; **Osborne, C. A.**; Moore, C. E.; Morrissette, N. S.; Jarvo, E. R. *Angew. Chem. Int. Ed.* **2014**, *53*, 2422.
*Article highlighted as "Synfact of the Month" in *Synfacts*, **2014**, *10*, 515.

PRESENTATIONS

Osborne, C. A.; Yonova, I. M.; Johnson, A. G.; Tollefson, E. J.; Morrissette, N. S.; Jarvo, E. R.
Identification of Enantioenriched Diarylalkanes as Selective Anti-Cancer Agents
Chao Family Comprehensive Cancer Center Scientific Retreat (Poster), September 2014

Osborne, C. A.; Tollefson, E. J.; Yonova, I. M.; Johnson, A. G.; Morrissette, N. S.; Jarvo, E. R.
Identification of Selective Anticancer Agents Synthesized by Stereospecific Nickel-Catalyzed Cross-Coupling Reactions
248th National Meeting of the American Chemical Society (Oral Presentation), August 2014

Osborne, C. A.; Yonova, I. M.; Johnson, A. G.; Morrissette, N. S.; Jarvo, E. R.
Synthesis, Biological Evaluation, and Anti-Breast Cancer Activity of Enantioenriched 1,1-Diarylalkanes and Diaryl Sulfides
247th National Meeting of the American Chemical Society (Poster Presentation), March 2014

Osborne, C. A.; Yonova, I. M.; Johnson, A. G.; Morrissette, N. S.; Jarvo, E. R.
Synthesis, Biological Testing, and Anti-Breast Cancer Activity of Enantioenriched Diarylalkanes
Chao Family Comprehensive Cancer Center Scientific Retreat (Poster), November 2013

AWARDS AND HONORS

2014	ACS Division of Organic Chemistry Travel Award for 248th National Meeting
2013–2015	NIH Ruth L. Kirschstein NRSA Predoctoral Fellowship
2011, 2012, 2013	NSF GRFP Honorable Mention
2011	AIC Senior Award in Chemistry (Willamette University)
2010	Barry M. Goldwater Scholarship
2010	Dick Van Santen ACS Scholarship
2008	CRC Freshman Chemistry Achievement Award (Willamette University)

TEACHING EXPERIENCE

Summer 2012	Lecture Teaching Assistant, *General Chemistry*
Spring 2012	Laboratory Teaching Assistant, *General Chemistry*
Winter 2012	Laboratory Teaching Assistant, *Organic Chemistry*
Fall 2011	Lecture Teaching Assistant, *General Chemistry*
2010–2011	Willamette University Chemistry Department Tutor, *Organic Chemistry*
2008–2009	Willamette University Dean's Office Tutor, *General Chemistry*

PROFESSIONAL MEMBERSHIPS

American Chemical Society
Iota Sigma Pi (National Honor Society for Women in Chemistry)
Phi Beta Kappa

SCIENCE OUTREACH

2012–2014	Iota Sigma Pi Calcium Chapter Historian
2011–2015	Iota Sigma Pi Calcium Chapter Member & Outreach Volunteer
2011–2015	LEAPS (Lab Experiments & Activities in the Physical Sciences) Volunteer
2011–2012	UCI Chemistry Outreach Program Volunteer
2010–2011	Willamette Chemistry Club President
2009–2010	Willamette Chemistry Club Outreach Coordinator
2009–2010	Willamette Science Outreach Program (Webber Scholar)

ABSTRACT OF DISSERTATION

Development of Transition Metal-Catalyzed Reactions for the Synthesis and Biological Evaluation of Enantioenriched Diarylalkanes and Homopropargylic Sultams

by

Charlotte A. Osborne

Doctor of Philosophy in Chemistry

University of California, Irvine, 2015

Prof. Elizabeth R. Jarvo, Chair

Methodology for the synthesis of enantioenriched compounds is critical to the discovery of new pharmaceuticals. To access single enantiomers of biologically relevant molecules for evaluation, the Jarvo laboratory has developed both enantiospecific and enantioselective reactions. Herein, we report the development of transition metal-catalyzed methodology to generate diarylalkanes and homopropargylic sultams in high enantiomeric excess.

Diaryl sulfides and 1,1-diarylalkanes are known to exhibit a wide variety of therapeutic applications, including treatment of breast cancer. These compound classes were synthesized for biological evaluation against a range of cancer cell lines. Heteroaromatic diaryl thioethers were prepared by the reaction of sulfenyl chlorides with arylzinc bromides, while enantioenriched 1,1-diarylalkanes were synthesized through the nickel-catalyzed cross-coupling reactions of alkyl Grignard reagents. Several lead compounds were identified that selectively inhibited breast

cancer cell proliferation in the low micromolar range. In particular, a diarylalkane containing a thiophene moiety exhibited selective activity against a triple-negative breast cancer line.

Stereospecific nickel-catalyzed cross-coupling methodology has also been applied to the synthesis of tubulin-binding diarylethane derivatives. Upon evaluation for inhibition of tubulin polymerization, the (*S*)-enantiomer of a trimethoxyphenyl-containing diarylethane exhibited higher levels of tubulin disruption than the (*R*)-enantiomer. These results show proof of concept that enantioenriched diarylethanes exhibit marked differences in tubulin-binding activity.

We developed a different type of nickel-catalyzed reaction for the stereospecific ring-opening of *O*-heterocycles in order to provide acyclic alcohols with controlled formation of a new C–C bond. Aryl-substituted tetrahydropyrans underwent nickel-catalyzed Kumada coupling reactions with a range of Grignard reagents to furnish acyclic alcohols with high diastereoselectivity. A furan-substituted lactone underwent a Negishi cross-coupling reaction to provide the corresponding carboxylic acid in high enantiospecificity. Biological evaluation of the products identified several lead compounds with selective activity against a triple-negative breast cancer line.

In the final Chapter of this dissertation, we describe the synthesis of enantioenriched homopropargylic α-chiral sulfonamides via the enantioselective silver-catalyzed propargylation of *N*-sulfonyl ketimines. This reaction proceeded in high yield and excellent enantiomeric excess, and was compatible with a wide variety of diaryl and alkyl ketimines. Synthetic transformations of homopropargylic products via enyne ring-closing metathesis and reduction reactions proceeded with high stereochemical fidelity. Both allenyl and propargyl borolane reagents could be used to obtain propargylic products, most consistent with a mechanism involving transmetallation of the silver catalyst with the borolane reagent.

Chapter One

Biological Evaluation of Diaryl Sulfides and Enantioenriched Diarylalkanes as Anti-Breast-Cancer Agents

1.1 Introduction

Breast cancer is an extremely heterogeneous disease.[1,2] In order to provide varied treatment options for different breast cancer patients, numerous types of pharmaceuticals have been developed. One class of pharmaceuticals includes colchicine and combretastatin A-4 (Figure 1.1a), which act by inhibiting microtubule polymerization so cancer cells cannot divide and proliferate.[3,4] The Jarvo laboratory's goal was to synthesize combretastatin A-4 analogues containing the diaryl motif (**1.3**, Figure 1.1b) in order to investigate their anti-breast-cancer activity. Specifically, we wanted to target diaryl sulfides and diarylalkanes (Figure 1.1c), as these compound classes have been reported to exhibit anti-breast-cancer activity.[5,6] In this Chapter, we disclose the biological evaluation of diaryl sulfides and diarylalkanes synthesized using cross-coupling methods developed by the Jarvo laboratory.

---

[1] Portions of this Chapter were originally published as: (a) Yonova, I. M.; Osborne, C. A.; Morrissette, N. S.; Jarvo, E. R. *J. Org. Chem.* **2014**, *79*, 1947; (b) Yonova, I. M.; Osborne, C. A.; Morrissette, N. S.; Jarvo, E. R. U. S. Patent Appl. No. 14/666,088, 2015; (c) Yonova, I. M.; Johnson, A. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. M.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2422.

[2] Harbeck, N.; Salem, M.; Nitz, U.; Gluz, O.; Liedtke, C. *Cancer Treat. Rev.* **2010**, *36*, 584.

[3] Lin, C. M.; Ho, H. H.; Pettit, G. R.; Hamel, E. *Biochemistry* **1989**, *28*, 6984.

[4] Tron, G. C.; Pirali, T.; Sorba, G.; Pagliai, F.; Busacca, S.; Genazzani, A. A. *J. Med. Chem.* **2006**, *49*, 3033.

[5] Representative diaryl sulfide possessing anti-breast-cancer activity: De Martino, G.; La Regina, G; Coluccia, A; Edler, M. C.; Barbera, M. C.; Brancale, A.; Wilcox, E.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2004**, *47*, 6120.

[6] Representative diarylalkane possessing anti-breast-cancer activity: (a) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870; (b) Pathak, T. P.; Osiak, J. G.; Vaden, R. M.; Welm, B. E.; Sigman, M. S. *Tetrahedron* **2012**, *68*, 5203.

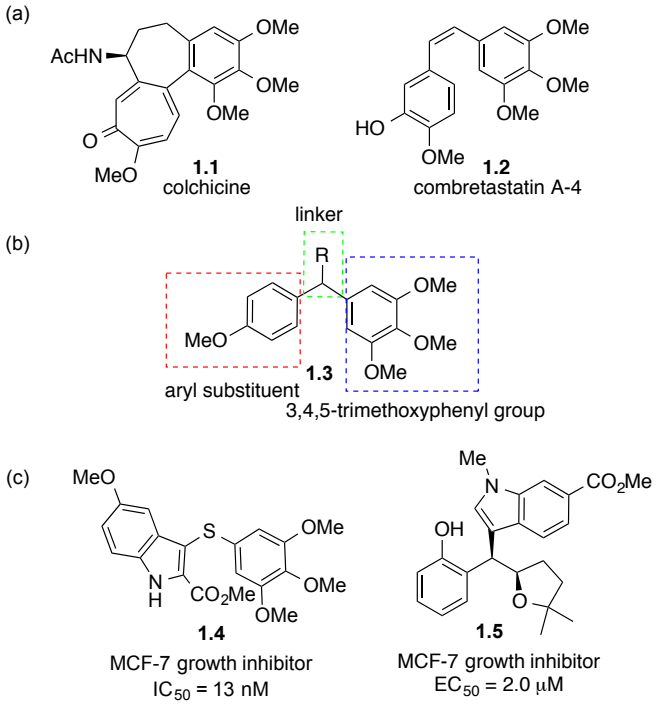


Figure 1.1. Compounds exhibiting anti-breast-cancer activity: (a) colchicine and combretastatin A-4, (b) representative diarylethane, and (c) representative diaryl sulfide and diarylalkane.

Diaryl sulfides abound as potential therapeutic treatments for a variety of diseases, including breast cancer,[5] inflammatory diseases,[7,8] diabetes,[9] HIV,[10] and Alzheimer's disease[11] (Figure 1.2). Thioethers possessing N-heterocyclic functionalities are especially prevalent; however, these sensitive moieties were poorly tolerated in previous syntheses of diaryl sulfides that relied on harsh methodology. We postulated that developing milder reaction conditions

[7] Liu, G.; Link, J. T.; Pei, Z.; Reilly, E. B.; Leitza, S.; Nguyen, B.; Marsh, K. C.; Okasinski, G. F.; von Geldern, T. W.; Ormes, M.; Fowler, K.; Gallatin, M. *J. Med. Chem.* **2000**, *43*, 4025.
[8] Alcaraz, M. L.; Atkinson, S.; Cornwall, P.; Foster, A. C.; Gill, D. M.; Humphries, L. A.; Keegan, P. S.; Kemp, R.; Merifield, E.; Nixon, R. A.; Noble, A. J.; O'Beirne, D.; Patel, Z. M.; Perkins, J.; Rowan, P.; Sadler, P.; Singleton, J. T.; Tornos, J.; Watts, A. J.; Woodland, I. A. *Org. Process Res. Dev.* **2005**, *9*, 555.
[9] Tang, P. C.; Ramphal, J. Y.; Harris, G. D. Jr.; Nematalla, A. S. Patent WO/1998/27092 A1, June 25, 1998.
[10] Pasquini, S.; Mugnaini, C.; Tintori, C.; Botta, M.; Trejos, A.; Arvela, R. K.; Larhed, M.; Witvrouw, M.; Michiels, M.; Christ, F.; Debyser, Z.; Corelli, F. *J. Med. Chem.* **2008**, *51*, 5125.
[11] Nielsen, S. F.; Nielsen, E. O.; Olsen, G. M.; Liljefors, T.; Peters, D. *J. Med. Chem.* **2000**, *43*, 2217.

would allow for the synthesis and biological evaluation of functionalized diaryl thioethers structurally analogous to combretastatin A-4. To this end, we recently reported the coupling of in situ-generated sulfenyl chlorides with arylzinc reagents to provide diaryl thioethers in high yield (Scheme 1.1).

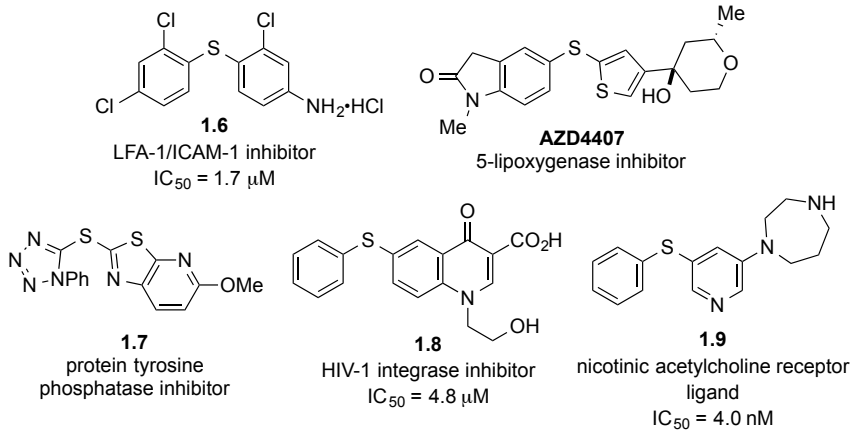
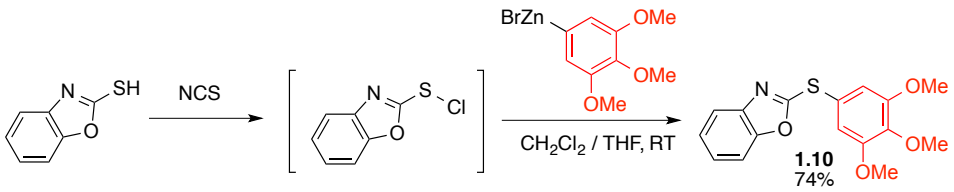


Figure 1.2. Representative bioactive diaryl sulfides.

Scheme 1.1. Coupling reaction developed by the Jarvo laboratory to synthesize diaryl sulfides for biological evaluation.



In contrast to diaryl sulfides, diarylalkanes are chiral and can be synthesized and evaluated as single enantiomers. The Jarvo laboratory has previously developed nickel-catalyzed stereospecific cross-coupling methodology for the construction of enantioenriched

diarylethanes.[12] We hypothesized that developing a method to synthesize enantioenriched 1,1-diarylalkanes, pharmacophores found in a range of bioactive molecules (Figure 1.3),[6,13] would provide improved lead compounds for the identification of anti-cancer drugs. Synthesis of both enantiomers of diarylalkanes would also allow us to determine whether one enantiomer exhibits greater activity than the other. Recently, the Jarvo laboratory developed the stereospecific nickel-catalyzed Kumada cross-coupling reaction of benzylic ethers to generate diarylalkanes in high enantiomeric excess (ee) (Scheme 1.2).

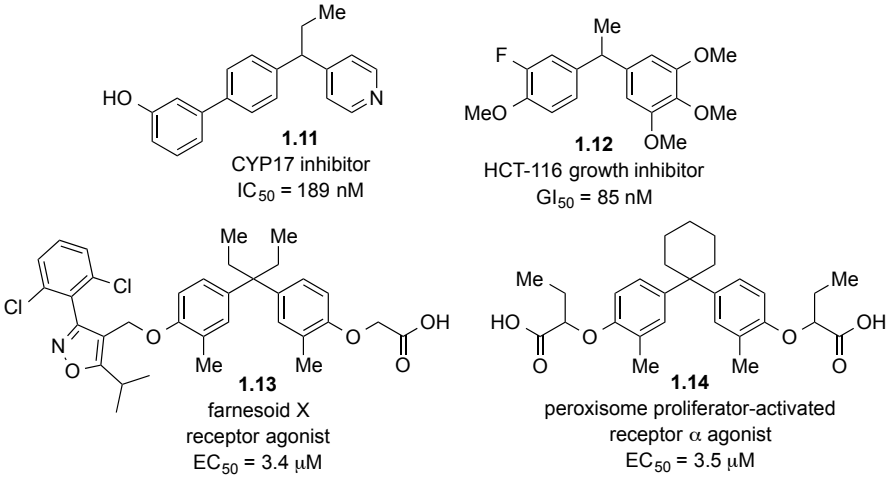
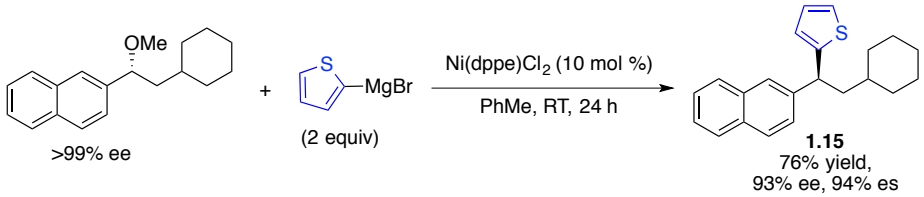


Figure 1.3. Representative bioactive diarylalkanes.

[12] (a) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389; (b) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293; (c) Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083.

[13] Representative examples: (a) as ligands for nuclear receptors, see: Kainuma, M; Kasuga, J.-i.; Hosoda, S; Wakabayashi, K.-i.; Tanatani, A; Nagasawa, K.; Miyachi, H.; Makishima, M; Hashimoto, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3213; (b) as combretastatin analogues for colon cancer, see: Messaoudi, S.; Hamze, A.; Provot, O.; Tréguier, B.; Rodrigo De Losada, J.; Bignon, J.; Liu, J.-M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *ChemMedChem.* **2011**, *6*, 488; (c) prostate cancer: Hu, Q. Z.; Yin, L. N.; Jagusch, C.; Hille, U. E.; Hartmann, R. W. *J. Med. Chem.* **2010**, *53*, 5049; (d) diabetes: Kim, R. M.; Parmee, E. R.; Tan, Q.; Yang, C.; Lins, A. R. U. S. Patent 12/227,030, May 11, 2007.

Scheme 1.2. Nickel-catalyzed cross-coupling reaction developed by the Jarvo laboratory to synthesize enantioenriched diarylalkanes for biological evaluation.



In this Chapter, we report the anti-breast-cancer activity of diaryl sulfides and diarylalkanes synthesized using the methodology in Schemes 1.1 and 1.2. Functionalized diaryl thioethers were formed from in situ-generated sulfenyl chlorides and mild organozinc reagents. A series of heterocyclic diaryl thioethers were designed and prepared as combretastatin A-4 analogues; two of these compounds demonstrated micromolar activity against the MCF-7 breast cancer cell line. We also report the discovery of several enantioenriched diarylalkanes as selective inhibitors of breast cancer cell proliferation.

1.2 Synthesis of Diaryl Sulfides via Sulfenyl Chlorides

Synthetic methods for the formation of diaryl thioethers have received significant attention in recent years. Numerous metal-catalyzed reactions for the generation of carbon–sulfur bonds, including copper- and palladium-catalyzed transformations, have been disclosed (Figure 1.4a).[14] However, these reactions typically require elevated temperatures. A milder copper-catalyzed synthesis of diaryl sulfides that proceeds at 0 °C was published in 2013.[15]

[14] (a) For a review, see: Eichman, C. C.; Stambuli, J. P. *Molecules* **2011**, *16*, 590; (b) for a representative example of a copper-catalyzed reaction, see: Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517; (c) for a representative example of a palladium-catalyzed reaction, see: Fernández-Rodríguez, M. A.; Hartwig, J. F. *J. Org. Chem.* **2009**, *74*, 1663.
[15] Uyeda, C.; Tan, Y.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 9548.

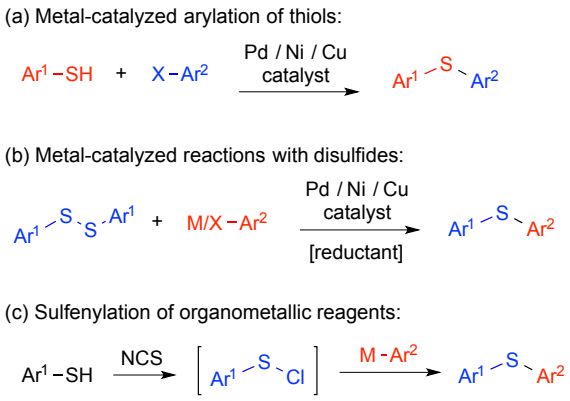


Figure 1.4. Strategies for the synthesis of diaryl sulfides.

Electrophilic sulfur reagents have also been employed (Figure 1.4b and c). Reactions of disulfides with aryl iodides, boronic acids, or silanes proceed with stoichiometric reducing reagents to generate the desired diaryl sulfides (Figure 1.4b).[16] In addition, sulfenyl chlorides formed in situ from aryl thiols and *N*-chlorosuccinimide can be utilized as highly reactive starting materials. Schlosser and co-workers have reported reactions of sulfenyl chlorides with indoles.[17] Recently, a related transformation for the sulfenylation of Grignard reagents, employing in situ-generated sulfenyl chlorides, was reported by Lee and co-workers (Figure 1.4c).[18]

Based on our previous work with *N*-chloroamines,[19] our laboratory concurrently developed the sulfenylation of organozinc reagents as a functional-group tolerant[20] strategy for formation of diaryl sulfides. Our approach provides a synthesis for diaryl thioethers containing

[16] (a) For a review, see: Wladislaw, B.; Marzorati, L.; Di Vitta, C. *Org. Prep. Proc. Int.* **2007**, *39*, 447; (b) for representative examples with aryl iodides, see: Taniguchi, N.; Onami, T. *J. Org. Chem.* **2004**, *69*, 915; (c) for representative examples with aryl boronic acids, see: Taniguchi, N. *Synlett* **2006**, 1351; (d) for representative examples with aryl trimethoxysilanes, see: Luo, P.-S.; Yu, M.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *Tetrahedron Lett.* **2009**, *50*, 1066.

[17] Schlosser, K. M.; Krasutski, A. P.; Hamilton, H. W.; Reed, J. E.; Sexton, K. *Org. Lett.* **2004**, *6*, 819.

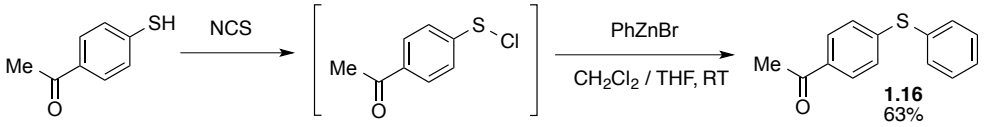
[18] While this work was in progress, Lee and co-workers disclosed a method for the synthesis of diaryl sulfides utilizing in situ-formed sulfenyl chlorides and organomagnesium reagents: Cheng, J.-H.; Ramesh, C.; Kao, H.-L.; Wamg, Y.-J.; Chan, C.-C.; Lee, C.-F. *J. Org. Chem.* **2012**, *77*, 10369.

[19] (a) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598; (b) Barker, T. J.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 8325.

[20] For demonstration of functional group tolerance of organozinc reagents, see: Bernhardt, S.; Manolikakes, G.; Kunz, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 9205.

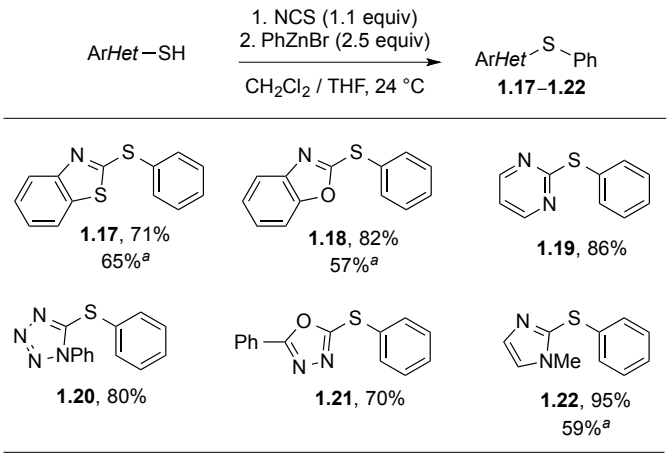
sensitive functional groups, including ketones and N-heterocycles. For example, 1-(4-mercapto-phenyl)-ethanone reacted smoothly to provide desired diaryl sulfide **1.16** with no observed competitive addition to the ketone (Scheme 1.3).

Scheme 1.3. Formation of ketone-containing diaryl sulfide **1.16**.



A broad range of heterocycles react with phenylzinc bromide to provide good to excellent yields of the corresponding sulfides, including benzothiazole, benzoxazole, pyrimidine, tetrazole, oxadiazole, and imidazole functional groups (Scheme 1.4). Notably, when phenylmagnesium bromide was used instead of phenylzinc bromide, compounds **1.17**, **1.18,** and **1.22** were obtained in diminished yields (65%, 57%, and 59%, respectively), highlighting the improved functional group tolerance of organozinc reagents.

Scheme 1.4. Reactivity of heteroaryl thiols.[21]

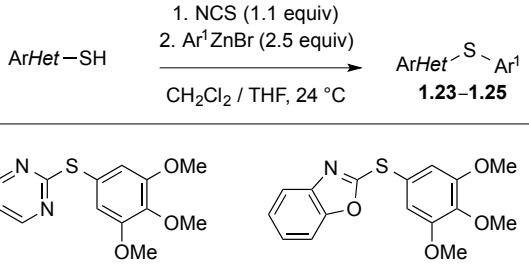


[a]Yield obtained using PhMgBr.

[21] Products **1.17**–**1.22** were synthesized using phenylzinc bromide by Ivelina Yonova; see: Yonova, I. M.; Osborne, C. A.; Morrissette, N. S.; Jarvo, E. R. *J. Org. Chem.* **2014**, *79*, 1947.

We sought to synthesize combretastatin A-4 analogues[3,4] using our method since it tolerates a diverse range of heterocycles and would further SAR studies of these compounds. Diaryl sulfide analogues of combretastatin containing N-heterocyclic moieties have been reported to be active against MCF-7 breast cancer cell lines (e.g., **1.4**).[5,22–25] We examined reactions of a variety of heteroaryl sulfides with 3,4,5-trimethoxyphenylzinc bromide, biasing our small library of analogues toward inclusion of the 3,4,5-trimethoxyphenyl scaffold, a privileged motif commonly found in anti-cancer compounds that target microtubules.[13b, 26] We were gratified to see that the corresponding arylzinc bromide reacts with a variety of heteroaryl sulfenyl chlorides to afford the respective trimethoxyphenyl-substituted thioethers in modest to good yields (Scheme 1.5).

Scheme 1.5. Combretastatin A-4 analogues.[27]



[22] Barbosa, E. G.; Bega, L. A. S.; Beatriz, A.; Sarkar, T.; Hamel, E.; do Amaral, M. S.; de Lima, D. P. *Eur. J. Med. Chem.* **2009**, *44*, 2685.
[23] La Regina, G.; Bai, R.; Rensen, W. M.; Di Cesare, E.; Coluccia, A.; Piscitelli, F.; Famiglini, V.; Reggio, A.; Nalli, M.; Pelliccia, S.; Da Pozzo, E.; Costa, B.; Granata, I.; Porta, A.; Maresca, B.; Soriani, A.; Iannitto, M. L.; Santoni, A.; Li, J.; Cona, M. M.; Chen, F.; Ni, Y.; Brancale, A.; Dondio, G.; Vultaggio, S.; Varasi, M.; Mercurio, C.; Martini, C.; Hamel, E.; Lavia, P.; Novellino, E.; Silvestri, R. *J. Med. Chem.* **2013**, *56*, 123.
[24] Lu, Y.; Li, C.-M.; Wang, Z.; Chen, J.; Mohler, M. L.; Li, W.; Dalton, J. T.; Miller, D. D. *J. Med. Chem.* **2011**, *54*, 4678.
[25] Lee, H.-Y.; Chang, J.-Y.; Nien, C.-Y.; Kuo, C.-C.; Shih, K.-H.; Wu, C.-H.; Chang, C.-Y.; Lai, W.-Y.; Liou, J.-P. *J. Med. Chem.* **2011**, *54*, 8517.
[26] Jordan, A.; Hadfield, J. A.; Lawrence, N. J.; McGown, A. T. *Med. Res. Rev.* **1998**, *18*, 259.
[27] Products **1.10** and **1.23–1.25** were synthesized by Ivelina Yonova; see reference 21.

1.3 Biological Evaluation of Diaryl Sulfides

We set out to evaluate these combretastatin A-4 analogues for anti-breast-cancer activity. Select products from Schemes 1.4 and 1.5 were tested for anti-cancer activity against the MCF-7 breast cancer cell line relative to the normal MCF-10A stromal cell line using a proliferation-based procedure (Figure 1.5).[6a] Results are compared to activity of the estrogen receptor antagonist, faslodex (ICI 182,780).[28] Two compounds demonstrated selective inhibition of cancer cell proliferation. Diaryl sulfide **1.10**, containing benzoxazole and 3,4,5-trimethoxyphenyl moieties, was a potent inhibitor of MCF-7 cell proliferation (EC_{50} = 4.5 μM, Figure 1.6a). In comparison, the simple phenyl analogues **1.18** and **1.17** were inactive. In contrast, trimethoxyphenyl-containing thioether **1.25** performed poorly, while its phenyl analogue **1.21** was a more potent cell proliferation inhibitor (EC_{50} = 7.9 μM, Figure 1.6b). Further studies to evaluate the biological activity of **1.10** and **1.21** against a broad panel of cancer cell lines are ongoing.

[28] For a discussion of faslodex and estrogen receptor antagonists, see: (a) Howell, A. *Endocr. Relat. Cancer* **2006**, *13*, 689; (b) Wakeling, A. E.; Dukes, M.; Bowler, J. *Cancer Res.* **1991**, *51*, 3867.

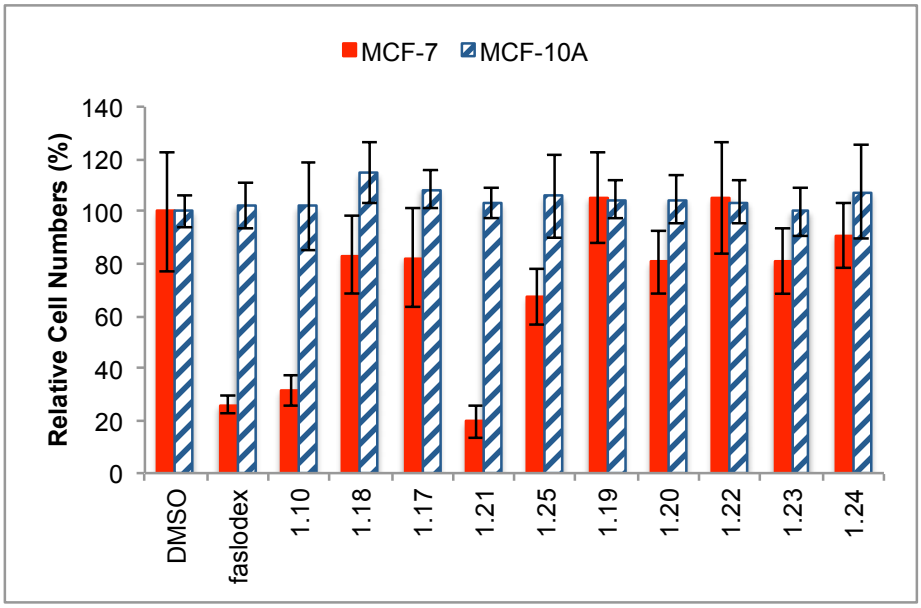


Figure 1.5. Evaluation of diaryl sulfides for anti-breast-cancer activity. Compounds were evaluated at 10 μM against breast cancer (MCF-7) and normal breast cell lines (MCF-10A). Cell proliferation is represented as relative cell numbers after treatment, where a low percentage indicates potent anti-proliferative activity for that compound. All data are normalized to the DMSO vehicle control.

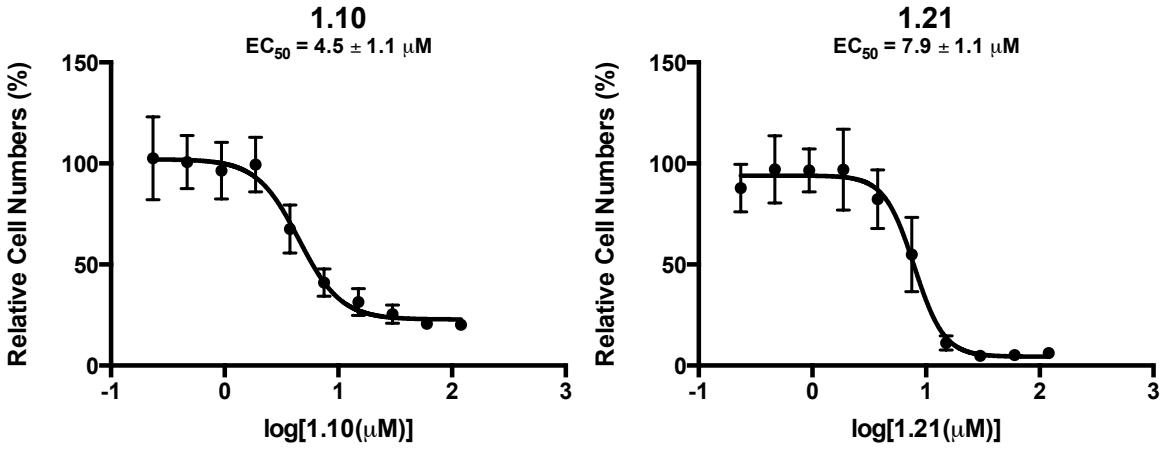


Figure 1.6. Dose response curves to determine half-maximal effective concentration (EC_{50}) values for (a) compound **1.10** and (b) compound **1.21**.

1.4 Biological Evaluation of Enantioenriched Diarylalkanes

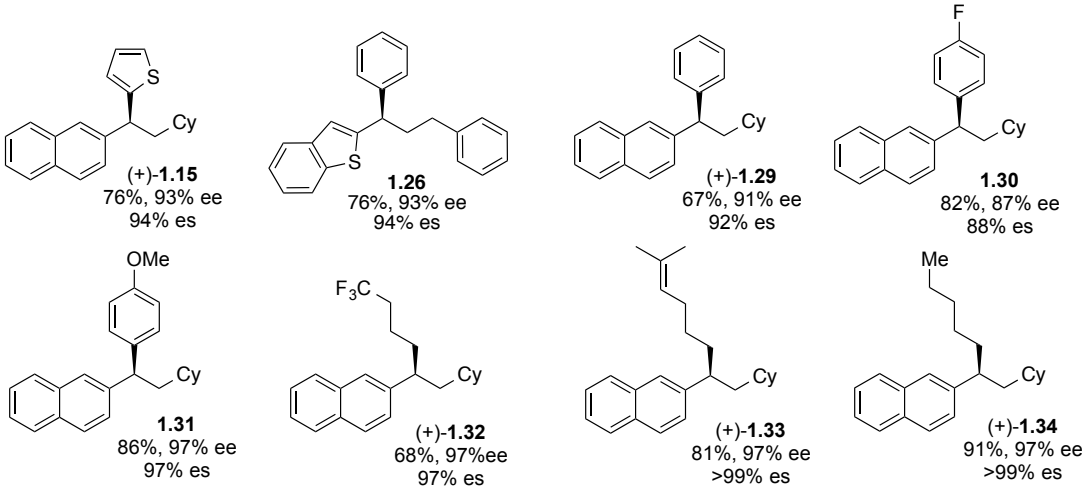
Another class of anti-cancer agents is diarylalkanes. Compounds containing this scaffold have demonstrated bioactivity against a wide range of indications, including breast cancer.[6,13] To access enantioenriched 1,1-diarylalkanes for biological evaluation, our laboratory developed the stereospecific cross-coupling reaction of benzylic ethers with arylmagnesium reagents (Scheme 1.2).[29,30] The Jarvo laboratory has previously developed nickel-catalyzed cross-coupling reactions of aryl Grignard reagents with benzhydryl alcohol derivatives to provide triarylmethanes;[31] however, this method failed to afford satisfactory yields with benzylic alcohol derivatives containing β-hydrogens. Changing catalysts from $Ni(cod)_2$ and dppo to $Ni(dppe)Cl_2$ allowed for incorporation of a variety of substituted aryl Grignard reagents to generate the compounds shown in Scheme 1.6.

[29] For a similar disconnection, see: (a) Lopez-Perez, A.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 5514; (b) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024; (c) Li, J.; Burke, M. D. *J. Am. Chem. Soc.* **2011**, *133*, 13774; (d) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 280.

[30] For representative alternative strategies for enantioselective synthesis of 1,1-diarylalkanes, see: (a) reference 6a; (b) Saini, V.; Liao, L.; Wang, Q.; Jana, R.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 5008; (c) Wang, X.; Guram, A.; Caille, S.; Hu, J.; Preston, J. P.; Ronk, M.; Walker, S. *Org. Lett.* **2011**, *13*, 1881; (d) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9331.

[31] (a) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790; stereospecific Suzuki couplings of arylboronic esters: (b) Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303; (c) Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307.

Scheme 1.6. 1,1-Diarylalkanes synthesized by stereospecific nickel-catalyzed cross-coupling reactions.[32]



Having obtained a variety of enantioenriched alkanes and diarylalkanes, we set out to evaluate these compounds for biological activity. The cross-coupling products in Scheme 1.6 were tested for selective anti-breast-cancer activity against the MCF-7 breast cancer cell line relative to the normal MCF-10A stromal cell line using a proliferation-based procedure.[6a] Selected results of the broad compound screen are shown in Figure 1.7. Several compounds demonstrated selectivity for the inhibition of breast cancer cell proliferation; results were compared to those obtained with estrogen receptor antagonist faslodex (ICI 182,780).[28] Thiophene-containing diarylalkane (+)-**1.15** inhibited MCF-7 cell proliferation with an EC_{50} of 5.3 μM (Figure 1.8a). We observed that (–)-**1.15** (EC_{50} = 6.5 μM, Figure 1.8b) and the racemic mixture (EC_{50} = 7.3 μM, Figure 1.8c) were both nearly as efficacious as the (+)-enantiomer. Interestingly, the isomeric diarylalkane **1.26** exhibited a similar level of inhibition. Control experiments confirmed that thiophene (**1.27**) and benzothiophene (**1.28**) did not inhibit cell

[32] Compounds in Scheme 1.6 were synthesized by Ivelina Yonova and A. George Johnson; see: Yonova, I. M.; Johnson, A. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. M.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2422.

growth. Replacing the thiophene moiety with different aryl groups, such as phenyl (**1.29**), *para*-methoxyphenyl (**1.30**), or *para*-fluorophenyl (**1.31**) resulted in similar selective inhibition of cancer cell proliferation. Furthermore, compounds containing hydrocarbon chains (**1.33** and **1.34**) were much less potent. These results provide new lead compounds with selective inhibition of breast cancer cell growth.

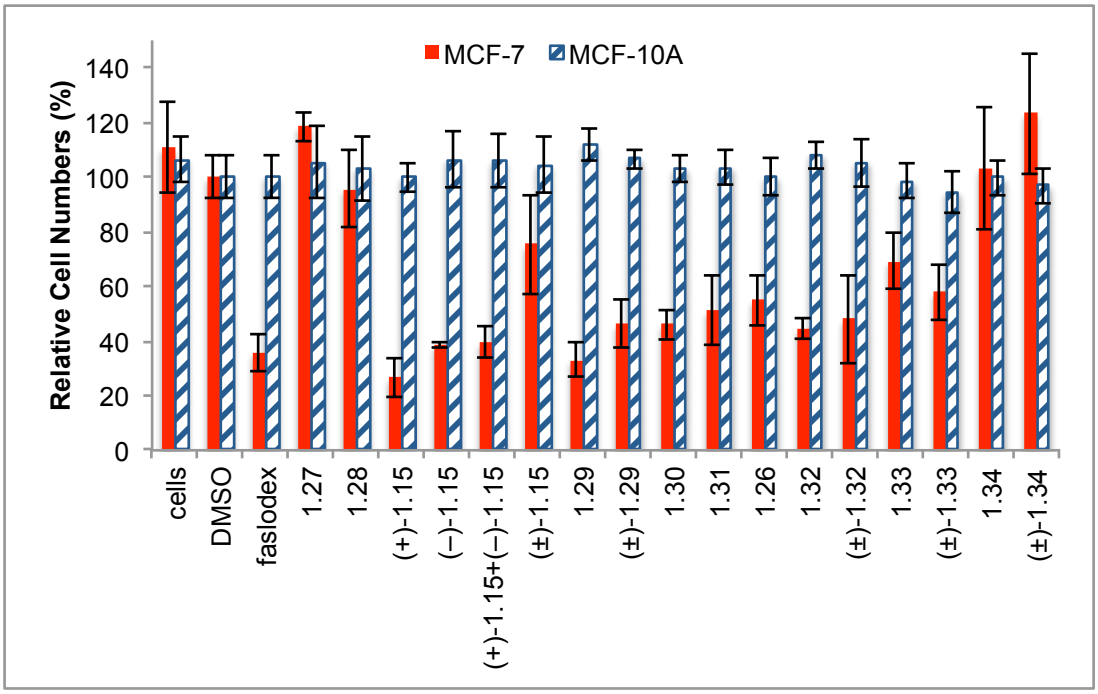


Figure 1.7. Evaluation of diarylalkanes for anti-breast-cancer activity. Compounds were evaluated at 10 μM against breast cancer (MCF-7) and normal breast cell lines (MCF-10A). Cell proliferation is represented as relative cell numbers after treatment, where a low percentage indicates potent anti-proliferative activity for that compound. All data are normalized to the DMSO vehicle control.

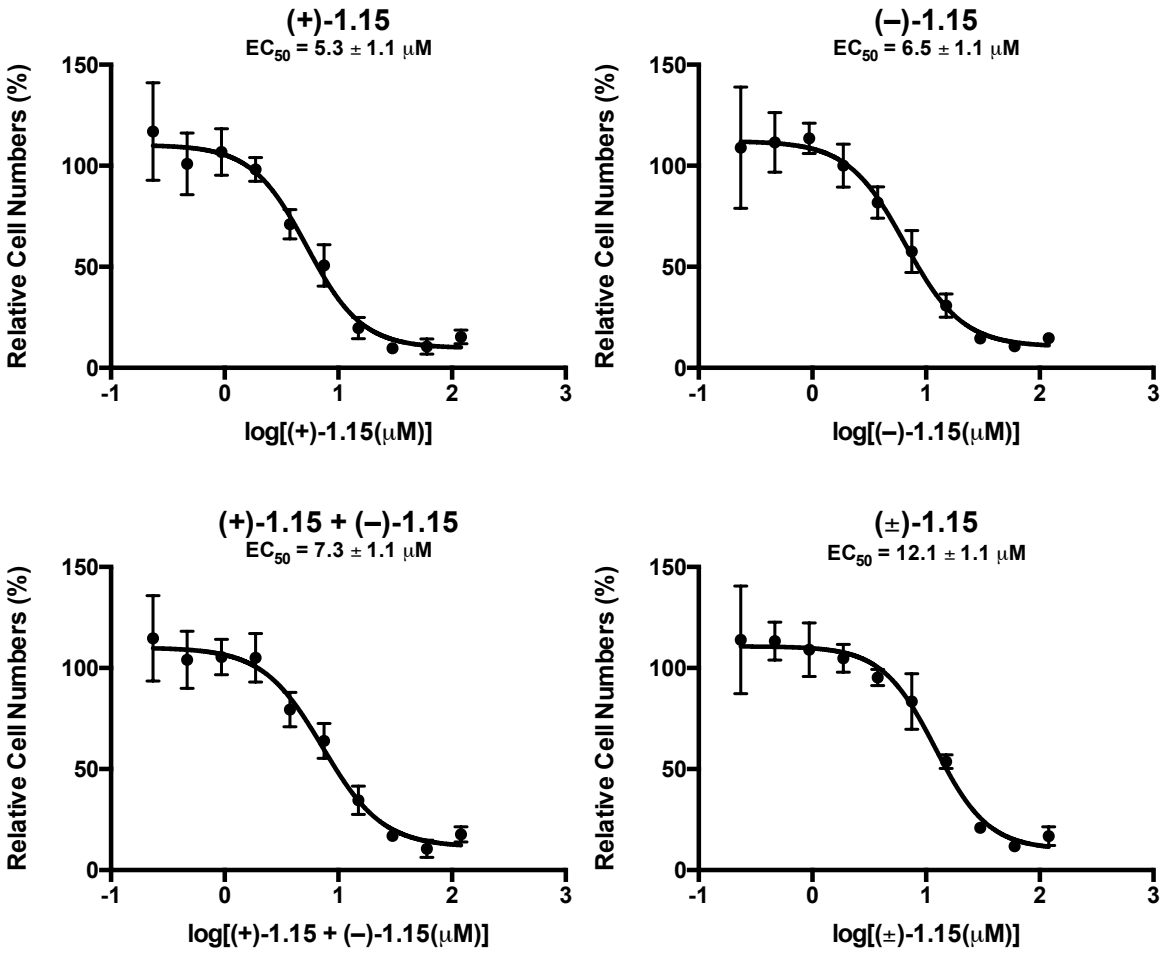


Figure 1.8. Dose response curves to determine half-maximal effective concentration (EC_{50}) values for (a) enantiomer (+)-**1.15**, (b) enantiomer (–)-**1.15**, and (c) the racemic mixture (+)-**1.15** + (–)-**1.15**.

Given the potency of (+)-**1.15**, we sought to pursue further biological testing of this lead compound. (+)-**1.15** was evaluated against a panel of cancer cell lines including prostate, kidney, ovarian, and triple-negative breast cancer cells using an MTT assay.[33] We found (+)-**1.15** to be highly selective for anti-breast-cancer activity: it was inactive against prostate, kidney, or ovarian

[33] MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay: Alley, M. C.; Scudiero, D. A.; Monks, A.; Hursey, M. L.; Czerwinski, M. J.; Fine, D. L.; Abbott, B. J.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 589.

cancer cell lines. In contrast, thiophene (+)-**1.15** strongly inhibited proliferation of MDA-MB-468 triple-negative breast cancer cells (Figure 1.9). This activity is significant because triple-negative breast cancer is a particularly aggressive and difficult cancer to treat: it does not express genes for the estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor (Her2).[34]

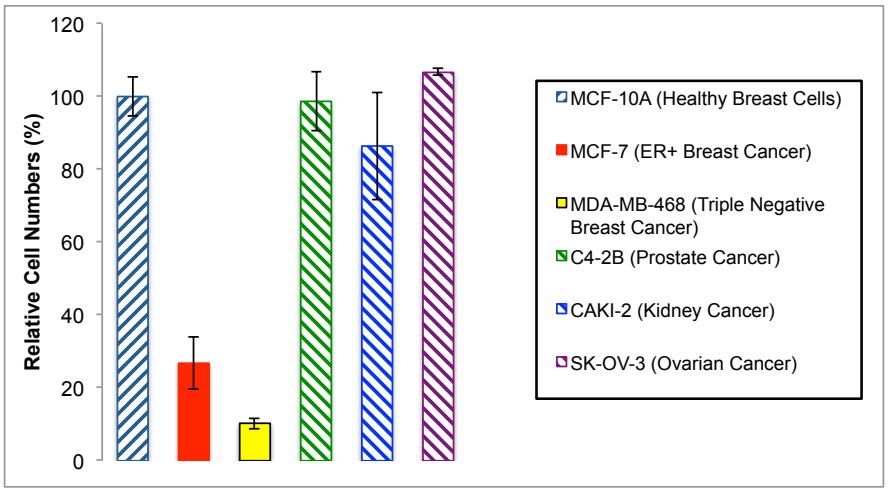


Figure 1.9. Evaluation of (+)-**1.15** for anti-cancer activity at 10 μM. Cell proliferation is represented as relative cell numbers after treatment, where a low percentage indicates potent anti-proliferative activity. All data are normalized to the DMSO vehicle control.

We hypothesize that the mechanism of action for our lead compound is independent of estrogen receptor alpha (ERα) since (+)-**1.15** inhibits both ER+ (MCF-7) and ER– (MDA-MB-468) breast cancer cell lines. However, while the triple-negative MDA-MB-468 line does not express ERα, it still expresses the other protein isoform estrogen receptor beta (ERβ).[35] Our working hypothesis is that (+)-**1.15** targets ERβ, the protein isoform expressed by both breast

[34] (a) Irvin, W. J., Jr.; Carey, L. A. *Eur. J. Cancer* **2008,** *44*, 2799; (b) Carey, L. A. *The Oncologist* **2011,** *16*, 71.
[35] Skliris, G. P.; Leygue, E.; Watson, P. H.; Murphy, L. C. *J. Steroid Biochem. Mol. Biol.* **2008**, *109*, 1.

cancer cell lines we tested. Ongoing studies will refine our understanding of the mechanism by which thiophene (+)-**1.15** demonstrates selectivity for breast cancer.

1.5 Biological Evaluation of Triarylmethane Analogues

Having established a robust method for the biological evaluation of diaryl sulfides and diarylalkanes, we sought to evaluate triarylmethane analogues synthesized by the Jarvo laboratory. Triarylmethanes have been established as potent anti-cancer agents.[36] For example, triarylmethanes are analogues of tamoxifen, an estrogen receptor antagonist that has been used to treat breast cancer for more than 30 years.[37] Despite showing promise as anti-breast-cancer agents, access to single enantiomers of diarylmethanes has been limited.

The Jarvo laboratory has developed stereospecific nickel-catalyzed Kumada and Suzuki cross-coupling methodology for the construction of enantioenriched triarylmethanes. The Kumada cross-coupling reaction of benzylic ethers with arylmagnesium reagents generated triarylmethanes in high yield and high es.[31a] The Suzuki cross-coupling reaction of benzylic alcohol derivatives with arylboronic esters allowed for greater functional group tolerance. Notably, this reaction afforded either enantiomer of product from a single chiral intermediate, by judicious choice of ligand.[31b]

We evaluated both enantiomers of triarylmethane analogues for anti-breast-cancer activity using the proliferation-based protocol.[6a] MCF-7 cell growth with 10 μM of compound was compared to activity of the estrogen receptor antagonist faslodex (ICI 182,780).[28] Two compounds exhibited different levels of breast cancer cell inhibition based on which enantiomer was evaluated. (*S*)-**1.35** proved more potent than (*R*)-**1.35**, while (*R*)-**1.36** was more efficacious

[36] Shagufta; Srivastava, A. K.; Sharma, R.; Mishra, R.; Balapure, A. K.; Murthy, P. S. R.; Panda, G. *Bioorg. Med. Chem.* **2006**, *14*, 1497.
[37] Jordan, V. C.; Collins, M. M.; Rowsby, L.; Prestwich, G. *J. Endocr.* **1977**, *75*, 305.

than *rac*-**1.36** (Figure 1.10). These preliminary data provide incentive to further develop methodology for the synthesis of enantioenriched triarylmethanes. Future work will determine EC_{50} values for these triarylmethanes, as well as confirm their selectivity for the MCF-7 breast cancer line compared to the MCF-10A normal breast line.

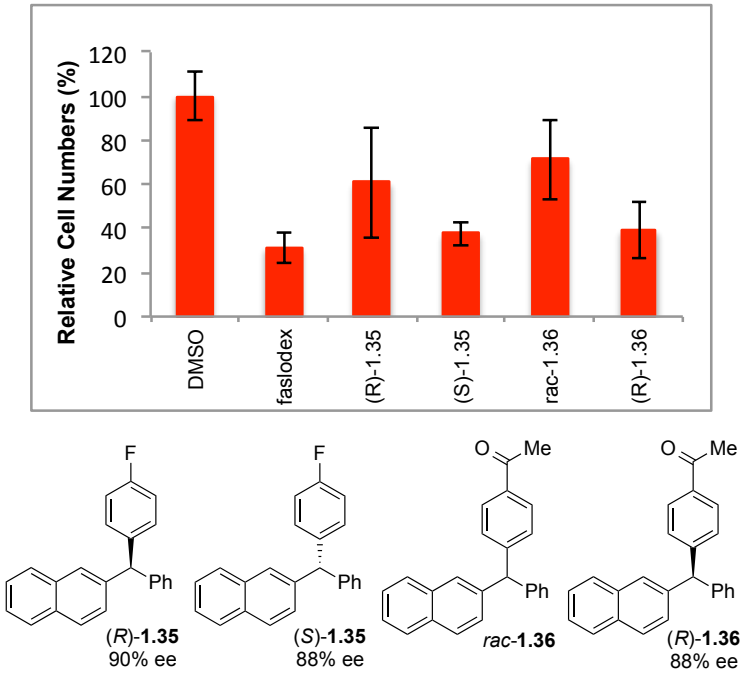


Figure 1.10. Evaluation of enantioenriched triarylmethanes for anti-breast-cancer activity.[38] Compounds were evaluated at 10 μM against the MCF-7 breast cancer cell line. Cell proliferation is represented as relative cell numbers after treatment, where a low percentage indicates potent anti-proliferative activity for that compound. All data are normalized to the DMSO vehicle control.

[38] Compounds **1.35** and **1.36** were synthesized by Michael Harris; see references 31a and 31b.

1.6 Conclusions

We have developed a mild and efficient protocol for the synthesis of diaryl thioethers. This method tolerates a wide array of heterocyclic moieties and is amenable to the construction of highly functionalized diaryl and diheteroaryl sulfides. Biological studies of select compounds have identified two promising inhibitors of MCF-7 breast cancer cell proliferation. Future efforts will focus on using this methodology to create a larger library of functionalized heterocyclic sulfides and investigating their biological activity against a broad range of cancer cell lines.

The Jarvo laboratory has developed a stereospecific nickel-catalyzed Kumada cross-coupling reaction for the synthesis of enantioenriched 1,1-diarylalkanes. Biological testing of compounds synthesized using this methodology identified several promising leads that exhibit selective inhibition of breast cancer cell proliferation in the low micromolar range.

1.7 Experimental Details

General Procedures

All reactions were carried out under an atmosphere of N_2 using glassware that was either oven- or flame-dried prior to use. Dichloromethane (CH_2Cl_2) and tetrahydrofuran (THF) were degassed with argon and then passed through two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 ºC for 12 h) to remove H_2O. ^1H NMR spectra were recorded on Bruker CRYO-500 (500 MHz ^1H, 125.7 MHz ^{13}C) or DRX-400 (400 MHz ^1H, 100 MHz ^{13}C) spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.00). Data are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), doublet of triplets (dt), quartet (q), multiplet (m), apparent singlet (ap s), and apparent

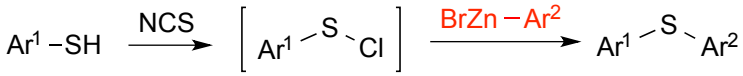
doublet (ap d)], coupling constants [Hz], integration. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.16 ppm). Unless otherwise indicated, NMR data were collected at 25 ºC. Infrared spectra were obtained on a Mattson Instruments *Galaxy 5000* spectrometer (thin film) and are reported in terms of frequency of absorption (cm^{-1}). Melting points (m.p.) were obtained using a Mel-Temp melting point apparatus and are uncorrected. High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F_{254} pre-coated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$ solution. Flash chromatography was performed using Silica Gel 60Å (170-400 mesh) from Fisher Scientific.

Phenylmagnesium bromide[39] and phenylzinc bromide[40] were prepared according to reported procedures. Molarities of organomagnesium and organozinc reagents were determined by titration.[41] N-Chlorosuccinimide (NCS) was recrystallized from benzene and stored in an amber vial for up to two weeks.

[39] Bollmann, A.; Blann, K.; Dixon, J. T.; Hess, F. M.; Killian, E.; Maumela, H.; McGuinness, D. S.; Morgan, D. H.; Neveling, A.; Otto, S.; Overett, M.; Slawin, A. M. Z.; Wasserscheid, P.; Kuhlmann, S. *J. Am. Chem. Soc.* **2004**, *126*, 14712.
[40] Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799.
[41] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890.

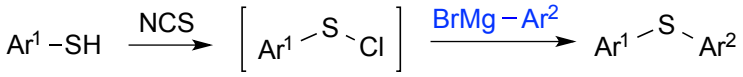
General Procedures for Sulfenylation Reactions

General Procedure A for Sulfenylation of Arylzinc Reagents



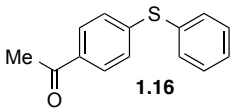
To a solution of NCS (0.073 g, 0.55 mmol) in DCM (1.0 mL) was added thiol (0.50 mmol) and the solution was stirred for 30 min in the absence of direct light. The solution was taken up using a Teflon needle and added drop-wise to a solution of arylzinc reagent in THF (1.25 mmol). Upon completion, as judged by TLC, the reaction mixture was quenched with MeOH, concentrated in vacuo, and the residue was adsorbed onto 3 mL of silica gel and purified by flash column chromatography.

General Procedure B for Sulfenylation of Arylmagnesium Reagents



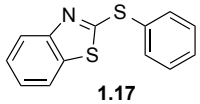
To a solution of NCS (0.073 g, 0.55 mmol) in DCM (1.0 mL) was added thiol (0.50 mmol) and the solution was stirred for 30 min in the absence of direct light. The solution was taken up using a Teflon needle and added drop-wise to a solution of arylmagnesium reagent in THF (1.25 mmol). Upon completion, as judged by TLC, the reaction mixture was quenched with MeOH, concentrated in vacuo, and the residue was adsorbed onto 3 mL of silica gel and purified by flash column chromatography.

Characterization Data for Products



1.16

4-Phenylsulfanylacetophenone (1.16) was prepared according to general procedure A from 1-(4-sulfanylphenyl)ethan-1-one (60 μL, 0.5 mmol), NCS (0.073 g, 0.55 mmol), and PhZnBr (1.3 mmol, 2.6 mL). Purification by flash column chromatography (5% EtOAc in hexanes) afforded the title compound as a pale yellow solid (0.072 g, 63%). Spectral data were consistent with reported values.[42] **TLC** R_f = 0.3 (5% EtOAc in hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.5 Hz, 2H), 7.50–7.47 (m, 2H), 7.40–7.38 (m, 3H), 7.20 (d, *J* = 8.5 Hz, 2H), 2.54 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 197.3, 145.0, 134.5, 134.0, 132.1, 129.8, 129.0, 128.9, 127.5, 26.5; **IR** (neat) 2922, 1677, 1589, 690 cm^{-1}.

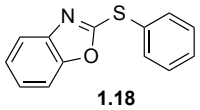


1.17

2-Phenylthio-benzothiazole (1.17) was prepared according to general procedure A from 2-mercaptobenzothiazole (0.084 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol), and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (15% EtOAc in hexanes) afforded the title compound as a colorless oil (0.087 g, 71%). Compound **1.17** was also prepared from PhMgBr according to general procedure B to afford 65% yield (determined by ^{1}H NMR in comparison to the internal standard phenyltrimethylsilane). Spectral data were consistent with reported values.[43] **TLC** R_f = 0.5 (30% EtOAc in hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.72 (m, 2H), 6.63 (d, *J* = 8.0 Hz, 1H), 7.52–7.43 (m, 3H), 7.38 (m, 1H),

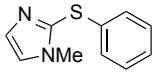
[42] Park, N.; Park, K.; Jang, M.; Lee, S. *J. Org. Chem.* **2011**, *76*, 4371.
[43] Zhou, A.-X.; Liu, X.-Y.; Yang, K.; Zhao, S.-C.; Liang, Y.-M. *Org. Biomol. Chem.* **2011**, *9*, 5456.

7.25 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 169.8, 154.0, 135.6, 135.4, 130.6, 130.01, 129.98, 126.2, 124.4, 122.0, 120.9.



1.18

2-Phenylthio-benzoxazole (1.18) was prepared according to general procedure A from 2-mercaptobenzoxazole (0.076 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol), and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (15% EtOAc in hexanes) afforded the title compound as a colorless oil (0.093 g, 82%). Compound **1.18** was also prepared from PhMgBr according to general procedure B to afford 57% yield (determined by ^{1}H NMR in comparison to the internal standard phenyltrimethylsilane). Spectral data were consistent with reported values.[43] **TLC** R_f = 0.5 (30% EtOAc in hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (m, 2H), 7.59 (m, 1H), 7.47–7.42 (m, 3H), 7.39 (m, 1H), 7.27–7.21 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.4, 152.0, 142.1, 134.5, 130.0, 129.8, 127.3, 124.5, 124.4, 119.2, 110.2.



1.22

1-Methyl-2-(phenylthio)-1*H*-imidazole (1.22) was prepared according to general procedure A from 2-mercapto-1-methylimidazole (0.057 g, 0.50 mmol), NCS (0.073 g, 0.55 mmol), and PhZnBr (1.3 mmol, 1.7 mL). Purification by flash column chromatography (10% EtOAc in hexanes) afforded the title compound as a colorless oil (0.081 g, 95%). Compound **1.22** was also prepared from PhMgBr according to general procedure B to afford 59% yield (determined by ^{1}H NMR in comparison to the internal standard phenyltrimethylsilane). Spectral data were

consistent with reported values.[43] **TLC** R_f = 0.2 (30% EtOAc in hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (m, 2H), 7.18–7.13 (m, 4H), 7.06 (d, *J* = 1.0 Hz, 1H), 3.62 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.1, 135.0, 130.2, 129.3, 128.0, 126.6, 123.9, 33.9.

General Procedures for Biological Experiments with Fluorescence Assay

Fluorescence assay experiments were performed according to a modified procedure by Sigman and co-workers.[6a]

Materials

The following reagents were obtained from commercial sources as indicated: Dulbecco's Modified Eagle's Medium (DMEM)/high glucose containing 4.5 g/L glucose and 4.0 mM L-glutamine (HyClone); fetal bovine serum (FBS), heat-inactivated (Omega Scientific); L-glutamine, 200 mM (Gibco); penicillin/streptomycin solution 50X (Mediatech); DMEM/Ham's Nutrient Mixture F12 containing 2.5 mM L-glutamine, 3151 mg/L dextrose, and 55 mg/L sodium pyruvate (Sigma-Aldrich); horse serum (Sigma-Aldrich); 50 μM hydrocortisone solution (Sigma-Aldrich); human insulin solution (Sigma-Aldrich); cholera toxin (Sigma-Aldrich); human Epidermal Growth Factor (EGF), recombinant (Sigma-Aldrich); 0.25% Trypsin-EDTA (Gibco); nuclease-free sterile water (Fisher Scientific); molecular biology grade DMSO (Sigma-Aldrich); ICI 182,780 (faslodex) (Tocris Bioscience).

Cell Lines and Culture Conditions

MCF-7 cells were maintained in DMEM/high glucose supplemented with 10% FBS, L-glutamine, and penicillin/streptomycin. Experiments with MCF-7 cells were performed in

DMEM/high glucose supplemented with 2% FBS, L-glutamine, and penicillin/streptomycin. MCF-10A cells were maintained in standard medium according to a modified recipe by Brugge and co-workers:[44] DMEM/F12 supplemented with 5% horse serum, 10 μg/mL human insulin, 0.5 μg/mL hydrocortisone, 10 ng/mL EGF, 100 ng/mL cholera toxin, and penicillin/ streptomycin. Experiments with MCF-10A cells were performed in the same medium.

Evaluation of Compounds Against MCF-7 Cells

MCF-7 cells were centrifuged in 1X PBS for 20 min, then the pellet was resuspended in DMEM supplemented with 10% FBS and filtered through a 40 μm nylon cell strainer (Fisher Scientific) to prevent clumping. The cells were seeded at 1,500 cells per well in 96-well flat bottom plates suitable for fluorimetry, using 175 μL per well DMEM supplemented with 10% FBS, and grown for 24 h in 5% CO_2 at 37 °C. The compounds (including the faslodex positive control) were dissolved in molecular biology grade DMSO to achieve a 3.5 mM stock solution, then sterile filtered through a 0.45 μm PVDF syringe filter unit (Fisher Scientific). The 3.5 mM stock solutions were subsequently diluted to a final concentration of 10 μM in DMEM supplemented with 2% FBS. Additionally, the corresponding DMSO vehicle control was diluted using the same medium.

After 24 h growth, the cells were treated by replacing the normal media with fresh media containing the individual compounds or vehicle control (day 0). The outer rows of wells were not used to eliminate the possibility of effects due to evaporation of media. The cells were incubated with compound for 48 h then treated again by aspirating the media and adding fresh media containing the compounds and controls (day 2). This procedure was repeated after an additional

[44] Debnath, J.; Muthuswamy, S. K.; Brugge, J. S. *Methods* **2003**, *30*, 256.

48 h (day 4). After incubating a final 24 h, the 96-well plates were rinsed with 1X PBS, blotted dry, and then frozen at –78 °C overnight (day 5). On day 6, cell proliferation was measured using the fluorescence-based CyQUANT Cell Proliferation Assay Kit (Invitrogen).

Fluorimetry analysis was performed according to a modified procedure by McGowan and co-workers.[45] Cells were stained with 200 μL/well of 1X CyQUANT GR dye in cell lysis buffer for 10 min in the dark at room temperature and quantified by fluorimetry at 535 nm with 485 nm excitation. The fluorescence values were normalized to the DMSO vehicle control. The normalized values were plotted as an average ± standard deviation of 6 wells per compound.

Evaluation of Compounds Against MCF-10A Cells

MCF-10A cells were centrifuged in 1X PBS for 20 min, then the pellet was resuspended in DMEM/F12 and filtered through a 40 μm nylon cell strainer (Fisher Scientific) to prevent clumping. The cells were seeded at 9,000 cells per well in 96-well flat bottom plates suitable for fluorimetry, using 175 μL per well DMEM/F12, and grown for 24 h in 5% CO_2 at 37 °C. The 3.5 mM stock solutions of compound in DMSO were subsequently diluted to a final concentration of 10 μM in DMEM/F12. Additionally, the corresponding DMSO vehicle control was diluted using the same medium.

Addition of compounds was performed as specified above for days 0 through 6. Fluorimetry analysis was performed as specified above for MCF-7 cells, with the exception of staining MCF-10A cells with 200 μL/well of 5X CyQUANT GR dye in cell lysis buffer for 10 min in the dark at room temperature before quantification by fluorimetry. The fluorescence values were

[45] McGowan, E. M.; Alling, N.; Jackson, E. A.; Yagoub, D.; Haass, N. K.; Allen, J. D.; Martinello-Wilks, R. *PLoS ONE* **2011**, *6*, e20623.

normalized to the DMSO vehicle control. The normalized values were plotted as an average ± standard deviation of 6 wells per compound.

*Dose Response of Compounds **1.10** and **1.21***

MCF-7 cells were centrifuged in 1X PBS for 20 min, then the pellet was resuspended in DMEM supplemented with 10% FBS and filtered through a 40 μm nylon cell strainer (Fisher Scientific) to prevent clumping. The cells were seeded at 1,500 cells per well in 96-well flat bottom plates suitable for fluorimetry, using 175 μL per well DMEM supplemented with 10% FBS, and grown for 24 h in 5% CO_2 at 37 °C. The compounds **1.10** and **1.21** were dissolved in molecular biology grade DMSO to achieve a 42 mM stock, then sterile filtered through a 0.45 μm PVDF syringe filter unit (Fisher Scientific). The 42 mM stock solutions in DMSO were subsequently diluted to 120 μM in DMEM supplemented with 2% FBS, and then serially diluted to achieve 10 different concentrations. Additionally, the corresponding DMSO vehicle controls for each concentration were serially diluted using the same medium.

Addition of compounds was performed as specified above for days 0 through 6. Fluorimetry analysis was performed as specified above for the evaluation of compounds against MCF-7 cells. The fluorescence values were normalized to the DMSO vehicle controls corresponding to each concentration. The normalized values were plotted as an average ± standard deviation of 4 wells per concentration and these data were analyzed using the dose response nonlinear regression fitting function (log[inhibitor] vs. response with variable slope (four parameters)) with GraphPad Prism 6.

*Dose Response of Compounds (+)-**1.15**, (–)-**1.15**, (+)-**1.15** + (–)-**1.15**, and (±)-**1.15***

MCF-7 cells were centrifuged in 1X PBS for 20 min, then the pellet was resuspended in DMEM supplemented with 10% FBS and filtered through a 40 μm nylon cell strainer (Fisher Scientific) to prevent clumping. The cells were seeded at 1,500 cells per well in 96-well flat bottom plates suitable for fluorimetry, using 175 μL per well DMEM supplemented with 10% FBS, and incubated with 5% CO_2 at 37 °C for 24 h. The compounds (+)-**1.15**, (–)-**1.15**, (+)-**1.15** + (–)-**1.15**, and (±)-**1.15**[46] were dissolved in molecular biology grade DMSO to achieve a 42 mM stock, then sterile filtered through a 0.45 μm PVDF syringe filter unit (Fisher Scientific). The 42 mM stock solutions in DMSO were subsequently diluted to 120 μM in DMEM supplemented with 2% FBS, and then serially diluted to achieve 10 different concentrations. Additionally, the corresponding DMSO vehicle controls for each concentration were serially diluted using the same medium.

Addition of compounds was performed as specified above for days 0 through 6. Fluorimetry analysis was performed as specified above for the evaluation of compounds against MCF-7 cells. The fluorescence values were normalized to the DMSO vehicle controls corresponding to each concentration. The normalized values were plotted as an average ± standard deviation of 4 wells per concentration and these data were analyzed using the dose response nonlinear regression fitting function (log[inhibitor] vs. response with variable slope (four parameters)) with GraphPad Prism 6.

[46] (+)-**1.15** and (–)-**1.15** are samples of each single enantiomer with 93% ee and 92% ee, respectively; (±)-**1.15** is a sample of the racemic standard; (+)-**1.15** + (–)-**1.15** is a sample containing an equimolar ratio of the two enantiomers, combined in DMSO prior to biological testing.

General Procedures for Biological Experiments with MTT Assay

MTT assay experiments were performed according to a modified procedure by Alley and co-workers.[33]

Materials

The following reagents were obtained from commercial sources as indicated: RPMI 1640 medium (HyClone); McCoy's 5A medium (HyClone); fetal bovine serum (FBS), heat-inactivated (Omega Scientific); L-glutamine, 200 mM (Gibco); penicillin/streptomycin solution 50X (Mediatech); amphotericin B (HyClone); DMEM/Ham's Nutrient Mixture F12 containing 2.5 mM L-glutamine, 3151 mg/L dextrose, and 55 mg/L sodium pyruvate (Sigma-Aldrich); horse serum (Sigma-Aldrich); 50 μM hydrocortisone solution (Sigma-Aldrich); human insulin solution (Sigma-Aldrich); cholera toxin (Sigma-Aldrich); human Epidermal Growth Factor (EGF), recombinant (Sigma-Aldrich); 0.25% Trypsin-EDTA (Gibco); nuclease-free sterile water (Fisher Scientific); molecular biology grade DMSO (Sigma-Aldrich); MTT (3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide) (Sigma-Aldrich).

Cell Lines and Culture Conditions

MCF-10A cells were maintained in standard medium according to a modified recipe by Brugge and co-workers:[44] DMEM/F12 supplemented with 5% horse serum, 10 μg/mL human insulin, 0.5 μg/mL hydrocortisone, 10 ng/mL EGF, 100 ng/mL cholera toxin, and penicillin/streptomycin. Experiments with MCF-10A cells were performed in the same medium.

MCF-7 cells were maintained in RPMI 1640 supplemented with 10% FBS, L-glutamine, and penicillin/streptomycin. Experiments with MCF-7 cells were performed in the same medium.

MDA-MB-468 cells were maintained in RPMI 1640 supplemented with 10% FBS, L-glutamine, penicillin/streptomycin, and amphotericin B. Experiments with MDA-MB-468 cells were performed in the same medium.

C4-2B cells were maintained in RPMI 1640 supplemented with 10% FBS, L-glutamine, and penicillin/streptomycin. Experiments with C4-2B cells were performed in the same medium.

CAKI-2 cells were maintained in McCoy's 5A supplemented with 10% FBS, L-glutamine, and penicillin/streptomycin. Experiments with CAKI-2 cells were performed in the same medium.

SK-OV-3 cells were maintained in RPMI 1640 supplemented with 10% FBS, L-glutamine, and penicillin/streptomycin. Experiments with SK-OV-3 cells were performed in the same medium.

Evaluation of Compounds Against Cell Lines

Preparation of Cell Lines

MCF-10A cells were centrifuged in DMEM/F12 at 1.0 rcf for 8 min, then the pellet was resuspended in DMEM/F12. The cells were seeded at 20,000 cells per well in 24-well flat bottom plates, using 500 μL per well DMEM/F12, and grown for 24 h in 5% CO_2 at 37 °C.

MCF-7 cells were centrifuged in RPMI at 1.0 rcf for 8 min, then the pellet was resuspended in RPMI. The cells were seeded at 20,000 cells per well in 24-well flat bottom plates, using 500 μL per well RPMI, and grown for 24 h in 5% CO_2 at 37 °C.

MDA-MB-468 cells were centrifuged in RPMI with amphotericin B at 1.0 rcf for 8 min, then the pellet was resuspended in RPMI with amphotericin B. The cells were seeded at 20,000 cells per well in 24-well flat bottom plates, using 500 μL per well RPMI with amphotericin B, and grown for 24 h in 5% CO_2 at 37 °C.

C4-2B cells were centrifuged in RPMI at 1.0 rcf for 8 min, then the pellet was resuspended in RPMI. The cells were seeded at 20,000 cells per well in 24-well flat bottom plates, using 500 μL per well RPMI, and grown for 24 h in 5% CO_2 at 37 °C.

CAKI-2 cells were centrifuged in McCoy's 5A at 1.0 rcf for 8 min, then the pellet was resuspended in McCoy's 5A. The cells were seeded at 12,500 cells per well in 24-well flat bottom plates, using 500 μL per well McCoy's 5A, and grown for 24 h in 5% CO_2 at 37 °C.

SK-OV-3 cells were centrifuged in RPMI at 1.0 rcf for 8 min, then the pellet was resuspended in RPMI. The cells were seeded at 20,000 cells per well in 24-well flat bottom plates, using 500 μL per well RPMI, and grown for 24 h in 5% CO_2 at 37 °C.

Preparation of Compounds

The compounds were dissolved in molecular biology grade DMSO to achieve a 100 mM stock solution, and then sterile filtered through a 0.45 μm PVDF syringe filter unit (Fisher Scientific). The 100 mM stock solutions were subsequently diluted to 20 mM stock solutions, then diluted to a final concentration of 10 μM in the corresponding medium for each cell line. Additionally, the corresponding DMSO vehicle control was diluted using the same medium.

After 24 h growth, the medium was carefully aspirated from each of the wells containing cells. The cells were treated by replacing the normal medium with 600 μL fresh medium per well containing the individual compounds or vehicle control (day 0). The plates were gently agitated, then the cells were incubated with compound at 37 °C with 5% CO_2 for 72 h. On day 3, cell proliferation was measured using the MTT absorbance assay.

MTT Absorbance Assay

Quantitative analysis was performed according to a modified procedure by Alley and co-workers.[33] After 72 h incubation with compound, 200 μL of MTT dye solution (3 mg MTT/ 1 mL PBS) was carefully added to each well containing cells. The plates were incubated at 37 °C for 1 h 15 min, after which the MTT dye was aspirated from each well. 300 μL of MTT dissolve solution (4% 1M HCl in IPA) was added to each well and the plates were agitated 15 min. From each well, 200 μL of cell lysate solution was carefully transferred to a new well in a clear-bottom 96-well plate suitable for UV-Vis spectroscopy. Cells were quantified by absorbance at 570 nm. The absorbance values were normalized to the DMSO vehicle control. The normalized values were plotted as an average ± standard deviation of 3 wells per compound.

Chapter Two

Synthesis and Biological Evaluation of Enantioenriched Diarylethanes as Tubulin Polymerization Disruptors

2.1 Introduction

Microtubules are essential for the cell cycle: they facilitate mitosis, transport, and maintenance of cell structures.[1] Monomers of the protein tubulin assemble together to form microtubule polymers, which are dynamic, growing or shrinking as required to perform tasks around the cell.[2] Due to their significance in cell division, microtubules are an important focus for anti-cancer therapeutics. Drugs targeting microtubules prevent cancer cells from proliferating and because cancer cells divide more rapidly than healthy cells, they are more impacted by anti-mitotic therapeutics.

There are three main classes of anti-mitotic drugs: the vinca alkaloids, the taxanes, and compounds related to colchicine. These mitotic inhibitors limit tumor proliferation by preventing cancer cell division, but each drug category targets microtubules in a different manner. The vinca alkaloids, for example, destroy the mitotic spindles to prevent cell division from taking place. The taxane family includes natural products such as paclitaxel (Taxol), which act by stabilizing microtubules so mitosis cannot occur. Compounds that interact with the colchicine binding site of tubulin prevent assembly of tubulin subunits into functional microtubules, and thus also inhibit cell division. In this Chapter we will focus on synthesis of compounds in the third class of anti-mitotic drugs, colchicine analogues.

---

[1] Jordan, A.; Hadfield, J. A.; Lawrence, N. J.; McGown, A. T. *Med. Res. Rev.* **1998**, *18*, 259.
[2] Jordan, M. A.; Wilson, L. *Nat. Rev. Cancer* **2004**, *4*, 253.

Multiple tubulin-binding agents that target the colchicine binding site have been identified. The ancient anti-gout remedy colchicine (**1.1**) was one of the first molecules discovered to bind to tubulin. Like a number of related diaryl natural products, including combretastatin A-4 (**1.2**, Figure 2.1a), it inhibits tubulin polymerization by interacting with β-tubulin at a site now known as the colchicine binding pocket.[3] 3,4,5-Trimethoxyphenyl ring A is necessary to retain activity as a tubulin disruptor, but the identity of ring B is more modular; for example, phenstatin and naphthylphenstatin (Figure 2.1b) are well tolerated in the colchicine binding site.[4] Diaryl analogues containing ethylene[5] or ethane[6] linkers are also active tubulin disruptors. In particular, racemic isoerianin derivatives (Figure 2.1c) are potent inhibitors of cancer cell division.[6]

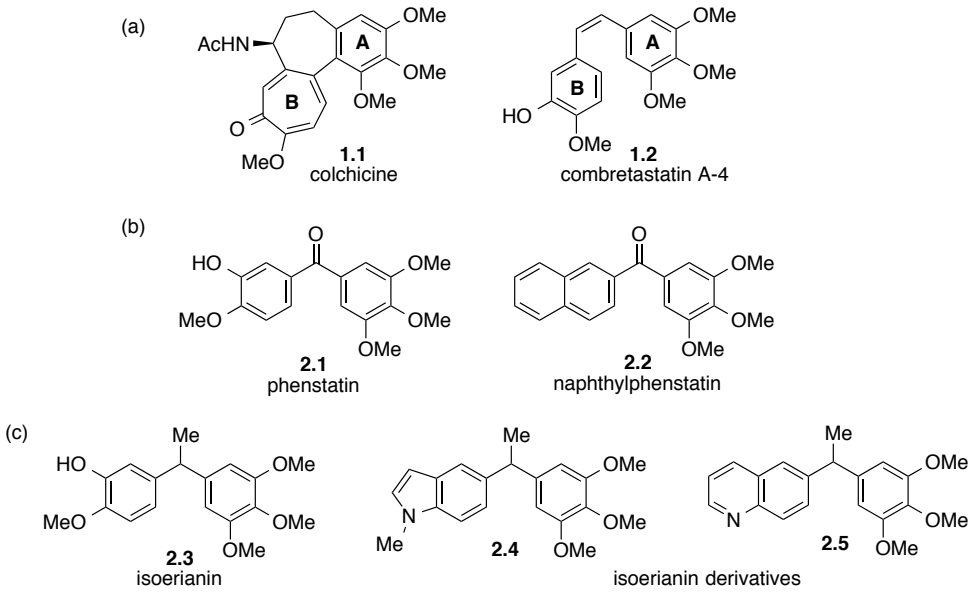


Figure 2.1. Tubulin-binding agents that interact with the colchicine binding site.

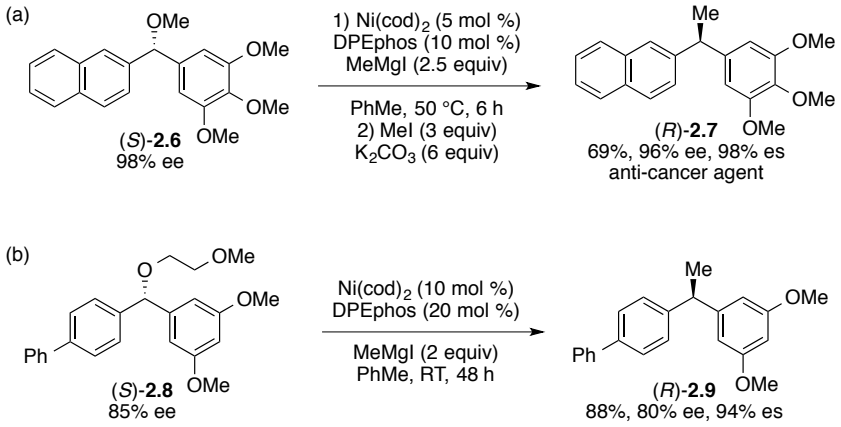
[3] Álvarez, R.; Álvarez, C.; Mollinedo, F.; Sierra, B. G.; Medarde, M.; Peláez, R. *Bioorg. Med. Chem.* **2009**, *17*, 6422.
[4] Álvarez, C.; Álvarez, R.; Corchete, P.; Pérez-Melero, C.; Peláez, R.; Medarde, M. *Bioorg. Med. Chem.* **2008**, *16*, 8999.
[5] Hamze, A.; Giraud, A.; Messaoudi, S.; Provot, O.; Peyrat, J.-F.; Bignon, J.; Liu, J.-M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *Chem. Med. Chem.* **2009**, *4*, 1912.
[6] Messaoudi, S.; Hamze, A.; Provot, O.; Tréguier, B.; Rodrigo De Losada, J.; Bignon, J.; Liu, J.-M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *Chem. Med. Chem.* **2011**, *6*, 488.

While the 1,1-diarylethane motif has been established as a potent tubulin polymerization inhibitor, this class of compound has yet to be synthesized and examined as single enantiomers. It is well known that the difference between enantiomers of pharmaceuticals can dramatically affect their binding ability and efficacy as drugs.[7] Methodology developed in the Jarvo laboratory would allow efficient access to both enantiomers of bioactive diarylethanes. We hypothesized that use of enantioenriched diarylethanes would further refine three-dimensional structure-activity relationships and provide improved lead compounds for the identification of anti-cancer drugs.

The Jarvo laboratory has previously demonstrated the stereospecific synthesis of several 1,1-diarylethanes via the nickel-catalyzed Kumada cross-coupling reactions of diaryl alcohol derivatives. The cross-coupling reaction of enantioenriched diaryl ether (*S*)-**2.6** with methylmagnesium iodide provided (*R*)-**2.7**, a known tubulin-binding compound,[4] in high enantiomeric excess (ee) and enantiospecificity (es) (Scheme 2.1a).[8,9] Less reactive substrates containing methoxyphenyl substituents, such as (*S*)-**2.8**, underwent smooth cross-coupling reactions when a methoxyethyl ether leaving group was used in the transformation (Scheme 2.1b).[10] We postulated that we could apply this cross-coupling methodology to prepare a series of trimethoxyphenyl-substituted diarylethane analogues for tubulin-binding studies.

[7] Ariëns, E. J. *Eur. J. Clin. Pharmacol.* **1984**, *26*, 663.
[8] Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389.
[9] es = ee $_{\text{product}}$/ee $_{\text{starting material}}$; see: Denmark, S. E.; Vogler, T. *Chem.–Eur. J.* **2009**, *15*, 11737.
[10] Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293.

Scheme 2.1. Enantiospecific nickel-catalyzed cross-coupling methods for the synthesis of methoxyphenyl-substituted 1,1-diarylethanes.



In this Chapter, we report the synthesis of both enantiomers of naphthyl-substituted diarylethane **2.7** using nickel-catalyzed Kumada cross-coupling methods. Subsequent biological evaluation for tubulin polymerization disruption was performed to determine relative tubulin-binding affinities. We hypothesized that one enantiomer would exhibit greater potency as a tubulin polymerization disruptor. In addition, we report the synthesis and biological evaluation of diarylethane **2.10**. We chose to target this more challenging diarylethane in order to expand our cross-coupling methodology, and because this compound is an anti-cancer agent: **2.10** has demonstrated cytotoxic activity toward colon carcinoma cells[6] and has been identified as a smallpox anti-viral agent.[11] Finally, we report the first synthesis of indole-substituted diarylethane **2.4** achieved using a cross-coupling reaction.

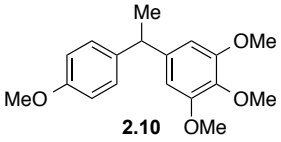


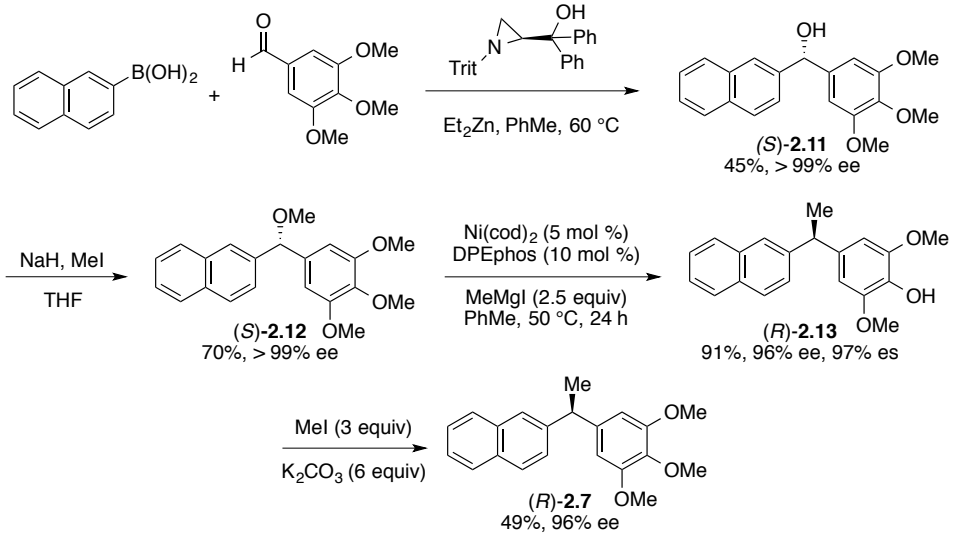
Figure 2.2. Structure of diarylethane **2.10**.

[11] Cheltsov, A. V.; Aoyagi, M.; Aleshin, A.; Yu, E. C.-W.; Gilliland, T.; Zhai, D.; Bobkov, A. A.; Reed, J. C.; Liddington, R. C.; Abagyan, R. *J. Med. Chem.* **2010**, *53*, 3899.

2.2 Synthesis of Enantioenriched Naphthyl-Substituted Diarylethanes

The synthesis of naphthyl-substituted diarylethane (*R*)-**2.7** was undertaken according to the procedure shown in Scheme 2.2.[8] The stereogenic center was installed via an asymmetric arylation reaction of 3,4,5-trimethoxybenzaldehyde with 2-naphthylboronic acid using a chiral aziridine catalyst.[12] Protection of diaryl alcohol (*S*)-**2.11** with iodomethane proceeded in 70% yield with retention of stereochemistry to generate diaryl methyl ether (*S*)-**2.12** for the Kumada cross-coupling reaction.

Scheme 2.2. Synthesis of diarylethane (*R*)-**2.7**.



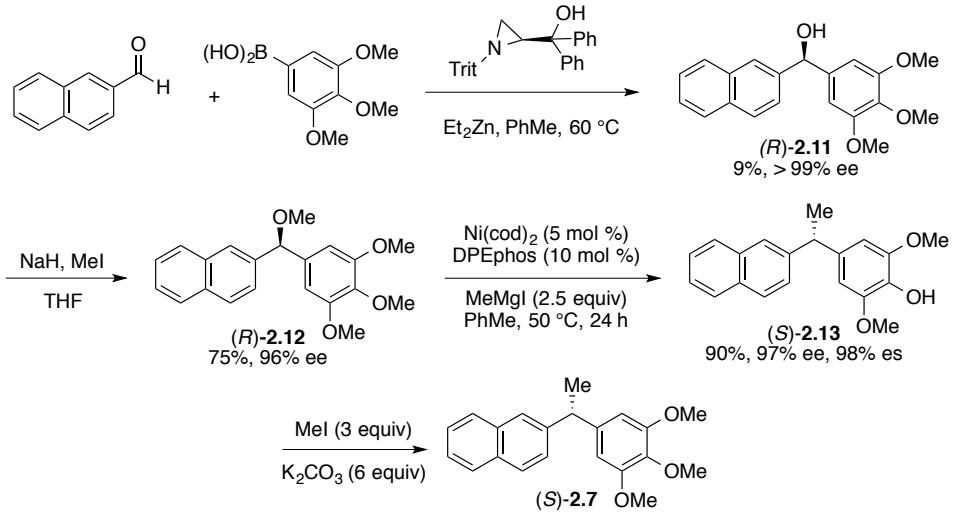
Upon subjecting (*S*)-**2.12** to the cross-coupling conditions, the reaction formed demethylated compound (*R*)-**2.13** in 91% yield and 96% ee; this phenol could be remethylated by treatment with iodomethane in the presence of potassium carbonate to furnish the intended diarylethane (*R*)-**2.7** (Scheme 2.2). It was proposed that during the course of the cross-coupling reaction, methoxy substituents *ortho* to one another chelate excess magnesium ions, activating the *para*-methoxyphenyl group for cleavage by methylmagnesium iodide.[8] While previous work in the Jarvo laboratory showed only partial demethylation after 6 hours, we observed quantitative

[12] Braga, A. L.; Paixão, M. W.; Westermann, B.; Schneider P. H.; Wessjohan, L. A. *J. Org. Chem.* **2008**, *73*, 2879.

demethylation after longer reaction times, an observation consistent with the coordination of excess magnesium ions in solution.

The synthetic sequence to obtain enantiomer (*S*)-**2.7** has never been reported, and was performed according to Scheme 2.3. By switching the identity of the arylboronic acid and aldehyde, the same enantiomer of chiral aziridine catalyst can be used to generate the other enantiomer of **2.11**.[12] The low yield of (*R*)-**2.11** after asymmetric arylation can be accounted for by the poor solubility of 3,4,5-trimethoxyphenylboronic acid in toluene; additional recrystallizations were required to obtain material of suitable ee. Methylation to generate benzylic ether (*R*)-**2.12** followed by the nickel-catalyzed cross-coupling reaction formed phenol (*S*)-**2.13** in 80% yield and 97% ee. As with (*R*)-**2.13**, subsequent remethylation using iodomethane resulted in the desired diarylethane (*S*)-**2.7**.[13]

Scheme 2.3. Synthesis of diarylethane (*S*)-**2.7**.



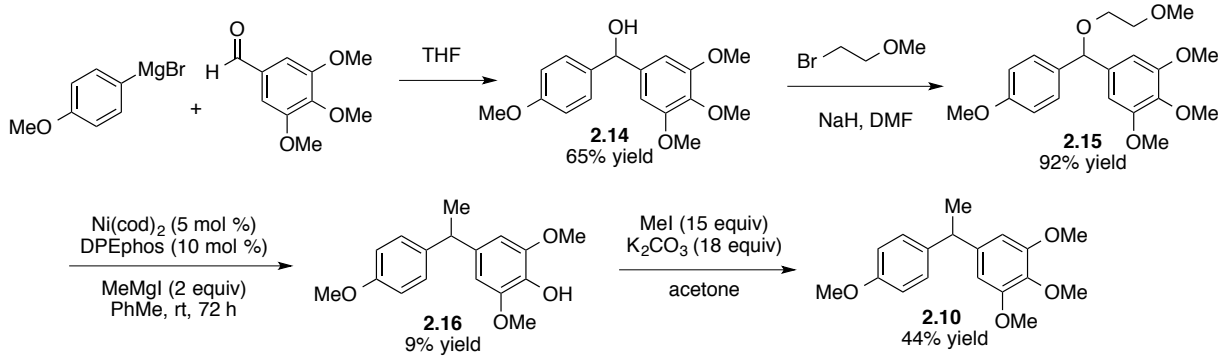
[13] Remethylation of (*S*)-**2.13** to obtain (*S*)-**2.7** was performed by LuisRuben Martinez.

2.3 Synthesis of *para*-Methoxyphenyl-Substituted Diarylethane 2.10

We also prepared diarylethane **2.10**, an analogue of diarylethane **2.7**, for tubulin-binding studies. Guided by the Jarvo laboratory's previous reaction design for substrates lacking an extended aromatic system (Scheme 2.1b), we postulated that the cross-coupling reaction to obtain **2.10** would require a more activated leaving group.[10] As with (*S*)-**2.8**, we designed substrate **2.15** to contain a methoxyethyl ether leaving group instead of a simple methyl ether. We hypothesized that the methoxyethyl ether group would chelate excess magnesium ions to provide increased activation for oxidative addition.

The racemic synthesis of **2.10** involved addition of *para*-methoxyphenylmagnesium bromide to 3,4,5-trimethoxybenzaldehyde in order to generate alcohol **2.14** (Scheme 2.4). Alkylation using 2-(bromoethyl)methyl ether formed **2.15** in 92% yield.[10] Upon subjecting **2.15** to the cross-coupling conditions, the reaction yielded demethylated compound **2.16**, which could be remethylated to provide **2.10** (vide supra).

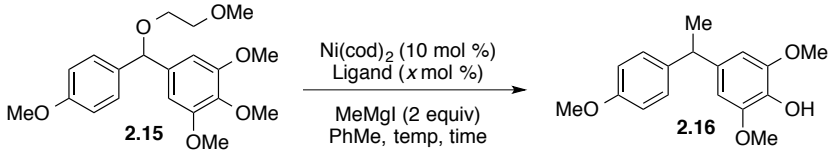
Scheme 2.4. Racemic synthesis of diarylethane **2.10**.



Initial attempts to develop the cross-coupling reaction resulted in low yield and significant background reaction, which lead us to conclude that the reaction of electron-rich substrates would be challenging (Scheme 2.4 and Table 2.1, entries 1 and 2). Electron-donating *para*-methoxyphenyl groups can facilitate carbocation formation, which leads to racemization of

starting material. We reasoned that investigating other catalyst systems with increased nickel loading would enable the cross-coupling reaction to outcompete the background reaction. Nickel catalysts ligated by *rac*-BINAP and CyDPEphos produced the highest yields at room temperature (entries 5 and 6). In order to improve reactivity, the cross-coupling reaction was performed at elevated temperatures. Heating the reaction to 40 °C afforded higher yields while keeping background reactivity low (entry 7); however, at 60 °C we observed background reactivity comparable to that of the nickel-catalyzed reaction (entry 11). The optimized reaction conditions, 24 hours at 40 °C with DPEphos, produced phenol **2.16** in 49% yield (entry 8).

Table 2.1. Ligand screen and effect of increased temperature and reaction time on the cross-coupling reaction of **2.15**.



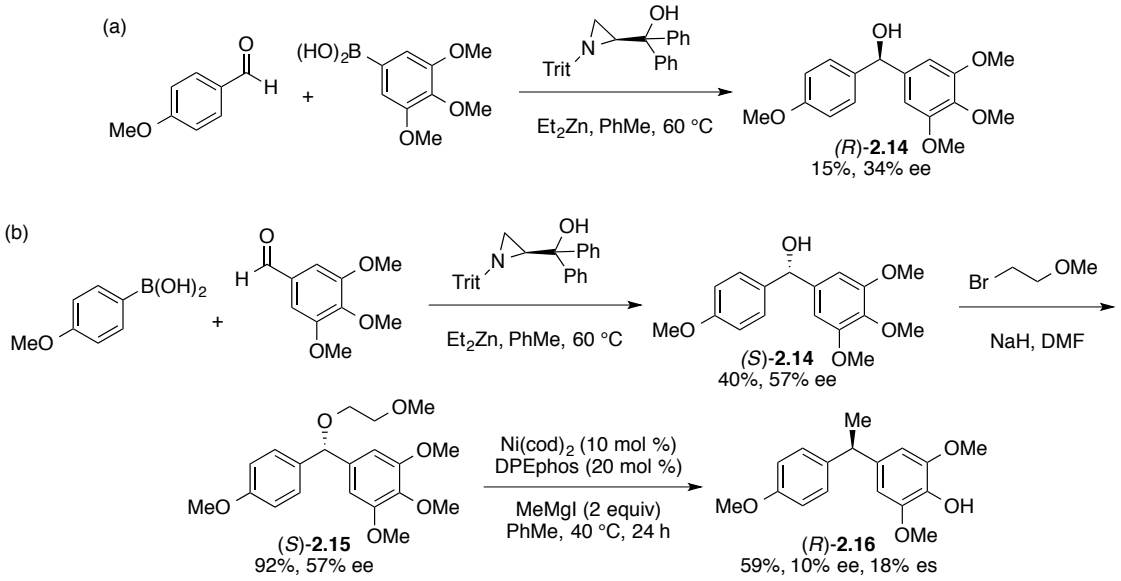
entry	ligand	ligand loading (%)	time (h)	temp (°C)	SM yield (%)[a]	yield **2.16** (%)[a]
1[b]	none, no Ni	--	72	rt	31	8
2[b]	DPEphos	10	72	rt	37	9
3	DPEphos	10	48	rt	65	16
4	Xantphos	10	48	rt	61	22
5	*rac*-BINAP	10	48	rt	62	24
6	CyDPEphos	10	48	rt	56	25
7	**none, no Ni**	**--**	**6**	**40**	**71**	**5**
8	**DPEphos**	**20**	**24**	**40**	**28**	**49**
9	*rac*-BINAP	20	6	40	15	31
10	CyDPEphos	20	6	40	27	33
11	none, no Ni	--	6	60	50	54
12	*rac*-BINAP	20	6	60	37	nd
13	CyDPEphos	20	6	60	29	51

[a]Yield determined by ^{1}H NMR spectroscopy by comparison to an internal standard (PhTMS).
[b]Employed 5 mol % $Ni(cod)_2$.

With optimized reaction conditions in hand, our next goal was to determine the enantiospecificity of the reaction. Synthesis of enantioenriched substrate **2.15** was accomplished

using the asymmetric aziridine-catalyzed arylation reaction (Scheme 2.5).[12] The reaction to generate (*R*)-**2.14** alcohol gave only 15% yield and 34% ee after recrystallization (Scheme 2.5a; the low yield can be accounted for by the low solubility of 3,4,5-trimethoxyphenylboronic acid in toluene, vide supra). In contrast, the reaction to make (*S*)-**2.14** alcohol provided 40% yield and 57% ee (Scheme 2.5b). We chose to move forward with the latter alcohol and synthesized the ether (*S*)-**2.15** in 92% yield. Subjecting (*S*)-**2.15** to the cross-coupling reaction conditions generated **2.16** in 59% yield; however, the resulting diarylethane was formed in only 10% ee and 18% es. We attribute the loss of stereochemistry to a background racemization pathway caused by the electron-rich *para*-methoxyphenyl group.

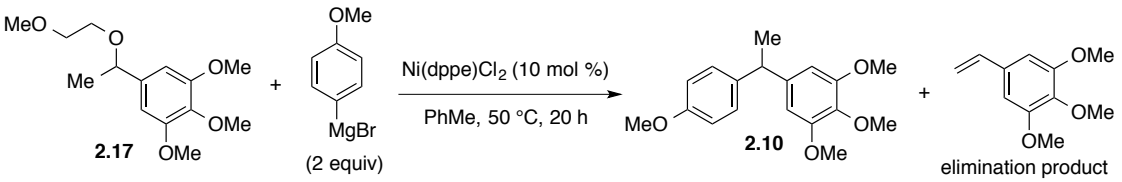
Scheme 2.5. Attempted enantioenriched synthesis of diarylethane **2.10**.



To circumvent having the electron-donating *para*-methoxyphenyl substituent in the ether substrate, we devised a synthetic plan for the cross-coupling reaction to incorporate the *para*-methoxyphenyl moiety as the transmetallating partner instead. The proposed transformation would involve the Kumada cross-coupling reaction of ether **2.17** with *para*-methoxyphenylmagnesium bromide to generate diarylethane **2.10** (Table 2.2). Our reaction

design was inspired by previous work in the Jarvo laboratory using the Ni(dppe)Cl_2 catalyst to minimize β-hydride elimination.[14] We attempted the Kumada cross-coupling reaction of substrate **2.17** with *para*-methoxyphenylmagnesium bromide using Ni(dppe)Cl_2, but the reaction yielded < 2% desired product and 7% β-hydride elimination product (entry 1). Incorporating one equivalent of magnesium iodide increased the yield of desired product to 18%, but generated additional β-hydride elimination product (entry 2).[15]

Table 2.2. Attempted Kumada cross-coupling reaction using Ni(dppe)Cl_2.



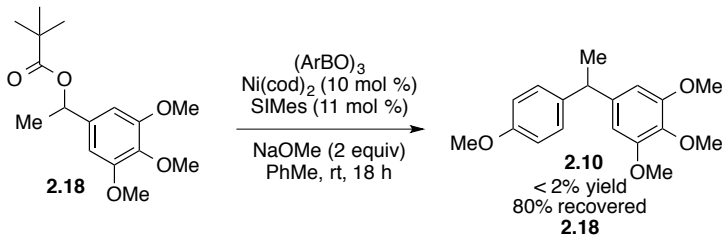
entry	SM yield (%)[a]	yield **2.10** (%)[a]	elimination yield (%)[a]	additive
1	68	< 2	7	--
2	49	18	16	MgI_2

[a]Yield determined by ^{1}H NMR spectroscopy by comparison to an internal standard (PhTMS).

An alternative strategy to access diarylethane **2.10** involved the Suzuki cross-coupling reaction of ester **2.18** with *para*-methoxyphenylboronic ester (Scheme 2.6). Based on previous methods developed in the Jarvo laboratory, we postulated that incorporation of a pivolyl leaving group in the substrate would allow for use of an arylboroxine as the transmetallating agent.[16] When subjected to the reaction conditions, substrate **2.18** provided only recovered starting material.

[14] Yonova, I. M.; Johnson, A. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. S.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2422.
[15] Greene, M. A. Diastereoselective Synthesis of Seven Membered Ring *trans*-Alkenes and Development of Stereospecific Nickel-Catalyzed Cross-Coupling Reactions. Ph.D. Thesis, The University of California, Irvine, May 2013.
[16] Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 3303.

Scheme 2.6. Attempted Suzuki cross-coupling reaction to synthesize **2.10**.



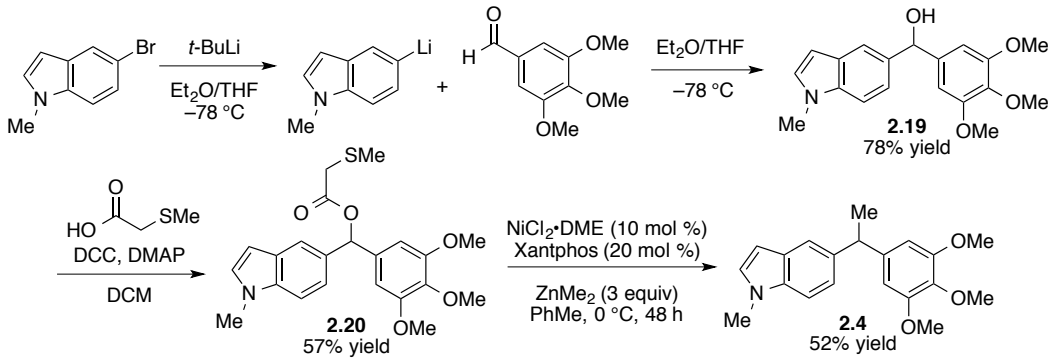
2.4 Synthesis of Indole-Substituted Diarylethane 2.4

We were interested in pursuing the synthesis of indole-substituted diarylethane **2.4** because it potently inhibits tubulin polymerization and demonstrates bioactivity against colon, lung, breast, and triple-negative breast cancer cell lines.[6,17] Typically, synthesis of diarylethane **2.4** is achieved by hydrogenation of the diarylethylene precursor. Our proposed synthetic route to prepare **2.4** would incorporate a stereospecific nickel-catalyzed Negishi cross-coupling reaction to generate single enantiomers of **2.4**. Herein, we report the first synthesis of diarylethane **2.4** achieved using a cross-coupling reaction; these results have set the stage for the enantiospecific synthesis and subsequent biological evaluation of (*R*)- and (*S*)-**2.4**.

The Jarvo laboratory has previously developed the nickel-catalyzed Negishi cross-coupling reactions of diaryl 2-(methylthio)esters with dimethylzinc to generate diarylethanes.[18] To access diarylethane **2.4**, the requisite 2-(methylthio)acetate **2.20** was obtained by a DCC coupling reaction of alcohol **2.19** with 2-(methylthio)acetic acid (Scheme 2.7).[19] After evaluating several ligands for the transformation of **2.20** to **2.4**, we found that a combination of $NiCl_2 \cdot DME$ and Xantphos provided the highest yields. Performing the cross-coupling reaction at 0 °C for 48 h furnished diarylethane **2.4** in 52% yield.

[17] Álvarez, R.; Puebla, R.; Fernando Díaz, J.; Bento, A. C. García-Navas, R.; de la Iglesia-Vicente, J.; Mollinedo, F.; Andreu, J. M.; Medarde, M.; Peláez, R. *J. Med. Chem.* **2013**, *56*, 2813.
[18] Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083.
[19] Stayshich, R. M.; Meyer, T. Y. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 4704.

Scheme 2.7. Synthesis of diarylethane **2.4**.



Initial attempts to generate either (*R*)- or (*S*)-**2.20** for the stereospecific cross-coupling reaction were unsuccessful: the asymmetric arylation reaction did not provide the desired enantioenriched diaryl alcohol **2.19**. Efforts to obtain (*R*)- or (*S*)-**2.19** via other synthetic pathways are in progress.

2.5 Biological Evaluation as Tubulin Polymerization Disruptors

Having utilized our cross-coupling methodology to synthesize the six diarylethanes shown in Figure 2.3, we performed a qualitative tubulin-binding assay.[20] Polymerized microtubules are visualized in vivo using fluorescence microscopy with a cell line containing green fluorescent protein (GFP)-tagged tubulin.[21] When the tubulin-binding agent is introduced, microtubule fibers are no longer visible by fluorescence microscopy because they have been depolymerized into tubulin monomers.

[20] Lyons-Abbott, S.; Sackett, D. L.; Wloga, D.; Gaertig, J.; Morgan, R. E.; Werbovetz, K. A.; Morrissette, N. S. *Eukaryot. Cell* **2010**, *9*, 1825.
[21] Freitag, M.; Hickey, P. C.; Raju, N. B.; Selker, E. U.; Read, N. D. *Fungal Genet. Biol.* **2004**, *41*, 897.

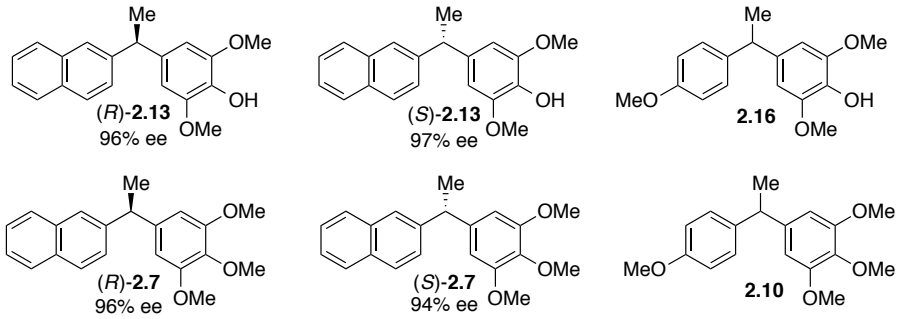


Figure 2.3. Diarylethanes for biological testing.

In collaboration with the Morrissette laboratory at UC Irvine, our six diarylethanes were evaluated against an LLCPK cell line containing GFP-tagged tubulin. Our preliminary goal was to classify the substrates as active, inactive, or somewhat active tubulin disruptors. Samples were dissolved in DMSO and diluted to 10 μM concentration in media before incubating with cells (0.1% DMSO). Fluorescence microscopy images were collected of the cells before compound exposure, after incubation for 15 minutes, then after incubation for 30 minutes.

The positive control, 10 μM colchicine (**1.1**), showed significant tubulin disruption after 15 minutes, while the negative vehicle control of DMSO showed no microtubule disruption (Figure 2.4). Racemic compound **2.10** was the only substrate besides colchicine to demonstrate activity as a potent tubulin disruptor; its phenol counterpart **2.16** showed no tubulin disruption. Compound (*S*)-**2.7** demonstrated fair activity as a tubulin disruptor, while (*R*)-**2.7** showed no tubulin depolymerization. The remaining two phenol compounds, (*S*)-**2.13** and (*R*)-**2.13**, did not show activity as tubulin-binding agents. These results reflect the necessity of the trimethoxyphenyl motif for tubulin binding. The increased potency of compound (*S*)-**2.7** demonstrates the significance of stereochemical differentiation in the colchicine binding site.

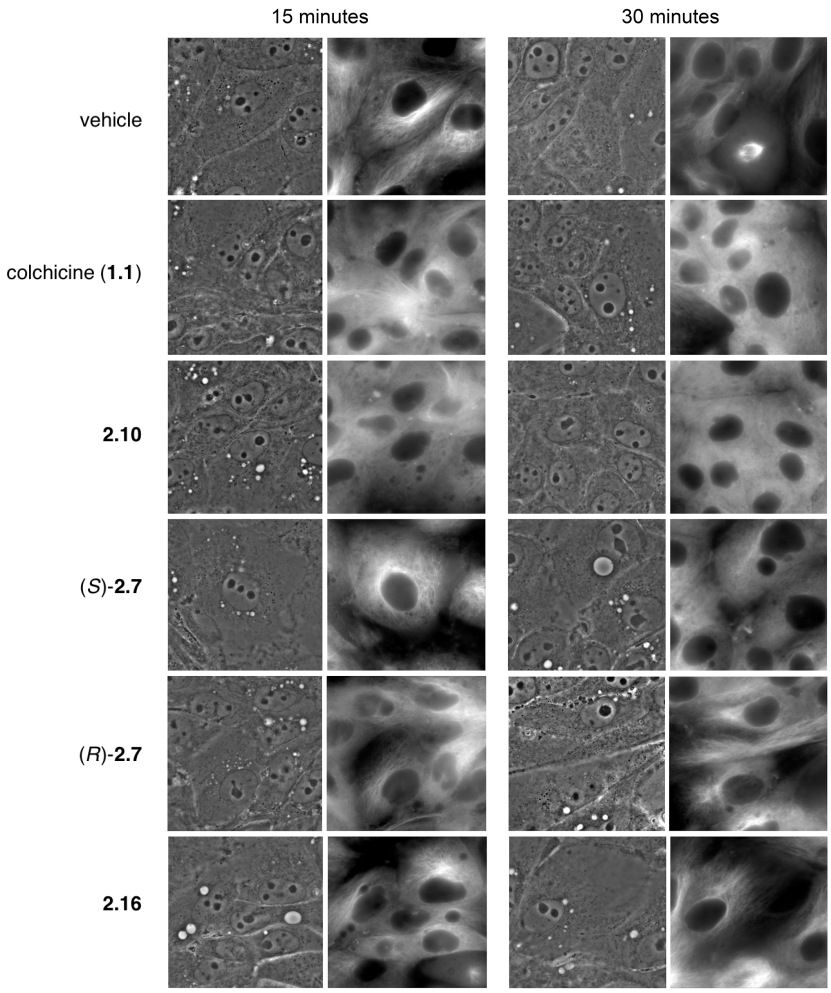


Figure 2.4. Fluorescence microscopy images of LLCPK cells, containing GFP-tagged tubulin, upon incubation with diarylethane compounds.

2.6 Conclusions

The tubulin disruption studies confirm that **2.10** is a potent inhibitor of tubulin polymerization in the LLCPK cell line. Preliminary results show a marked difference in tubulin binding between (*S*)-**2.7** and (*R*)-**2.7**, and support our assertion that the colchicine binding site recognizes absolute stereochemistry. We have established that compounds containing a 2,6-dimethoxy-phenol motif (**2.16**, (*S*)-**2.13**, and (*R*)-**2.13**) do not exhibit activity as tubulin polymerization inhibitors, confirming the 3,4,5-trimethoxyphenyl ring is important for binding in

the colchicine site. Finally, we have completed the racemic synthesis of **2.4** utilizing a Negishi cross-coupling reaction.

Synthesis of enantioenriched (*R*)-**2.10**, (*S*)-**2.10**, (*R*)-**2.4**, and (*S*)-**2.4** is under way. These compounds will be evaluated for activity as tubulin polymerization disruptors to determine whether a single enantiomer demonstrates greater affinity for tubulin binding, and to assign IC_{50} values to these substrates.

2.7 Experimental Details

General Procedures

All reactions were carried out under an atmosphere of N_2. All glassware was oven- or flame-dried prior to use. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), and toluene (PhMe) were degassed with Ar and then passed through two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 ºC for 12 h) to remove H_2O. All other solvents used were purchased "anhydrous" commercially, or purified as described (vide infra). ^{1}H NMR spectra were recorded on Bruker DRX-400 (400 MHz ^{1}H, 100 MHz ^{13}C), GN-500 (500 MHz ^{1}H, 125.7 MHz ^{13}C), or CRYO-500 (500 MHz ^{1}H, 125.7 MHz ^{13}C) spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.00). Data are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), doublet of triplets (dt), doublet of doublet of triplets (ddt), triplet of triplets (tt), quartet (q), multiplet (m)], coupling constants [Hz], integration). Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.16 ppm). Unless otherwise indicated, NMR data were collected at 25 ºC. Infrared spectra

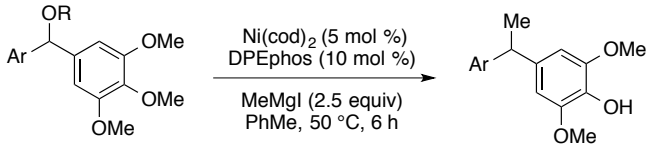
were obtained on a Thermo Scientific Nicolet iS5 FT-IR Spectrometer. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F_{254} precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$, ceric ammonium molybdate (CAM), or *p*-anisaldehyde (PAA) solutions. Flash chromatography was performed using Silica Gel 60Å (170-400 mesh) from Fisher Scientific. Melting points (m.p.) were obtained using a Mel-Temp melting point apparatus and are uncorrected. Optical rotations were measured on a Rudolph Research Analytical Autopol III Automatic Polarimeter. SFC determinations of enantiopurity were performed on a Berger Analytical instrument using a Daicel™ Chiralpak® column (OD-H, OJ-H, AD-H, or AS-H; 100 bar, 50 °C). High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center.

$Ni(cod)_2$ was purchased from Strem, stored in a glovebox freezer (–20 °C) under an atmosphere of N_2, and used as received. All ligands were purchased from Strem, Aldrich, or Solvias and stored in a glovebox under an atmosphere of N_2. Dimethyl zinc ($ZnMe_2$) was purchased from Aldrich and stored under N_2 at 4 °C. Grignard reagents were freshly prepared from the halide precursor. All Grignard reagents and $ZnMe_2$ were titrated with iodine prior to use.[22] All other chemicals were purchased commercially and used as received.

[22] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890.

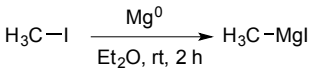
General Cross-Coupling Procedures

Method A: Cross-Coupling with Methyl Grignard



Performed according to a procedure reported by Jarvo and co-workers.[8] In a glovebox, a flame-dried bomb flask equipped with a stir bar was charged with $Ni(cod)_2$ (0.05 equiv) and DPEphos (0.10 equiv). A solution of substrate (1.0 equiv) in PhMe was added and the reaction mixture was stirred for 5 min. MeMgI (2.5 equiv) was added dropwise and the vial was sealed, removed from the glovebox, and stirred for 24 h at 40 °C or 50 °C. The reaction was quenched with saturated aqueous ammonium chloride, extracted with EtOAc (x 3), washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Phenyltrimethylsilane (PhTMS) was added as internal standard and a ^1H NMR yield was obtained before purification by flash column chromatography.

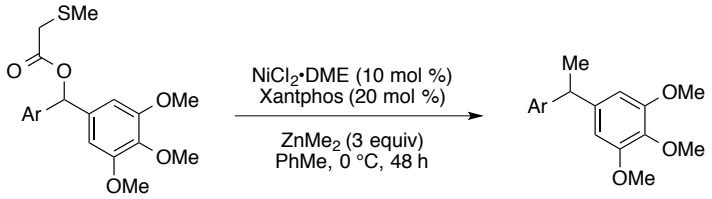
Preparation of Methyl Grignard Reagent



Under a N_2 atmsophere, a 3-necked flask equipped with a stir bar, reflux condenser, and Schlenk filtration apparatus was charged with magnesium turnings (1.1 g, 45 mmol, 1.5 equiv). The flask and magnesium turnings were then flame-dried under vacuum and the flask was back-filled with N_2. Anhydrous Et_2O (7 mL) and a crystal of iodine (ca. 2 mg) were added to the flask. Freshly distilled iodomethane (1.9 mL, 31 mmol, 1.0 equiv) was slowly added over 30 min to maintain a gentle reflux. The mixture was stirred for 2 h at room temperature then filtered through the fritted Schlenk filter into the Schlenk bomb under N_2 atmosphere. The magnesium turnings were

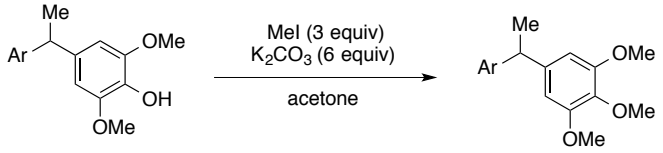
washed with Et_2O (2 x 1.0 mL) then the Schlenk bomb was sealed, removed, and placed under an argon atmosphere. The resulting methyl Grignard reagent was typically between 2.4 and 3.0 M as titrated by Knochel's method[22] and could be stored (sealed under argon atmosphere or in a glovebox) for up to 4 weeks.

Method B: Cross-Coupling with Dimethylzinc



Performed according to a procedure reported by Jarvo and co-workers.[18] In a glovebox, a flame-dried 7 mL vial equipped with a stir bar was charged with $NiCl_2 \cdot DME$ (0.10 equiv) and Xantphos (0.20 equiv). A solution of substrate (1.0 equiv) in PhMe was added and the reaction mixture was stirred for 5 min before being sealed and removed from the glovebox. The vial was equipped with a N_2 line, cooled to 0 °C, and $ZnMe_2$ (3.0 equiv) was added, which resulted in an immediate color change from green to orange. The reaction was allowed to stir at 0 °C for 48 h, then it was quenched with isopropyl alcohol, filtered through a plug of silica gel (neat Et_2O), and concentrated in vacuo. Phenyltrimethylsilane (PhTMS) was added as internal standard and a ^1H NMR yield was obtained before purification by flash column chromatography.

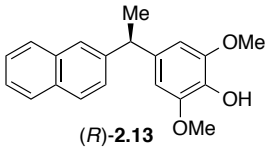
Method C: Remethylation with Iodomethane



Performed according to a procedure reported by Jarvo and co-workers.[8] Substrate (1.0 equiv)

was dissolved in acetone and K_2CO_3 (6.0 equiv) was added, followed by iodomethane (3.0 equiv). The reaction mixture was heated to reflux and stirred overnight, after which the reaction was cooled to room temperature, filtered, washed with acetone, and concentrated in vacuo. H_2O was added and the mixture was extracted with EtOAc (x 3). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated in vacuo.

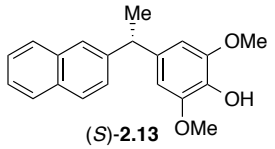
Characterization Data for Products



(*R*)-**2.13**

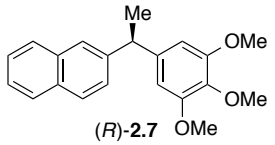
2,6-Dimethoxy-4-((*R*)-1-naphthalen-3-yl)ethyl)phenol ((*R*)-2.13). Prepared according to Method A, using the following amounts of reagents: $Ni(cod)_2$ (6.5 mg, 0.024 mmol, 0.050 equiv), DPEphos (25 mg, 0.047 mmol, 0.10 equiv), ether (*S*)-**2.12** (0.16 g, 0.47 mmol, 1.0 equiv), PhMe (5.0 mL), and MeMgI (0.59 mL, 1.2 mmol, 2.0 M in Et_2O, 2.5 equiv). The product was purified by flash column chromatography using 25% EtOAc/hexanes to afford the title compound as a colorless oil (0.13 g, 0.42 mmol, 91%). Analytical data are consistent with literature values.[8] **TLC R_f** = 0.3 (20% EtOAc/hexanes); **m.p.** 88–90 °C; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.80–7.78 (m, 2H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.66 (s, 1H), 7.45–7.41 (m, 2H), 7.30 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.47 (s, 2H), 5.40 (s, 1H), 4.23 (q, *J* = 7.2 Hz, 1H), 3.81 (s, 6H), 1.70 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 147.0, 144.0, 137.4, 133.6, 133.1, 132.2, 128.0, 127.8, 127.7, 126.8, 126.0, 125.5, 125.2, 104.6, 56.4, 44.9, 22.1; **IR** (neat) 3420, 2962, 1612, 1243, 1226, 1111 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{20}H_{20}O_3$ $(M + Na)^+$ 331.1310, found 331.1317; **$[\alpha]^{24}_D$** +22.2 (*c* 1.45, $CHCl_3$), literature $[\alpha]^{23}_D$ +23.6 (*c* 0.42, $CHCl_3$); **SFC**

analysis (AD-H, 15% MeOH, 2.5 mL/min, 215 nm) indicated 96% ee: t_R (minor) = 12.11 min, t_R (major) = 13.25 min.



(*S*)-**2.13**

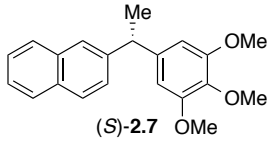
2,6-Dimethoxy-4-((*S*)-1-naphthalen-3-yl)ethyl)phenol ((*S*)-2.13). Prepared according to Method A, using the following amounts of reagents: $Ni(cod)_2$ (1.6 mg, 6.0 μmol, 0.050 equiv), DPEphos (6.2 mg, 0.012 mmol, 0.10 equiv), ether (*R*)-**2.12** (39 mg, 0.12 mmol, 1.0 equiv), PhMe (1.0 mL), and MeMgI (0.13 mL, 0.29 mmol, 2.3 M in Et_2O, 2.5 equiv). The product was purified by flash column chromatography using 10–25% EtOAc/hexanes to afford the title compound as a colorless oil (32 mg, 0.11 mmol, 90%). Analytical data are consistent with the values listed for (*R*)-**2.13** (vide supra). $\mathbf{[\alpha]^{24}_D}$ –26.6 (*c* 1.40, $CHCl_3$); **SFC** analysis (AD-H, 15% MeOH, 2.5 mL/min, 215 nm) indicated 97% ee: t_R (major) = 12.10 min, t_R (minor) = 13.33 min.



(*R*)-**2.7**

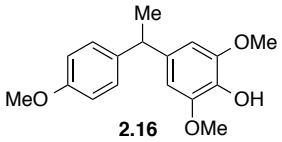
2-((*R*)-1-(3,4,5-Trimethoxyphenyl)ethyl)naphthalene ((*R*)-2.7). Prepared according to Method C, using the following amounts of reagents: phenol (*R*)-**2.13** (55 mg, 0.18 mmol, 1.0 equiv), K_2CO_3 (0.447 g, 3.24 mmol, 18.0 equiv), iodomethane (102 μL, 1.62 mmol, 9.00 equiv), and acetone (3.0 mL). The product was purified by flash column chromatography using 15% Et_2O/pentanes to afford the title compound as a colorless oil (28 mg, 0.088 mmol, 49%). Analytical data are consistent with literature values.[8] **TLC** $\mathbf{R_f}$ = 0.4 (40% Et_2O/hexanes); **^{1}H**

NMR ($CDCl_3$, 400 MHz) δ 7.81–7.79 (m, 2H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.68 (s, 1H), 7.46–7.42 (m, 2H), 7.32 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.47 (s, 2H), 4.24 (q, *J* = 7.2 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 6H), 1.71 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 153.2, 143.7, 142.1, 136.4, 133.6, 132.2, 128.1, 127.9, 127.7, 126.8, 126.1, 125.5, 125.3, 105.0, 60.9, 56.2, 45.2, 22.0; **IR** (neat) 2932, 1588, 1506, 1417, 1232, 1124, 1008 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{21}H_{22}O_3$ $(M + Na)^+$ 345.1467, found 345.1454; **$[\alpha]^{24}_D$** +26.9 (*c* 1.29, $CHCl_3$), literature $[\alpha]^{23}_D$ +24.9 (*c* 0.78, $CHCl_3$); **SFC** analysis (AD-H, 15% MeOH, 2.5 mL/min, 215 nm) indicated 96% ee: t_R (minor) = 3.86 min, t_R (major) = 4.20 min.



(*S*)-**2.7**

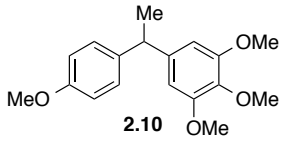
2-((*S*)-1-(3,4,5-Trimethoxyphenyl)ethyl)naphthalene ((*S*)-2.7). Prepared according to Method C by LuisRuben Martinez. The product was further purified by flash columm chromatography using 40% Et_2O/hexanes to afford the title compound as a colorless oil. Analytical data are consistent with the values listed for (*R*)-**2.7** (vide supra). **$[\alpha]^{24}_D$** –26.5 (*c* 0.70, $CHCl_3$); **SFC** analysis (AD-H, 15% MeOH, 2.5 mL/min, 215 nm) indicated 94% ee: t_R (major) = 3.83 min, t_R (minor) = 4.25 min.



2.16

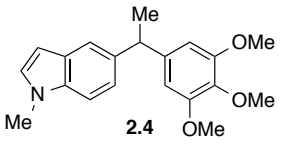
2,6-Dimethoxy-4-(1-(4-methoxyphenyl)ethyl)phenol (2.16). Prepared according to Method A, using the following amounts of reagents: $Ni(cod)_2$ (16 mg, 0.058 mmol, 0.10 equiv), DPEphos (63 mg, 0.12 mmol, 0.20 equiv), ether **2.15** (0.21 g, 0.58 mmol, 1.0 equiv), PhMe (6.0 mL), and

MeMgI (0.58 mL, 1.2 mmol, 2.0 M in Et_2O, 2.0 equiv). The product was purified by flash column chromatography using 40% Et_2O/hexanes to afford the title compound as a yellow oil (98 mg, 0.34 mmol, 59%). **TLC R_f** = 0.2 (40% Et_2O/hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.12 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.42 (s, 2H), 5.37 (s, 1H), 4.02 (q, *J* = 7.2 Hz, 1H), 3.83 (s, 6H), 3.78 (s, 3H), 1.58 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 157.9, 147.0, 138.7, 138.0, 133.0, 128.4, 113.8, 104.4, 56.3, 55.3, 44.0, 22.4; **IR** (neat) 3430, 2962, 2836, 1509, 1240, 1212, 1111 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{17}H_{20}O_4$ $(M + Na)^+$ 311.1259, found 311.1265.



2.10

1,2,3-Trimethoxy-5-(1-(4-methoxyphenyl)ethyl)benzene (2.10). Prepared according to Method C, using the following amounts of reagents: phenol **2.16** (36 mg, 0.13 mmol, 1.0 equiv), K_2CO_3 (0.310 g, 2.25 mmol, 18.0 equiv), iodomethane (94.0 μL, 1.50 mmol, 12.0 equiv), and acetone (3.0 mL). The product was purified by flash chromatography (10–40% Et_2O/pentanes) to afford the title compound as a colorless oil (17 mg, 0.055 mmol, 44%). Analytical data are consistent with literature values.[6] **TLC R_f** = 0.2 (10% Et_2O/hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.14 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.42 (s, 2H), 4.04 (q, *J* = 7.2 Hz, 1H), 3.82 (s, 9H), 3.79 (s, 3H), 1.60 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 157.9, 153.1, 142.5, 138.4, 136.2, 128.4, 113.8, 104.6, 60.9, 56.1, 55.3, 44.3, 22.3; **IR** (neat) 2933, 2835, 1508, 1235, 1123, 1008 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{18}H_{22}O_4$ $(M + Na)^+$ 325.1416, found 325.1427.

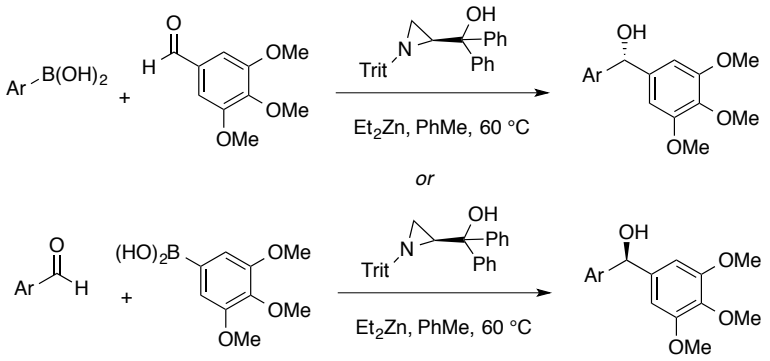


2.4

1-Methyl-5-(1-(3,4,5-trimethoxyphenyl)ethyl)-1*H*-indole (2.4). Prepared according to Method B, using the following amounts of reagents: $NiCl_2 \cdot DME$ (3.0 mg, 0.014 mmol, 0.10 equiv), Xantphos (16 mg, 0.027 mmol, 0.20 equiv), ester **2.20** (50 mg, 0.12 mmol, 1.0 equiv), PhMe (1.7 mL), and $ZnMe_2$ (0.34 mL, 0.41 mmol, 1.2 M in pentanes, 3.0 equiv). The product was purified by flash column chromatography using 20–40% EtOAc/hexanes to afford the title compound as a colorless oil (20 mg, 0.062 mmol, 52%). Analytical data are consistent with literature values.[6] **TLC R_f** = 0.5 (20% EtOAc/hexanes); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48 (s, 1H), 7.24 (d, *J* = 8.5 Hz, 1H), 7.08 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.02 (d, *J* = 3.0 Hz, 1H), 6.49 (s, 2H), 6.43 (dd, *J* = 3.0, 0.9 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 1H), 3.81–3.80 (m, 9H), 3.76 (s, 3H), 1.68 (d, *J* = 7.1 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 153.1, 143.3, 137.4, 136.1, 135.5, 129.1, 128.6, 122.0, 119.1, 109.2, 104.8, 100.9, 61.0, 56.2, 45.2, 33.0, 22.7; **IR** (neat) 2932, 1417, 1233, 1123, 721 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{20}H_{23}NO_3$ $(M + Na)^+$ 348.1576, found 348.1567.

General Procedures for Starting Materials Synthesis

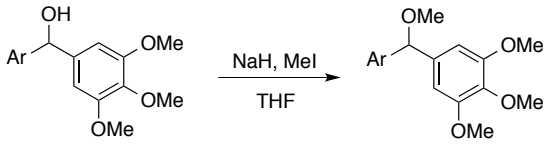
Method D: Asymmetric Aziridine-Catalyzed Arylation



Modified from a procedure reported by Braga and co-workers.[12] To a solution of arylboronic

acid (2.4 equiv) in anhydrous PhMe was added diethylzinc (1.0 M in PhMe, 7.2 equiv), and the solution was allowed to stir at 60 °C for 18 h. Upon cooling to room temperature, (*S*)-α,α-diphenyl-1-(triphenylmethyl)-2-aziridinemethanol (0.10 equiv) was added as a solution in PhMe and the reaction mixture was allowed to stir for 10 minutes before the addition of a solution of arylaldehyde (1.0 equiv) in PhMe. After stirring 18 h at room temperature, 1M HCl was added and the product was extracted with EtOAc (x 3). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated in vacuo.

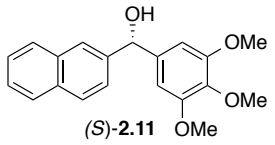
Method E: Alkylation with Iodomethane



Modified from a procedure reported by Jarvo and co-workers.[8] To a suspension of NaH (1.5 equiv) in anhydrous THF was added a solution of substrate (1.0 equiv) in THF. The mixture was stirred for 1 h before addition of iodomethane (1.02 equiv) and then the reaction was stirred overnight. Excess NaH was quenched with saturated aqueous ammonium chloride, and the product was extracted with EtOAc (x 3). The combined organics were washed with brine, dried over Na_2SO_4 and concentrated in vacuo.

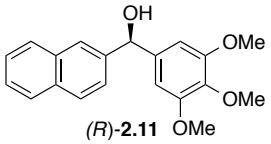
Synthesis & Characterization Data for Starting Materials

*Synthesis of Starting Materials for **2.7***



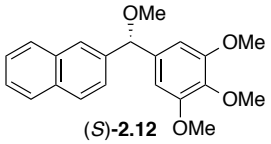
(S)-**2.11**

(*S*)-(3,4,5-Trimethoxyphenyl)(naphthalen-3-yl)methanol ((*S*)-2.11). Prepared according to Method D, using the following amounts of reagents: 3,4,5-trimethoxybenzaldehyde (0.49 g, 2.5 mmol, 1.0 equiv), 2-naphthylboronic acid (1.0 g, 6.0 mmol, 2.4 equiv), diethylzinc (18.0 mL, 18.0 mmol, 1.00 M in toluene, 7.20 equiv), (*S*)-α,α-diphenyl-1-(triphenylmethyl)-2-aziridinemethanol (0.12 g, 0.25 mmol, 0.10 equiv), and PhMe (43 mL). The product was purified by flash column chromatography using 25% EtOAc/hexanes, then recrystallized from 50% CH_2Cl_2/hexanes to afford the title compound as a white solid (0.36 g, 1.1 mmol, 45%). Analytical data are consistent with literature values.[8] **TLC** $\mathbf{R_f}$ = 0.1 (40% Et_2O/hexanes); **m.p.** 135–136 °C; $^{\mathbf{1}}$**H NMR** ($CDCl_3$, 500 MHz) δ 7.85–7.77 (m, 4H), 7.49–7.41 (m, 3H), 6.62 (s, 2H), 5.88 (s, 1H), 3.81 (s, 3H), 3.79 (s, 6H), 2.63 (br s, 1H); $^{\mathbf{13}}$**C NMR** ($CDCl_3$, 125 MHz) δ 153.3, 141.0, 139.4, 137.3, 133.3, 133.0, 128.4, 128.2, 127.8, 126.3, 126.1, 125.1, 124.8, 103.7, 76.4, 60.9, 56.1; **IR** (neat) 3357, 2938, 2838, 1590, 1233, 1128, 997 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{20}H_{20}O_4$ $(M + Na)^+$ 347.1259, found 347.1261; $\mathbf{[\alpha]^{26}_D}$ –1.5 (*c* 1.17, $CHCl_3$), literature $[\alpha]^{23}_D$ –1.07 (*c* 0.95, $CHCl_3$); **SFC** analysis (AD-H, 30% MeOH, 2.5 mL/min, 215 nm) indicated >99% ee: t_R (minor) = 3.25 min, t_R (major) = 3.55 min.



(*R*)-**2.11**

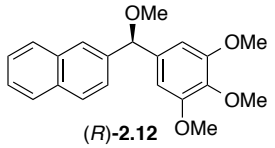
(*R*)-(3,4,5-Trimethoxyphenyl)(naphthalen-3-yl)methanol ((*R*)-2.11). Prepared according to Method D, using the following amounts of reagents: 2-naphthaldehyde (0.39 g, 2.5 mmol, 1.0 equiv), 3,4,5-trimethoxyphenylboronic acid (1.3 g, 6.0 mmol, 2.4 equiv), diethylzinc (18.0 mL, 18.0 mmol, 1.00 M in toluene, 7.20 equiv), (*S*)-α,α-diphenyl-1-(triphenylmethyl)-2-aziridinemethanol (0.12 g, 0.25 mmol, 0.10 equiv), and PhMe (43 mL). The product was purified by flash column chromatography using 50% EtOAc/hexanes, then recrystallized twice from 50% CH_2Cl_2/hexanes to afford the title compound as a white solid (70 mg, 0.22 mmol, 9%). Analytical data are consistent with the values listed for (*S*)-**2.11** (vide supra). $\mathbf{[\alpha]^{26}_D}$ –0.7 (*c* 0.20, $CHCl_3$); **SFC** analysis (AD-H, 30% MeOH, 2.5 mL/min, 215 nm) indicated >99% ee: t_R (major) = 3.34 min, t_R (minor) = 3.67 min.



(*S*)-**2.12**

2-((*S*)-Methoxy(3,4,5-trimethoxyphenyl)methyl)naphthalene ((*S*)-2.12). Prepared according to Method E, using the following amounts of reagents: alcohol (*S*)-**2.11** (0.31 g, 0.96 mmol, 1.0 equiv), NaH (35 mg, 1.4 mmol, 1.5 equiv), iodomethane (60 µL, 0.98 mmol, 1.02 equiv), and THF (5.5 mL). The product was purified by flash column chromatography using 40% Et_2O/pentanes to afford the title compound as a white solid (0.24 g, 0.71 mmol, 70%). Analytical data are consistent with literature values.[8] **TLC** $\mathbf{R_f}$ = 0.3 (40% Et_2O/hexanes); **m.p.** 88–89 °C; $^{\mathbf{1}}$**H NMR** ($CDCl_3$, 400 MHz) δ 7.85–7.79 (m, 4H), 7.47–7.43 (m, 3H), 6.63 (s, 2H), 5.32 (s, 1H), 3.82 (s, 3H), 3.81 (s, 6H), 3.43 (s, 3H); $^{\mathbf{13}}$**C NMR** ($CDCl_3$, 125 MHz) δ 153.4, 139.3, 137.7,

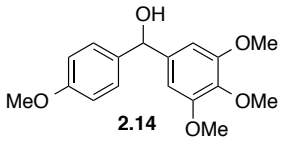
137.3, 133.3, 133.0, 128.4, 128.1, 127.8, 126.3, 126.1, 125.8, 125.0, 104.0, 85.6, 60.9, 57.2, 56.2; **IR** (neat) 2937, 1587, 1230, 1126, 1088 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{21}H_{22}O_4$ $(M + Na)^+$ 361.1416, found 361.1419; $\mathbf{[\alpha]^{26}_D}$ +25.2 (*c* 1.35, $CHCl_3$), literature $[\alpha]^{23}_D$ +28.0 (*c* 0.57, $CHCl_3$); **SFC** analysis (AD-H, 20% MeOH, 2.5 mL/min, 215 nm) indicated >99% ee: t_R (major) = 2.97 min, t_R (minor) = 3.23 min.



(*R*)-**2.12**

2-((*R*)-Methoxy(3,4,5-trimethoxyphenyl)methyl)naphthalene ((*R*)-2.12). Prepared according to Method E, using the following amounts of reagents: alcohol (*R*)-**2.11** (67 mg, 0.2 mmol, 1.0 equiv), NaH (7.2 mg, 0.3 mmol, 1.5 equiv), iodomethane (13 μL, 0.21 mmol, 1.02 equiv), and THF (2.0 mL). The product was purified by flash column chromatography using 40% Et_2O/pentanes to afford the title compound as a white solid (51 mg, 0.15 mmol, 75%). Analytical data are consistent with the values listed for (*S*)-**2.12** (vide supra). $\mathbf{[\alpha]^{26}_D}$ –25.3 (*c* 0.57, $CHCl_3$); **SFC** analysis (AD-H, 20% MeOH, 2.5 mL/min, 215 nm) indicated 99% ee: t_R (minor) = 2.94 min, t_R (major) = 3.21 min.

*Synthesis of Starting Materials for **2.10***

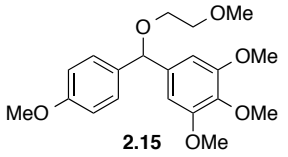


2.14

(3,4,5-Trimethoxyphenyl)(4-methoxyphenyl)methanol (2.14). THF (27 mL) was added to magnesium turnings (1.46 g, 60.0 mmol, 1.50 equiv) and catalytic I_2. 4-Bromoanisole (5.00 mL, 40.0 mmol, 1.00 equiv) was added slowly over 30 min at 0 °C, so as to maintain a gentle reflux.

The mixture was stirred for 20 min at 0 °C, then 40 min at room temperature. The resulting dark black Grignard reagent was titrated[22] and used immediately.

To a solution of 3,4,5-trimethoxybenzaldehyde (1.8 g, 9.3 mmol, 1.0 equiv) in THF (8.0 mL) at 0 °C was added *p*-methoxyphenylmagnesium bromide (16.0 mL, 13.9 mmol, 0.87 M in THF, 1.50 equiv). After stirring for 10 min at 0 °C, then 1.5 h at room temperature, the reaction was quenched with saturated aqueous ammonium chloride (10 mL). H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash column chromatography using 50% CH_2Cl_2/EtOAc to afford the title compound as a white solid (1.9 g, 6.1 mmol, 65%). **TLC** $\mathbf{R_f}$ = 0.3 (50% CH_2Cl_2/EtOAc); **m.p.** 94–95 °C; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.24 (d, *J* = 8.8, 2H), 6.83 (d, *J* = 8.8, 2H), 6.56 (s, 2H), 5.64 (s, 1H), 3.79 (s, 3H), 3.77 (s, 6H), 3.75 (s, 3H), 2.93 (s, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 159.0, 153.1, 140.0, 136.9, 136.1, 127.9, 113.8, 103.4, 75.7, 60.8, 56.0, 55.3; **IR** (neat) 3347, 2936, 2838, 1508, 1235, 1124 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{17}H_{20}O_5$ $(M + Na)^+$ 327.1208, found 327.1208.

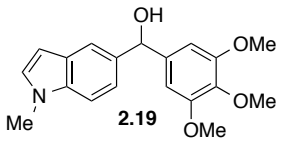


2.15

1-((2-Methoxyethoxy)(3,4,5-trimethoxyphenyl)methyl)-4-methoxybenzene (2.15). To a slurry of NaH (0.22 g, 9.0 mmol, 3.0 equiv) in DMF (2.0 mL) was added a solution of alcohol **2.14** (0.91 g, 3.0 mmol, 1.0 equiv) in DMF (3.0 mL). The mixture was stirred at room temperature for 20 min before addition of DMF (10 mL) and one equivalent of 2-bromoethyl methyl ether (0.28 mL, 3.0 mmol). After stirring for 10 min, a second equivalent of 2-bromoethyl methyl ether

(0.28 mL, 3.0 mmol) was added and the reaction stirred for 30 min. Excess NaH was quenched with saturated aqueous ammonium chloride (5 mL). H_2O (10 mL) was added and the mixture was extracted with EtOAc (4 x 10 mL). The combined organics were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The product was purified by flash column chromatography using 25–50% EtOAc/hexanes to afford the title compound as a yellow oil (1.0 g, 2.8 mmol, 92%). **TLC R_f** = 0.2 (20% EtOAC/hexanes); **^{1}H NMR** ($CDCl_3$, 500 MHz) δ 7.27 (d, *J* = 8.7, 2H), 6.85 (d, *J* = 8.7, 2H), 6.60 (s, 2H), 5.31 (s, 1H), 3.81 (s, 9H), 3.76 (s, 3H), 3.64–3.59 (m, 4H), 3.38 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 159.1, 153.2, 138.0, 137.0, 134.2, 128.4, 113.8, 103.9, 83.6, 72.1, 68.4, 60.8, 59.0, 56.0, 55.2; **IR** (neat) 2935, 1506, 1232, 1123, 1088 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{20}H_{26}O_6$ $(M + Na)^+$ 385.1627, found 385.1620.

*Synthesis of Starting Materials for **2.4***

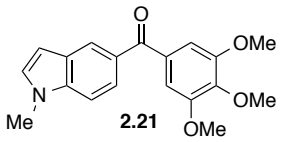


2.19

(1-Methyl-1*H*-indol-5-yl)(3,4,5-trimethoxyphenyl)methanol (2.19). Prepared according to a modified procedure reported by Rapoport and co-workers.[23] To a flame-dried flask charged with a stir bar was carefully added *tert*-butyllithium (10.4 mL, 17.6 mmol, 1.70 M in pentanes, 2.20 equiv), and the flask was cooled to –78 °C. A solution of 5-bromo-1-methylindole (1.7 g, 8.0 mmol, 1.0 equiv) in anhydrous 1:1 Et_2O/THF (20 mL) was slowly added to the reaction flask at –78 °C, and the reaction was stirred at –78 °C for 15 min then used directly in the next step.

[23] Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106.

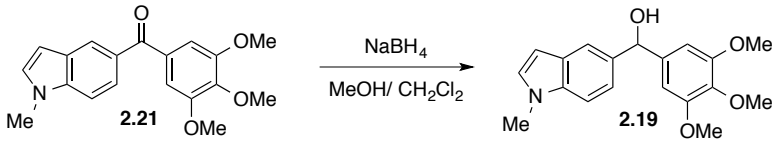
To this mixture was slowly added a solution of 3,4,5-trimethoxybenzaldehyde (3.92 g, 20.0 mmol, 2.50 equiv) in 1:1 Et_2O/THF (15 mL) via syringe at –78 °C. The reaction was allowed to warm to –20 °C slowly over several hours, then stirred at –20 °C overnight. The reaction was quenched with saturated aqueous ammonium chloride (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by flash column chromatography using 20–50% EtOAc/hexanes to afford the title compound as a white solid (2.0 g, 6.2 mmol, 78%). Analytical data are consistent with literature values.[17] **TLC** $\mathbf{R_f}$ = 0.4 (40% EtOAc/hexanes); **m.p.** 125–126 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.68 (s, 1H), 7.36–7.28 (m, 2H), 7.13 (d, *J* = 3.2 Hz, 1H), 6.73 (s, 2H), 6.54 (d, *J* = 3.2 Hz, 1H), 5.94 (d, *J* = 3.3 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 6H), 3.84 (s, 3H), 2.44 (d, *J* = 3.3 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 153.2, 140.3, 136.9, 136.4, 135.1, 129.5, 128.4, 120.7, 119.2, 109.5, 103.4, 101.2, 76.9, 60.9, 56.1, 33.0; **IR** (neat) 3478 (br), 2938, 1123, 907, 724 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{19}H_{21}NO_4$ $(M + Na)^+$ 350.1368, found 350.1358.



2.21

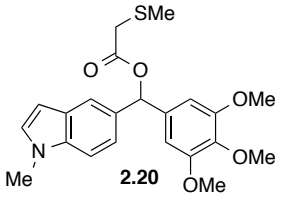
(1-Methyl-1*H*-indol-5-yl)(3,4,5-trimethoxyphenyl)methanone (2.21). Isolated as a byproduct from the lithiation reaction intended to form alcohol **2.19**, if the reaction was warmed to room temperature before quenching. The following amounts of reagents were used: *tert*-butyllithium (10.4 mL, 17.6 mmol, 1.70 M in pentanes, 2.20 equiv), 5-bromo-1-methylindole (1.7 g, 8.0 mmol, 1.0 equiv), 3,4,5-trimethoxybenzaldehyde (3.92 g, 20.0 mmol, 2.50 equiv), and anhydrous 1:1 Et_2O/THF (35 mL). The product was purified by flash column chromatography using 20–30–

40% EtOAc/hexanes to afford the title compound as a white solid (1.9 g, 5.9 mmol, 74%). Analytical data are consistent with literature values.[17] **TLC R_f** = 0.5 (40% EtOAc/hexanes); **m.p.** 115–116 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.14 (d, *J* = 1.6 Hz, 1H), 7.80 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 3.2 Hz, 1H), 7.08 (s, 2H), 6.61 (d, *J* = 3.1 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 6H), 3.86 (s, 3H); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 196.5, 152.8, 141.3, 139.0, 134.3, 130.6, 129.4, 127.8, 125.2, 123.9, 109.1, 107.7, 103.0, 61.1, 56.4, 33.2; **IR** (neat) 2941, 1652, 1581, 1324, 1119 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{19}H_{19}NO_4$ $(M + Na)^+$ 326.1392, found 326.1382.



(1-Methyl-1*H*-indol-5-yl)(3,4,5-trimethoxyphenyl)methanol (2.19) could alternatively be prepared by reduction of ketone **2.21** according to a modified procedure reported by Franzén and co-workers.[24] Ketone **2.21** (0.98 g, 3.0 mmol, 1.0 equiv) was dissolved in 1:1 MeOH/CH_2Cl_2 (20 mL) and the reaction cooled to 0 °C. $NaBH_4$ (0.18 g, 4.8 mmol, 1.6 equiv) was added in one portion and the reaction stirred 30 min at 0 °C, then 3 h at room temperature. The reaction was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by flash column chromatography using 20–30–40% EtOAc/hexanes to afford the title compound as a white solid (0.80 g, 2.5 mmol, 82%). Analytical data are consistent with the values listed for **2.19** (vide supra).

[24] Wang. Y.; Franzén, R. *Synlett.* **2012**, *23*, 925.



2.20

(1-Methyl-1*H*-indol-5-yl)(3,4,5-trimethoxyphenyl)methyl 2-(methylthio)acetate (2.20). Prepared according to a modified procedure reported by Meyer and co-workers.[19] To a stirring solution of alcohol **2.19** (0.46 g, 1.4 mmol, 1.0 equiv), N,N'-dicyclohexylcarbodiimide (DCC, 0.32 g, 1.5 mmol, 1.1 equiv), and 4-dimethylaminopyridine (DMAP, 94 mg, 0.77 mmol, 0.55 equiv) in anhydrous CH_2Cl_2 (10 mL) was added 2-(methylthio)acetic acid (0.11 mL, 1.5 mmol, 1.1 equiv). The opaque reaction mixture was allowed to stir at room temperature for 20 h. The mixture was passed through a plug of Celite, rinsed with CH_2Cl_2, and concentrated in vacuo. The product was purified by flash column chromatography using 20–30% EtOAc/hexanes to afford the title compound a white solid (0.33 g, 0.79 mmol, 57%). **TLC** $\mathbf{R_f}$ = 0.7 (40% EtOAc/hexanes); **m.p.** 92–93 °C; ^{1}**H NMR** ($CDCl_3$, 400 MHz) δ 7.62 (s, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.21 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.03 (d, *J* = 3.2 Hz, 1H), 6.99 (s, 1H), 6.66 (s, 2H), 6.45 (d, *J* = 3.1 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 6H), 3.72 (s, 3H), 3.30 (d, *J* = 14.1 Hz, 1H), 3.24 (d, *J* = 14.1 Hz, 1H), 2.15 (s, 3H); ^{13}**C NMR** ($CDCl_3$, 125 MHz) δ 169.2, 153.1, 137.1, 136.3 (2C), 130.5, 129.6, 128.2, 121.1, 120.1, 109.3, 103.8, 101.2, 78.4, 60.7, 56.0, 35.9, 32.8, 16.2; **IR** (neat) 2935, 1729, 1243, 1116, 727 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{22}H_{25}NO_5S$ $(M + Na)^+$ 438.1351, found 438.1344.

General Procedures for Biological Experiments

Materials

DMEM/high glucose media (containing 10% FBS and supplemented with L-glutamine and gentamycin) was purchased from HyClone.

Tubulin Polymerization Disruption Experiments

Fluorescence imaging was performed on glass-bottom 3 mL plates suitable for microscopy that were seeded with near-confluent monolayers of an LLCPK cell line containing GFP-tagged tubulin. The cells were cultured in 10% DMEM media and imaged prior to substrate exposure. The compounds (*R*)-**2.7**, (*S*)-**2.7**, **2.10**, (*R*)-**2.13**, (*S*)-**2.13**, **2.15**, and colchicine control (**1.1**) were dissolved in molecular biology grade DMSO to achieve 10 mM stock solutions. The 10 mM DMSO stock solutions were subsequently diluted to a final concentration of 10 μM in 3 mL of 10% DMEM media. The media was aspirated from the plates containing the LLCPK cells and the media containing the compounds or DMSO vehicle controls were added. After culturing for 15 min, tubulin disruption was measured using a deconvolution fluorescence microscope. The cells were cultured for another 15 min and imaged again. Tubulin disruption was qualitatively determined by the degree of tubulin depolymerization relative to the colchicine and DMSO vehicle controls. This assay was repeated with all compounds to confirm the results.

Fluorescence imaging was performed on a Zeiss Axiovert 200 M using the Axiovision camera and software, and images were processed in Photoshop 8.0.

Chapter Three

Stereospecific Nickel-Catalyzed Cross-Coupling Reactions of Aryl-Substituted Tetrahydropyrans for the Synthesis and Biological Evaluation of 3,5-Diaryl Alcohols

3.1 Introduction

The structural complexity of unnatural polyketide analogues provides an intriguing challenge with respect to their synthesis.[1,2,3,4] A major obstacle is controlling the relative configuration of substituents during the synthesis of acyclic polyketides. In the total synthesis of erythromycin A, Woodward and co-workers presented an innovative solution: implementing a dithiadecalin system to control the relative stereochemistry of the cyclic molecule, followed by subsequent ring-opening to reveal the highly functionalized, acyclic natural product.[5] Similarly, others have utilized this approach to synthesize substituted polyketides.[6]

---

[1] Portions of this Chapter were originally published as: Tollefson, E. J.; Dawson, D. D.; Osborne, C. A.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 14951.

[2] (a) Rohr, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2847; (b) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461; (c) Cragg, G. M.; Grothaus, P. G.; Newman, D. J. *Chem. Rev.* **2009**, *109*, 3012.

[3] For selected reviews, see: (a) ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2010**, *46*, 2535; (b) Hanessian, S.; Giroux, S.; Mascitti, V. *Synthesis* **2006**, *7*, 1057; (c) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506; (d) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Gao, X.; Itoh, T.; Krische, M. J. *Nat. Prod. Rep.* **2014**, *31*, 504.

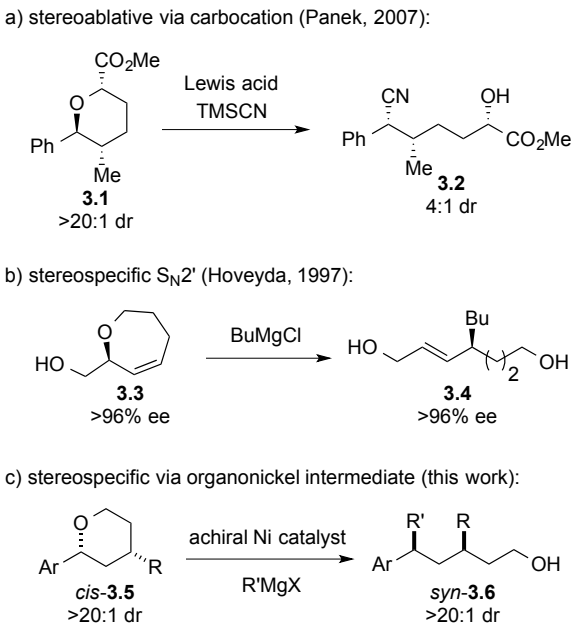
[4] For biosynthetic strategies for synthesis of unnatural polyketides, see: (a) Tang, Y.; Khosla, C. Biosynthesis of "Unnatural" Natural Products. In *Exploiting Chemical Diversity for Drug Discovery*; Bartlett, P. A.; Entzeroth, M., Eds.; Royal Society of Chemistry: Dorset, U.K., 2006; (b) Zhang, W.; Tang, Y. *J. Med. Chem.* **2008**, *51*, 2629.

[5] Woodward, R. B.: Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, A. T.; Vasella, W. C.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210.

[6] Ward, D. E. *Chem. Commun.* **2011**, *47*, 11375.

To access substituted unnatural polyketides, the ring-opening reactions of tetrahydropyrans have been developed,[7] although few examples of ring-opening by forming a new C_{sp^3}–C_{sp^3} bond exist.[8,9] Notably, Panek and co-workers disclosed the diastereoselective, Lewis acid-catalyzed ring-opening reaction of tetrahydropyrans using cyanide, where the stereochemical outcome of the reaction is consistent with carbocation formation (Scheme 3.1a).[8a]

Scheme 3.1. Stereoselective ring-opening and C–C bond formation strategy.



While diastereoselective ring-opening reactions constitute one method of controlling relative stereochemistry, a complementary approach involves stereospecific transformations. Here, stereochemical information is conserved throughout the reaction. For example, Hoveyda and co-workers showed that unsaturated cyclic ethers activated by pendant alcohols could

[7] (a) Burwell, R. L., Jr. *Chem. Rev.* **1954**, *54*, 615; (b) Maercker, A. *Angew. Chem., Int. Ed.* **1987**, *26*, 972; (c) For a recent example, see: Mack, D. J.; Guo, B.; Njarðarson, J. T. *Chem. Commun.* **2012**, *48*, 7844.
[8] (a) Qin, H.-L.; Lowe, J. T.; Panek, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 38; (b) Sawama, Y.; Shibata, K.; Sawama, Y.; Takubo, M.; Monguchi, Y.; Krause, N.; Sajiki, H. *Org. Lett.* **2013**, *15*, 5282; (c) Oku, A.; Homoto, Y.; Harada, T. *Chem. Lett.* **1986**, 1495; (d) Christensen, S. H.; Holm, T.; Madsen, R. *Tetrahedron* **2014**, *70*, 4942.
[9] For examples of allylic substitution reactions that open dihydropyrans and lactones, see: (a) Sawama, Y.; Sawama, Y.; Krause, N. *Org. Lett.* **2009**, *11*, 5034; (b) Matsushita, H.; Negishi, E.-i. *J. Chem. Soc., Chem. Commun.* **1982**, 160.

undergo stereospecific S_N2' displacements by Grignard reagents to provide enantioenriched acyclic products (Scheme 3.1b).[10]

Our goal was to expand the scope of stereospecific ring-opening reactions to include *saturated* cyclic ethers, such as tetrahydropyrans, that are not activated by ring strain.[11,12] Based on the Jarvo laboratory's enantiospecific Kumada cross-coupling reaction of ethers,[13,14] we anticipated that we could develop the stereospecific nickel-catalyzed ring-opening reactions of cyclic ethers (Scheme 3.1c). We envisioned that this stereospecific methodology would provide complex acyclic fragments containing both a medicinally relevant benzylic methyl substituent[15] and a pendant alcohol for further derivatization.

In this Chapter, we report the stereospecific Kumada cross-coupling reaction of tetrahydropyrans with a range of Grignard reagents. We also report the derivatization of an enantioenriched furan-containing carboxylic acid formed via the stereospecific Negishi cross-coupling reaction of a benzylic lactone with dimethyl zinc. This methodology has generated a range of unnatural polyketide analogues for biological testing. We report the discovery of several

---

[10] (a) Heron, N. M.; Adams, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 6205; (b) Adams, J. A.; Heron, N. M.; Koss, A.-M.; Hoveyda, A. H. *J. Org. Chem.* **1999**, *64*, 854; (c) The Hoveyda group has also reported enantioselective, catalyst controlled ring-opening of cyclic unsaturated ethers with chiral zirconium-based catalysts. For a lead reference, see: Didiuk, M. T.; Johannes, C. W.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7097.

[11] For nickel-catalyzed cross-coupling reaction of dihydrofurans with Grignard reagents, see: Cornella, J.; Martin, R. *Org. Lett.* **2013**, *24*, 6298.

[12] For examples of nickel-catalyzed addition to strained heterocycles, e.g., epoxides and aziridines, see: (a) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076; (b) Lin, B. L.; Clough, C. R.; Hillhouse G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890; (c) Nielsen, D. K.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2011**, *50*, 6056; (d) Nielsen, D. K.; Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 13605; (e) Jensen, K. L.; Standley, E. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2014**, *136*, 11145; (f) Takeda, Y.; Ikeda, Y.; Kuroda, A.; Tanaka, S.; Minakata, S. *J. Am. Chem. Soc.* **2014**, *136*, 8544.

[13] (a) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389; (b) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790; (c) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293; (d) Yonova, I. M.; Johnson, A. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. S.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2422.

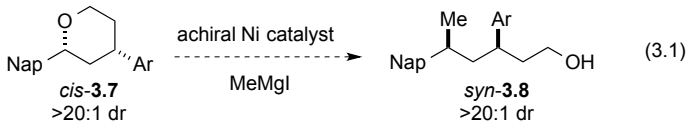
[14] For a recent review of nickel-catalyzed reactions, see: Tasker, S. Z.; Standley, E. A.; Jamison T. F. *Nature* **2014**, *509*, 299.

[15] For a review, see: Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215.

compounds that exhibit selective anti-breast cancer activity against the MCF-7 (ER+ breast cancer) and MDA-MB-468 (triple-negative breast cancer) cell lines.

3.2 Stereospecific Kumada Cross-Coupling Reactions of Tetrahydropyrans

We sought to develop this methodology as a powerful strategy for the cross-coupling reactions of heterocycles containing multiple stereogenic centers. Toward this end, we applied our reaction to the opening of *cis*-(±)-2,4-disubstituted tetrahydropyrans, subunits of the calyxin family of natural products.[16] These cross-coupling reactions would provide synthetic access to *syn*-3,5-disubstituted alcohols (eq. 3.1).



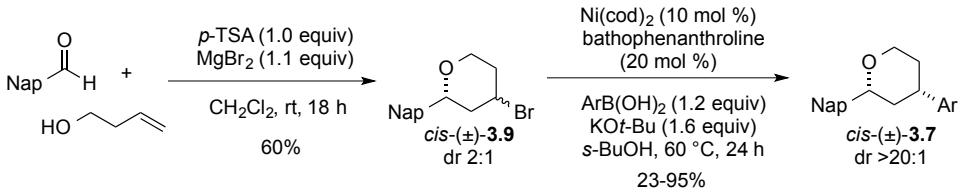
cis-**3.7** >20:1 dr → *syn*-**3.8** >20:1 dr (3.1)

There are several elegant methods for the diastereoselective synthesis of highly substituted tetrahydropyrans,[17] including diastereoselective Prins cyclization reactions.[18] We developed the two-step diastereoselective strategy outlined in Scheme 3.2 to easily obtain tetrahydropyrans containing a broad range of aryl substituents at the C4 position. First, a $MgBr_2$ and *p*-TsOH-promoted Prins cyclization afforded 4-bromotetrahydropyran **3.9** as a 2:1 mixture of diastereomers.[19] Then, we employed a diastereoselective nickel-catalyzed Suzuki cross-coupling reaction to install an array of aryl substituents.[20] This approach takes advantage of Fu

[16] Prasain, J. K.; Li, J.-X.; Tezuka, Y.; Tanaka, K.; Basnet, P.; Dong, H.; Namba, T.; Kadota, S. *J. Nat. Prod.* **1998**, *61*, 212.
[17] (a) Nicolas, L.; Butkevich, A. N.; Guérinot, A.; Corbu, A.; Reymond, S.; Cossy, J. *Pure Appl. Chem.* **2013**, *85*, 1203; (b) Pastor, I. M.; Yus, M. *Curr. Org. Chem*. **2012**, *16*, 1277.
[18] (a) For a recent review, see reference 17b; (b) Jasti, R.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2006**, *128*, 13640; (c) Alder, R. W.; Harvey, J. N.; Oakley, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4960.
[19] Borkar, P; van de Weghe, P.; Subba Reddy, B. V.; Yadav, J. S.; Grée, R. *Chem. Commun.* **2012**, *48*, 9316.
[20] Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624.

and co-workers' seminal stereoconvergent Suzuki reaction.[21] In this transformation, diastereoselectivity stems from the preferred conformation of the radical intermediate.[22] The thermodynamically-favored cis diastereomer is predicted as the major product; indeed, the cross-coupling reactions of **3.9** with a range of commercially available aryl boronic acids afforded a variety of 4-aryltetrahydropyrans in high diastereoselectivity. The relative configurations of these *cis*-2,4-diaryl tetrahydropyrans were assigned by NOE NMR experiments.[23]

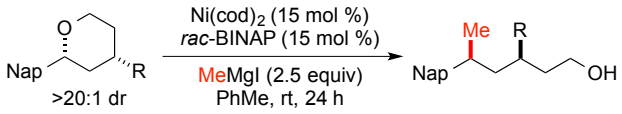
Scheme 3.2. Diastereoselective synthesis of tetrahydropyrans.

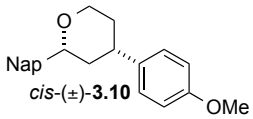
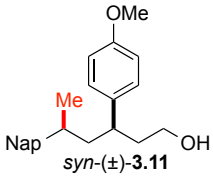
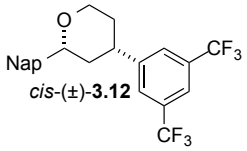
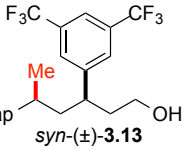
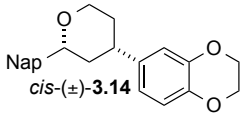
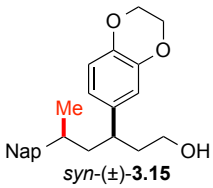
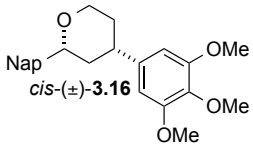
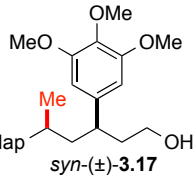
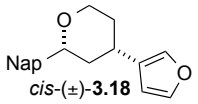
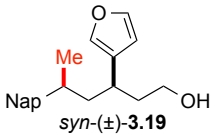
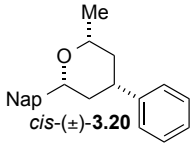
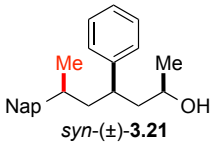


Development of the nickel-catalyzed ring-opening reactions of cyclic ethers was guided by our prior experience developing Kumada cross-coupling reactions of benzylic ethers. We observed that 15 mol % catalyst loading of $Ni(cod)_2$ and *rac*-BINAP in the presence of methylmagnesium iodide resulted in good to excellent yields of the desired 3,5-diaryl alcohols (Table 3.1). We also examined the transfer of stereochemical information in the cross-coupling reaction by comparing the diastereomeric ratios of the starting materials to those of the acyclic products. For example, tetrahydropyran **3.10** (dr >20:1) afforded *syn*-**3.11** in 76% yield and >20:1 dr (entry 1), indicating the complete transfer of stereochemical information in the cross-coupling reaction.

[21] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340.
[22] (a) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362; (b) Stille, J. K.; Cowell, A. B. *J. Organomet. Chem.* **1977**, *124*, 253.
[23] See Experimental Section for details.

Table 3.1. Scope of cross-coupling reaction of tetrahydropyrans.



Entry	Starting Material	Product	Yield (%)[a]	Prod. dr[b]
1	 *cis*-(±)-**3.10**	 *syn*-(±)-**3.11**	76[c]	>20:1
2	 *cis*-(±)-**3.12**	 *syn*-(±)-**3.13**	72	>20:1
3	 *cis*-(±)-**3.14**	 *syn*-(±)-**3.15**	81[c]	>20:1
4	 *cis*-(±)-**3.16**	 *syn*-(±)-**3.17**	42[c]	>20:1
5	 *cis*-(±)-**3.18**	 *syn*-(±)-**3.19**	74	>20:1
6	 *cis*-(±)-**3.20**	 *syn*-(±)-**3.21**	63	>20:1

[a]Isolated yield after column chromatography. [b]Determined by ^{1}H NMR. [c]Calculated yield; see Experimental Section for details. Nap = 2-naphthyl.

We evaluated the scope of the cross-coupling reaction and found that both electron-rich and electron-poor aryl substituents at the C4 position of the tetrahydropyran are well tolerated (Table 3.1, entries 1 and 2). To challenge this methodology, we sought to incorporate biologically-relevant moieties in our substrates. For example, the cross-coupling reaction of tetrahydropyran *cis*-**3.14** proceeded in 81% yield and >20:1 dr to form benzodioxane-substituted product *syn*-**3.15** (entry 3). 1,4-Benzodioxanes are present in a range of pharmaceutical agents such as piperoxan and idazoxan.[24] The reaction of tetrahydropyran **3.16** afforded product **3.17** in modest yield (entry 4); the 3,4,5-trimethoxyphenyl functionality is commonly found in compounds that inhibit tubulin polymerization, such as colchicine and combretastatin A-4.[25] We were also gratified to see that 3-furan-substituted tetrahydropyran *cis*-**3.18** was well tolerated in the reaction. Product *syn*-**3.19** was formed in high yield and dr, and contains a furan substituent that can be readily derivatized by oxidation or cycloaddition reactions (entry 5).[26]

To further challenge this method, we synthesized a stereotriad by the Kumada coupling of 2,4,6-trisubstituted tetrahydropyran *cis*-**3.20**. Subjecting *cis*-**3.20** to the reaction conditions afforded the secondary alcohol *syn*-**3.21**, containing three stereogenic centers, as a single diastereomer and with good yield (Table 3.1, entry 6). This strategy introduces a modular three-step synthesis of polyketide analogues where substituents in the C2, C4, and C6 positions can be easily altered by the use of commercially available aldehydes, arylboronic acids, and homoallylic alcohols, respectively.

---

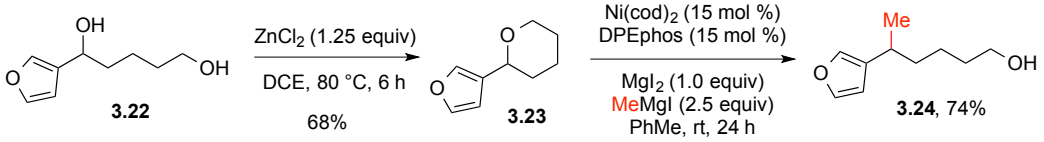
[24] (a) Piperoxan: Fourneau, E.; Bovet, D. *Arch. Int. Pharmacodyn. Thér.* **1933**, *46*, 178; (b) Idazoxan synthesis and pharmacology: Chapleo, C. B.; Myers, P. L.; Butler, R. C. M.; Doxey, J. C.; Roach, A. G.; Smith, C. F. C. *J. Med. Chem.* **1983**, *26*, 823.

[25] (a) Jordan, M. A.; Wilson, L. *Nat. Rev. Cancer* **2004**, *4*, 253; (b) Lin, C. M.; Ho, H. H.; Pettit, G. R.; Hamel, E. *Biochemistry* **1989**, *28*, 6984; (c) Tron, G. C.; Pirali, T.; Sorba, G.; Pagliai, F.; Busacca, S.; Genazzani, A. A. *J. Med. Chem.* **2006**, *49*, 3033.

[26] (a) Kobayashi, Y.; Kumar, G. B.; Kurachi, T.; Acharya, H. P.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **2001**, *66*, 2011; (b) Diels, O.; Alder, K. *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 554.

We were interested in determining whether this cross-coupling reaction could be performed using substrates containing aryl substituents other than naphthyl. We hypothesized that tetrahydropyran **3.23** would undergo a nickel-catalyzed Kumada cross-coupling reaction due to the lower aromatic stabilization energy of furan.[27] Our laboratory has observed a strong dependence of cross-coupling rates on the identity of the aryl substituent, and we predict that arenes possessing lower aromatic stabilization energy provide better ligation of the nickel catalyst and greater stabilization of the transition state for oxidative addition. Benzylic ethers and esters activated by extended aromatic rings such as naphthalene and benzofuran are sufficiently reactive, as are those activated by furan.[28] The synthesis of compound **3.23** is easily achieved by a Lewis acid-promoted cyclization of the corresponding 1,5-diol (**3.22**, Scheme 3.3).[29] Subjecting 3-furan-substituted tetrahydropyran **3.23** to the nickel-catalyzed Kumada reaction formed the desired product **3.24** in 74% yield. We found DPEphos to be a more effective ligand than *rac*-BINAP for this transformation, consistent with our observation that DPEphos provides the highest yields for heteroaromatic-containing substrates.[30] In addition, using one equivalent of MgI_2 in the reaction slightly increased the yield from 70% to 74%.[31]

Scheme 3.3. Synthesis and Kumada cross-coupling reaction of 3-furan-substituted tetrahydropyran **3.23**.



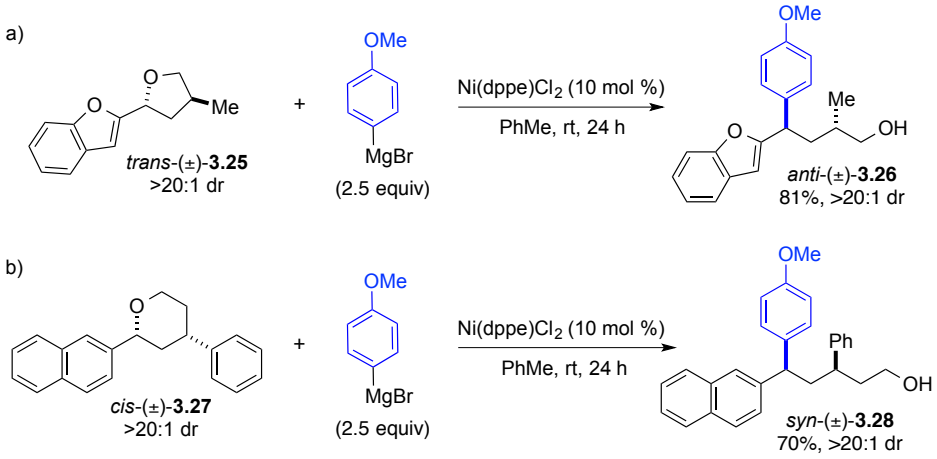
[27] (a) For thermodynamic parameters of bonding of arenes to nickel complexes, see: Brauer, D. J.; Krüger, C. *Inorg. Chem.* **1977**, *16*, 884; (b) For resonance energies of arenes, see: Smith, M. B.; March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; John Wiley & Sons, Inc.: New York, 2007; pp 60–62.
[28] Harris, M. R.; Konev, M. O.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 7825.
[29] Kim, S.; Chung, K. N.; Yang. S. *J. Org. Chem.* **1987**, *52*, 3917.
[30] Tollefson, E. J.; Dawson, D. D.; Osborne, C. A.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 14951.
[31] Greene, M. A. Diastereoselective Synthesis of Seven Membered Ring *trans*-Alkenes and Development of Stereospecific Nickel-Catalyzed Cross-Coupling Reactions. Ph.D. Thesis, The University of California, Irvine, May 2013.

3.3 Grignard Reagent Scope

It is critical for synthetic methodology to provide access to analogues with a range of substituent patterns to achieve the long-term goal of determining structure-activity relationships (SAR). To this end, we were interested in examining the scope of our reaction with respect to the transmetallating agent. Successful incorporation of other Grignard reagents would provide modular access to acyclic products containing a variety of benzylic substituents.

The Jarvo laboratory has recently demonstrated that Ni(dppe)Cl_2 is a broadly applicable catalyst for cross-coupling reactions of alkyl and aryl Grignard reagents with benzylic ethers.[13d] We applied this catalyst system to the ring-opening reactions of a representative tetrahydrofuran and tetrahydropyran and found that aryl Grignard reagents were well tolerated in the synthesis of complex diarylalkanes (Scheme 3.4). For example, 4-methoxyphenylmagnesium bromide underwent smooth cross-coupling reactions with both tetrahydrofuran **3.25** and tetrahydropyran **3.27**. Products *anti*-**3.26** and *syn*-**3.28** were formed in high yield and dr (Scheme 3.4).

Scheme 3.4. Use of aryl Grignard reagent in the stereospecific Kumada cross-coupling reaction of (a) tetrahydrofuran **3.25** and (b) tetrahydropyran **3.27**.



3.4 Derivatization of a Furan-Containing Product Synthesized via the Negishi Cross-Coupling Reaction of Lactones

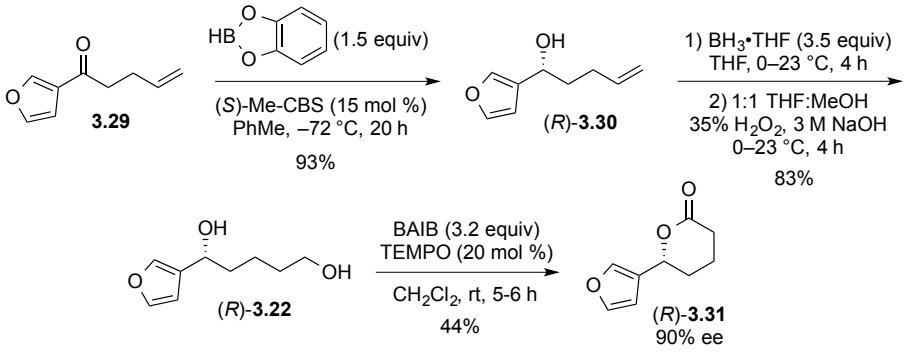
Based on our recently reported nickel-catalyzed Negishi cross-coupling reaction of benzylic esters,[32] we hypothesized that a similar reaction could be applied to the ring-opening of benzylic lactones. Utilizing alkyl zinc reagents in the transformation would allow for greater functional group tolerance as compared to Grignard reagents. Furthermore, the ring-opening reaction of enantioenriched lactones would provide products containing a benzylic stereocenter and a pendant carboxylic acid available for derivatization. Recently, Sawama and co-workers have disclosed the Lewis acid-catalyzed ring-opening reaction of aryl-substituted lactones with allylsilane.[8b] However, stereospecific ring-opening of lactones with other carbon-based nucleophiles has not been reported.

The required starting lactone (*R*)-**3.31** can be readily accessed as a single enantiomer (Scheme 3.5).[33] Corey–Bakshi–Shibata (CBS) reduction of benzylic ketone **3.29**[34] followed by hydroboration/ oxidation and cyclization of 1,5-diol (*R*)-**3.22** provided (*R*)-**3.31** in 90% ee.[35] The absolute configuration of the lactone was assigned as *R* based on the accepted CBS model of selectivity for intermediate alcohol (*R*)-**3.30** (see Experimental Section for details).[34]

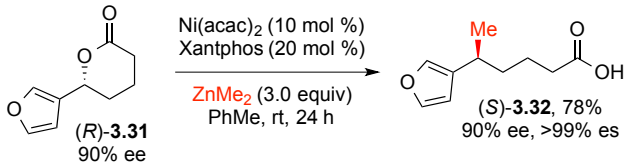
---

[32] Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083.
[33] (a) For a review, see: Boucard, V.; Broustal, G.; Campagne, J. M. *Eur. J. Org. Chem.* **2007**, 225. For recent examples, see: (b) Murphy, S. K.; Dong, V. M. *J. Am. Chem. Soc.* **2013**, *135*, 5553; (c) Moran, J.; Smith, A. G.; Carris, R. M.; Johnson, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 18618.
[34] Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
[35] (a) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Letters* **2003**, *44*, 57; (b) This type of oxidative cylization is known to proceed with retention of stereochemical information; see: Kamal, A.; Sandbhor, M.; Shaik, A. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1575.

Scheme 3.5. Synthesis of valerolactone (*R*)-**3.31**.[36]



Natural products including ricciocarpin A and salvinorin B contain δ-valerolactones with furan substituents, such as **3.31**.[37] Methods to open such aryl-substituted valerolactones would provide a strategic synthesis of analogues for biological evaluation.[38] We predicted that, as with tetrahydropyran **3.23**, lactone **3.31** would undergo a stereospecific nickel-catalyzed cross-coupling reaction. Therefore, we evaluated 3-furan-substituted lactone (*R*)-**3.31** and found that $Ni(acac)_2$ and Xantphos afforded the cross-coupled carboxylic acid in 78% yield and >99% es (eq. 3.2).[39]

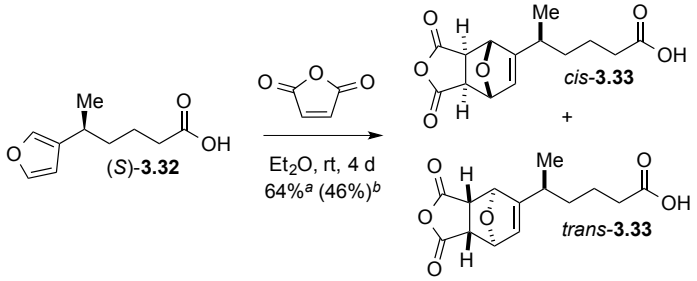


(3.2)

[36] (*R*)-**3.30** was synthesized by Emily Tollefson; see reference 30.
[37] (a) Wurzel, G.; Becker, H. *Phytochemistry* **1990**, *29*, 2565; (b) Ortega, A.; Blount, J. F.; Manchand, P. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, *10*, 2505.
[38] (a) Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829; (b) Boldi, A. M. *Curr. Opin. Chem. Biol.* **2004**, *8*, 281; (c) Li, J.; Cisar, J. S.; Zhou, C.-Y.; Vera, B.; Williams, H.; Rodríguez, A. D.; Cravatt, B. F.; Romo, D. *Nat. Chem.* **2013**, *5*, 510; (d) Huigens, R. W.; Morrison, K. C.; Hicklin, R. W.; Flood, T. A., Jr.; Richter, M. F.; Hergenrother, P. J. *Nat. Chem.* **2013**, *5*, 195.
[39] es = ee $_{product}$/ee $_{starting\ material}$; see: Denmark, S. E.; Vogler, T. *Chem.–Eur. J.* **2009**, *15*, 11737.

To highlight the furan's functional utility, we derivatized product (*S*)-**3.32** by a Diels–Alder reaction with maleic anhydride (Scheme 3.6).[26b,40] The cycloaddition reaction furnished the enantioenriched bicycle **3.33** in 64% yield as a 1:1 mixture of diastereomers. Based on Woodward's analysis of the thermodynamic product of the reaction, the Diels–Alder reaction is anticipated to be highly exo-selective.[40] Notably, this derivatization has generated an unnatural polyketide analogue containing no aromatic substituents.

Scheme 3.6. Diels–Alder reaction of furan (*S*)-**3.32**.



[a]Yield determined by ^{1}H NMR based on comparison to PhTMS as internal standard. [b]Isolated yield after column chromatography.

3.5 Biological Evaluation of Cross-Coupling Products

We hypothesized that the 3,5-diaryl alcohol moiety would exhibit anti-cancer activity because of its structural similarity to the 1,1-diarylalkane pharmacophore. The latter scaffold is found in a range of bioactive molecules,[41, 42] and we have previously demonstrated in Chapter 1

[40] Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1948**, *70*, 1161.

[41] Representative examples: (a) as ligands for nuclear receptors, see: Kainuma, M; Kasuga, J.-i.; Hosoda, S; Wakabayashi, K.-i.; Tanatani, A; Nagasawa, K.; Miyachi, H.; Makishima, M; Hashimoto, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3213; (b) as combretastatin analogs for colon cancer, see: Messaoudi, S.; Hamze, A.; Provot, O.; Tréguier, B.; Rodrigo De Losada, J.; Bignon, J.; Liu, J.-M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *ChemMedChem.* **2011**, *6*, 488; (c) prostate cancer: Hu, Q. Z.; Yin, L. N.; Jagusch, C.; Hille, U. E.; Hartmann, R. W. *J. Med. Chem.* **2010**, *53*, 5049; (d) diabetes: Kim, R. M.; Parmee, E. R.; Tan, Q.; Yang, C.; Lins, A. R. U. S. Patent 12/227,030, May 11, 2007.

that enantioenriched diarylalkanes provide lead compounds with selective anti-breast-cancer activity.[13d] We evaluated several 3,5-diaryl alcohols, synthesized using our nickel-catalyzed cross-coupling reaction, against a range of cancer cell lines using an MTT assay.[43] Preliminary biological studies indicated that *syn*-**3.34** was selective for anti-proliferation of the MCF-7 breast cancer line compared to the MDA-MB-468 breast cancer line and prostate, kidney, and ovarian cancer lines (Figure 3.1a).

To generate analogues of this lead compound, we biased our library of tetrahydropyrans to include different aryl derivatives at the C4 position (Table 3.1). Upon evaluating analogues for biological activity, we determined that *syn*-**3.11**, *syn*-**3.13**, *syn*-**3.15**, *syn*-**3.17**, and *syn*-**3.19** did not exhibit significant anti-cancer activity. However, **3.17** proved extremely potent toward all cell lines, including the healthy MCF-10A breast cell line (Figure 3.1b). We hypothesize that the 3,4,5-trimethoxyphenyl motif of **3.17** interacts with the colchicine binding site of β-tubulin and thus demonstrates general cytotoxic activity.[44]

---

[42] For breast cancer: (a) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870; (b) Pathak, T. P.; Osiak, J. G.; Vaden, R. M.; Welm, B. E.; Sigman, M. S. *Tetrahedron* **2012**, *68*, 5203.

[43] MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay: Alley, M. C.; Scudiero, D. A.; Monks, A.; Hursey, M. L.; Czerwinski, M. J.; Fine, D. L.; Abbott, B. J.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 589.

[44] (a) see reference 25a; (b) Álvarez, R.; Álvarez, C.; Mollinedo, F.; Sierra, B. G.; Medarde, M.; Peláez, R. *Bioorg. Med. Chem.* **2009**, *17*, 6422.

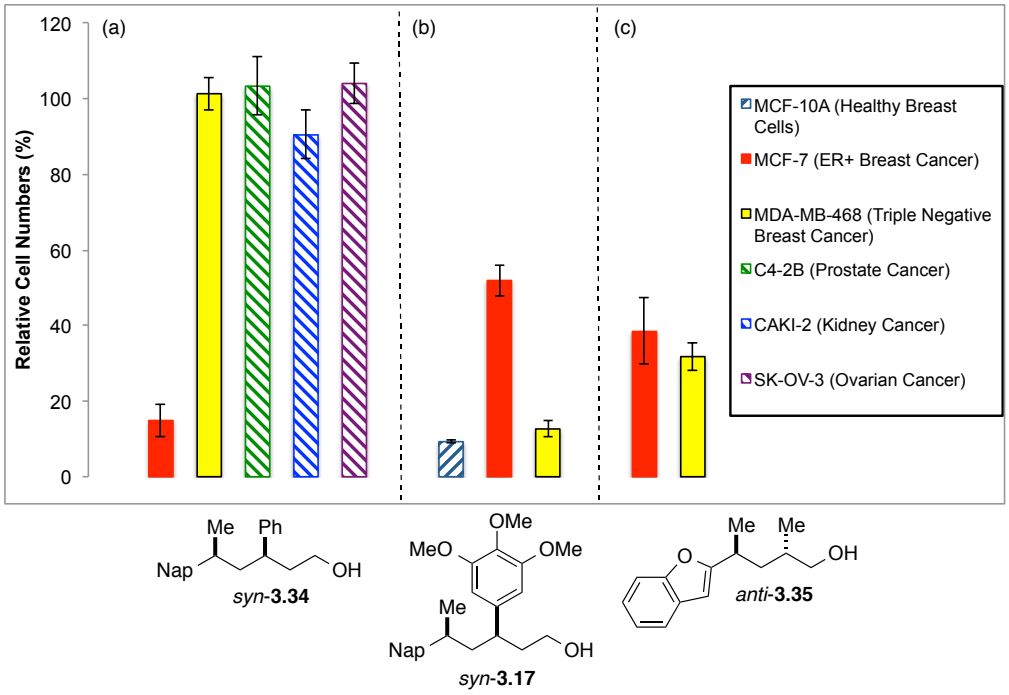


Figure 3.1. Evaluation of compounds for anti-cancer activity at 10 μM.[45] Cell proliferation is represented as relative cell numbers after treatment, where a low percentage indicates potent anti-proliferative activity. All data are normalized to the DMSO vehicle control.

Examination of additional compounds isolated from our cross-coupling reactions identified *anti*-**3.35** as displaying potent activity toward both ER+ breast cancer (MCF-7) and triple-negative breast cancer (MDA-MB-468) cell lines (Figure 3.1c). Establishing activity against the latter cell line is a significant result because it is a particularly challenging cancer to treat.[46] These results have set the stage for future SAR studies of unnatural polyketide analogues.

[45] Products *syn*-**3.34** and *anti*-**3.35** were synthesized by Emily Tollefson; see reference 30.
[46] (a) Irvin, W. J., Jr.; Carey, L. A. *Eur. J. Cancer* **2008,** *44*, 2799; (b) Carey, L. A. *The Oncologist* **2011,** *16*, 71.

3.6 Conclusions

We have developed the nickel-catalyzed, stereospecific cross-coupling reactions of aryl-substituted tetrahydropyrans. Through judicious choice of starting materials, cyclic ether intermediates have been utilized to set the desired relative stereochemical relationships. We have demonstrated the high stereospecificity of the reaction, where the dr of the product matches the dr of the starting tetrahydropyrans and tetrahydrofurans. The Negishi cross-coupling reaction of a benzylic lactone has also been established to synthesize an enantioenriched carboxylic acid. Evaluation of products for activity against a range of cancer cell lines identified several compounds that were selectively potent toward the MCF-7 ER+ breast cancer line and the MDA-MB-468 triple-negative breast cancer line. We are currently investigating the application of these methods toward the implementation of natural product editing to generate unnatural polyketides.

3.7 Experimental Details

General Procedures

All reactions were carried out under a N_2 atmosphere, unless otherwise stated. All glassware was either oven dried or flame-dried prior to use. Toluene (PhMe), diethyl ether (Et_2O), dichloromethane (DCM), benzene (C_6H_6), and tetrahydrofuran (THF) were degassed with argon and then passed through two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 °C for 12 hours) to remove H_2O. Other solvents were purchased "anhydrous" commercially, or were purified as described. ^1H NMR were recorded on Bruker DRX-400 (400 MHz ^1H, 100 MHz ^{13}C), GN-500 (500 MHz ^1H, 125.7 MHz ^{13}C), or CRYO-500 (500 MHz ^1H, 125.7 MHz ^{13}C) spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal trimethylsilane (TMS, δ 0.00). Data

are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet (t), doublet of triplets (dt), triplet of doublets (td), doublet of doublet of triplets (ddt), quartet (q), quintet (quint), quintet of triplets (quintt), quintet of doublets (quintd), sextet (sext), septet (sept), multiplet (m), apparent doublet (ad), apparent triplet (at), apparent quartet (aq), apparent quintet (aquint)], coupling constants [Hz], integration). Carbon chemical shifts are reported in ppm (δ) relative to TMS with the solvent resonance as the internal standard ($CDCl_3$, δ 77.16 ppm). NMR data were collected at 25 °C. Infrared spectra were obtained on a Thermo Scientific Nicolet iS5 spectrometer with an iD5 ATR tip (neat) and are reported in terms of frequency of absorption (cm^{-1}). Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60Å F254 precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with *p*-anisaldehyde (PAA), cerium ammonium molybdate (CAM), or potassium permanganate ($KMnO_4$) solutions. Flash chromatography was performed using Silica Gel 60 (170-400 mesh) from Fisher Scientific or silver impregnated silica gel.[47] Melting points (m.p.) were obtained using a Mel-Temp melting point apparatus and are uncorrected. Optical rotations were measured with a Rudolph Research Analytical Autopol III Automatic Polarimeter. SFC determinations of enantiopurity were performed on a Berger Analytical instrument and an Aurora A5 Fusion instrument using a Daicel™ Chiralpak® column (OD-H, AD-H, OJ-H, or (*R*,*R*)-Whelk-O; 100 bar, 215 nm, 50 °C). High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center.

[47] Shaghafi, M. B.; Kohn, B. L.; Jarvo, E. R. *Org. Lett.* **2008**, *10*, 4743.

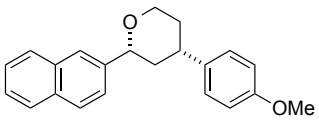
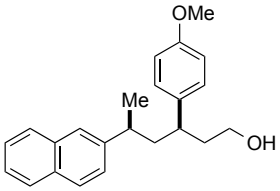
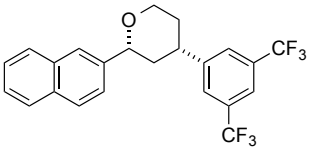
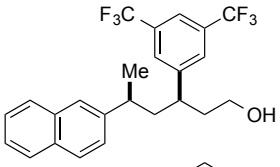
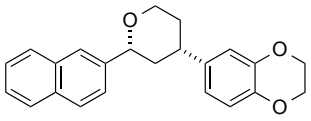
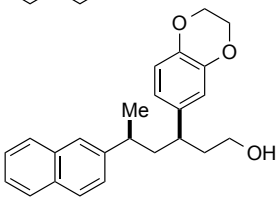
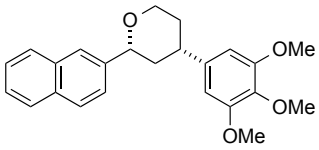
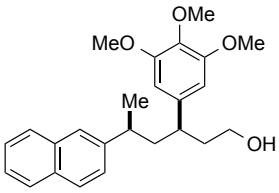
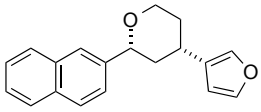
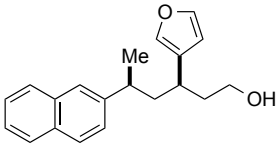
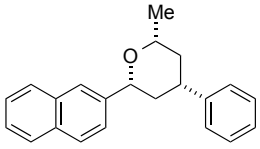
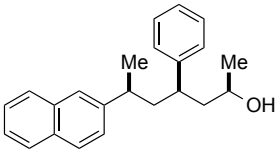
Bis(1,5-cyclooctadiene)nickel was purchased from Strem, stored in a glove box freezer (–20 °C) under an atmosphere of N_2 and used as received. Zinc (II) chloride was purchased from Strem and stored under an atmosphere of N_2. 1,2-Dichloroethane (DCE) was purchased from EMD Chemicals and distilled from CaH_2 through a short-path distillation head (80 °C, 40 torr). All ligands were purchased from Strem or Sigma Aldrich and were stored under N_2 atmosphere and used as received. Dimethyl zinc ($ZnMe_2$) was purchased from Sigma Aldrich and stored under N_2 at 4 °C. All Grignard reagents and $ZnMe_2$ were titrated with iodine prior to use.[48] Activated manganese oxide was prepared according to a procedure reported by Attenburrow.[49] All other chemicals were purchased commercially and used as received, unless otherwise noted.

Stereochemical Proofs

The relative or absolute configurations of all starting materials and cross-coupling reaction products were assigned by analogy based on the assumption that the reactions proceed with inversion of stereochemistry at the benzylic position. These stereochemical assignments are summarized in Tables 3.2, 3.3, and 3.4. These tables also summarize how the configuration of each compound was assigned.

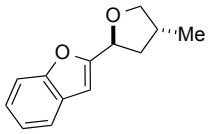
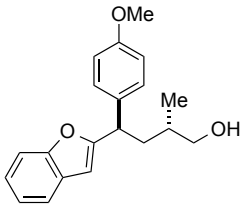
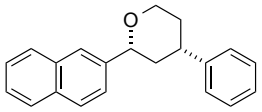
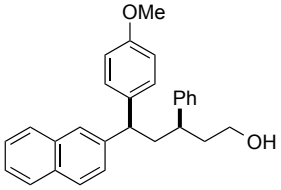
[48] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890.
[49] Attenburrow, J.; Cameron, A. F. B.; Chapman, J. H.; Evans, R. M.; Hems, B. A.; Jansen, A. B. A.; Walker, T. *J. Chem. Soc.* **1952**, 1094.

Table 3.2. Configuration of starting materials and products for Table 3.1.

Tetrahydropyran	Configuration[a] assigned by:	Product	Configuration[b] assigned by:
Table 3.1:			
	**3.10** *cis* NOE		**3.11** *syn* by analogy
	**3.12** *cis* NOE		**3.13** *syn* by analogy
	**3.14** *cis* NOE		**3.15** *syn* by analogy
	**3.17** *cis* by analogy		**3.18** *syn* by analogy
	**3.19** *cis* by analogy		**3.20** *syn* by analogy
	**3.21** *cis,cis* NOE		**3.22** *syn,syn* by analogy

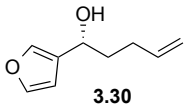
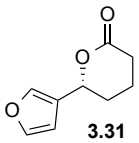
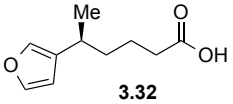
[a]For NOE values for each compound, see the characterization data. For comparison to literature values of derivatives, see the characterization data. [b]In the absence of known relative or absolute configurations, the product configurations were assigned based on the assumption that the cross-coupling reaction proceeds with inversion.

Table 3.3. Configuration of starting materials and products for Scheme 3.4.

Tetrahydrofuran/ Tetrahydropyran	Configuration[a] assigned by:	Product	Configuration[b] assigned by:
Scheme 3.4: 	**3.25** *trans* by analogy		**3.26** *anti* by analogy
	**3.27** *cis* NOE lit ^{1}H NMR X-ray		**3.28** *syn* by analogy

[a]For NOE values for each compound, see the characterization data. [b]For configuration assignment for products derived from tetrahydrofurans, see the Breit model.[50] In the absence of known relative or absolute configurations, the product configurations were assigned based on the assumption that the cross-coupling reaction proceeds with inversion.

Table 3.4. Configuration of starting materials and products for Scheme 3.5.

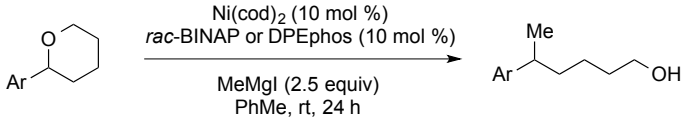
Alcohol	Corresponding Lactone:	Configuration[a] assigned by:	Product	Configuration[b] assigned by:
Scheme 3.5:  **3.30**	 **3.31**	*R* (+) CBS model	 **3.32**	*S* (+) by analogy

[a]For the optical rotation of each compound, see the characterization data. For the CBS model, see reference 34. For retention of stereochemistry of diol cyclizations to the corresponding lactones, see reference 35b. [b]In the absence of known optical rotations, the product configurations were assigned based on the assumption that the cross-coupling reaction proceeds with inversion.

[50] Schmidt, Y.; Lehr, K.; Colas, L.; Breit, B. *Chem. Eur. J.* **2012**, *18*, 7071.

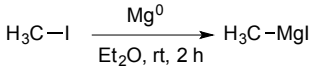
General Cross-Coupling Procedures

Method A: Cross-Coupling with Methyl Grignard



In a glovebox, a flame-dried 7 mL vial equipped with a stir bar was charged with substrate (1.0 equiv), $Ni(cod)_2$ (0.10 equiv), *rac*-BINAP or DPEphos (0.10 equiv), and PhMe. MeMgI (2.5 equiv) was then added dropwise. After 24 h the reaction was removed from the glovebox, quenched with isopropyl alcohol, filtered through a plug of silica gel (neat Et_2O), and concentrated in vacuo. Phenyltrimethylsilane (PhTMS) was added as internal standard and a ^1H NMR yield was obtained before purification by flash column chromatography.

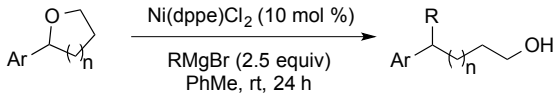
Preparation of Methyl Grignard Reagent



Under a N_2 atmsophere, a 3-necked flask equipped with a stir bar, reflux condenser, and Schlenk filtration apparatus was charged with magnesium turnings (1.1 g, 45 mmol, 1.5 equiv). The flask and magnesium turnings were then flame-dried under vacuum and the flask was back-filled with N_2. Anhydrous Et_2O (7 mL) and a crystal of iodine (ca. 2 mg) were added to the flask. Freshly distilled iodomethane (1.9 mL, 31 mmol, 1.0 equiv) was slowly added over 30 min to maintain a gentle reflux. The mixture was stirred for 2 h at room temperature then filtered through the fritted Schlenk filter into the Schlenk bomb under N_2 atmosphere. The magnesium turnings were washed with Et_2O (2 x 1.0 mL) then the Schlenk bomb was sealed, removed, and placed under an argon atmosphere. The resulting methyl Grignard reagent was typically between 2.4 and 3.0

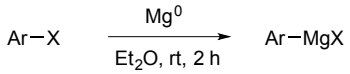
M as titrated by Knochel's method[48] and could be stored (sealed under argon atmosphere or in a glovebox) for up to 4 weeks.

Method B: Cross-Coupling with Aryl Grignard



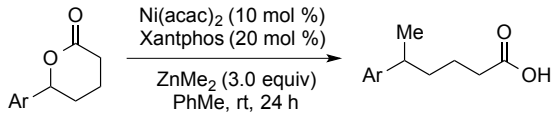
On the benchtop, a flame-dried 7 mL vial was charged with substrate (1.0 equiv) and $Ni(dppe)Cl_2$ (0.10 equiv), flushed with N_2, and capped with a Teflon-lined septum. PhMe was added, followed by the alkyl or aryl Grignard reagent (2.5 equiv). The reaction was allowed to stir at room temperature for 24 h, then it was quenched with isopropyl alcohol, filtered through a plug of silica gel (neat Et_2O), and concentrated in vacuo. Phenyltrimethylsilane (PhTMS) was added as internal standard and a ^1H NMR yield was obtained before purification by flash column chromatography.

Preparation of Aryl Grignard Reagent



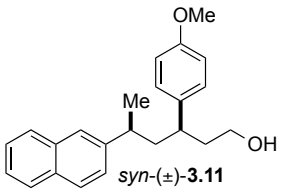
A 2-necked flask equipped with a stir bar and reflux condenser was charged with magnesium turnings (3.0 equiv). The reaction apparatus was flame-dried under vacuum and cooled under N_2. Anhydrous Et_2O and a crystal of I_2 (ca. 2 mg) were added to the flask. The organohalide (1.0 equiv) was added slowly over 30 min to maintain a gentle reflux. The mixture was stirred for 2 h at room temperature. The resulting Grignard reagent was typically between 1.5 and 2.5 M as titrated by Knochel's method.[48]

Method C: Cross-Coupling with Dimethylzinc



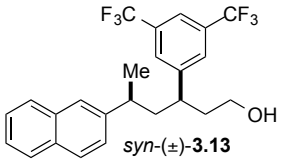
In a glovebox, a flame-dried 7 mL vial equipped with a stir bar was charged with substrate (1.0 equiv). To a separate flame-dried 7 mL vial equipped with a stir bar was added $Ni(acac)_2$ (0.10 equiv), Xantphos (0.20 equiv), and PhMe in the glovebox. After a 5 min prestir, half of the catalyst mixture was transferred to the vial containing substrate, which was then capped with a screw-cap fitted with a septum and removed from the glovebox. The reaction vial was equipped with a N_2 line and $ZnMe_2$ (3.0 equiv) was added, which resulted in an immediate color change from green to dark orange. The reaction was allowed to stir at room temperature for 2 h under N_2 before being sealed with Teflon tape and taken back into the glovebox. In the glovebox, the remaining catalyst mixture was added to the reaction vial. The reaction was allowed to stir at room temperature for an additional 22 h, then it was removed from the glovebox and quenched with 1M HCl (2 mL). The aqueous layer was extracted with E_2O (3 x 2 mL), the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Phenyltrimethylsilane (PhTMS) was added as internal standard and a ^1H NMR yield was obtained before purification by flash column chromatography.

Characterization Data for Products



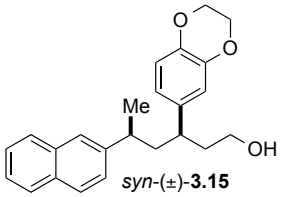
syn-(±)-**3.11**

***syn*-(±)-3-(4-Methoxyphenyl)-5-(naphthalen-2-yl)hexan-1-ol (*syn*-3.11)** was prepared according to Method A. The following amounts of reagents were used: $Ni(cod)_2$ (8.6 mg, 0.030 mmol, 0.15 equiv), *rac*-BINAP (19 mg, 0.030 mmol, 0.15 equiv), substrate *cis*-(±)-**3.10** (63.7 mg, 0.200 mmol, 1.00 equiv, dr >20:1), PhMe (2.0 mL), and MeMgI (0.19 mL, 0.50 mmol, 2.7 M in Et_2O, 2.5 equiv). The compound was purified by flash column chromatography using silver-impregnated silica gel (20% EtOAc/hexanes) to afford a colorless oil (53.8 mg) containing the title compound (76% calculated yield, dr >20:1). The dr was determined based on integration of the benzylic methines in the ^{1}H NMR spectrum. A small amount of analytically pure material was obtained for characterization. **TLC R_f** = 0.3 (20% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82–7.76 (m, 3H), 7.47–7.41 (m, 3H), 7.29 (dd, *J* = 8.5, 1.6, 1H), 7.24 (t, *J* = 7.7, 1H), 6.78 (dd, *J* = 8.1, 2.6, 1H), 6.68 (d, *J* = 7.7, 1H), 6.61, (m, 1H), 3.79 (s, 3H), 3.41–3.30 (m, 2H), 2.66–2.59 (m, 1H), 2.41 (sept, *J* = 5.0, 1H), 2.08–2.03 (m, 1H), 1.99–1.93 (m, 1H), 1.86–1.72 (m, 2H), 1.23 (d, *J* = 7.2, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 159.8, 146.5, 144.4, 133.7, 132.4, 129.6, 128.2, 127.8, 127.6, 126.0, 125.8, 125.3, 120.4, 113.8, 111.6, 61.2, 55.3, 45.2, 40.6, 40.4, 37.7, 23.9; **IR** (neat) 3361 (br), 3051, 2925, 1599, 1486, 1257 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{23}H_{26}O_2Na$ $(M + Na)^+$ 357.1830, found 357.1831.



syn-(±)-**3.13**

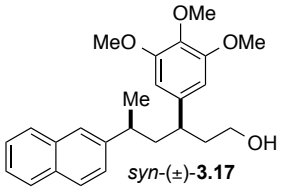
***syn*-(±)-3-(3,5-Bis(trifluoromethyl)phenyl)-5-(naphthalen-2-yl)hexan-1-ol (*syn*-3.13)** was prepared according to Method A. The following amounts of reagents were used: $Ni(cod)_2$ (8.3 mg, 0.030 mmol, 0.15 equiv), *rac*-BINAP (19 mg, 0.030 mmol, 0.15 equiv), substrate *cis*-(±)-**3.12** (85 mg, 0.20 mmol, 1.0 equiv, dr >20:1), PhMe (2.0 mL), and MeMgI (0.21 mL, 0.50 mmol, 2.4 M in Et_2O, 2.5 equiv). The compound was purified by flash column chromatography using silver-impregnated silica gel (5–10% EtOAc/hexanes) to afford the title compound as a colorless oil (63 mg, 0.14 mmol, 72%, dr >20:1). The dr was determined based on integration of the benzylic methines in the ^{1}H NMR spectrum. **TLC R_f** = 0.3 (10% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3, 2H), 7.76–7.74 (m, 2H), 7.50–7.44 (m, 4H), 7.35 (s, 1H), 7.24 (dd, *J* = 8.5, 1.5, 1H), 3.45–3.40 (m, 1H), 3.33–3.28 (m, 1H), 2.65–2.59 (m, 1H), 2.50–2.43 (m, 1H), 2.18 (ddd, *J* = 14.2, 11.4, 4.2, 1H), 1.99–1.89 (m, 2H), 1.82–1.75 (m, 1H), 1.25 (d, *J* = 6.9, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 147.5, 143.1, 133.7, 132.5, 131.7 (q, *J* = 32.7), 128.7, 128.3 (q, *J* = 2.8), 127.8, 127.7, 126.3, 126.1, 125.6, 125.1, 123.6 (q, *J* = 272.8), 120.6 (septet, *J* = 3.9), 60.4, 44.6, 40.1, 39.7, 37.9, 23.8; **IR** (neat) 3330 (br), 2927, 1277, 1171 cm^{-1}; **HRMS** (TOF MS ES–) *m / z* calcd for $C_{24}H_{21}F_6O$ $(M - H)^-$ 439.1497, found 439.1489.



syn-(±)-**3.15**

***syn*-(±)-3-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-5-(naphthalen-2-yl)hexan-1-ol (*syn*-3.15)** was prepared according to Method A. The following amounts of reagents were used: $Ni(cod)_2$

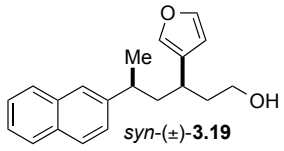
(8.3 mg, 0.030 mmol, 0.15 equiv), *rac*-BINAP (19 mg, 0.030 mmol, 0.15 equiv), substrate *cis*-(±)-**3.14** (69.3 mg, 0.200 mmol, 1.00 equiv, dr >20:1), PhMe (2.0 mL), and MeMgI (0.21 mL, 0.50 mmol, 2.4 M in Et_2O, 2.5 equiv). The compound was purified by flash column chromatography (20% EtOAc/hexanes) to afford a white foam (60.0 mg) containing a mixture of the title compound (81% calculated yield, dr >20:1) and β-H elimination (1% calculated yield). The dr was determined based on integration of the benzylic methines in the ^{1}H NMR spectrum. A small amount of analytically pure material was obtained for characterization. **TLC R_f** = 0.2 (20% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81–7.76 (m, 3H), 7.48 (s, 1H), 7.46–7.40 (m, 2H), 7.28 (dd, *J* = 8.5, 1.3, 1H), 6.79 (d, *J* = 8.3, 1H), 6.62 (d, *J* = 2.0, 1H), 6.50 (dd, *J* = 8.3, 2.0, 1H), 4.24 (s, 4H), 3.37–3.26 (m, 2H), 2.67–2.60 (m, 1H), 2.33–2.27 (m, 1H), 2.00 (ddd, *J* = 14.5, 10.9, 4.2, 1H), 1.89 (ddd, *J* = 14.8, 11.1, 4.3, 1H), 1.79–1.72 (m, 1H), 1.70–1.63 (m, 1H), 1.22 (d, *J* = 7.0, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 144.4, 143.6, 142.0, 138.0, 133.7, 132.3, 128.1, 127.69, 127.65, 125.92, 125.88, 125.8, 125.2, 121.2, 117.1, 116.1, 64.5, 64.4, 61.2, 45.4, 40.4, 39.7, 37.6, 23.8; **IR** (neat) 3427 (br), 2926, 1453, 906, 729 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{24}H_{26}ONa$ $(M + Na)^+$ 341.1881, found 341.1886.



syn-(±)-**3.17**

***syn*-(±)-4-(1-Hydroxy-5-(naphthalen-2-yl)hexan-3-yl)-2,6-dimethoxyphenol (*syn*-3.17)** was prepared according to Method A. The following amounts of reagents were used: $Ni(cod)_2$ (8.3 mg, 0.030 mmol, 0.15 equiv), *rac*-BINAP (18.7 mg, 0.030 mmol, 0.15 equiv), substrate *cis*-(±)-**3.16** (75.7 mg, 0.20 mmol, 1.0 equiv, dr >20:1), PhMe (2.0 mL), and MeMgI (0.21 mL, 0.50

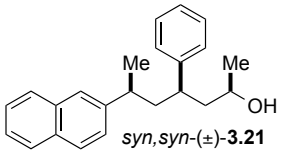
mmol, 2.4 M in Et_2O, 2.5 equiv). The compound was purified by flash column chromatography using silver-impregnated silica gel (15–40% EtOAc in hexanes) to afford a colorless oil (43.7 mg) containing a mixture of the title compound (42% calculated yield, dr >20:1) and β-H elimination (14% calculated yield). A small amount of analytically pure material was obtained for characterization. **TLC R_f** = 0.2 (40% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83–7.79 (m, 2H), 7.75–7.73 (m, 1H), 7.45–7.41 (m, 3H), 7.30 (dd, *J* = 8.4, 1.8, 1H), 6.23 (s, 2H), 3.86 (s, 3H), 3.81 (s, 6H), 3.45–3.33 (m, 2H), 2.68–2.59 (m, 1H), 2.39–2.31 (m, 1H), 2.07 (ddd, *J* = 13.9, 10.8, 4.2, 1H), 1.95–1.71 (m, 3H), 1.24 (d, *J* = 6.9, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 153.3, 144.3, 140.4, 136.3, 133.7, 132.4, 128.2, 127.8, 127.5, 126.14, 126.09, 125.7, 125.3, 104.6, 61.3, 61.0, 56.2, 45.0, 40.9, 40.3, 37.7, 24.0; **IR** (neat) 3504 (br), 2931, 1590, 1456, 1128 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{25}H_{30}O_4$ $(M + Na)^+$ 417.2042, found 417.2049.



syn-(±)-**3.19**

***syn*-(±)-3-(Furan-3-yl)-5-(naphthalen-2-yl)hexan-1-ol (*syn*-3.19)** was prepared according to Method A. The following amounts of reagents were used: $Ni(cod)_2$ (7.9 mg, 0.029 mmol, 0.15 equiv), *rac*-BINAP (18 mg, 0.029 mmol, 0.15 equiv), substrate *cis*-(±)-**3.18** (53 mg, 0.19 mmol, 1.0 equiv, dr >20:1), PhMe (1.9 mL), and MeMgI (0.18 mL, 0.48 mmol, 2.7 M in Et_2O, 2.5 equiv). The compound was purified by flash column chromatography using silver-impregnated silica gel (20% EtOAc/hexanes) to afford the title compound as a white oil (42 mg, 0.14 mmol, 74%, dr >20:1). The dr was determined based on integration of the benzylic methines in the ^{1}H NMR spectrum. **TLC R_f** = 0.3 (20% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81–7.76

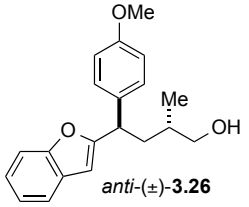
(m, 3H), 7.51 (s, 1H), 7.46–7.40 (m, 3H), 7.29 (dd, *J* = 8.5, 1.6, 1H), 7.10 (s, *J* = 7.2, 2H), 6.27 (s, 1H), 3.45–3.41 (m, 1H), 3.38–3.33 (m, 1H), 2.78–2.71 (m, 1H), 2.38 (septet, *J* = 5.0, 1H), 2.00–1.95 (m, 1H), 1.80 (ddd, *J* = 13.8, 10.9, 4.3, 1H), 1.76–1.71 (m, 1H), 1.67–1.59 (m, 1H), 1.25 (d, *J* = 7.0, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 144.3, 143.4, 139.6, 133.7, 132.4, 128.3, 127.7, 127.63, 127.60, 126.0, 125.8, 125.7, 125.3, 109.0, 61.1, 44.4, 39.5, 37.7, 30.4, 23.8; **IR** (neat) 3422 (br), 2927, 1455, 906, 728 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{20}H_{22}O_2Na$ $(M + Na)^+$ 317.1518, found 317.1517.



syn,syn-(±)-**3.21**

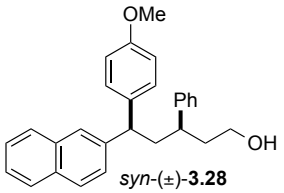
***syn,syn*-(±)-6-(Naphthalen-2-yl)-4-phenylheptan-2-ol (*syn*-3.21)** was prepared according to Method A. The following amounts of reagents were used: $Ni(cod)_2$ (8.3 mg, 0.030 mmol, 0.15 equiv), *rac*-BINAP (19 mg, 0.030 mmol, 0.15 equiv), substrate *cis*-(±)-**3.20** (61 mg, 0.20 mmol, 1.0 equiv, dr >20:1), PhMe (2.0 mL), and MeMgI (0.21 mL, 0.50 mmol, 2.4 M in Et_2O, 2.5 equiv). The compound was purified by flash column chromatography using silver-impregnated silica gel (10% EtOAc/hexanes) to afford the title compound as a colorless oil (40. mg, 0.13 mmol, 63%, dr >20:1). The dr was determined based on integration of the benzylic methines in the ^{1}H NMR spectrum. **TLC R_f** = 0.3 (10% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82–7.75 (m, 3H), 7.47–7.40 (m, 3H), 7.33–7.21 (m, 4H), 7.08 (dd, *J* = 8.4, 1.4, 2H), 3.41–3.33 (m, 1H), 2.65–2.54 (m, 2H), 2.05 (ddd, *J* = 13.9, 10.4, 4.6, 1H), 1.95 (ddd, *J* = 13.8, 10.6, 4.7, 1H), 1.72–1.59 (m, 2H), 1.22 (d, *J* = 7.0, 3H), 0.99 (d, *J* = 6.3, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 144.9, 144.4, 133.7, 132.4, 128.6, 128.20, 128.15, 127.74, 127.68, 126.4, 125.94, 125.93, 125.8, 125.2, 65.7, 47.1, 45.5, 40.3, 37.8, 24.2, 23.9; **IR** (neat) 3427 (br), 2926, 1453,

906, 729 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{23}H_{26}ONa$ $(M + Na)^+$ 341.1881, found 341.1886.



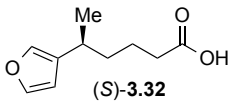
anti-(±)-**3.26**

***anti*-(±)-4-(Benzofuran-2-yl)-4-(4-methoxyphenyl)-2-methylbutan-1-ol (*anti*-3.26)** was prepared according to Method B. The following amounts of reagents were used: $Ni(dppe)Cl_2$ (9.1 mg, 0.017 mmol, 0.10 equiv), *trans*-(±)-**3.25** (35 mg, 0.17 mmol, 1.0 equiv, dr >20:1), phenylmagnesium bromide (0.31 mL, 0.43 mmol, 1.4 M in Et_2O, 2.5 equiv), PhMe (1.6 mL). The crude product was purified via flash column chromatography (10–20% EtOAc/hexanes) to afford the title compound as a pale yellow oil (43 mg, 0.14 mmol, 81%, dr >20:1). The dr was determined based on integration of the benzylic methines in the ^1H NMR spectrum. **TLC R_f** = 0.3 (20% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.24–7.23 (m, 2H), 7.20–7.13 (m, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.38 (s, 1H), 4.15 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.77 (s, 3H), 3.46 (d, *J* = 6.0 Hz, 2H), 2.18–2.12 (m, 1H), 1.98–1.92 (m, 1H), 1.58–1.49 (m, 1H), 1.40 (br s, 1H), 0.97 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 162.0, 158.6, 154.8, 133.5, 129.1, 128.8, 123.5, 122.6, 120.6, 114.1, 111.0, 102.1, 68.4, 55.4, 42.3, 37.9, 33.3, 16.3; **IR** (neat) 3367 (br), 2929, 1510, 1247, 750 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{20}H_{22}O_3Na$ $(M + Na)^+$ 333.1467, found 333.1473.



syn-(±)-**3.28**

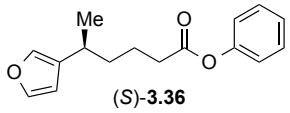
***syn*-(±)-5-(4-Methoxyphenyl)-5-(naphthalen-2-yl)-3-phenylpentan-1-ol (*syn*-3.28)** was prepared according to Method B. The following amounts of reagents were used: Ni(dppe)Cl_2 (11 mg, 0.020 mmol, 0.10 equiv), *cis*-(±)-**3.27** (58 mg, 0.20 mmol, 1.0 equiv, dr >20:1), phenylmagnesium bromide (0.36 mL, 0.50 mmol, 1.4 M in Et_2O, 2.5 equiv), PhMe (2.0 mL). The crude product was purified via flash column chromatography (10–20% EtOAc/hexanes) to afford the title compound as a white foam (55 mg, 0.14 mmol, 70%, dr >20:1). The dr was determined based on integration of the benzylic methines in the ^{1}H NMR spectrum. **TLC R_f** = 0.3 (20% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.57 (s, 1H), 7.45–7.39 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.26–7.19 (m, 2H), 7.09–7.05 (m, 4H), 6.75 (d, *J* = 8.7 Hz, 2H), 3.80 (dd, *J* = 10.5, 4.9 Hz, 1H), 3.70 (s, 3H), 3.40–3.36 (m, 1H), 3.34–3.29 (m, 1H), 2.59–2.49 (m, 2H), 2.40–2.31 (m, 1H), 1.97–1.91 (m, 1H), 1.85–1.78 (m, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 157.9, 144.4, 141.8, 137.6, 133.6, 132.3, 128.71, 128.65, 128.4, 128.0, 127.8, 127.7, 126.8, 126.6, 126.1, 125.5, 113.9, 61.1, 55.3, 47.6, 42.8, 40.2, 40.1; **IR** (neat) 3388 (br), 2930, 1509, 907, 728 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{28}H_{28}O_2Na$ $(M + Na)^+$ 419.1987, found 419.1970.



(*S*)-**3.32**

(*S*)-5-(Furan-3-yl)hexanoic acid ((*S*)-3.32) was prepared according to Method C. The following amounts of reagent were used: substrate (*R*)-**3.31** (58.5 mg, 0.350 mmol, 1.00 equiv, 90% ee),

$Ni(acac)_2$ (9.0 mg, 0.035 mmol, 0.10 equiv), Xantphos (41 mg, 0.070 mmol, 0.20 equiv), $ZnMe_2$ (0.59 mL, 1.8 M in PhMe, 1.1 mmol, 3.0 equiv), and PhMe (5.6 mL). The product was purified by flash column chromatography (10–50% Et_2O/pentane) to afford the title compound as a clear, colorless oil (49.5 mg, 0.272 mmol, 78%). The enantiomers of **3.32** could not be separated by SFC. The ee of (*S*)-**3.32** was determined by derivatization to ester (*S*)-**3.36**, which indicated 90% ee and >99% es. **TLC R_f** = 0.2 (20% Et_2O/pentanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 (t, *J* = 1.5, 1H), 7.21 (d, *J* = 0.8, 1H), 6.27 (d, *J* = 0.8, 1H), 2.65 (sext, *J* = 6.8, 1H), 2.33 (t, *J* = 7.2, 2H), 1.64–1.51 (m, 4H), 1.19 (d, *J* = 6.9, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 180.3, 143.0, 138.2, 130.5, 109.5, 36.9, 34.2, 30.0, 22.6, 21.4; **IR** (neat) 2959, 2930, 2872, 1708, 909 cm^{-1}; **HRMS** (TOF MS ES–) *m / z* calcd for $C_{10}H_{12}O_3$ $(M - H)^-$ 181.0865, found 181.0868; **$[\alpha]_D^{26}$** +9.9 (*c* 1.5, $CDCl_3$).



(*S*)-**3.36**

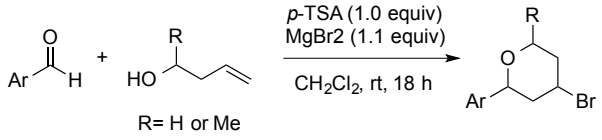
Phenyl (*S*)-5-(furan-3-yl)hexanoate ((*S*)-3.36) was prepared according to a modified procedure reported by Meyer.[51] To a stirring solution of substrate (*S*)-**3.32** (28 mg, 0.15 mmol, 1.0 equiv) in anhydrous DCM (2.0 mL) was added phenol (14 mg, 0.15 mmol, 1.0 equiv), N,N'-dicyclohexylcarbodiimide (DCC, 31 mg, 0.15 mmol, 1.0 equiv), and 4-dimethylaminopyridine (DMAP, 9.3 mg, 0.076 mmol, 0.50 equiv). The reaction mixture was allowed to stir at room temperature for 20 h. The mixture was passed through a plug of Celite, rinsed with DCM, and concentrated in vacuo. The product was purified by flash column chromatography (1% Et_2O/hexanes) to afford the title compound as a clear, colorless oil (26 mg, 0.10 mmol, 67%, 90% ee). **TLC R_f** = 0.5 (5% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 3H),

[51] Stayshich, R. M.; Meyer, T. Y. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 4704.

7.25–7.19 (m, 2H), 7.07–7.03 (m, 2H), 6.29 (d, J = 0.9, 1H), 2.69 (sext, J = 6.9, 1H), 2.54 (t, J = 7.3, 2H), 1.75–1.69 (m, 2H), 1.65–1.57 (m, 2H), 1.21 (d, J = 6.9, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ172.2, 150.8, 143.0, 138.2, 130.5, 129.5, 125.9, 121.7, 109.5, 37.0, 34.5, 30.0, 22.8, 21.5; **IR** (neat) 2959, 2927, 1758, 1496 1135, 873 cm^{-1}; **HRMS** (TOF MS ES+) m/z calcd for $C_{16}H_{18}O_3Na$ $(M + Na)^+$ 281.1154, found 281.1152; **$[\alpha]_D^{26}$** + 8.2 (c 0.8, $CDCl_3$); **SFC** analysis (AD-H, 10% MeOH, 3.0 mL/min, 215 nm) indicated 90% ee: t_R (major) = 2.0 minutes, t_R (minor) = 2.2 minutes.

General Procedures for Starting Materials Synthesis

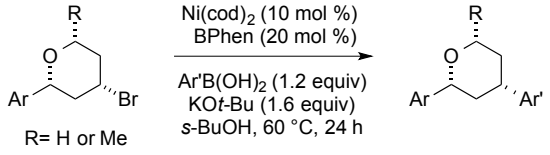
Method D: Prins Cyclization with $MgBr_2$



Modified from a procedure reported by Grée.[19] Magnesium bromide (1.1 equiv) was added to a flame-dried flask equipped with a stir bar and then flame dried again under vacuum. *p*-Toluene sulfonic acid monohydrate (1.0 equiv) and anhydrous DCM (20 mL) were added and the reaction mixture was set to stir at ambient temperature. To a separate flame dried flask was added aldehyde (1.0 equiv). Anhydrous DCM (20 mL) and homoallylic alcohol (1.1 equiv) were added and the mixture was stirred for 5 min at room temperature. The aldehyde solution was added to the magnesium bromide solution and the reaction mixture was allowed to stir at room temperature for 18 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) and was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo.

To remove unreacted aldehyde that was difficult to separate from the desired product, the crude mixture was subjected to $NaBH_4$ reduction by a modified procedure reported by Franzén.[52] The crude mixture was dissolved in 1:1 MeOH/DCM and the reaction cooled to 0 °C. $NaBH_4$ (1.6 equiv relative to 1.0 equiv of aldehyde as determined by ^1H NMR integration) was added in one portion and the reaction stirred 30 min at 0 °C, then 30 min at room temperature. The reaction was quenched with water and extracted with DCM (x 3). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo.

Method E: Suzuki-Type Cross-Coupling of Alkyl Bromides



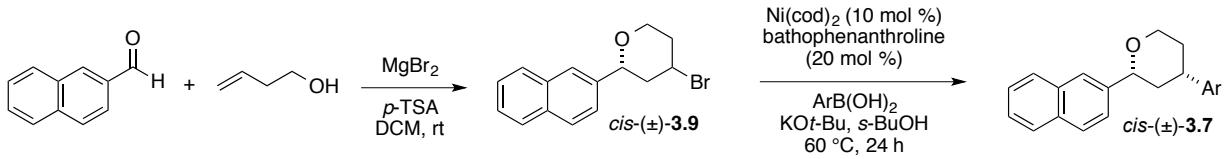
Modified from a procedure reported by Fu.[21] In a glove box, $Ni(cod)_2$ (0.10 equiv), bathophenanthroline (BPhen, 0.20 equiv), anhydrous KO^t-Bu (1.6 equiv), arylboronic acid (1.2 equiv), and freshly distilled *s*-butanol (3.0 mL) were added to a flame dried 7 mL vial equipped with a stir bar and stirred at ambient temperature for 10 min. Substrate (1.0 equiv) was added to the reaction vial, which was then capped with a septum and removed from the glove box. The reaction vial was put under N_2 in a 60 °C oil bath. After stirring for 24 h, the reaction was allowed to cool to ambient temperature before it was passed through a silica gel plug (50% Et_2O/hexanes). The filtrate was concentrated in vacuo.

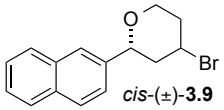
[52] Wang. Y.; Franzén, R. *Synlett.* **2012**, *23*, 925.

Characterization Data for Starting Materials

Synthesis of Tetrahydropyrans

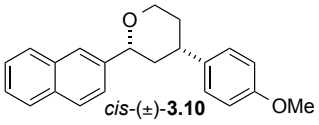
Scheme 3.7. Two-step synthesis of 2,4-disubstituted tetrahydropyrans.



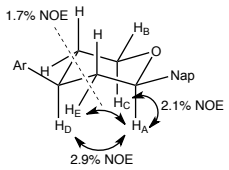


(±)-4-Bromo-2-(2-naphthyl)-tetrahydropyran (*cis*-3.9) was prepared according Method D. The following amounts of reagents were used: magnesium bromide (1.97 g, 10.7 mmol, 1.1 equiv), *p*-toluene sulfonic acid monohydrate (1.7 g, 9.7 mmol, 1.0 equiv), 2-naphthaldehyde (1.5 g, 9.7 mmol, 1.0 equiv), 3-buten-1-ol (0.92 mL, 10.7 mmol, 1.1 equiv), and anhydrous DCM (100 mL). The product was purified by flash column chromatography (2% EtOAc/hexanes) to afford the title compound as a white solid (1.84 g, 65%). The dr was determined based on integration of the benzylic methines in the ^{1}H NMR spectrum. ^{1}H NMR analysis indicated **3.9** was an inseparable 2:1 mixture of cis and trans diastereomers.[19] **m.p.** 55–57 °C; **TLC** $\mathbf{R_f}$ = 0.6 (2% EtOAc/hexanes); **IR** (neat) 3059, 2956, 2927, 2853, 1601, 1505, 1445 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{15}H_{15}BrONH_4$ $(M + NH_4)^+$ 308.0650, found 308.0640. ***cis*-(±)-3.9** (68% by ^{1}H NMR integration): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84–7.79 (m, 4H), 7.49–7.43 (m, 3H), 4.50 (d, *J* = 11.1, 1H), 4.37–4.30 (m, 1H), 4.24–4.19 (m, 1H), 3.66 (td, *J* = 12.1, 2.2, 1H), 2.56 (ddd, *J* = 13.0, 4.5, 2.2, 1H), 2.31–2.12 (m, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 138.7, 133.4, 133.2, 128.4, 128.2, 127.82, 126.3, 126.1, 124.7, 124.0, 80.4, 68.5, 46.6, 45.7, 37.9. ***trans*-**

(±)-3.9 (32% by ^{1}H NMR integration): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84–7.79 (m, 4H), 7.49–7.43 (m, 3H), 5.08 (dd, *J* = 10.6, 1.8 1H), 4.84–4.82 (m, 1H), 4.24–4.19 (m, 1H), 4.08 (dd, *J* = 11.8, 5.0, 1H), 2.31–2.12 (m, 3H), 2.01 (app d, *J* = 15.1, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 139.4, 133.5, 133.1, 128.3, 128.1, 127.79, 126.2, 126.0, 124.7, 124.19, 74.6, 63.7, 50.3, 42.0, 34.2.

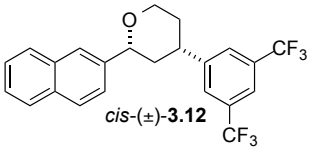


cis-(±)-**3.10**

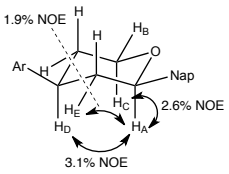


***cis*-(±)-4-(4-Methoxyphenyl)-2-(2-naphthyl)-tetrahydropyran** (*cis*-**3.10**) was prepared according to Method E. The following amounts of reagents were used: $Ni(cod)_2$ (14 mg, 0.050 mmol, 0.10 equiv), bathophenanthroline (33 mg, 0.10 mmol, 0.20 equiv), anhydrous KO^t-Bu (90. mg, 0.80 mmol, 1.6 equiv), 4-methoxyphenylboronic acid (91 mg, 0.60 mmol, 1.2 equiv), *s*-butanol (3.0 mL) and substrate *cis*-(±)-**3.9** (150 mg, 0.50 mmol, 1.0 equiv). The compound was purified by flash column chromatography (5% Et_2O/hexanes) to afford the title compound as a white solid (110 mg, 0.34 mmol, 68%, dr >20:1). The dr was determined based on integration of the benzylic methines in the ^{1}H NMR spectrum. The relative configuration was assigned as cis by COSY and NOE NMR experiments. Irradiation of the benzylic proton (H_A) gave an NOE enhancement of 2.1% of H_C, an enhancement of 2.9% of H_D, and an enhancement of 1.7% of H_E. **m.p.** 69–70 °C; **TLC R_f** = 0.3 (5% Et_2O/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.83–7.79 (m, 3H), 7.49 (dd, *J* = 8.4, 1.6, 1H), 7.46–7.41 (m, 2H), 7.17 (d, *J* = 8.7, 2H), 6.85 (d, *J* = 8.8, 2H), 4.62 (dd, *J* = 11.2, 1.6, 1H), 4.33 (ddd, *J* = 11.5, 4.2, 1.6, 1H), 3.80 (td, *J* = 11.5, 2.9, 1H), 3.76 (s, 3H), 2.95 (tt, *J* = 11.9, 4.0, 1H), 2.14 (adt, *J* = 13.2, 1.6, 1H), 1.93–1.76 (m, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 158.2, 140.4, 137.8, 133.5, 133.0, 128.14, 128.12, 127.75, 127.74, 126.1, 125.8, 124.4, 124.3, 114.0, 80.1, 68.9, 55.4, 41.8, 41.4, 33.8; **IR** (neat) 2937,

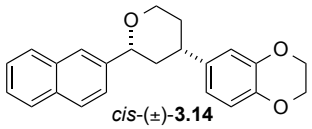
2836, 1600, 1258, 1083 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{22}H_{22}O_2Na$ $(M + Na)^+$ 341.1518, found 341.1512.

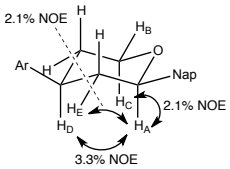


cis-(±)-**3.12**

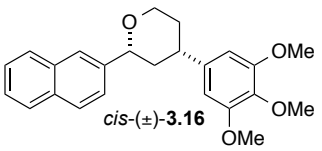


***cis*-(±)-4-(3,5-Bis(trifluoromethyl)phenyl)-2-(2-naphthyl)-tetrahydropyran** (*cis*-**3.12**) was prepared according to Method E. The following amounts of reagents were used: $Ni(cod)_2$ (14 mg, 0.050 mmol, 0.10 equiv), bathophenanthroline (33 mg, 0.10 mmol, 0.20 equiv), anhydrous KO^t-Bu (90. mg, 0.80 mmol, 1.6 equiv), 3,5-bis(trifluoromethyl)phenylboronic acid (155 mg, 0.600 mmol, 1.2 equiv), *s*-butanol (3.0 mL) and substrate *cis*-(±)-**3.9** (150 mg, 0.50 mmol, 1.0 equiv). The compound was purified by flash column chromatography (2% Et_2O/hexanes) to afford the title compound as a white solid (130 mg, 0.31 mmol, 62%, dr >20:1). The dr was determined based on integration of the benzylic methines in the ^1H NMR spectrum. The relative configuration was assigned as cis by COSY and NOE NMR experiments. Irradiation of the benzylic proton (H_A) gave an NOE enhancement of 2.6% of H_C, an enhancement of 3.1% of H_D, and an enhancement of 1.9% of H_E. **m.p.** 73–74 °C; **TLC R_f** = 0.3 (5% Et_2O/hexanes); **^1H NMR** (500 MHz, $CDCl_3$) δ 7.86–7.81 (m, 4H), 7.75 (s, 1H), 7.71 (s, 2H), 7.50 (dd, *J* = 8.5, 1.5, 1H), 7.48–7.45 (m, 2H), 4.67 (dd, *J* = 10.9, 1.8, 1H), 4.38 (ddd, *J* = 11.5, 4.2, 1.8, 1H), 3.84 (td, *J* = 11.4, 3.3, 1H), 3.20–3.14 (m, 1H), 2.20 (adt, *J* = 13.2, 1.9, 1H), 2.00–1.91 (m, 2H), 1.85 (q, *J* = 12.3, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 147.8, 139.7, 133.5, 133.1, 132.0 (q, *J* = 33.4), 128.4, 128.1, 127.8, 127.2 (q, *J* = 2.8), 126.3, 126.0, 124.5, 124.1, 123.5 (q, *J* = 272.8), 120.7, (septet, *J* = 3.9), 79.8, 68.4, 42.1, 41.2, 33.1; **IR** (neat) 2920, 2848, 1277, 1171 cm^{-1}; **HRMS** (TOF MS CI+) *m / z* calcd for $C_{23}H_{18}F_6ONH_4$ $(M + NH_4)^+$ 442.1606, found 442.1609.



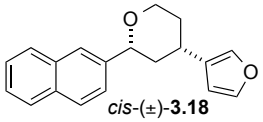


***cis*-(±)-6-(2-(Naphthyl)-tetrahydropyranyl)-2,3-dihydrobenzo[*b*][1,4]dioxine (*cis*-3.14)** was prepared according to Method E. The following amounts of reagents were used: $Ni(cod)_2$ (14 mg, 0.050 mmol, 0.10 equiv), bathophenanthroline (33 mg, 0.10 mmol, 0.20 equiv), anhydrous KO^t-Bu (90. mg, 0.80 mmol, 1.6 equiv), 1,4-benzodioxane-6-boronic acid (110 mg, 0.60 mmol, 1.2 equiv), *s*-butanol (3.0 mL) and substrate *cis*-(±)-**3.9** (150 mg, 0.50 mmol, 1.0 equiv). The compound was purified by flash column chromatography (5% Et_2O/hexanes) to afford the title compound as a faintly pink oil (95 mg, 0.27 mmol, 55%, dr >20:1). The dr was determined based on integration of the benzylic methines in the ^1H NMR spectrum. The relative configuration was assigned as cis by COSY and NOE NMR experiments. Irradiation of the benzylic proton (H_A) gave an NOE enhancement of 2.1% of H_C, an enhancement of 3.3% of H_D, and an enhancement of 2.1% of H_E. **TLC R_f** = 0.2 (5% Et_2O/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84–7.80 (m, 4H), 7.49 (dd, *J* = 8.6, 1.3, 1H), 7.47–7.42 (m, 2H), 6.82–6.77 (m, 2H), 6.73 (dd, *J* = 8.3, 1.9, 1H), 4.62 (dd, *J* = 11.1, 1.1, 1H), 4.32 (ddd, *J* = 11.5, 3.7, 2.0, 1H), 4.22 (s, 4H), 3.80 (td, *J* = 11.1, 3.6, 1H), 2.94–2.88 (m, 1H), 2.14 (add, *J* = 13.2, 2.0, 1H), 1.91–1.84 (m, 2H), 1.78 (q, *J* = 12.2, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 143.6, 142.1, 140.3, 139.1, 133.5, 133.0, 128.1, 127.8, 126.1, 125.8, 124.5, 124.4, 119.8, 117.3, 115.6, 80.1, 68.9, 64.54, 64.45, 41.7, 41.5, 33.7; **IR** (neat) 2933, 1508, 1284, 1068 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{23}H_{22}O_3Na$ $(M + Na)^+$ 369.1467, found 369.1469.



cis-(±)-**3.16**

***cis*-(±)-2-(Naphthalen-2-yl)-4-(3,4,5-trimethoxyphenyl)tetrahydro-2*H*-pyran (*cis*-3.16)** was prepared according to Method E. The following amounts of reagents were used: $Ni(cod)_2$ (20.6 mg, 0.075 mmol, 0.15 equiv), bathophenanthroline (50.0 mg, 0.15 mmol, 0.30 equiv), anhydrous KO^t-Bu (90 mg, 0.80 mmol, 1.6 equiv), 3,4,5-trimethoxyphenylboronic acid (127 mg, 0.60 mmol, 1.2 equiv), *s*-butanol (3.0 mL) and substrate *cis*-(±)-**3.9** (146 mg, 0.5 mmol, 1.0 equiv). The compound was purified by flash column chromatography (20% EtOAc in hexanes) to afford the title compound as a colorless oil (133 mg, 0.35 mmol, 70%, dr >20:1). The dr was determined based on integration of the benzylic methines in the ^{1}H NMR spectrum. The relative configuration was assigned as cis by analogy to *cis*-**3.10**. **TLC R_f** = 0.4 (20% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.83–7.80 (m, 3H), 7.50 (dd, *J* = 8.6, 1.3, 1H), 7.47–7.43 (m, 2H), 6.48 (s, 2H), 4.64 (dd, *J* = 11.1, 1.5, 1H), 4.36 (ddd, *J* = 11.3, 4.0, 1.6 1H), 3.85 (s, 6H), 3.83–3.79 (m, 4H), 3.00–2.94 (m, 1H), 2.18 (add, *J* = 13.4, 1.7, 1H), 1.96–1.87 (m, 2H), 1.81 (q, *J* = 12.5, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 153.4, 141.4, 140.3, 136.5, 133.4, 133.0, 128.15, 128.07, 127.7, 126.1, 125.8, 124.3, 124.2, 103.7, 80.0, 68.8, 60.9, 56.2, 42.7, 41.8, 33.7; **IR** (neat) 2936, 2838, 1588, 1124 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{24}H_{26}O_4$ $(M + Na)^+$ 401.1729, found 401.1717.



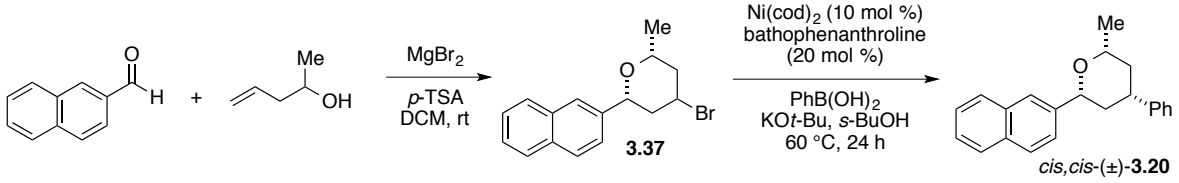
cis-(±)-**3.18**

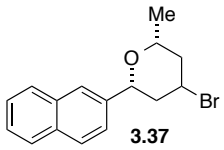
***cis*-(±)-4-(Furan-3-yl)-2-(naphthyl)-tetrahydropyran** (*cis*-**3.18**) was prepared according to Method E. The following amounts of reagents were used: $Ni(cod)_2$ (21 mg, 0.075 mmol, 0.15

equiv), bathophenanthroline (50. mg, 0.15 mmol, 0.30 equiv), anhydrous KO^t-Bu (90. mg, 0.80 mmol, 1.6 equiv), 3-furanylboronic acid (67 mg, 0.60 mmol, 1.2 equiv), *s*-butanol (3.0 mL) and substrate *cis*-(±)-**3.9** (150 mg, 0.50 mmol, 1.0 equiv). The compound was purified by flash column chromatography (5% Et_2O/hexanes) to afford a mixture of desired product and dimer of the starting material; this mixture was further purified by flash column chromatography (40% benzene/hexanes) to afford the title compound as an opaque oil (31 mg, 0.11 mmol, 23%, dr >20:1). The dr was determined based on integration of the benzylic methines in the ^{1}H NMR spectrum. The relative configuration was assigned as cis by analogy to *cis*-**3.10**. **TLC R_f** = 0.4 (5% Et_2O/hexanes), 0.2 (40% benzene/hexanes), R_f (dimer) = 0.3 (40% benzene/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84–7.80 (m, 4H), 7.49 (dd, *J* = 8.4, 1.6, 1H), 7.48–7.43 (m, 2H), 7.36 (m, 1H), 7.24 (s, 1H), 6.33 (s, 1H), 4.61 (dd, *J* = 11.3, 1.7, 1H), 4.30 (ddd, *J* = 11.6, 4.5, 1.1, 1H), 3.79 (td, *J* = 12.0, 2.2, 1H), 2.94 (tt, *J* = 12.1, 3.8, 1H), 2.20 (adt, *J* = 13.2, 1.7, 1H), 1.92 (adq, *J* = 13.2, 2.0, 1H), 1.79 (qd, *J* = 12.6, 4.5, 1H), 1.71 (q, *J* = 12.3, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 143.1, 140.3, 137.9, 133.5, 133.0, 129.6, 128.2, 128.1, 127.8, 126.1, 125.9, 124.5, 124.3, 109.4, 79.9, 68.6, 41.1, 33.0, 32.8; **IR** (neat) 2935, 2846, 1085, 907 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{19}H_{18}O_2Na$ $(M + Na)^+$ 301.1205, found 301.1206.

Synthesis of cis,cis-*(±)-**3.20***

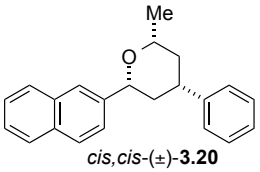
Scheme 3.8. Two-step synthesis of *cis,cis*-(±)-**3.20**.



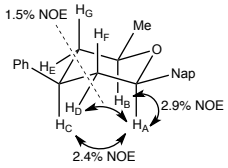


3.37

(±)-4-Bromo-6-methyl-2-(2-naphthyl)-tetrahydropyran (3.37) was prepared according to Method D. The following amounts of reagents were used: magnesium bromide (1.6 g, 8.7 mmol, 1.1 equiv), *p*-toluene sulfonic acid monohydrate (1.4 g, 7.4 mmol, 1.0 equiv), 2-naphthaldehyde (1.2 g, 7.7 mmol, 1.0 equiv), 4-penten-2-ol (0.82 mL, 7.9 mmol, 1.0 equiv), and anhydrous DCM (80 mL). The compound was purified by flash column chromatography (0–1% EtOAc in hexanes) to afford the title compound as a white solid (0.91 g, 3.0 mmol, 39%). The dr was determined based on integration of the benzylic methines in the ^{1}H NMR spectrum. ^{1}H NMR analysis indicated the title compound was an inseparable mixture of *cis* and *trans* diastereomers by comparison to literature ^{1}H NMR of the reported analogues.[19] The *cis*:*trans* ratios ranged from 1:1.1 to 1:1.7 for different batches. **m.p.** 78–80 °C; **TLC** $\mathbf{R_f}$ = 0.6 (2% EtOAc/hexanes, stains blue with PAA); **IR** (neat) 3060, 2966, 1312, 1069 cm^{-1}; **HRMS** (TOF MS CI+) *m / z* calcd for $C_{16}H_{17}BrONH_4$ $(M + NH_4)^+$ 322.0807, found 322.0815. ***cis*-(±)-3.37** (37% by ^{1}H NMR integration): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77–7.70 (m, 4H), 7.41–7.33 (m, 3H), 4.30 (dd, *J* = 11.4, 1.5, 1H), 4.15–4.07 (m, 1H), 3.48–3.40 (m, 1H), 2.37 (dt, *J* = 12.9, 2.2, 1H), 2.15 (dd, *J* = 14.4, 2.2, 1H), 2.02–1.86 (m, 1H), 1.79–1.64 (m, 1H), 1.21 (d, *J* = 6.3, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 138.8, 133.4, 133.1, 128.4, 128.13, 127.77, 126.2, 126.0, 124.76, 124.2, 79.7, 74.3, 46.6, 45.0, 41.0, 21.8. ***trans*-(±)-3.37** (63% by ^{1}H NMR integration): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77–7.70 (m, 4H), 7.41–7.33 (m, 3H), 5.06 (dd, *J* = 10.9, 1.4, 1H), 6.46 (t, *J* = 2.9, 1H), 4.24–4.16 (m, 1H), 2.15 (dd, *J* = 14.4, 2.2, 1H), 2.02–1.86 (m, 2H), 1.79–1.64 (m, 1H), 1.25 (d, *J* = 6.4, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 139.6, 133.5, 133.1, 128.3, 128.10, 127.75, 126.1, 125.9, 124.77, 124.4, 74.5, 69.0, 50.7, 44.8, 41.5, 21.6.



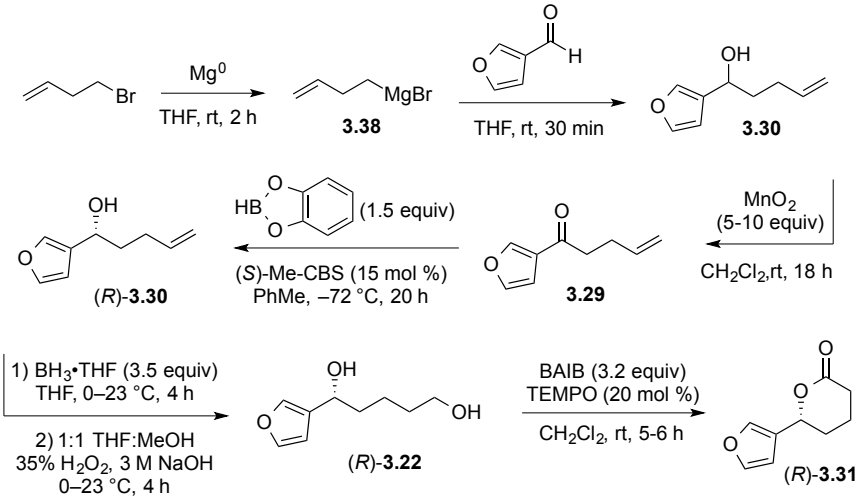
cis,cis-(±)-**3.20**

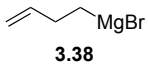


***cis,cis*-(±)-6-Methyl-4-phenyl-2-(2-naphthyl)-tetrahydropyran (*cis,cis*-3.20)** was prepared according to Method E. The following amounts of reagents were used: $Ni(cod)_2$ (14 mg, 0.050 mmol, 0.10 equiv), bathophenanthroline (33 mg, 0.10 mmol, 0.20 equiv), anhydrous KO^t-Bu (90. mg, 0.80 mmol, 1.6 equiv), phenylboronic acid (73 mg, 0.60 mmol, 1.2 equiv), *s*-butanol (3.0 mL) and substrate **3.37** (150 mg, 0.50 mmol, 1.0 equiv). The compound was purified by flash column chromatography (2% Et_2O/hexanes) to afford the title compound as a white solid (99 mg, 0.33 mmol, 66%, dr >20:1). The dr was determined based on integration of the benzylic methines in the ^{1}H NMR spectrum. The relative configuration was assigned as cis by COSY and NOE NMR experiments. Irradiation of the benzylic proton (H_A) gave an NOE enhancement of 2.9% of H_B, an enhancement of 2.4% of H_C, and an enhancement of 1.5% of H_D. **m.p.** 67–69 °C; **TLC R_f** = 0.5 (5% Et_2O/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.83–7.79 (m, 3H), 7.52 (dd, *J* = 8.6, 1.5, 1H), 7.46–7.41 (m, 2H), 7.32–7.29 (m, 2H), 7.26–7.19 (m, 3H), 4.70 (dd, *J* = 11.1, 1.7, 1H), 3.89–3.83 (m, 1H), 3.03 (tt, *J* = 12.3, 3.7, 1H), 2.15 (dt, *J* = 13.2, 1.8, 1H), 1.93 (dt, *J* = 13.2, 1.8, 1H), 1.77 (q, *J* = 12.3, 1H), 1.56 (q, *J* = 11.8, 1H), 1.37 (d, *J* = 6.4, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 145.6, 140.5, 133.5, 133.0, 128.7, 128.16, 128.15, 127.7, 126.9, 126.5, 126.0, 125.7, 124.59, 124.58, 79.8, 74.4, 42.3, 41.0, 40.8, 22.3; **IR** (neat) 3058, 2930, 1132, 757 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{22}H_{22}O$ $(M + Na)^+$ 325.1568, found 325.1563.

*Synthesis of Enantioenriched Valerolactone (*R*)-**3.31**.*

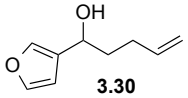
Scheme 3.9. Synthetic scheme for (*R*)-**3.31**.





3.38

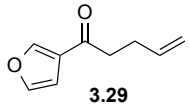
3-Butenylmagnesium bromide (3.38). Magnesium turnings (3.65 g, 150 mmol, 2.00 equiv.) were added to a round-bottom flask equipped with a stir bar. The reaction apparatus was flame-dried under vacuum and cooled under N_2. A single crystal of I_2 (ca. 2 mg) was added to the flask, followed by anhydrous Et_2O (30 mL). 4-Bromo-1-butene (7.5 mL, 74 mmol, 1.0 equiv.) was added portion-wise over 1 h at 0 °C. The reaction was stirred at 0 °C for 10 min, then at ambient temperature for 2 h, and titrated.[48]



3.30

1-(3-Furyl)-pent-4-en-1-ol (3.30). A solution of freshly prepared Grignard reagent **3.38** (13 mL, 20 mmol, 1.5 M in Et_2O, 1.1 equiv) at 0 °C was treated in a dropwise manner with 3-furaldehyde

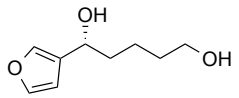
(1.60 mL, 18.4 mmol, 1.00 equiv) to maintain a gentle reflux. The reaction mixture was stirred at room temperature 1 h, and then cooled to 0 °C and quenched with saturated aqueous NH_4Cl (30 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash column chromatography (5–10–20% Et_2O/hexanes) to afford the title compound as a light yellow oil (2.78 g, 18.3 mmol, 99%). **TLC R_f** = 0.4 (20% EtOAc/hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39–7.38 (m, 2H), 6.40 (s, 1H), 5.88–5.80 (m, 1H), 5.05 (dq, *J* = 17.1, 1.7, 1H), 4.99 (dq, *J* = 1.4, 10.2, 1H), 4.70–4.66 (m, 1H), 2.20–2.09 (m, 2H), 1.91–1.77 (m, 2H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 143.5, 139.2, 138.2, 129.1, 115.2, 108.5, 66.6, 36.9, 30.0; **IR** (neat) 3364 (br), 2936, 1502, 1159, 1022 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_9H_{12}O_2$ $(M + Na)^+$ 151.0759, found 151.0756.



3.29

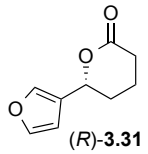
1-(3-Furyl)-pent-4-en-1-one (3.29). Activated MnO_2 (15.9 g, 183 mmol, 10.0 equiv) was added to a solution of substrate **3.30** (2.78 g, 18.3 mmol, 1.00 equiv) in wet DCM (200 mL). The reaction was stirred at ambient temperature for 18 h, then filtered through a bed of Celite with additional DCM and concentrated in vacuo. The product was purified by flash column chromatography (1% Et_2O/hexanes) to afford the title compound as a clear, colorless oil (2.06 g, 13.7 mmol, 75%). **TLC R_f** = 0.6 (10% Et_2O/pentanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (as, 1H), 7.44 (at, *J* = 1.7, 1H), 6.77 (add, *J* = 1.9, 0.8, 1H), 5.91–5.82 (m, 1H), 5.09 (dq, *J* = 17.0, 1.6, 1H), 5.00 (dq, *J* = 10.2, 1.4, 1H), 2.85 (t, *J* = 7.5, 2H), 2.47 (qt, *J* = 7.1, 1.3, 2H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 194.3, 147.2, 144.3, 137.2, 127.8, 115.5, 108.7, 39.6, 28.2; **IR** (neat)

3137, 1676, 1562, 1511, 1155, 873 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_9H_{10}O_2H$ $(M + H)^+$ 151.0759, found 151.0765.



(*R*)-**3.22**

(*R*)-1-(2-Furyl)-1,5-pentanediol ((*R*)-3.22). Anhydrous THF (75 mL) was added to a flame-dried round-bottom flask equipped with a stir bar. Substrate (*R*)-**3.30** (1.22 g, 8.00 mmol, 1.00 equiv) was added and the reaction mixture cooled to 0 °C. $BH_3 \cdot THF$ (20 mL, 20 mmol, 1.0 M in THF, 2.5 equiv) was slowly added and the reaction mixture was stirred at ambient temperature for 4 h. The reaction was then cooled to 0 °C, diluted with 1:1 THF/MeOH (120 mL), and treated with 30% w/w H_2O_2 (40 mL) and 3 M NaOH (75 mL) before stirring at ambient temperature another 4 h. The reaction mixture was partitioned between H_2O and EtOAc and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by flash column chromatography (20–70% EtOAc/hexanes) to afford the title compound as a pale yellow oil (1.13 g, 6.64 mmol, 83%). Enantiomeric excess could not be determined for the title compound using chiral SFC and GC instrumentation. **TLC R_f** = 0.6 (10% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 1.5, 2H), 6.41 (s, 1H), 4.68 (at, *J* = 6.6, 1H), 3.65 (t, *J* = 6.4, 2H), 1.91–1.38 (m, 8H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 143.5, 139.2, 129.2, 108.5, 67.0, 62.9, 37.6, 32.5, 22.0; **IR** (neat) 3329, 2926, 2861, 1020, 874 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_9H_{14}O_3Na$ $(M + Na)^+$ 193.0841, found 193.0842; **$[\alpha]_D^{28}$** + 13.6 (*c* 0.9, $CHCl_3$).

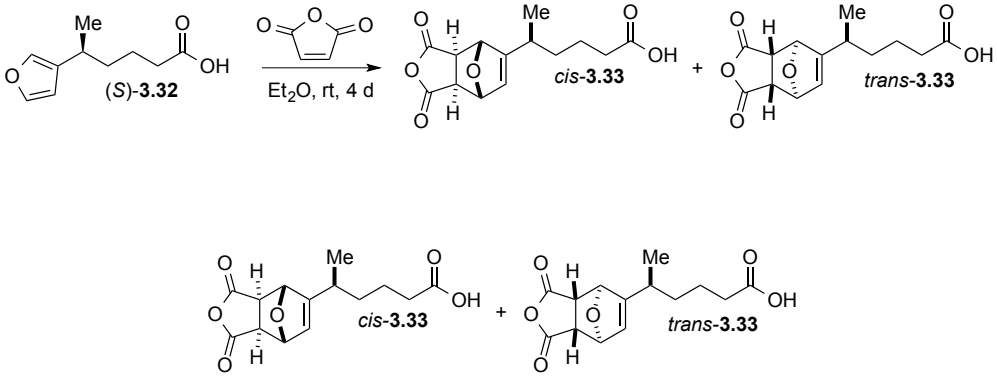


(*R*)-**3.31**

(*R*)-δ-(3-Furyl)-δ-valerolactone ((*R*)-3.31) was prepared according to a modified procedure reported by Forsyth.[35a] We found for this substrate in particular that the preceding diol **3.22** had to be pure for cyclization to proceed. To a stirring solution of diol (*R*)-**3.22** (0.16 g, 0.92 mmol, 1.0 equiv), in DCM (10 mL) was added bis-acetoxyiodobenzene (BAIB, 0.89 g, 2.8 mmol, 3.0 equiv) followed by 2,2,6,6-tetramethylpiperidinyloxy (TEMPO, 29 mg, 0.18 mmol, 0.20 equiv). After stirring for 5 h at ambient temperature, sat. aq. $Na_2S_2O_3$ (10 mL) and Et_2O (10 x mL) were added and the organic phase was washed with sat. aq. $NaHCO_3$ (10 mL) and then H_2O (10 mL). The combined aqueous layers were extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash column chromatography (20–50% Et_2O/pentanes) to afford the title compound as a pale yellow oil (0.67 g, 0.40 mmol, 44%, 90% ee). Absolute configuration was assigned as *R* from the preceding CBS reduction to (*R*)-**3.30**.[34] This type of oxidative cyclization is known to proceed with retention of stereochemical information from the requisite diol.[35b] **TLC** $\mathbf{R_f}$ = 0.3 (50% Et_2O/pentanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (as, 1H), 7.42 (as, 1H), 6.42 (as, 1H), 5.36 (dd, *J* = 9.5, 3.4, 1H), 2.70–2.63 (m, 1H), 2.58–2.51 (m, 1H), 2.19–2.14 (m, 1H), 2.03–1.87 (m, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 171.2, 143.8, 139.7, 125.1, 108.5, 75.2, 29.6, 28.8, 18.5; **IR** (neat) 2922, 1727, 1504, 1346, 1227, 1156 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_9H_{10}O_3Na$ $(M + Na)^+$ 189.0528, found 189.0529; $\mathbf{[\alpha]_D^{29}}$ – 18.6 (*c* 1.1, $CHCl_3$); **SFC** analysis (Whelk-(*R,R*), 5% IPA, 2.5 mL/min, 215 nm) indicated 90% ee: t_R (major) = 16.8 minutes, t_R (minor) = 13.9 minutes.

Synthesis of* cis-** ***and **trans-*3.33***

Scheme 3.10. Diels–Alder cycloaddition of (*S*)-**3.32**.



5-(1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-4,7-epoxyisobenzofuran-5-yl)hexanoic acid (3.33) was prepared according to a modified procedure by Woodward.[40] To a flame-dried 7 mL reaction vial equipped with a N_2 line was added maleic anhydride (31 mg, 0.31 mmol, 3.0 equiv) and 0.5 mL Et_2O, and the mixture stirred vigorously until dissolution of maleic anhydride. Substrate (*S*)-**3.32** (19 mg, 0.10 mmol, 1.0 equiv) was added as a solution in 0.5 mL Et_2O, and the reaction was stirred at ambient temperature for 4 d, whereupon the solvent was removed in vacuo. Phenyltrimethylsilane (PhTMS) was added as internal standard and a ^{1}H NMR yield (64%) was obtained before purification. The crude mixture was purified by flash column chromatography in 50% EtOAc/hexanes to afford a colorless oil (13.3 mg) containing a mixture of the title compound (46% calculated yield) and maleic anhydride. A small amount of analytically pure sample was obtained for characterization. The dr (1:1.1) was determined based on integration of diastereotopic carbons in the ^{13}C NMR spectrum. **TLC** $\mathbf{R_f}$ = 0.2 (50% EtOAc/hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.10 (t, *J* = 1.5, 1H), 5.38, (s, 1H), 5.29 (s, 1H), 3.25–3.19 (m, 2H), 2.49–2.43 (m, 1H), 2.41–2.35 (m, 2H), 1.66–1.51 (m, 3H), 1.49–1.39 (m, 1H), 1.12 (d, *J* = 7.0, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 178.12, 178.10, 170.53, 170.49, 170.2, 157.0, 156.8, 128.68, 128.65, 83.5, 83.4, 83.23, 83.21, 50.2, 50.1, 49.1, 49.0, 34.2, 34.0, 33.54, 33.48, 32.8,

32.5, 22.1, 22.0, 18.8, 18.4; **IR** (neat) 2931, 1781, 905, 728 cm^{-1}; **HRMS** (TOF MS ES–) *m / z* calcd for $C_{14}H_{15}O_6$ $(M - H)^-$ 279.0869, found 279.0870; $\mathbf{[\alpha]_D^{28}}$ + 7.1 (*c* 0.2, $CDCl_3$).

General Procedures for Biological Experiments

Biological experiments were performed according to a modified procedure by Alley.[43]

Materials

The following reagents were obtained from commercial sources as indicated: RPMI 1640 medium (HyClone); McCoy's 5A medium (HyClone); fetal bovine serum (FBS), heat-inactivated (Omega Scientific); L-glutamine, 200 mM (Gibco); penicillin/streptomycin solution 50X (Mediatech); amphotericin B (HyClone); DMEM/Ham's Nutrient Mixture F12 containing 2.5 mM L-glutamine, 3151 mg/L dextrose, and 55 mg/L sodium pyruvate (Sigma-Aldrich); horse serum (Sigma-Aldrich); 50 μM hydrocortisone solution (Sigma-Aldrich); human insulin solution (Sigma-Aldrich); cholera toxin (Sigma-Aldrich); human Epidermal Growth Factor (EGF), recombinant (Sigma-Aldrich); 0.25% Trypsin-EDTA (Gibco); nuclease-free sterile water (Fisher Scientific); molecular biology grade DMSO (Sigma-Aldrich); MTT (3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyltetrazolium bromide) (Sigma-Aldrich).

Cell Lines and Culture Conditions

MCF-10A cells were maintained in standard medium according to a modified recipe by Brugge:[53] DMEM/F12 supplemented with 5% horse serum, 10 μg/mL human insulin, 0.5 μg/mL

[53] Debnath, J.; Muthuswamy, S. K.; Brugge, J. S. *Methods* **2003**, *30*, 256.

hydrocortisone, 10 ng/mL EGF, 100 ng/mL cholera toxin, and penicillin/streptomycin. Experiments with MCF-10A cells were performed in the same medium.

MCF-7 cells were maintained in RPMI 1640 supplemented with 10% FBS, L-glutamine, and penicillin/streptomycin. Experiments with MCF-7 cells were performed in the same medium.

MDA-MB-468 cells were maintained in RPMI 1640 supplemented with 10% FBS, L-glutamine, penicillin/streptomycin, and amphotericin B. Experiments with MDA-MB-468 cells were performed in the same medium.

C4-2B cells were maintained in RPMI 1640 supplemented with 10% FBS, L-glutamine, and penicillin/streptomycin. Experiments with C4-2B cells were performed in the same medium.

CAKI-2 cells were maintained in McCoy's 5A supplemented with 10% FBS, L-glutamine, and penicillin/streptomycin. Experiments with CAKI-2 cells were performed in the same medium.

SK-OV-3 cells were maintained in RPMI 1640 supplemented with 10% FBS, L-glutamine, and penicillin/streptomycin. Experiments with SK-OV-3 cells were performed in the same medium.

Evaluation of Compounds Against Cell Lines

Preparation of Cell Lines

MCF-10A cells were centrifuged in DMEM/F12 at 1.0 rcf for 8 min, then the pellet was resuspended in DMEM/F12. The cells were seeded at 20,000 cells per well in 24-well flat bottom plates, using 500 μL per well DMEM/F12, and grown for 24 h in 5% CO_2 at 37 °C.

MCF-7 cells were centrifuged in RPMI at 1.0 rcf for 8 min, then the pellet was resuspended in RPMI. The cells were seeded at 20,000 cells per well in 24-well flat bottom plates, using 500 μL per well RPMI, and grown for 24 h in 5% CO_2 at 37 °C.

MDA-MB-468 cells were centrifuged in RPMI with amphotericin B at 1.0 rcf for 8 min, then the pellet was resuspended in RPMI with amphotericin B. The cells were seeded at 20,000 cells per well in 24-well flat bottom plates, using 500 μL per well RPMI with amphotericin B, and grown for 24 h in 5% CO_2 at 37 °C.

C4-2B cells were centrifuged in RPMI at 1.0 rcf for 8 min, then the pellet was resuspended in RPMI. The cells were seeded at 20,000 cells per well in 24-well flat bottom plates, using 500 μL per well RPMI, and grown for 24 h in 5% CO_2 at 37 °C.

CAKI-2 cells were centrifuged in McCoy's 5A at 1.0 rcf for 8 min, then the pellet was resuspended in McCoy's 5A. The cells were seeded at 12,500 cells per well in 24-well flat bottom plates, using 500 μL per well McCoy's 5A, and grown for 24 h in 5% CO_2 at 37 °C.

SK-OV-3 cells were centrifuged in RPMI at 1.0 rcf for 8 min, then the pellet was resuspended in RPMI. The cells were seeded at 20,000 cells per well in 24-well flat bottom plates, using 500 μL per well RPMI, and grown for 24 h in 5% CO_2 at 37 °C.

Preparation of Compounds

The compounds were dissolved in molecular biology grade DMSO to achieve a 100 mM stock solution, and then sterile filtered through a 0.45 μm PVDF syringe filter unit (Fisher Scientific). The 100 mM stock solutions were subsequently diluted to 20 mM stock solutions, then diluted to a final concentration of 10 μM in the corresponding medium for each cell line. Additionally, the corresponding DMSO vehicle control was diluted using the same medium.

After 24 h growth, the medium was carefully aspirated from each of the wells containing cells. The cells were treated by replacing the normal medium with 600 μL fresh medium per well containing the individual compounds or vehicle control (day 0). The plates were gently agitated,

then the cells were incubated with compound at 37 °C with 5% CO_2 for 72 h. On day 3, cell proliferation was measured using the MTT absorbance assay.

MTT Absorbance Assay

Quantitative analysis was performed according to a modified procedure by Alley.[43] After 72 h incubation with compound, 200 μL of MTT dye solution (3 mg MTT/ 1 mL PBS) was carefully added to each well containing cells. The plates were incubated at 37 °C for 1 h 15 min, after which the MTT dye was aspirated from each well. 300 μL of MTT dissolve solution (4% 1M HCl in IPA) was added to each well and the plates were agitated 15 min. From each well, 200 μL of cell lysate solution was carefully transferred to a new well in a clear-bottom 96-well plate suitable for UV-Vis spectroscopy. Cells were quantified by absorbance at 570 nm. The absorbance values were normalized to the DMSO vehicle control. The normalized values were plotted as an average ± standard deviation of 3 wells per compound.

Raw Data for Cell Assays

Table 3.5. Relative cell numbers for compound *syn*-**3.34**.

MCF-7 cell line	**Trial:**	**1**	**2**	**3**	**4**	**Average**	**SD**
Fluorescence counts (DMSO)		1177201	1525796	1288876	1409215	1350272	150561
Fluorescence counts (*syn*-**3.34**)		138743	165322	255419	243509	200748	57495
Relative cell numbers (*syn*-**3.34**), normalized (%)		10.3	12.2	18.9	18.0	14.9	4.3
MDA-MB-468 cell line	**Trial:**	**1**	**2**	**3**		**Average**	**SD**
Absorbance values (DMSO)		1.6433	1.5081	1.4655		1.5390	0.0928
Absorbance values (*syn*-**3.34**)		1.5390	1.5651	1.6679		1.5907	0.0681
Relative cell numbers (*syn*-**3.34**), normalized (%)		98.0	99.7	106.2		101.3	4.3

C4-2B cell line	Trial:	1	2	3	Average	SD
Absorbance values (DMSO)		0.9790	0.9650	0.9612	0.9684	0.0094
Absorbance values (*syn*-**3.34**)		1.0003	0.9264	1.0744	1.0004	0.0740
Relative cell numbers (*syn*-**3.34**), normalized (%)		103.3	95.7	110.9	103.3	7.6

CAKI-2 cell line	Trial:	1	2	3	Average	SD
Absorbance values (DMSO)		1.2051	0.9685	0.9101	1.0279	0.1562
Absorbance values (*syn*-**3.34**)		0.8728	0.9132	1.0017	0.9292	0.0659
Relative cell numbers (*syn*-**3.34**), normalized (%)		84.9	88.8	97.5	90.4	6.4

SK-OV-3 cell line	Trial:	1	2	3	Average	SD
Absorbance values (DMSO)		2.0732	1.8405	1.5620	1.8252	0.2559
Absorbance values (*syn*-**3.34**)		1.9432	2.0110	2.1475	2.0339	0.1041
Relative cell numbers (*syn*-**3.34**), normalized (%)		99.4	102.8	109.8	104.0	5.3

Table 3.6. Relative cell numbers for compound *syn*-**3.17**.

MCF-10A cell line	Trial:	1	2	3	Average	SD
Absorbance values (DMSO)		2.7994	2.7073	2.7361	2.7476	0.0471
Absorbance values (*syn*-**3.17**)		0.2520	0.2484	0.2635	0.2546	0.0079
Relative cell numbers (*syn*-**3.17**), normalized (%)		9.2	9.0	9.6	9.3	0.3

MCF-7 cell line	Trial:	1	2	3	Average	SD
Absorbance values (DMSO)		0.4127	0.3514	0.3336	0.3659	0.0415
Absorbance values (*syn*-**3.17**)		0.1770	0.1858	0.2070	0.1899	0.0154
Relative cell numbers (*syn*-**3.17**), normalized (%)		48.4	50.8	56.6	51.9	4.2

MDA-MB-468 cell line	Trial:	1	2	3	Average	SD
Absorbance values (DMSO)		1.2696	1.1288	1.2005	1.1996	0.0704
Absorbance values (*syn*-**3.17**)		0.1797	0.1338	0.1412	0.1516	0.0246
Relative cell numbers (*syn*-**3.17**), normalized (%)		15.0	11.2	11.8	12.6	2.1

Table 3.7. Relative cell numbers for compound *anti*-**3.35**.

MCF-7 cell line	**Trial:**	**1**	**2**	**3**	**Average**	**SD**
Absorbance values (DMSO)		0.9522	0.6718	0.7772	0.8004	0.1416
Absorbance values (*anti*-**3.35**)		0.2498	0.2870	0.3857	0.3075	0.0702
Relative cell numbers (*anti*-**3.35**), normalized (%)		31.2	35.9	48.2	38.4	8.8

MDA-MB-468 cell line	**Trial:**	**1**	**2**	**3**	**Average**	**SD**
Absorbance values (DMSO)		1.3253	1.2975	1.2052	1.2760	0.0629
Absorbance values (*anti*-**3.35**)		0.3928	0.4578	0.3655	0.4054	0.0474
Relative cell numbers (*anti*-**3.35**), normalized (%)		30.8	35.9	28.6	31.8	3.7

Chapter Four

Silver-Catalyzed Enantioselective Propargylation Reactions of *N*-Sulfonyl Ketimines

4.1 Introduction

Nearly half of the top 200 pharmaceuticals in 2012 contain functional groups that can be prepared from α-chiral amines.[1,2] To access this moiety, numerous enantioselective methods for the synthesis of chiral amines have been developed, many of which involve addition of organometallic nucleophiles to aldimines.[3] Additions to ketimines pose specific challenges. For example, mixtures of E and Z isomers can lead to low levels of enantioinduction.[4] These obstacles have inspired creative approaches[5] including use of cyclic *N*-sulfonyl ketimines (e.g., **4.1**), which do not undergo E/Z isomerization and are synthesized in one step from saccharin.[6,7] Hayashi and co-workers have pioneered the rhodium-catalyzed enantioselective arylation reactions of *N*-sulfonyl ketimines; other elegant examples of arylation, allylation, and

[1] Portions of this Chapter were originally published as: Osborne, C. A.; Endean, T. B. D.; Jarvo, E. R. *Org. Lett.* **2015**, *17*, 5340.

[2] 94 of the top 200 pharmaceuticals by U.S. retail sales in 2012 contained functional groups that could be prepared from α-chiral amines, while 25 of the top 200 pharmaceuticals contained α-chiral amines. See: (a) Njarðarson Group. *Top Pharmaceuticals Poster*. http://jon.oia.arizona.edu/top-pharmaceuticals-poster (accessed May 30, 2015); (b) McGrath, N. A.; Brichacek, M.; Njarðarson, J. T. *J. Chem. Ed.* **2010**, *87*, 1348.

[3] For reviews on catalytic enantioselective methods for generating chiral amines, see: (a) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753; (b) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626.

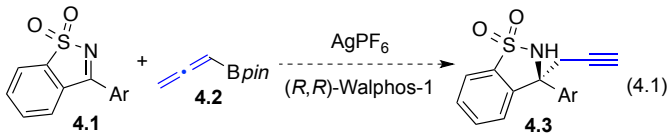
[4] For a discussion and review, see: Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873.

[5] For a lead reference, see: Yin, L.; Otsuka, Y.; Takada, H.; Mouri, S.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2013**, *15*, 698.

[6] (a) For enantioselective hydrogenation, see: Oppolzer, W.; Wills, M.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1990**, *31*, 4117; (b) For homoenolate additions, see: Rommel, M.; Fukuzumi, T.; Bode, J. W. *J. Am. Chem. Soc.* **2008**, *130*, 17266; (c) For enantioselective arylation, see: Nishimura, T.; Noishiki, A.; Tsui, G. C.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 5056; (d) For formal [3+2] cycloadditions with TMM, see: Trost, B. M.; Silverman, S. M. *J. Am. Chem. Soc.* **2012**, *134*, 4941.

[7] Synthesis of *N*-sulfonyl ketimines from saccharin: Davis, F. A.; Towson, J. C.; Vashi, D. B.; ThimmaReddy, R.; McCauley, Jr., J. P.; Harakal, M. E.; Gosciniak, D. J. *J. Org. Chem.* **1990**, *55*, 1254.

alkenylation reactions have also been reported.[6c,8] An enantioselective propargylation reaction would afford a chiral sultam with a pendant terminal alkyne, a valuable functional group handle that can be easily derivatized for further synthetic elaboration.[9] In this Chapter, we report the first enantioselective propargylation reaction of ketimines (eq. 4.1).



Building on early advances in enantioselective propargylation reactions of aldehydes, in the past five years there has been rapid development of enantioselective propargylation reactions of ketones and aldimines.[10,11,12] The Jarvo laboratory has reported the silver-catalyzed enantioselective propargylation reactions of aldimines and diarylketones.[11b,13,14] Using AgF and chiral phosphine ligands from the Walphos family provided a variety of homopropargylic amines and alcohols in good yield and high enantiomeric excess (ee). We hypothesized that a

[8] For enantioselective arylation, see: (a) Jiang, C.; Lu, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 9936; (b) Yang, G.; Zhang, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 7540; (c) Wang, H.; Jiang, T.; Xu, M.-H. *J. Am. Chem. Soc.* **2013**, *135*, 971; (d) Jiang, T.; Wang, Z.; Xu, M.-H. *Org. Lett.* **2015**, *17*, 528; (e) For enantioselective allylation, see: Luo, Y.; Hepburn, H. B.; Chotsang, N.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 8309; (f) For enantioselective alkenylation, see: Luo, Y.; Carnell, A. J.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 6762.

[9] For recent examples in synthesis of polyketides, see: (a) Mailhol, D.; Willwacher, J.; Kausch-Busies, N.; Rubitski, E. E.; Sobol, Z.; Schuler, M.; Lam, M.-H.; Musto, S.; Loganzo, F.; Maderna, A.; Fürstner, A. *J. Am. Chem. Soc.* **2014**, *136*, 15719; (b) Reznik, S. K.; Marcus, B. S.; Leighton, J. L. *Chem. Sci.* **2012**, *3*, 3326.

[10] (a) For a comprehensive review, see: Ding, C.-H.; Hou, X.-L. *Chem. Rev.* **2011**, *111*, 1914; (b) For a synopsis of catalytic enantioselective propargylation reactions of ketones and imines, see: Wisniewska, H. M.; Jarvo, E. R. *J. Org. Chem.* **2013**, *78*, 11629.

[11] For catalyst-controlled, enantioselective propargylation of imines, see: (a) Kagoshima, H.; Uzawa, T.; Akiyama, T. *Chem. Lett.* **2002**, *31*, 298; (b) Wisniewska, H. M.; Jarvo, E. R. *Chem. Sci.* **2011**, *2*, 807; (c) Viera, E. M.; Haeffner, F.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 6618.

[12] For examples of diastereoselective propargylation of imines, see: (a) Gonzalez, A. Z.; Soderquist, J. A. *Org. Lett.* **2007**, *9*, 1081; (b) Fandrick, D. R.; Johnson, C. S.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Lee, H.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 748; (c) García-Muñoz, M. J.; Zacconi, F.; Foubelo, F.; Yus, M. *Eur. J. Org. Chem.* **2013**, 1287; (d) Guo, T.; Song, R.; Yuan, B.-H.; Chen, X.-Y.; Sun, X.-W.; Lin, G.-Q. *Chem. Commun.* **2013**, *49*, 5402; (e) Chen, D.; Xu, M.-H. *Chem. Commun.* **2013**, *49*, 1327.

[13] Kohn, B. L.; Ichiishi, N.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 4414.

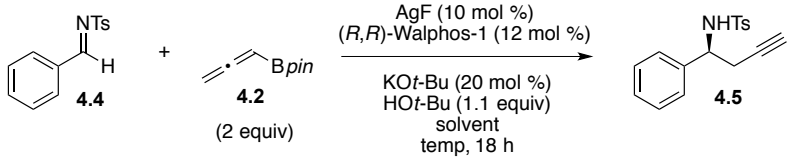
[14] For silver-catalyzed enantioselective allylation reactions of ketones, see: Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556.

Ag/Walphos catalyst would be able to differentiate between the *Re* and *Si* faces of diaryl ketimines, based on their structural similarity to diarylketones.

4.2 Optimization of Reactions of Aryl and Alkyl Ketimines

Previous methods in the Jarvo laboratory for preparing the Ag/Walphos catalyst were time and labor intensive. Catalyst preparation involved formation of the silver phosphine complex in methanol followed by solvent replacement with THF.[15] We turned to the silver-catalyzed enantioselective propargylation of aldimine **4.4** as a well-developed model system to improve catalyst preparation. Heating AgF and Walphos-1 in DMF for a 30 minute pre-stir increased the solubility of AgF and simplified reaction set-up; these results (Table 4.1, entries 1 and 2) were comparable to previously published results obtained using a methanol pre-stir (entries 3 and 4).

Table 4.1. Optimization of catalyst formation.



entry	solvent	temp (°C)	yield **4.5** (%)[a]	ee **4.5** (%)[b]	note
1	DMF	22	75	91	pre-stir heated
2	DMF	–20	89	97	pre-stir heated
3[c]	MeOH then THF	22	85	88	
4[c]	MeOH then THF	–20	90	97	

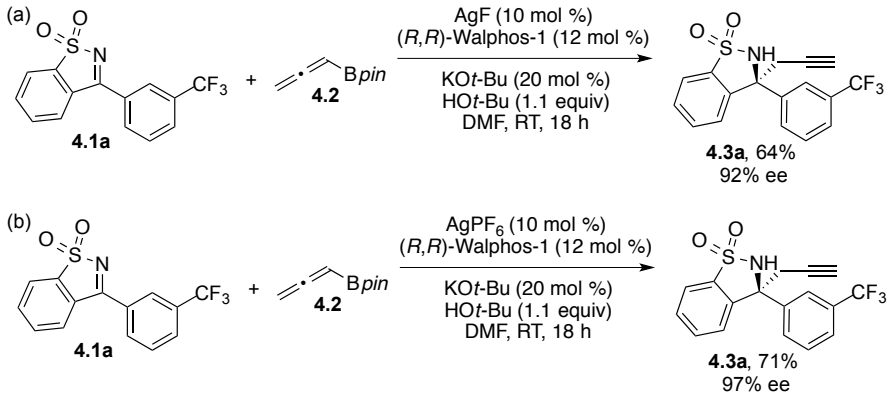
[a]Determined using ^{1}H NMR by comparison to PhTMS as internal standard. [b]Determined using chiral SFC chromatography. [c]See reference 11b.

With an improved method for catalyst preparation, we began to optimize reaction conditions for the enantioselective propargylation of diaryl ketimines. Employing AgF as the

[15] See references 11b, 13, and 14 for full details.

precatalyst and Walphos-1 as the ligand formed homopropargylic sultam **4.3a** in 64% yield and 92% ee (Scheme 4.1a). A survey of alternate silver sources found that $AgPF_6$ provided higher yield, likely due to increased solubility. Furthermore, $AgPF_6$ provided higher ee than AgF. Employing $AgPF_6$ as the precatalyst and Walphos-1 as the ligand provided **4.3a** in 71% yield and 97% ee (Scheme 4.1b).

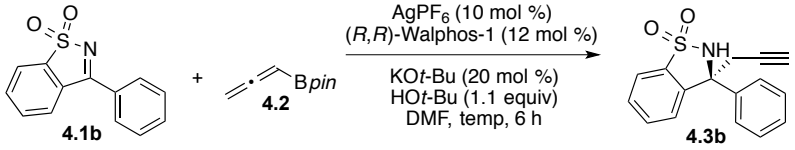
Scheme 4.1. Enantioselective propargylation of ketimine **4.1a** with (a) AgF or (b) $AgPF_6$.



We were interested in improving reaction conditions for the propargylation of substrate **4.1b** (Table 4.2). Initial reaction at –20 °C resulted in low conversion to sulfonamide **4.3b** (entry 1). We hypothesized that protodeborylation of allenylboronic acid pinacol ester **4.2** to allene (C_3H_4) was competitive with the desired addition reaction and thus resulted in modest yields.[16] Use of two additional equivalents of allenylboronic acid pinacol ester **4.2** via slow addition improved the yield and provided **4.3b** in 98% ee (entry 2). We increased the temperature and found that at ambient temperature, **4.3b** was formed in a modest yield; fortunately, the ee remained high (entry 3). Increasing the equivalents of **4.2** at room temperature further improved the yield, providing **4.3b** in 71% yield and 97% ee (entry 4).

[16] Kohn, B. L.; Jarvo, E. R. *Org. Lett.* **2011**, *13*, 4858.

Table 4.2. Optimization of silver-catalyzed propargylation reaction.



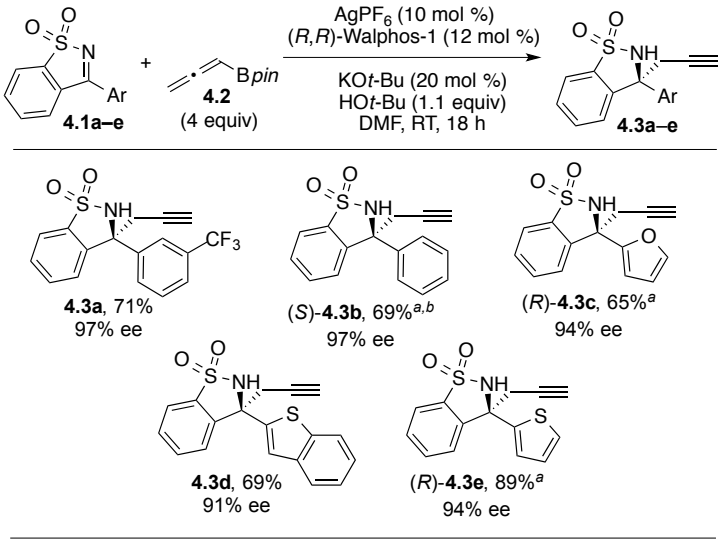
entry	temp (°C)	equiv **4.2**	yield **4.1b** (%)[a]	yield **4.3b** (%)[a]	ee **4.3b** (%)[b]
1	–20	2	57	12	nd
2	–20	4	49	52	98
3	22	2	43	52	96
4	22	4	34	71	97

[a]Determined using ^{1}H NMR by comparison to PhTMS as internal standard. [b]Determined using chiral SFC.

Having determined optimized conditions for this reaction, we proceeded to evaluate the substrate scope. A wide range of aryl ketimines underwent enantioselective propargylation in high yield and >91% ee (Scheme 4.2). Ketimines containing electron-withdrawing groups formed products in excellent ee (**4.3a**). We found that several heterocycles were also tolerated in the reaction. Ketimines containing furan, thiophene, and benzothiophene functionalities reacted smoothly to provide the corresponding homopropargylic sulfonamides (**4.3c**–**e**) in high ee. The absolute configurations of **4.3b**, **4.3c**, and **4.3e** were determined by X-ray crystallographic analysis.[17]

[17] For supplementary crystallographic data, see the Experimental Section and CCDC 1405841, 1405894 and 1405895.

Scheme 4.2. Scope of diaryl sultams.

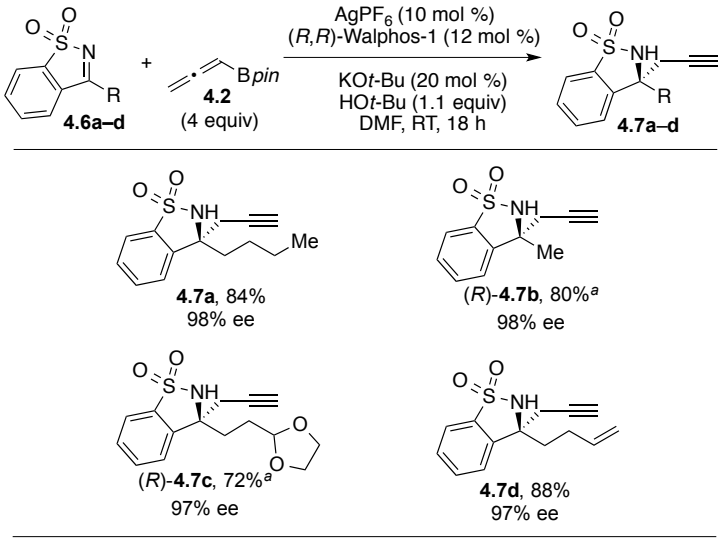


[a]Absolute configuration assigned by X-ray crystallographic analysis.[17] [b]Reaction performed for 6 hours.

We were gratified to find that alkyl ketimines were also well tolerated in the reaction (Scheme 4.3), since we were concerned that these substrates would tautomerize to enamines in the presence of potassium *tert*-butoxide. Several alkyl ketimines reacted to give homopropargylic products in excellent ee (**4**.**7a**–**c**). Furthermore, we found that other functional groups are compatible with this methodology: sultam **4.7c**, containing an acetal protecting group, was formed in high yield. The absolute configuration of **4.7c** was determined by X-ray crystallographic analysis.[18]

[18] For supplementary crystallographic data, see the Experimental Section and CCDC 1410049 and 1405843.

Scheme 4.3. Scope of alkyl sultams.



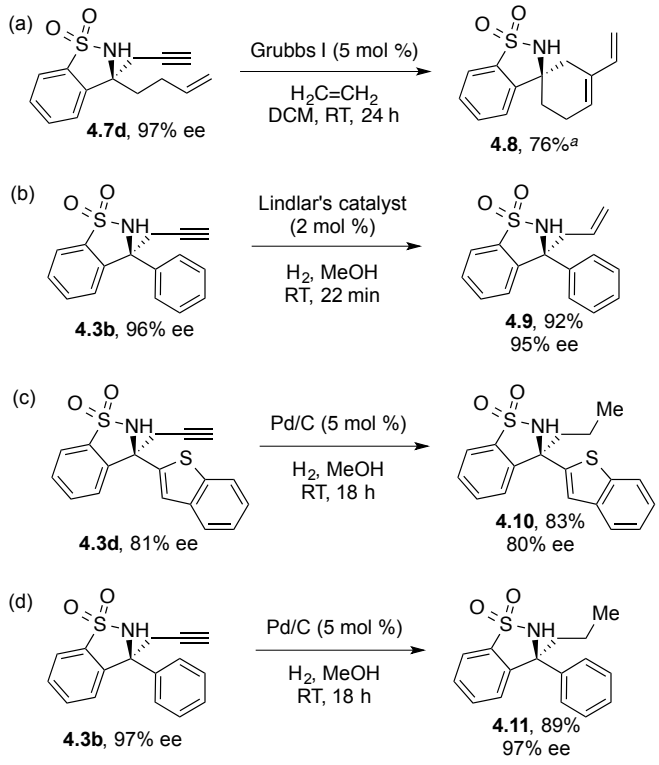
[a]Absolute configuration assigned by X-ray crystallographic analysis.[18]

4.3 Synthetic Transformations of Homopropargylic Sultams

To emphasize the utility of the pendant terminal alkyne, we synthesized derivatives of several alkyl and aryl homopropargylic sulfonamides (Scheme 4.4). We prepared compound **4.7d** for an enyne ring-closing metathesis (Scheme 4.4a).[19] In the presence of 5 mol % Grubbs I catalyst and under an atmosphere of ethylene, the desired spirocycle **4.8** was obtained in 76% yield. Lindlar reduction of **4.3a** provided the corresponding enantioenriched diaryl allyl sultam **4.9**, a moiety that has not been previously reported (Scheme 4.4b).[8e,20]

[19] Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317.
[20] For enantioselective allylation of alkyl cyclic *N*-sulfonyl ketimines, see: Hepburn, H. B.; Chotsaeng, N.; Luo, Y.; Lam, H. W. *Synthesis* **2013**, *45*, 2649.

Scheme 4.4. Synthetic transformations of homopropargylic sultams.



[a]Enantiomeric excess could not be determined using chiral SFC instrumentation.

We further highlighted the versatility of the alkyne moiety by reducing several alkynes to their corresponding alkanes. Alkyne **4.3d** was fully reduced to alkane **4.10** using palladium on carbon for 18 hours, without reduction of the cyclic benzylic sulfonamide (Scheme 4.4c). Likewise, reduction of **4.3b** afforded alkane **4.11** in 89% yield without racemization (Scheme 4.4d).

4.4 Mechanism of Propargylation

We sought to establish a reasonable mechanism for this propargylation reaction; two of the most likely possibilities are presented in Figure 4.1.[21] Our approach to distinguish between these mechanisms was to compare product distributions from reactions employing isomeric

[21] For a discussion of these mechanistic possibilities, including representative examples, see references 10a and 10b.

borolane reagents, allenyl borolane **4.2** and propargyl borolane **4.12**. Importantly, both mechanisms take into account our experimental observation that allenyl borolane **4.2** and propargyl borolane **4.12** are not in equilibrium under the reaction conditions during the time frame of the reaction (vide infra).

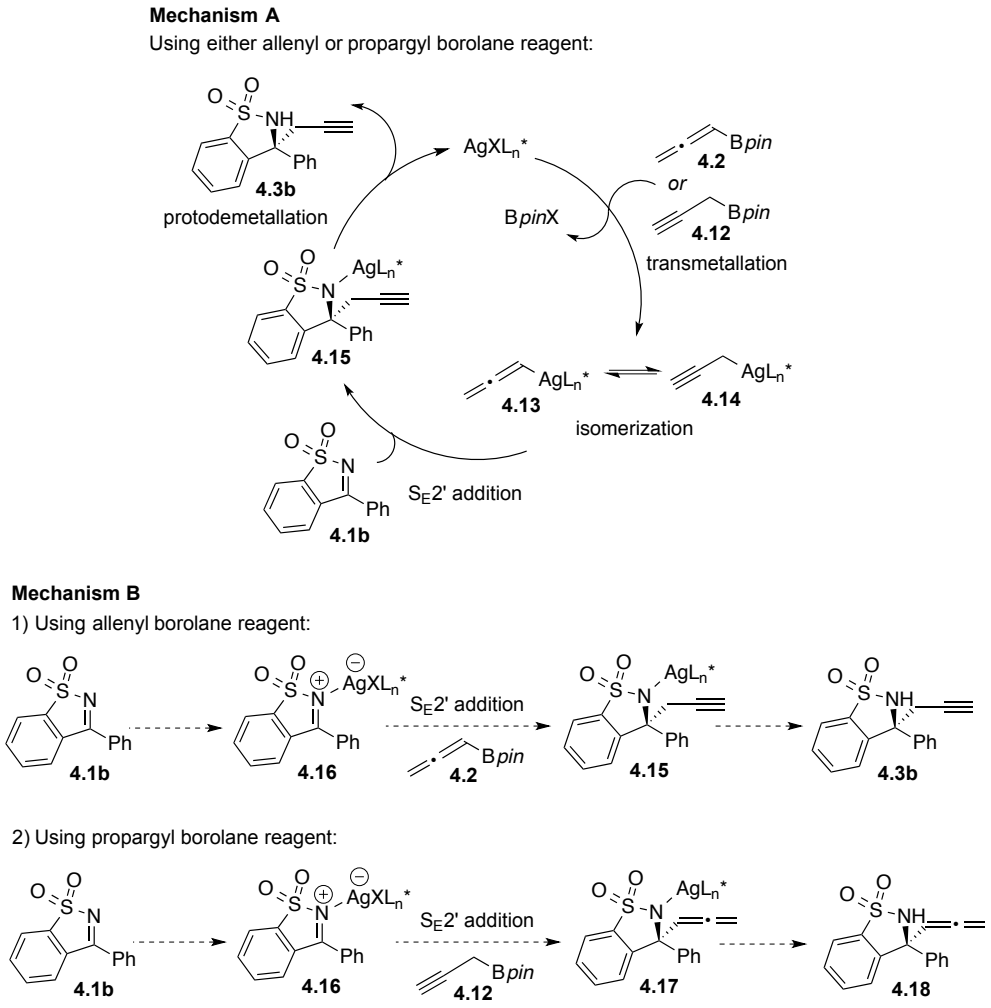


Figure 4.1. Possible mechanisms for silver-catalyzed propargylation reaction. (a) Proposed catalytic cycle involving transmetallation of silver catalyst with borolane reagent. (b) Lewis acid catalysis.

Mechanism A involves transmetallation and isomerization of the allenylmetal intermediates.[22] Transmetallation of the silver catalyst with the borolane reagent forms the key nucleophilic allenylsilver complex (**4.13**) in situ. Allenylsilver complex **4.13** is in equilibrium with propargylsilver complex **4.14**.[23,24] Addition of allenylsilver complex **4.13** to the ketimine via S_E2' mechanism is favored to form alkyne **4.3b**. Therefore, if Mechanism A is operative, using either allenyl borolane **4.2** or propargyl borolane **4.12** would result in formation of alkyne **4.3b** via equilibration of **4.13** and **4.14** (Figure 4.1a).

An alternative pathway is Mechanism B, involving direct addition of the borolane reagent to the ketimine.[10] In this scenario, the silver catalyst acts as a chiral Lewis acid in the reaction (Figure 4.1b-1). Coordination of the silver catalyst to form intermediate **4.16** followed by S_E2' addition of allenyl borolane **4.2** results in formation of alkyne **4.3b**. In this possible mechanism, isomerization of the allenyl- and propargylboron species is slower than attack on the activated electrophile (**4.16**). Therefore, using propargyl borolane **4.12** would provide a different product, allene **4.18** (Figure 4.1b-2).

[22] For selected examples of reactions that likely proceed through a similar mechanism, see: (a) Tamaru, Y.; Goto, S.; Tanaka, A.; Shimizu, N.; Kimura, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 878; (b) Hameury, T.; Guillemont, J.; Van Hijfte, L.; Bellosta, V.; Cossy, J. *Org. Lett.* **2009**, *11*, 2397; (c) Fandrick, D. R.; Saha, J.; Fandrick, K. R.; Sanyal, S.; Ogikubo, J.; Lee, H.; Roschangar, F.; Song, J. J.; Senanayake, C. H. *Org. Lett.* **2011**, *13*, 5616; (d) Fandrick, K. R.; Ogikubo, J.; Fandrick, D. R.; Patel, N. D.; Saha, J.; Lee, H.; Ma, S.; Grinberg, N.; Busacca, C. A.; Senanayake, C. H. *Org. Lett.* **2013**, *15*, 1214; (e) Mszar, N. W.; Haeffner, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 3362.

[23] For selected examples of isomerization of allenyl- and propargylmetal complexes, see: (a) Elsevier, C. J.; Kleijn, H.; Boersma, J.; Vermeer, P. *Organometallics* **1986**, *5*, 716; (b) Ogoshi, S.; Fukunishi, Y.; Tsutsumi, K.; Kurosawa, H. *J. Chem. Soc., Chem. Commun*. **1995**, 2485; (c) Ogoshi, S.; Nishida, T.; Fukunishi, Y.; Tsutsumi, K.; Kurosawa, H. *J. Organomet. Chem.* **2001**, *620*, 190.

[24] For examples in the context of palladium-catalyzed cross-coupling reactions, see: (a) Moriya, T.; Miyaura, N.; Suzuki, A. *Synlett* **1994**, 149; (b) Ma, S.; Zhang, A. *J. Org. Chem.* **2002**, *67*, 2287; (c) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.

To rule out one of these two mechanisms, we set out to examine reactions employing propargyl borolane **4.12**.[25] We synthesized **4.12** using a procedure recently published by Fandrick and co-workers, employing iodomethyl borolane **4.19** in a Matteson homologation in the presence of ethynylmagnesium bromide.[22c] This reaction proved extremely sensitive to trace moisture. All reagents and solvents were distilled over molecular sieves but additional attempts at the homologation reaction were plagued by isomerization to allenyl borolane **4.2**.[26] Excess Grignard reagent could catalyze bimolecular isomerization, so DMSO was added as a Lewis basic reagent to coordinate excess magnesium and prevent its chelation with the borolane.[27] To slow isomerization, the number of equivalents of Grignard reagent was scaled down to 0.95 equivalents; however, the reaction yielded primarily starting iodomethyl borolane **4.19**.[28] Further investigation of the effect of the number of equivalents of Grignard reagent on product formation showed a narrow range in which propargyl borolane **4.12** is the primary product of this reaction (Figure 4.2). The optimal number of equivalents of Grignard reagent was determined to be 1.02 equivalents ethynylmagnesium bromide, above which there is significant isomerization to allenyl borolane **4.2**, and below which almost no conversion was observed. The desired product was isolated in a 96:4 propargyl : allenyl ratio at 1.02 equivalents Grignard reagent.

[25] See reference 22c. A related strategy has been employed to elucidate the mechanistic details of transition-metal-catalyzed allylation reactions. See: (a) reference 14; (b) Shaghafi, M. B.; Kohn, B. L.; Jarvo, E. R. *Org. Lett.* **2008**, *10*, 4743.
[26] Soundararajan, R.; Li, G.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 8961.
[27] Fandrick, D. R.; *Personal communication*.
[28] Soundararajan, R.; Li, G.; Brown, H. C. *Tetrahedron Lett.* **1994**, *35*, 8957.

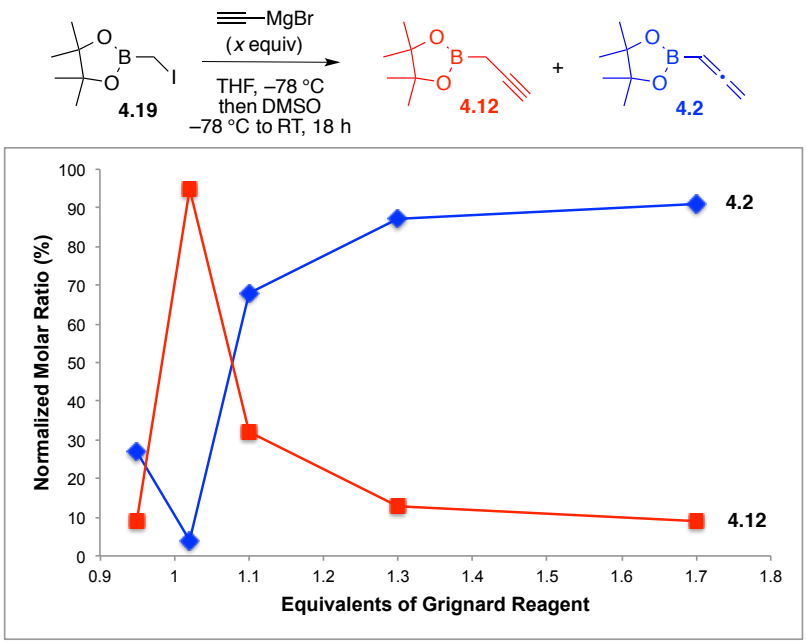
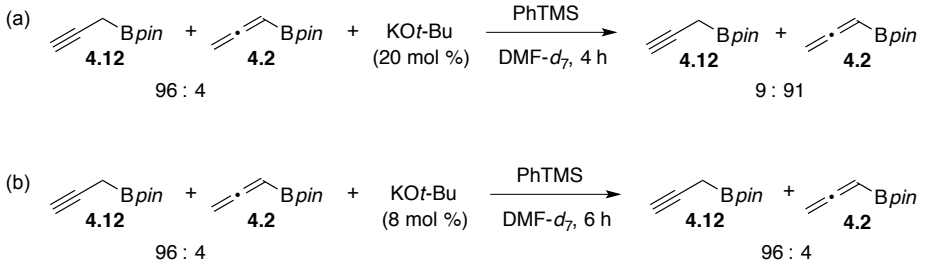


Figure 4.2. Isomerization of propargyl borolane **4.12** to allenyl borolane **4.2** in the presence of excess Grignard reagent.

Having established that excess Grignard reagent causes the isomerization of propargyl borolane **4.12** to allenyl borolane **4.2**, we reasoned that potassium *tert*-butoxide could also accelerate isomerization. We were concerned that equilibration might occur under the propargylation reaction conditions. To determine whether **4.12** could isomerize to **4.2** under the propargylation conditions, we performed control experiments employing different amounts of base. In the presence of 20 mol % potassium *tert*-butoxide, we observed the rapid isomerization of propargyl borolane **4.12** to allenyl borolane **4.2** (Scheme 4.5a). However, in the presence of 8 mol % potassium *tert*-butoxide, we observed no discernable isomerization after 6 hours (Scheme 4.5b).[29]

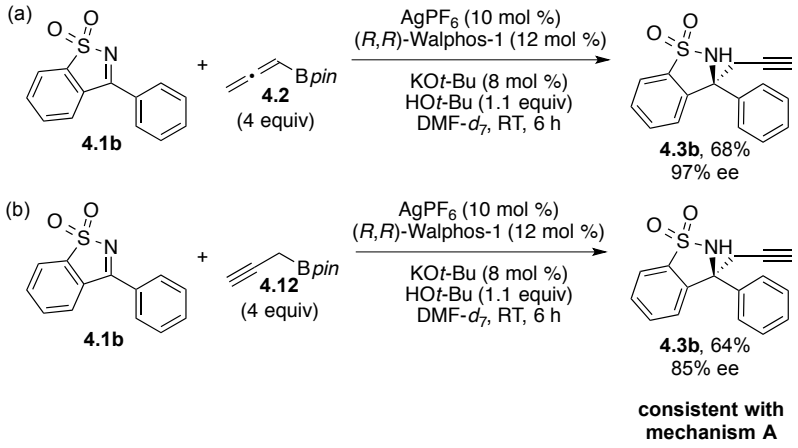
[29] See the Experimental Section for full details.

Scheme 4.5. Isomerization of propargyl borolane **4.12** to allenyl borolane **4.2** in the presence of (a) 20 mol % KO*t*-Bu, or (b) 8 mol % KO*t*-Bu.



With propargyl borolane **4.12** in hand, we performed the silver-catalyzed addition reaction to ketimine **4.1b**. Use of **4.12** in the reaction afforded alkyne **4.3b** in 64% yield (Scheme 4.6b). We found that the ee of the product remained high, with a slight decrease from 97% to 85% ee when using propargyl borolane **4.12**. Both allenyl borolane **4.2** and propargyl borolane **4.12** provide similar product distributions, most consistent with Mechanism A, where the silver catalyst undergoes transmetallation with the borolane reagent. The reaction was performed in deuterated DMF and the ratio of propargyl to allenyl borolane was analyzed by ^{1}H NMR directly from the reaction mixture. The ratio of **4.12**:**4.2** before the reaction was 96:4, and after the reaction it was 94:6. This observation is most consistent with negligible equilibration of **4.12** and **4.2** over the time course of the propargylation reactions.

Scheme 4.6. Silver-catalyzed propargylation reaction using (a) allenylboronic acid pinacol ester **4.2**, or (b) propargylboronic acid pinacol ester **4.12**.



4.5 Conclusions

We have developed an enantioselective silver-catalyzed propargylation reaction of cyclic *N*-sulfonyl ketimines. Using a catalyst prepared from $AgPF_6$ and Walphos-1, we found that many aryl and alkyl homopropargylic amines, including several heterocyclic products, were formed in high yield and excellent ee. Derivatization of the terminal alkyne yielded spirocyclic, alkenyl, or alkyl products. Mechanistic experiments employing propargyl borolane reagent are most consistent with a mechanism in which the silver catalyst undergoes transmetallation with the borolane reagent to generate a nucleophilic allenylboron reagent.

4.6 Experimental Details

General Procedures

NMR spectra were recorded on Bruker DRX-400 (400 MHz ^{1}H, 100 MHz ^{13}C, 376.5 MHz ^{19}F), GN-500 (500 MHz ^{1}H, 125.7 MHz ^{13}C, 160.2 MHz ^{11}B), or CRYO-500 (500 MHz

^{1}H, 125.7 MHz ^{13}C) spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal trimethylsilane (TMS, δ 0.00). Data are reported as follows: chemical shift (multiplicity [singlet (s), broad singlet (br s), doublet (d), apparent doublet (ad), doublet of doublets (dd), doublet of doublets of doublets (ddd), triplet (t), apparent triplet (at), doublet of triplets (dt), triplet of doublets (td), quartet (q), quintet (quint), apparent quintet of doublets (aquintd), sextet (sext), multiplet (m)], coupling constants [Hz], integration). Carbon chemical shifts are reported in ppm (δ) relative to TMS with the solvent resonance as the internal standard ($CDCl_3$, δ 77.16 ppm or DMF-d_7, δ 163.15 ppm). NMR data were collected at 25 °C. Infrared spectra were obtained on a Thermo Scientific Nicolet iS5 spectrometer with an iD5 ATR tip (neat) and are reported in terms of frequency of absorption (cm^{-1}). Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60Å F254 precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with *p*-anisaldehyde (PAA) or potassium permanganate ($KMnO_4$) solutions. Flash chromatography was performed using Silica Gel 60 (170-400 mesh) from Fisher Scientific. Melting points (m.p.) were obtained using a Mel-Temp melting point apparatus and are uncorrected. Optical rotations were measured with a Rudolph Research Analytical Autopol III Automatic Polarimeter. SFC determinations of enantiopurity were performed on a Berger Analytical instrument using a Daicel™ Chiralpak® column (OD-H, AD-H, AS-H, or (*R*,*R*)-Whelk-O); 100 bar, 215 nm, 50 °C). High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center.

All reactions were carried out under a N_2 atmosphere, unless otherwise stated. All glassware was either oven-dried or flame-dried prior to use. *N*,*N*-Dimethylformamide (DMF), tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (DCM), triethylamine (TEA),

methanol (MeOH), and *N*,*N*-dimethylacetamide (DMA) were degassed with argon and then passed through two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 °C for 12 hours) to remove H_2O. Other solvents were purchased "anhydrous" commercially, or were purified as described.

$AgPF_6$ was purchased as a white powder from Strem, stored in the dark in a glove box under an atmosphere of N_2, and discarded upon turning to a brown powder.

(*R*,*R*)-Walphos W001-1 was purchased from Strem or Acros, stored in a glove box under an atmosphere of N_2, and used as received. All other ligands were purchased from Strem or Sigma Aldrich and were stored under N_2 atmosphere and used as received.

Saccharin was purchased from Sigma Aldrich and used as received. All Grignard reagents were titrated with iodine prior to use.[30] *n*-Butyllithium and methyllithium solutions were purchased from Acros, stored at 4 °C, and titrated prior to use.[31]

tert-Butanol was purchased from Fisher and distilled every two weeks over CaH_2 through a short-path distillation head onto activated 4Å mol sieves.

Allenylboronic acid pinacol ester **4.2** was prepared according to Yoshida and co-workers[32] and distilled every month.

Propargylboronic acid pinacol ester **4.12** was prepared according to Fandrick and co-workers (vide infra).[22c] Ethynylmagnesium bromide was purchased from Sigma Aldrich, stored at 4 °C, and used within one week of opening the bottle.

N,*N*-Dimethylformamide-d_7 was purchased from Cambridge Isotope Laboratories and used as received.

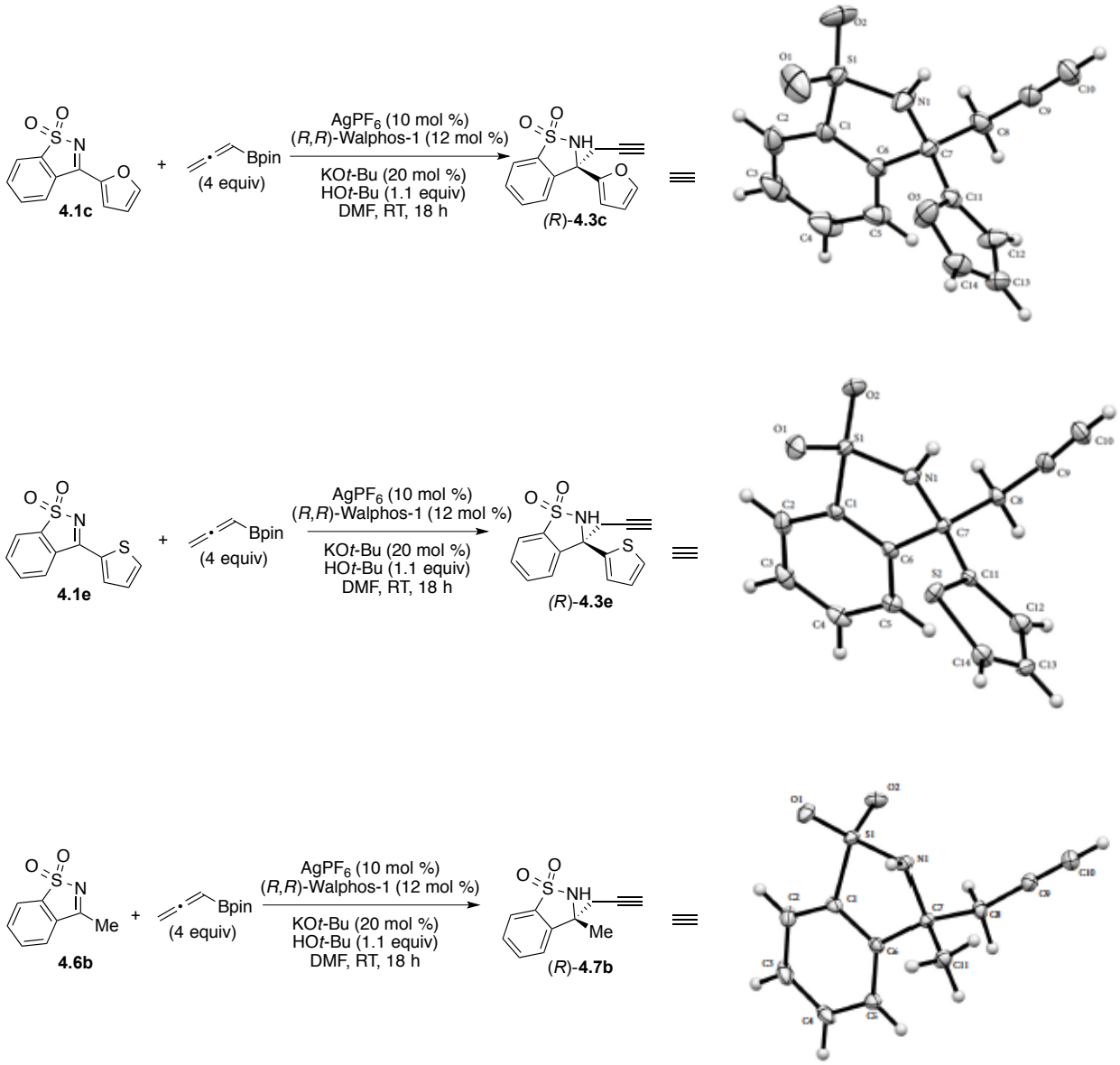
All other chemicals were purchased commercially and used as received.

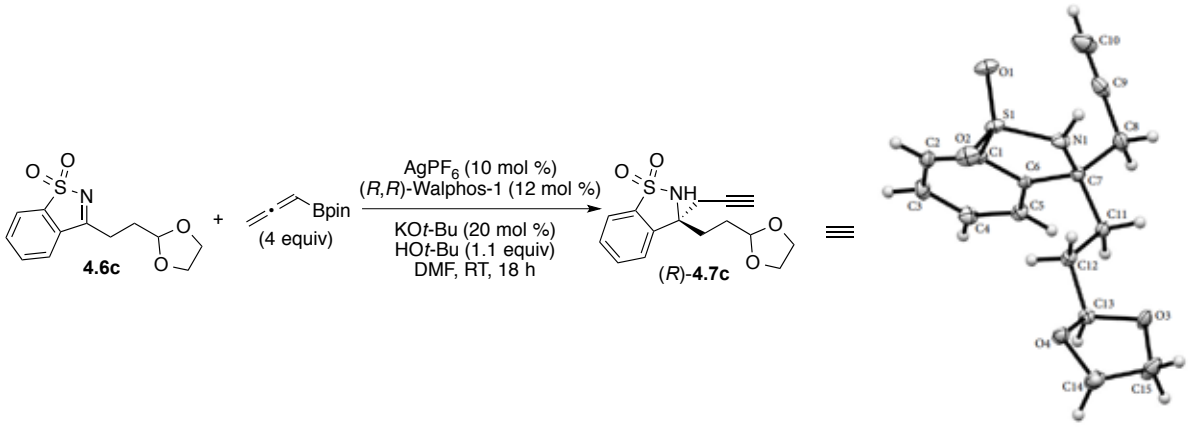
[30] Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *5*, 890.
[31] Love, B. E.; Jones, E. G. *J. Org. Chem.* **1999**, *64*, 3755.
[32] Tonogaki, K.; Itami, K.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2006**, *128*, 1464.

Stereochemical Proofs

The absolute configurations of products **4.3c**, **4.3e**, **4.7b**, and **4.7c** were assigned by X-ray crystallographic analysis (Scheme 4.7). The absolute configurations of all other products were assigned by analogy.

Scheme 4.7. Absolute configurations of products determined by X-ray crystallography.

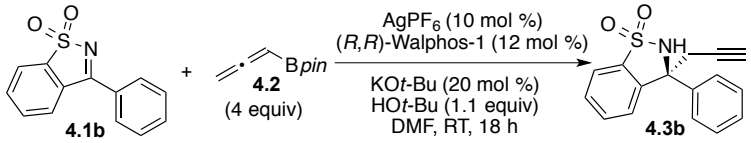




Representative Addition Procedures

Method A: Enantioselective Addition to Ketimines

Note: All manipulations involving silver-catalyzed reactions were performed in the absence of direct light, using vials wrapped in aluminum foil.



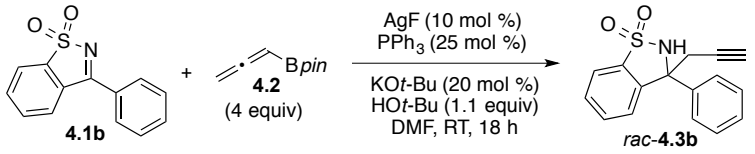
In a glovebox, an oven-dried 1.0 mL conical vial equipped with a triangular stir bar was charged with $AgPF_6$ (5.0 mg, 0.020 mmol, 0.10 equiv) and Walphos W001-1 (22.3 mg, 0.0240 mmol, 0.120 equiv). The vial was sealed with a screw-top cap fit with a septum and removed from the glovebox. Anhydrous DMF (400 μL) was added and the solution was stirred for 5 min at RT. The N_2 line was then removed and the solution was stirred for 30 min at 70 °C, then cooled to RT over 15 min.

To the catalyst solution was added *tert*-butanol (21 μL, 0.22 mmol, 1.1 equiv), followed by potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv) and phenyl ketimine **4.1b** (48.6 mg, 0.200 mmol, 1.00 equiv) under a flow of N_2. The reaction was stirred at RT for 5 min to dissolve the ketimine. Allenylboronic acid pinacol ester **4.2** (72 μL, 0.40 mmol, 2.0 equiv) was

added via syringe, followed by another portion of allenylboronic acid pincol ester (72 μL, 0.40 mmol, 2.0 equiv) added via slow addition over 3 h using a syringe pump. The N_2 line was removed and the reaction was stirred at 22 °C for 18 h. The reaction mixture was filtered through a plug of silica gel eluting with 100% Et_2O to remove the catalyst. Et_2O was removed in vacuo and the resulting residue was purified by silica gel chromatography.

Method B: Racemic Standards

Note: All manipulations involving silver-catalyzed reactions were performed in the absence of direct light, using vials wrapped in aluminum foil.



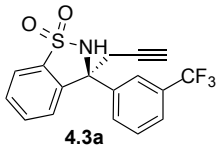
In a glovebox, a flame-dried 7 mL vial equipped with a stir bar was charged with AgF (2.5 mg, 0.020 mmol, 0.10 equiv) and PPh_3 (13 mg, 0.050 mmol, 0.25 equiv). The vial was sealed with a screw-top cap fit with a septum and removed from the glovebox. Anhydrous DMF (800 μL) was added and the solution was stirred for 5 min at RT. The N_2 line was then removed and the solution was stirred for 30 min at 70 °C, then cooled to RT over 15 min.

To the catalyst solution was added *tert*-butanol (21 μL, 0.22 mmol, 1.1 equiv), followed by potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv) and phenyl ketimine **4.1b** (48.6 mg, 0.200 mmol, 1.00 equiv) under a flow of N_2. The reaction was stirred at RT for 5 min to dissolve the ketimine. Allenylboronic acid pinacol ester **4.2** (72 μL, 0.40 mmol, 2.0 equiv) was added via syringe. The N_2 line was removed and the reaction was stirred at 22 °C for 18 h. The reaction mixture was filtered through a plug of silica gel eluting with 100% Et_2O to remove the

catalyst. Et_2O was removed in vacuo and the resulting residue was purified by silica gel chromatography.

Characterization Data for Products

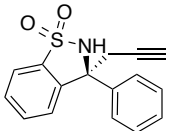
Note: The yield of homoallenylic sultam is typically less than 5–10% in these reactions and can be separated from the homopropargylic sultam using the column chromatography conditions specified below. The TLC R_f of the homoallenylic sultam is generally 0.1 higher than the R_f of the homopropargylic sultam. The diagnostic peaks for the homoallenylic sultam are found in the ^{1}H NMR range of δ 5.96 to 5.48 (t, J = 6.6 Hz, 1H) and δ 5.11 to 5.01 (d, J = 6.6 Hz, 2H).



4.3a

Sultam 4.3a was prepared according to Method A, using the following amounts of reagents: $AgPF_6$ (5.0 mg, 0.020 mmol, 0.10 equiv), Walphos W001-1 (22.3 mg, 0.0240 mmol, 0.120 equiv), *tert*-butanol (21 μL, 0.22 mmol, 1.1 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), substrate **4.1a** (62.3 mg, 0.200 mmol, 1.00 equiv), DMF (400 μL), and allenylboronic acid pincol ester (144 μL, 0.800 mmol, 4.00 equiv). The resulting mixture was purified by flash column chromatography using 0–1% TEA/benzene to separate product from unreacted starting material. The mixture was purified again by flash column chromatography using 5–10–20% EtOAc/hexanes (1% TEA) to separate product from excess ligand and afford the title compound as a beige solid (49.8 mg, 0.142 mmol, 71%, 97% ee). **TLC R_f** = 0.1 (20% EtOAc/hexanes, stains pink with PAA); **m.p.** = 125–127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85–7.82 (m, 2H), 7.78 (d, J = 7.9 Hz, 1H), 7.70–7.58 (m, 3H), 7.52 (t, J = 7.9 Hz, 1H), 7.37 (d,

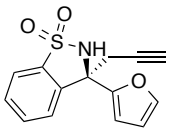
J = 7.9 Hz, 1H), 5.35 (br s, 1H), 3.32 (dd, J = 17.3, 2.7 Hz, 1H), 3.24 (dd, J = 17.3, 2.7 Hz, 1H), 2.10 (t, J = 2.7 Hz, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 141.6, 141.5, 135.1, 133.8, 131.4 (q, J = 32.4 Hz), 130.4, 130.3, 129.8, 125.6 (q, J = 3.7 Hz), 124.6, 123.9 (q, J = 272.4 Hz), 123.3 (q, J = 4.0 Hz), 121.8, 77.7, 73.9, 66.7, 31.5; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –62.6; **IR** (neat) 3302, 1329, 1164, 1125, 731 cm^{-1}; **HRMS** (TOF MS ES+) m/z calcd for $C_{17}H_{12}F_3NO_2S$ $(M + Na)^+$ 374.0439, found 374.0433; **$[\alpha]^{26}_D$** +47 (c 1.2, $CDCl_3$); **SFC** analysis (Whelk-O (R,R), 5% IPA, 3.0 mL/min, 215 nm) indicated 97% ee: t_R (minor) = 10.8 min, t_R (major) = 11.3 min.



(*S*)-**4.3b**

Sultam (*S*)-4.3b was prepared according to Method A, using the following amounts of reagents: $AgPF_6$ (5.0 mg, 0.020 mmol, 0.10 equiv), Walphos W001-1 (22.3 mg, 0.0240 mmol, 0.120 equiv), *tert*-butanol (21 μL, 0.22 mmol, 1.1 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), substrate **4.1b** (48.6 mg, 0.200 mmol, 1.00 equiv), DMF (400 μL), and allenylboronic acid pincol ester (144 μL, 0.800 mmol, 4.00 equiv). The resulting mixture was purified by flash column chromatography using 0–1% TEA/benzene to separate product from unreacted starting material. The mixture was purified again by flash column chromatography using 5–10–20% EtOAc/hexanes (1% TEA) to separate product from excess ligand and afford the title compound as a white solid (39.3 mg, 0.139 mmol, 69%, 97% ee). **TLC R_f** = 0.2 (20% EtOAc/hexanes, stains pink with PAA); **m.p.** = 139–142 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (ad, J = 7.3 Hz, 1H), 7.62–7.53 (m, 4H), 7.41–7.30 (m, 4H), 5.23 (br s, 1H), 3.30 (dd, J = 17.2, 2.6 Hz, 1H), 3.24 (dd, J = 17.2, 2.6 Hz, 1H), 2.06 (t, J = 2.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.3, 140.4, 135.0, 133.5, 130.0, 129.1, 128.7, 126.6, 125.0, 121.5, 78.5, 73.3, 67.1,

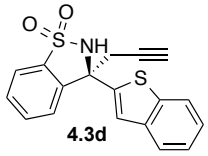
31.3; **IR** (neat) 3286, 2923, 1713, 1293, 1165 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{16}H_{13}NO_2S$ $(M + Na)^+$ 306.0565, found 306.0564; $[\alpha]^{24}_D$ +42 (*c* 0.7, $CHCl_3$); **SFC** analysis (OD-H, 10% IPA, 3.0 mL/min, 215 nm) indicated 97% ee: t_R (minor) = 11.5 min, t_R (major) = 14.3 min.



(*R*)-**4.3c**

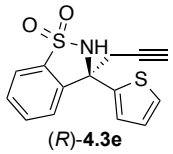
Sultam (*R*)-4.3c was prepared according to Method A, using the following amounts of reagents: $AgPF_6$ (5.0 mg, 0.020 mmol, 0.10 equiv), Walphos W001-1 (22.3 mg, 0.0240 mmol, 0.120 equiv), *tert*-butanol (21 μL, 0.22 mmol, 1.1 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), substrate **4.1c** (46.6 mg, 0.200 mmol, 1.00 equiv), DMF (400 μL), and allenylboronic acid pincol ester (144 μL, 0.800 mmol, 4.00 equiv). The resulting mixture was purified by flash column chromatography using 0–1% TEA/benzene to separate product from unreacted starting material. The mixture was purified again by flash column chromatography using 5–20–40% EtOAc/hexanes (1% TEA) to separate product from excess ligand and afford the title compound as a white solid (35.4 mg, 0.130 mmol, 65%, 94% ee). **TLC** $\mathbf{R_f}$ = 0.3 (20% EtOAc/hexanes, stains purple with PAA); **m.p.** = 126–127 °C; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.6 Hz, 1H), 7.66 (td, *J* = 7.6, 1.1 Hz, 1H), 7.60–7.58 (m, 2H), 7.40 (d, *J* = 1.1 Hz, 1H), 6.48 (d, *J* = 3.3 Hz, 1H), 6.35 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.29 (br s, 1H), 3.25 (dd, *J* = 17.0, 2.6 Hz, 1H), 3.19 (dd, *J* = 17.0, 2.6 Hz, 1H), 2.07 (t, *J* = 2.6 Hz, 1H); ^{13}**C NMR** (125.7 MHz, $CDCl_3$) δ 152.1, 143.6, 139.7, 135.2, 133.5, 130.4, 124.8, 121.5, 110.8, 108.8, 77.8, 73.1, 63.3, 30.6; **IR** (neat) 3283, 1295, 1166, 1132, 735 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{14}H_{11}NO_3S$ $(M + Na)^+$ 296.0357, found 296.0363; $[\alpha]^{26}_D$ +7.0 (*c* 1.0, $CDCl_3$); **SFC** analysis

(OD-H, 10% IPA, 3.0 mL/min, 215 nm) indicated 94% ee: t_R (minor) = 7.2 min, t_R (major) = 8.6 min.



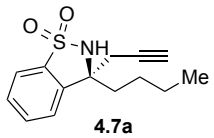
4.3d

Sultam 4.3d was prepared according to Method A, using the following amounts of reagents: $AgPF_6$ (5.0 mg, 0.020 mmol, 0.10 equiv), Walphos W001-1 (22.3 mg, 0.0240 mmol, 0.120 equiv), *tert*-butanol (21 μL, 0.22 mmol, 1.1 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), substrate **4.1d** (59.9 mg, 0.200 mmol, 1.00 equiv), DMF (400 μL), and allenylboronic acid pincol ester (144 μL, 0.800 mmol, 4.00 equiv). The resulting mixture was purified by flash column chromatography using 0–1% TEA/benzene to separate product from unreacted starting material. The mixture was purified again by flash column chromatography using 5–10–20% EtOAc/hexanes (1% TEA) to separate product from excess ligand and afford the title compound as a pale yellow oil (46.7 mg, 0.138 mmol, 69%, 91% ee). **TLC** $\mathbf{R_f}$ = 0.3 (20% EtOAc/hexanes, stains purple with PAA); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.8 Hz, 1H), 7.77–7.73 (m, 2H), 7.67 (td, *J* = 7.6, 1.1 Hz, 1H), 7.62–7.56 (m, 2H), 7.45 (s, 1H), 7.34 (aquintd, *J* = 7.5, 1.4 Hz, 2H), 5.44 (s, 1H), 3.36 (dd, *J* = 17.1, 2.7 Hz, 1H), 3.29 (dd, *J* = 17.1, 2.7 Hz, 1H), 2.12 (t, *J* = 2.7 Hz, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 145.5, 141.0, 139.9, 139.3, 134.9, 133.7, 130.5, 125.3, 124.9, 124.8, 124.3, 123.0, 122.5, 121.7, 77.8, 73.8, 65.4, 32.8; **IR** (neat) 3288, 1294, 1166, 1131, 726 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{18}H_{13}NO_2S_2$ $(M + Na)^+$ 362.0285, found 362.0279; $\mathbf{[\alpha]^{28}_D}$ +17 (*c* 1.1, $CDCl_3$); **SFC** analysis (AS-H, 20% IPA, 3.0 mL/min, 215 nm) indicated 91% ee: t_R (major) = 11.0 min, t_R (minor) = 16.5 min.



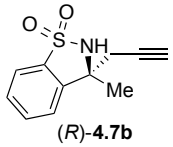
(*R*)-**4.3e**

Sultam (*R*)-4.3e was prepared according to Method A, using the following amounts of reagents: $AgPF_6$ (5.0 mg, 0.020 mmol, 0.10 equiv), Walphos W001-1 (22.3 mg, 0.0240 mmol, 0.120 equiv), *tert*-butanol (21 μL, 0.22 mmol, 1.1 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), substrate **4.1e** (49.9 mg, 0.200 mmol, 1.00 equiv), DMF (400 μL), and allenylboronic acid pincol ester (144 μL, 0.800 mmol, 4.00 equiv). The resulting mixture was purified by flash column chromatography using 0–1% TEA/benzene to separate product from unreacted starting material. The mixture was purified again by flash column chromatography using 5–10–20% EtOAc/hexanes (1% TEA) to separate product from excess ligand and afford the title compound as a yellow solid (51.3 mg, 0.177 mmol, 89%, 94% ee). **TLC** $\mathbf{R_f}$ = 0.3 (20% EtOAc/hexanes, stains purple with PAA); **m.p.** = 155–157 °C; $^{\mathbf{1}}$**H NMR** (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.7 Hz, 1H), 7.66 (td, *J* = 7.6, 1.3 Hz, 1H), 7.59 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.30 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.18 (dd, *J* = 3.7, 1.3 Hz, 1H), 6.98 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.34 (br s, 1H), 3.27 (d, *J* = 2.6 Hz, 2H), 2.09 (t, *J* = 2.6 Hz, 1H); $^{\mathbf{13}}$**C NMR** (125.7 MHz, $CDCl_3$) δ 145.1, 141.6, 135.0, 133.6, 130.3, 127.4, 126.6, 126.2, 124.8, 121.5, 78.0, 73.5, 65.0, 33.2; **IR** (neat) 3305, 2925, 1302, 1168, 906, 728 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{14}H_{11}NO_2S_2$ $(M + Na)^+$ 312.0129, found 312.0142; $\mathbf{[\alpha]^{28}_D}$ –12 (*c* 0.9, $CDCl_3$); **SFC** analysis (OD-H, 10% IPA, 3.0 mL/min, 215 nm) indicated 94% ee: t_R (minor) = 12.5 min, t_R (major) = 15.7 min.



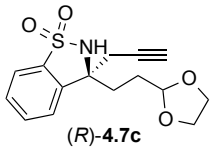
4.7a

Sultam 4.7a was prepared according to Method A, using the following amounts of reagents: $AgPF_6$ (5.0 mg, 0.020 mmol, 0.10 equiv), Walphos W001-1 (22.3 mg, 0.0240 mmol, 0.120 equiv), *tert*-butanol (21 μL, 0.22 mmol, 1.1 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), substrate **4.6a** (44.7 mg, 0.200 mmol, 1.00 equiv), DMF (400 μL), and allenylboronic acid pincol ester (144 μL, 0.800 mmol, 4.00 equiv). The resulting mixture was purified by flash column chromatography using 0–1% TEA/benzene to separate product from unreacted starting material. The mixture was purified again by flash column chromatography using 5–10% EtOAc/hexanes (1% TEA) to separate product from excess ligand and afford the title compound as a colorless oil (44.3 mg, 0.168 mmol, 84%, 98% ee). **TLC** $\mathbf{R_f}$ = 0.6 (20% EtOAc/hexanes, stains pink with PAA); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.6, 1.0 Hz, 1H), 7.56 (t, *J* = 7.7, 0.9 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 4.87 (s, 1H), 2.82 (dd, *J* = 16.9, 2.7 Hz, 1H), 2.77 (dd, *J* = 16.9, 2.7 Hz, 1H), 2.13 (t, *J* = 2.7 Hz, 1H), 2.14–2.08 (m, 1H), 2.02–1.96 (m, 1H), 1.45–1.35 (m, 1H), 1.34–1.24 (m, 2H), 1.04–0.96 (m, 1H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}**C NMR** (125.7 MHz, $CDCl_3$) δ 141.9, 135.8, 133.4, 129.8, 123.6, 121.6, 78.8, 72.8, 65.2, 38.5, 31.8, 25.8, 22.7, 14.0; **IR** (neat) 3306, 2959, 1289, 1168, 907, 728 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{14}H_{17}NO_2S$ $(M + Na)^+$ 286.0878, found 286.0884; $\mathbf{[\alpha]^{28}_D}$ –2.4 (*c* 1.1, $CDCl_3$); **SFC** analysis (AS-H, 10% IPA, 3.0 mL/min, 215 nm) indicated 98% ee: t_R (major) = 7.5 min, t_R (minor) = 8.3 min.



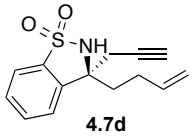
(*R*)-**4.7b**

Sultam (*R*)-4.7b was prepared according to Method A, using the following amounts of reagents: $AgPF_6$ (5.0 mg, 0.020 mmol, 0.10 equiv), Walphos W001-1 (22.3 mg, 0.0240 mmol, 0.120 equiv), *tert*-butanol (21 μL, 0.22 mmol, 1.1 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), substrate **4.6b** (36.2 mg, 0.200 mmol, 1.00 equiv), DMF (400 μL), and allenylboronic acid pincol ester (144 μL, 0.800 mmol, 4.00 equiv). The resulting mixture was purified by flash column chromatography using 0–1% TEA/benzene to separate product from unreacted starting material. The mixture was purified again by flash column chromatography using 5–10–20% EtOAc/hexanes (1% TEA) to separate product from excess ligand and afford the title compound as a white solid (35.7 mg, 0.161 mmol, 80%, 98% ee). **TLC R_f** = 0.3 (20% EtOAc/hexanes, stains pink with PAA); **m.p.** = 91–93 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 1H), 7.65 (td, *J* = 7.8, 1.1 Hz, 1H), 7.56 (td, *J* = 7.7, 1.0 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 4.93 (s, 1H), 2.82 (dd, *J* = 17.0, 2.7 Hz, 1H), 2.77 (dd, *J* = 17.0, 2.7 Hz, 1H), 2.15 (t, *J* = 2.7 Hz, 1H), 1.76 (s, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 143.3, 135.6, 133.5, 129.8, 123.4, 121.5, 78.8, 72.7, 62.0, 32.6, 26.9; **IR** (neat) 3274, 2980, 2342, 1281, 1156, 1132 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{11}H_{11}NO_2S$ $(M + Na)^+$ 244.0408, found 244.0410; **$[\alpha]^{27}_D$** +16 (*c* 0.9, $CDCl_3$); **SFC** analysis (OD-H, 10% IPA, 3.0 mL/min, 215 nm) indicated 98% ee: t_R (minor) = 5.8 min, t_R (major) = 6.3 min.



(*R*)-**4.7c**

Sultam (*R*)-4.7c was prepared according to Method A, using the following amounts of reagents: $AgPF_6$ (5.0 mg, 0.020 mmol, 0.10 equiv), Walphos W001-1 (22.3 mg, 0.0240 mmol, 0.120 equiv), *tert*-butanol (21 μL, 0.22 mmol, 1.1 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), substrate **4.6c** (53.5 mg, 0.200 mmol, 1.00 equiv), DMF (400 μL), and allenylboronic acid pincol ester (144 μL, 0.800 mmol, 4.00 equiv). The resulting mixture was purified by flash column chromatography using 0–1% TEA/benzene to separate product from unreacted starting material. The mixture was purified again by flash column chromatography using 10–20–30% EtOAc/hexanes (1% TEA) to separate product from excess ligand and afford the title compound as a white solid (43.9 mg, 0.143 mmol, 72%, 97% ee). **TLC R_f** = 0.2 (20% EtOAc/hexanes, stains yellow then pink with PAA); **m.p.** = 128–129 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.57–7.53 (m, 2H), 5.86 (s, 1H), 4.87 (t, *J* = 3.8 Hz, 1H), 4.03–3.95 (m, 2H), 3.91–3.83 (m, 2H), 2.83 (dd, *J* = 17.0, 2.7 Hz, 1H), 2.77 (dd, *J* = 17.0, 2.7 Hz, 1H), 2.33–2.20 (m, 2H), 2.14 (t, *J* = 2.7 Hz, 1H), 1.70–1.63 (m, 1H), 1.62–1.56 (m, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 141.7, 136.4, 133.3, 129.9, 123.8, 121.5, 103.2, 79.0, 72.7, 65.3, 65.2, 64.6, 32.4, 31.1, 27.5; **IR** (neat) 3269, 2890, 1286, 1164, 1131, 729 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{15}H_{17}NO_4S$ $(M + Na)^+$ 330.0776, found 330.0781; **$[\alpha]^{27}_D$** –26 (*c* 1.2, $CDCl_3$); **SFC** analysis (AS-H, 10% IPA, 3.0 mL/min, 215 nm) indicated 97% ee: t_R (major) = 12.4 min, t_R (minor) = 13.8 min.



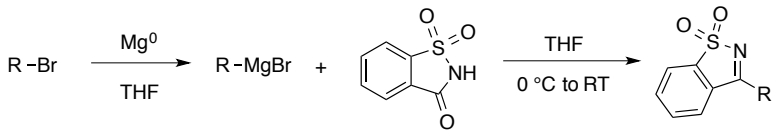
4.7d

Sultam 4.7d was prepared according to Method A, using the following amounts of reagents: $AgPF_6$ (5.0 mg, 0.020 mmol, 0.10 equiv), Walphos W001-1 (22.3 mg, 0.0240 mmol, 0.120 equiv), *tert*-butanol (21 μL, 0.22 mmol, 1.1 equiv), potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv), substrate **4.6d** (44.3 mg, 0.200 mmol, 1.00 equiv), DMF (400 μL), and allenylboronic acid pincol ester (144 μL, 0.800 mmol, 4.00 equiv). The resulting mixture was purified by flash column chromatography using 0–1% TEA/benzene to separate product from unreacted starting material. The mixture was purified again by flash column chromatography using 5–10% EtOAc/hexanes (1% TEA) to separate product from excess ligand and afford the title compound as a white solid (46.2 mg, 0.177 mmol, 88%, 97% ee). **TLC R_f** = 0.4 (20% EtOAc/hexanes, stains pink with PAA); **m.p.** = 80–81 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.66 (td, *J* = 7.6, 1.3 Hz, 1H), 7.57 (td, *J* = 7.6, 1.0 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 5.79–5.69 (m, 1H), 5.02–4.93 (m, 3H), 2.86–2.76 (m, 2H), 2.27–2.16 (m, 2H), 2.15 (t, *J* = 2.6 Hz, 1H), 2.13–2.05 (m, 1H), 1.87–1.76 (m, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 141.4, 137.0, 135.8, 133.4, 129.9, 123.6, 121.6, 115.7, 78.6, 72.9, 65.0, 37.8, 32.0, 28.0; **IR** (neat) 3273, 1285, 1165, 1131, 730 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{14}H_{15}NO_2S$ $(M + Na)^+$ 284.0721, found 284.0728; **$[\alpha]^{24}_D$** +0.5 (*c* 1.3, $CDCl_3$); **SFC** analysis (AS-H, 10% IPA, 3.0 mL/min, 215 nm) indicated 97% ee: t_R (major) = 7.5 min, t_R (minor) = 8.6 min.

General Procedures for Starting Material Synthesis

Note: When possible, Method D was preferentially used instead of Method C in order to minimize side reactions and obtain reaction mixtures that were easier to purify. The yields for starting material synthesis are unoptimized.

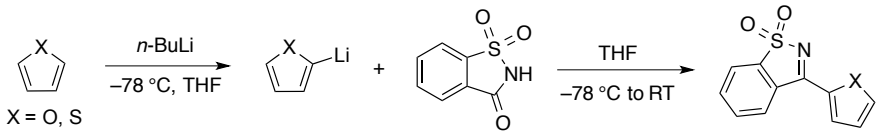
Method C: Grignard Addition into Saccharin



Prepared according to a modified procedure described by Hayashi and co-workers.[6c] The Grignard reagent was typically prepared using flame-dried magnesium turnings (2.0 equiv) with a few crystals of I_2 in anhydrous THF (10 mL). The aryl halide (1.0 equiv) was added to the solution until initiation of the Grignard reagent, after which the remaining aryl halide was added dropwise at 0 °C. The reaction was stirred 2 h at RT, then titrated.[30]

The Grignard reagent (2.0 equiv) was then slowly added to a solution of saccharin (1.0 equiv) in THF (6 mL) at 0 °C. The reaction was allowed to warm to RT and stirred at 22 °C overnight. The reaction was quenched at 0 °C with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified either by recrystallization (if the unpurified material was already crystalline) or by flash column chromatography using silica gel (generally, the unpurified material was first adsorbed onto silica).

Method D: Organolithium Addition into Saccharin

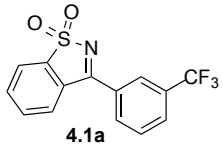


Prepared according to a modifed procedure described by Bode and co-workers.[6b] The organolithium reagent was typically prepared by slow addition *n*-butyllithium (2.75 equiv) to a solution of heterocycle (2.5 equiv) in anhydrous THF (10 mL) at –78 °C. The reaction was stirred at –78 °C for 15 min then used directly in the next step.

To this mixture was slowly added a solution of saccharin (1.0 equiv) in THF (6 mL) via syringe at –78 °C. The reaction was allowed to warm to RT slowly over several hours, then stirred at 22 °C overnight. The reaction was quenched at 0 °C with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified either by recrystallization (if the unpurified material was already crystalline) or by flash column chromatography using silica gel (generally, the unpurified material was first adsorbed onto silica).

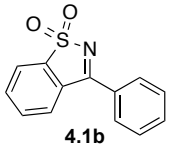
Note: In the case of compounds **4.6a** or **4.6b**, *n*-butyllithium or methyllithium (2.2 equiv) was slowly added directly to a solution of saccharin (1.0 equiv) in THF at –78 °C.

Characterization Data for Starting Materials



4.1a

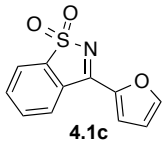
***N*-Sulfonyl ketimine 4.1a** was prepared according Method C, using the following amounts of reagents: saccharin (0.46 g, 2.5 mmol, 1.0 equiv), (3-(trifluoromethyl)phenyl)magnesium iodide (4.00 mL, 5.00 mmol, 1.25 M in THF, 2.00 equiv) and THF (2.5 mL). The product was recrystallized from hot Et_2O in $CHCl_3$ (1:1 $Et_2O/CHCl_3$) to afford the title compound as a pale yellow solid (0.21 g, 0.68 mmol, 27%). **TLC R_f** = 0.4 (20% EtOAc/hexanes, UV active); **m.p.** = 154–156 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.84–7.81 (m, 2H), 7.80–7.76 (m, 2H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 169.9, 141.3, 134.1, 133.9, 132.7, 132.2 (q, *J* = 33.3 Hz), 131.5, 130.14, 130.09, 129.9 (q, *J* = 3.7 Hz), 126.4 (q, *J* = 3.7 Hz), 126.3, 123.55, 123.54 (q, *J* = 272.8 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ –62.9; **IR** (neat) 1614, 1325, 1281, 1166, 1123 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{14}H_8F_3NO_2S$ $(M + Na)^+$ 334.0125, found 334.0131.



4.1b

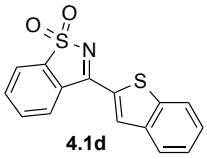
***N*-Sulfonyl ketimine 4.1b** was prepared according Method C, using the following amounts of reagents: saccharin (1.10 g, 6.00 mmol, 1.00 equiv), phenylmagnesium bromide (6.0 mL, 12 mmol, 2.0 M in THF, 2.0 equiv) and THF (25 mL). The product was recrystallized from hot Et_2O in $CHCl_3$ (1:1 $Et_2O/CHCl_3$) to afford the title compound as a white solid (0.715 g, 2.94

mmol, 49% yield). Analytical data are consistent with literature values.[6c] **TLC R_f** = 0.2 (20% EtOAc/hexanes, UV active); **m.p.** = 163–165 ˚C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.5 Hz, 1H), 7.98 (d, *J* = 7.3 Hz, 2H), 7.91 (d, *J* = 7.3 Hz, 1H), 7.80 (t, *J* = 7.3 Hz, 1H), 7.75 (t, *J* = 7.3 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.2, 141.3, 133.8, 133.6, 133.5, 130.7, 130.6, 129.7, 129.4, 126.7, 123.3; **IR** (neat) 1599, 1531, 1332, 1171 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{13}H_9NO_2S$ $(M + Na)^+$ 266.0252, found 266.0255.



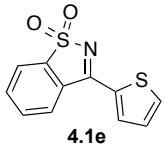
4.1c

***N*-Sulfonyl ketimine 4.1c** was prepared according Method D, using the following amounts of reagents: furan (0.910 mL, 12.5 mmol, 2.50 equiv), *n*-BuLi (5.50 mL, 13.8 mmol, 2.50 M in hexanes, 2.75 equiv), saccharin (0.92 g, 5.0 mmol, 1.0 equiv), and THF (15 mL). The product was recrystallized from hot Et_2O in $CHCl_3$ (1:1 $Et_2O/CHCl_3$) to afford the title compound as a yellow solid (0.16 g, 0.70 mmol, 14%). Analytical data are consistent with literature values.[6c] **TLC R_f** = 0.2 (20% EtOAc/hexanes, UV active); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 5.5, 3.0 Hz, 1H), 7.98 (dd, *J* = 5.5, 3.0 Hz, 1H), 7.91 (s, 1H), 7.79–7.76 (m, 3H), 6.79 (dd, *J* = 3.7, 1.6 Hz, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 158.1, 149.4, 148.2, 141.0, 133.9, 133.6, 129.8, 127.6, 122.8, 122.2, 114.1; **IR** (neat) 1600, 1571, 1516, 1320, 1165 cm^{-1}; **HRMS** (TOF MS ES+) *m* / *z* calcd for $C_{11}H_7NO_3S$ $(M + Na)^+$ 256.0044, found 256.0043.



4.1d

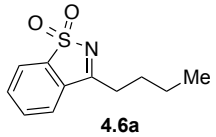
***N*-Sulfonyl ketimine 4.1d** was prepared according Method D, using the following amounts of reagents: benzothiophene (1.46 mL, 12.5 mmol, 2.50 equiv), *n*-BuLi (5.50 mL, 13.8 mmol, 2.50 M in hexanes, 2.75 equiv), saccharin (0.92 g, 5.0 mmol, 1.0 equiv), and THF (16 mL). The product was purified by flash column chromatography using 20–30–50% EtOAc/hexanes to afford the title compound as a yellow solid (0.29 g, 0.96 mmol, 19%). **TLC R_f** = 0.2 (20% EtOAc/hexanes, UV active); **m.p.** = 266–268 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.30–8.28 (m, 1H), 8.05–8.03 (m, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.83–7.81 (m, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 164.0, 142.9, 141.4, 139.2, 133.9, 133.7, 132.7, 130.4, 128.6, 126.1, 126.0, 125.8, 123.3, 122.9; **IR** (neat) 1593, 1526, 1316, 1171, 744 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{15}H_9NO_2S_2$ $(M + Na)^+$ 321.9973, found 321.9986.



4.1e

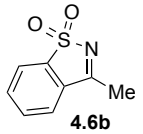
***N*-Sulfonyl ketimine 4.1e** was prepared according Method C, using the following amounts of reagents: saccharin (0.92 g, 5.0 mmol, 1.0 equiv), 2-thienylmagnesium bromide (8.00 mL, 10.0 mmol, 1.25 M in THF, 2.00 equiv) and THF (5 mL). The product was recrystallized from hot Et_2O in $CHCl_3$ (1:1 $Et_2O/CHCl_3$) to afford the title compound as an orange solid (0.22 g, 0.90 mmol, 18%). Analytical data are consistent with literature values.[6b] **TLC R_f** = 0.2 (20% EtOAc/hexanes, UV active); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 3.9 Hz, 1H), 8.21–8.18

(m, 1H), 8.03–8.00 (m, 1H), 7.88 (d, J = 5.0 Hz, 1H), 7.82–7.77 (m, 2H), 7.34 (t, J = 4.4 Hz, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 163.1, 141.4, 135.8, 135.3, 134.0, 133.8, 133.6, 130.5, 129.2, 125.8, 123.2; **IR** (neat) 1594, 1416, 1316, 1164, 725 cm^{-1}; **HRMS** (TOF MS ES+) m/z calcd for $C_{11}H_7NO_2S_2$ $(M + Na)^+$ 271.9816, found 271.9816.



4.6a

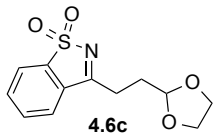
***N*-Sulfonyl ketimine 4.6a** was prepared according Method D, using the following amounts of reagents: saccharin (0.92 g, 5.0 mmol, 1.0 equiv), *n*-BuLi (5.50 mL, 13.8 mmol, 2.50 M in hexanes, 2.75 equiv), and THF (18 mL). The product was purified by flash column chromatography using 20% EtOAc/hexanes to afford the title compound as a yellow solid (0.40 g, 1.8 mmol, 36%). Analytical data are consistent with literature values.[6b] **TLC R_f** = 0.4 (20% EtOAc/hexanes, stains with $KMnO_4$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93–7.90 (m, 1H), 7.77–7.68 (m, 3H), 2.97 (t, J = 7.4 Hz, 2H), 1.88 (quint, J = 7.4 Hz, 2H), 1.51 (sext, J = 7.4 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 176.5, 140.0, 134.0, 133.6, 131.5, 124.0, 122.6, 31.0, 27.6, 22.5, 13.9; **IR** (neat) 2342, 1604, 1558, 1332, 1172 cm^{-1}; **HRMS** (TOF MS ES+) m/z calcd for $C_{11}H_{13}NO_2S$ $(M + Na)^+$ 246.0565, found 246.0568.



4.6b

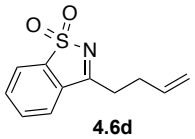
***N*-Sulfonyl ketimine 4.6b** was prepared according Method D, using the following amounts of reagents: saccharin (1.83 g, 10.0 mmol, 1.00 equiv), MeLi (15.7 mL, 22.0 mmol, 1.40 M in Et_2O, 2.20 equiv) and THF (10 mL). The product was purified by flash column chromatography using

20% EtOAc/hexanes to afford the title compound as a white solid (1.13 g, 6.21 mmol, 62%). Analytical data are consistent with literature values.[6b] **TLC R_f** = 0.3 (20% EtOAc/hexanes, stains with $KMnO_4$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.99–7.97 (m, 1H), 7.84–7.79 (m, 2H), 7.76–7.75 (m, 1H), 2.73 (s, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 173.4, 139.7, 134.1, 133.7, 131.7, 124.3, 122.5, 17.7; **IR** (neat) 2341, 1558, 1316, 1168, 771 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_8H_7NO_2S$ $(M + Na)^+$ 204.0095, found 204.0098.



4.6c

***N*-Sulfonyl ketimine 4.6c** was prepared according Method C, using the following amounts of reagents: saccharin (1.2 g, 6.5 mmol, 1.0 equiv), (2-(1,3-dioxolan-2-yl)ethyl)magnesium bromide (14.0 mL, 13.0 mmol, 0.900 M in THF, 2.00 equiv) and THF (17 mL). The product was purified by flash column chromatography using 50% EtOAc/hexanes to afford the title compound as a white solid (0.80 g, 3.0 mmol, 46%). **TLC R_f** = 0.5 (50% EtOAc/hexanes, UV active); **m.p.** = 68–70 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93–7.90 (m, 1H), 7.77–7.71 (m, 3H), 5.07 (t, *J* = 4.0 Hz, 1H), 4.01–3.95 (m, 2H), 3.93–3.87 (m, 2H), 3.12 (t, *J* = 7.4 Hz, 2H), 2.31 (td, *J* = 7.4, 4.0 Hz, 2H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 176.2, 139.8, 134.0, 133.6, 131.3, 124.1, 122.5, 102.6, 65.2, 29.0, 25.1; **IR** (neat) 1607, 1333, 1172, 909, 726 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{12}H_{13}NO_4S$ $(M + Na)^+$ 290.0463, found 290.0465.

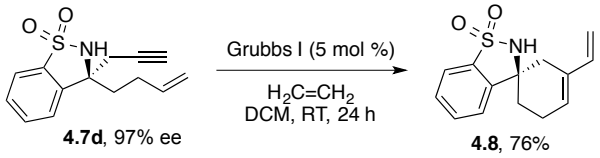


4.6d

***N*-Sulfonyl ketimine 4.6d** was prepared according Method C, using the following amounts of reagents: saccharin (0.82 g, 4.5 mmol, 1.0 equiv), 4-butenylmagnesium bromide (5.0 mL, 4.5 mmol, 0.90 M in THF, 1.0 equiv) and THF (6 mL). The product was purified by flash column chromatography using 10–20% EtOAc/hexanes to afford the title compound as a white solid (0.16 g, 0.71 mmol, 16%). Analytical data are consistent with literature values.[33] **TLC** $\mathbf{R_f}$ = 0.3 (20% EtOAc/hexanes, stains with $KMnO_4$); **m.p.** = 81 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93–7.88 (m, 1H), 7.78–7.68 (m, 3H), 5.99–5.89 (m, 1H), 5.15 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.09 (dd, *J* = 10.2, 1.4 Hz, 1H), 3.07 (t, *J* = 7.5 Hz, 2H), 2.69–2.63 (m, 2H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 175.7, 139.9, 135.9, 134.1, 133.7, 131.3, 124.0, 122.6, 116.7, 30.6, 29.2; **IR** (neat) 2923, 2257, 1558, 1334, 907, 726 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{11}H_{11}NO_2S$ $(M + Na)^+$ 244.0408, found 244.0419.

Synthetic Transformations of Homopropargylic Sultams (Scheme 4.4)

*Enyne Ring-Closing Metathesis to Form **4.8***



4.7d, 97% ee

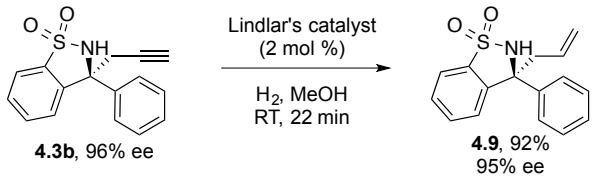
4.8, 76%

Sultam 4.8 was prepared according to a modified procedure described by Mori and co-workers.[34] To a flame-dried 7 mL reaction vial equipped with a N_2 line and Grubbs 1st generation catalyst (6.0 mg, 0.0070 mmol, 0.050 equiv) was added substrate **4.7d** (36.8 mg, 0.140 mmol,

[33] Paderes M. C.; Chemler, S. R. *Org. Lett.* **2009**, *11*, 1915.
[34] Mori, M.; Sakakibara N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082.

1.00 equiv) in anhydrous DCM (5 mL). The N_2 atmosphere was exchanged with ethylene (1 atm, balloon), taking care to fully purge the vial of N_2. After stirring 24 h at room temperature, the reaction mixture was concentrated in vacuo. The product was purified by flash column chromatography using 5–10% EtOAc/hexanes (1% TEA) to afford the title compound as a colorless oil (28.0 mg, 0.110 mmol, 76%). Enantiomeric excess could not be determined for the title compound using chiral SFC instrumentation due to lack of separation of the enantiomers. **TLC R_f** = 0.4 (20% EtOAc/hexanes, stains blue with PAA); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 6.42 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.94 (s, 1H), 5.04–4.97 (m, 2H), 4.72 (s, 1H), 2.69 (d, *J* = 17.4 Hz, 1H), 2.58–2.49 (m, 2H), 2.45–2.37 (m, 1H), 2.07–1.94 (m, 2H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 144.6, 138.6, 135.5, 133.6, 133.2, 129.6, 128.7, 123.4, 121.6, 111.7, 61.9, 37.0, 33.3, 23.4; **IR** (neat) 3455, 3251, 2926, 1161, 1061, 744 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{14}H_{15}NO_2S$ $(M + Na)^+$ 284.0721, found 284.0712; **$[\alpha]^{24}_D$** –14 (*c* 0.9, $CDCl_3$).

*Lindlar Reduction to Form **4.9***

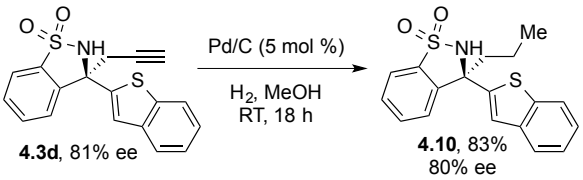


Sultam 4.9 was prepared according to a modified procedure described by Jarvo and co-workers.[35] To a flame-dried 7 mL reaction vial equipped with a N_2 line, substrate **4.3b** (41.0 mg, 0.145 mmol, 1.00 equiv), and palladium, 5% on calcium carbonate, lead poisoned (6.4 mg, 2 mol % palladium relative to **4.3b**) was added anhydrous MeOH (2 mL). The N_2 atmosphere was exchanged with H_2 (1 atm, balloon) and the reaction was allowed to stir at room temperature.

[35] Harris, M. R.; Konev, M. O.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 7825.

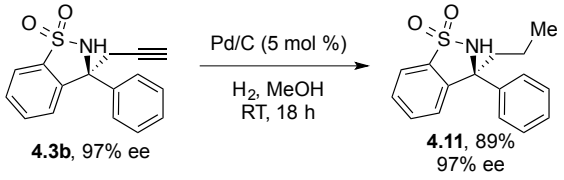
After 22 min, the H_2 atmosphere was exchanged with N_2 and the reaction mixture was filtered through a pad of Celite using 50% EtOAc/hexanes, and then concentrated in vacuo. The product was purified by flash column chromatography using 5–10% EtOAc/hexanes (1% TEA) to afford the title compound as a white solid (38.2 mg, 0.134 mmol, 92%, 95% ee). **TLC R_f** = 0.1 (10% EtOAc/hexanes, stains blue with PAA); **m.p.** = 125–127 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 1H), 7.62–7.58 (m, 3H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 3H), 7.30 (m, 1H), 5.66–5.57 (m, 1H), 5.28–5.21 (m, 2H), 5.00 (s, 1H), 3.25 (dd, *J* = 14.3, 6.6 Hz, 1H), 3.03 (dd, *J* = 14.3, 7.7 Hz, 1H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 143.2, 141.7, 134.8, 133.5, 131.7, 129.6, 129.1 128.3, 126.3, 124.6, 122.0, 121.6, 67.7, 45.2; **IR** (neat) 3290, 3069, 1295, 1168, 906, 729 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{16}H_{15}NO_2S$ $(M + Na)^+$ 308.0721, found 308.0723; **$[\alpha]^{24}_D$** +72 (*c* 0.9, $CDCl_3$); **SFC** analysis (OD-H, 10% IPA, 3.0 mL/min, 215 nm) indicated 95% ee: t_R (minor) = 9.9 min, t_R (major) = 12.6 min.

*Pd/C Reduction to Form **4.10** and **4.11***



Sultam 4.10. To a flame-dried 7 mL reaction vial equipped with a N_2 line and palladium, 10% on carbon (5.6 mg, 5 mol % palladium relative to **4.3d**) was added substrate **4.3d** (35.7 mg, 0.105 mmol, 1.00 equiv) in anhydrous MeOH (2 mL). The vial was evacuated and refilled with N_2 three times. The N_2 atmosphere was exchanged with H_2 (1 atm, balloon) and the reaction was allowed to stir at room temperature. After 18 h, the H_2 atmosphere was exchanged with N_2 and the reaction mixture was filtered through a pad of Celite using MeOH, and then concentrated in

vacuo. The product was purified by flash column chromatography using 5–10–20% EtOAc/hexanes (1% TEA) to afford the title compound as a colorless oil (29.8 mg, 0.0870 mmol, 83%, 80% ee). **TLC R_f** = 0.4 (20% EtOAc/hexanes, UV active); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.70 (dd, *J* = 6.8, 1.8 Hz, 1H), 7.63 (td, *J* = 7.6, 1.2 Hz, 1H), 7.55 (td, *J* = 7.5, 1.1 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.37 (s, 1H), 7.31 (aquintd, *J* = 7.2, 1.5 Hz, 2H), 5.07 (br s, 1H), 2.47–2.31 (m, 2H), 1.64–1.51 (m, 1H), 1.23–1.10 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 148.0, 142.1, 139.6, 139.4, 134.4, 133.7, 130.0, 125.0, 124.8, 124.5, 124.1, 122.4, 121.8, 121.7, 67.3, 44.1, 17.6, 14.0; **IR** (neat) 3258, 2961, 1456, 1287, 1157, 725 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{18}H_{17}NO_2S_2$ $(M + Na)^+$ 366.0598, found 366.0601; **$[\alpha]^{25}_D$** +47 (*c* 1.0, $CDCl_3$); **SFC** analysis (AS-H, 20% IPA, 3.0 mL/min, 215 nm) indicated 80% ee: t_R (major) = 9.9 min, t_R (minor) = 15.7 min.



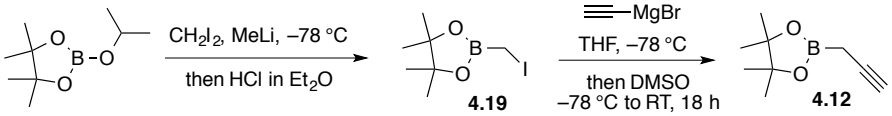
Sultam 4.11. To a flame-dried 7 mL reaction vial equipped with a N_2 line and palladium, 10% on carbon (6.3 mg, 5 mol % palladium relative to **4.3b**) was added substrate **4.3b** (32.3 mg, 0.114 mmol, 1.00 equiv) in anhydrous MeOH (1.0 mL). The vial was evacuated and refilled with N_2 three times. The N_2 atmosphere was exchanged with H_2 (1 atm, balloon) and the reaction was allowed to stir at room temperature. After 18 h, the H_2 atmosphere was exchanged with N_2 and the reaction mixture was filtered through a pad of Celite using MeOH, and then concentrated in vacuo. The product was purified by flash column chromatography using 5–10–20%

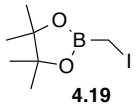
EtOAc/hexanes (1% TEA) to afford the title compound as a white solid (29.2 mg, 0.102 mmol, 89%, 97% ee). **TLC** $\mathbf{R_f}$ = 0.5 (20% EtOAc/hexanes, stains blue with PAA); **m.p.** = 160–162 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.60–7.49 (m, 4H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.0 Hz, 2H), 4.86 (br s, 1H), 2.44–2.36 (m, 1H), 2.33–2.26 (m, 1H), 1.57–1.46 (m, 1H), 1.24–1.02 (m, 1H), 0.94 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (125.7 MHz, $CDCl_3$) δ 143.6, 142.5, 134.5, 133.5, 129.4, 129.1, 128.2, 126.1, 124.4, 121.4, 68.9, 42.6, 17.5, 14.1; **IR** (neat) 3251, 2958, 1450, 1281, 1157, 765 cm^{-1}; **HRMS** (TOF MS ES+) *m / z* calcd for $C_{16}H_{17}NO_2S$ $(M + Na)^+$ 310.0878, found 310.0883; $\mathbf{[\alpha]^{25}_D}$ +95 (*c* 0.9, $CDCl_3$); **SFC** analysis (OD-H, 10% IPA, 3.0 mL/min, 215 nm) indicated 97% ee: t_R (minor) = 11.0 min, t_R (major) = 13.9 min.

Mechanistic Studies (Scheme 4.6)

*Synthesis of Propargyl Borolane Reagent **4.12***

Scheme 4.8. Synthesis of propargyl borolane **4.12**.

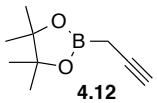




Iodomethyl borolane 4.19 was prepared according to a modified procedure by Brown and co-workers,[36] using the following amounts of reagents: 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (17.7 mL, 86.9 mmol, 1.00 equiv), diiodomethane (7.00 mL, 86.9 mmol, 1.00

[36] Roy, C. D.; Soundararajan, R.; Brown, H. C. *Monatsch. Chem.* **2008**, *139*, 241.

equiv), methyllithium (52.3 mL, 86.9 mmol, 1.66 M in Et_2O, 1.00 equiv), THF (45 mL), and anhydrous HCl (93.0 mL, 93.0 mmol, 1.00 M in Et_2O, 1.07 equiv). The resulting red solution was filtered through a plug of silica gel (40 mL) eluting with 10% Et_2O/pentanes and concentrated in vacuo. Distillation twice through a short path distillation apparatus onto activated 4Å molecular sieves at 13.7 mmHg and T_{vap} = 95 °C provided the title compound as a clear, colorless liquid (7.64 g, 28.5 mmol, 33%). Analytical data are consistent with literature values.[36] **TLC R_f** = 0.7 (10% Et_2O/pentanes, stains blue with PAA); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.16 (s, 2H), 1.28 (s, 12 H); **^{13}C NMR** ($CDCl_3$, 125.7 MHz) δ 84.1, 24.5; **^{11}B NMR** ($CDCl_3$, 160.2 MHz) δ 31.7; **IR** (neat) 2977, 1322, 1142, 844, 673, 577 cm^{-1}; **HRMS** (TOF MS CI+) *m* / *z* calcd for $C_7H_{14}BIO_2$ $(M)^+$ 268.0133, found 268.0143.



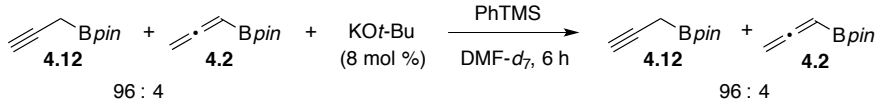
4.12

Propargylboronic acid pinacol ester 4.12 was prepared according to a literature procedure by Fandrick and co-workers,[22c] using the following amounts of reagents: **4.19** (2.0 mL, 11 mmol, 1.0 equiv), ethynylmagnesium bromide (19.8 mL, 11.2 mmol, 0.566 M in THF, 1.02 equiv), THF (15 mL), and 1:1 THF/DMSO (24 mL). Distillation using a Kugelrohr distillation apparatus at 3–6 torr and T_{vap} = 60 °C provided the title compound as a 96:4 mixture of propargyl borolane **4.12** and allenyl borolane **4.2** as a clear, colorless oil (0.37 g, 2.2 mmol, 20%). Analytical data for allenyl borolane **4.2** are consistent with literature values.[32] **TLC R_f** = 0.9 (10% Et_2O/hexanes, stains blue with PAA); **^{1}H NMR** (400 MHz, DMF-d_7) δ 4.90 (t, J = 7.0 Hz, 1H), 4.71 (d, J = 7.0 Hz, 2H), 1.26 (s, 12H). Analytical data for propargyl borolane **4.12** are consistent with literature values.[22c] **^{1}H NMR** (400 MHz, DMF-d_7) δ 2.46 (t, J = 2.9 Hz, 1H), 1.78 (d, J = 2.9 Hz, 2H), 1.26 (s, 12H); **^{13}C NMR** (125.7 MHz, DMF-d_7) δ 84.9, 81.9, 69.5, 25.3.

Note: We found that in order to obtain high ratios of propargyl borolane to allenyl borolane, it was necessary to use precisely 1.02 equivalents of ethynylmagnesium bromide relative to iodomethyl borolane **4.19**. Excess Grignard reagent (1.1 equivalents) causes isomerization to allenyl borolane, while fewer than 1.0 equivalents of Grignard reagent results in low conversion to product (Figure 4.2).

Control Reactions with 4.12

Isomerization in Presence of 8 mol % Base



In a glovebox, a flame-dried vial was charged with potassium *tert*-butoxide (1.7 mg, 0.015 mmol, 0.076 equiv). *N*,*N*-Dimethylformamide-d_7 (+0.05% V/V TMS, 0.6 mL) was added from an ampule opened in the glovebox and the solution was transferred into an oven-dried NMR tube. The NMR tube was capped with a rubber septum, sealed with parafilm, and removed from the glovebox. Phenyltrimethylsilane (PhTMS, internal standard) (17.2 μL, 0.100 mmol, 0.500 equiv) was added via syringe to the NMR tube through the septum, and the NMR tube was inverted to mix. An initial ^{1}H NMR spectrum was collected of the solution, after which propargyl borolane **4.12** (72 μL, 0.40 mmol, 2.0 equiv) was added via syringe to the NMR tube through the septum, and the NMR tube was inverted to mix. A ^{1}H NMR spectrum was collected (1 minute after adding **4.12**, Figure 4.3a), followed by sequential ^{1}H NMR spectra collected at the time points listed in Table 4.3.

Table 4.3. Absence of isomerization of propargyl borolane **4.12** in the presence of 8 mol % KO*t*-Bu at RT.

time elapsed	ratio **4.12** : **4.2**
1 min	96:4
4 min	96:4
7 min	96:4
9 min	96:4
10 min	96:4
15 min	96:4
20 min	96:4
30 min	96:4
40 min	96:4
1 h	96:4
3 h	96:4
6 h	96:4

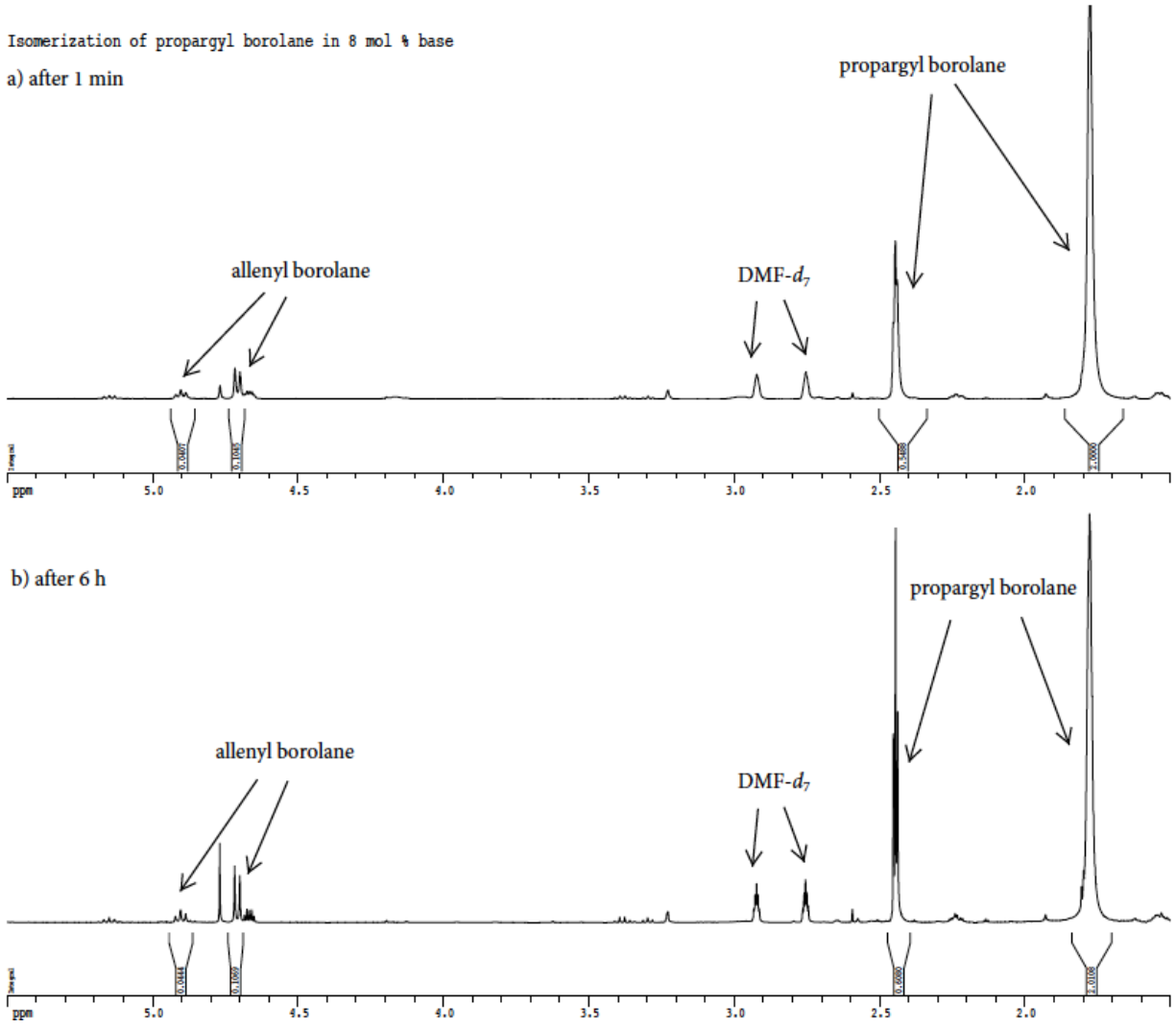
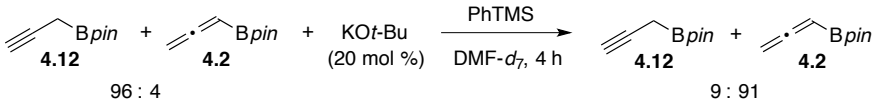


Figure 4.3. Absence of isomerization of propargyl borolane **4.12** in the presence of 8 mol % KO*t*-Bu at RT.

Isomerization in Presence of 20 mol % Base



96 : 4 9 : 91

In a glovebox, a flame-dried vial was charged with potassium *tert*-butoxide (4.5 mg, 0.040 mmol, 0.20 equiv). *N*,*N*-Dimethylformamide-d_7 (+0.05% V/V TMS, 0.6 mL) was added

from an ampule opened in the glovebox and the solution was transferred into an oven-dried NMR tube. The NMR tube was capped with a rubber septum, sealed with parafilm, and removed from the glovebox. Phenyltrimethylsilane (PhTMS, internal standard) (17.2 μL, 0.100 mmol, 0.500 equiv) was added via syringe to the NMR tube through the septum, and the NMR tube was inverted to mix. An initial ^{1}H NMR spectrum was collected, after which propargyl borolane **4.12** (72 μL, 0.40 mmol, 2.0 equiv) was added via syringe to the NMR tube through the septum, and the NMR tube was inverted to mix. A ^{1}H NMR spectrum was collected (1 minute after adding **4.12**, Figure 4.4a), followed by sequential ^{1}H NMR spectra collected at the time points listed in Table 4.4.

Table 4.4. Isomerization of propargyl borolane **4.12** to allenyl borolane **4.2** in the presence of 20 mol % KO*t*-Bu at RT.

time elapsed	ratio **4.12** : **4.2**
1 min	92:8
5 min	87:13
8 min	84:16
10 min	82:18
20 min	69:31
30 min	64:36
35 min	60:40
40 min	57:43
1 h	46:54
2 h	27:73
3 h	18:82
4 h	9:91

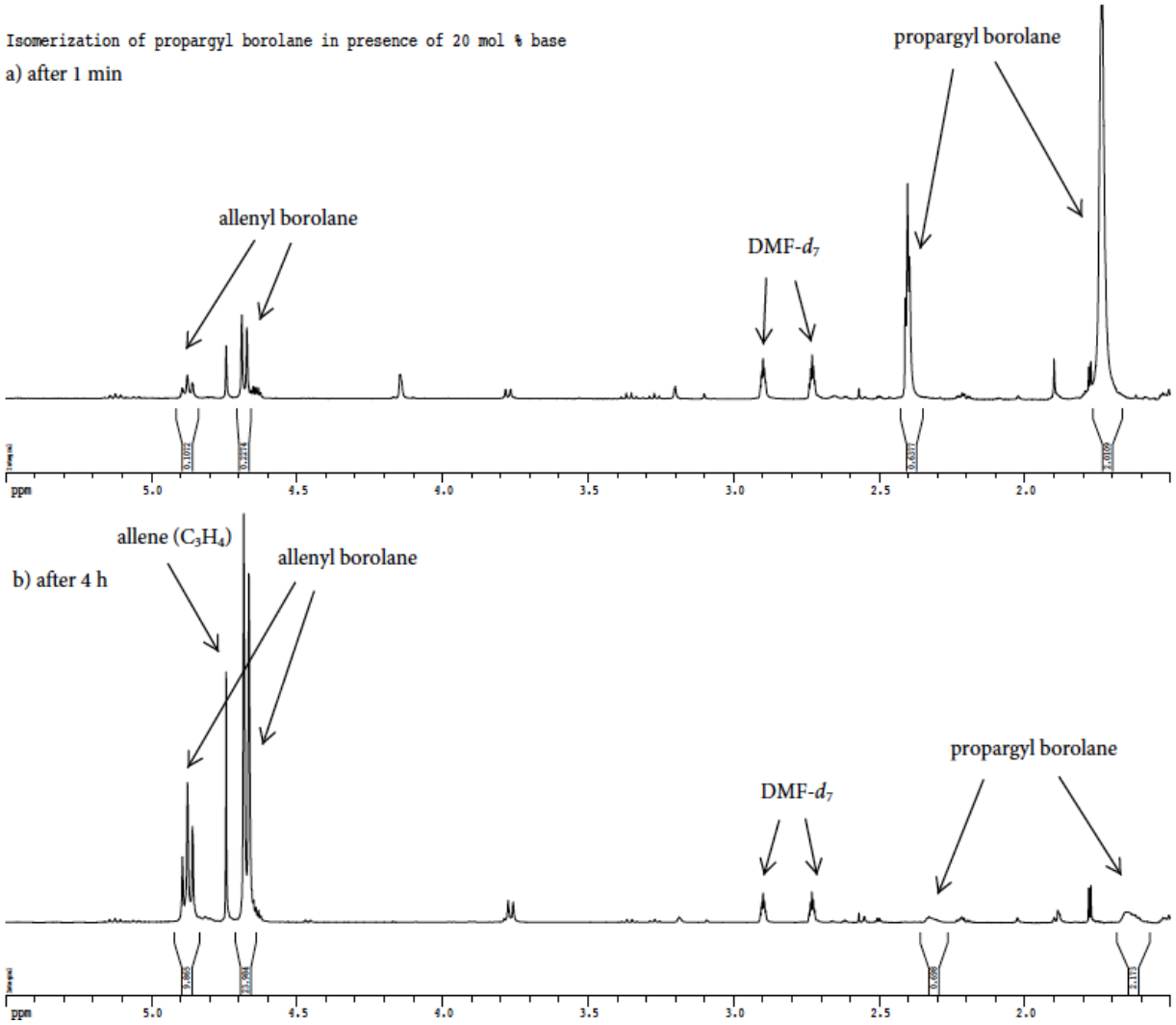


Figure 4.4. Isomerization of propargyl borolane **4.12** to allenyl borolane **4.2** in the presence of 20 mol % KO*t*-Bu at RT.

Mechanistic Studies with Borolane Reagents

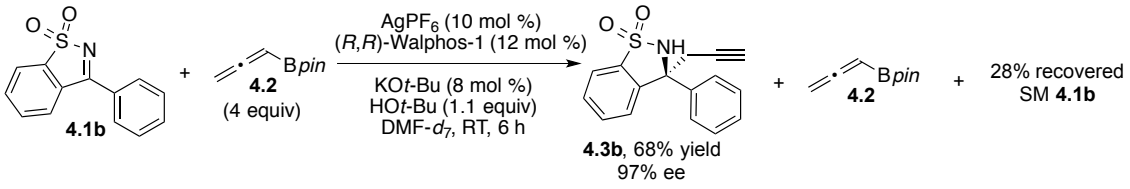
We were interested in distinguishing between two possible mechanisms for this propargylation reaction: transmetallation of the silver catalyst with the borolane reagent (Mechanism A), or Lewis acid catalysis (Mechanism B). To distinguish between these mechanisms, we examined reactions employing propargyl borolane reagent **4.12** while lowering

the base loading to 8 mol %. This experimental modification was performed to minimize isomerization of **4.12** to allenyl borolane **4.2** (vide supra). We also performed the reactions in deuterated solvent in order to determine the ratio of **4.12** to **4.2** by ^{1}H NMR immediately after the reaction.

A control reaction using allenyl borolane **4.2** (Scheme 4.6a) demonstrated that under these conditions, alkyne **4.3b** was formed in 68% yield with 28% recovered starting material **4.1b** (vide infra). Using propargyl borolane **4.12** in the reaction (Scheme 4.6b) yielded alkyne **4.3b** in 64% yield with 32% recovered starting material **4.1b** (vide infra). This product distribution is consistent with Mechanism A.

Note: All manipulations involving silver-catalyzed reactions were performed in the absence of direct light, using vials and NMR tubes wrapped in aluminum foil.

*Reaction using Allenyl Borolane **4.2** (Scheme 4.6a)*



In a glovebox, an oven-dried 1.0 mL conical vial equipped with a triangular stir bar was charged with $AgPF_6$ (5.0 mg, 0.020 mmol, 0.10 equiv) and Walphos W001-1 (22.3 mg, 0.0240 mmol, 0.102 equiv). The vial was sealed with a screw-top cap fit with a septum and DMF-d_7 (+0.05% V/V TMS, 400 μL) was added from an ampule opened in the glovebox. The vial was removed from the glovebox and the solution was stirred for 5 min at RT. The N_2 line was then removed and the solution was stirred for 30 min at 70 °C, then cooled to RT over 15 min.

To the catalyst solution was added *tert*-butanol (21 μL, 0.22 mmol, 1.1 equiv), followed by potassium *tert*-butoxide (1.7 mg, 0.015 mmol, 0.076 equiv) and phenyl ketimine **4.1b** (48.6 mg, 0.200 mmol, 1.00 equiv) under a flow of N_2. The reaction was stirred at RT for 5 min to dissolve the ketimine. Allenylboronic acid pinacol ester **4.2** (72 μL, 0.40 mmol, 2.0 equiv) was added via syringe, followed by another portion of allenylboronic acid pincol ester (72 μL, 0.40 mmol, 2.0 equiv) added via slow addition over 3 h using a syringe pump. The N_2 line was removed and the reaction was stirred at 22 °C for another 3 h. The reaction mixture in DMF-d_7 was transferred to an NMR tube and the ratio of allenyl borolane **4.2** to propargyl borolane **4.12** was determined to be 94:6 by ^{1}H NMR (Figure 4.5). The mixture was then filtered through a plug of silica gel eluting with 100% Et_2O to remove the catalyst. Et_2O was removed in vacuo and the resulting residue was purified by flash column chromatography using 0–1% TEA/benzene to separate product from unreacted starting material. The mixture was purified again by flash column chromatography using 5–10–20% EtOAc/hexanes (1% TEA) to separate product from excess ligand and afford alkyne **4.3b** as a white solid (38.5 mg, 0.136 mmol, 68%, 97% ee). Analytical data are consistent with the values listed for **4.3b** (vide supra). **SFC** analysis (OD-H, 10% IPA, 3.0 mL/min, 215 nm) indicated 97% ee: t_R (minor) = 11.8 min, t_R (major) = 13.7 min.

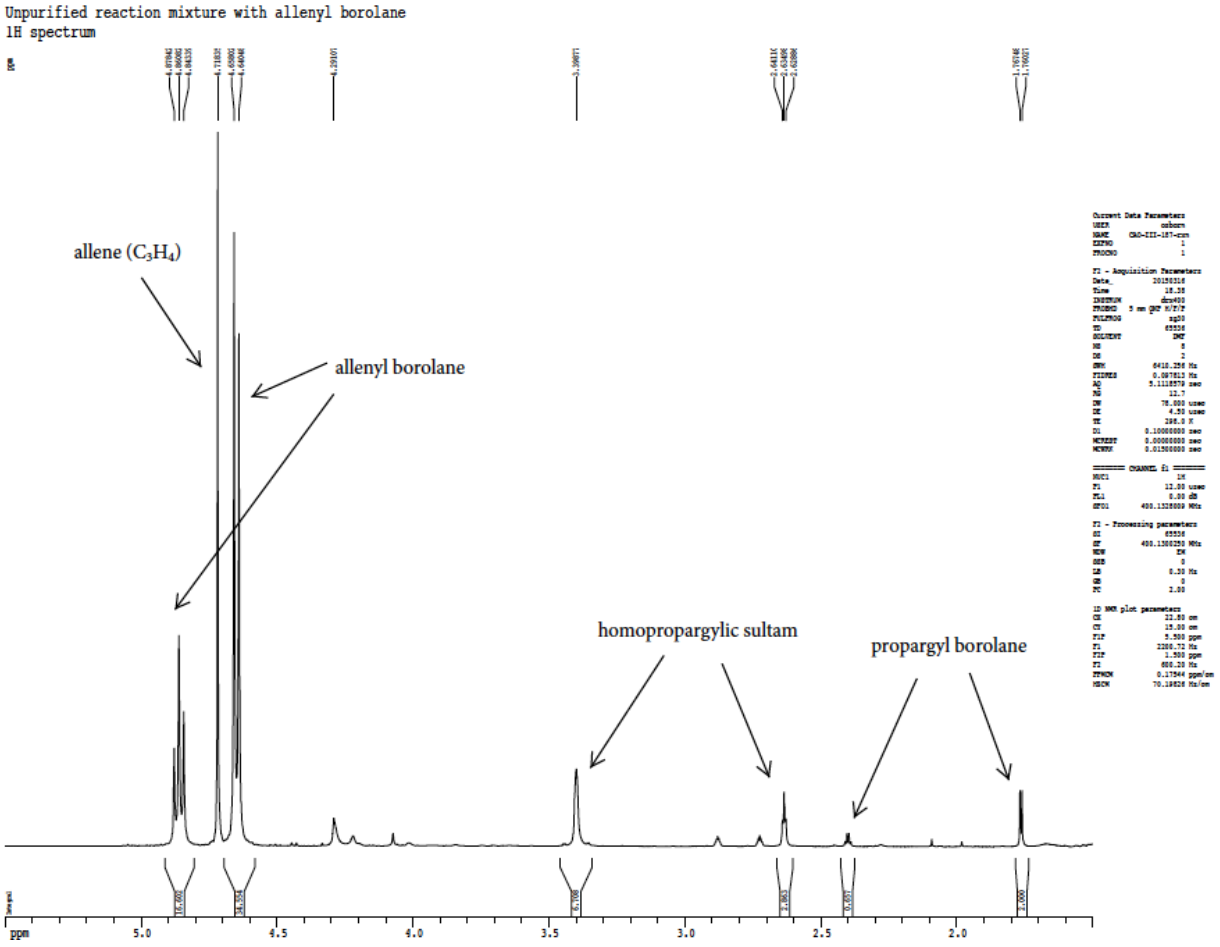
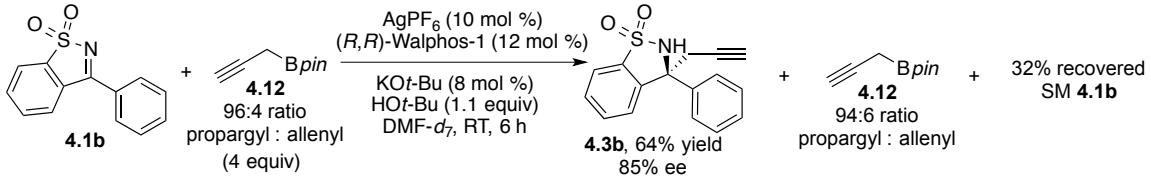


Figure 4.5. Unpurified reaction mixture in DMF-d_7.

*Reaction using Propargyl Borolane **4.12** (Scheme 4.6b)*



In a glovebox, an oven-dried 1.0 mL conical vial equipped with a triangular stir bar was charged with $AgPF_6$ (5.0 mg, 0.020 mmol, 0.10 equiv) and Walphos W001-1 (22.3 mg, 0.0240 mmol, 0.120 equiv). The vial was sealed with a screw-top cap fit with a septum and DMF-d_7

(+0.05% V/V TMS, 400 μL) was added from an ampule opened in the glovebox. The vial was removed from the glovebox and the solution was stirred for 5 min at RT. The N_2 line was then removed and the solution was stirred for 30 min at 70 °C, then cooled to RT over 15 min.

To the catalyst solution was added *tert*-butanol (21 μL, 0.22 mmol, 1.1 equiv), followed by potassium *tert*-butoxide (1.7 mg, 0.015 mmol, 0.076 equiv) and phenyl ketimine **4.1b** (48.6 mg, 0.200 mmol, 1.00 equiv) under a flow of N_2. The reaction was stirred at RT for 5 min to dissolve the ketimine. Propargylboronic acid pinacol ester **4.12** (72 μL, 0.40 mmol, 2.0 equiv) was added via syringe, followed by another portion of propargylboronic acid pincol ester (72 μL, 0.40 mmol, 2.0 equiv) added via slow addition over 3 h using a syringe pump. The N_2 line was removed and the reaction was stirred at 22 °C for another 3 h. The reaction mixture in DMF-d_7 was transferred to an NMR tube and the ratio of propargyl borolane **4.12** to allenyl borolane **4.2** was determined to be 94:6 by ^{1}H NMR (Figure 4.6). The mixture was then filtered through a plug of silica gel eluting with 100% Et_2O to remove the catalyst. Et_2O was removed in vacuo and the resulting residue was purified by flash column chromatography using 0–1% TEA/benzene to separate product from unreacted starting material. The mixture was purified again by flash column chromatography using 5–10–20% EtOAc/hexanes (1% TEA) to separate product from excess ligand and afford alkyne **4.3b** as a white solid (36.5 mg, 0.129 mmol, 64%, 85% ee). Analytical data are consistent with the values listed for **4.3b** (vide supra). **SFC** analysis (OD-H, 10% IPA, 3.0 mL/min, 215 nm) indicated 85% ee: t_R (minor) = 11.8 min, t_R (major) = 13.7 min.

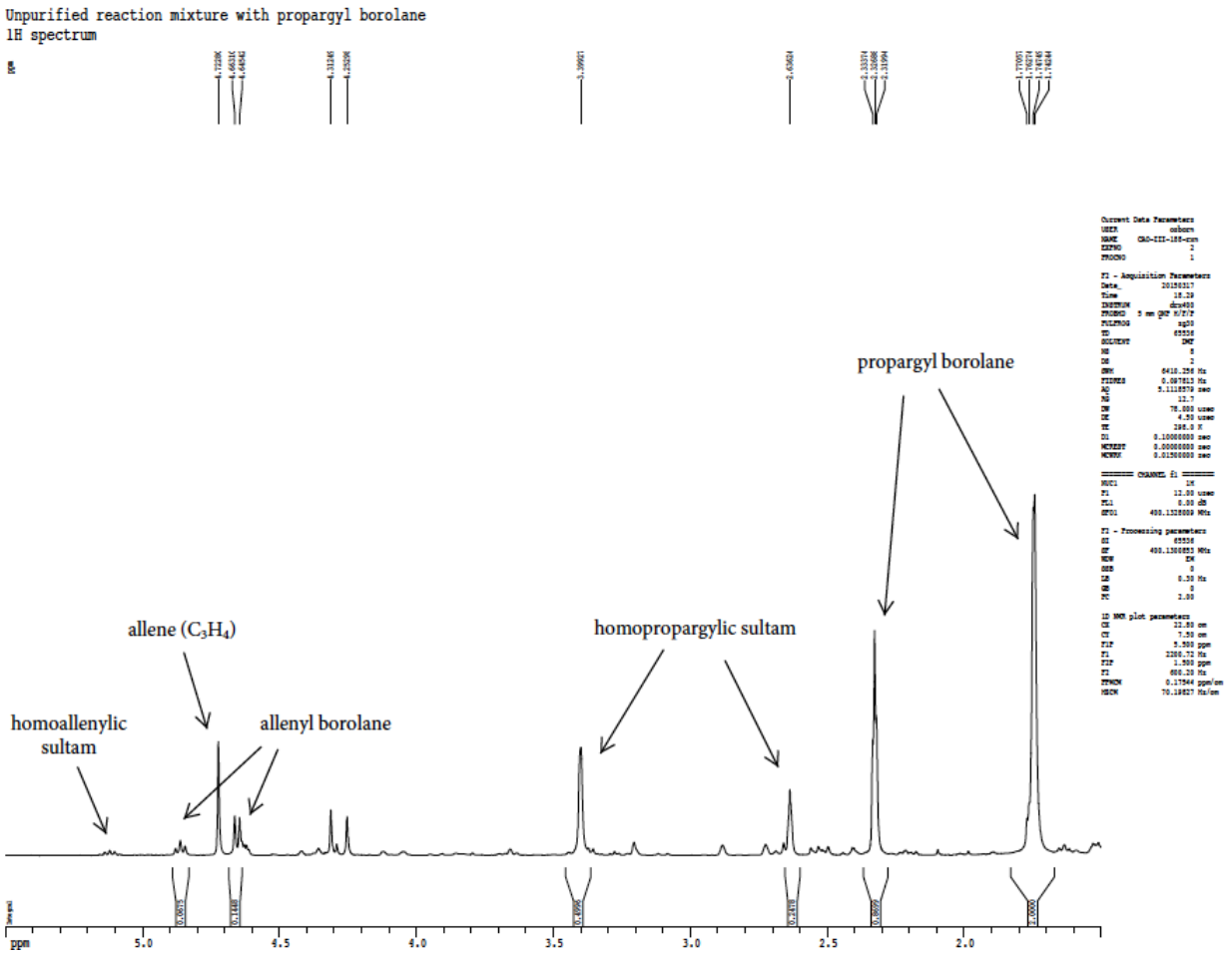
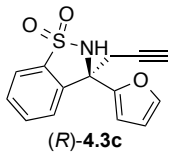


Figure 4.6. Unpurified reaction mixture in DMF-d_7.

Crystallographic Data

*A. X-ray Data Collection, Structure Solution and Refinement for (R)-**4.3c**:*



(*R*)-**4.3c**

A single crystal was grown from EtOAc with slow diffusion of pentanes at room temperature. A colorless crystal of approximate dimensions 0.202 x 0.333 x 0.426 mm was mounted on a glass fiber and transferred to a Bruker SMART APEX II diffractometer. The APEX2[37] program package was used to determine the unit-cell parameters and for data collection (15 sec/frame scan time for a sphere of diffraction data). The raw frame data was processed using SAINT[38] and SADABS[39] to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL[40] program. The diffraction symmetry was *mmm* and the systematic absences were consistent with the orthorhombic space group $P2_12_12_1$ that was later determined to be correct.

The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques. The analytical scattering factors[41] for neutral atoms were used throughout the analysis. Hydrogen atoms H(1) and H(10) were located from a difference-Fourier map and refined (x,y,z and U_{iso}). The remaining hydrogen atoms were included using a riding model. O(3) and C(12) were disordered and included using partial site-occupancy-factors. The disorder was included to account for the approximate distribution of carbon (50%) and oxygen (50%) over the two sites.

At convergence, wR2 = 0.0909 and Goof = 1.070 for 180 variables refined against 3100 data (0.74 Å), R1 = 0.0363 for those 2870 data with $I > 2.0\sigma(I)$. The absolute structure was assigned by refinement of the Flack parameter.[42]

[37] APEX2 Version 2014.11-0, Bruker AXS, Inc.; Madison, WI 2014.
[38] SAINT Version 8.34a, Bruker AXS, Inc.; Madison, WI 2013.
[39] Sheldrick, G. M. SADABS, Version 2014/5, Bruker AXS, Inc.; Madison, WI 2014.
[40] Sheldrick, G. M. SHELXTL, Version 2014/7, Bruker AXS, Inc.; Madison, WI 2014.
[41] International Tables for Crystallography 1992, Vol. C., Dordrecht: Kluwer Academic Publishers.
[42] Parsons, S., Flack, H. D., Wagner, T. Acta Cryst. B69, 249-259, 2013.

Definitions:

$wR2 = [\Sigma[w(F_o^2-F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

$R1 = \Sigma||F_o|-|F_c|| / \Sigma|F_o|$

$Goof = S = [\Sigma[w(F_o^2-F_c^2)^2] / (n-p)]^{1/2}$ where n is the number of reflections and p is the total number of parameters refined.

The thermal ellipsoid plot is shown at the 30% probability level.

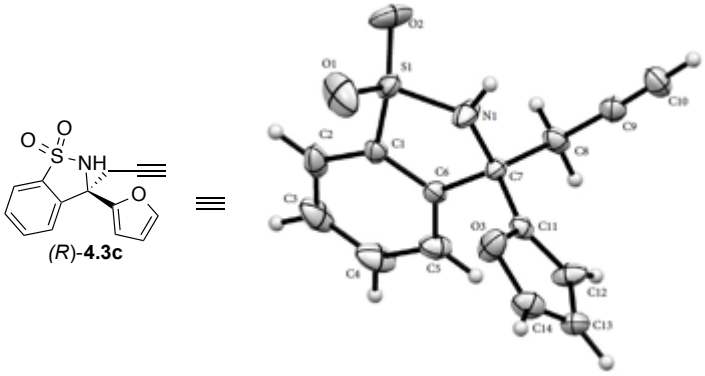


Table 4.5. Crystal data and structure refinement for (*R*)-**4.3c**.

Identification code	erj23 (Charlotte Osborne)	
Empirical formula	$C_{14}\ H_{11}\ N\ O_3\ S$	
Formula weight	273.30	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.5472(5) Å	a= 90°.
	b = 10.3052(7) Å	b= 90°.
	c = 16.2327(10) Å	g = 90°.
Volume	1262.51(14) $Å^3$	
Z	4	
Density (calculated)	1.438 Mg/m^3	
Absorption coefficient	0.259 mm^{-1}	
F(000)	568	
Crystal color	colorless	
Crystal size	0.426 x 0.333 x 0.202 mm^3	
Theta range for data collection	2.341 to 28.839°	
Index ranges	$-10 \le h \le 10$, $-13 \le k \le 13$, $-21 \le l \le 20$	
Reflections collected	15206	
Independent reflections	3100 [R(int) = 0.0274]	
Completeness to theta = 25.500°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8621 and 0.8165	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3100 / 0 / 180	
Goodness-of-fit on F^2	1.070	
Final R indices [I>2sigma(I) = 2870 data]	R1 = 0.0363, wR2 = 0.0881	
R indices (all data, 0.74Å)	R1 = 0.0403, wR2 = 0.0909	

Absolute structure parameter	0.04(2)
Largest diff. peak and hole	0.298 and -0.366 e.Å^{-3}

Table 4.6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (*R*)-**4.3c**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	3053(1)	7602(1)	8953(1)	25(1)
N(1)	4347(4)	6393(2)	9154(2)	36(1)
O(1)	1714(3)	7709(3)	9570(1)	58(1)
O(2)	4026(4)	8766(2)	8781(1)	48(1)
O(3)	3159(3)	3886(2)	9539(2)	38(1)
C(1)	2206(3)	6903(2)	8057(2)	24(1)
C(2)	897(3)	7416(3)	7551(2)	37(1)
C(3)	430(4)	6713(3)	6868(2)	47(1)
C(4)	1240(4)	5532(3)	6696(2)	46(1)
C(5)	2551(4)	5035(3)	7203(2)	33(1)
C(6)	3040(3)	5741(2)	7897(1)	22(1)
C(7)	4499(3)	5402(2)	8508(1)	20(1)
C(8)	6309(3)	5461(3)	8061(2)	28(1)
C(9)	7799(3)	5308(2)	8617(2)	28(1)
C(10)	8994(4)	5223(3)	9089(2)	34(1)
C(11)	4214(3)	4100(2)	8891(2)	22(1)
C(12)	4765(3)	2981(2)	8580(1)	32(1)
C(13)	4119(3)	1987(3)	9100(2)	31(1)
C(14)	3160(4)	2544(3)	9680(2)	33(1)

Table 4.7. Bond lengths [Å] and angles [°] for (*R*)-**4.3c**.

S(1)-O(1)	1.426(2)
S(1)-O(2)	1.435(2)
S(1)-N(1)	1.616(2)
S(1)-C(1)	1.745(3)
N(1)-C(7)	1.468(3)
O(3)-C(11)	1.338(3)
O(3)-C(14)	1.402(4)
C(1)-C(6)	1.378(3)
C(1)-C(2)	1.389(4)
C(2)-C(3)	1.371(5)
C(3)-C(4)	1.390(5)
C(4)-C(5)	1.385(4)
C(5)-C(6)	1.391(4)
C(6)-C(7)	1.522(3)
C(7)-C(11)	1.494(3)
C(7)-C(8)	1.548(3)
C(8)-C(9)	1.451(4)
C(9)-C(10)	1.186(4)
C(11)-C(12)	1.326(3)
C(12)-C(13)	1.414(3)
C(13)-C(14)	1.319(4)
O(1)-S(1)-O(2)	115.75(16)
O(1)-S(1)-N(1)	110.28(16)
O(2)-S(1)-N(1)	112.00(15)
O(1)-S(1)-C(1)	110.97(13)
O(2)-S(1)-C(1)	111.74(12)
N(1)-S(1)-C(1)	94.07(12)

C(7)-N(1)-S(1)	116.09(18)
C(11)-O(3)-C(14)	106.9(2)
C(6)-C(1)-C(2)	123.0(3)
C(6)-C(1)-S(1)	110.40(18)
C(2)-C(1)-S(1)	126.6(2)
C(3)-C(2)-C(1)	117.4(3)
C(2)-C(3)-C(4)	120.8(3)
C(5)-C(4)-C(3)	121.3(3)
C(4)-C(5)-C(6)	118.5(3)
C(1)-C(6)-C(5)	119.1(2)
C(1)-C(6)-C(7)	114.0(2)
C(5)-C(6)-C(7)	126.8(2)
N(1)-C(7)-C(11)	108.4(2)
N(1)-C(7)-C(6)	104.41(19)
C(11)-C(7)-C(6)	111.9(2)
N(1)-C(7)-C(8)	112.1(2)
C(11)-C(7)-C(8)	111.0(2)
C(6)-C(7)-C(8)	108.93(19)
C(9)-C(8)-C(7)	112.8(2)
C(10)-C(9)-C(8)	177.4(3)
C(12)-C(11)-O(3)	110.0(2)
C(12)-C(11)-C(7)	125.2(2)
O(3)-C(11)-C(7)	124.2(2)
C(11)-C(12)-C(13)	107.2(2)
C(14)-C(13)-C(12)	107.5(2)
C(13)-C(14)-O(3)	108.3(2)

Table 4.8. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for (*R*)-**4.3c**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	26(1)	19(1)	30(1)	-2(1)	8(1)	2(1)
N(1)	44(1)	26(1)	38(1)	-13(1)	-19(1)	10(1)
O(1)	38(1)	91(2)	45(1)	-20(1)	19(1)	1(1)
O(2)	74(2)	19(1)	50(1)	4(1)	-6(1)	-12(1)
O(3)	38(1)	28(1)	48(1)	4(1)	21(1)	3(1)
C(1)	19(1)	22(1)	32(1)	6(1)	2(1)	0(1)
C(2)	24(1)	35(2)	53(2)	18(1)	-2(1)	5(1)
C(3)	36(2)	52(2)	53(2)	23(2)	-24(2)	-9(1)
C(4)	50(2)	48(2)	39(2)	10(1)	-26(2)	-16(2)
C(5)	38(2)	30(1)	32(1)	2(1)	-11(1)	-7(1)
C(6)	21(1)	21(1)	25(1)	5(1)	-4(1)	-2(1)
C(7)	23(1)	18(1)	20(1)	-2(1)	-3(1)	2(1)
C(8)	24(1)	28(1)	31(1)	6(1)	0(1)	-4(1)
C(9)	25(1)	25(1)	35(1)	5(1)	3(1)	-2(1)
C(10)	24(1)	38(2)	40(2)	10(1)	-2(1)	-4(1)
C(11)	18(1)	25(1)	23(1)	4(1)	-5(1)	-2(1)
C(12)	44(1)	25(1)	27(1)	-6(1)	12(1)	-10(1)
C(13)	29(1)	22(1)	43(2)	-1(1)	-4(1)	-5(1)
C(14)	36(1)	33(1)	31(1)	9(1)	4(1)	-9(1)

Table 4.9. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for (*R*)-**4.3c**.

	x	y	z	U(eq)
H(1)	5160(50)	6570(30)	9490(20)	44(10)
H(2B)	346	8222	7674	45
H(3A)	-457	7037	6507	57
H(4A)	887	5056	6223	55
H(5A)	3105	4230	7079	40
H(8A)	6353	4769	7639	33
H(8B)	6414	6306	7774	33
H(10)	9950(60)	5160(40)	9500(30)	69(13)
H(12A)	5464	2869	8098	38
H(13A)	4336	1084	9042	38
H(14A)	2571	2110	10117	40

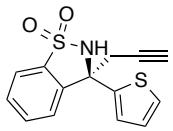
Table 4.10. Hydrogen bonds for (*R*)-**4.3c** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(1)#1	0.84(4)	2.06(4)	2.888(3)	167(3)

Symmetry transformations used to generate equivalent atoms:

#1 x+1/2,-y+3/2,-z+2

*B. X-ray Data Collection, Structure Solution and Refinement for (R)-**4.3e**:*



(*R*)-**4.3e**

A single crystal was grown from EtOAc with slow diffusion of pentanes at room temperature. A colorless crystal of approximate dimensions 0.573 x 0.369 x 0.266 mm was mounted on a glass fiber and transferred to a Bruker SMART APEX II diffractometer. The APEX2[37] program package was used to determine the unit-cell parameters and for data collection (5 sec/frame scan time for a sphere of diffraction data). The raw frame data was processed using SAINT[38] and SADABS[39] to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL[40] program. The diffraction symmetry was *mmm* and the systematic absences were consistent with the orthorhombic space group $P2_12_12_1$ that was later determined to be correct.

The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques. The analytical scattering factors[41] for neutral atoms were used throughout the analysis. S(2) and C(12) were disordered and included using partial site-occupancy-factors. The disorder was included to account for the approximate distribution of carbon (25%) / sulfur (75%) at the position of S(2) and carbon (75%) / sulfur (25%) at the position of C(12). H(1) and H(10) were located from a difference-Fourier map and refined (x,y,z and U_{iso}). All other hydrogen atoms were included using a riding model.

At convergence, wR2 = 0.0762 and Goof = 1.076 for 180 variables refined against 3338 data (0.73 Å), R1 = 0.0275 for those 3263 data with $I > 2.0\sigma(I)$. The absolute structure was assigned by refinement of the Flack parameter.[42]

Definitions:

$wR2 = [\Sigma[w(F_o^2-F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

$R1 = \Sigma||F_o|-|F_c|| / \Sigma|F_o|$

$Goof = S = [\Sigma[w(F_o^2-F_c^2)^2] / (n-p)]^{1/2}$ where n is the number of reflections and p is the total number of parameters refined.

The thermal ellipsoid plot is shown at the 50% probability level.

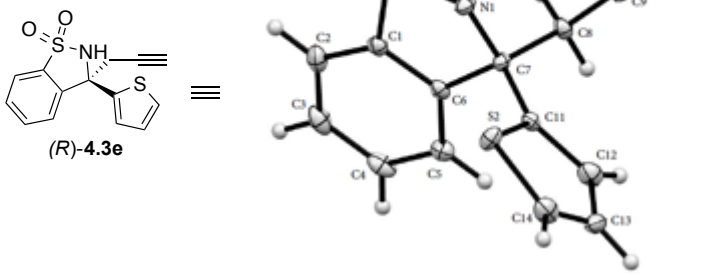


Table 4.11. Crystal data and structure refinement for (*R*)-**4.3e**.

Identification code	erj24 (Charlotte Osborne)	
Empirical formula	$C_{14}\ H_{11}\ N\ O_2\ S_2$	
Formula weight	289.36	
Temperature	88(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.5169(3) Å	a= 90°.
	b = 10.5263(5) Å	b= 90°.
	c = 16.5993(8) Å	g = 90°.
Volume	1313.42(10) $Å^3$	
Z	4	
Density (calculated)	1.463 Mg/m^3	
Absorption coefficient	0.401 mm^{-1}	
F(000)	600	
Crystal color	colorless	
Crystal size	0.573 x 0.369 x 0.266 mm^3	
Theta range for data collection	2.291 to 29.140°	
Index ranges	$-9 \le h \le 10$, $-14 \le k \le 14$, $-22 \le l \le 22$	
Reflections collected	16368	
Independent reflections	3338 [R(int) = 0.0221]	
Completeness to theta = 25.500°	99.9 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9277 and 0.8316	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3338 / 0 / 180	
Goodness-of-fit on F^2	1.076	
Final R indices [I>2sigma(I) = 3263 data]	R1 = 0.0275, wR2 = 0.0754	
R indices (all data, 0.73Å)	R1 = 0.0283, wR2 = 0.0762	

Absolute structure parameter	0.040(17)
Largest diff. peak and hole	0.529 and -0.343 e.Å^{-3}

Table 4.12. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (*R*)-**4.3e**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	3023(1)	2396(1)	1085(1)	14(1)
S(2)	2903(1)	6156(1)	301(1)	14(1)
O(1)	1668(2)	2128(2)	496(1)	25(1)
O(2)	4157(2)	1338(1)	1302(1)	23(1)
N(1)	4166(2)	3658(2)	827(1)	15(1)
C(1)	2139(3)	3119(2)	1943(1)	14(1)
C(2)	841(3)	2609(2)	2448(1)	20(1)
C(3)	343(3)	3334(2)	3112(1)	23(1)
C(4)	1123(3)	4508(2)	3257(1)	21(1)
C(5)	2439(3)	4994(2)	2750(1)	17(1)
C(6)	2945(3)	4280(2)	2079(1)	13(1)
C(7)	4410(3)	4602(2)	1480(1)	12(1)
C(8)	6241(3)	4446(2)	1908(1)	15(1)
C(9)	7722(3)	4540(2)	1342(1)	18(1)
C(10)	8858(3)	4545(2)	845(2)	24(1)
C(11)	4195(2)	5919(2)	1128(1)	12(1)
C(12)	4882(2)	7120(2)	1456(1)	23(1)
C(13)	4238(3)	8128(2)	940(1)	21(1)
C(14)	3182(3)	7740(2)	320(1)	22(1)

Table 4.13. Bond lengths [Å] and angles [°] for (*R*)-**4.3e**.

S(1)-O(1)	1.4387(15)
S(1)-O(2)	1.4478(16)
S(1)-N(1)	1.6393(18)
S(1)-C(1)	1.747(2)
S(2)-C(14)	1.682(2)
S(2)-C(11)	1.6990(19)
N(1)-C(7)	1.482(2)
C(1)-C(6)	1.382(3)
C(1)-C(2)	1.394(3)
C(2)-C(3)	1.392(3)
C(3)-C(4)	1.389(3)
C(4)-C(5)	1.396(3)
C(5)-C(6)	1.396(3)
C(6)-C(7)	1.522(3)
C(7)-C(11)	1.513(3)
C(7)-C(8)	1.557(3)
C(8)-C(9)	1.460(3)
C(9)-C(10)	1.187(3)
C(11)-C(12)	1.470(2)
C(12)-C(13)	1.447(3)
C(13)-C(14)	1.363(3)

O(1)-S(1)-O(2)	115.80(10)
O(1)-S(1)-N(1)	110.63(10)
O(2)-S(1)-N(1)	112.31(10)
O(1)-S(1)-C(1)	111.70(10)
O(2)-S(1)-C(1)	110.87(9)
N(1)-S(1)-C(1)	93.38(9)

C(14)-S(2)-C(11)	93.42(10)
C(7)-N(1)-S(1)	114.66(13)
C(6)-C(1)-C(2)	123.30(19)
C(6)-C(1)-S(1)	110.61(14)
C(2)-C(1)-S(1)	126.07(16)
C(3)-C(2)-C(1)	117.0(2)
C(4)-C(3)-C(2)	120.8(2)
C(3)-C(4)-C(5)	121.4(2)
C(6)-C(5)-C(4)	118.5(2)
C(1)-C(6)-C(5)	119.15(18)
C(1)-C(6)-C(7)	114.06(16)
C(5)-C(6)-C(7)	126.69(18)
N(1)-C(7)-C(11)	108.54(15)
N(1)-C(7)-C(6)	103.80(15)
C(11)-C(7)-C(6)	112.32(15)
N(1)-C(7)-C(8)	111.86(16)
C(11)-C(7)-C(8)	111.52(16)
C(6)-C(7)-C(8)	108.58(15)
C(9)-C(8)-C(7)	111.95(16)
C(10)-C(9)-C(8)	174.7(2)
C(12)-C(11)-C(7)	127.37(16)
C(12)-C(11)-S(2)	111.95(13)
C(7)-C(11)-S(2)	120.48(14)
C(13)-C(12)-C(11)	107.10(15)
C(14)-C(13)-C(12)	114.98(18)
C(13)-C(14)-S(2)	112.53(16)

Table 4.14. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for (*R*)-**4.3e**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	15(1)	12(1)	16(1)	-1(1)	-2(1)	0(1)
S(2)	20(1)	11(1)	12(1)	3(1)	-5(1)	-2(1)
O(1)	21(1)	31(1)	24(1)	-9(1)	-7(1)	-2(1)
O(2)	25(1)	14(1)	31(1)	2(1)	0(1)	4(1)
N(1)	18(1)	12(1)	14(1)	-2(1)	3(1)	-1(1)
C(1)	13(1)	15(1)	15(1)	2(1)	-1(1)	2(1)
C(2)	15(1)	23(1)	23(1)	7(1)	-1(1)	-4(1)
C(3)	17(1)	32(1)	21(1)	11(1)	4(1)	1(1)
C(4)	20(1)	30(1)	13(1)	3(1)	3(1)	7(1)
C(5)	17(1)	19(1)	14(1)	0(1)	0(1)	3(1)
C(6)	11(1)	15(1)	12(1)	3(1)	-2(1)	2(1)
C(7)	13(1)	11(1)	12(1)	-1(1)	1(1)	0(1)
C(8)	13(1)	16(1)	16(1)	3(1)	-1(1)	1(1)
C(9)	15(1)	17(1)	22(1)	5(1)	-5(1)	1(1)
C(10)	15(1)	27(1)	29(1)	7(1)	2(1)	2(1)
C(11)	11(1)	13(1)	13(1)	2(1)	1(1)	1(1)
C(12)	21(1)	24(1)	24(1)	7(1)	1(1)	2(1)
C(13)	22(1)	13(1)	28(1)	-2(1)	8(1)	-1(1)
C(14)	20(1)	22(1)	22(1)	10(1)	3(1)	2(1)

Table 4.15. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for (*R*)-**4.3e**.

	x	y	z	U(eq)
H(1)	4980(40)	3440(30)	590(20)	34(9)
H(2B)	321	1803	2344	24
H(3A)	-542	3022	3470	28
H(4A)	754	4991	3711	25
H(5A)	2977	5793	2858	20
H(8A)	6368	5112	2325	18
H(8B)	6283	3610	2180	18
H(10)	9730(50)	4590(40)	510(20)	55(11)
H(12A)	5610	7216	1920	27
H(13A)	4530	8995	1027	25
H(14A)	2661	8303	-61	26

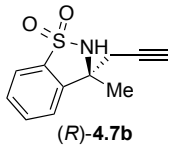
Table 4.16. Hydrogen bonds for (*R*)-**4.3e** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(1)#1	0.76(3)	2.28(3)	3.008(2)	159(3)
C(8)-H(8A)...O(2)#2	0.99	2.65	3.590(3)	158.9
C(13)-H(13A)...O(2)#3	0.95	2.52	3.432(3)	160.2

Symmetry transformations used to generate equivalent atoms:

#1 x+1/2,-y+1/2,-z #2 -x+1,y+1/2,-z+1/2 #3 x,y+1,z

*C. X-ray Data Collection, Structure Solution and Refinement for (R)-**4.7b**:*



(*R*)-**4.7b**

A single crystal was grown from Et_2O with slow diffusion of pentanes at room temperature. A colorless crystal of approximate dimensions 0.284 x 0.299 x 0.489 mm was mounted on a glass fiber and transferred to a Bruker SMART APEX II diffractometer. The APEX2[37] program package was used to determine the unit-cell parameters and for data collection (10 sec/frame scan time for a sphere of diffraction data). The raw frame data was processed using SAINT[38] and SADABS[39] to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL[40] program. The diffraction symmetry was *mmm* and the systematic absences were consistent with the orthorhombic space group $P2_12_12_1$ that was later determined to be correct.

The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques. The analytical scattering factors[41] for neutral atoms were used throughout the analysis. Hydrogen atoms were located from a difference-Fourier map and refined (x,y,z and U_{iso}).

At convergence, wR2 = 0.0679 and Goof = 1.058 for 180 variables refined against 2571 data (0.74Å), R1 = 0.0259 for those 2521 data with $I > 2.0\sigma(I)$. The absolute structure was assigned by refinement of the Flack parameter.[42]

Definitions:

$wR2 = [\Sigma[w(F_o^2-F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

$R1 = \Sigma||F_o|-|F_c|| / \Sigma|F_o|$

$Goof = S = [\Sigma[w(F_o^2-F_c^2)^2] / (n-p)]^{1/2}$ where n is the number of reflections and p is the total number of parameters refined.

The thermal ellipsoid plot is shown at the 50% probability level.

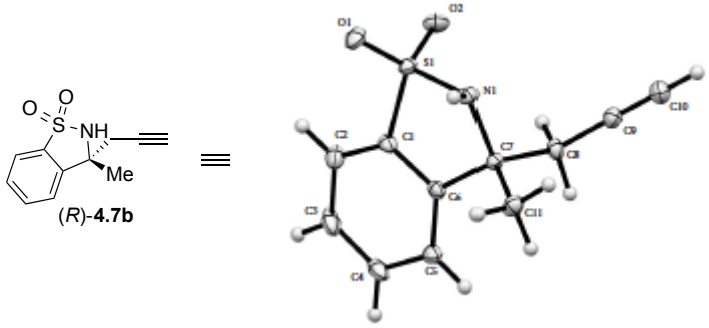


Table 4.17. Crystal data and structure refinement for (*R*)-**4.7b**.

Identification code	erj26 (Charlotte Osborne)	
Empirical formula	C_{11} H_{11} N O_2 S	
Formula weight	221.27	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.0916(6) Å	a= 90°.
	b = 9.4218(7) Å	b= 90°.
	c = 13.8016(10) Å	g = 90°.
Volume	1052.20(13) $Å^3$	
Z	4	
Density (calculated)	1.397 Mg/m^3	
Absorption coefficient	0.285 mm^{-1}	
F(000)	464	
Crystal color	colorless	
Crystal size	0.489 x 0.299 x 0.284 mm^3	
Theta range for data collection	2.617 to 28.724°	
Index ranges	$-10 \le h \le 10$, $-12 \le k \le 12$, $-18 \le l \le 18$	
Reflections collected	12648	
Independent reflections	2571 [R(int) = 0.0277]	
Completeness to theta = 25.500°	99.9 %	
Absorption correction	Numerical	
Max. and min. transmission	1.0000 and 0.8521	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2571 / 0 / 180	
Goodness-of-fit on F^2	1.058	
Final R indices [I>2sigma(I) = 2521 data]	R1 = 0.0259, wR2 = 0.0672	

R indices (all data, 0.74Å)	R1 = 0.0265, wR2 = 0.0679
Absolute structure parameter	0.01(3)
Largest diff. peak and hole	0.314 and -0.279 e.Å^{-3}

Table 4.18. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (*R*)-**4.7b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	995(1)	3781(1)	7431(1)	14(1)
O(1)	639(2)	4308(2)	8386(1)	21(1)
O(2)	360(2)	2389(1)	7201(1)	22(1)
N(1)	370(2)	4924(2)	6611(1)	14(1)
C(1)	3091(2)	3848(2)	7115(1)	15(1)
C(2)	4403(2)	3209(2)	7592(1)	22(1)
C(3)	5950(3)	3368(2)	7180(1)	26(1)
C(4)	6157(2)	4107(2)	6320(1)	24(1)
C(5)	4813(2)	4700(2)	5835(1)	19(1)
C(6)	3250(2)	4566(2)	6245(1)	14(1)
C(7)	1612(2)	5056(2)	5812(1)	14(1)
C(8)	1157(2)	4018(2)	4982(1)	17(1)
C(9)	-448(2)	4300(2)	4531(1)	18(1)
C(10)	-1745(2)	4511(2)	4149(1)	23(1)
C(11)	1642(3)	6587(2)	5455(1)	19(1)

Table 4.19. Bond lengths [Å] and angles [°] for (*R*)-**4.7b**.

S(1)-O(1)	1.4377(13)
S(1)-O(2)	1.4438(14)
S(1)-N(1)	1.6418(16)
S(1)-C(1)	1.7524(17)
N(1)-C(7)	1.497(2)
N(1)-H(1)	0.77(3)
C(1)-C(6)	1.384(2)
C(1)-C(2)	1.388(3)
C(2)-C(3)	1.384(3)
C(2)-H(2)	0.93(3)
C(3)-C(4)	1.386(3)
C(3)-H(3)	0.91(3)
C(4)-C(5)	1.394(3)
C(4)-H(4)	0.95(3)
C(5)-C(6)	1.392(2)
C(5)-H(5)	0.94(3)
C(6)-C(7)	1.525(2)
C(7)-C(11)	1.525(2)
C(7)-C(8)	1.550(2)
C(8)-C(9)	1.464(3)
C(8)-H(8A)	1.01(2)
C(8)-H(8B)	0.95(2)
C(9)-C(10)	1.192(3)
C(10)-H(10)	0.92(3)
C(11)-H(11A)	0.98(3)
C(11)-H(11B)	0.93(3)
C(11)-H(11C)	0.97(3)

O(1)-S(1)-O(2)	116.34(8)
O(1)-S(1)-N(1)	110.12(8)
O(2)-S(1)-N(1)	109.58(8)
O(1)-S(1)-C(1)	114.17(8)
O(2)-S(1)-C(1)	108.82(9)
N(1)-S(1)-C(1)	95.88(8)
C(7)-N(1)-S(1)	110.82(12)
C(7)-N(1)-H(1)	113.8(19)
S(1)-N(1)-H(1)	107.4(18)
C(6)-C(1)-C(2)	123.60(16)
C(6)-C(1)-S(1)	108.88(13)
C(2)-C(1)-S(1)	127.35(14)
C(3)-C(2)-C(1)	116.72(17)
C(3)-C(2)-H(2)	120.5(15)
C(1)-C(2)-H(2)	122.6(15)
C(2)-C(3)-C(4)	121.09(18)
C(2)-C(3)-H(3)	121.4(17)
C(4)-C(3)-H(3)	117.5(17)
C(3)-C(4)-C(5)	121.24(18)
C(3)-C(4)-H(4)	120.9(17)
C(5)-C(4)-H(4)	117.9(17)
C(6)-C(5)-C(4)	118.52(17)
C(6)-C(5)-H(5)	121.0(16)
C(4)-C(5)-H(5)	120.5(16)
C(1)-C(6)-C(5)	118.79(16)
C(1)-C(6)-C(7)	114.00(15)
C(5)-C(6)-C(7)	127.10(15)
N(1)-C(7)-C(11)	109.09(14)
N(1)-C(7)-C(6)	105.65(13)
C(11)-C(7)-C(6)	113.48(15)

N(1)-C(7)-C(8)	109.46(14)
C(11)-C(7)-C(8)	111.19(14)
C(6)-C(7)-C(8)	107.79(14)
C(9)-C(8)-C(7)	114.22(15)
C(9)-C(8)-H(8A)	109.7(14)
C(7)-C(8)-H(8A)	108.6(14)
C(9)-C(8)-H(8B)	109.7(15)
C(7)-C(8)-H(8B)	109.1(14)
H(8A)-C(8)-H(8B)	105.1(19)
C(10)-C(9)-C(8)	178.6(2)
C(9)-C(10)-H(10)	177.4(18)
C(7)-C(11)-H(11A)	109.3(16)
C(7)-C(11)-H(11B)	114.0(15)
H(11A)-C(11)-H(11B)	109(2)
C(7)-C(11)-H(11C)	109.1(17)
H(11A)-C(11)-H(11C)	107(2)
H(11B)-C(11)-H(11C)	108(2)

Table 4.20. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for (*R*)-**4.7b**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	13(1)	16(1)	14(1)	1(1)	3(1)	0(1)
O(1)	21(1)	27(1)	14(1)	1(1)	5(1)	4(1)
O(2)	22(1)	17(1)	26(1)	3(1)	4(1)	-4(1)
N(1)	14(1)	15(1)	14(1)	0(1)	2(1)	1(1)
C(1)	12(1)	19(1)	15(1)	-4(1)	1(1)	0(1)
C(2)	20(1)	30(1)	15(1)	-1(1)	-2(1)	5(1)
C(3)	15(1)	41(1)	22(1)	-6(1)	-6(1)	6(1)
C(4)	12(1)	36(1)	23(1)	-9(1)	1(1)	-2(1)
C(5)	16(1)	25(1)	16(1)	-3(1)	3(1)	-4(1)
C(6)	14(1)	16(1)	14(1)	-4(1)	-1(1)	-2(1)
C(7)	14(1)	16(1)	12(1)	0(1)	2(1)	-1(1)
C(8)	18(1)	19(1)	14(1)	-3(1)	-1(1)	0(1)
C(9)	20(1)	20(1)	14(1)	-1(1)	1(1)	-2(1)
C(10)	21(1)	28(1)	19(1)	1(1)	-3(1)	-3(1)
C(11)	23(1)	16(1)	18(1)	2(1)	2(1)	-1(1)

Table 4.21. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for (*R*)-**4.7b**.

	x	y	z	U(eq)
H(1)	190(30)	5630(30)	6875(19)	20(6)
H(2)	4280(30)	2750(30)	8185(18)	23(6)
H(3)	6870(30)	2970(30)	7450(20)	28(6)
H(4)	7230(30)	4240(30)	6048(19)	32(7)
H(5)	4960(30)	5170(30)	5240(20)	34(7)
H(8A)	2060(30)	4060(30)	4474(18)	21(6)
H(8B)	1180(30)	3070(20)	5224(17)	18(5)
H(10)	-2740(40)	4630(30)	3840(20)	36(7)
H(11A)	2430(30)	6670(30)	4925(19)	28(6)
H(11B)	1900(30)	7240(30)	5932(18)	23(6)
H(11C)	570(40)	6830(30)	5200(20)	36(7)

Table 4.22. Torsion angles [°] for (*R*)-**4.7b**.

O(1)-S(1)-N(1)-C(7)	138.66(12)
O(2)-S(1)-N(1)-C(7)	-92.16(13)
C(1)-S(1)-N(1)-C(7)	20.23(13)
O(1)-S(1)-C(1)-C(6)	-126.43(12)
O(2)-S(1)-C(1)-C(6)	101.75(14)
N(1)-S(1)-C(1)-C(6)	-11.27(14)
O(1)-S(1)-C(1)-C(2)	58.3(2)
O(2)-S(1)-C(1)-C(2)	-73.50(18)
N(1)-S(1)-C(1)-C(2)	173.48(17)
C(6)-C(1)-C(2)-C(3)	2.9(3)
S(1)-C(1)-C(2)-C(3)	177.46(15)
C(1)-C(2)-C(3)-C(4)	-1.4(3)
C(2)-C(3)-C(4)-C(5)	-0.7(3)
C(3)-C(4)-C(5)-C(6)	1.6(3)
C(2)-C(1)-C(6)-C(5)	-2.1(3)
S(1)-C(1)-C(6)-C(5)	-177.56(13)
C(2)-C(1)-C(6)-C(7)	174.41(17)
S(1)-C(1)-C(6)-C(7)	-1.05(18)
C(4)-C(5)-C(6)-C(1)	-0.2(3)
C(4)-C(5)-C(6)-C(7)	-176.18(17)
S(1)-N(1)-C(7)-C(11)	-144.84(13)
S(1)-N(1)-C(7)-C(6)	-22.51(16)
S(1)-N(1)-C(7)-C(8)	93.30(15)
C(1)-C(6)-C(7)-N(1)	14.5(2)
C(5)-C(6)-C(7)-N(1)	-169.29(17)
C(1)-C(6)-C(7)-C(11)	134.01(16)
C(5)-C(6)-C(7)-C(11)	-49.8(2)
C(1)-C(6)-C(7)-C(8)	-102.40(17)

C(5)-C(6)-C(7)-C(8)	73.8(2)
N(1)-C(7)-C(8)-C(9)	61.96(19)
C(11)-C(7)-C(8)-C(9)	-58.6(2)
C(6)-C(7)-C(8)-C(9)	176.40(14)

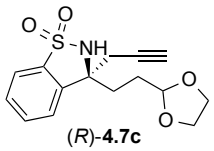
Table 4.23. Hydrogen bonds for (*R*)-**4.7b** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(2)#1	0.77(3)	2.14(3)	2.903(2)	171(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x,y+1/2,-z+3/2

*D. X-ray Data Collection, Structure Solution and Refinement for (R)-**4.7c**:*



(*R*)-**4.7c**

A single crystal was grown from EtOAc with slow diffusion of pentanes at room temperature. A colorless crystal of approximate dimensions 0.288 x 0.160 x 0.108 mm was mounted on a glass fiber and transferred to a Bruker SMART APEX II diffractometer. The APEX2[37] program package was used to determine the unit-cell parameters and for data collection (60 sec/frame scan time for a sphere of diffraction data). The raw frame data was processed using SAINT[38] and SADABS[39] to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL[40] program. The diffraction symmetry was *mmm* and the systematic absences were consistent with the orthorhombic space group $P2_12_12_1$ that was later determined to be correct.

The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques. The analytical scattering factors[41] for neutral atoms were used throughout the analysis. Hydrogen atoms were located from a difference-Fourier map and refined (x,y,z and U_{iso}).

At convergence, wR2 = 0.0706 and Goof = 1.040 for 258 variables refined against 3562 data (0.75 Å), R1 = 0.0294 for those 3283 data with $I > 2.0\sigma(I)$. The absolute structure was assigned by refinement of the Flack parameter.[42]

Definitions:

$wR2 = [\Sigma[w(F_o^2-F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

$R1 = \Sigma||F_o|-|F_c|| / \Sigma|F_o|$

$Goof = S = [\Sigma[w(F_o^2-F_c^2)^2] / (n-p)]^{1/2}$ where n is the number of reflections and p is the total number of parameters refined.

The thermal ellipsoid plot is shown at the 50% probability level.

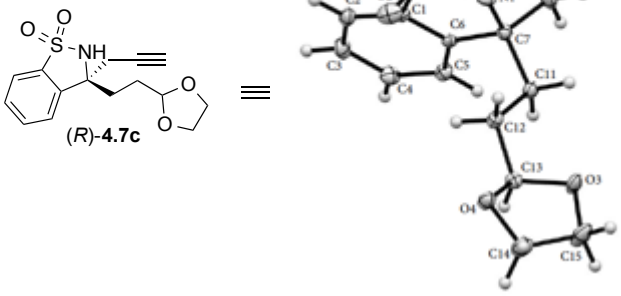


Table 4.24. Crystal data and structure refinement for (*R*)-**4.7c**.

Identification code	erj22 (Charlotte Osborne)	
Empirical formula	$C_{15}H_{17}NO_4S$	
Formula weight	307.35	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.7171(5) Å	a= 90°.
	b = 7.9486(5) Å	b= 90°.
	c = 23.8160(14) Å	g = 90°.
Volume	1460.88(16) $Å^3$	
Z	4	
Density (calculated)	1.397 Mg/m^3	
Absorption coefficient	0.237 mm^{-1}	
F(000)	648	
Crystal color	colorless	
Crystal size	0.288 x 0.160 x 0.108 mm^3	
Theta range for data collection	1.710 to 28.288°	
Index ranges	$-10 \leq h \leq 10$, $-10 \leq k \leq 10$, $-31 \leq l \leq 31$	
Reflections collected	17581	
Independent reflections	3562 [R(int) = 0.0306]	
Completeness to theta = 25.500°	100.0 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9980 and 0.9400	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3562 / 0 / 258	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I) = 3283 data]	R1 = 0.0294, wR2 = 0.0678	
R indices (all data, 0.75 Å)	R1 = 0.0342, wR2 = 0.0706	

Absolute structure parameter	0.07(2)
Largest diff. peak and hole	0.316 and -0.247 e.Å^{-3}

Table 4.25. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (*R*)-**4.7c**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	9619(1)	2605(1)	9054(1)	17(1)
N(1)	10456(2)	3214(2)	8456(1)	18(1)
O(1)	10861(2)	1665(2)	9377(1)	25(1)
O(2)	7974(2)	1792(2)	8972(1)	25(1)
O(3)	7309(2)	5275(2)	6830(1)	22(1)
O(4)	5065(2)	4151(2)	7301(1)	20(1)
C(1)	9266(2)	4647(2)	9298(1)	14(1)
C(2)	8545(3)	5077(3)	9810(1)	19(1)
C(3)	8250(3)	6771(3)	9908(1)	22(1)
C(4)	8676(3)	7967(3)	9505(1)	21(1)
C(5)	9407(2)	7505(2)	8996(1)	17(1)
C(6)	9706(2)	5809(2)	8890(1)	13(1)
C(7)	10489(3)	5054(2)	8361(1)	15(1)
C(8)	12367(3)	5666(3)	8281(1)	23(1)
C(9)	13497(3)	5248(3)	8757(1)	24(1)
C(10)	14373(3)	4848(3)	9138(1)	34(1)
C(11)	9414(3)	5506(3)	7836(1)	16(1)
C(12)	7675(3)	4603(3)	7816(1)	16(1)
C(13)	6485(3)	5257(3)	7365(1)	16(1)
C(14)	4400(3)	4455(4)	6752(1)	30(1)
C(15)	5922(3)	5167(4)	6424(1)	30(1)

Table 4.26. Bond lengths [Å] and angles [°] for (*R*)-**4.7c**.

S(1)-O(2)	1.4379(16)
S(1)-O(1)	1.4383(15)
S(1)-N(1)	1.6361(18)
S(1)-C(1)	1.746(2)
N(1)-C(7)	1.480(3)
O(3)-C(13)	1.425(2)
O(3)-C(15)	1.445(3)
O(4)-C(13)	1.413(2)
O(4)-C(14)	1.425(3)
C(1)-C(2)	1.383(3)
C(1)-C(6)	1.384(3)
C(2)-C(3)	1.385(3)
C(3)-C(4)	1.390(3)
C(4)-C(5)	1.387(3)
C(5)-C(6)	1.391(3)
C(6)-C(7)	1.521(3)
C(7)-C(8)	1.541(3)
C(7)-C(11)	1.543(3)
C(8)-C(9)	1.468(3)
C(9)-C(10)	1.175(3)
C(11)-C(12)	1.523(3)
C(12)-C(13)	1.505(3)
C(14)-C(15)	1.519(3)
O(2)-S(1)-O(1)	115.30(10)
O(2)-S(1)-N(1)	111.35(9)
O(1)-S(1)-N(1)	110.84(10)
O(2)-S(1)-C(1)	108.98(9)
O(1)-S(1)-C(1)	114.11(9)

N(1)-S(1)-C(1)	94.39(9)
C(7)-N(1)-S(1)	115.63(13)
C(13)-O(3)-C(15)	105.46(17)
C(13)-O(4)-C(14)	105.85(16)
C(2)-C(1)-C(6)	123.63(18)
C(2)-C(1)-S(1)	125.90(16)
C(6)-C(1)-S(1)	110.34(14)
C(1)-C(2)-C(3)	117.03(19)
C(2)-C(3)-C(4)	120.6(2)
C(5)-C(4)-C(3)	121.3(2)
C(4)-C(5)-C(6)	118.85(18)
C(1)-C(6)-C(5)	118.58(17)
C(1)-C(6)-C(7)	114.62(16)
C(5)-C(6)-C(7)	126.80(17)
N(1)-C(7)-C(6)	104.84(15)
N(1)-C(7)-C(8)	110.31(17)
C(6)-C(7)-C(8)	110.57(16)
N(1)-C(7)-C(11)	110.20(16)
C(6)-C(7)-C(11)	111.43(15)
C(8)-C(7)-C(11)	109.42(16)
C(9)-C(8)-C(7)	113.10(18)
C(10)-C(9)-C(8)	177.2(3)
C(12)-C(11)-C(7)	112.91(16)
C(13)-C(12)-C(11)	113.39(17)
O(4)-C(13)-O(3)	104.82(15)
O(4)-C(13)-C(12)	109.61(16)
O(3)-C(13)-C(12)	111.66(17)
O(4)-C(14)-C(15)	104.84(18)
O(3)-C(15)-C(14)	104.59(18)

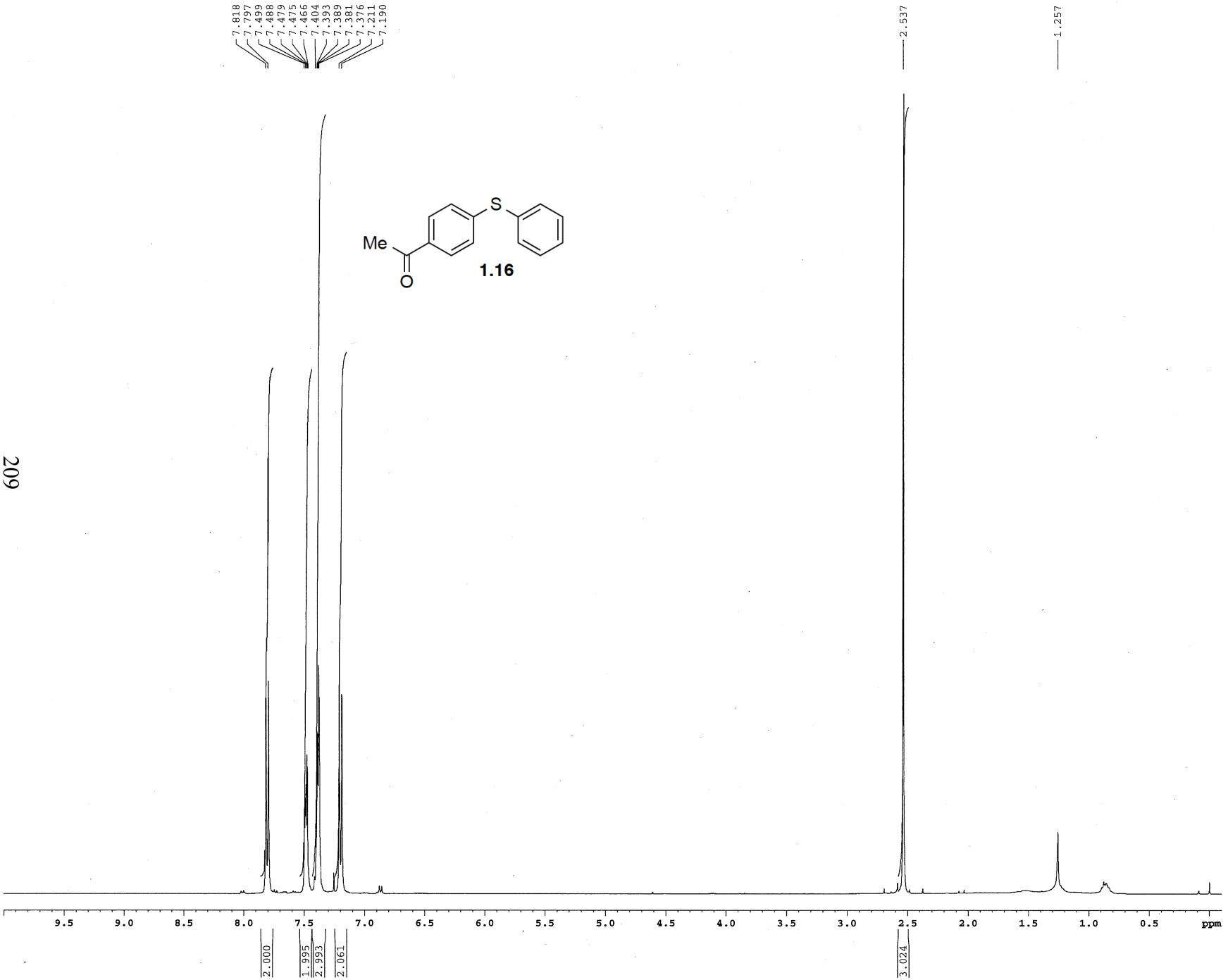
Table 4.27. Anisotropic displacement parameters ($Å^2$x 10^3) for (*R*)-**4.7c**. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	19(1)	12(1)	18(1)	1(1)	-6(1)	0(1)
N(1)	21(1)	17(1)	18(1)	-4(1)	-2(1)	6(1)
O(1)	28(1)	20(1)	27(1)	4(1)	-9(1)	5(1)
O(2)	26(1)	18(1)	32(1)	1(1)	-9(1)	-7(1)
O(3)	22(1)	31(1)	12(1)	5(1)	-3(1)	-6(1)
O(4)	17(1)	26(1)	17(1)	4(1)	-4(1)	-5(1)
C(1)	14(1)	13(1)	16(1)	0(1)	-3(1)	-1(1)
C(2)	17(1)	24(1)	15(1)	3(1)	1(1)	-5(1)
C(3)	22(1)	28(1)	15(1)	-6(1)	4(1)	0(1)
C(4)	24(1)	18(1)	21(1)	-4(1)	-2(1)	4(1)
C(5)	18(1)	16(1)	18(1)	1(1)	-2(1)	-2(1)
C(6)	11(1)	17(1)	11(1)	1(1)	-3(1)	-1(1)
C(7)	14(1)	16(1)	14(1)	-1(1)	0(1)	1(1)
C(8)	16(1)	34(1)	18(1)	-2(1)	3(1)	-3(1)
C(9)	14(1)	31(1)	28(1)	-8(1)	3(1)	-1(1)
C(10)	23(1)	43(1)	34(1)	-10(1)	-8(1)	4(1)
C(11)	17(1)	19(1)	12(1)	1(1)	0(1)	-1(1)
C(12)	19(1)	17(1)	14(1)	2(1)	0(1)	-1(1)
C(13)	17(1)	15(1)	16(1)	0(1)	0(1)	0(1)
C(14)	24(1)	45(2)	22(1)	9(1)	-8(1)	-5(1)
C(15)	33(1)	37(1)	19(1)	9(1)	-10(1)	-12(1)

Table 4.28. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for (*R*)-**4.7c**.

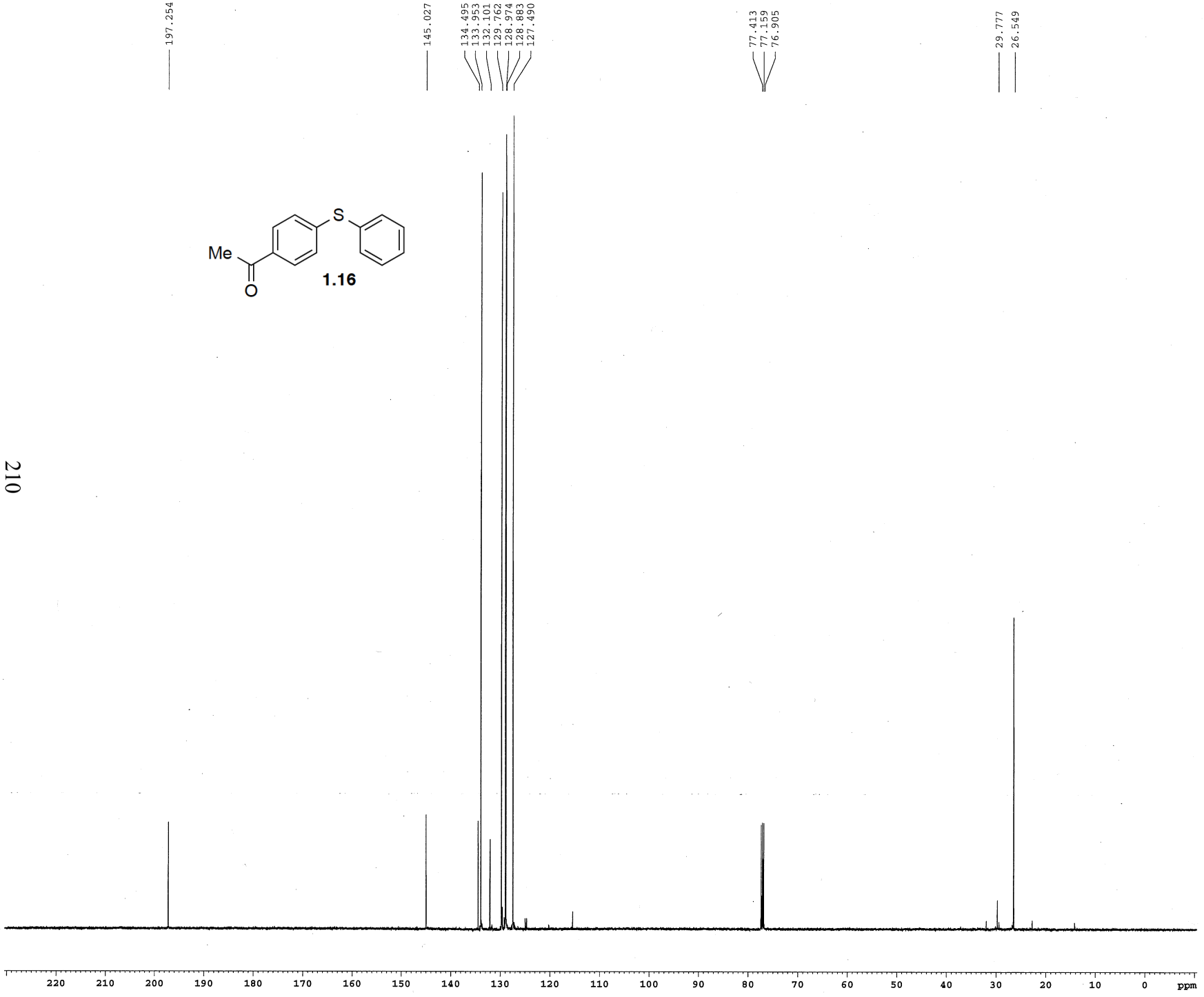
	x	y	z	U(eq)
H(1)	11280(40)	2610(40)	8381(11)	34(7)
H(2B)	8200(40)	4230(40)	10076(12)	37(8)
H(3A)	7770(30)	7090(30)	10250(10)	20(6)
H(4A)	8440(30)	9070(40)	9586(11)	28(7)
H(5A)	9700(30)	8340(30)	8715(10)	27(7)
H(8A)	12820(30)	5150(30)	7952(11)	23(6)
H(8B)	12330(30)	6880(40)	8216(10)	24(6)
H(10)	15060(40)	4580(40)	9411(13)	51(9)
H(11A)	9240(30)	6750(30)	7845(9)	21(6)
H(11B)	10110(30)	5230(30)	7509(10)	15(5)
H(12A)	7860(30)	3410(30)	7749(10)	20(6)
H(12B)	7070(30)	4720(30)	8154(11)	23(6)
H(13A)	6040(30)	6350(30)	7452(9)	12(5)
H(14A)	3410(40)	5190(40)	6780(12)	40(8)
H(14B)	4030(50)	3470(50)	6598(15)	67(11)
H(15A)	6290(40)	4470(40)	6122(14)	55(10)
H(15B)	5690(30)	6250(30)	6278(11)	27(7)

1H spectrum



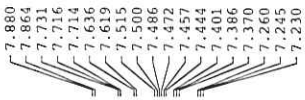

```
Current Data Parameters
USER                osborn
NAME       CAO-II-170 pure
EXPNO                    4
PROCNO                   1

F2 - Acquisition Parameters
Date_            20140121
Time                14.26
INSTRUM          drx400
PROBHD   5 mm QNP H/F/P
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     2
SWH           6410.256 Hz
FIDRES        0.097813 Hz
AQ            5.1118579 sec
RG                    64
DW               78.000 usec
DE                4.50 usec
TE                298.0 K
D1            0.10000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                  1H
P1               12.00 usec
PL1               0.00 dB
SFO1        400.1328009 MHz

F2 - Processing parameters
SI                 65536
SF          400.1300232 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                2.00
```

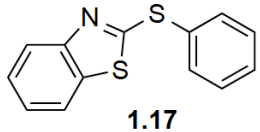
Z–restored spin–echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME          CAO-II-170 pure
EXPNO                    3
PROCNO                   1

F2 - Acquisition Parameters
Date_              20140121
Time                 13.05
INSTRUM            cryo500
PROBHD    5 mm CPTCI 1H-
PULPROG   SpinEchopg30gp.prd
TD                   65536
SOLVENT              CDCl3
NS                     321
DS                      16
SWH             30303.031 Hz
FIDRES              0.462388 Hz
AQ                1.0813940 sec
RG                   7298.2
DW                  16.500 usec
DE                   6.00 usec
TE                  298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec
P2                  31.00 usec

======== CHANNEL f1 ========
NUC1                   13C
P1                   15.50 usec
P11                 500.00 usec
P12                2000.00 usec
PL0                 120.00 dB
PL1                  -1.00 dB
SFO1           125.7942548 MHz
SP1                  3.20 dB
SP2                  3.20 dB
SPNAM1     Crp60,0.5,20.1
SPNAM2       Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2               100.00 usec
PL2                  1.60 dB
PL12                24.60 dB
SFO2           500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1            SINE.100
GPNAM2            SINE.100
GPX1                 0.00 %
GPX2                 0.00 %
GPY1                 0.00 %
GPY2                 0.00 %
GPZ1                30.00 %
GPZ2                50.00 %
p15                500.00 usec
p16               1000.00 usec

F2 - Processing parameters
SI                   65536
SF             125.7804196 MHz
WDW                    EM
SSB                    0
LB                   1.00 Hz
GB                     0
PC                   2.00
```

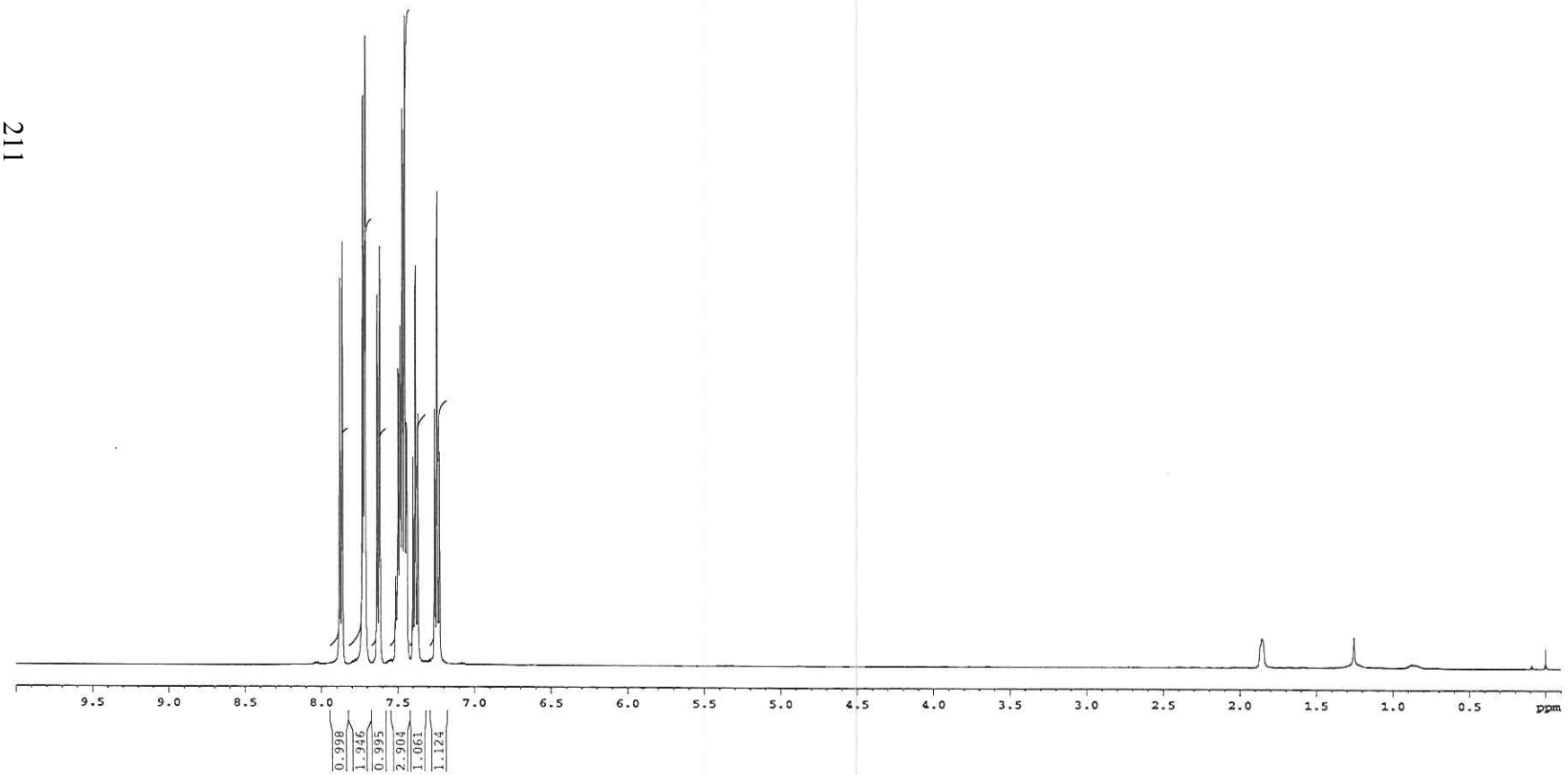
1H spectrum



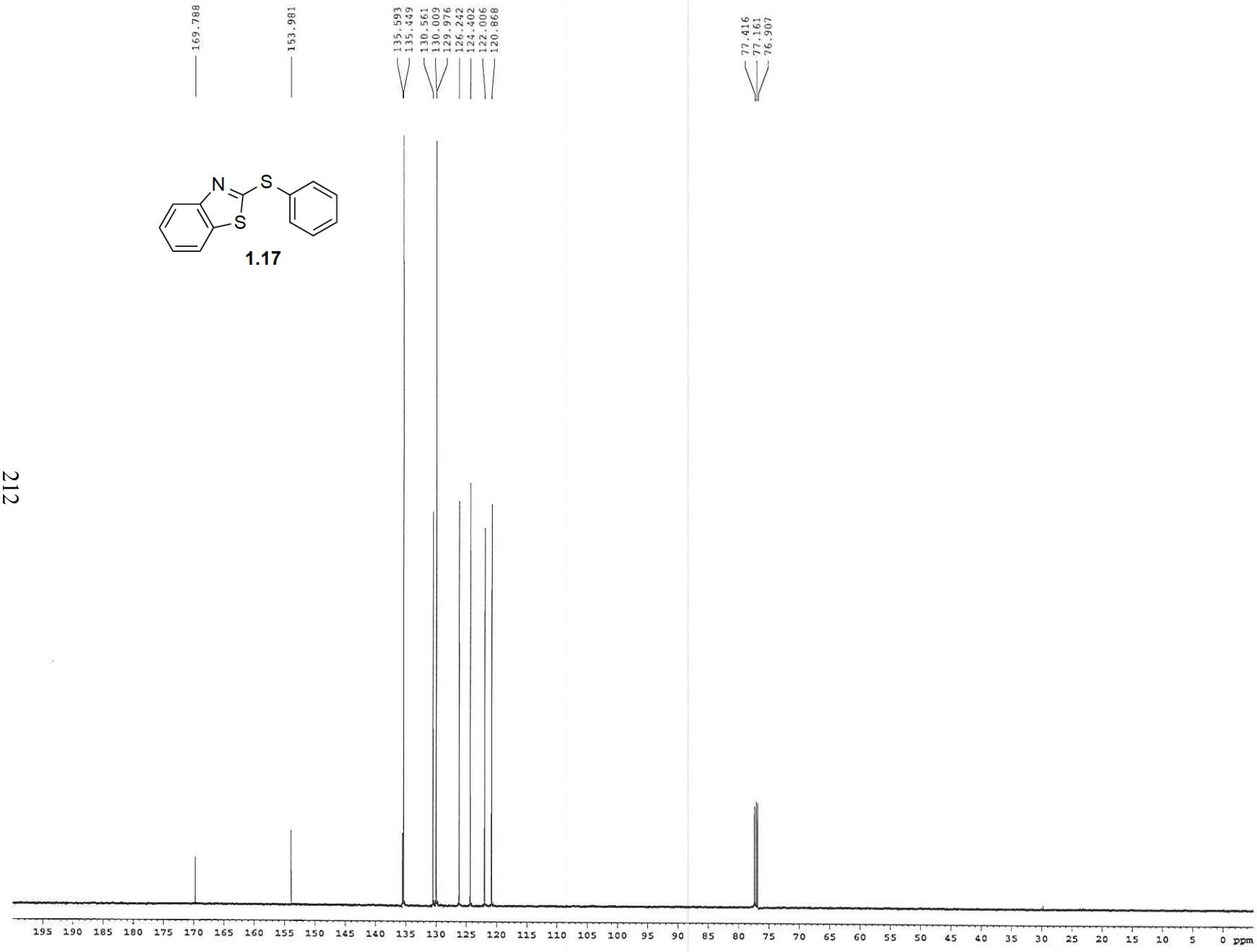


1.17


```
Current Data Parameters
USER              yonova
NAME      imy2 - Benzothiazole-f
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_          20100916
Time               17.05
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 81728
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             8012.820 Hz
FIDRES          0.098043 Hz
AQ              5.0998774 sec
RG                   5.7
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1             0.10000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 7.50 usec
PL1                1.60 dB
SFO1          500.2235015 MHz

F2 - Processing parameters
SI                 65536
SF            500.2200397 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  4.00
```



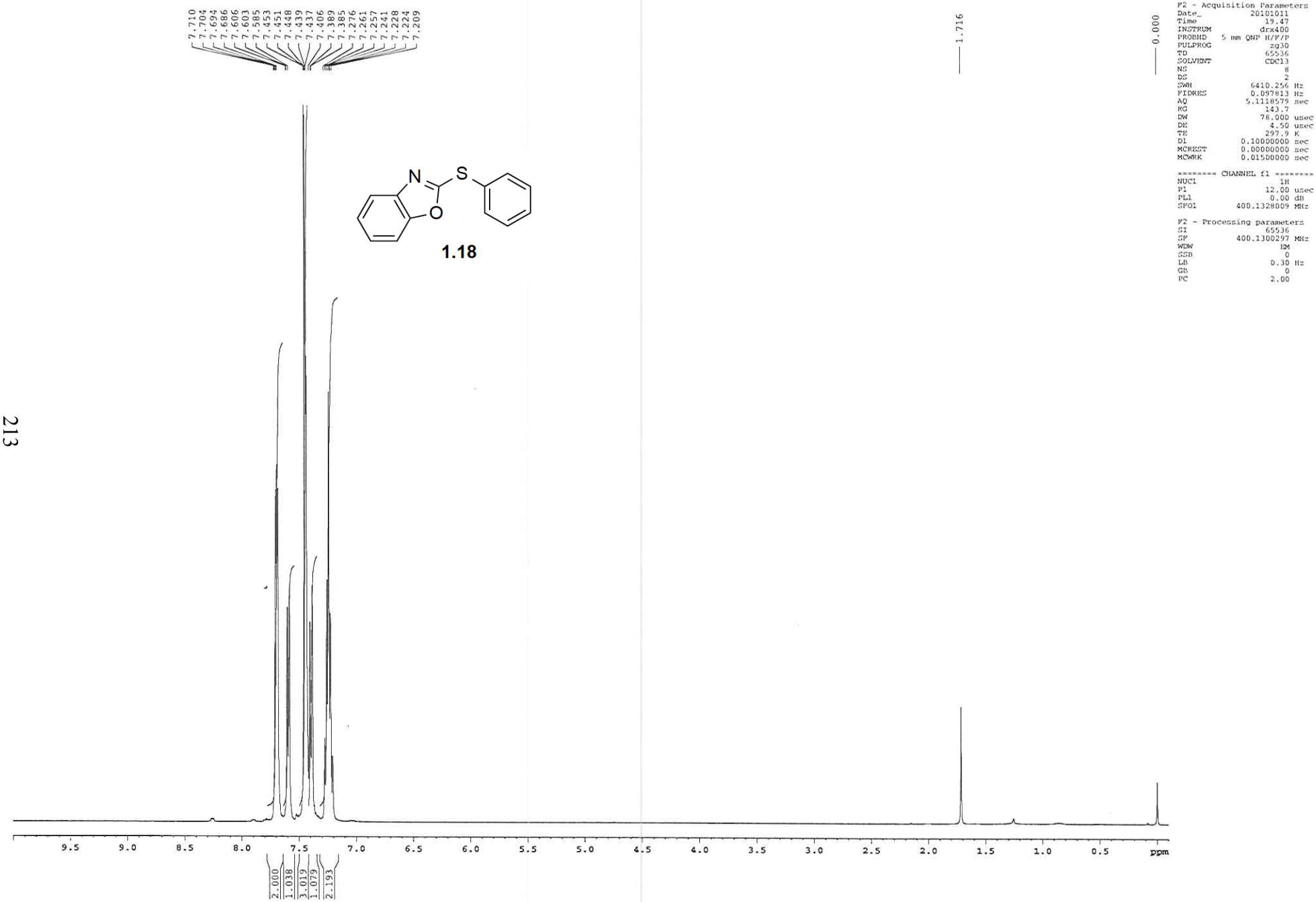
Z-restored spin-echo 13C spectrum with 1H decoupling



1.17

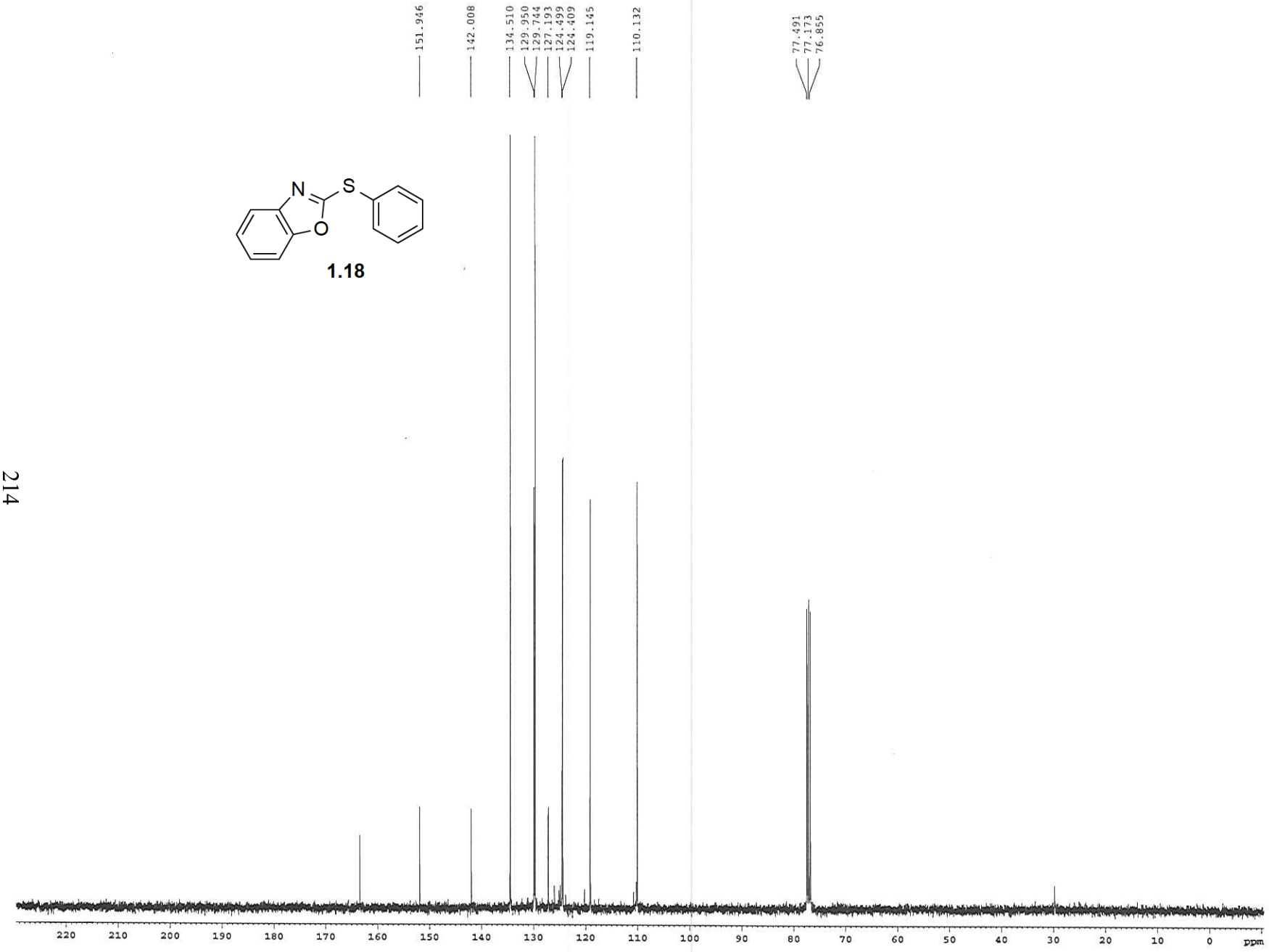
```
Current Data Parameters
USER                yonova
NAME      imy2 - Benzothiazole-S
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_            20100916
Time                17.09
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                  65536
SOLVENT             CDCl3
NS                    168
DS                     16
SWH              30303.031 Hz
FIDRES           0.462388 Hz
AQ               1.0813940 sec
RG                  7298.2
DW                 16.500 usec
DE                  6.00 usec
TE                298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec
P2                 31.00 usec

======== CHANNEL f1 ========
NUC1                 13C
P1                 15.50 usec
P11               500.00 usec
P12              2000.00 usec
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MHz
SP1                3.20 dB
SP2                3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7804210 MHz
WDW                    EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  2.00
```

1H spectrum




```
Current Data Parameters
USER                yonova
NAME      imy2 - benzoxazol
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20101011
Time                19.47
INSTRUM          drx400
PROBHD    5 mm QNP H/F/P
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     2
SWH              6410.256 Hz
FIDRES           0.097813 Hz
AQ               5.1118579 sec
RG                 143.7
DW                78.000 usec
DE                 4.50 usec
TE                297.9 K
D1            0.10000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                12.00 usec
PL1                0.00 dB
SFO1        400.1328009 MHz

F2 - Processing parameters
SI                 65536
SF          400.1300297 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 2.00
```

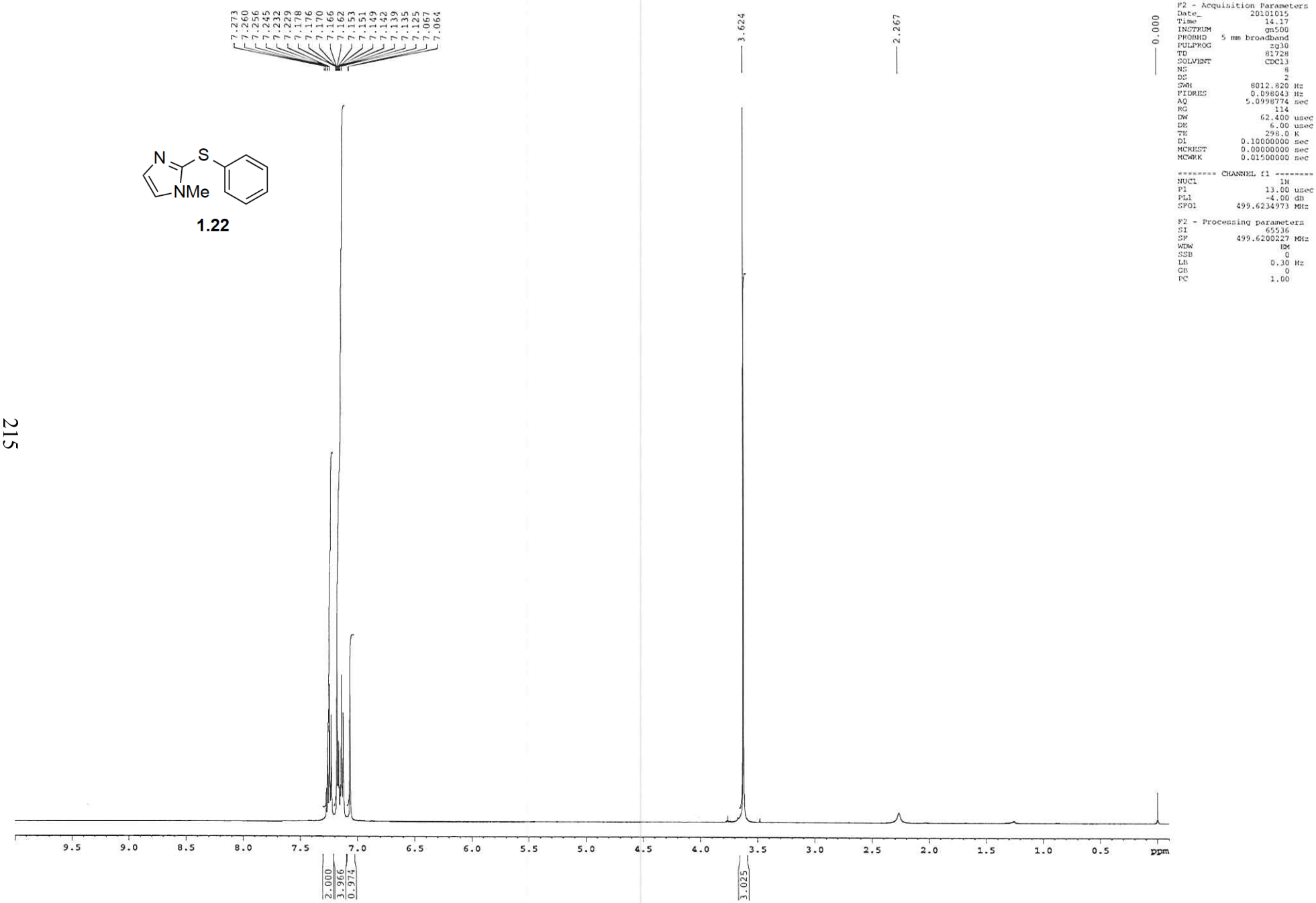
13C spectrum with 1H decoupling



1.18

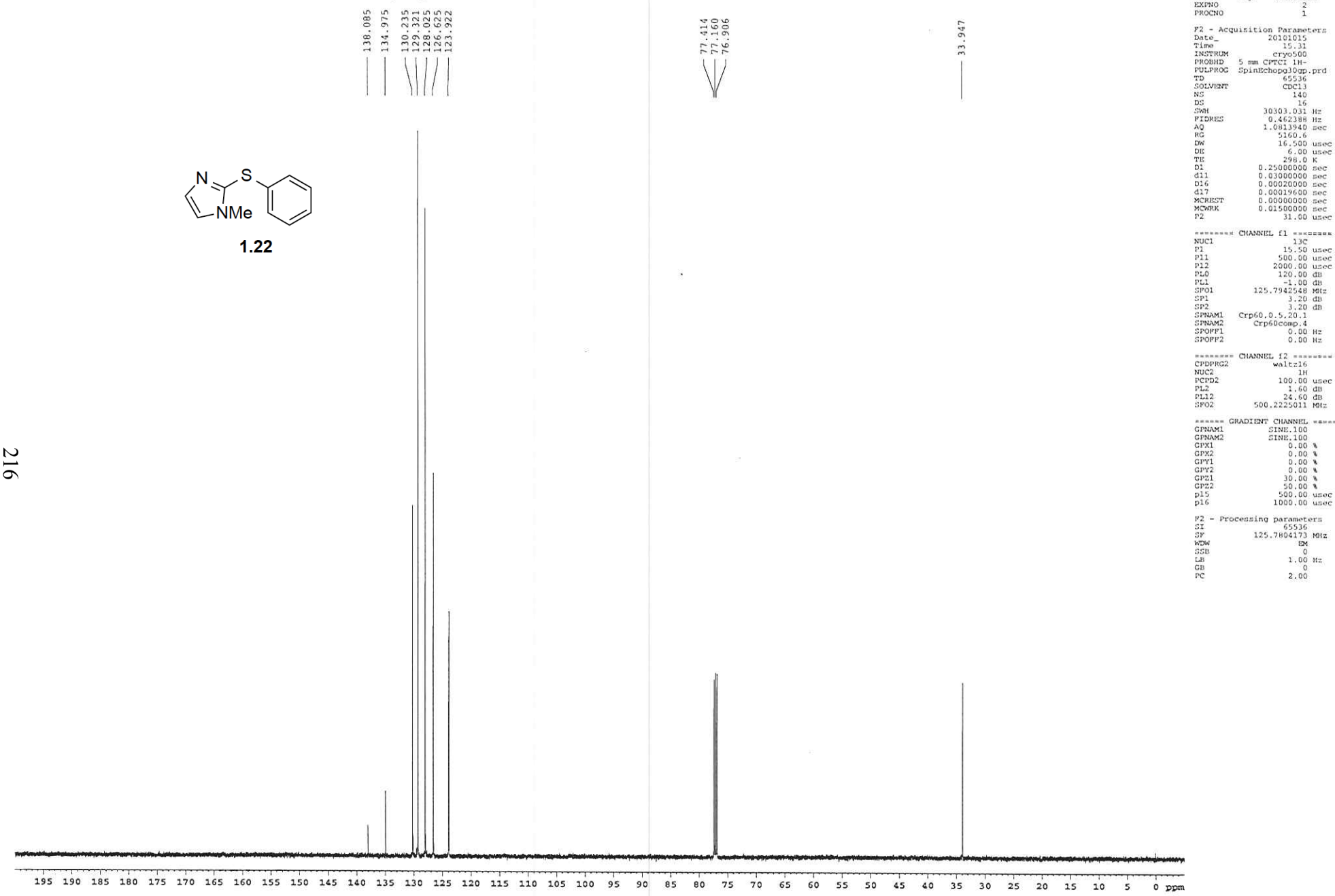
```
Current Data Parameters
USER                yonova
NAME            imy2 - 217
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20101007
Time                 3.20
INSTRUM            drx400
PROBHD   5 mm QNP H/F/P
PULPROG           zgdc30
TD                 65536
SOLVENT            CDCl3
NS                   337
DS                     4
SWH            24154.590 Hz
FIDRES         0.368570 Hz
AQ             1.3566452 sec
RG                14596.5
DW                20.700 usec
DE                20.39 usec
TE                297.9 K
D1             0.10000000 sec
d11            0.03000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                  13C
P1                10.75 usec
PL1                0.00 dB
SFO1          100.6237964 MHz

======== CHANNEL f2 ========
CPDPRG2             mlev16
NUC2                  1H
PCPD2             90.00 usec
PL2                0.00 dB
PL12              17.70 dB
SFO2          400.1328009 MHz

F2 - Processing parameters
SI                    65536
SF            100.6127672 MHz
WDW                      EM
SSB                       0
LB                 1.00 Hz
GB                        0
PC                     1.00
```

1H spectrum




```
Current Data Parameters
USER                yonova
NAME       imy2 - imidazole
EXPNO                     5
PROCNO                    1

F2 - Acquisition Parameters
Date_              20101015
Time                 14.17
INSTRUM              qm500
PROBHD  5 mm broadband
PULPROG               zg30
TD                   81728
SOLVENT              CDCl3
NS                       8
DS                       2
SWH             8012.820 Hz
FIDRES             0.098043 Hz
AQ              5.0998774 sec
RG                     114
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1             0.10000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                 13.00 usec
PL1                -4.00 dB
SFO1          499.6234973 MHz

F2 - Processing parameters
SI                   65536
SF            499.6200227 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

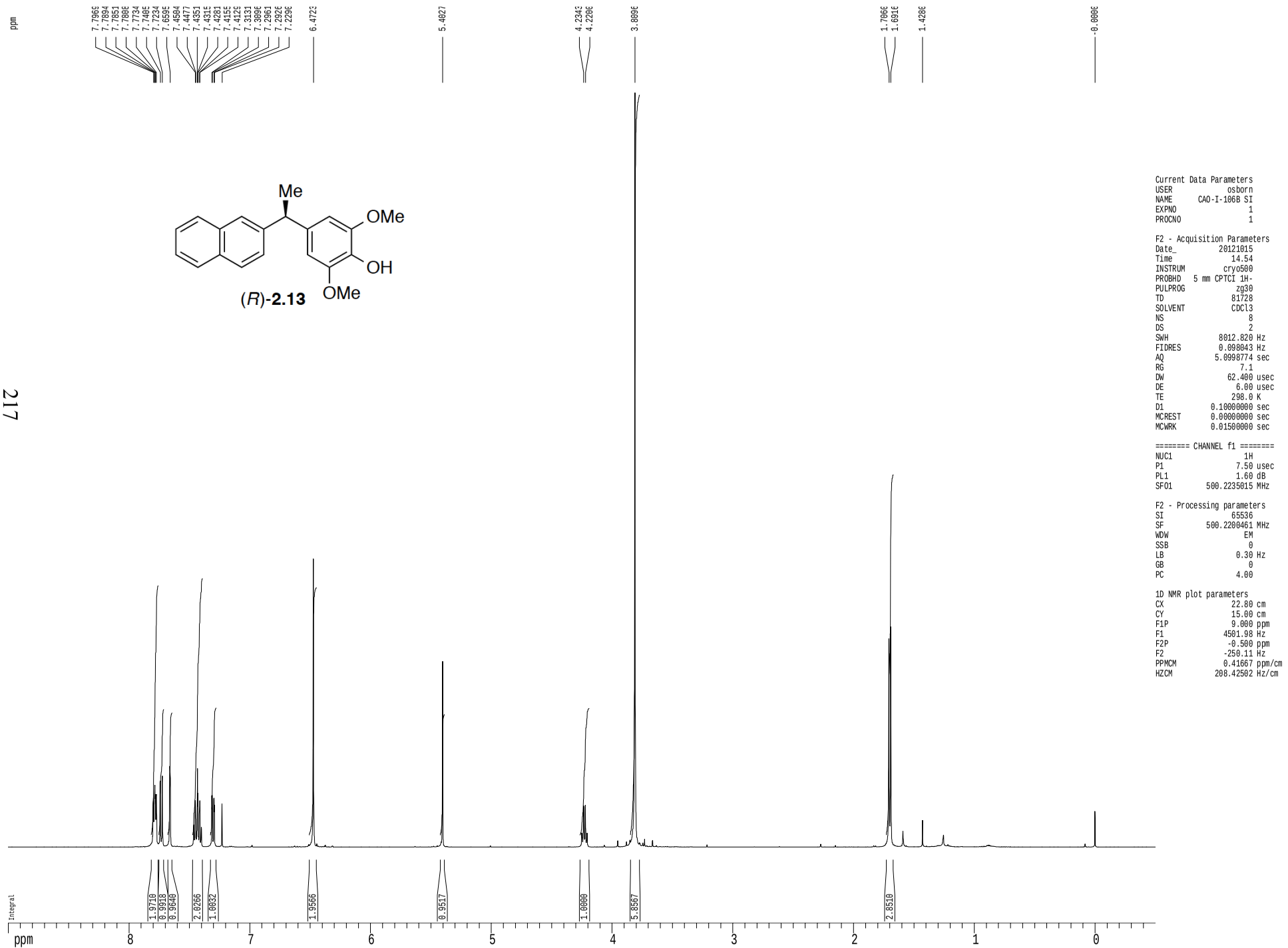
Z–restored spin–echo 13C spectrum with 1H decoupling



1.22

```
Current Data Parameters
USER                yonova
NAME       imy2 - imidazole
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_              20101015
Time                  15.31
INSTRUM             cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                   65536
SOLVENT               CDCl3
NS                      140
DS                       16
SWH               30303.031 Hz
FIDRES            0.462388 Hz
AQ                1.0813940 sec
RG                   5160.6
DW                   16.500 usec
DE                    6.00 usec
TE                   298.0 K
D1                0.25000000 sec
d11               0.03000000 sec
D16               0.00020000 sec
d17               0.00019600 sec
MCREST            0.00000000 sec
MCWRK             0.01500000 sec
P2                   31.00 usec

======== CHANNEL f1 ========
NUC1                    13C
P1                    15.50 usec
P11                  500.00 usec
P12                 2000.00 usec
PL0                  120.00 dB
PL1                   -1.00 dB
SFO1           125.7942548 MHz
SP1                   3.20 dB
SP2                   3.20 dB
SPNAM1     Crp60,0.5,20.1
SPNAM2       Crp60comp.4
SPOFF1                0.00 Hz
SPOFF2                0.00 Hz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2                100.00 usec
PL2                   1.60 dB
PL12                 24.60 dB
SFO2           500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1            SINE.100
GPNAM2            SINE.100
GPX1                  0.00 %
GPX2                  0.00 %
GPY1                  0.00 %
GPY2                  0.00 %
GPZ1                 30.00 %
GPZ2                 50.00 %
p15                 500.00 usec
p16                1000.00 usec

F2 - Processing parameters
SI                   65536
SF             125.7804173 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    2.00
```

CAO-I-106B SI
1H spectrum



Current Data Parameters
USER osborn
NAME CAO-I-106B SI
EXPNO 1
PROCNO 1

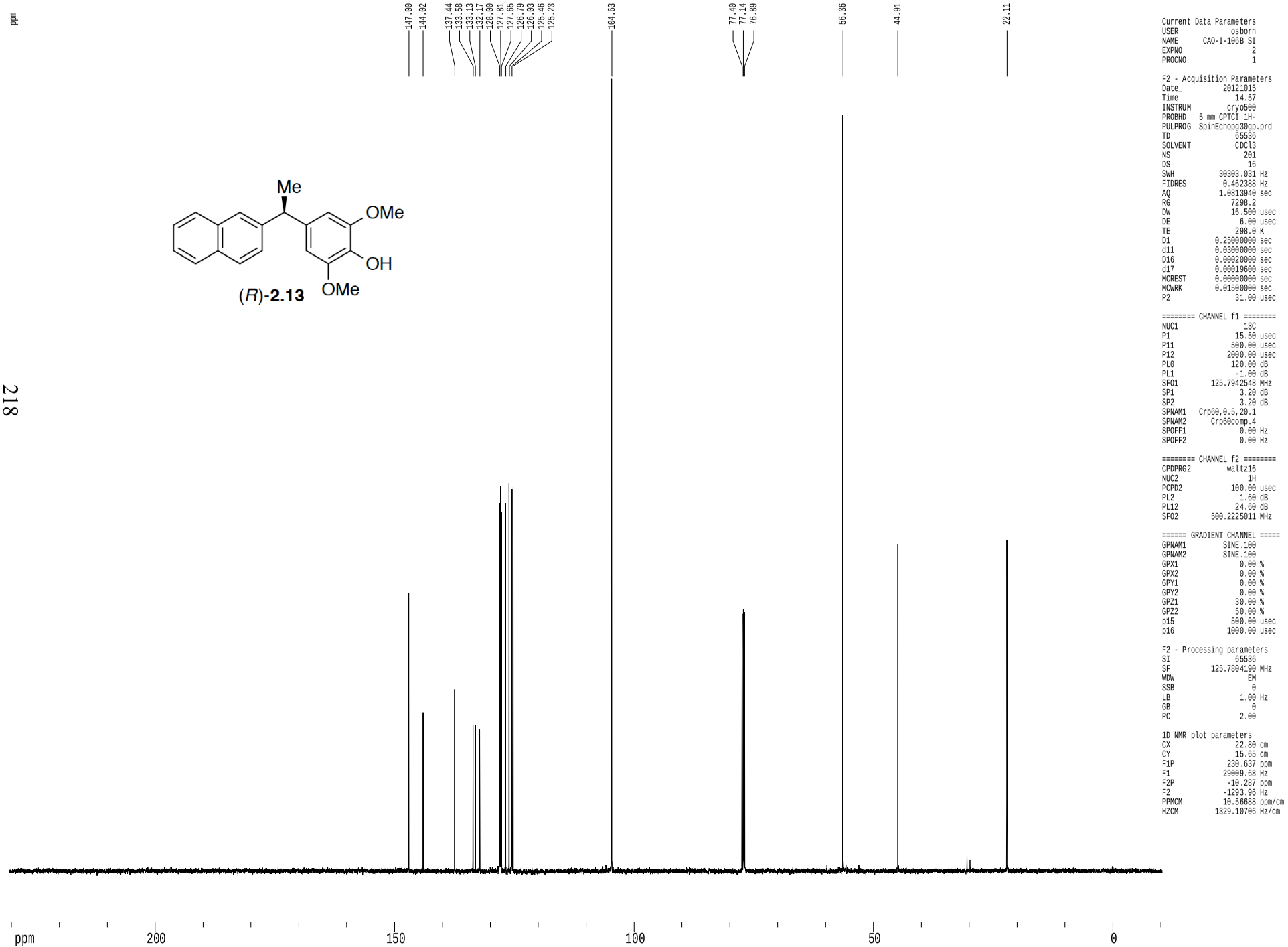
F2 - Acquisition Parameters
Date_ 20121015
Time 14.54
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 7.1
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz

F2 - Processing parameters
SI 65536
SF 500.2200461 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm

CAO-I-106B SI
Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME CAO-I-106B SI
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121015
Time 14.57
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 201
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 7298.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 31.00 usec

======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

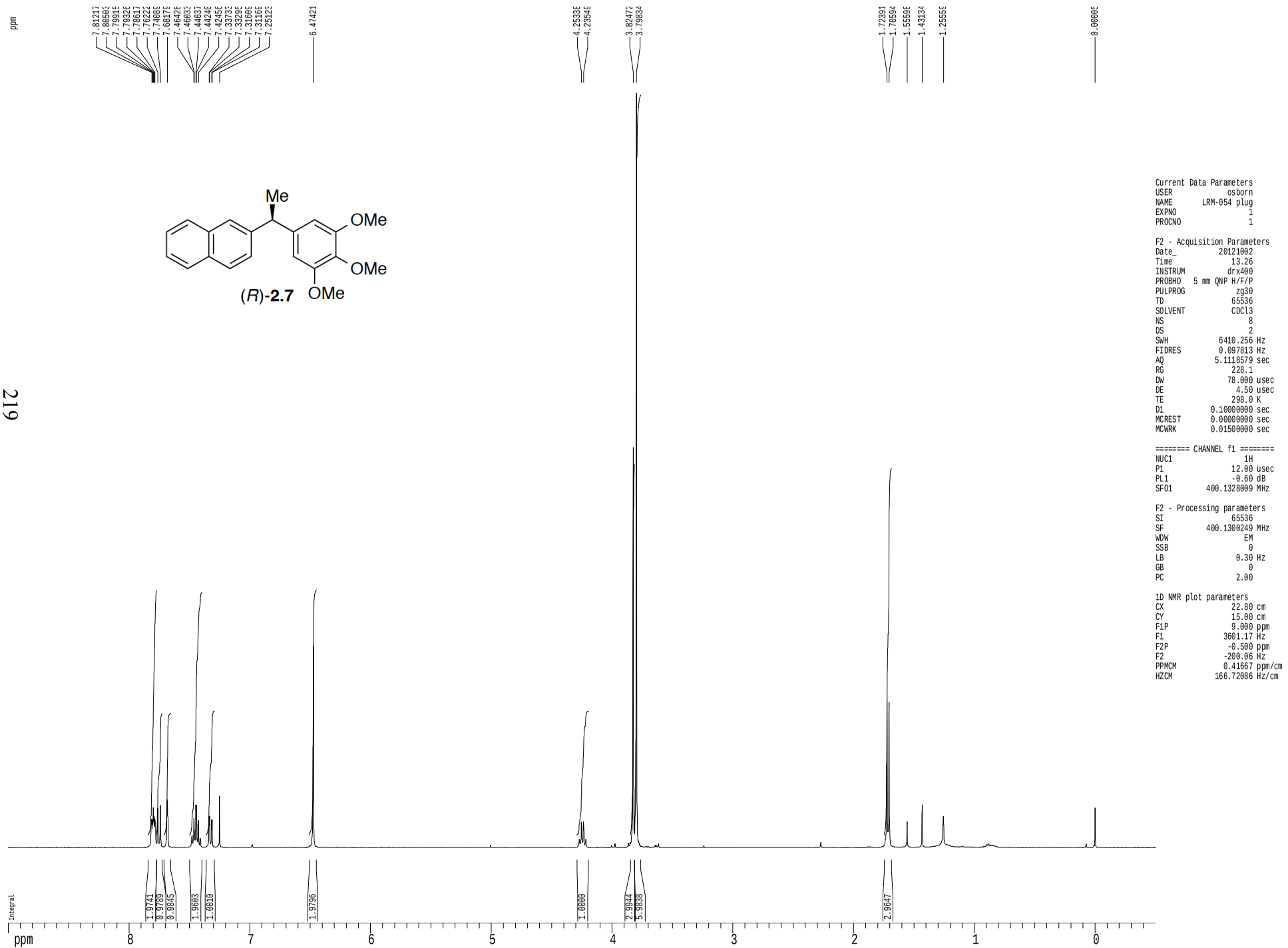
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 125.7804190 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10706 Hz/cm

1H spectrum



Current Data Parameters
USER osborn
NAME LRM-054 plug
EXPNO 1
PROCNO 1

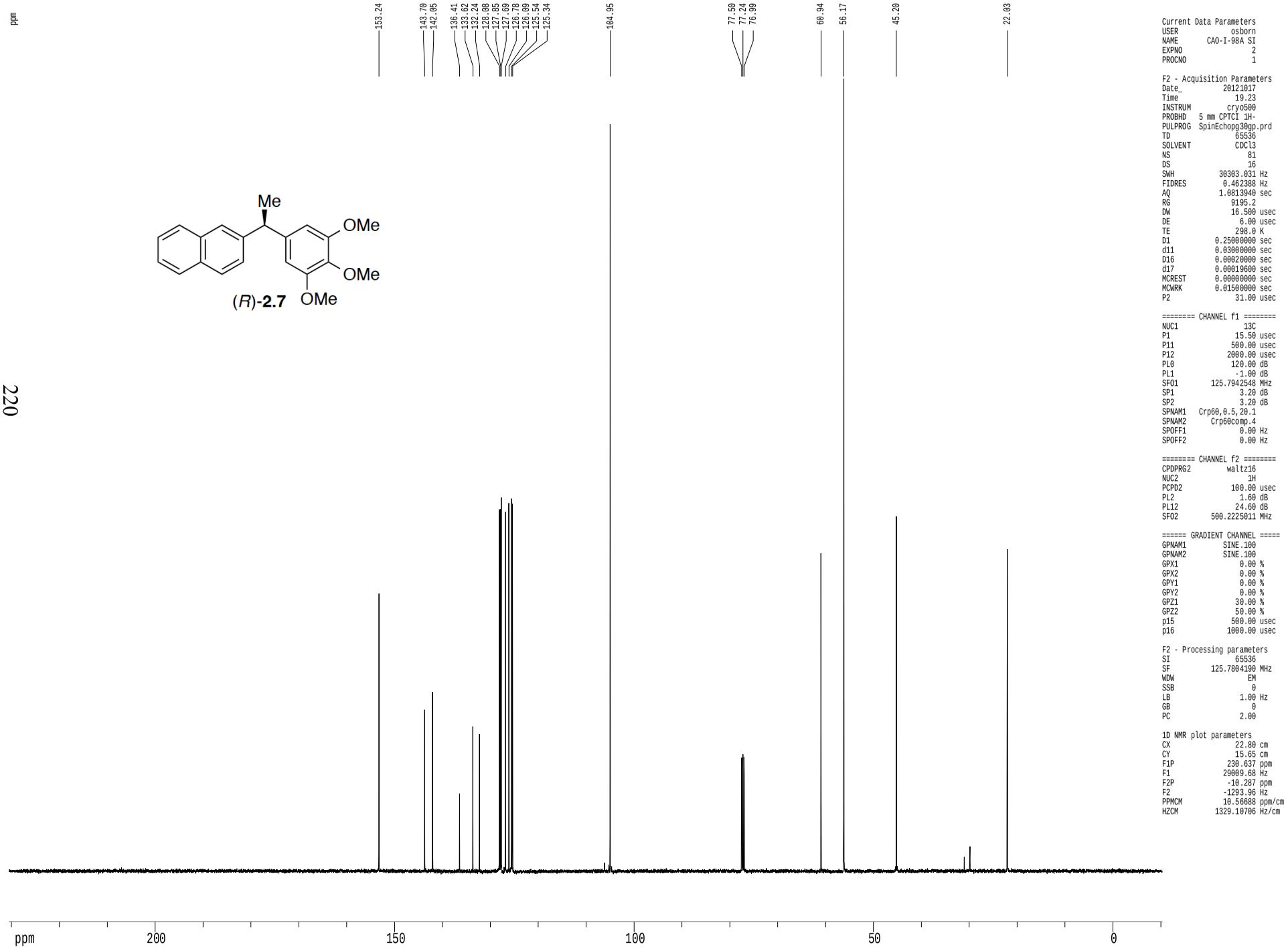
F2 - Acquisition Parameters
Date_ 20121002
Time 13.26
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 228.1
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 -0.60 dB
SFO1 400.1328009 MHz

F2 - Processing parameters
SI 65536
SF 400.1300249 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00

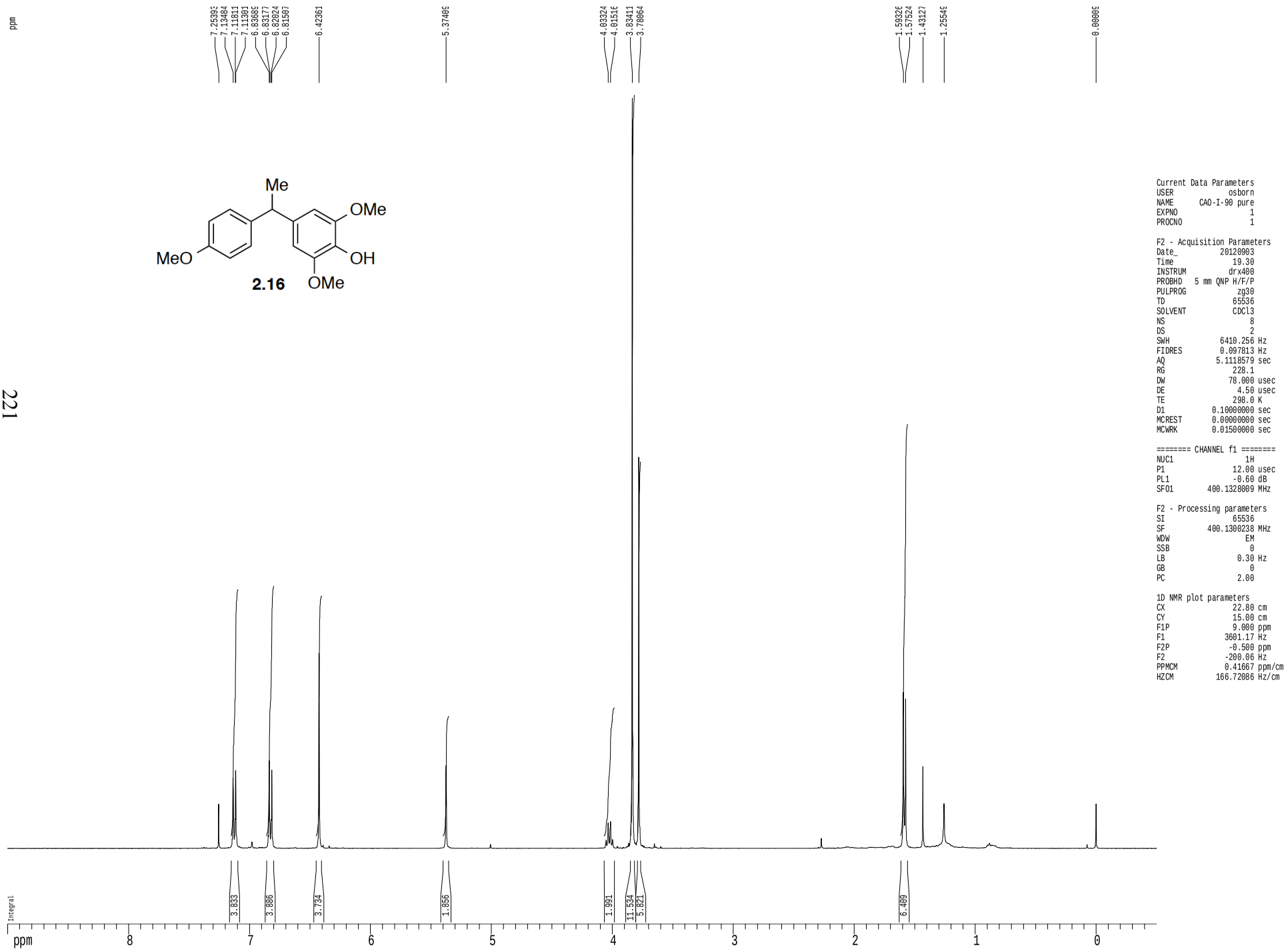
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72086 Hz/cm

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME         CAO-I-98A SI
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121017
Time                19.23
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                 65536
SOLVENT            CDCl3
NS                    81
DS                    16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.0813940 sec
RG                9195.2
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec
P2                31.00 usec

======== CHANNEL f1 ========
NUC1                 13C
P1                15.50 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1               3.20 dB
SP2               3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15              500.00 usec
p16             1000.00 usec

F2 - Processing parameters
SI                 65536
SF           125.7804190 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 2.00

1D NMR plot parameters
CX                22.80 cm
CY                15.65 cm
F1P             230.637 ppm
F1              29009.68 Hz
F2P             -10.287 ppm
F2              -1293.96 Hz
PPMCM          10.56688 ppm/cm
HZCM         1329.10706 Hz/cm
```

CAO-I-90 pure
1H spectrum



Current Data Parameters
USER osborn
NAME CAO-I-90 pure
EXPNO 1
PROCNO 1

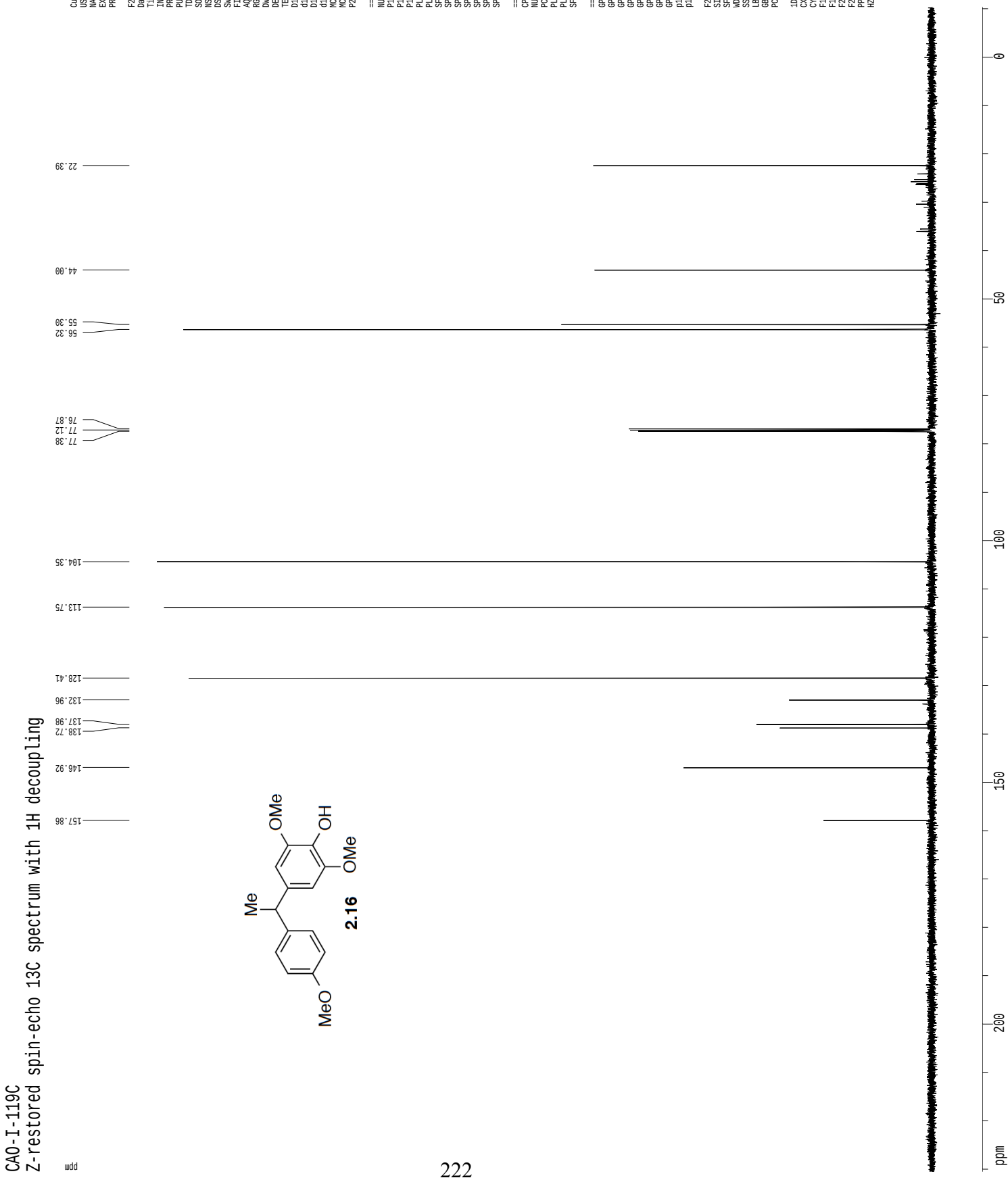
F2 - Acquisition Parameters
Date_ 20120903
Time 19.30
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 228.1
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 -0.60 dB
SFO1 400.1328009 MHz

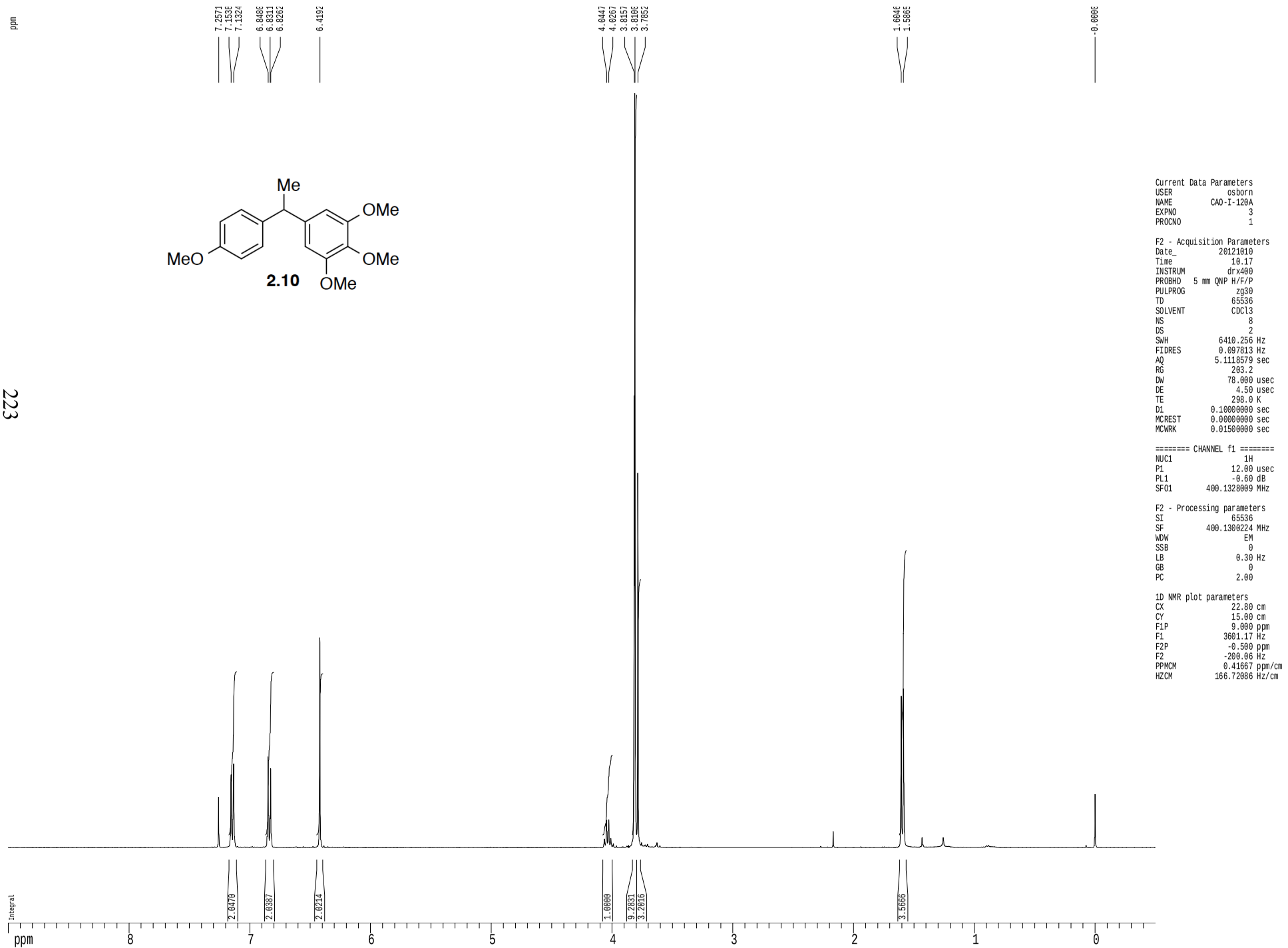
F2 - Processing parameters
SI 65536
SF 400.1300238 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72086 Hz/cm

CAO-I-119C
Z-restored spin-echo 13C spectrum with 1H decoupling



CAO-I-102A
1H spectrum



Current Data Parameters
USER osborn
NAME CAO-I-120A
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121010
Time 10.17
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 203.2
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

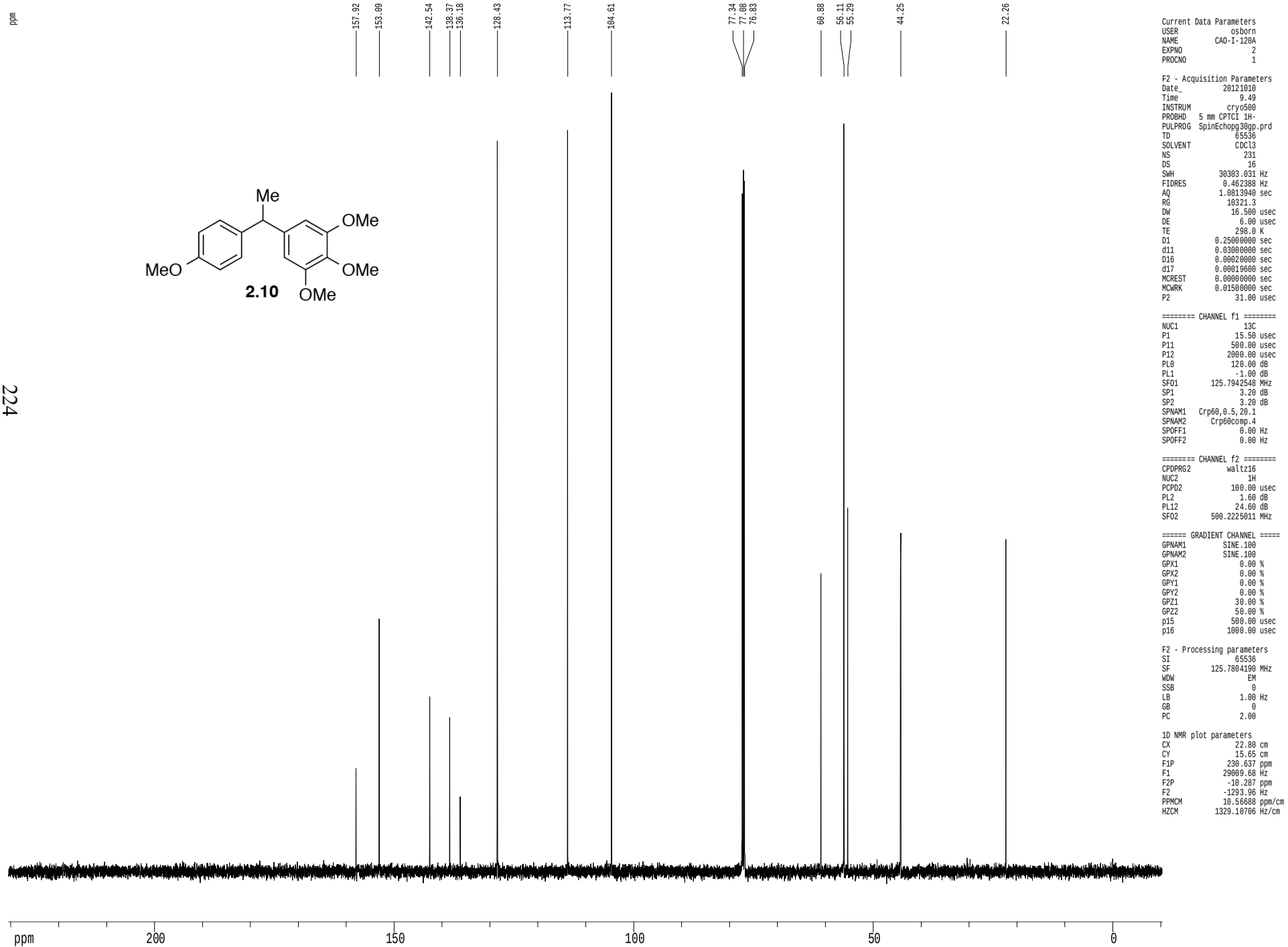
======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 -0.60 dB
SFO1 400.1328009 MHz

F2 - Processing parameters
SI 65536
SF 400.1300224 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72086 Hz/cm

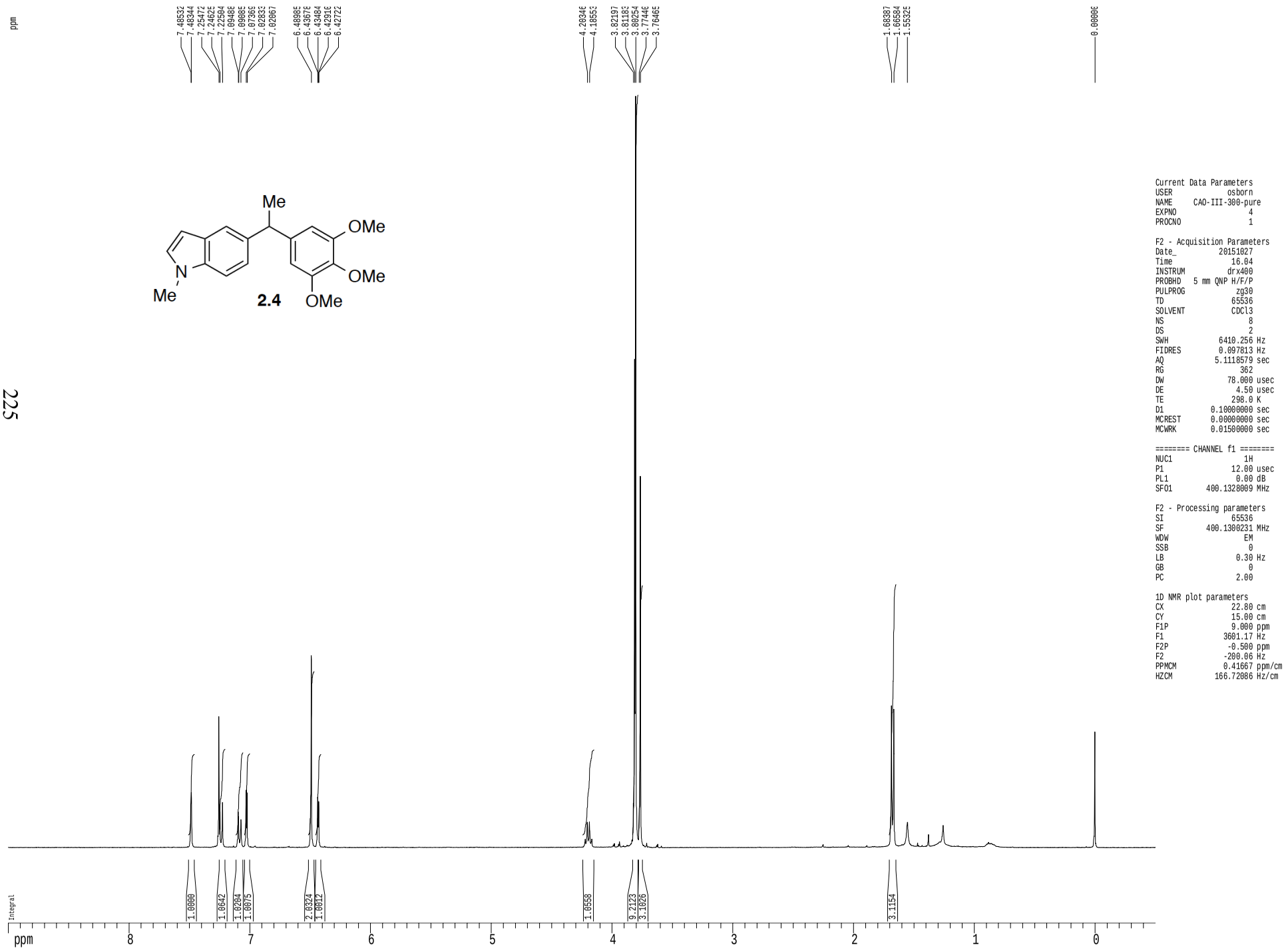
CAO-I-120A

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME             CAO-I-120A
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20121010
Time                 9.49
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                   65536
SOLVENT              CDCl3
NS                     231
DS                      16
SWH              30303.031 Hz
FIDRES           0.462388 Hz
AQ               1.0813940 sec
RG                 10321.3
DW                 16.500 usec
DE                  6.00 usec
TE                 298.0 K
D1               0.25000000 sec
d11              0.03000000 sec
D16              0.00020000 sec
d17              0.00019600 sec
MCREST           0.00000000 sec
MCWRK            0.01500000 sec
P2                  31.00 usec

======== CHANNEL f1 ========
NUC1                   13C
P1                  15.50 usec
P11                500.00 usec
P12               2000.00 usec
PL0                120.00 dB
PL1                 -1.00 dB
SFO1           125.7942548 MHz
SP1                  3.20 dB
SP2                  3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  1.60 dB
PL12                24.60 dB
SFO2           500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPX1                 0.00 %
GPX2                 0.00 %
GPY1                 0.00 %
GPY2                 0.00 %
GPZ1                30.00 %
GPZ2                50.00 %
p15                500.00 usec
p16               1000.00 usec

F2 - Processing parameters
SI                   65536
SF             125.7804190 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   2.00

1D NMR plot parameters
CX                  22.80 cm
CY                  15.65 cm
F1P               230.637 ppm
F1                29009.68 Hz
F2P               -10.287 ppm
F2                -1293.96 Hz
PPMCM             10.56688 ppm/cm
HZCM           1329.10706 Hz/cm
```

1H spectrum



Current Data Parameters
USER osborn
NAME CAO-III-300-pure
EXPNO 4
PROCNO 1

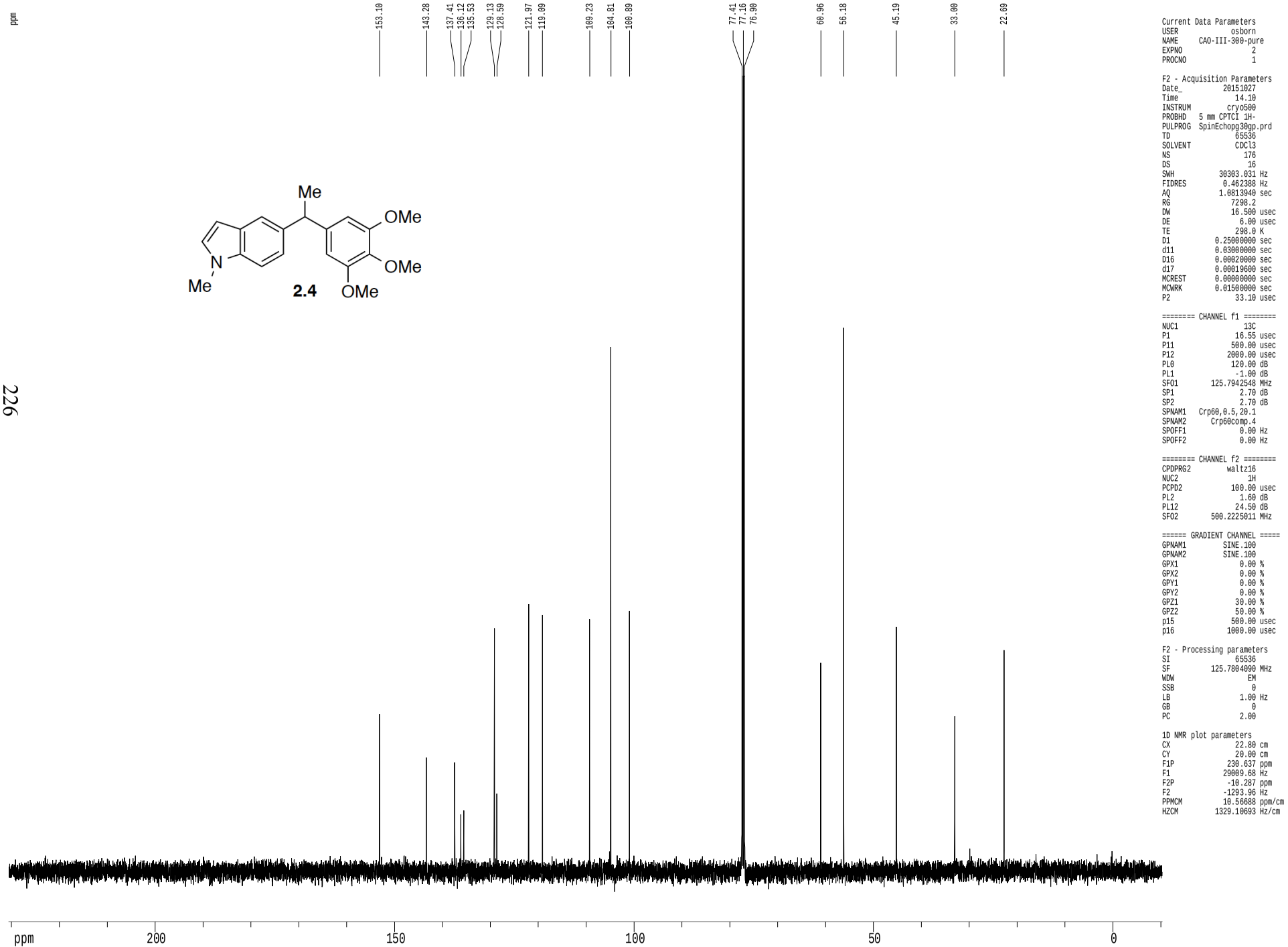
F2 - Acquisition Parameters
Date_ 20151027
Time 16.04
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 362
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz

F2 - Processing parameters
SI 65536
SF 400.1300231 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00

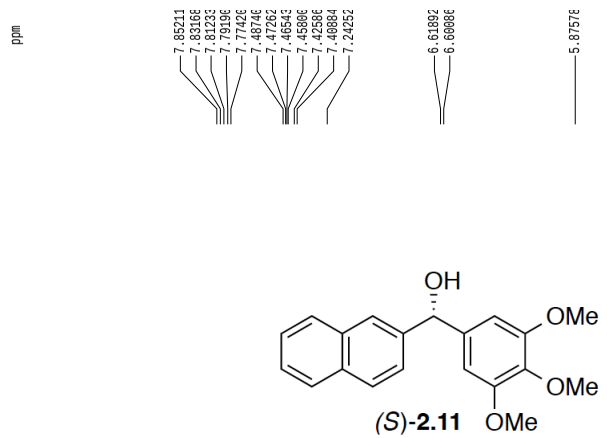
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72086 Hz/cm

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME      CAO-III-300-pure
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_           20151027
Time              14.10
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                65536
SOLVENT           CDCl3
NS                  176
DS                   16
SWH           30303.031 Hz
FIDRES         0.462388 Hz
AQ             1.0813940 sec
RG                7298.2
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1             0.25000000 sec
d11            0.03000000 sec
D16            0.00020000 sec
d17            0.00019600 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec
P2                33.10 usec

======== CHANNEL f1 ========
NUC1                 13C
P1                16.55 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1               2.70 dB
SP2               2.70 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                1.60 dB
PL12              24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15              500.00 usec
p16             1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7804090 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   2.00

1D NMR plot parameters
CX                  22.80 cm
CY                  20.00 cm
F1P              230.637 ppm
F1             29009.68 Hz
F2P              -10.287 ppm
F2             -1293.96 Hz
PPMCM           10.56688 ppm/cm
HZCM          1329.10693 Hz/cm
```

CAO-I-95 SI
1H spectrum

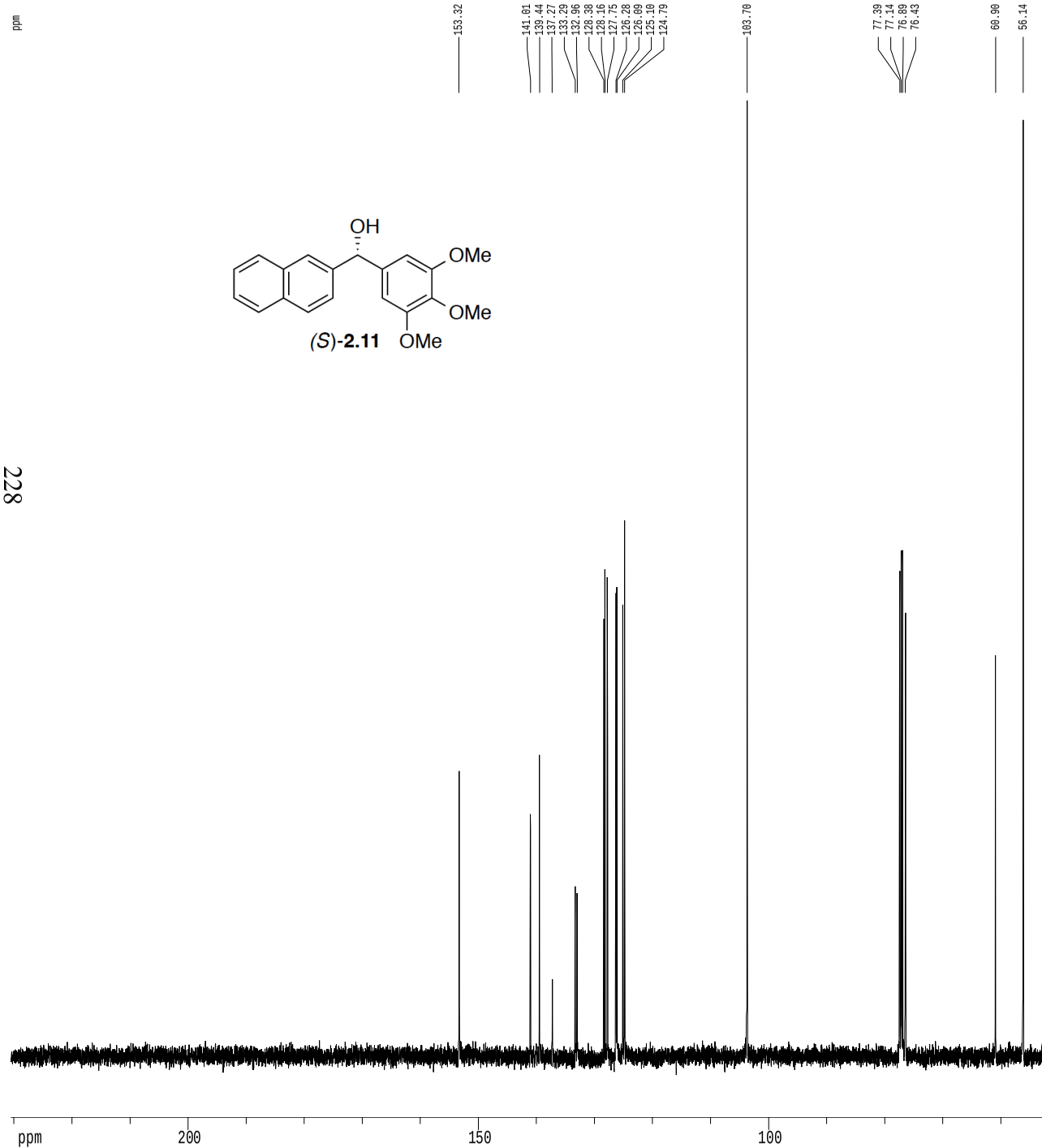


(*S*)-**2.11**

227

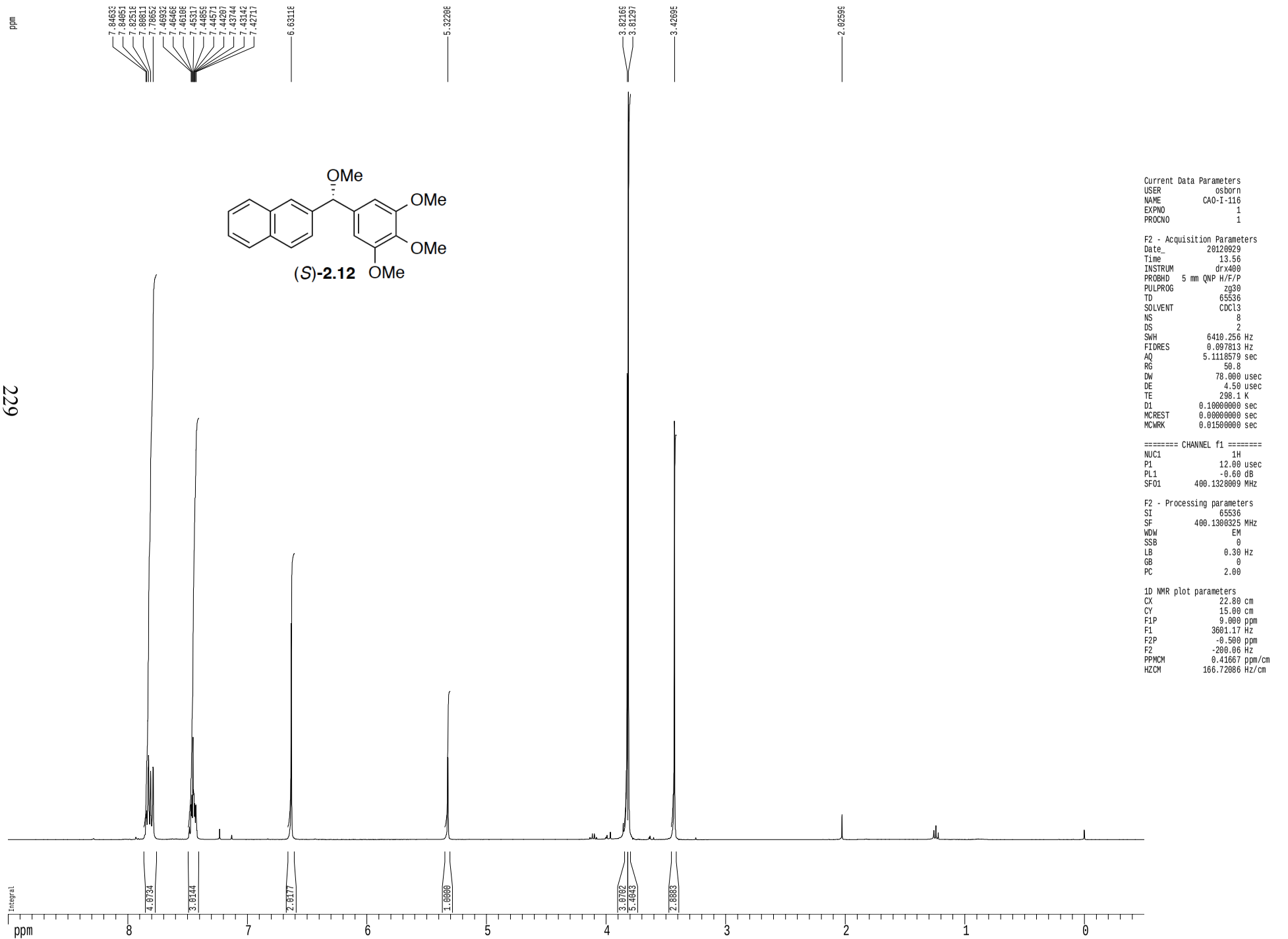
```
Current Data Parameters
USER              osborn
NAME         CAO-I-95 SI
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_          20121017
Time              19.05
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 81728
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             8012.820 Hz
FIDRES             0.098043 Hz
AQ              5.0998774 sec
RG                   3.2
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1             0.10000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  7.50 usec
PL1                 1.60 dB
SFO1          500.2235015 MHz

F2 - Processing parameters
SI                 65536
SF            500.2200395 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  4.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.00 cm
F1P                 9.000 ppm
F1               4501.98 Hz
F2P                -0.500 ppm
F2               -250.11 Hz
PPMCM           0.41667 ppm/cm
HZCM          208.42502 Hz/cm
```

CAO-I-95 SI
Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME          CAO-I-95 SI
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121017
Time                19.08
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                 65536
SOLVENT            CDCl3
NS                   131
DS                    16
SWH            30303.031 Hz
FIDRES         0.462388 Hz
AQ             1.0813940 sec
RG                7298.2
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1             0.25000000 sec
d11            0.03000000 sec
D16            0.00020000 sec
d17            0.00019600 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec
P2                31.00 usec

======== CHANNEL f1 ========
NUC1                 13C
P1                15.50 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1               3.20 dB
SP2               3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                 65536
SF           125.7804190 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 2.00

1D NMR plot parameters
CX                22.80 cm
CY                15.65 cm
F1P             230.637 ppm
F1              29009.68 Hz
F2P             -10.287 ppm
F2              -1293.96 Hz
PPMCM          10.56688 ppm/cm
HZCM         1329.10706 Hz/cm
```

CAO-I-116
1H spectrum



Current Data Parameters
USER osborn
NAME CAO-I-116
EXPNO 1
PROCNO 1

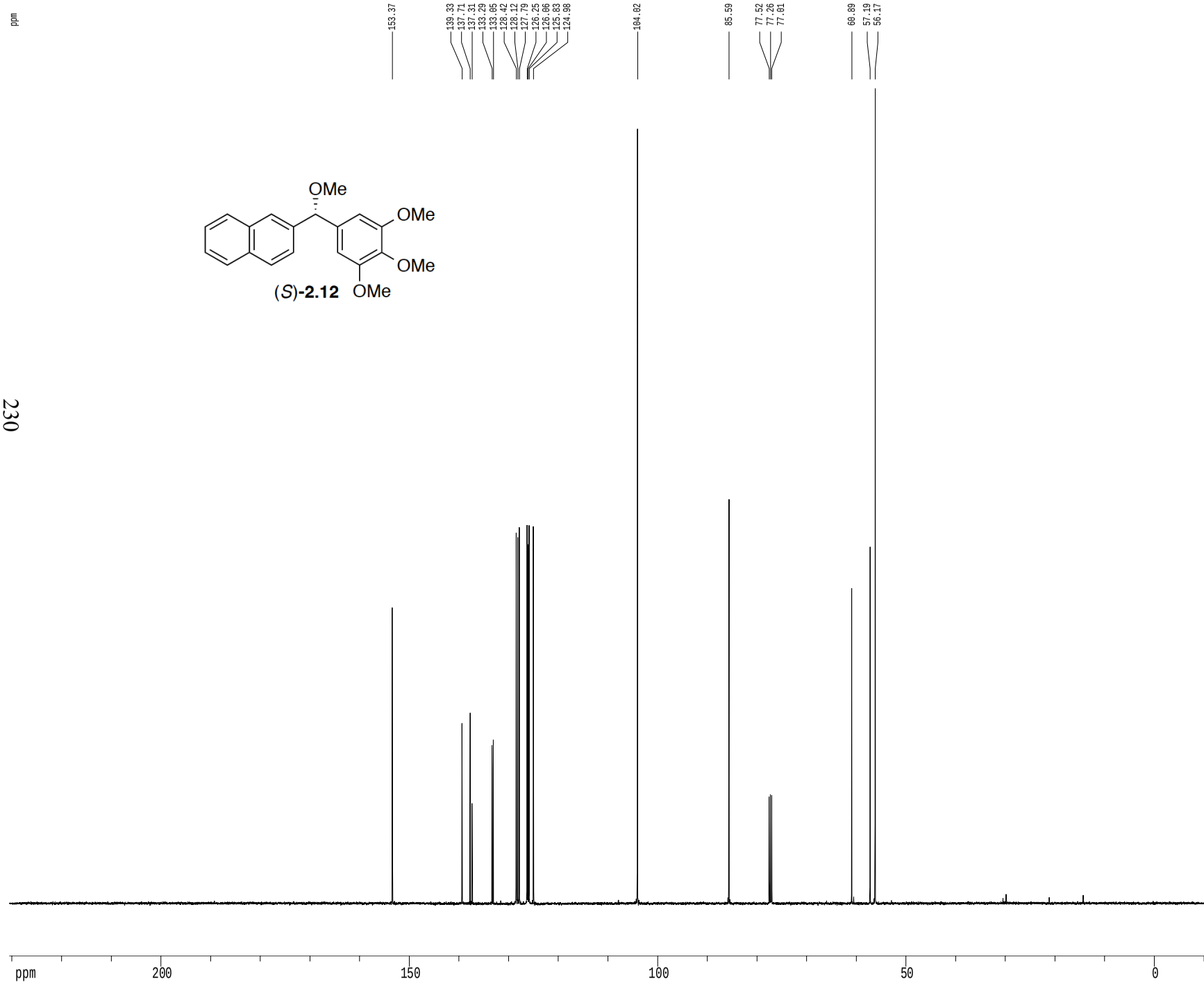
F2 - Acquisition Parameters
Date_ 20120929
Time 13.56
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 50.8
DW 78.000 usec
DE 4.50 usec
TE 298.1 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 -0.60 dB
SFO1 400.1328009 MHz

F2 - Processing parameters
SI 65536
SF 400.1300325 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00

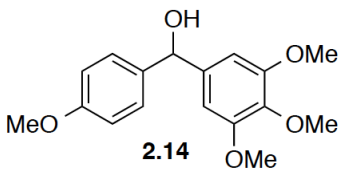
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72086 Hz/cm

CAO-I-96 SI
Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME          CAO-I-96 SI
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121017
Time                19.16
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                  65536
SOLVENT             CDCl3
NS                    106
DS                     16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.0813940 sec
RG                 7298.2
DW                16.500 usec
DE                 6.00 usec
TE                 298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec
P2                 31.00 usec

======== CHANNEL f1 ========
NUC1                  13C
P1                 15.50 usec
P11               500.00 usec
P12              2000.00 usec
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MHz
SP1                3.20 dB
SP2                3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7804190 MHz
WDW                    EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  2.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.65 cm
F1P              230.637 ppm
F1               29009.68 Hz
F2P              -10.287 ppm
F2               -1293.96 Hz
PPMCM            10.56688 ppm/cm
HZCM          1329.10706 Hz/cm
```

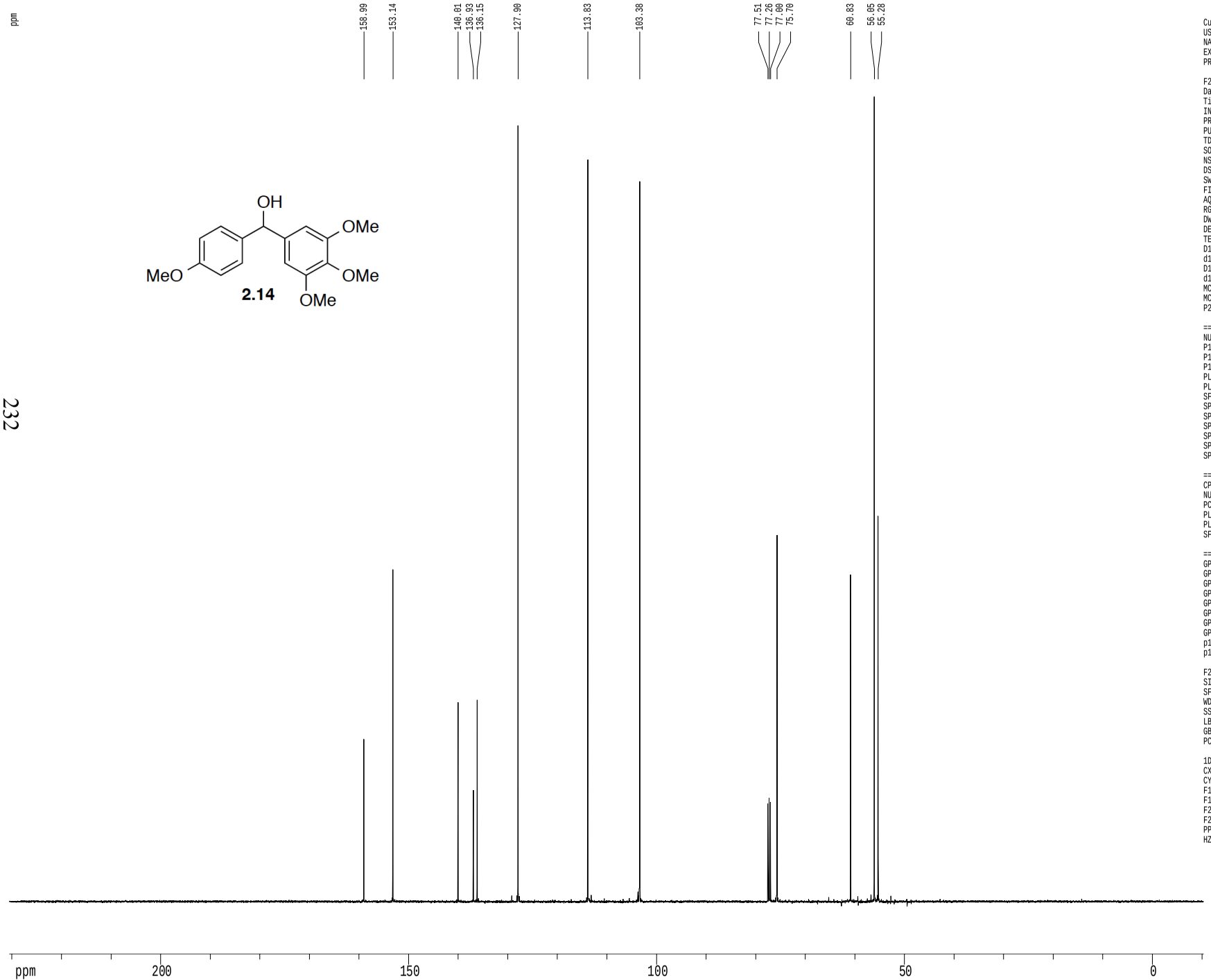
CAO-I-32 SI
1H spectrum



2.14

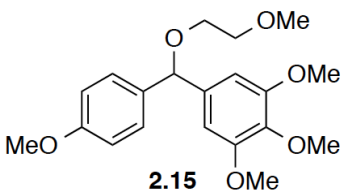

```
Current Data Parameters
USER              osborn
NAME         CAO-I-32 SI
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121015
Time               14.36
INSTRUM          cryo500
PROBHD    5 mm CPTCI 1H-
PULPROG             zg30
TD                 81728
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             8012.820 Hz
FIDRES          0.098043 Hz
AQ              5.0998774 sec
RG                     4
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1             0.10000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 =======
NUC1                   1H
P1                  7.50 usec
PL1                 1.60 dB
SFO1          500.2235015 MHz

F2 - Processing parameters
SI                 65536
SF            500.2200254 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  4.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.00 cm
F1P                 9.000 ppm
F1               4501.98 Hz
F2P                -0.500 ppm
F2               -250.11 Hz
PPMCM           0.41667 ppm/cm
HZCM          208.42502 Hz/cm
```

CAO-I-32 SI
Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME          CAO-I-32 SI
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121015
Time                14.39
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                  65536
SOLVENT             CDCl3
NS                    131
DS                     16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.0813940 sec
RG                 7298.2
DW                16.500 usec
DE                 6.00 usec
TE                 298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec
P2                 31.00 usec

======== CHANNEL f1 ========
NUC1                  13C
P1                 15.50 usec
P11               500.00 usec
P12              2000.00 usec
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MHz
SP1                3.20 dB
SP2                3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7804190 MHz
WDW                    EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  2.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.65 cm
F1P              230.637 ppm
F1               29009.68 Hz
F2P              -10.287 ppm
F2               -1293.96 Hz
PPMCM           10.56688 ppm/cm
HZCM          1329.10706 Hz/cm
```

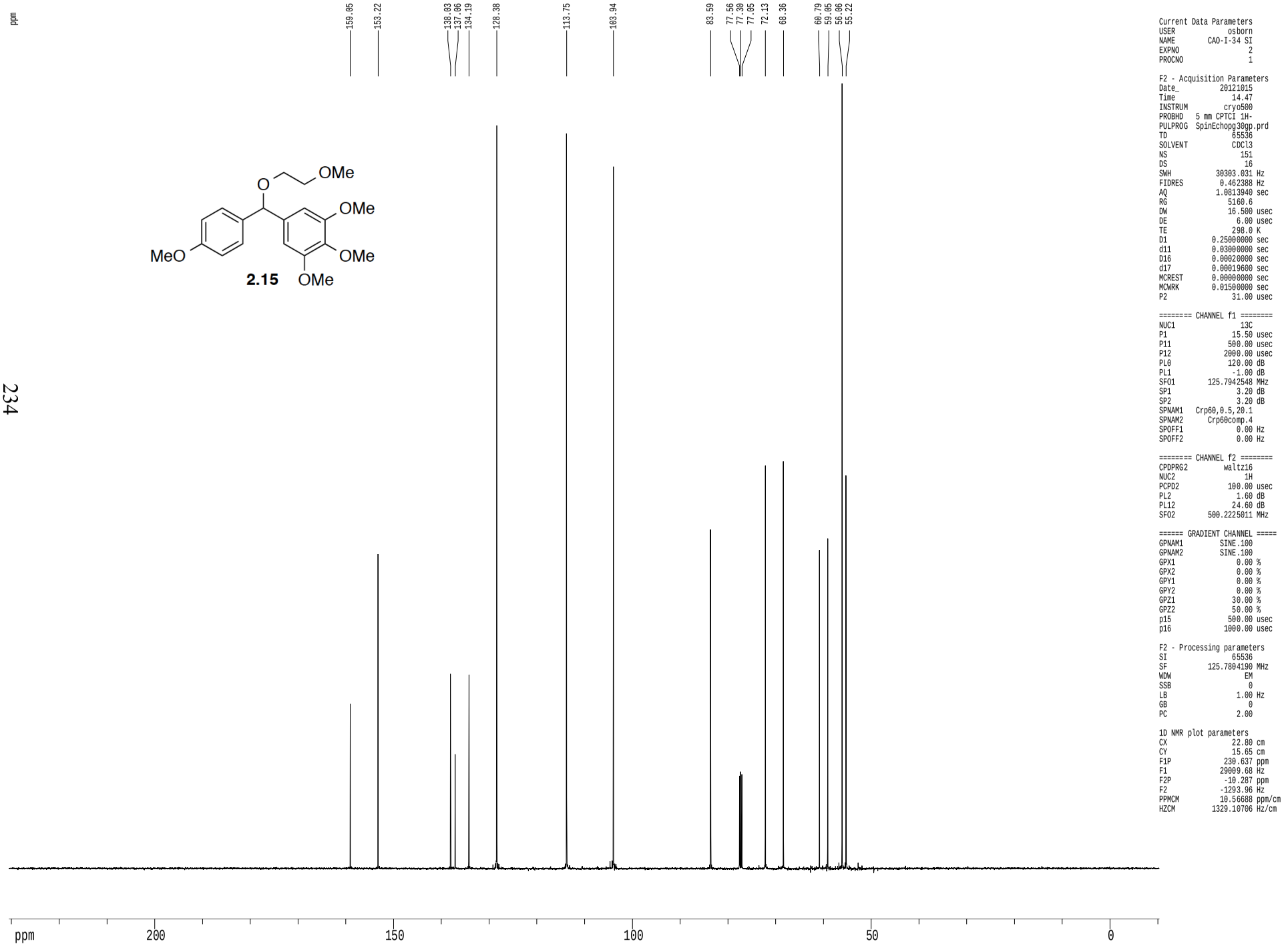
CAO-I-34 SI
1H spectrum



2.15

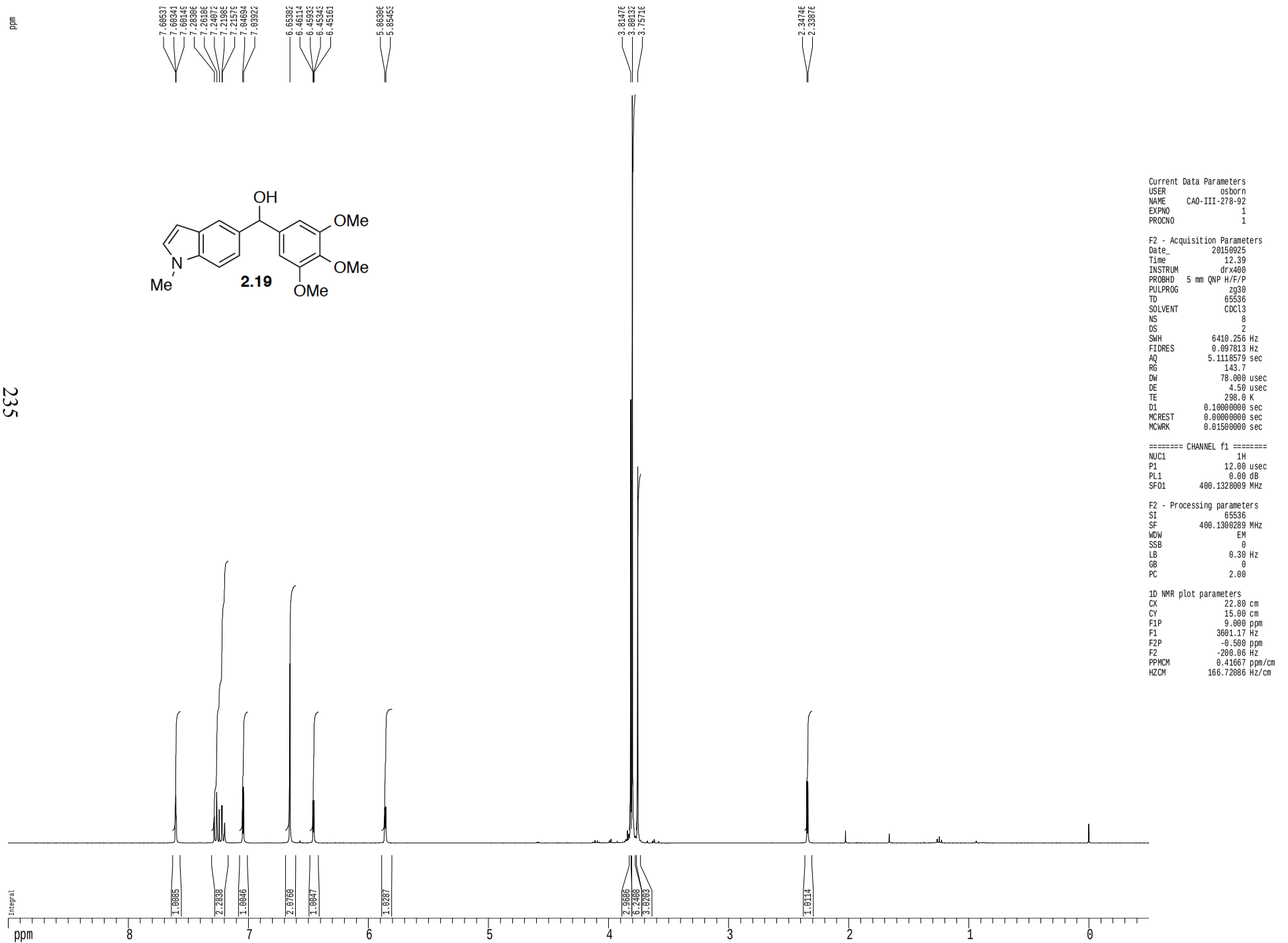

```
Current Data Parameters
USER              osborn
NAME         CAO-I-34 SI
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20121015
Time              14.44
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                81728
SOLVENT           CDCl3
NS                    8
DS                    2
SWH            8012.820 Hz
FIDRES         0.098043 Hz
AQ             5.0998774 sec
RG                    4
DW               62.400 usec
DE                6.00 usec
TE                298.0 K
D1           0.10000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 =======
NUC1                  1H
P1                 7.50 usec
PL1                1.60 dB
SFO1         500.2235015 MHz

F2 - Processing parameters
SI                 65536
SF           500.2200186 MHz
WDW                   EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 4.00

1D NMR plot parameters
CX                22.80 cm
CY                15.00 cm
F1P                9.000 ppm
F1              4501.98 Hz
F2P               -0.500 ppm
F2              -250.11 Hz
PPMCM          0.41667 ppm/cm
HZCM          208.42502 Hz/cm
```

CAO-I-34 SI
Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME          CAO-I-34 SI
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121015
Time                14.47
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                  65536
SOLVENT             CDCl3
NS                    151
DS                     16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.0813940 sec
RG                 5160.6
DW                16.500 usec
DE                 6.00 usec
TE                 298.0 K
D1             0.25000000 sec
d11            0.03000000 sec
D16            0.00020000 sec
d17            0.00019600 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec
P2                31.00 usec

======== CHANNEL f1 ========
NUC1                 13C
P1                15.50 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1                3.20 dB
SP2                3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15              500.00 usec
p16             1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7804190 MHz
WDW                    EM
SSB                     0
LB                 1.00 Hz
GB                      0
PC                 2.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.65 cm
F1P              230.637 ppm
F1               29009.68 Hz
F2P              -10.287 ppm
F2               -1293.96 Hz
PPMCM            10.56688 ppm/cm
HZCM          1329.10706 Hz/cm
```

1H spectrum



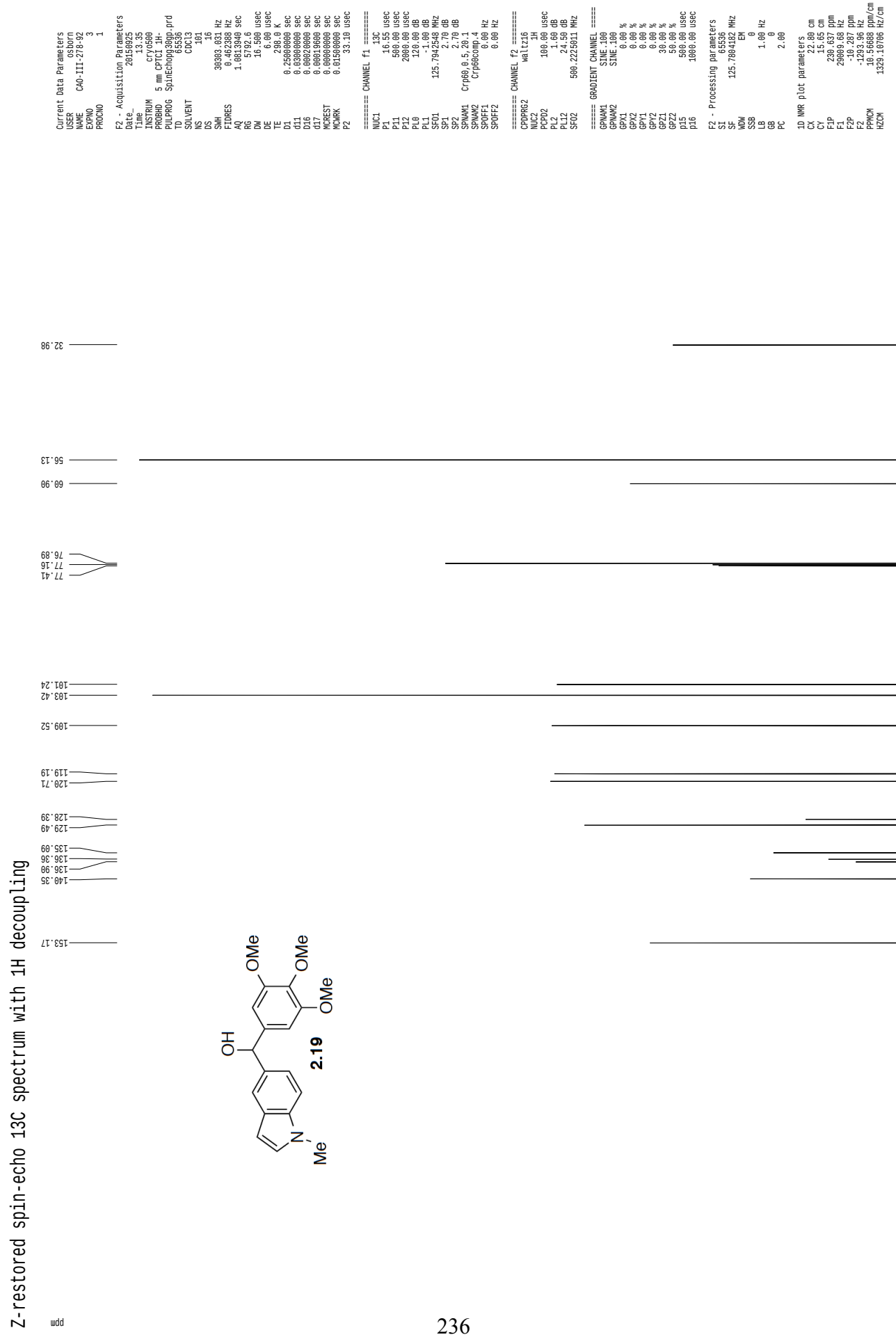
Current Data Parameters
USER osborn
NAME CAO-III-278-92
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150925
Time 12.39
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 143.7
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

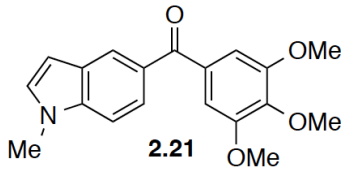
======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz

F2 - Processing parameters
SI 65536
SF 400.1300289 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72086 Hz/cm


Z-restored spin-echo 13C spectrum with 1H decoupling
Current Data Parameters
USER osborn
NAME CAO-III-278-02
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150925
Time 13.35
INSTRUM cryo600
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 101
DS 16
SWH 30303.031 Hz
FIDRES 0.462308 Hz
AQ 1.0813940 sec
RG 5792.6
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 33.10 usec
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM1 Crp80,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.00 dB
PL12 24.50 dB
SFO2 500.2225811 MHz
===== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7884102 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.00 cm
CY 15.65 cm
F1P 238.637 ppm
F1 29969.08 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56608 ppm/cm
HZCM 1329.10706 Hz/cm
32.98
56.13
60.90
76.89
77.16
77.41
101.24
103.42
109.52
119.19
120.71
128.39
129.49
135.09
136.36
136.90
140.35
153.17
OMe
OMe
OMe
OH
N
Me
2.19
ppm
0
50
100
150
200

1H spectrum

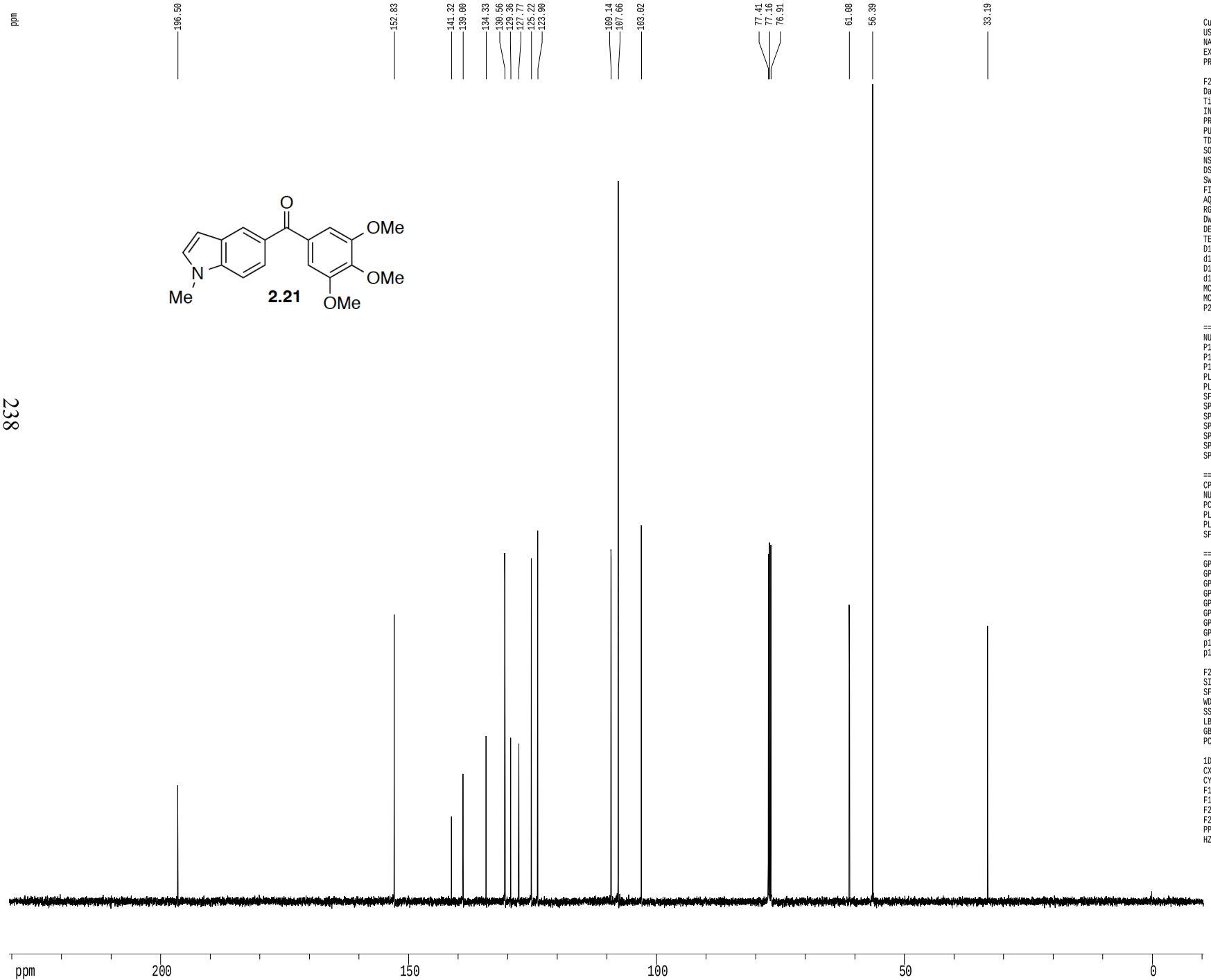


2.21

237

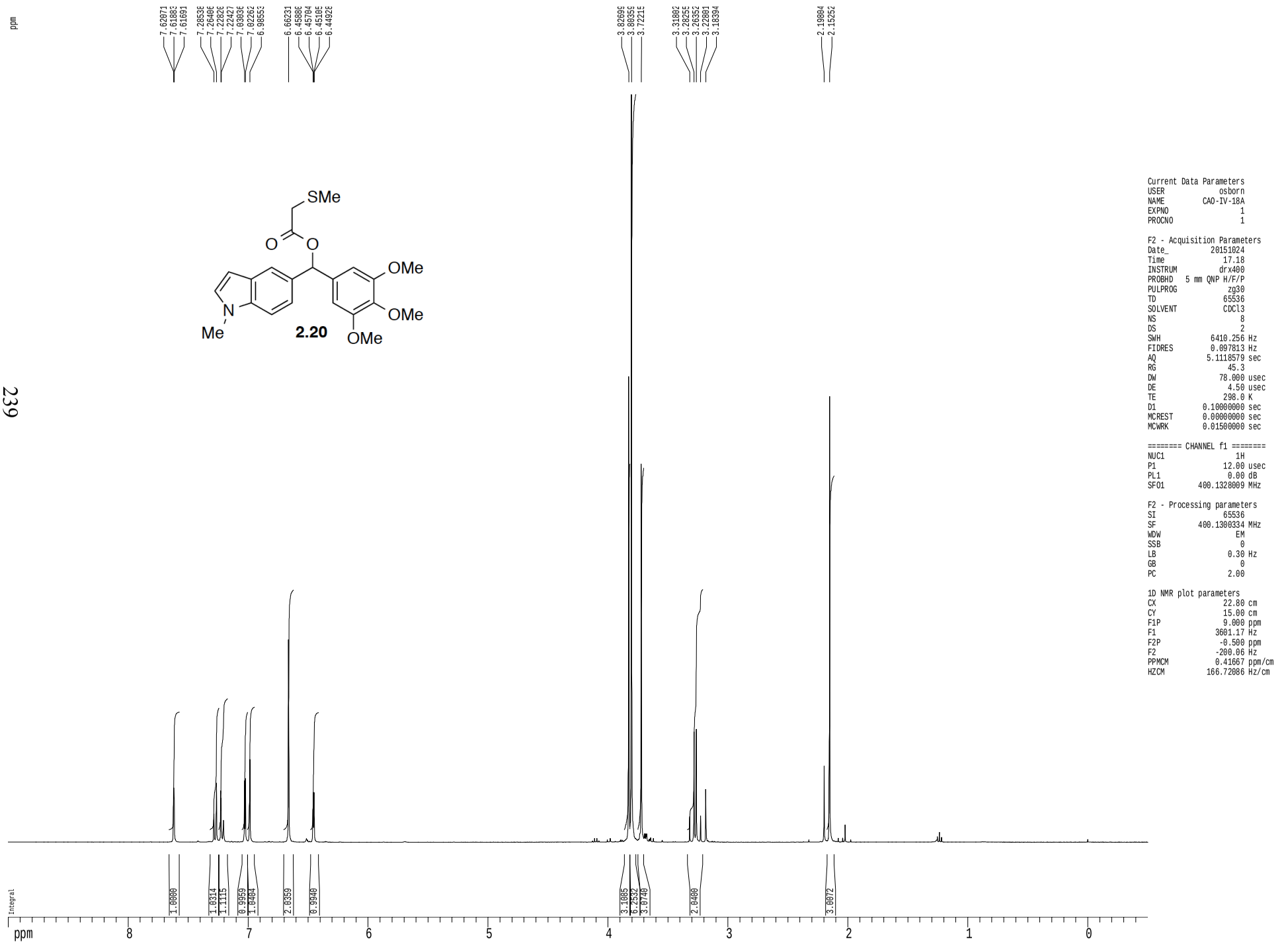
```
Current Data Parameters
USER              osborn
NAME      CAO-III-281-pure
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_           20150930
Time              17.16
INSTRUM         drx400
PROBHD   5 mm QNP H/F/P
PULPROG           zg30
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    2
SWH            6410.256 Hz
FIDRES        0.097813 Hz
AQ            5.1118579 sec
RG                912.3
DW               78.000 usec
DE                4.50 usec
TE                298.0 K
D1           0.10000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======= CHANNEL f1 =======
NUC1                 1H
P1                12.00 usec
PL1                0.00 dB
SFO1        400.1328009 MHz

F2 - Processing parameters
SI                65536
SF          400.1300212 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 2.00

1D NMR plot parameters
CX                22.80 cm
CY                15.00 cm
F1P               9.000 ppm
F1              3601.17 Hz
F2P              -0.500 ppm
F2              -200.06 Hz
PPMCM          0.41667 ppm/cm
HZCM         166.72086 Hz/cm
```

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME      CAO-III-281-pure
EXPNO                    3
PROCNO                   1

F2 - Acquisition Parameters
Date_           20151017
Time                14.34
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                  65536
SOLVENT             CDCl3
NS                    131
DS                     16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.0813940 sec
RG                10321.3
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1             0.25000000 sec
d11            0.03000000 sec
D16            0.00020000 sec
d17            0.00019600 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec
P2                33.10 usec

======== CHANNEL f1 ========
NUC1                  13C
P1                 16.55 usec
P11               500.00 usec
P12              2000.00 usec
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MHz
SP1                2.70 dB
SP2                2.70 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7804136 MHz
WDW                    EM
SSB                     0
LB                 1.00 Hz
GB                      0
PC                 2.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.65 cm
F1P              230.637 ppm
F1               29009.68 Hz
F2P              -10.287 ppm
F2               -1293.96 Hz
PPMCM            10.56688 ppm/cm
HZCM          1329.10693 Hz/cm
```

1H spectrum



Current Data Parameters
USER osborn
NAME CAO-IV-18A
EXPNO 1
PROCNO 1

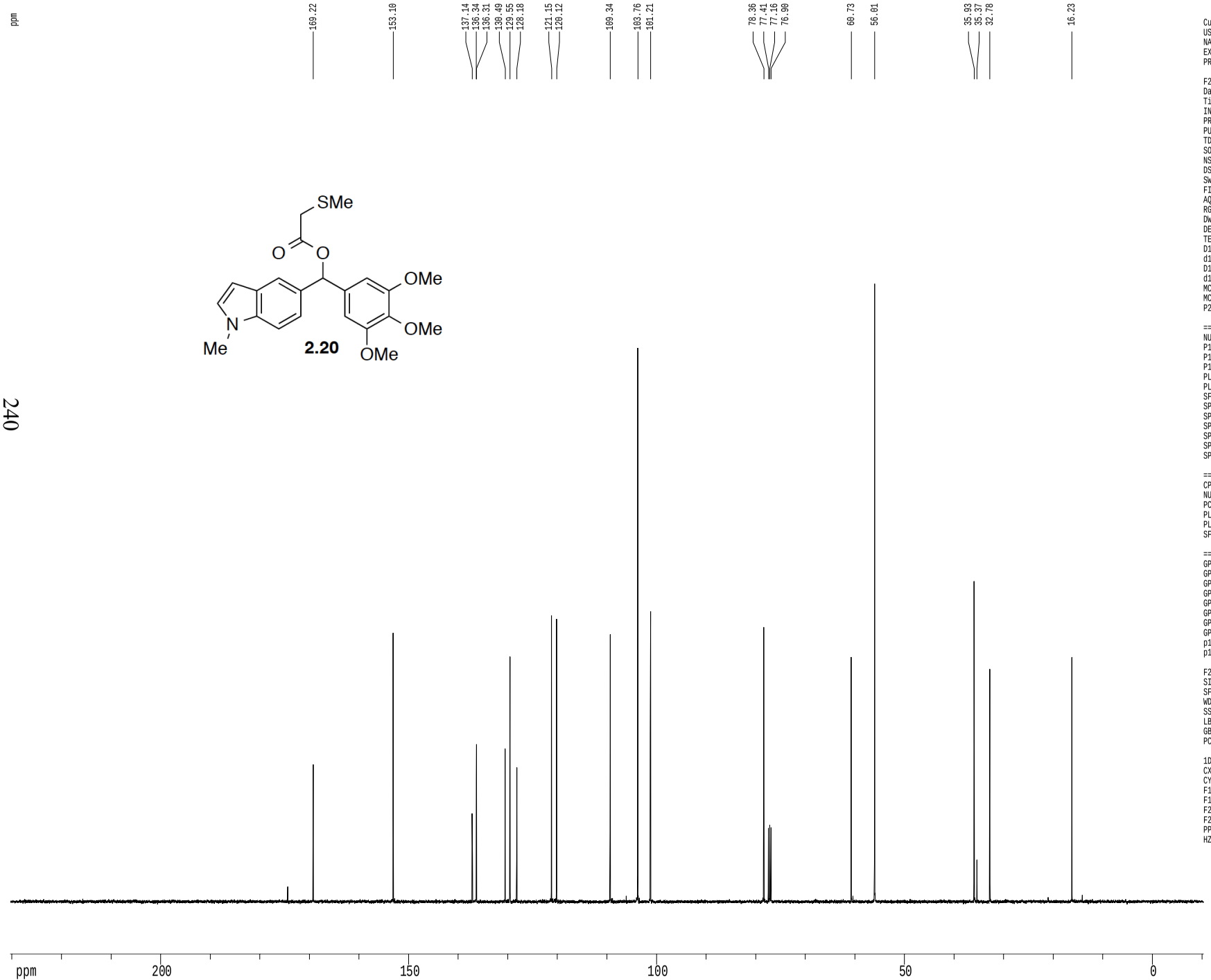
F2 - Acquisition Parameters
Date_ 20151024
Time 17.18
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 45.3
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz

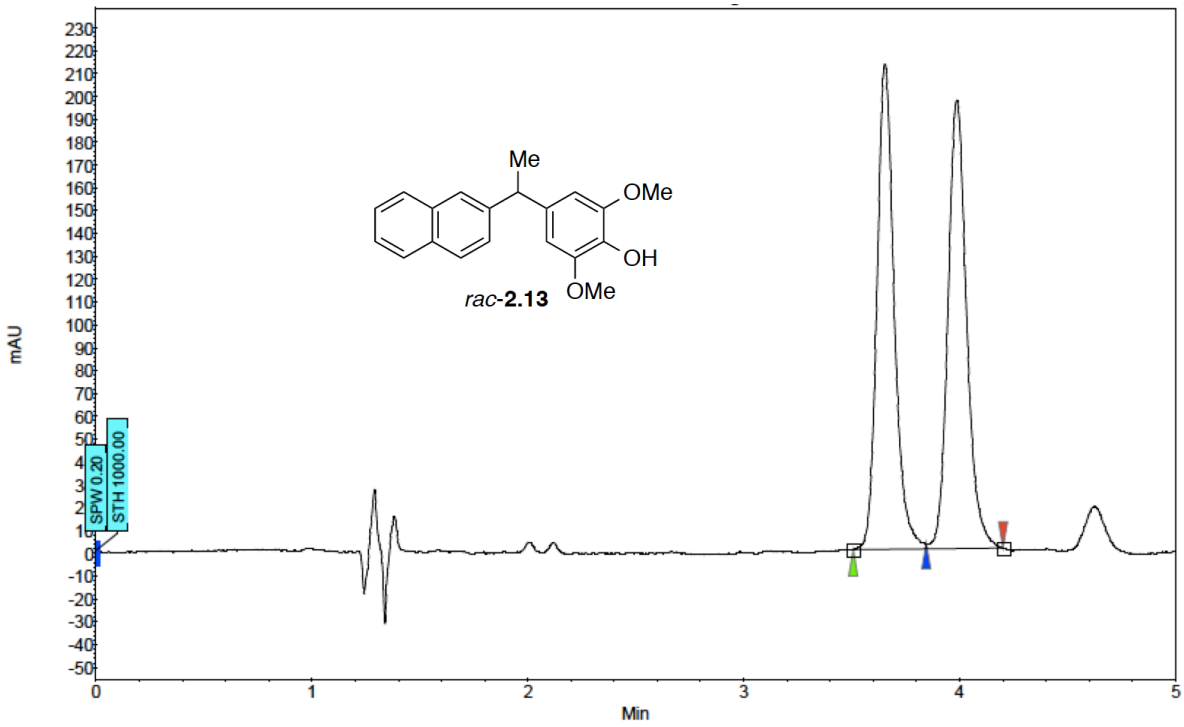
F2 - Processing parameters
SI 65536
SF 400.1300334 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00

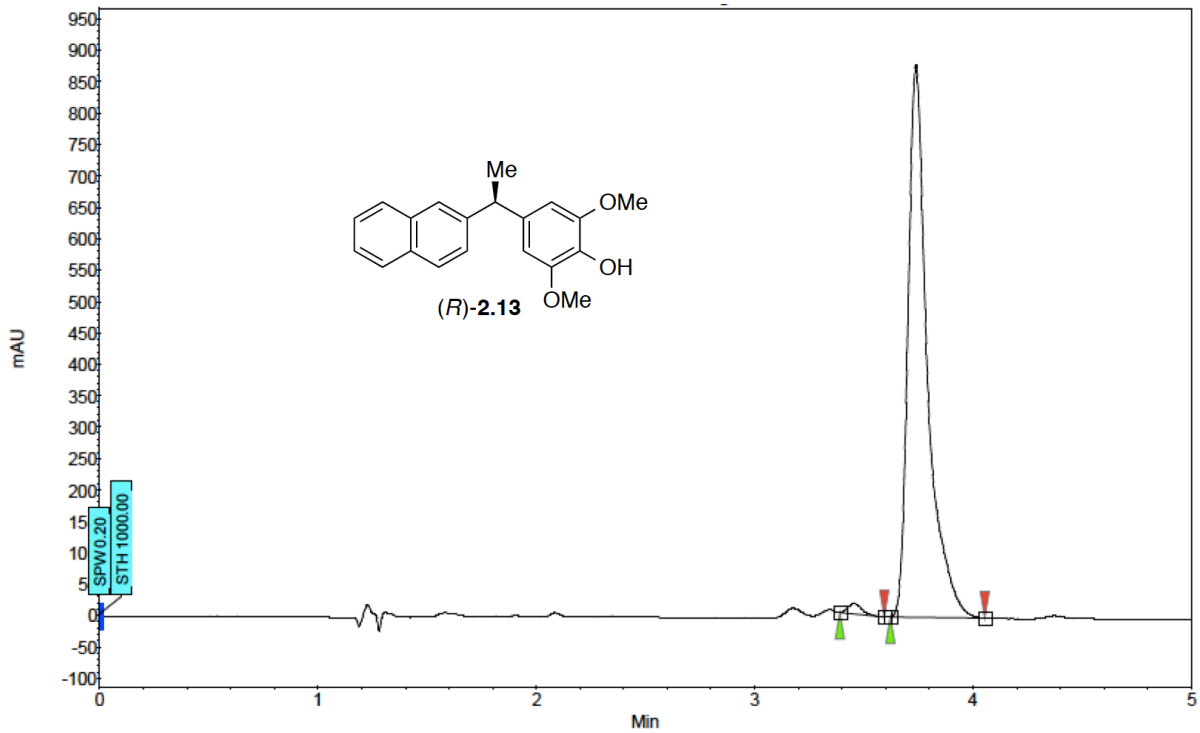
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72086 Hz/cm

Z-restored spin-echo 13C spectrum with 1H decoupling

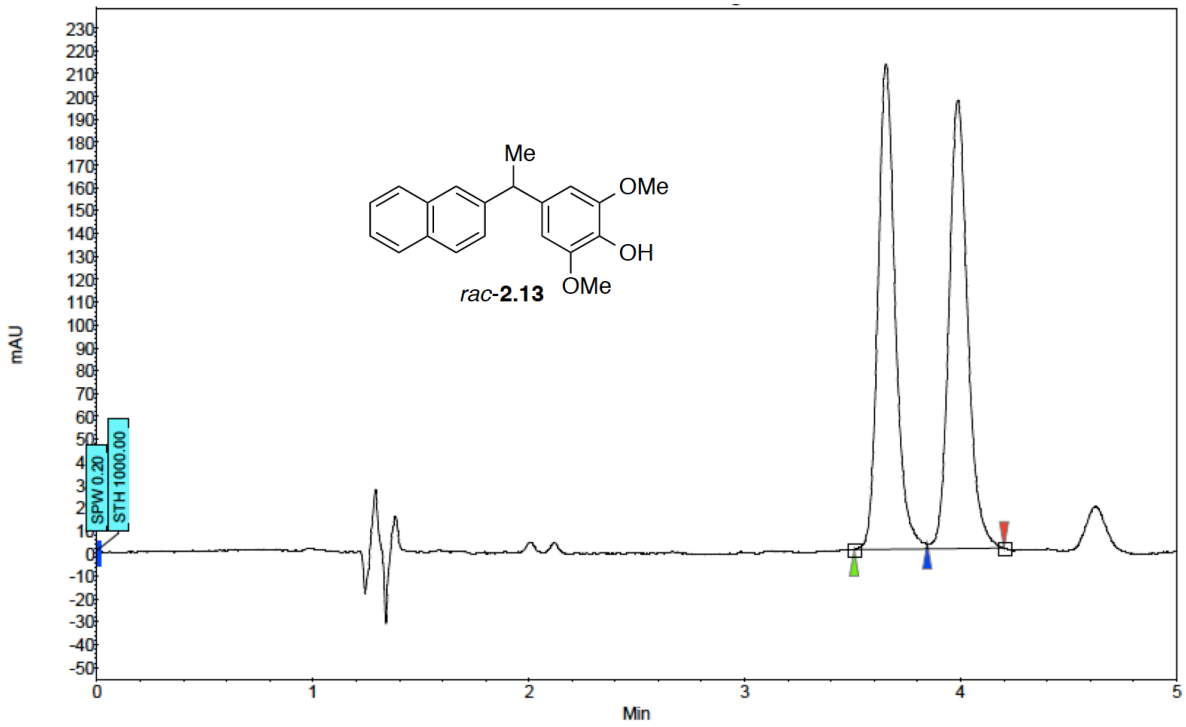


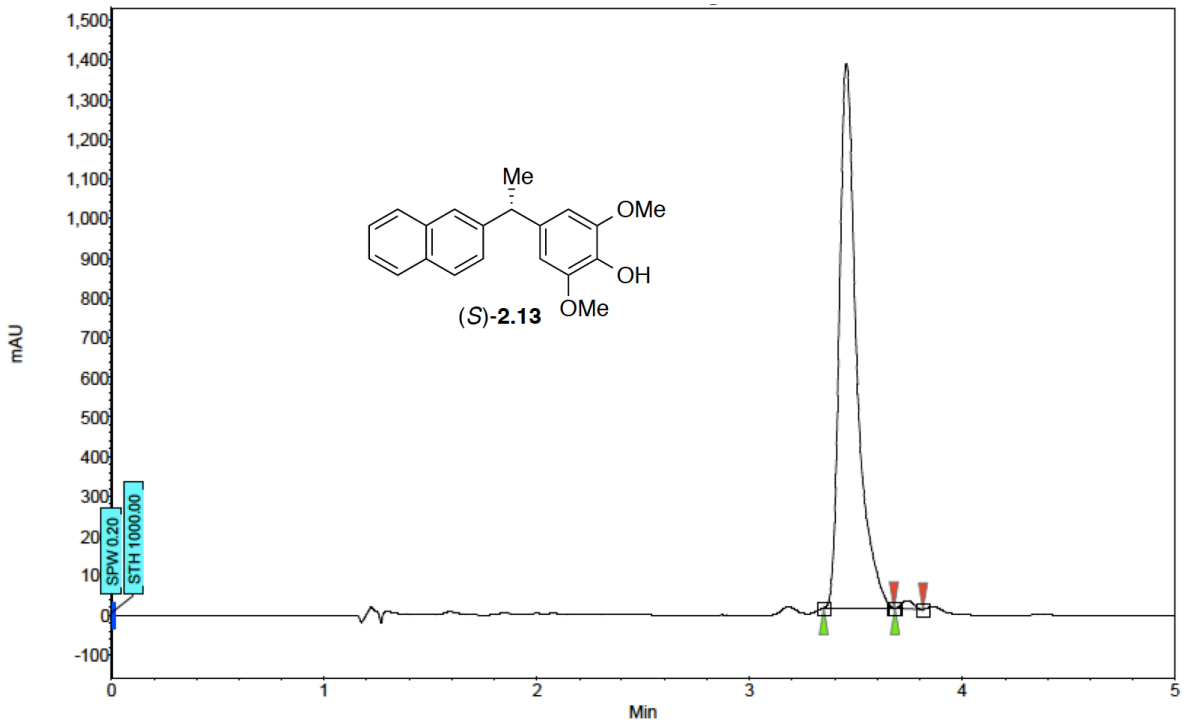

```
Current Data Parameters
USER                osborn
NAME          CAO-IV-18A
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_          20151024
Time              17.51
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                65536
SOLVENT           CDCl3
NS                   41
DS                   16
SWH           30303.031 Hz
FIDRES        0.462388 Hz
AQ            1.0813940 sec
RG               2298.8
DW               16.500 usec
DE                6.00 usec
TE                298.0 K
D1            0.25000000 sec
d11           0.03000000 sec
D16           0.00020000 sec
d17           0.00019600 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec
P2                33.10 usec

======== CHANNEL f1 ========
NUC1                 13C
P1                16.55 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1               2.70 dB
SP2               2.70 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2               1.60 dB
PL12             24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                 0.00 %
GPX2                 0.00 %
GPY1                 0.00 %
GPY2                 0.00 %
GPZ1                30.00 %
GPZ2                50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7804399 MHz
WDW                    EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  2.00

1D NMR plot parameters
CX                 22.80 cm
CY                 12.00 cm
F1P              230.637 ppm
F1             29009.68 Hz
F2P              -10.287 ppm
F2             -1293.96 Hz
PPMCM           10.56688 ppm/cm
HZCM          1329.10730 Hz/cm
```



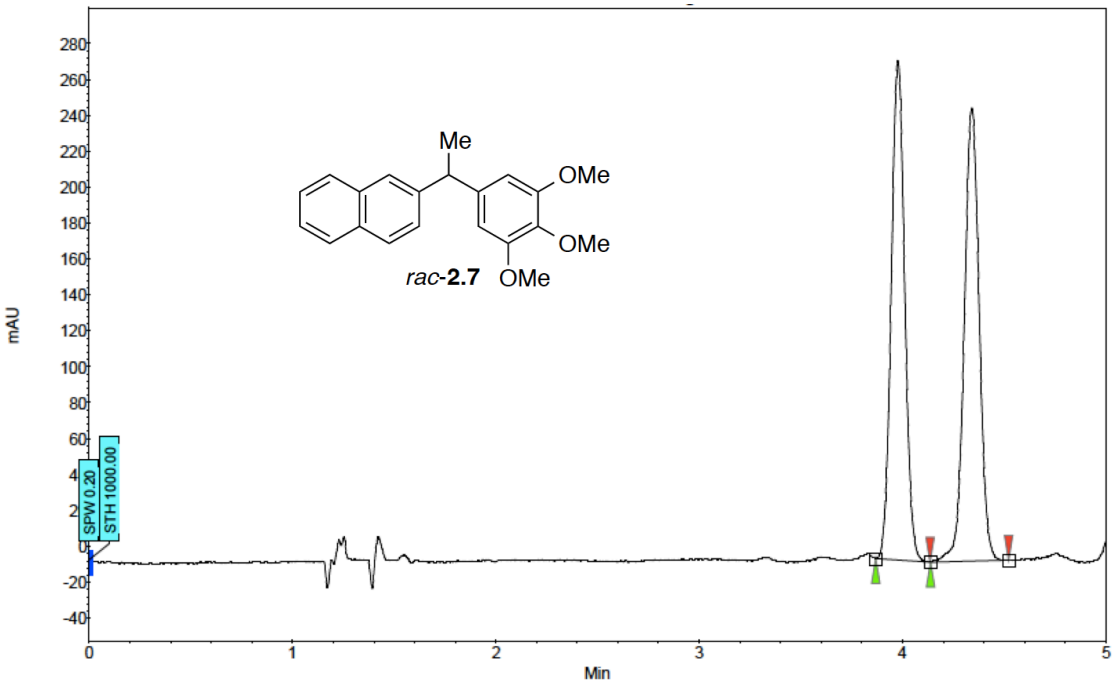


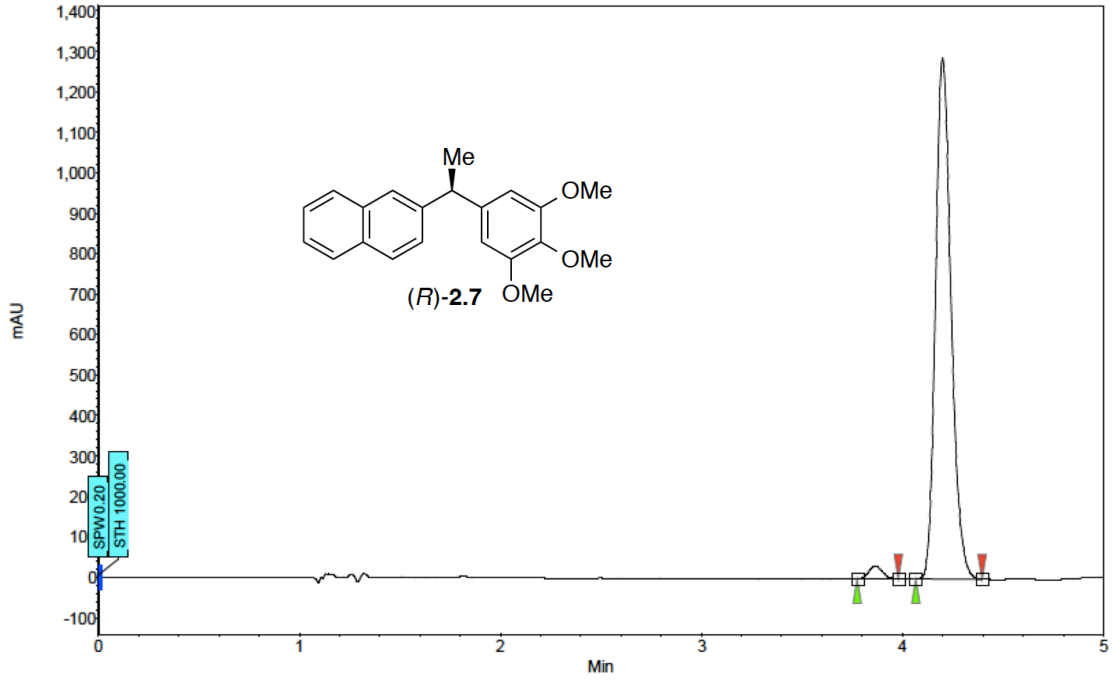
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	3.39	3.46	3.59	0.00	1.29	16.4	1.2	1.292
2	UNKNOWN	3.62	3.74	4.05	0.00	98.71	879.9	90.7	98.708
Total						100.00	896.2	91.9	100.000



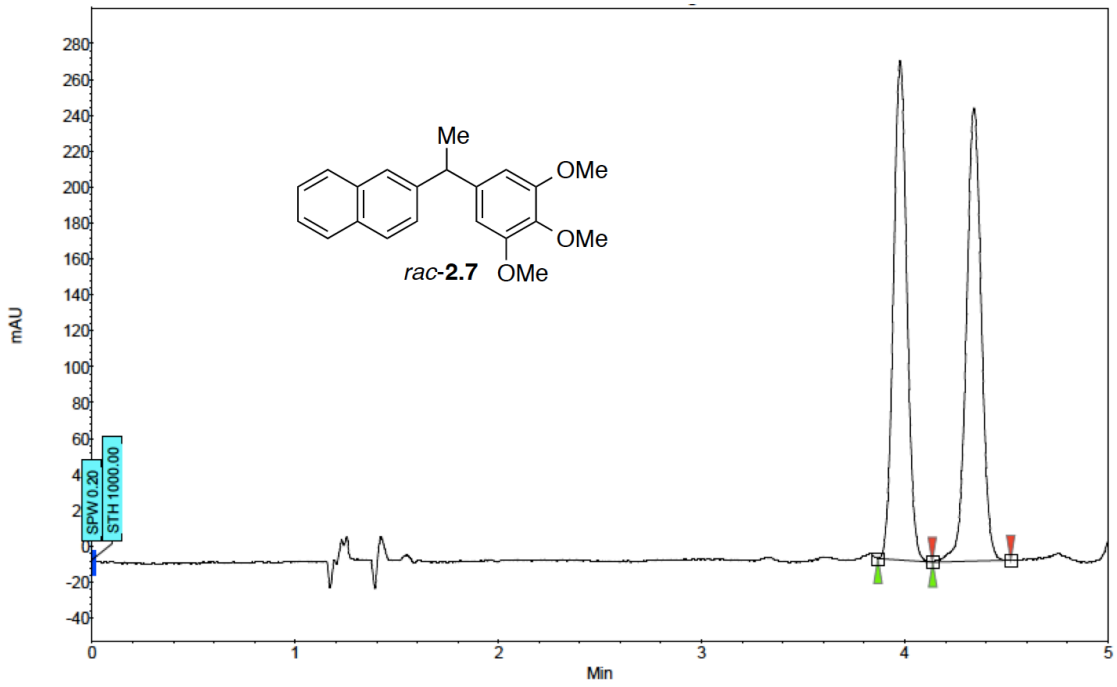


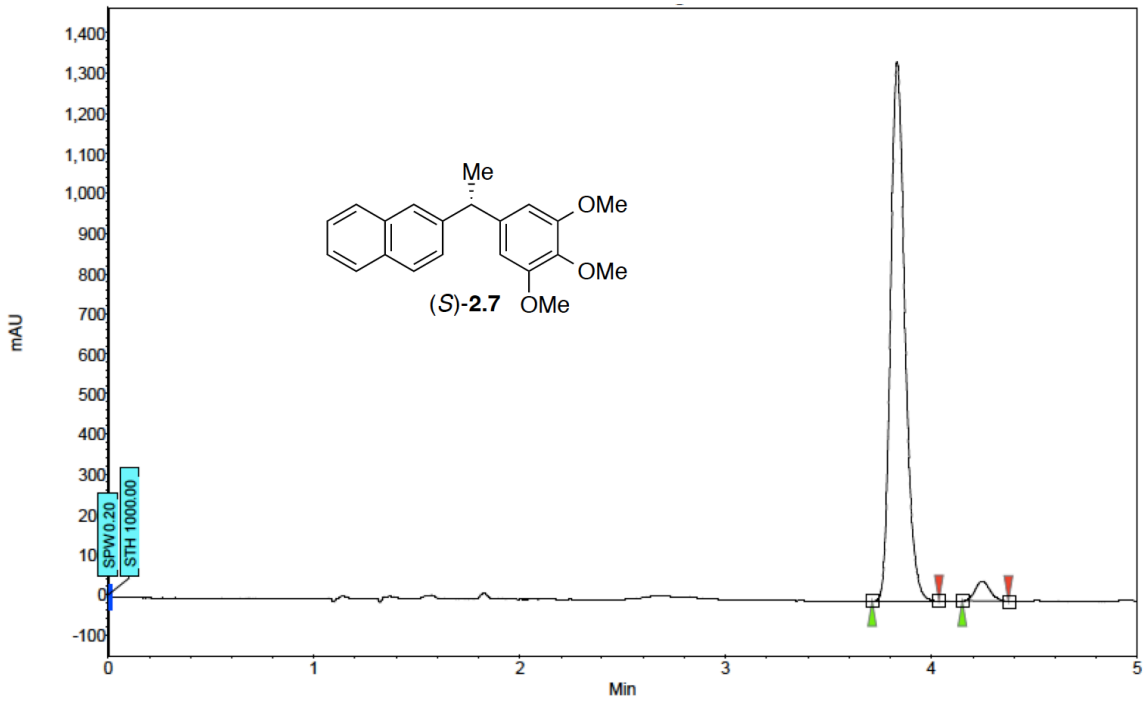
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	3.35	3.46	3.68	0.00	99.06	1372.2	129.7	99.060
2	UNKNOWN	3.68	3.74	3.82	0.00	0.94	20.3	1.2	0.940



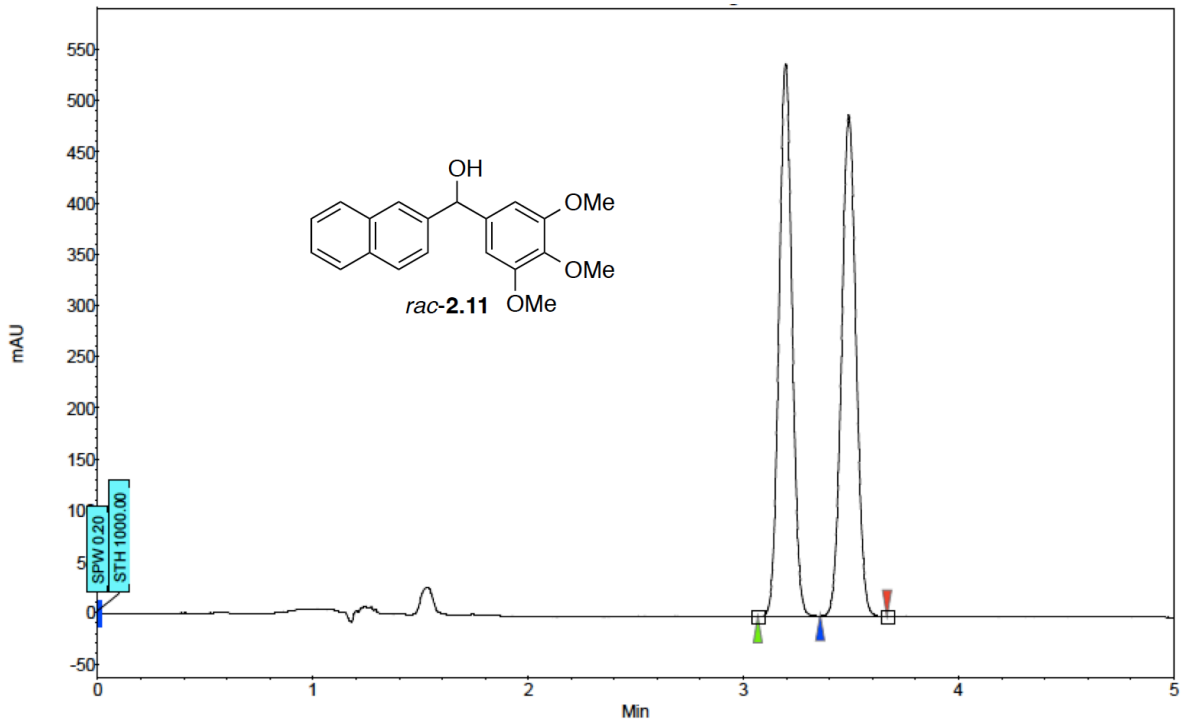


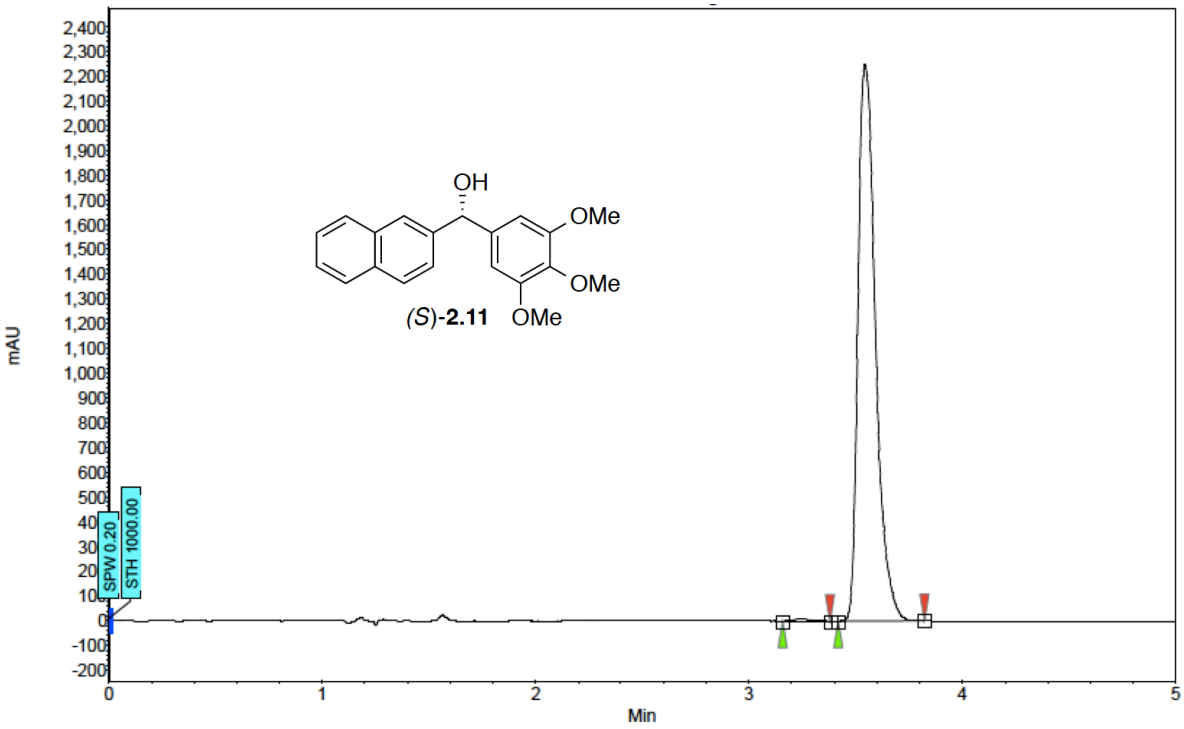
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	3.78	3.86	3.98	0.00	2.14	31.8	2.5	2.144
2	UNKNOWN	4.07	4.20	4.40	0.00	97.86	1288.9	115.4	97.856
Total						100.00	1320.7	118.0	100.000



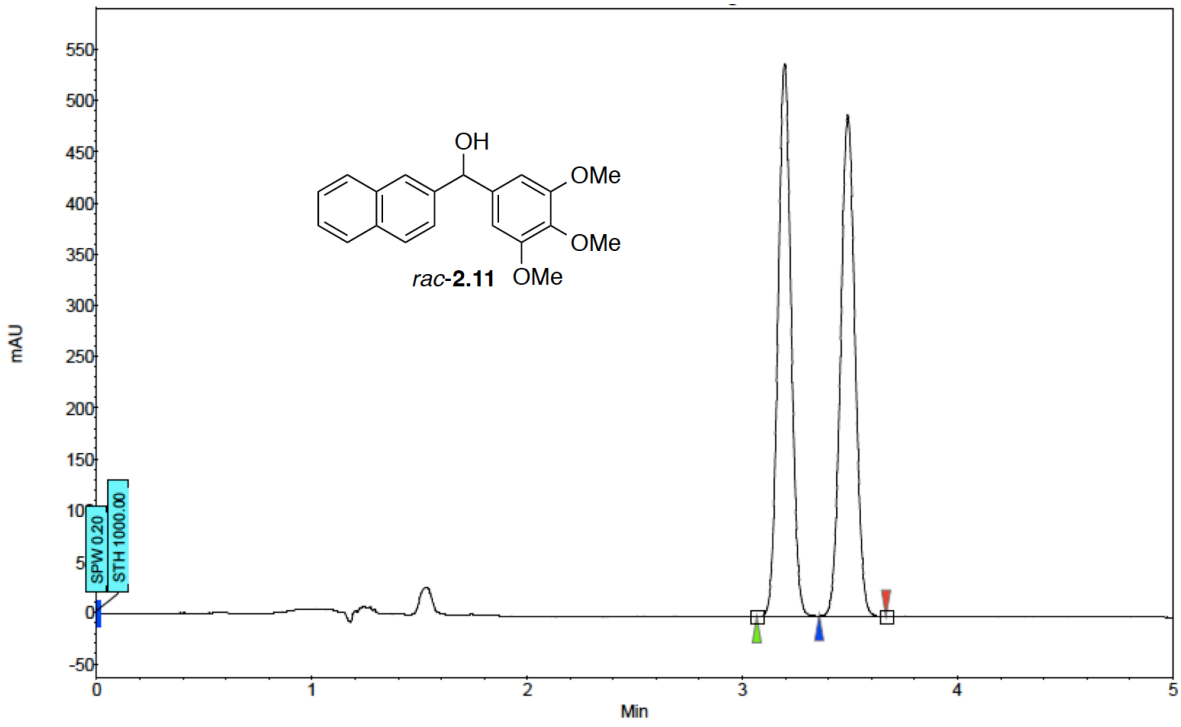


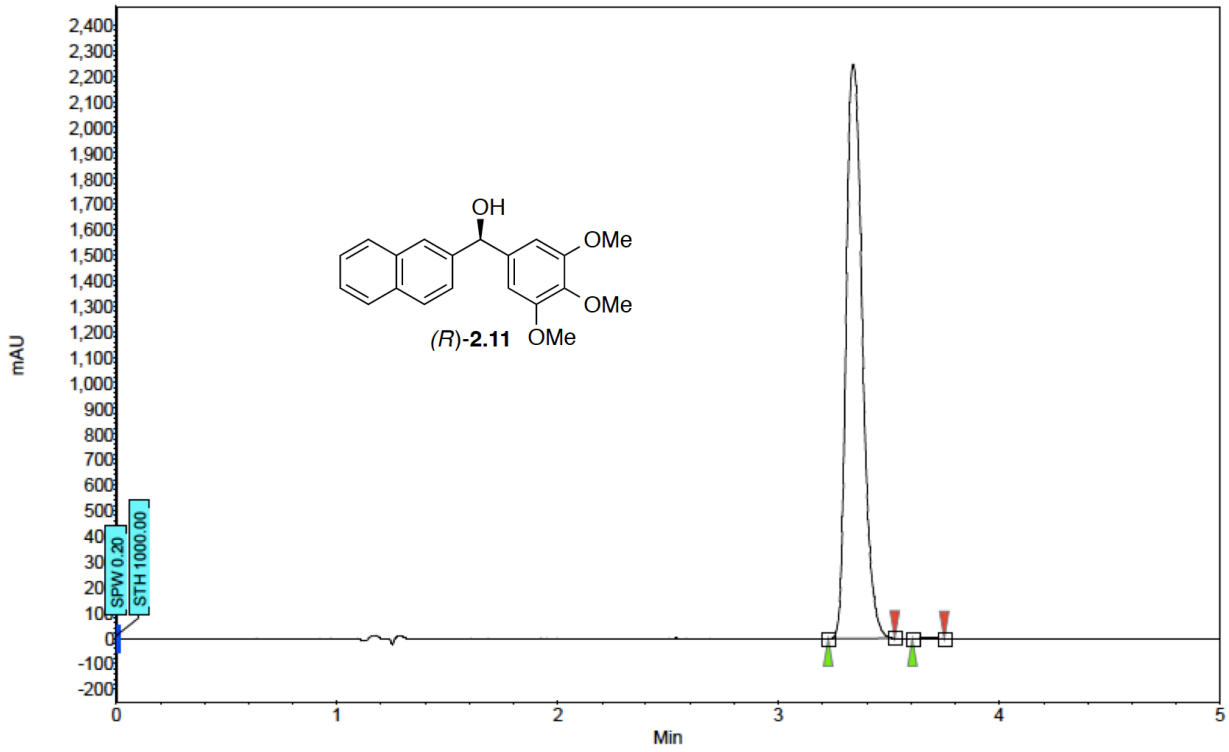
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	3.71	3.83	4.04	0.00	96.31	1344.1	108.6	96.310
2	UNKNOWN	4.15	4.25	4.37	0.00	3.69	49.8	4.2	3.690
Total						100.00	1393.9	112.8	100.000



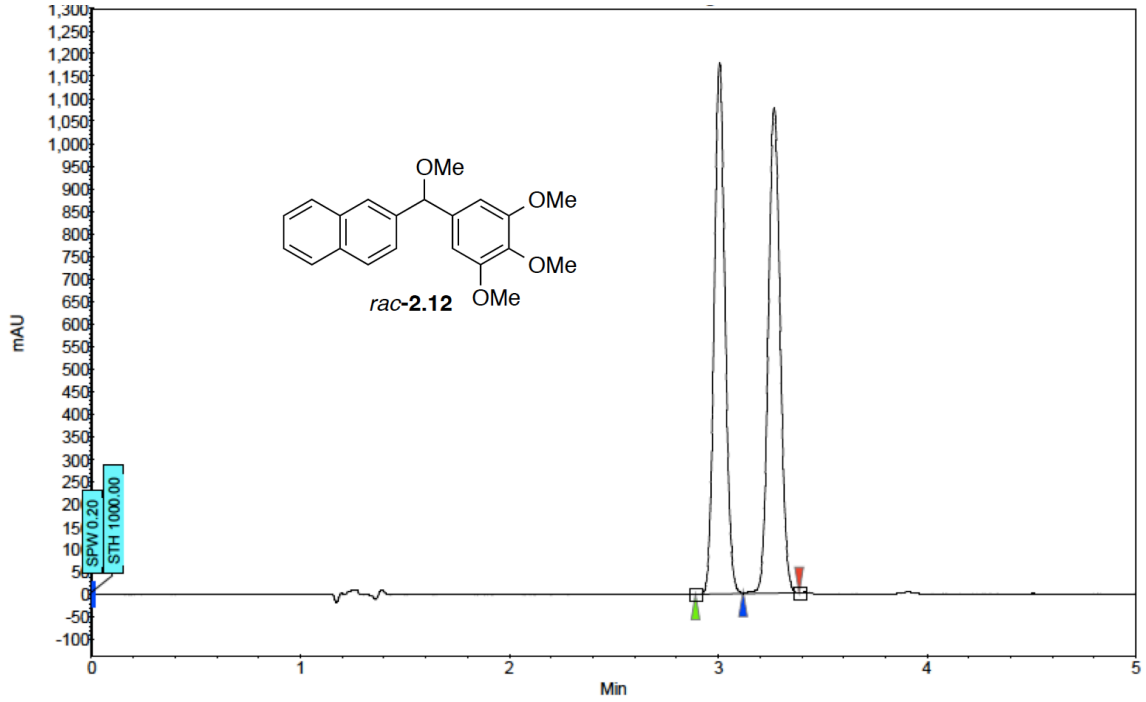


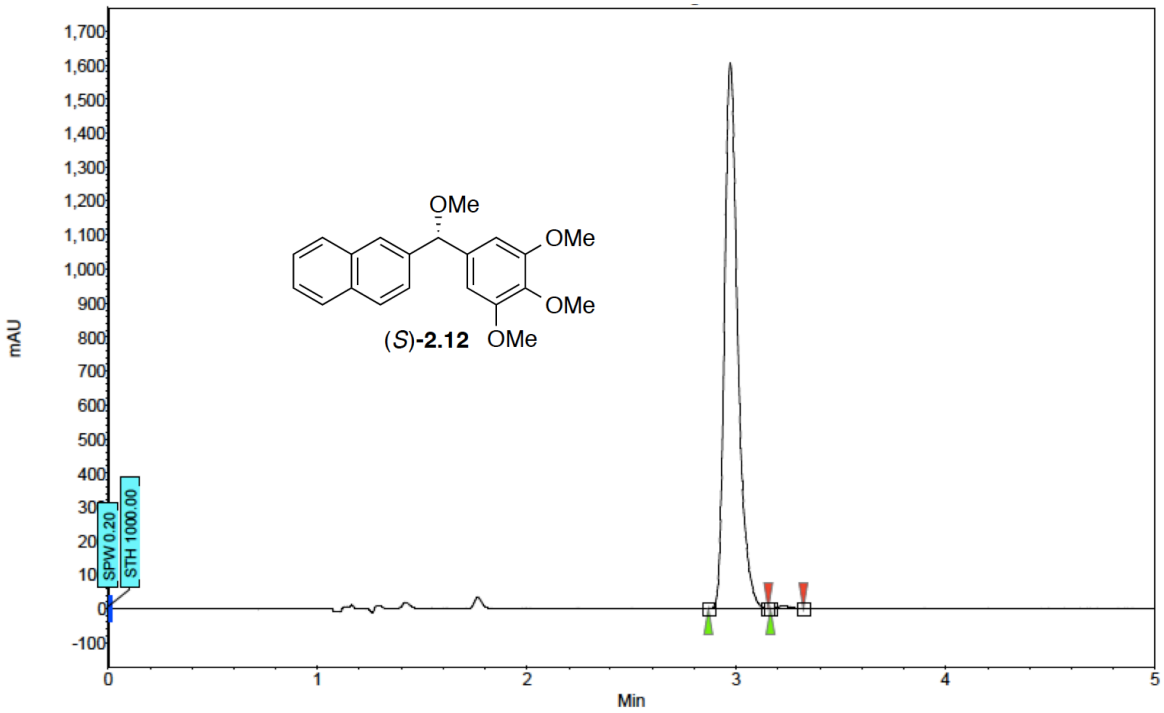
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	3.16	3.25	3.38	0.00	0.35	9.8	0.7	0.346
2	UNKNOWN	3.42	3.55	3.82	0.00	99.65	2248.5	212.7	99.654
Total						100.00	2258.3	213.4	100.000



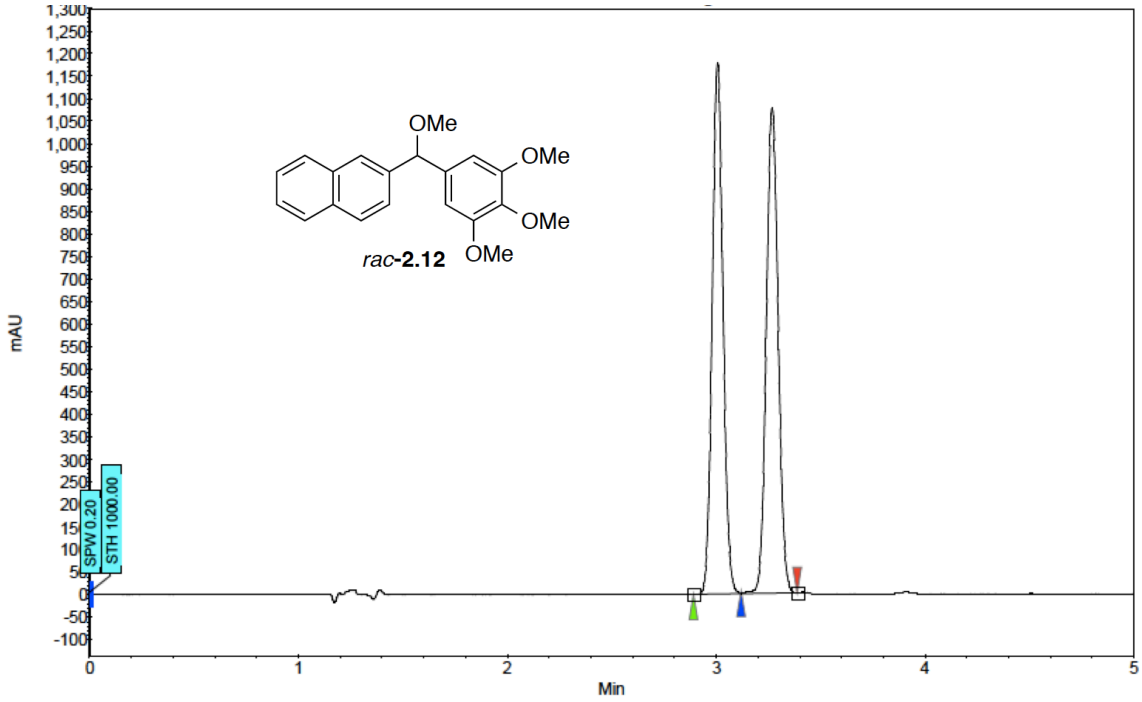


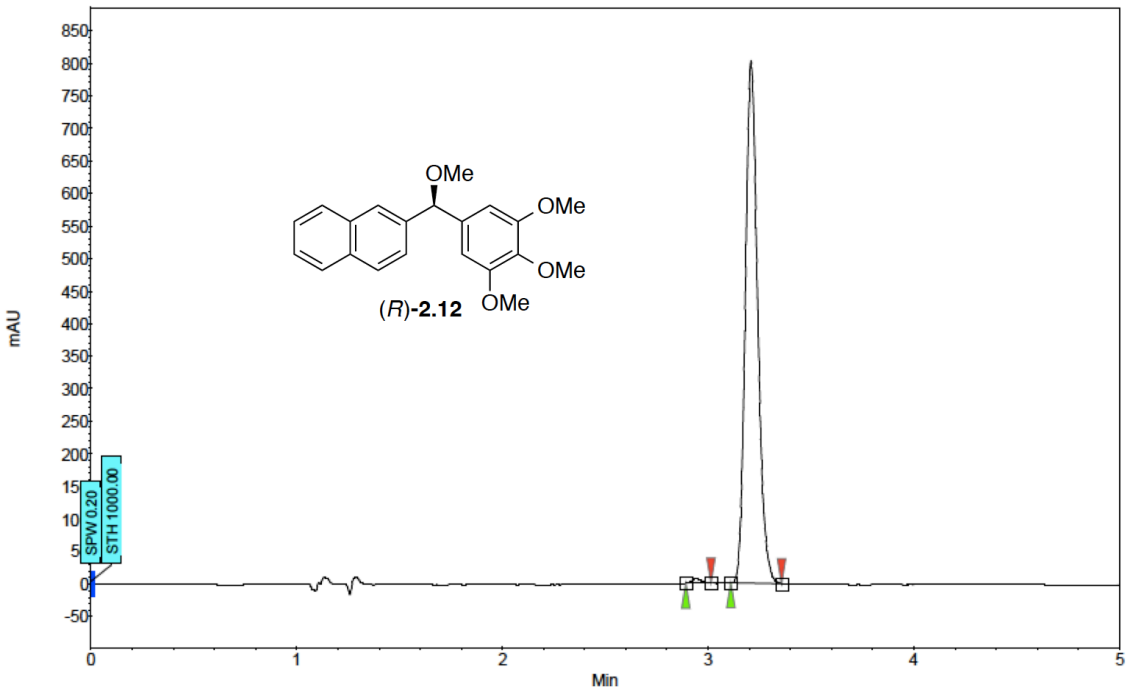
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	3.23	3.34	3.53	0.00	99.74	2246.9	190.7	99.738
2	UNKNOWN	3.61	3.67	3.75	0.00	0.26	7.1	0.5	0.262
Total						100.00	2254.1	191.2	100.000





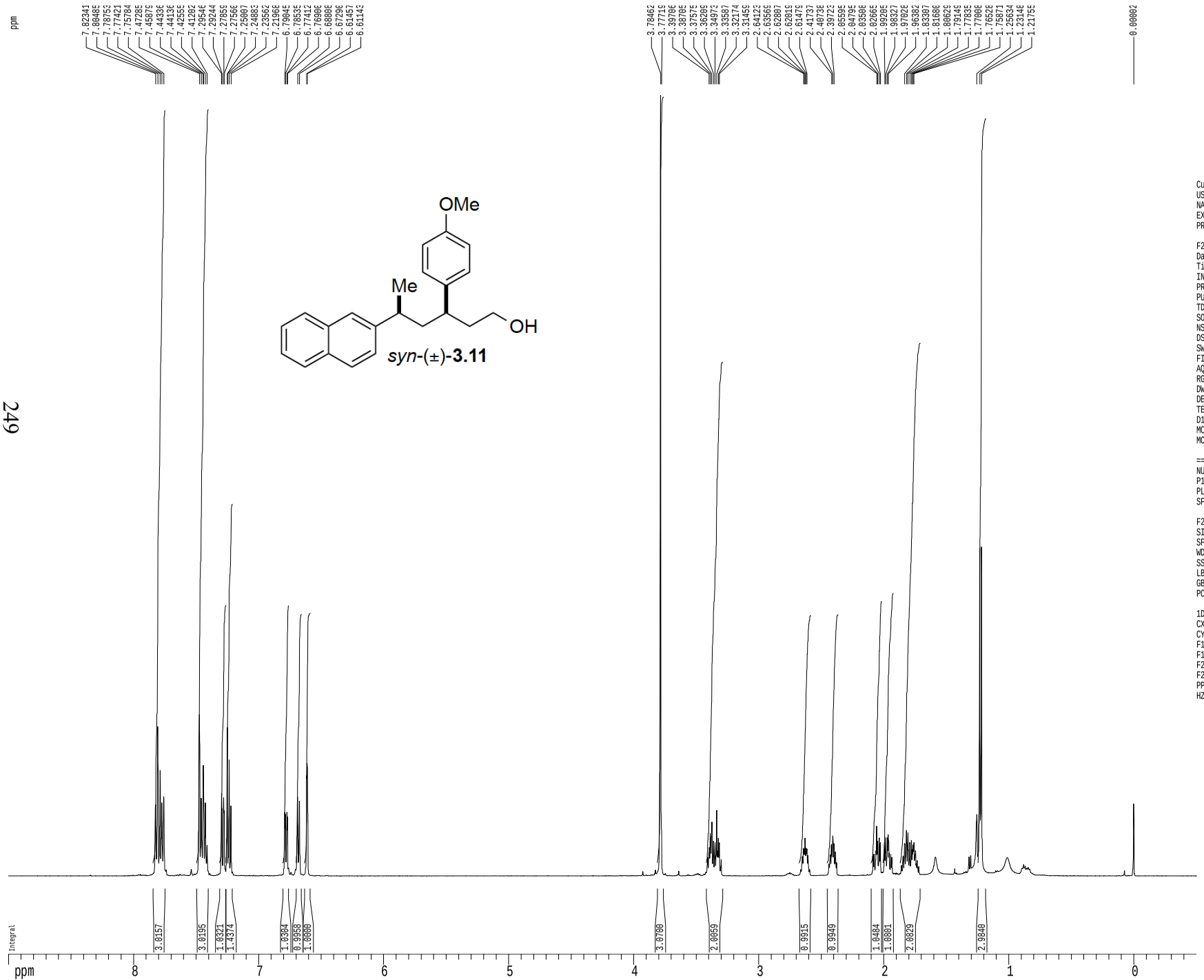
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	2.87	2.97	3.15	0.00	99.52	1606.5	117.9	99.518
2	UNKNOWN	3.16	3.23	3.32	0.00	0.48	8.6	0.6	0.482
Total						100.00	1615.1	118.5	100.000





Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	2.89	2.94	3.01	0.00	0.69	6.7	0.4	0.691
2	UNKNOWN	3.11	3.21	3.36	0.00	99.31	802.1	55.6	99.309
Total						100.00	808.8	56.0	100.000

1H spectrum



Current Data Parameters
USER osborn
NAME CAO-II-146A SI
EXPNO 1
PROCNO 1

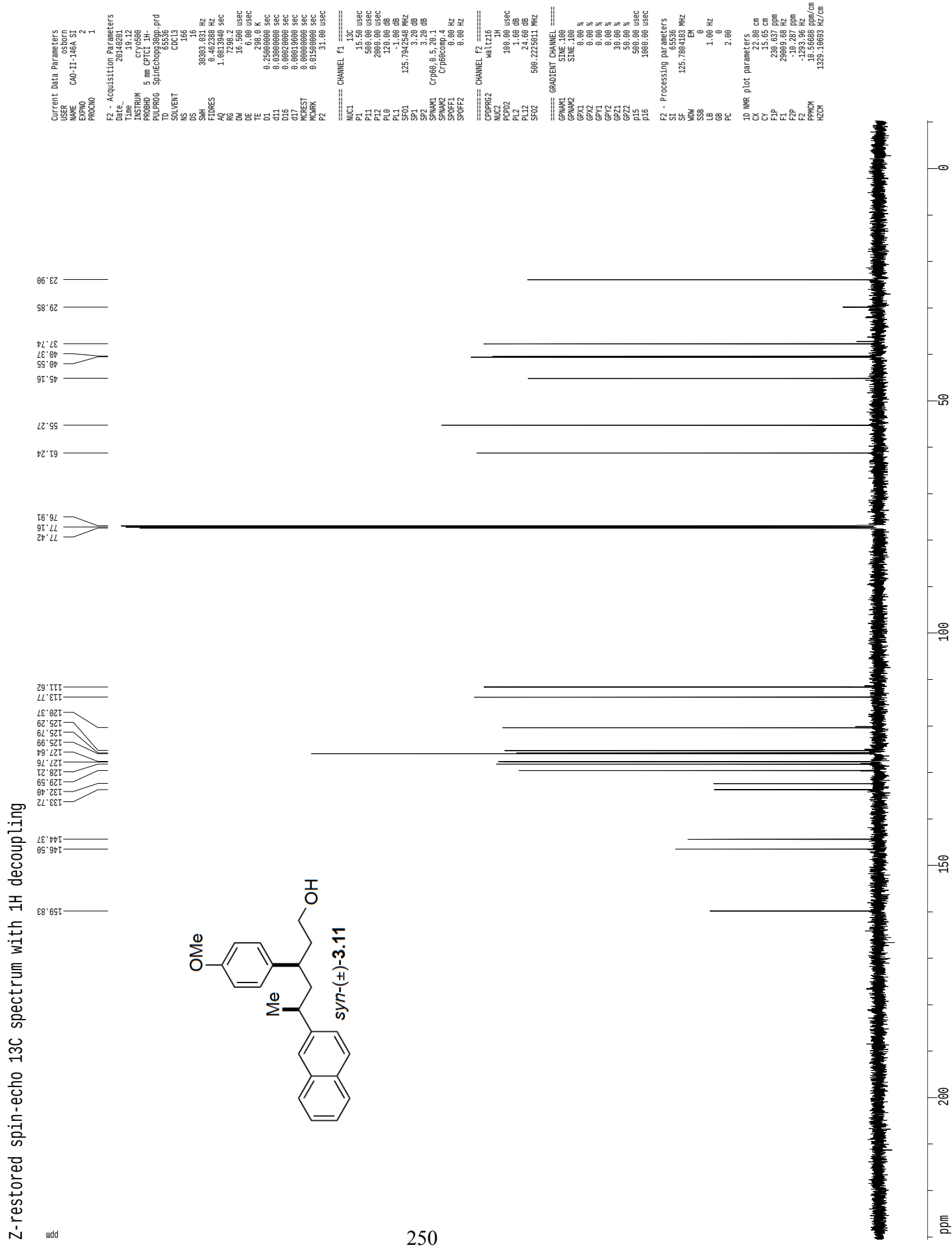
F2 - Acquisition Parameters
Date_ 20140201
Time 19.09
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 6.3
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

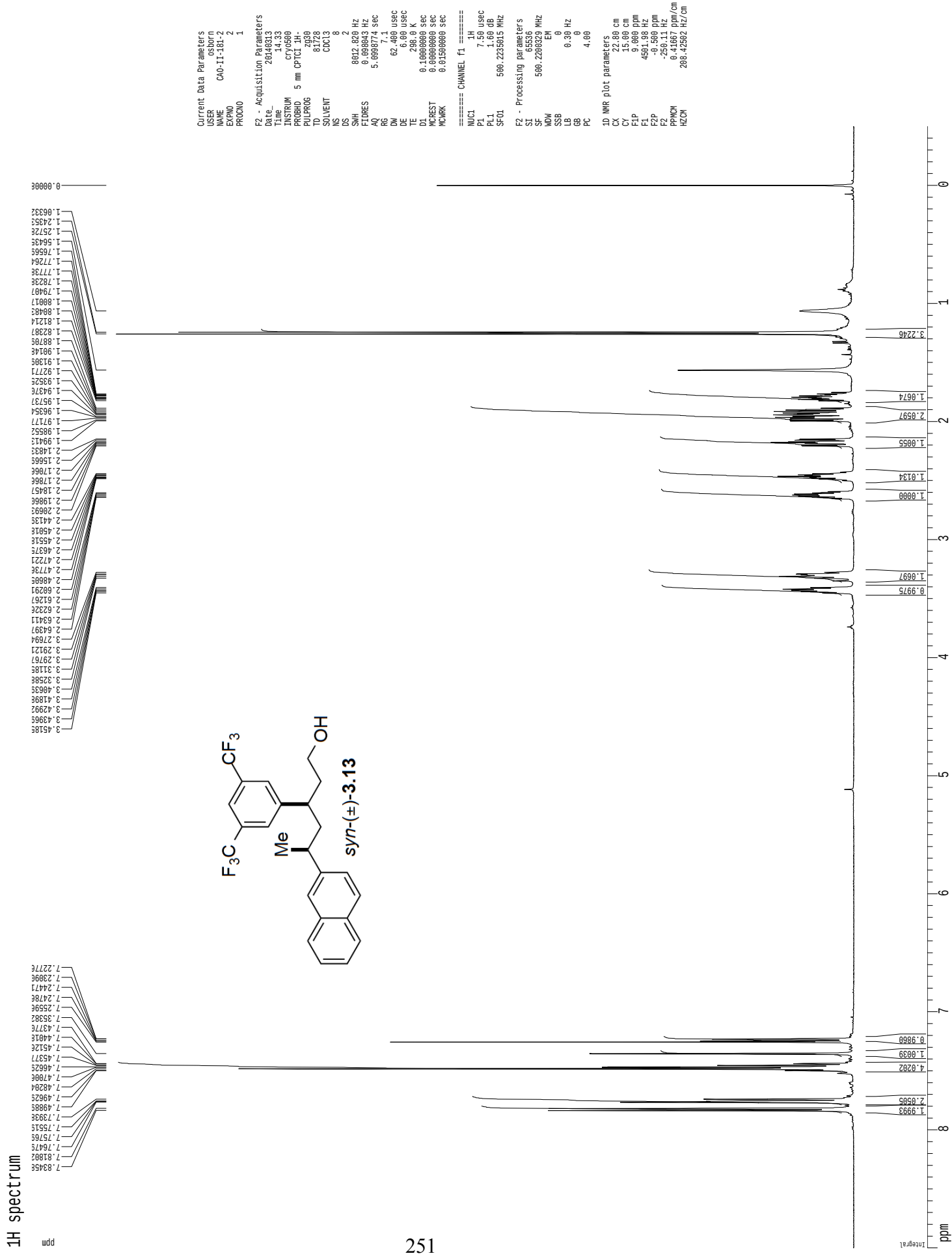
======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz

F2 - Processing parameters
SI 65536
SF 500.2200370 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

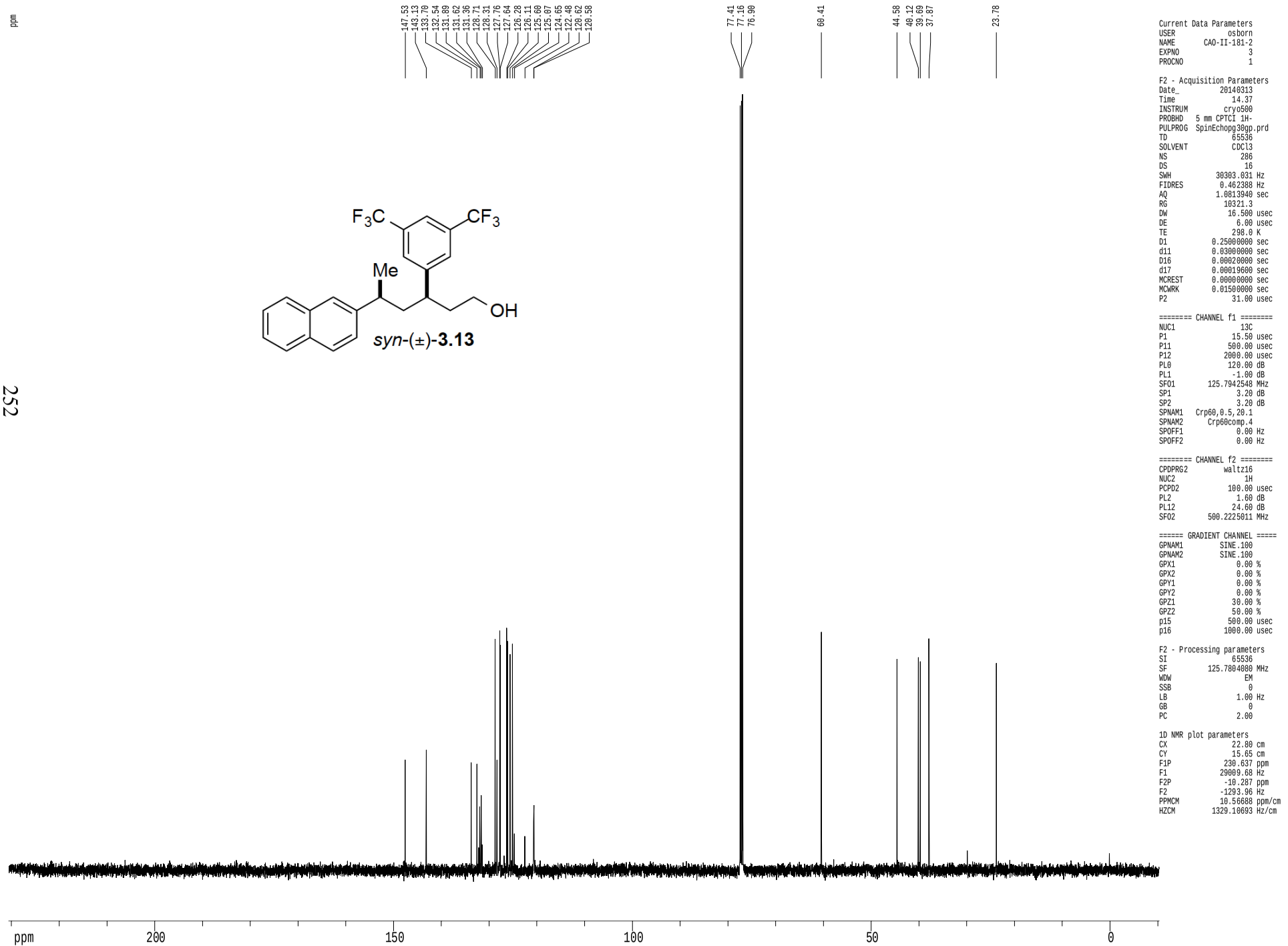
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm

Z-restored spin-echo 13C spectrum with 1H decoupling

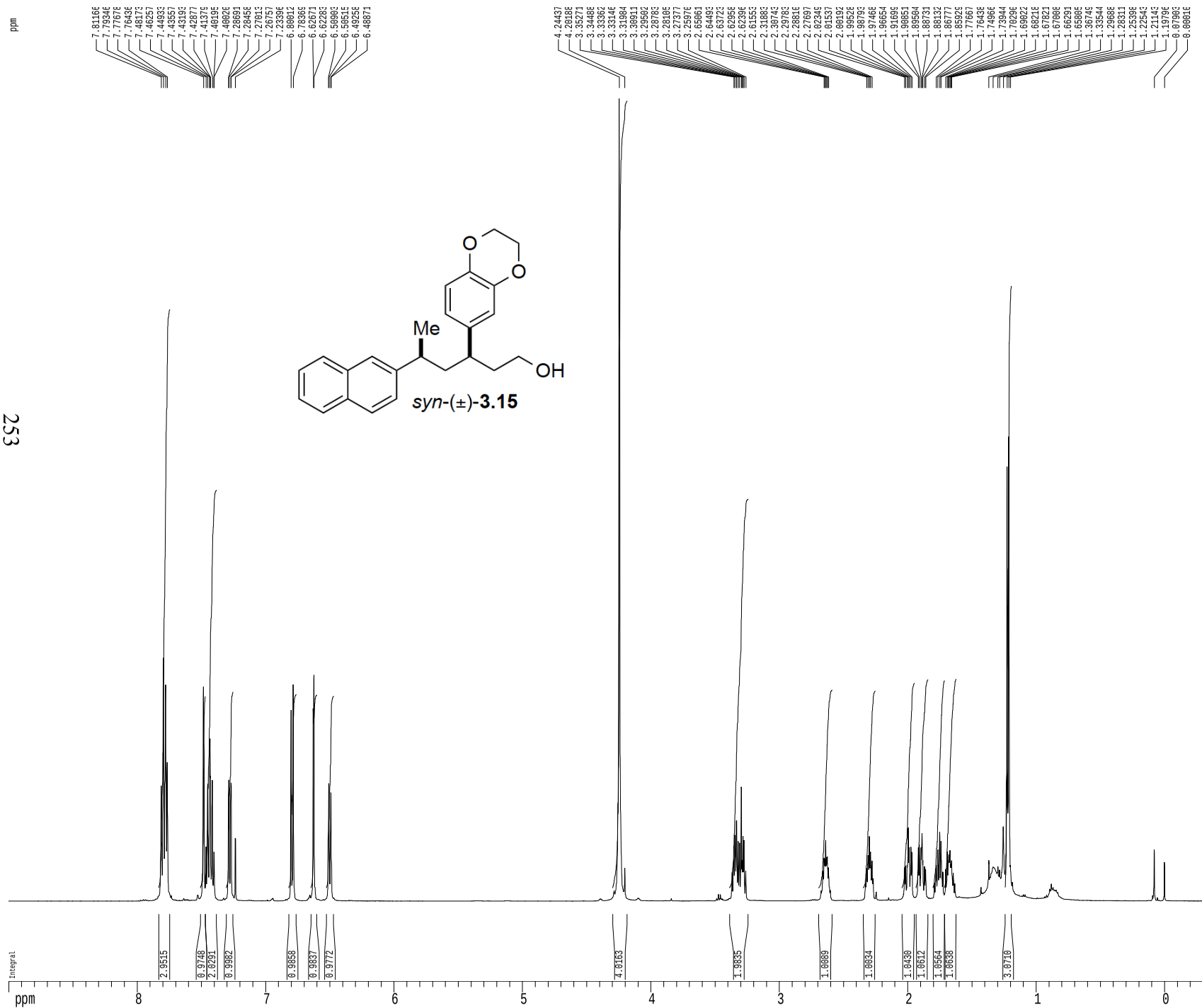



1H spectrum
Current Data Parameters
USER osborn
NAME CAO-II-181-2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140313
Time 14.33
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0999774 sec
RG 7.1
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200229 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm
CF3
F3C
Me
OH
syn-(±)-3.13
ppm
Integral

Z-restored spin-echo 13C spectrum with 1H decoupling

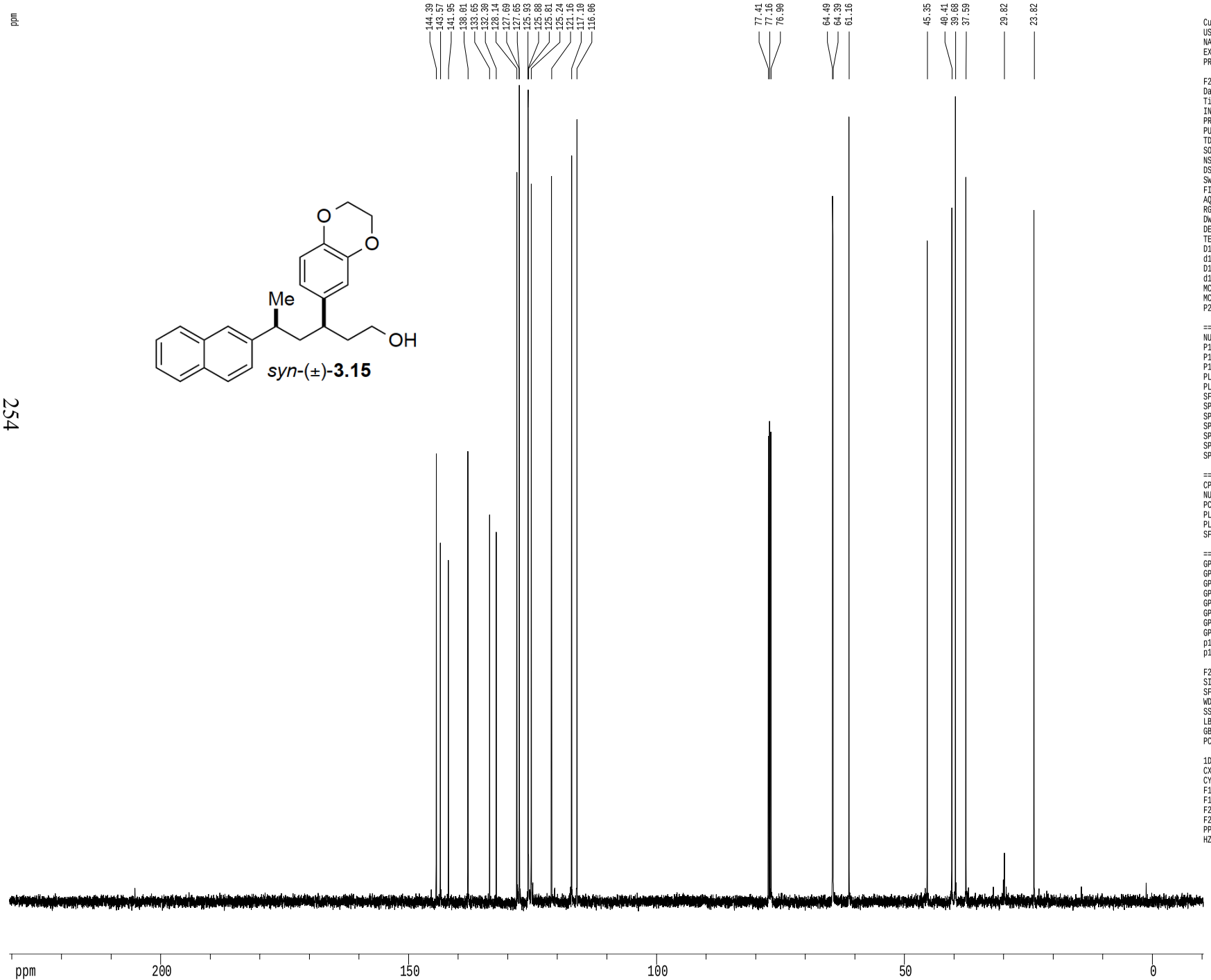


CAO-II-171A SI
1H spectrum



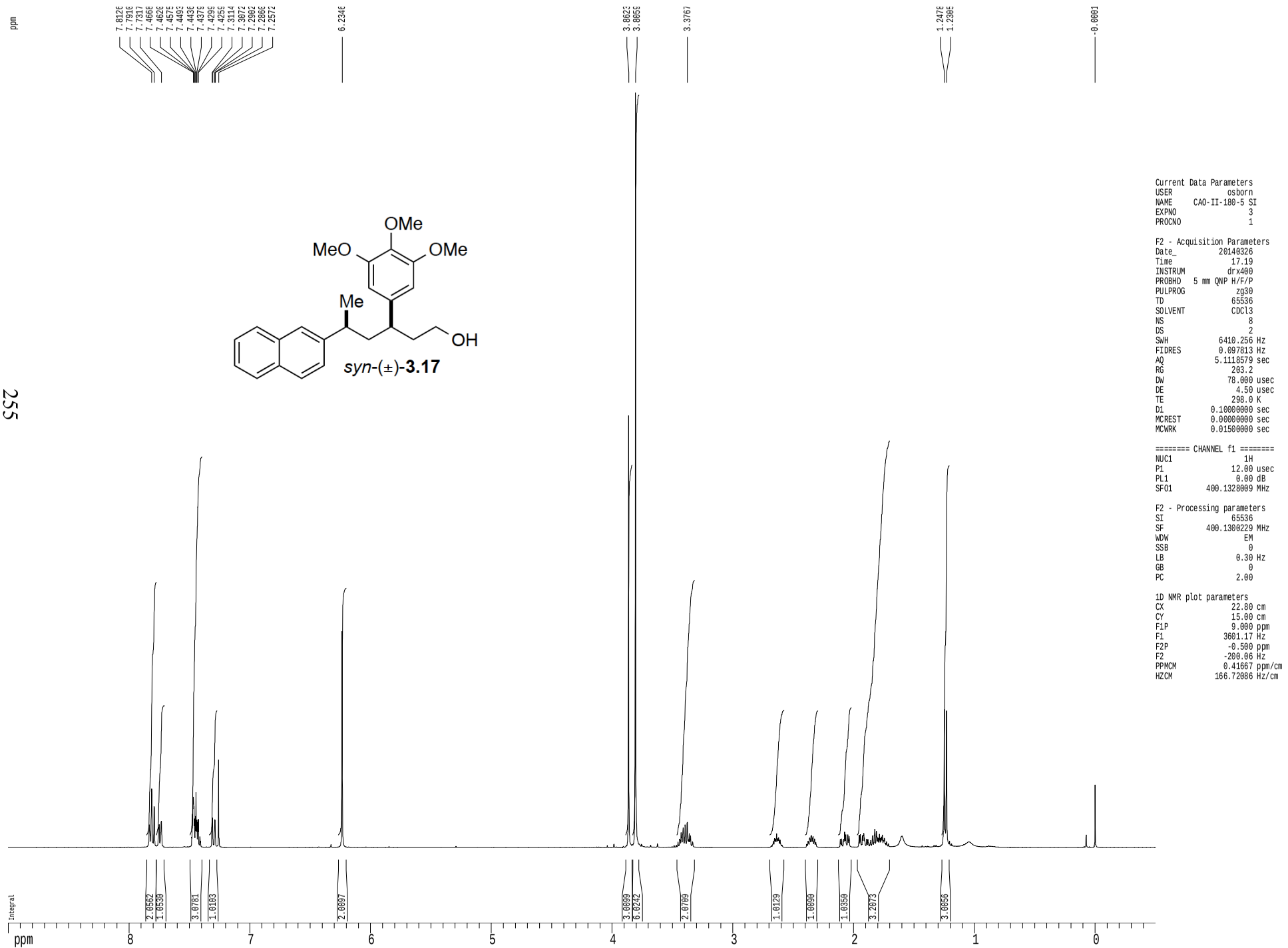

```
Current Data Parameters
USER                osborn
NAME      CAO-II-171A SI
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140328
Time               12.04
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 81728
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             8012.820 Hz
FIDRES             0.098043 Hz
AQ              5.0998774 sec
RG                   4.5
DW                62.400 usec
DE                 6.00 usec
TE                290.6 K
D1             0.10000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 =======
NUC1                  1H
P1                 7.50 usec
PL1                1.60 dB
SFO1         500.2235015 MHz

F2 - Processing parameters
SI                 65536
SF            500.2200437 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 4.00

1D NMR plot parameters
CX                22.80 cm
CY                15.00 cm
F1P                9.000 ppm
F1              4501.98 Hz
F2P               -0.500 ppm
F2              -250.11 Hz
PPMCM           0.41667 ppm/cm
HZCM          208.42502 Hz/cm
```

CAO-II-171A
Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME      CAO-II-171A SI
EXPNO                  5
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140328
Time              12.07
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                65536
SOLVENT           CDCl3
NS                  132
DS                   16
SWH           30303.031 Hz
FIDRES         0.462388 Hz
AQ            1.0813940 sec
RG               3649.1
DW               16.500 usec
DE                6.00 usec
TE                290.7 K
D1           0.25000000 sec
d11          0.03000000 sec
D16          0.00020000 sec
d17          0.00019600 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec
P2                31.00 usec

======== CHANNEL f1 ========
NUC1                13C
P1                15.50 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1        125.7942548 MHz
SP1               3.20 dB
SP2               3.20 dB
SPNAM1   Crp60,0.5,20.1
SPNAM2     Crp60comp.4
SPOFF1              0.00 Hz
SPOFF2              0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                1H
PCPD2            100.00 usec
PL2               1.60 dB
PL12              24.60 dB
SFO2        500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15              500.00 usec
p16             1000.00 usec

F2 - Processing parameters
SI                 65536
SF          125.7804182 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  2.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.65 cm
F1P              230.637 ppm
F1             29009.68 Hz
F2P              -10.287 ppm
F2             -1293.96 Hz
PPMCM           10.56688 ppm/cm
HZCM          1329.10706 Hz/cm
```

1H spectrum



Current Data Parameters
USER osborn
NAME CAO-II-180-5 SI
EXPNO 3
PROCNO 1

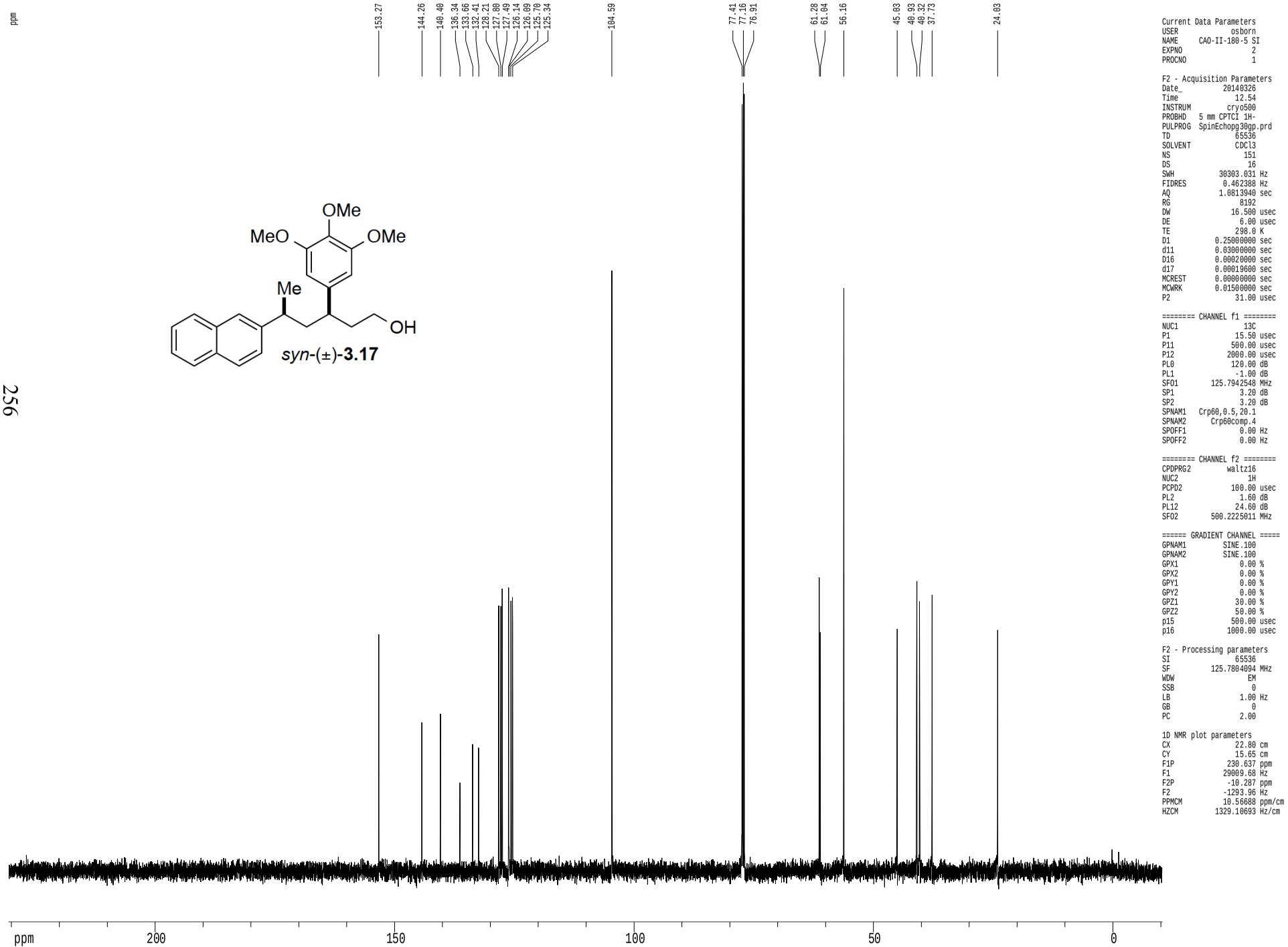
F2 - Acquisition Parameters
Date_ 20140326
Time 17.19
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 203.2
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz

F2 - Processing parameters
SI 65536
SF 400.1300229 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72086 Hz/cm

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME CAO-II-180-5 SI
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20140326
Time 12.54
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 151
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 8192
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 31.00 usec

======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

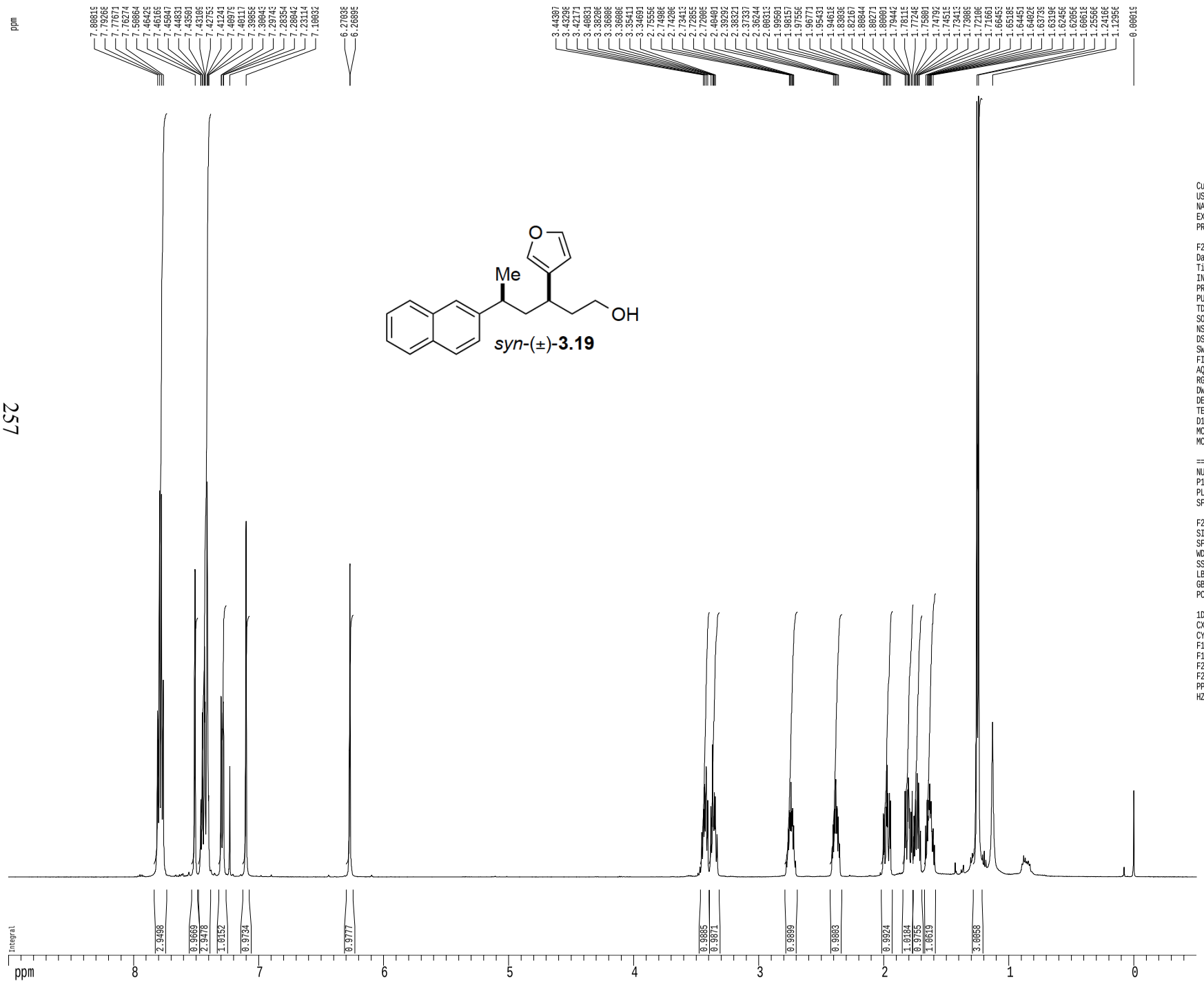
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 125.7804094 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

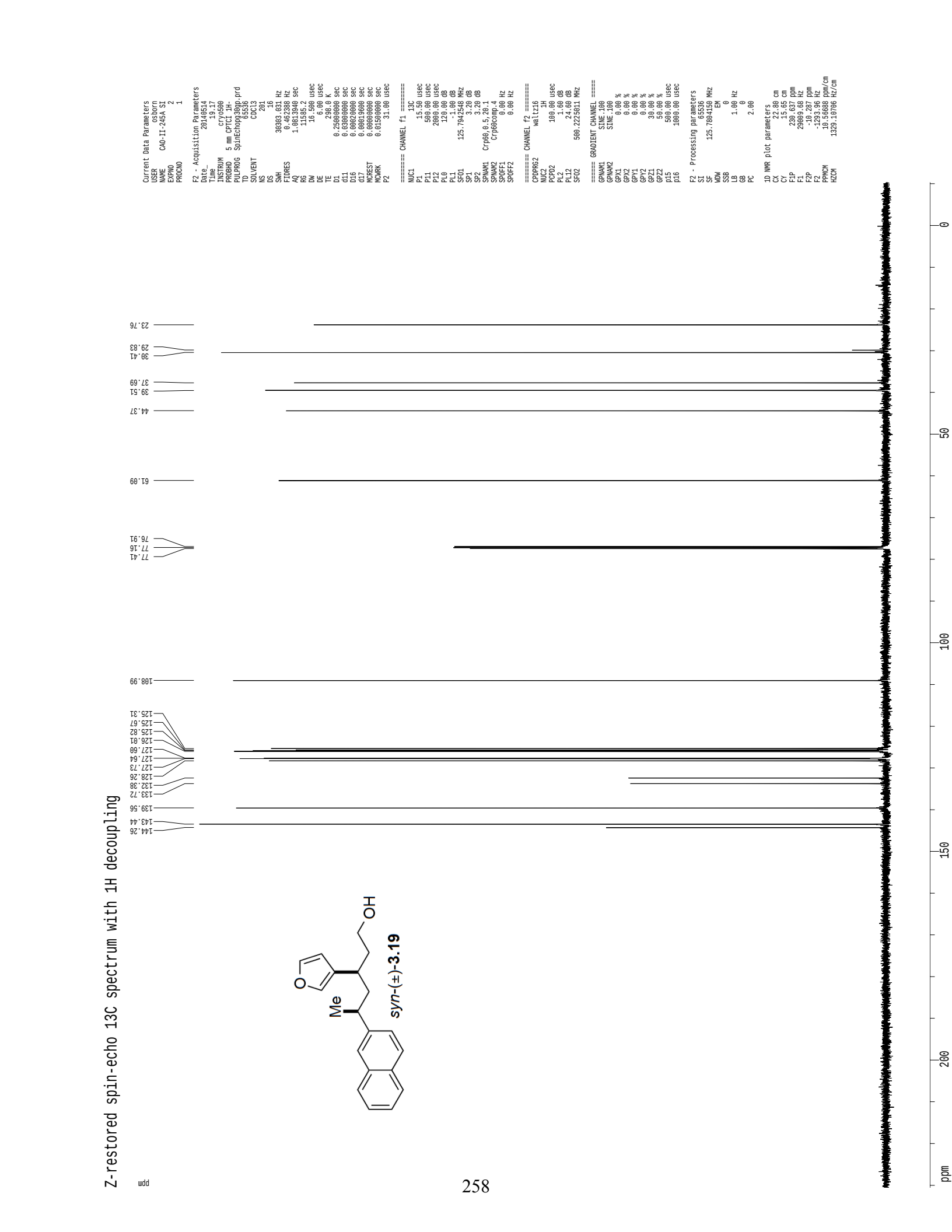
1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm

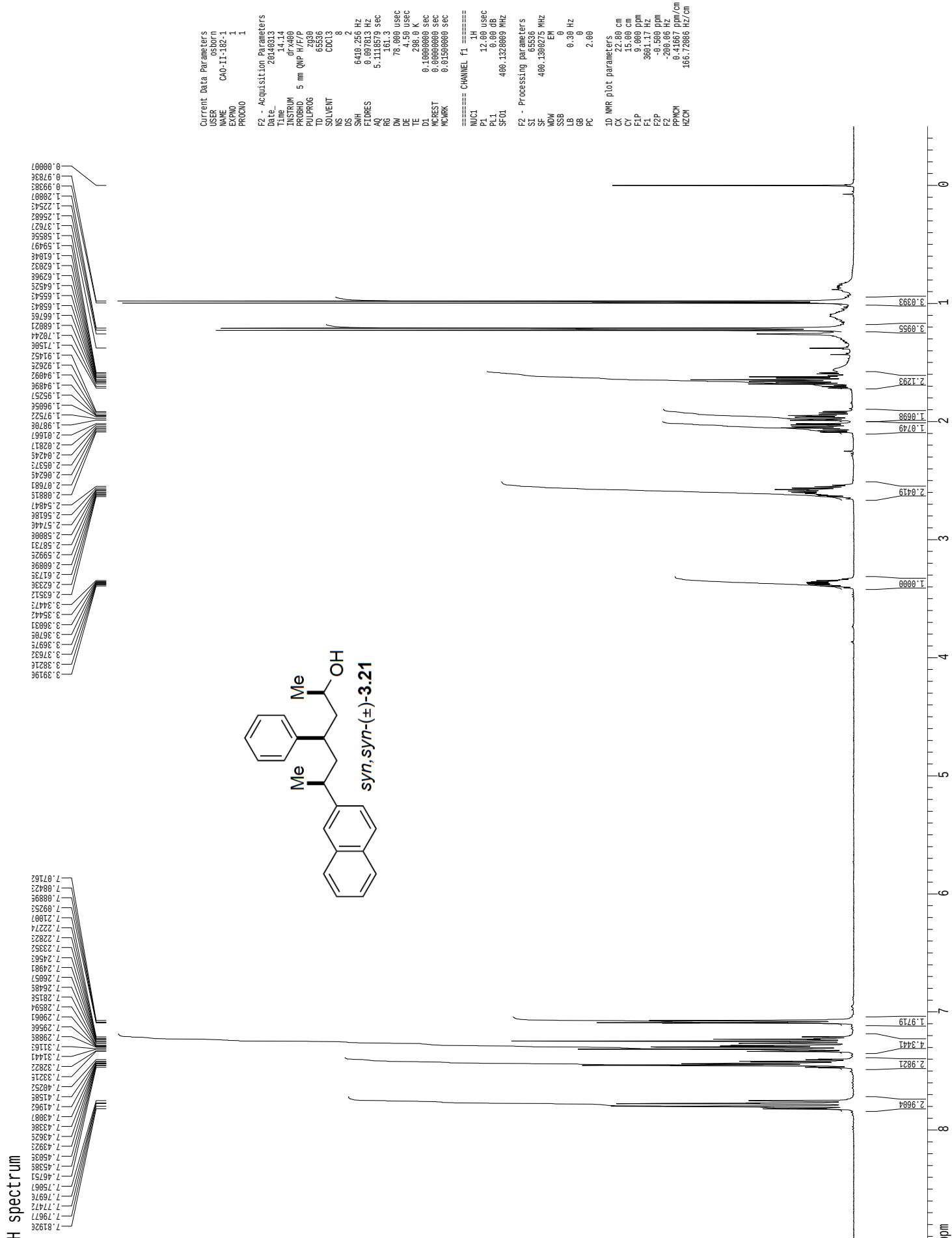
1H spectrum



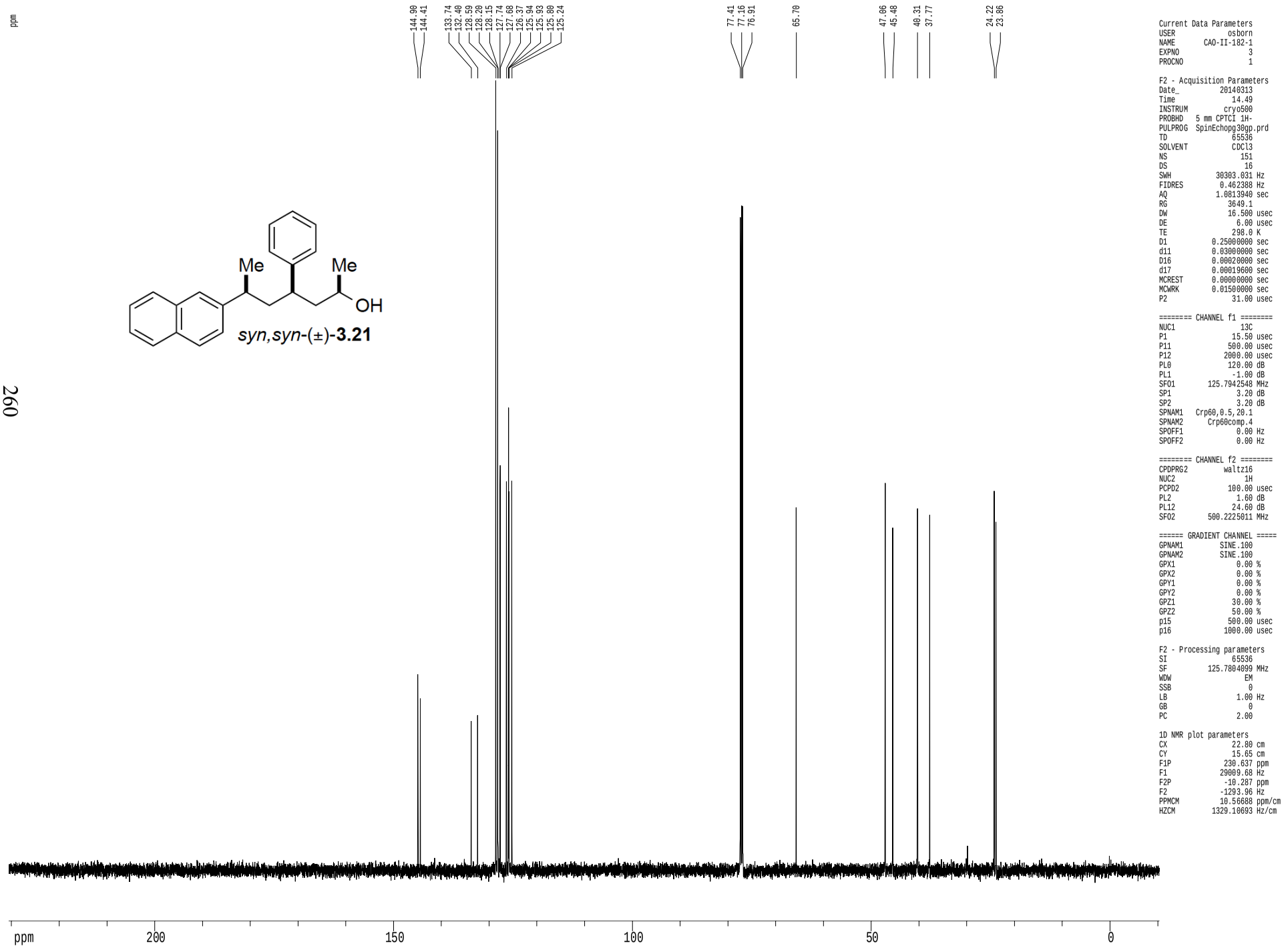

```
Current Data Parameters
USER                osborn
NAME      CAO-II-245A SI
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140514
Time               19.14
INSTRUM          cryo500
PROBHD    5 mm CPTCI 1H-
PULPROG             zg30
TD                 81728
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             8012.820 Hz
FIDRES          0.098043 Hz
AQ              5.0998774 sec
RG                   5.7
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1             0.10000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 =======
NUC1                  1H
P1                 7.50 usec
PL1                1.60 dB
SFO1         500.2235015 MHz

F2 - Processing parameters
SI                 65536
SF           500.2200466 MHz
WDW                   EM
SSB                    0
LB                 0.30 Hz
GB                     0
PC                 4.00

1D NMR plot parameters
CX                22.80 cm
CY                15.00 cm
F1P               9.000 ppm
F1              4501.98 Hz
F2P              -0.500 ppm
F2             -250.11 Hz
PPMCM          0.41667 ppm/cm
HZCM          208.42502 Hz/cm
```

Z-restored spin-echo 13C spectrum with 1H decoupling

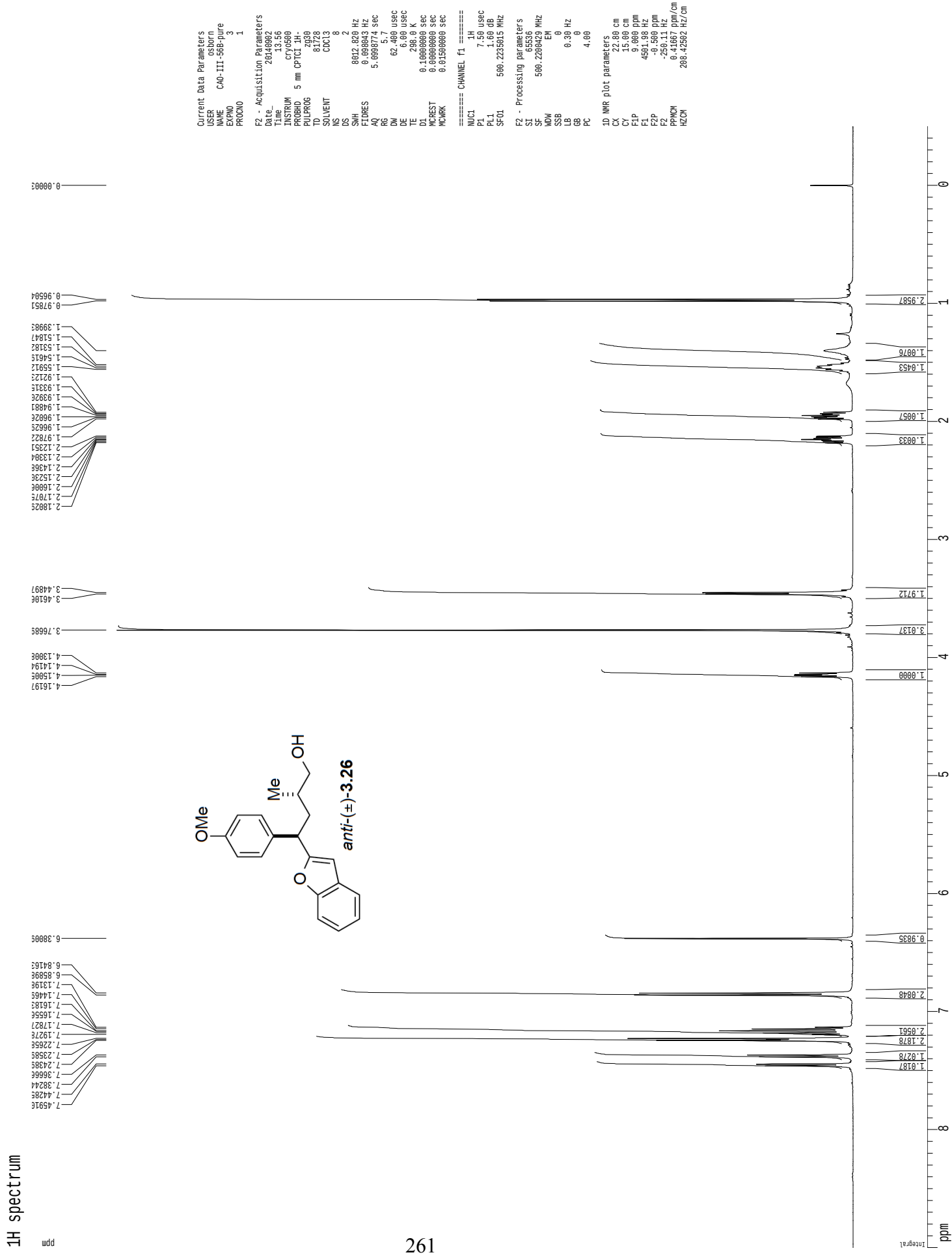



1H spectrum
Me
Me
OH
syn,syn-(±)-3.21

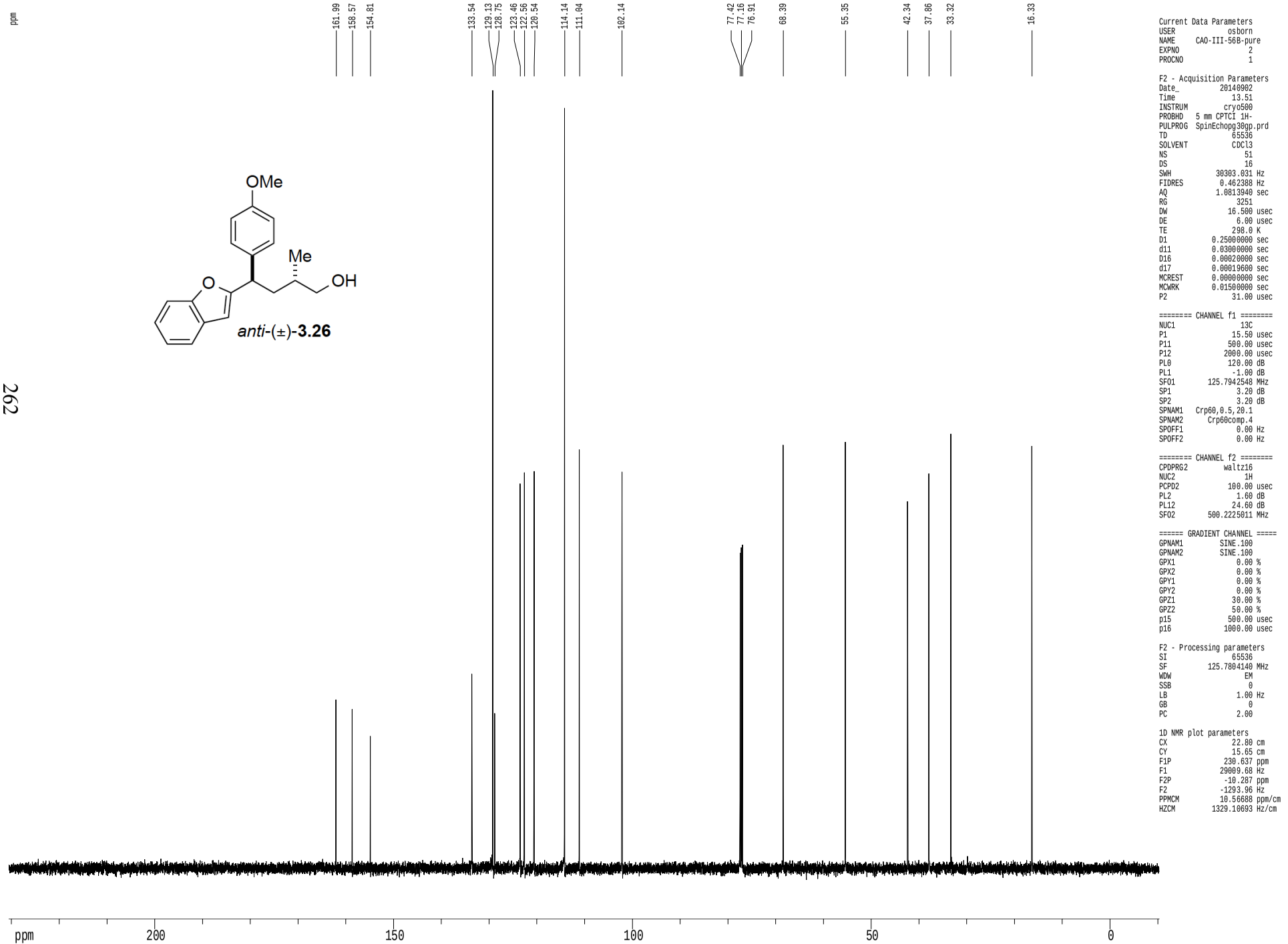
Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME          CAO-II-182-1
EXPNO                    3
PROCNO                   1

F2 - Acquisition Parameters
Date_             20140313
Time                 14.49
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                   65536
SOLVENT              CDCl3
NS                     151
DS                      16
SWH              30303.031 Hz
FIDRES           0.462388 Hz
AQ               1.0813940 sec
RG                  3649.1
DW                  16.500 usec
DE                   6.00 usec
TE                  298.0 K
D1               0.25000000 sec
d11              0.03000000 sec
D16              0.00020000 sec
d17              0.00019600 sec
MCREST           0.00000000 sec
MCWRK            0.01500000 sec
P2                  31.00 usec

======== CHANNEL f1 ========
NUC1                   13C
P1                   15.50 usec
P11                 500.00 usec
P12                2000.00 usec
PL0                 120.00 dB
PL1                  -1.00 dB
SFO1           125.7942548 MHz
SP1                  3.20 dB
SP2                  3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2       Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  1.60 dB
PL12                24.60 dB
SFO2           500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPX1                 0.00 %
GPX2                 0.00 %
GPY1                 0.00 %
GPY2                 0.00 %
GPZ1                30.00 %
GPZ2                50.00 %
p15                500.00 usec
p16               1000.00 usec

F2 - Processing parameters
SI                   65536
SF             125.7804099 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    2.00

1D NMR plot parameters
CX                   22.80 cm
CY                   15.65 cm
F1P                230.637 ppm
F1               29009.68 Hz
F2P                -10.287 ppm
F2               -1293.96 Hz
PPMCM             10.56688 ppm/cm
HZCM           1329.10693 Hz/cm
```

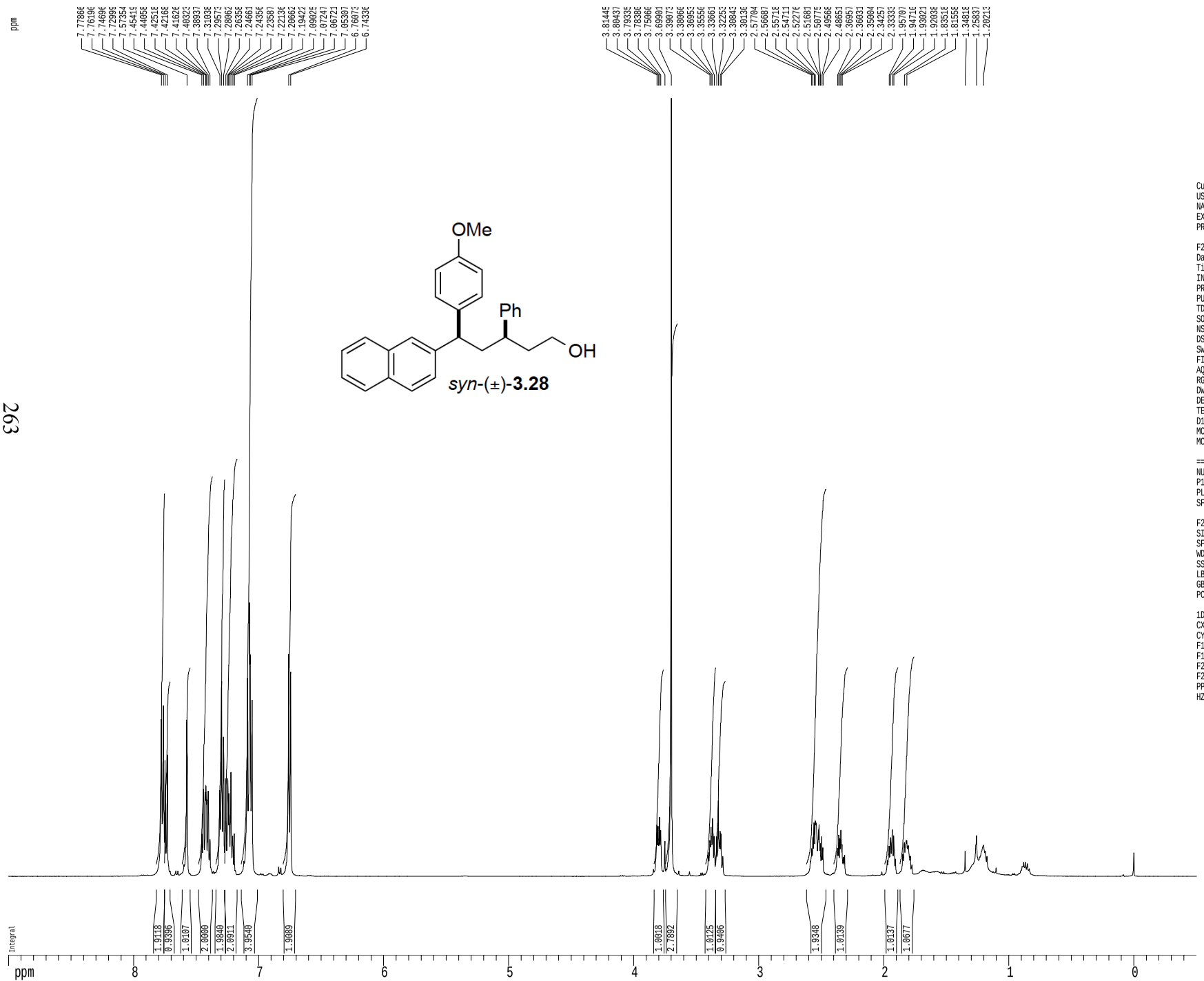

1H spectrum
Current Data Parameters
USER osborn
NAME CAO-III-56B-pure
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140902
Time 13.56
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0999774 sec
RG 5.7
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200429 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm
OMe
Me
OH
O
anti-(±)-3.26
ppm
Integral

Z-restored spin-echo 13C spectrum with 1H decoupling



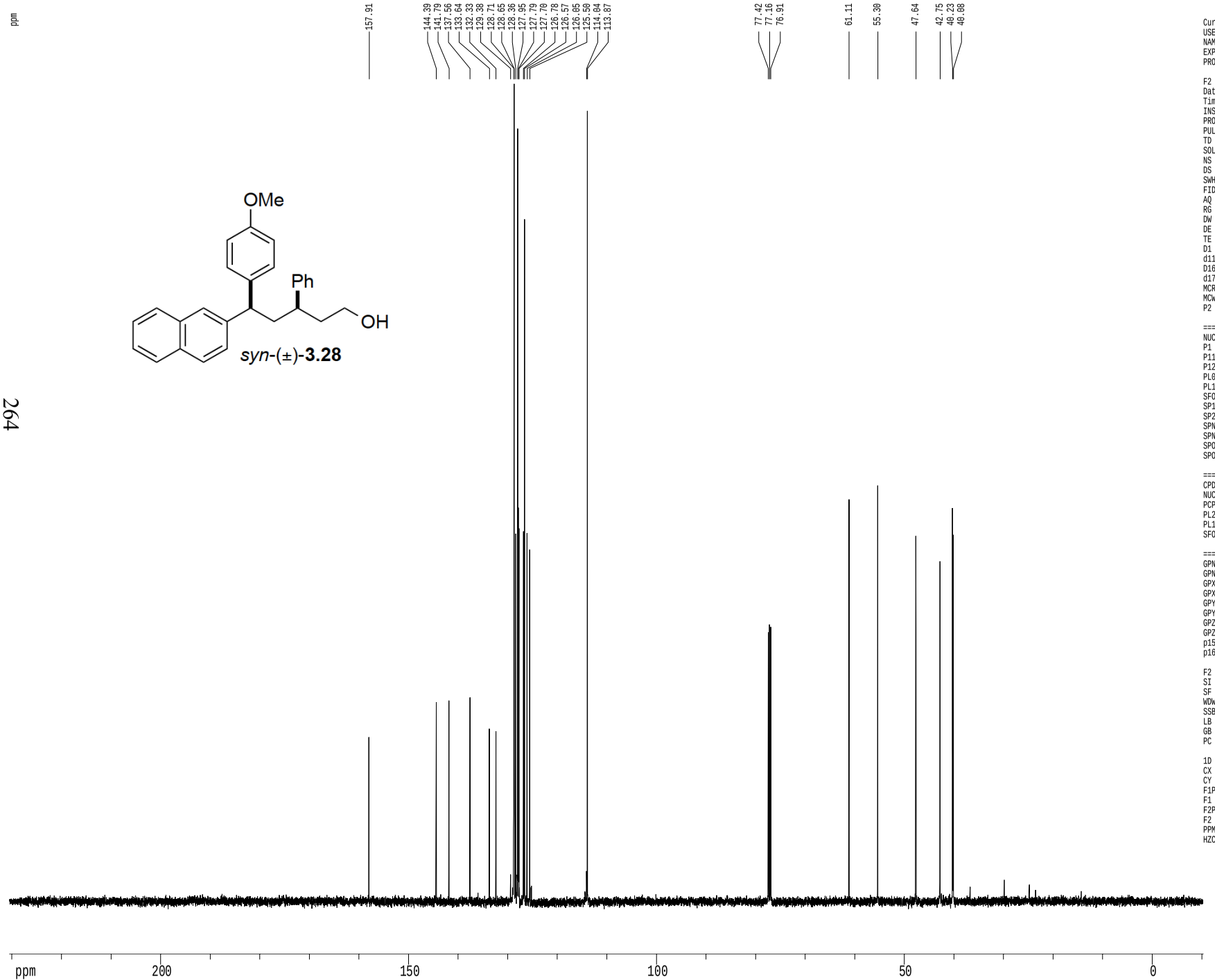

```
Current Data Parameters
USER                osborn
NAME      CAO-III-56B-pure
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20140902
Time                 13.51
INSTRUM            cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                   65536
SOLVENT              CDCl3
NS                      51
DS                      16
SWH              30303.031 Hz
FIDRES           0.462388 Hz
AQ               1.0813940 sec
RG                    3251
DW                 16.500 usec
DE                  6.00 usec
TE                  298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec
P2                  31.00 usec

======== CHANNEL f1 ========
NUC1                   13C
P1                  15.50 usec
P11                500.00 usec
P12               2000.00 usec
PL0                120.00 dB
PL1                 -1.00 dB
SFO1          125.7942548 MHz
SP1                  3.20 dB
SP2                  3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2       Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2             100.00 usec
PL2                 1.60 dB
PL12                24.60 dB
SFO2          500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                   65536
SF            125.7804140 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    2.00

1D NMR plot parameters
CX                  22.80 cm
CY                  15.65 cm
F1P               230.637 ppm
F1                29009.68 Hz
F2P               -10.287 ppm
F2                -1293.96 Hz
PPMCM             10.56688 ppm/cm
HZCM           1329.10693 Hz/cm
```

1H spectrum

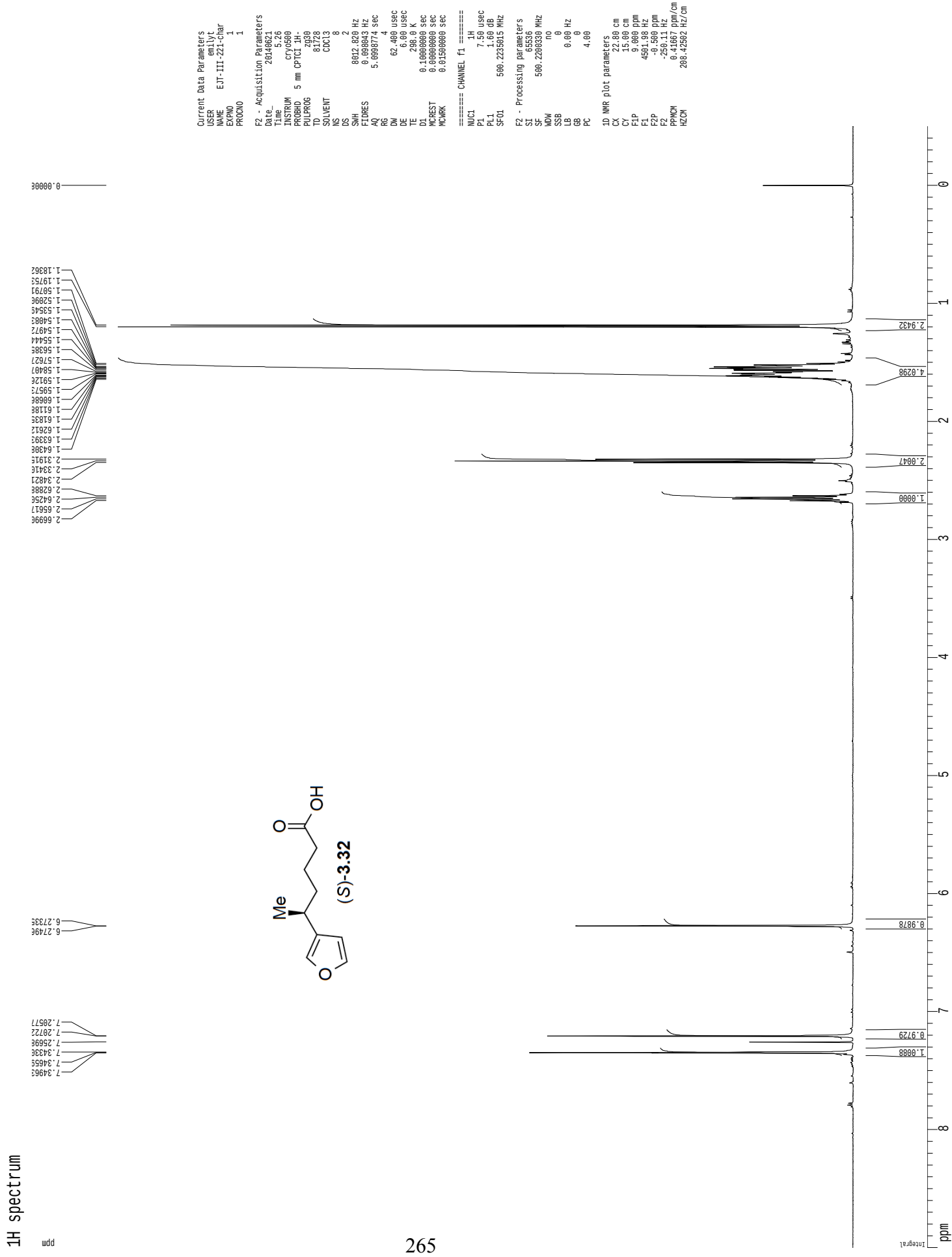



```
Current Data Parameters
USER                osborn
NAME      CAO-III-55-pure
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_            20140902
Time                13.42
INSTRUM          cryo500
PROBHD    5 mm CPTCI 1H-
PULPROG              zg30
TD                  81728
SOLVENT             CDCl3
NS                      8
DS                      2
SWH              8012.820 Hz
FIDRES           0.098043 Hz
AQ               5.0998774 sec
RG                    4.5
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1             0.10000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 =======
NUC1                   1H
P1                  7.50 usec
PL1                 1.60 dB
SFO1          500.2235015 MHz

F2 - Processing parameters
SI                  65536
SF            500.2200633 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   4.00

1D NMR plot parameters
CX                  22.80 cm
CY                  15.00 cm
F1P                 9.000 ppm
F1                4501.98 Hz
F2P                -0.500 ppm
F2                -250.11 Hz
PPMCM            0.41667 ppm/cm
HZCM           208.42503 Hz/cm
```

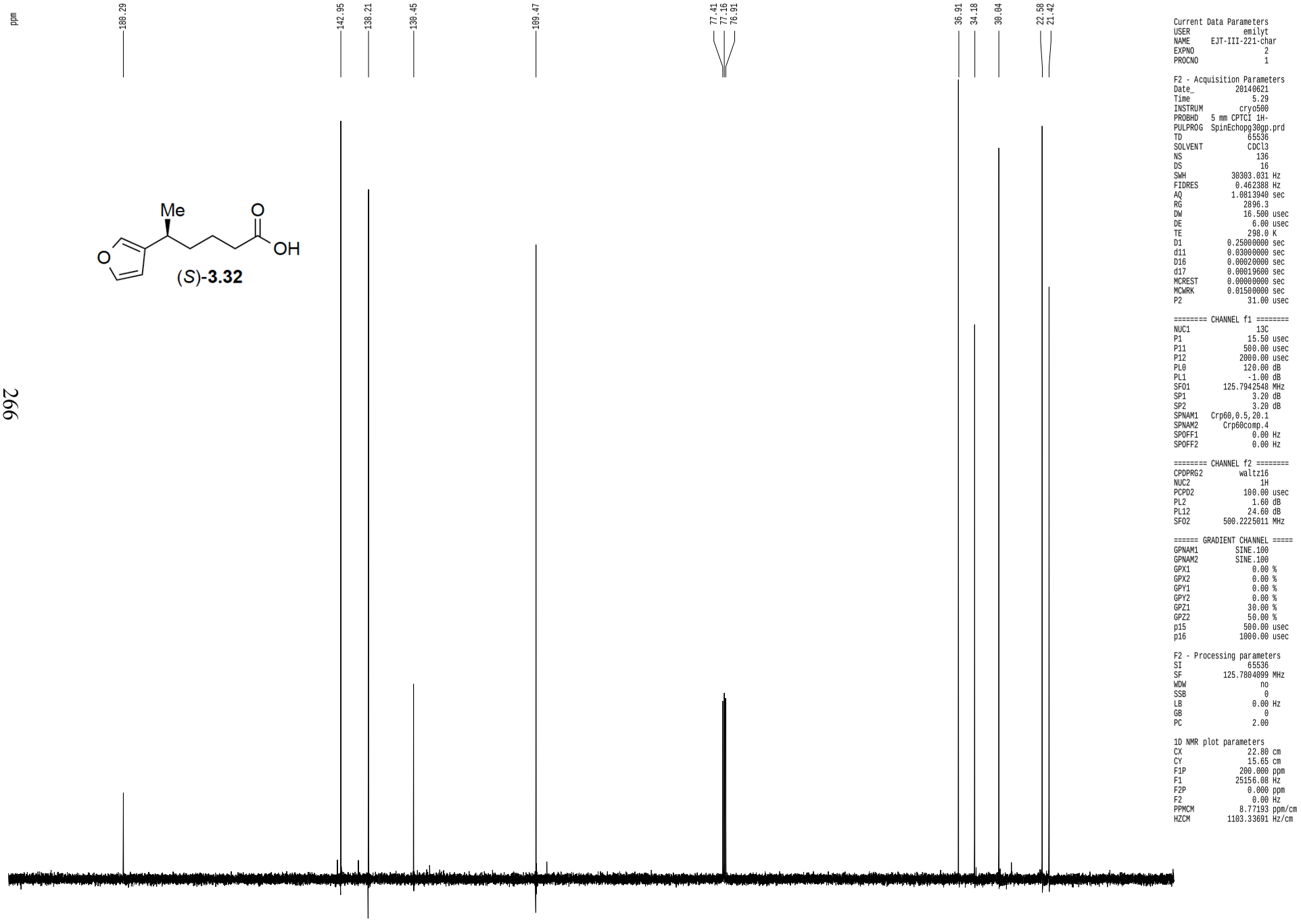
Z-restored spin-echo 13C spectrum with 1H decoupling



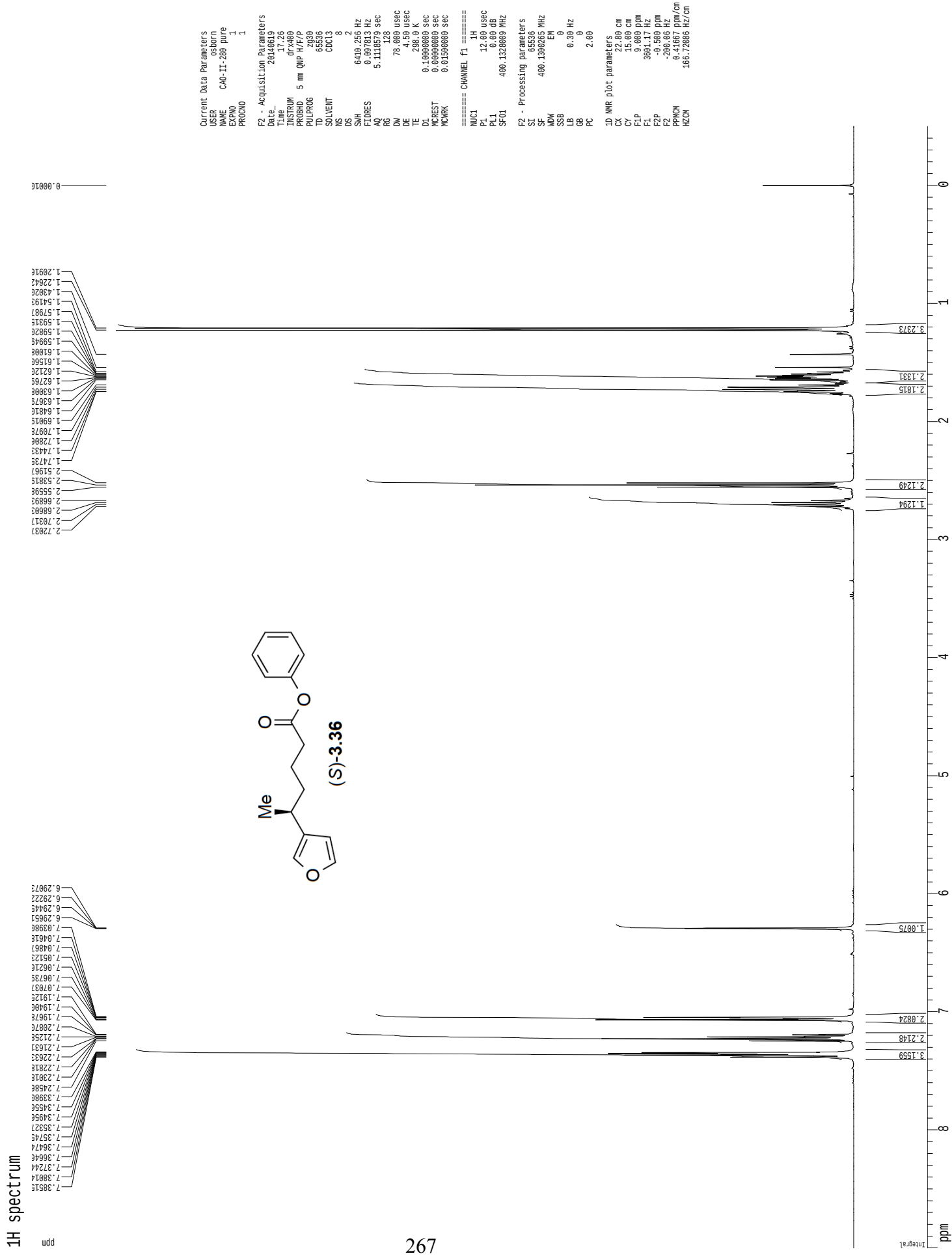

```
Current Data Parameters
USER                osborn
NAME      CAO-III-55-pure
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20140902
Time                 13.44
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                   65536
SOLVENT              CDCl3
NS                      91
DS                      16
SWH              30303.031 Hz
FIDRES           0.462388 Hz
AQ               1.0813940 sec
RG                 9195.2
DW                 16.500 usec
DE                  6.00 usec
TE                 298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec
P2                 31.00 usec

======== CHANNEL f1 ========
NUC1                   13C
P1                  15.50 usec
P11                500.00 usec
P12               2000.00 usec
PL0                120.00 dB
PL1                 -1.00 dB
SFO1          125.7942548 MHz
SP1                  3.20 dB
SP2                  3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2       Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  1.60 dB
PL12                24.60 dB
SFO2          500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPX1                 0.00 %
GPX2                 0.00 %
GPY1                 0.00 %
GPY2                 0.00 %
GPZ1                30.00 %
GPZ2                50.00 %
p15                500.00 usec
p16               1000.00 usec

F2 - Processing parameters
SI                   65536
SF            125.7804210 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    2.00

1D NMR plot parameters
CX                   22.80 cm
CY                   15.65 cm
F1P                230.637 ppm
F1               29009.68 Hz
F2P                -10.287 ppm
F2               -1293.96 Hz
PPMCM             10.56688 ppm/cm
HZCM           1329.10706 Hz/cm
```


1H spectrum
Current Data Parameters
USER emilyt
NAME EJT-III-221-char
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140821
Time 5.26
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0999774 sec
RG 4
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200330 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 4.00
1D NMR plot parameters
CX 22.00 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm
Me
(S)-3.32
ppm
Integral

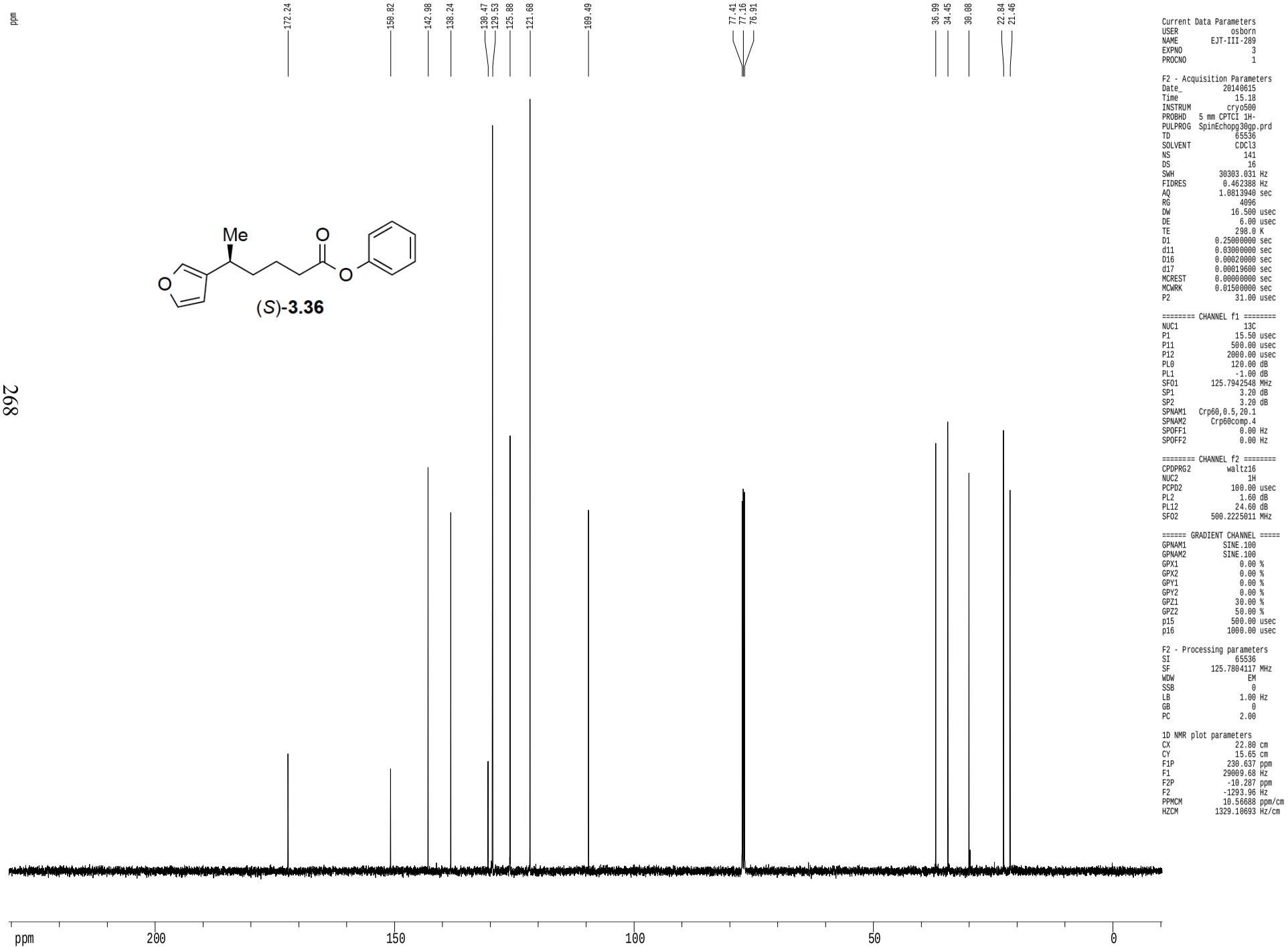
Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                emilyt
NAME      EJT-III-221-char
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_            20140621
Time                 5.29
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                   65536
SOLVENT              CDCl3
NS                     136
DS                      16
SWH              30303.031 Hz
FIDRES           0.462388 Hz
AQ               1.0813940 sec
RG                  2896.3
DW                  16.500 usec
DE                   6.00 usec
TE                  298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec
P2                  31.00 usec

======== CHANNEL f1 ========
NUC1                   13C
P1                  15.50 usec
P11                500.00 usec
P12               2000.00 usec
PL0                120.00 dB
PL1                 -1.00 dB
SFO1          125.7942548 MHz
SP1                  3.20 dB
SP2                  3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2       Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  1.60 dB
PL12                24.60 dB
SFO2          500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPX1                 0.00 %
GPX2                 0.00 %
GPY1                 0.00 %
GPY2                 0.00 %
GPZ1                30.00 %
GPZ2                50.00 %
p15                500.00 usec
p16               1000.00 usec

F2 - Processing parameters
SI                   65536
SF            125.7804099 MHz
WDW                     no
SSB                      0
LB                    0.00 Hz
GB                       0
PC                    2.00

1D NMR plot parameters
CX                   22.80 cm
CY                   15.65 cm
F1P                200.000 ppm
F1                25156.08 Hz
F2P                  0.000 ppm
F2                   0.00 Hz
PPMCM             8.77193 ppm/cm
HZCM           1103.33691 Hz/cm
```

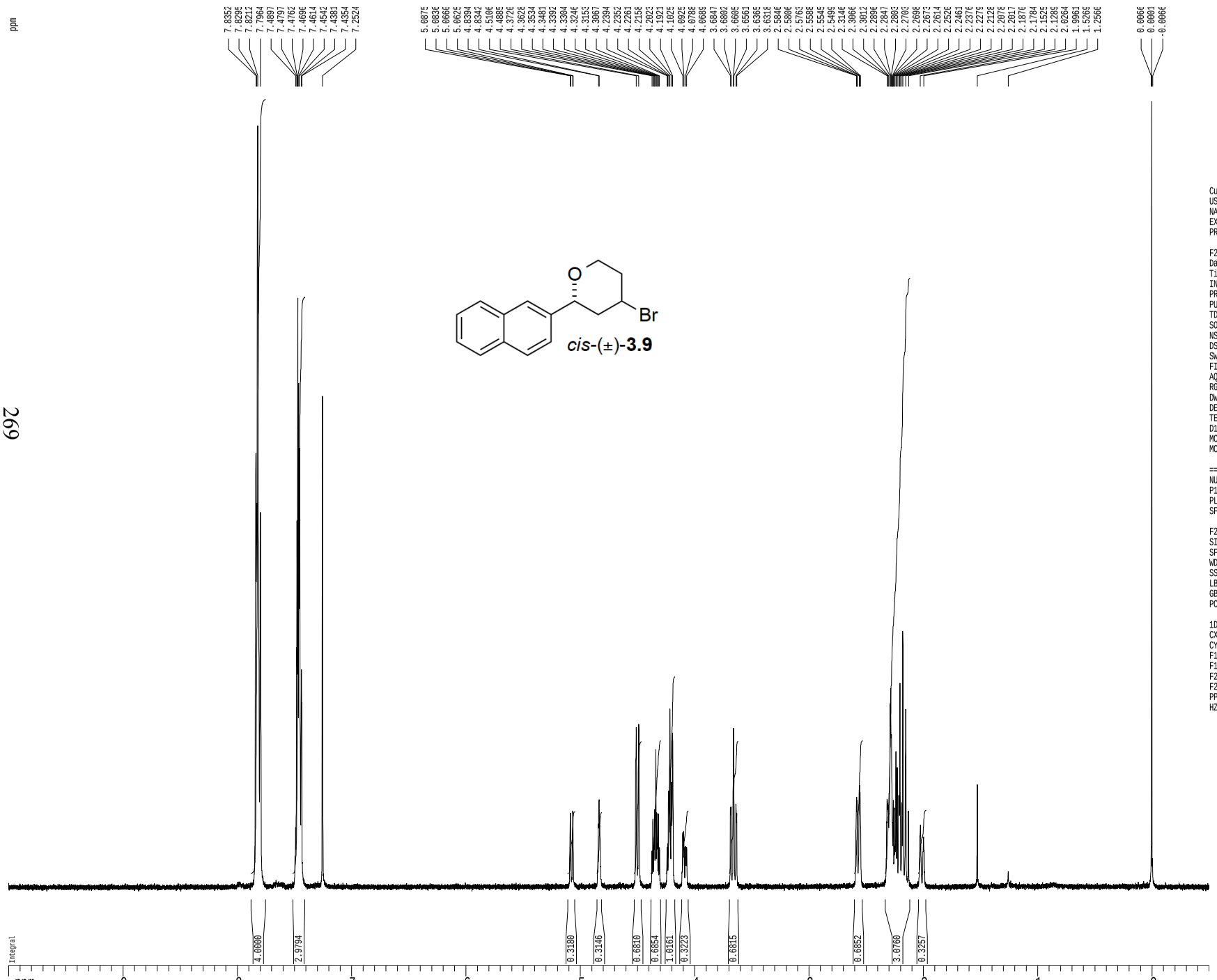

1H spectrum
(S)-3.36
Me
O
O
O
Current Data Parameters
USER osborn
NAME CAO-II-280 pure
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140619
Time_ 17.26
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 128
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300265 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72086 Hz/cm
ppm
Integral

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                 osborn
NAME              EJT-III-289
EXPNO                      3
PROCNO                     1

F2 - Acquisition Parameters
Date_              20140615
Time                  15.18
INSTRUM             cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                     65536
SOLVENT                CDCl3
NS                       141
DS                        16
SWH                30303.031 Hz
FIDRES             0.462388 Hz
AQ                 1.0813940 sec
RG                      4096
DW                    16.500 usec
DE                     6.00 usec
TE                   298.0 K
D1                 0.25000000 sec
d11                0.03000000 sec
D16                0.00020000 sec
d17                0.00019600 sec
MCREST             0.00000000 sec
MCWRK              0.01500000 sec
P2                    31.00 usec

======== CHANNEL f1 ========
NUC1                     13C
P1                    15.50 usec
P11                  500.00 usec
P12                 2000.00 usec
PL0                  120.00 dB
PL1                   -1.00 dB
SFO1             125.7942548 MHz
SP1                   3.20 dB
SP2                   3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1                0.00 Hz
SPOFF2                0.00 Hz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                100.00 usec
PL2                   1.60 dB
PL12                 24.60 dB
SFO2             500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1             SINE.100
GPNAM2             SINE.100
GPX1                  0.00 %
GPX2                  0.00 %
GPY1                  0.00 %
GPY2                  0.00 %
GPZ1                 30.00 %
GPZ2                 50.00 %
p15                 500.00 usec
p16                1000.00 usec

F2 - Processing parameters
SI                     65536
SF               125.7804117 MHz
WDW                       EM
SSB                        0
LB                    1.00 Hz
GB                         0
PC                    2.00

1D NMR plot parameters
CX                    22.80 cm
CY                    15.65 cm
F1P                 230.637 ppm
F1                29009.68 Hz
F2P                 -10.287 ppm
F2                -1293.96 Hz
PPMCM              10.56688 ppm/cm
HZCM             1329.10693 Hz/cm
```

1H spectrum



Current Data Parameters
USER emilyt
NAME EJT-I-164-A
EXPNO 5
PROCNO 1

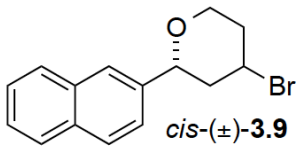
F2 - Acquisition Parameters
Date_ 20130412
Time 20.15
INSTRUM gn500
PROBHD 5 mm broadband
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 912.3
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 12.20 usec
PL1 -5.00 dB
SFO1 499.4034958 MHz

F2 - Processing parameters
SI 65536
SF 499.4000351 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 10.000 ppm
F1 4994.00 Hz
F2P -0.500 ppm
F2 -249.70 Hz
PPMCM 0.46053 ppm/cm
HZCM 229.98686 Hz/cm

13C spectrum with 1H decoupling



cis-(±)-**3.9**

270

Current Data Parameters
USER emilyt
NAME EJT-I-164-A
EXPNO 6
PROCNO 1

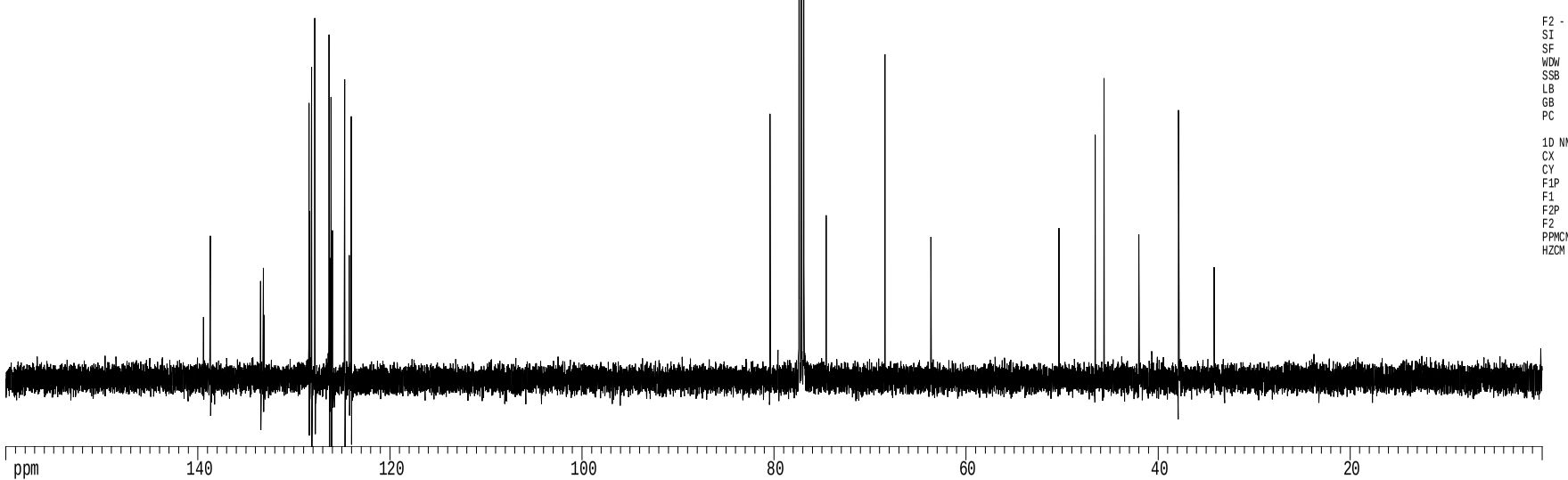
F2 - Acquisition Parameters
Date_ 20130412
Time 20.20
INSTRUM gn500
PROBHD 5 mm broadband
PULPROG zgdc30
TD 65536
SOLVENT CDCl3
NS 776
DS 4
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 13004
DW 16.500 usec
DE 4.50 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 13C
P1 7.70 usec
PL1 0.00 dB
SFO1 125.5880432 MHz

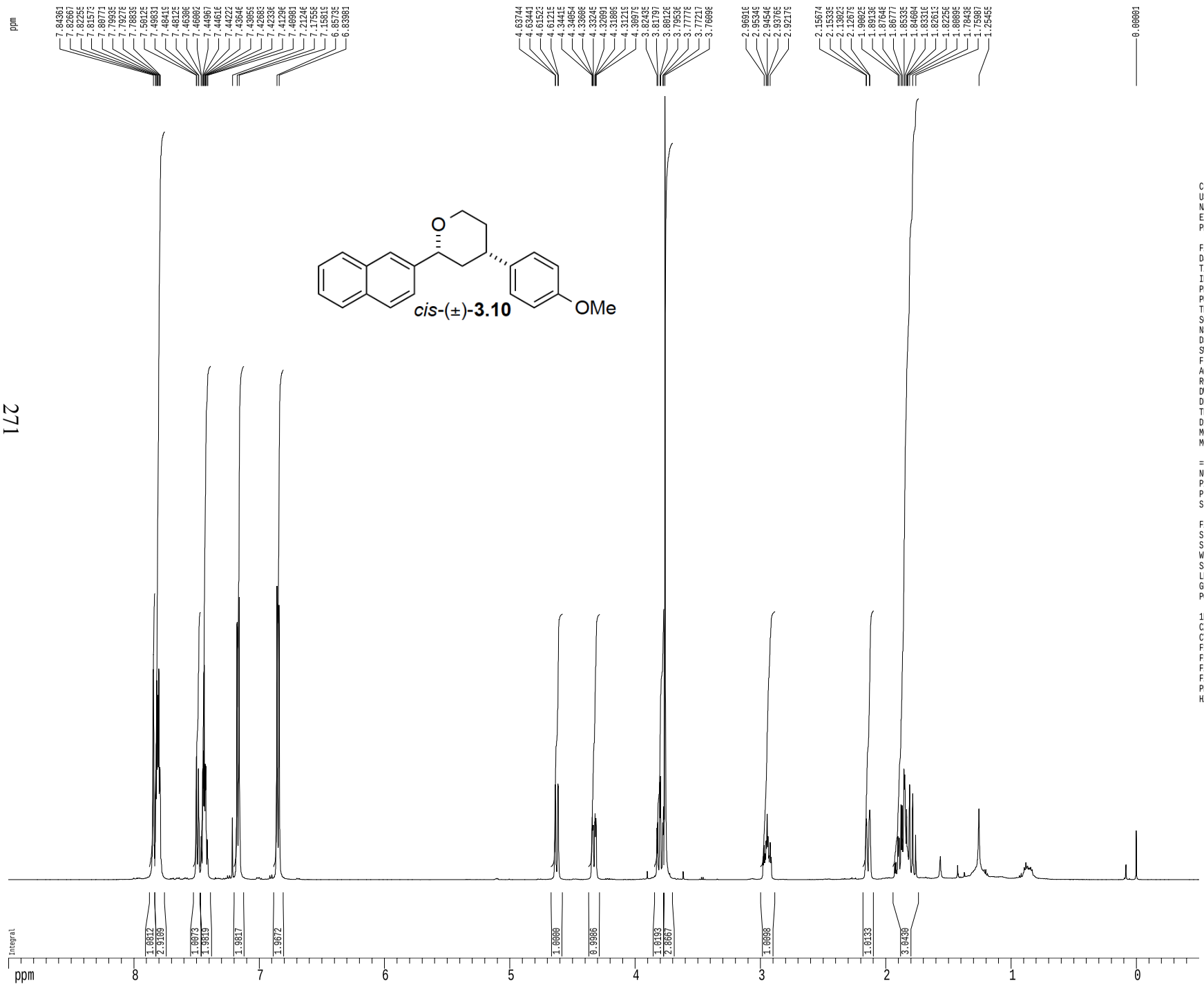
======= CHANNEL f2 =======
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -3.00 dB
PL12 13.20 dB
SFO2 499.4024970 MHz

F2 - Processing parameters
SI 65536
SF 125.5742187 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 160.000 ppm
F1 20091.88 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 7.01754 ppm/cm
HZCM 881.22260 Hz/cm



1H spectrum



271

Current Data Parameters
USER osborn
NAME CAO-II-177-2 SI
EXPNO 1
PROCNO 1

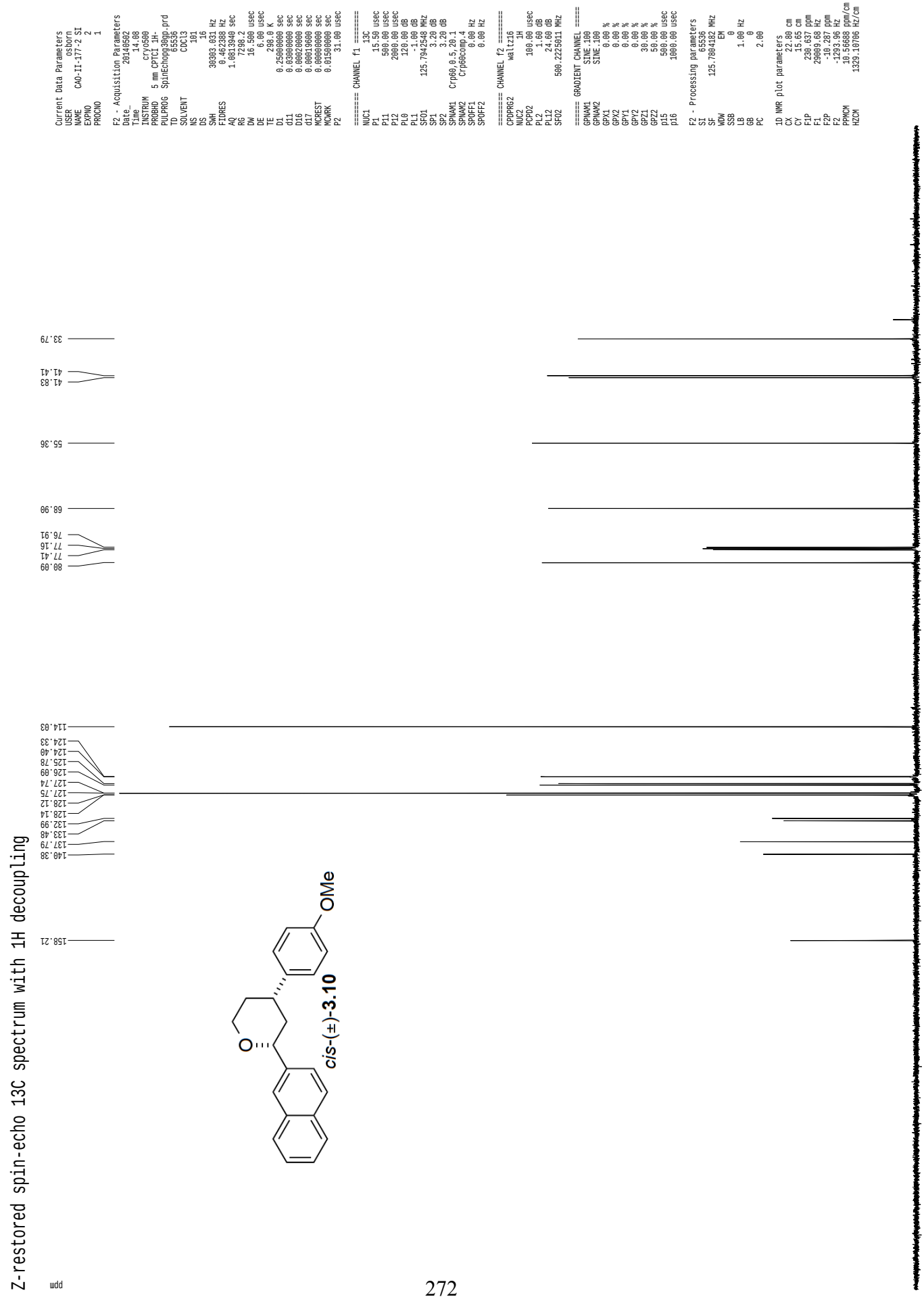
F2 - Acquisition Parameters
Date_ 20140502
Time 14.05
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 3.2
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz

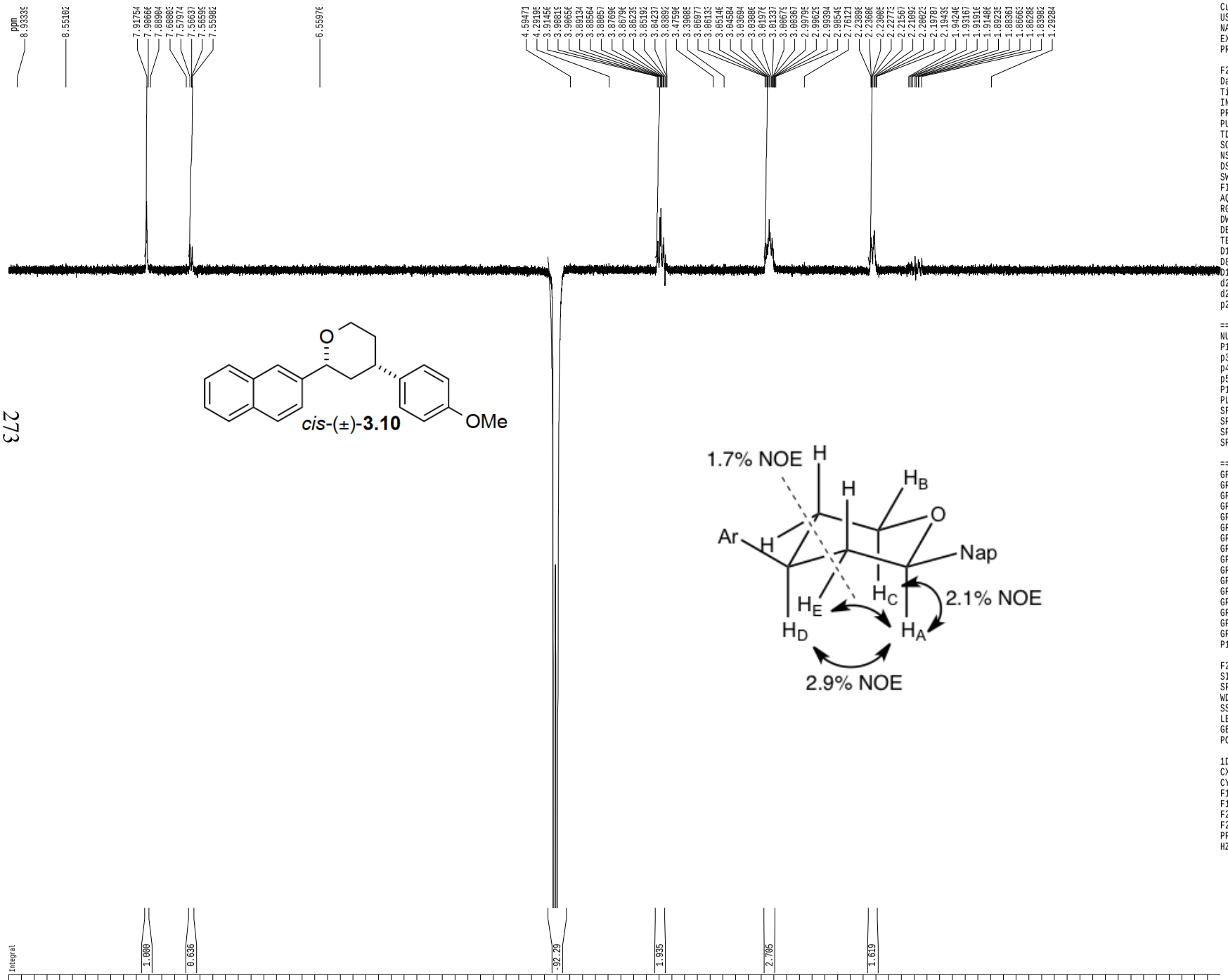
F2 - Processing parameters
SI 65536
SF 500.2200561 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42503 Hz/cm

Z-restored spin-echo 13C spectrum with 1H decoupling



gnoe



273

Current Data Parameters
USER osborn
NAME CAO-II-177-2
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20140719
Time 22.48
INSTRUM gn500
PROBHD 5 mm broadband
PULPROG gnoe1cc.wu
TD 65536
SOLVENT CDCl3
NS 256
DS 8
SWH 5482.456 Hz
FIDRES 0.083656 Hz
AQ 5.9769330 sec
RG 3649.1
DW 91.200 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
D8 0.50000000 sec
D16 0.00020000 sec
d21 0.33374399 sec
d22 0.16399699 sec
p2 24.00 usec

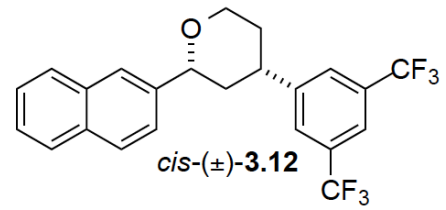
======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
p3 36.00 usec
p4 48.00 usec
p5 32.00 usec
P12 40000.00 usec
PL1 -5.80 dB
SFO1 499.2923529 MHz
SP1 53.60 dB
SPNAM1 gauss1.512
SPOFF1 0.00 Hz

===== GRADIENT CHANNEL =====
GPNAM1 sine.100
GPNAM2 sine.100
GPNAM3 sine.100
GPNAM4 sine.100
GPX1 0.00 %
GPX2 0.00 %
GPX3 0.00 %
GPX4 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPY3 0.00 %
GPY4 0.00 %
GPZ1 7.00 %
GPZ2 3.00 %
GPZ3 2.30 %
GPZ4 -2.30 %
P16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 499.2900000 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 22.80 cm
CY 50.00 cm
F1P 9.000 ppm
F1 4493.61 Hz
F2P -0.500 ppm
F2 -249.64 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.03751 Hz/cm

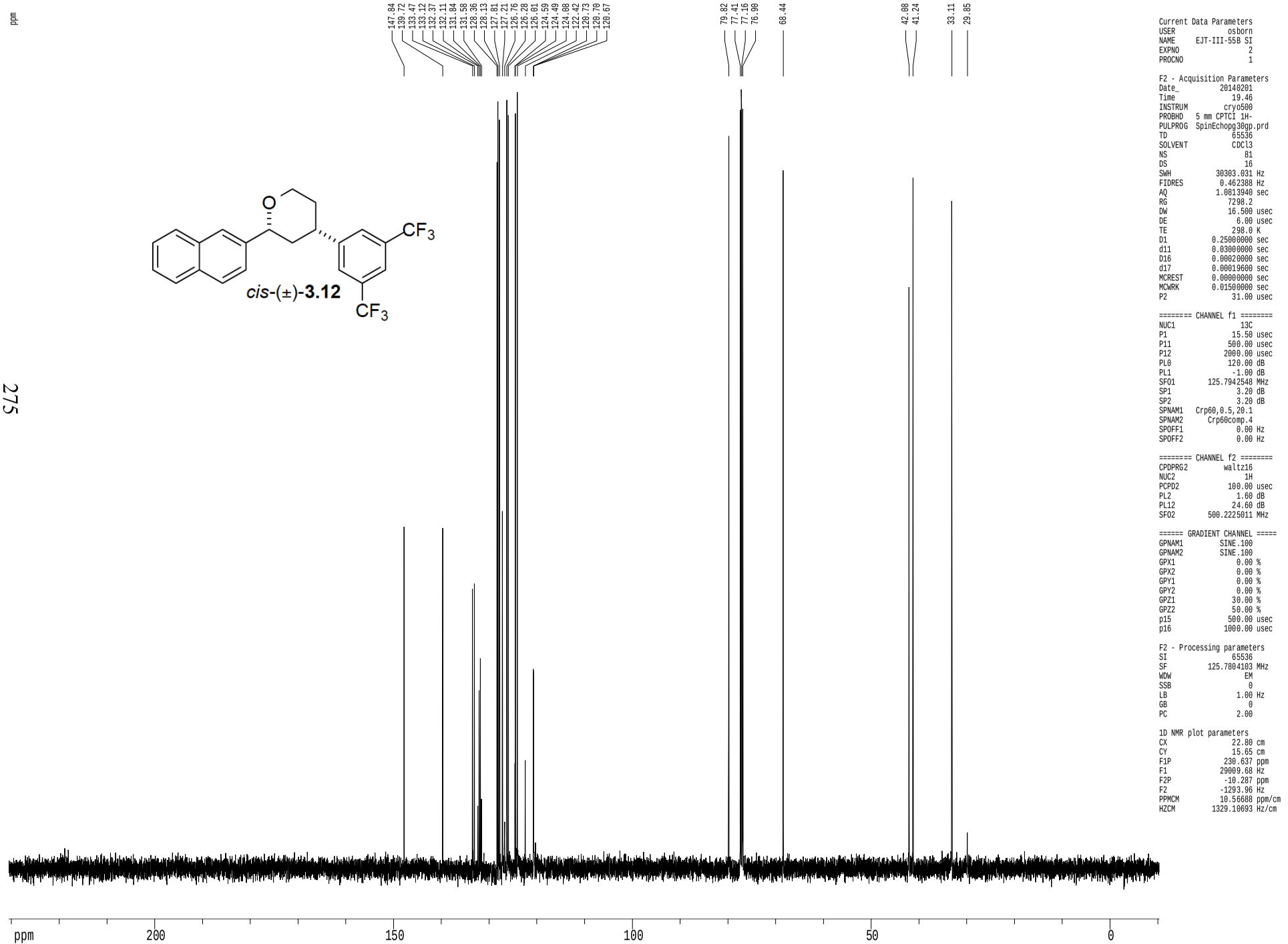
1H spectrum



cis-(±)-**3.12**


```
Current Data Parameters
USER                osborn
NAME      EJT-III-55B SI
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140201
Time               19.44
INSTRUM          cryo500
PROBHD    5 mm CPTCI 1H-
PULPROG             zg30
TD                 81728
SOLVENT            CDCl3
NS                     4
DS                     2
SWH             8012.820 Hz
FIDRES             0.098043 Hz
AQ              5.0998774 sec
RG                     8
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1             0.10000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 =======
NUC1                   1H
P1                  7.50 usec
PL1                 1.60 dB
SFO1          500.2235015 MHz

F2 - Processing parameters
SI                 65536
SF            500.2200406 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  4.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.00 cm
F1P                9.000 ppm
F1               4501.98 Hz
F2P               -0.500 ppm
F2               -250.11 Hz
PPMCM           0.41667 ppm/cm
HZCM          208.42502 Hz/cm
```

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME EJT-III-55B SI
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20140201
Time 19.46
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 81
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 7298.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 31.00 usec

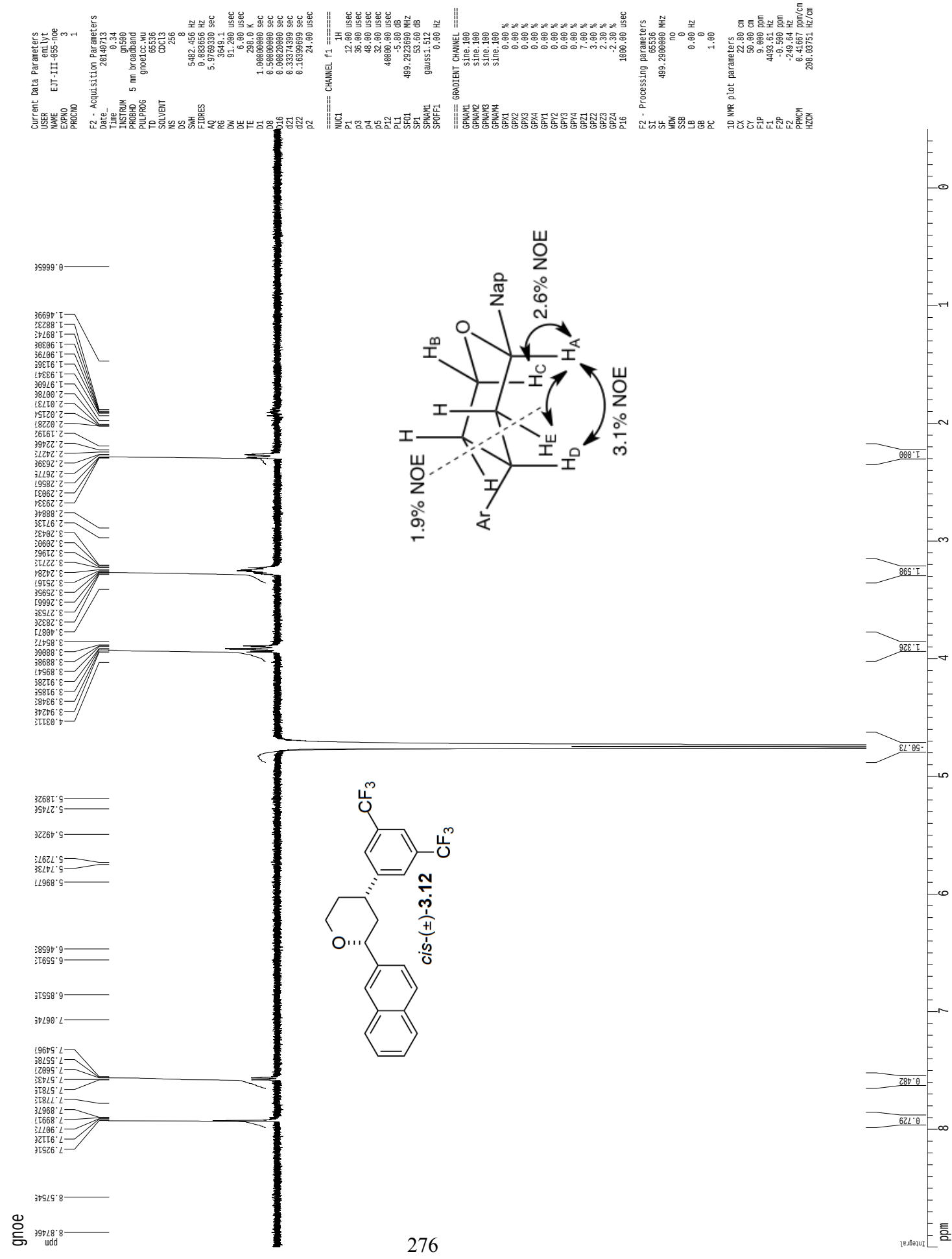
======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

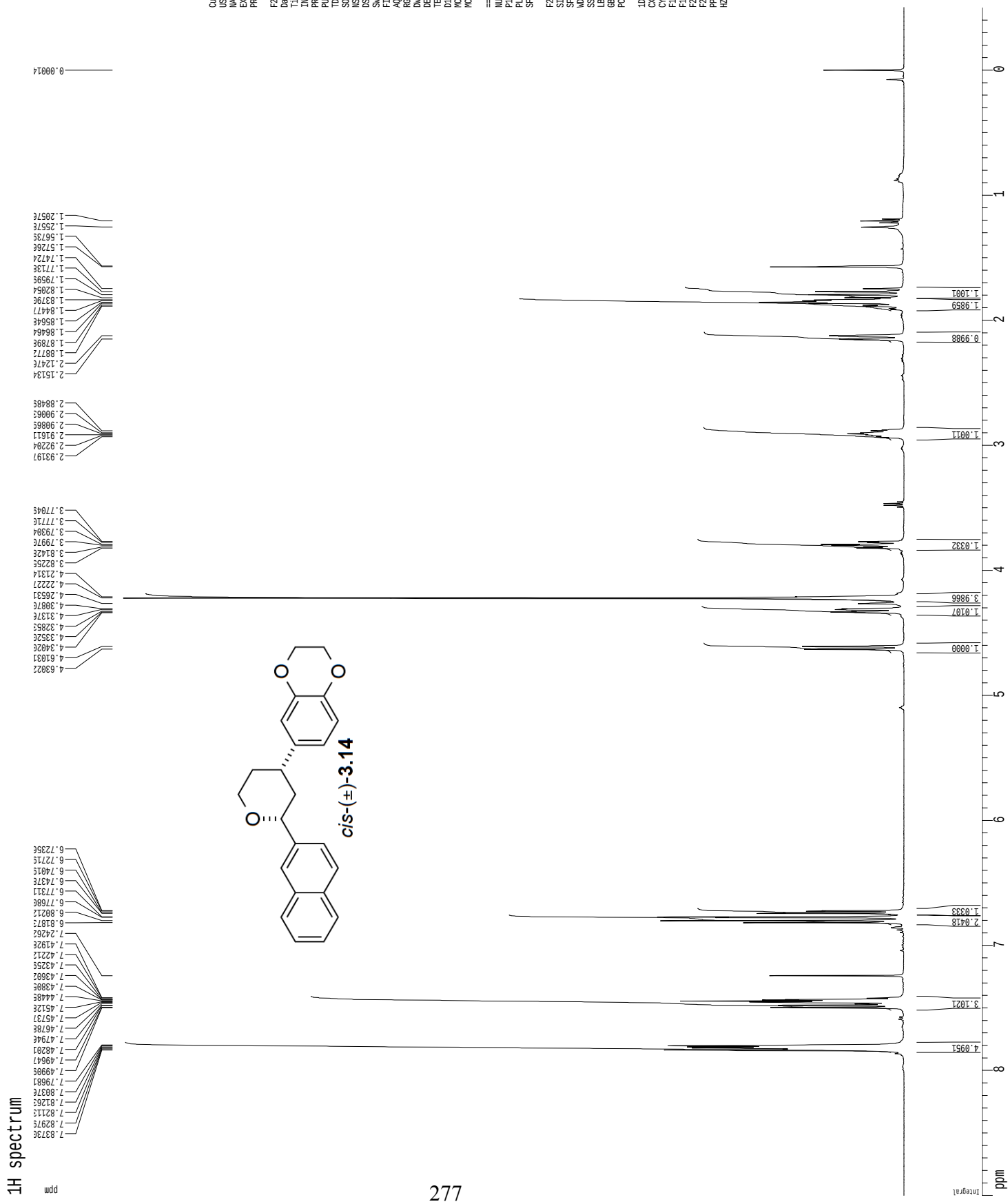
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

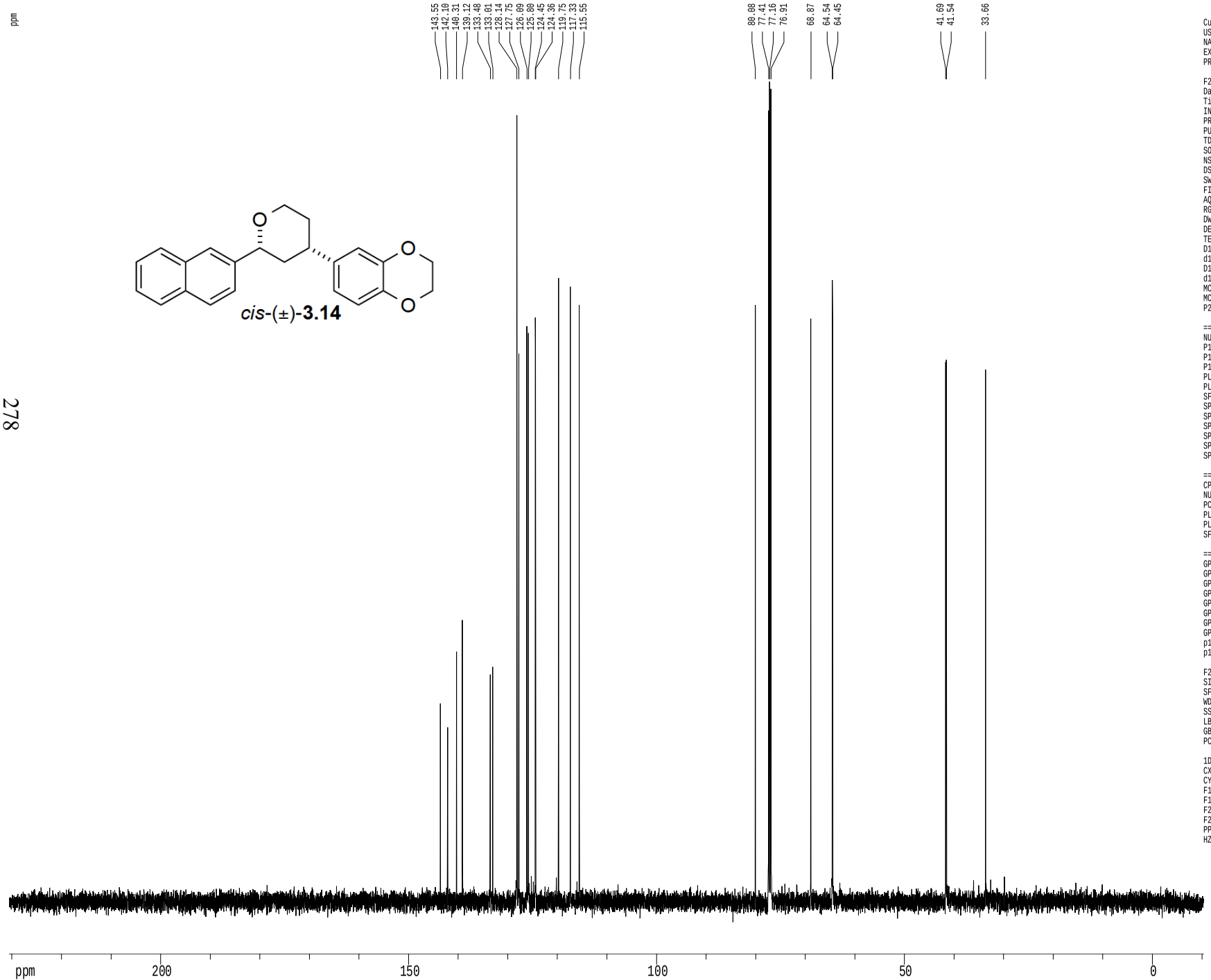
F2 - Processing parameters
SI 65536
SF 125.7804183 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm


gnoe
ppm
Integral
1.9% NOE
2.6% NOE
3.1% NOE
Nap
Ar
cis-(±)-3.12

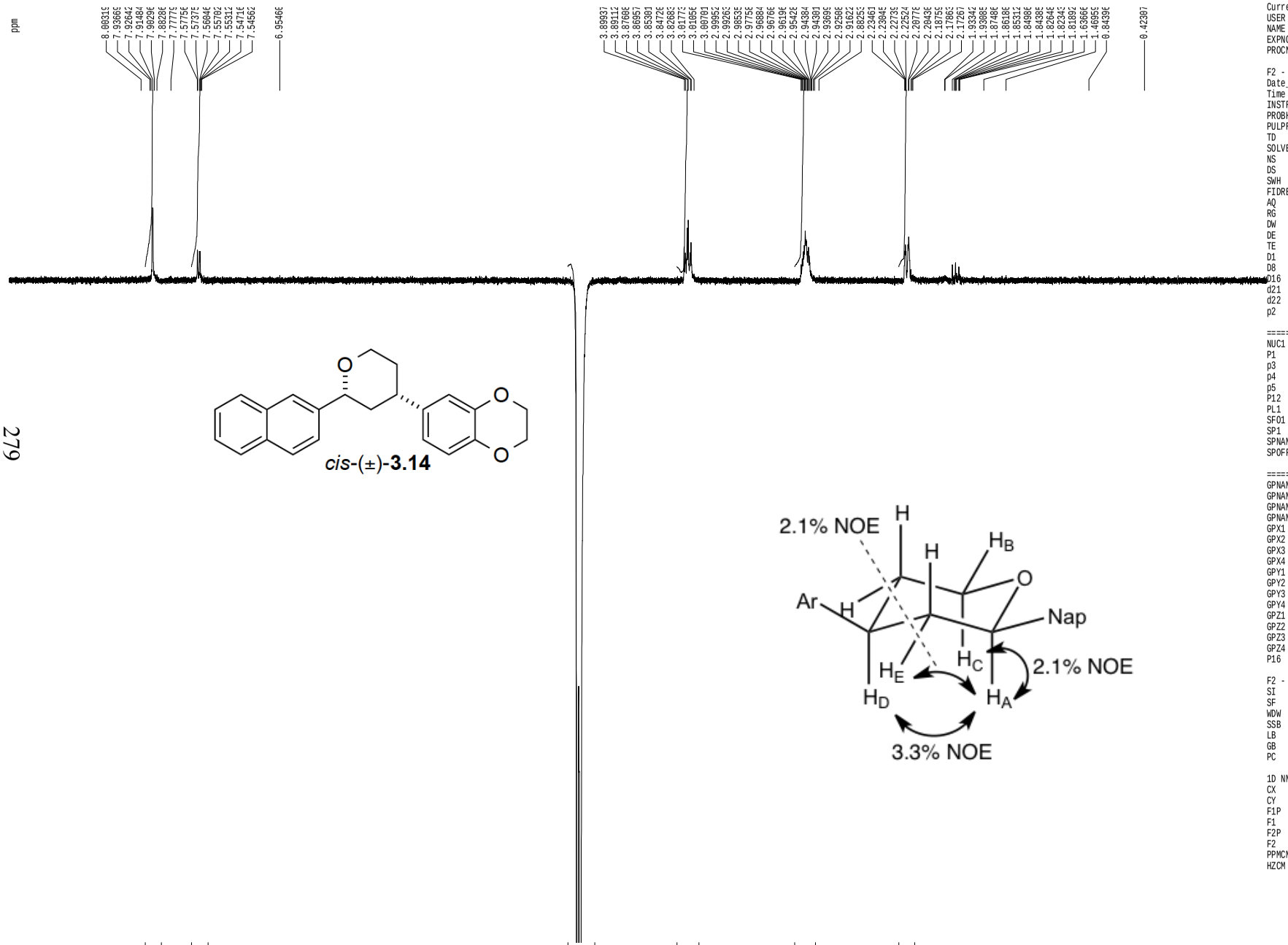

1H spectrum
cis-(±)-3.14
Current Data Parameters
USER osborn
NAME CAO-II-158A SI
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140206
Time 18.52
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0999774 sec
RG 7.1
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200403 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm
0.00014
1.20576
1.25576
1.56736
1.57266
1.74724
1.77136
1.79596
1.82054
1.83796
1.84477
1.85646
1.86464
1.87896
1.88772
2.12476
2.15134
2.88486
2.90063
2.90869
2.91611
2.92204
2.93197
3.77045
3.77716
3.79304
3.79976
3.81426
3.82256
4.21314
4.22227
4.26531
4.30876
4.31376
4.32853
4.33526
4.34026
4.61031
4.63022
6.72356
6.72716
6.74016
6.74376
6.77311
6.77686
6.80212
6.81873
7.24262
7.41926
7.42212
7.42526
7.43602
7.43866
7.44486
7.45126
7.45737
7.46786
7.47946
7.48201
7.49647
7.49905
7.79681
7.80376
7.81263
7.82113
7.82976
7.83736
1.1001
1.9859
0.9988
1.0011
1.0332
3.9866
1.0107
1.0000
1.0333
2.0418
3.1021
4.0951
ppm
Integral

Z-restored spin-echo 13C spectrum with 1H decoupling



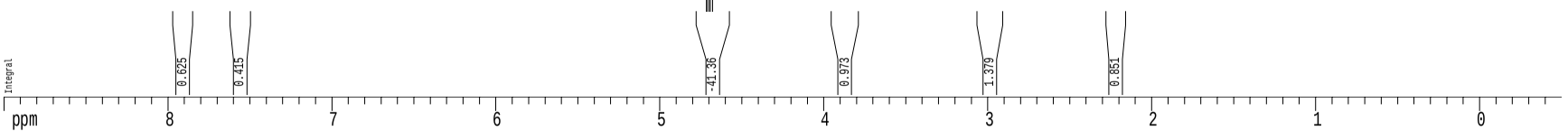

```
Current Data Parameters
USER              osborn
NAME      CAO-II-158A SI
EXPNO                2
PROCNO               1

F2 - Acquisition Parameters
Date_          20140206
Time              18.16
INSTRUM         cry0500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                65536
SOLVENT           CDCl3
NS                  126
DS                   16
SWH           30303.031 Hz
FIDRES        0.462388 Hz
AQ            1.0813940 sec
RG               7298.2
DW               16.500 usec
DE                6.00 usec
TE                298.0 K
D1            0.25000000 sec
d11           0.03000000 sec
D16           0.00020000 sec
d17           0.00019600 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec
P2                31.00 usec

======== CHANNEL f1 ========
NUC1                13C
P1                15.50 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1               3.20 dB
SP2               3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                1H
PCPD2            100.00 usec
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15              500.00 usec
p16             1000.00 usec

F2 - Processing parameters
SI                 65536
SF           125.7804122 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  2.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.65 cm
F1P              230.637 ppm
F1             29009.68 Hz
F2P              -10.287 ppm
F2             -1293.96 Hz
PPMCM           10.56688 ppm/cm
HZCM          1329.10693 Hz/cm
```

gnoe



279

cis-(±)-**3.14**



Current Data Parameters
USER dawson
NAME CAO-II-158-B-NOE
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20140714
Time 21.11
INSTRUM gn500
PROBHD 5 mm broadband
PULPROG gnoe1cc.wu
TD 65536
SOLVENT CDCl3
NS 256
DS 8
SWH 5482.456 Hz
FIDRES 0.083656 Hz
AQ 5.9769330 sec
RG 4096
DW 91.200 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
D8 0.50000000 sec
d16 0.00020000 sec
d21 0.33374399 sec
d22 0.16399699 sec
p2 24.00 usec

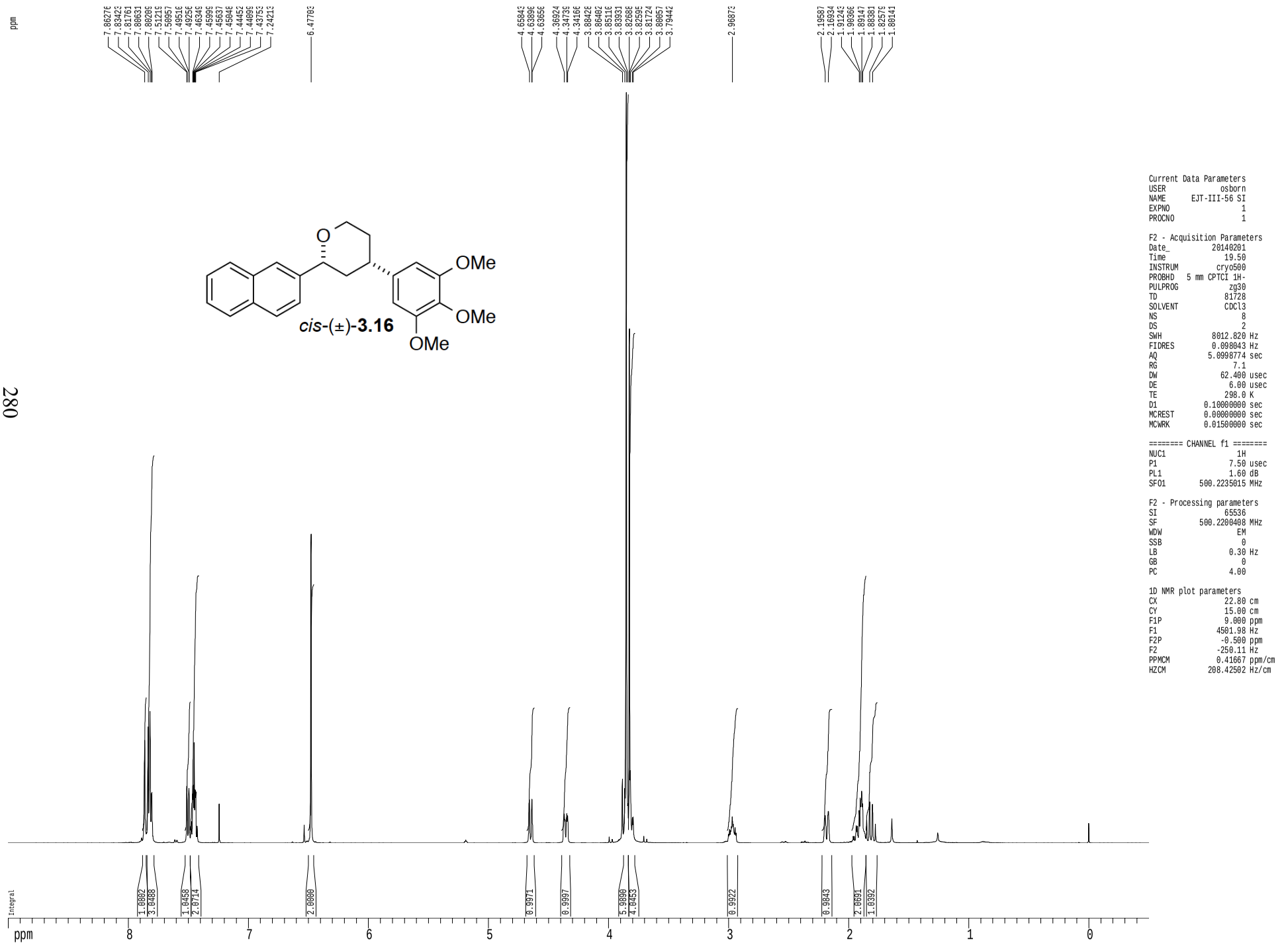
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
p3 36.00 usec
p4 48.00 usec
p5 32.00 usec
P12 40000.00 usec
PL1 -5.80 dB
SFO1 499.2923432 MHz
SP1 53.60 dB
SPNAM1 gauss1.512
SPOFF1 0.00 Hz

====== GRADIENT CHANNEL =====
GPNAM1 sine.100
GPNAM2 sine.100
GPNAM3 sine.100
GPNAM4 sine.100
GPX1 0.00 %
GPX2 0.00 %
GPX3 0.00 %
GPX4 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPY3 0.00 %
GPY4 0.00 %
GPZ1 7.00 %
GPZ2 3.00 %
GPZ3 2.30 %
GPZ4 -2.30 %
P16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 499.2900000 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 22.80 cm
CY 50.00 cm
F1P 9.000 ppm
F1 4493.61 Hz
F2P -0.500 ppm
F2 -249.64 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.03751 Hz/cm

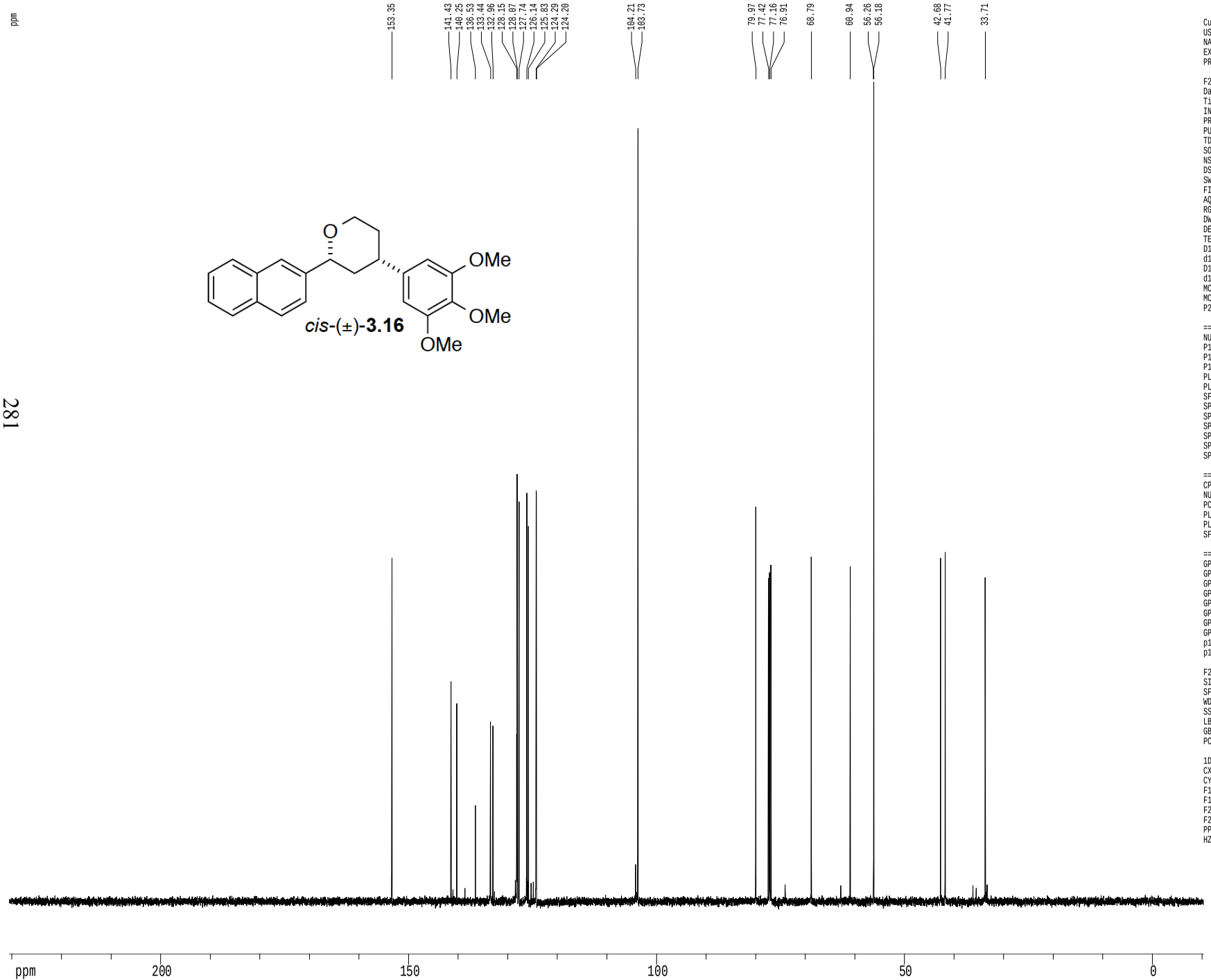
1H spectrum



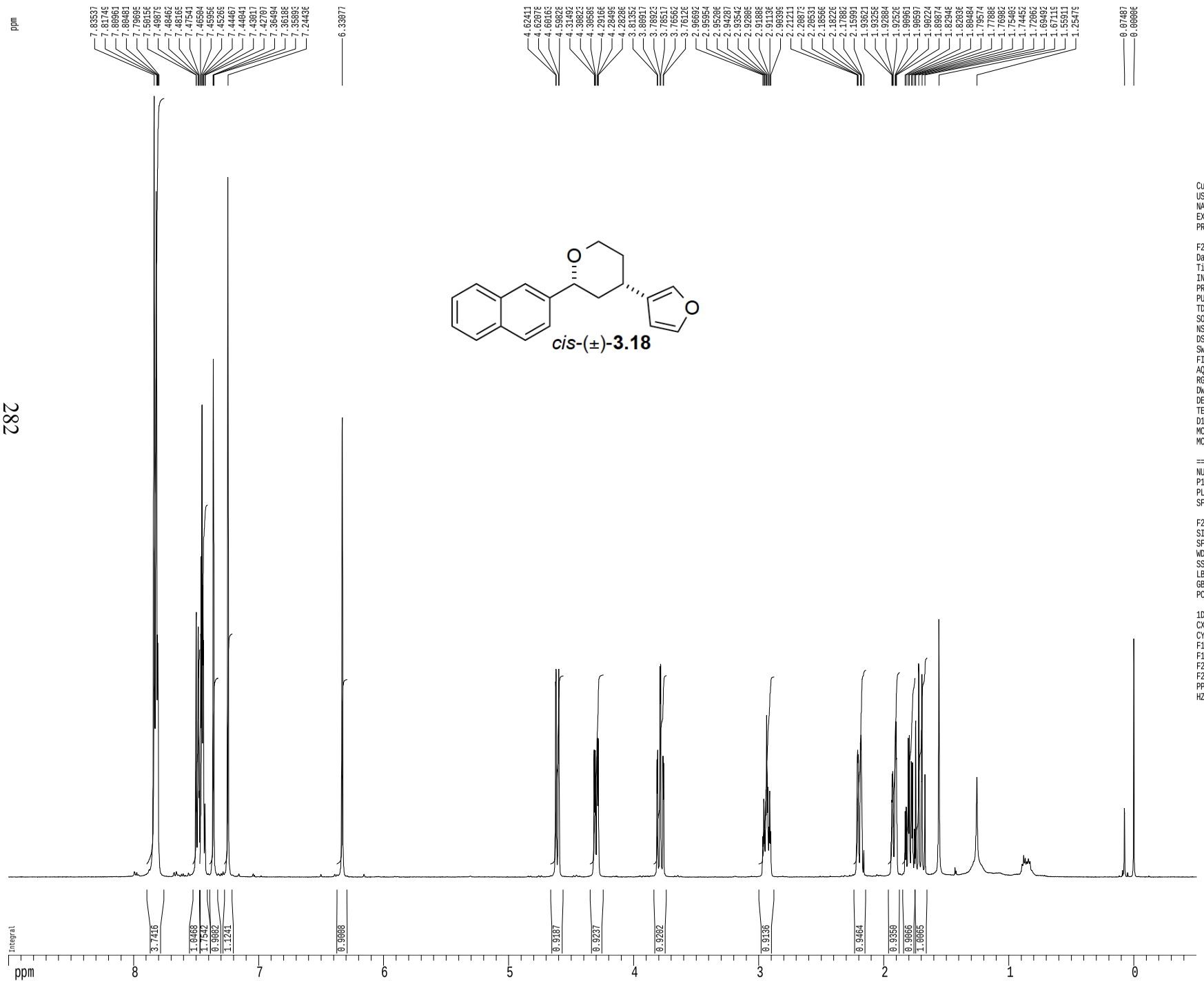
280

```
Current Data Parameters
USER              osborn
NAME      EJT-III-56 SI
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_          20140201
Time              19.50
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG            zg30
TD                81728
SOLVENT           CDCl3
NS                    8
DS                    2
SWH            8012.820 Hz
FIDRES         0.098043 Hz
AQ             5.0998774 sec
RG                  7.1
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1           0.10000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 =======
NUC1                1H
P1                7.50 usec
PL1               1.60 dB
SFO1        500.2235015 MHz

F2 - Processing parameters
SI                65536
SF          500.2200408 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 4.00

1D NMR plot parameters
CX                22.80 cm
CY                15.00 cm
F1P                9.000 ppm
F1              4501.98 Hz
F2P               -0.500 ppm
F2              -250.11 Hz
PPMCM          0.41667 ppm/cm
HZCM         208.42502 Hz/cm
```

Z-restored spin-echo 13C spectrum with 1H decoupling

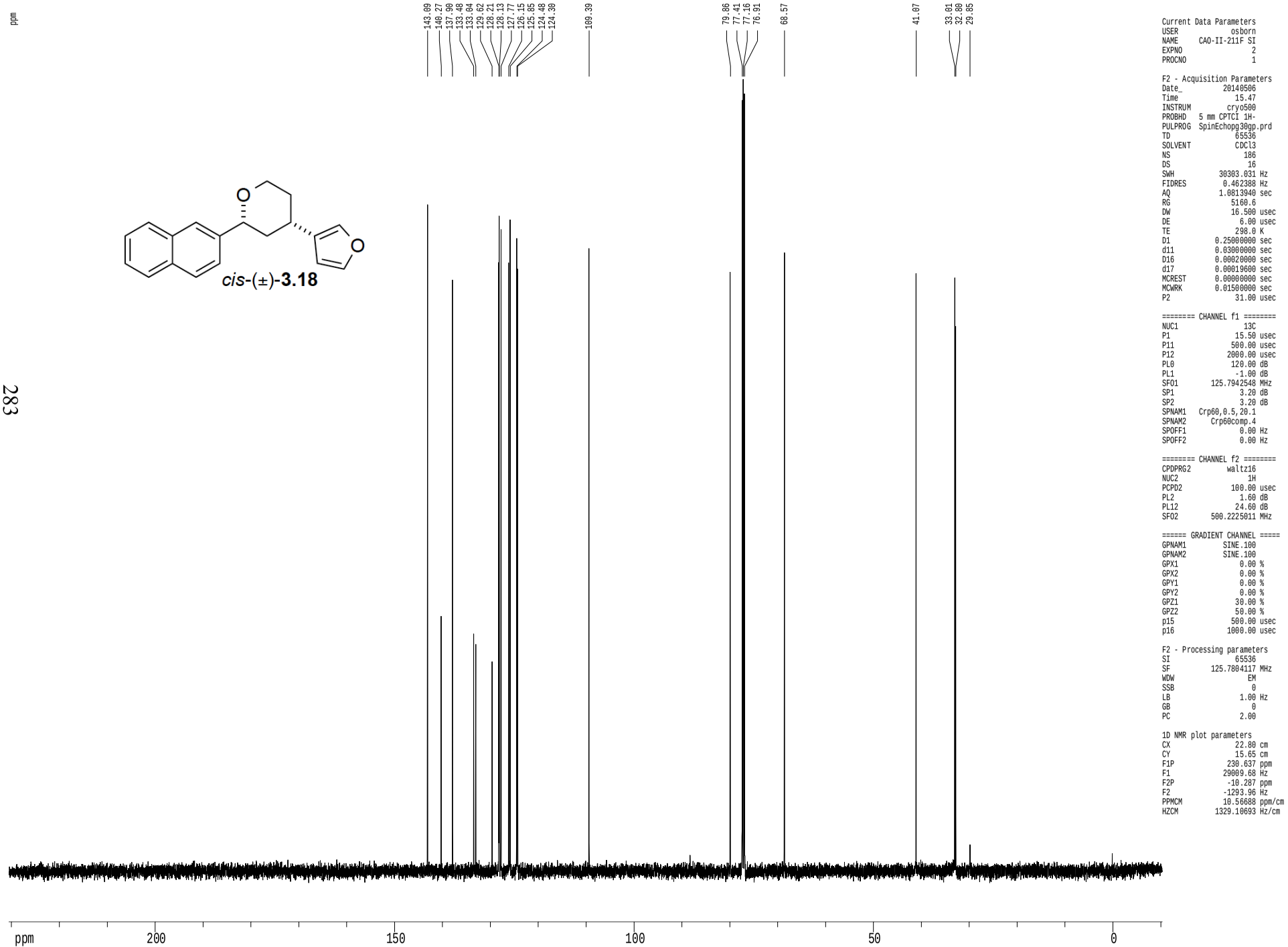


1H spectrum




```
Current Data Parameters
USER                osborn
NAME      CAO-II-211F SI
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140506
Time               15.44
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 81728
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             8012.820 Hz
FIDRES             0.098043 Hz
AQ              5.0998774 sec
RG                     8
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1              0.10000000 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 =======
NUC1                   1H
P1                  7.50 usec
PL1                 1.60 dB
SFO1          500.2235015 MHz

F2 - Processing parameters
SI                 65536
SF            500.2200403 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  4.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.00 cm
F1P                9.000 ppm
F1               4501.98 Hz
F2P               -0.500 ppm
F2              -250.11 Hz
PPMCM           0.41667 ppm/cm
HZCM          208.42502 Hz/cm
```

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME CAO-II-211F SI
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20140506
Time 15.47
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 186
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 5160.6
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 31.00 usec

======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

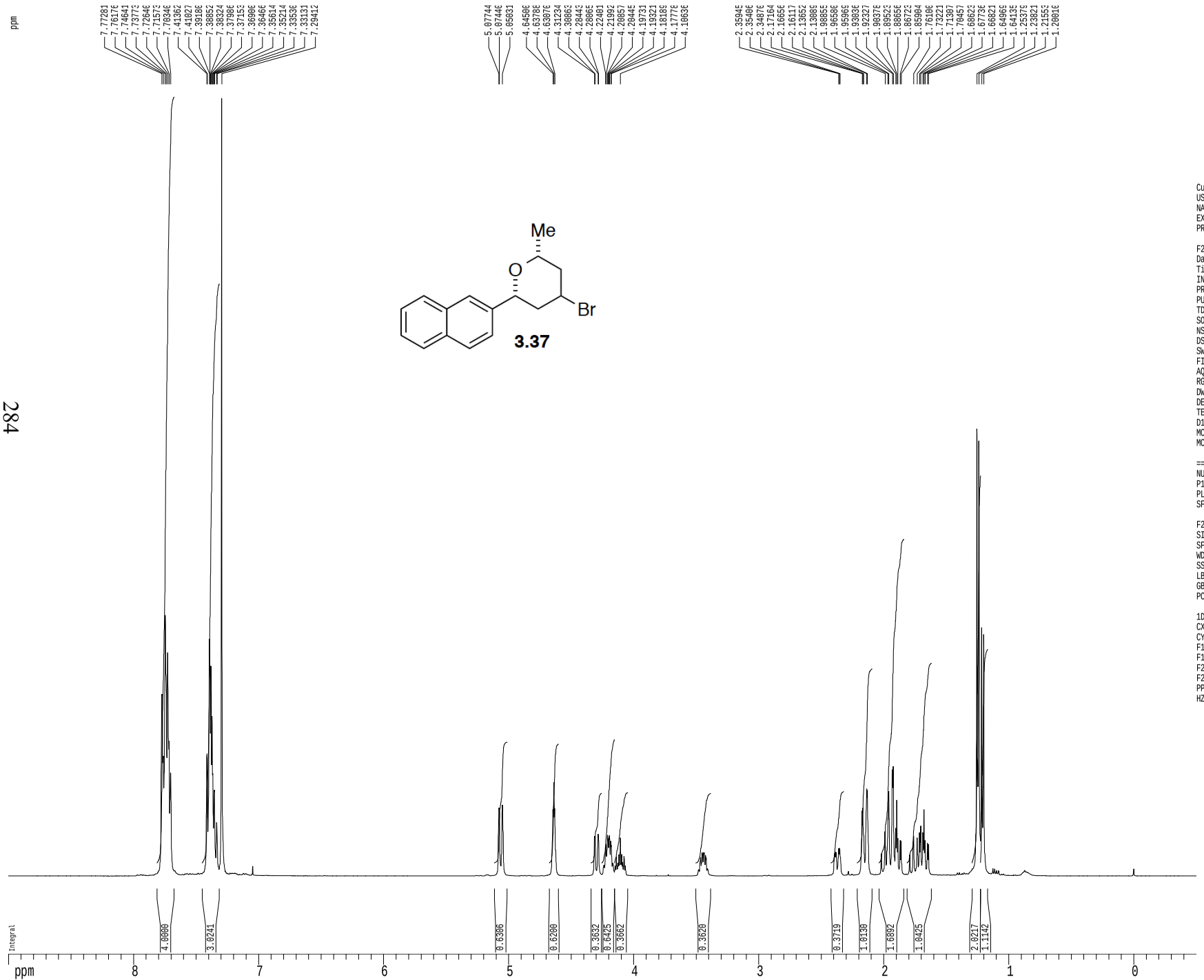
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 125.7804117 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm

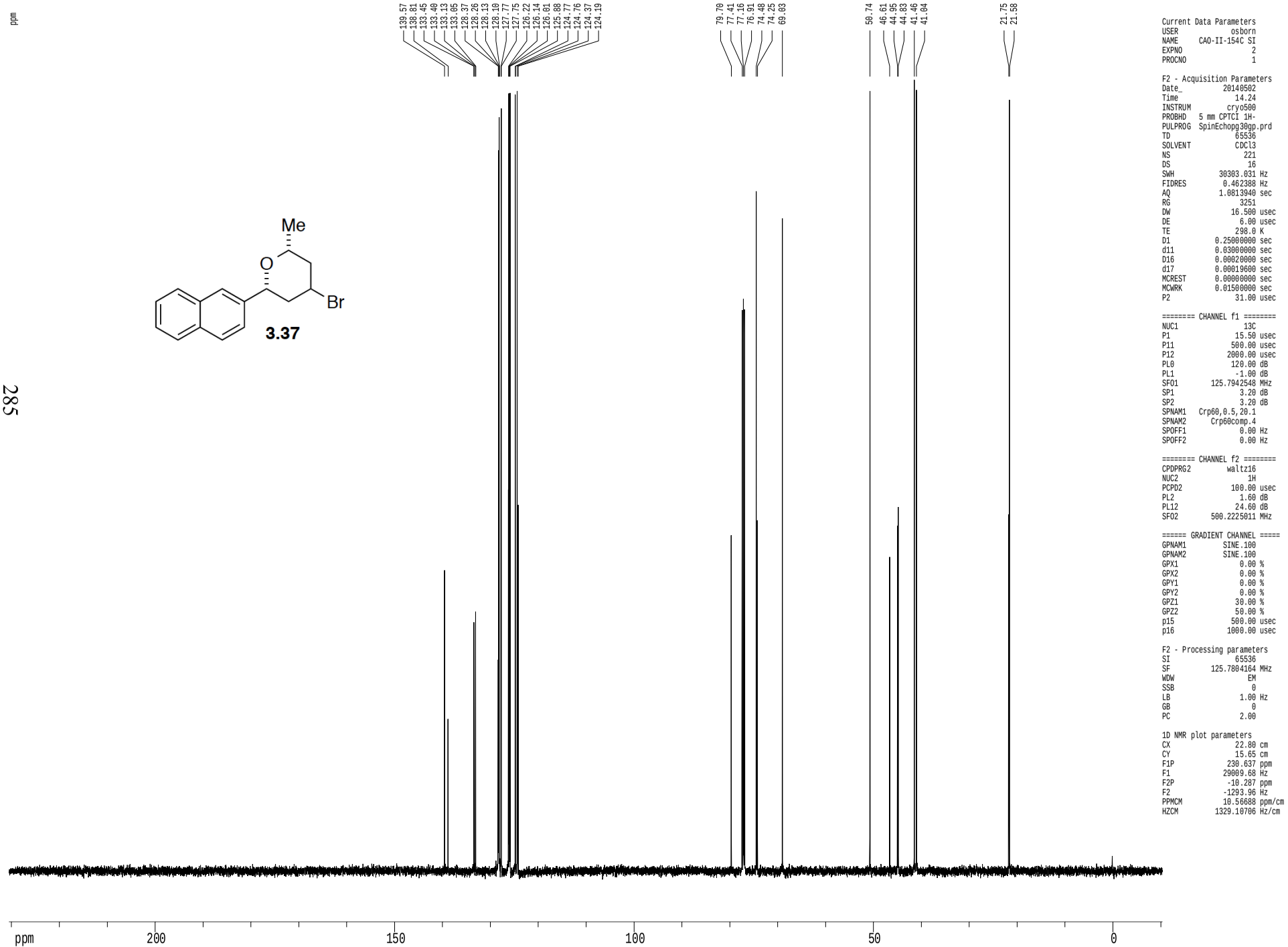
1H spectrum



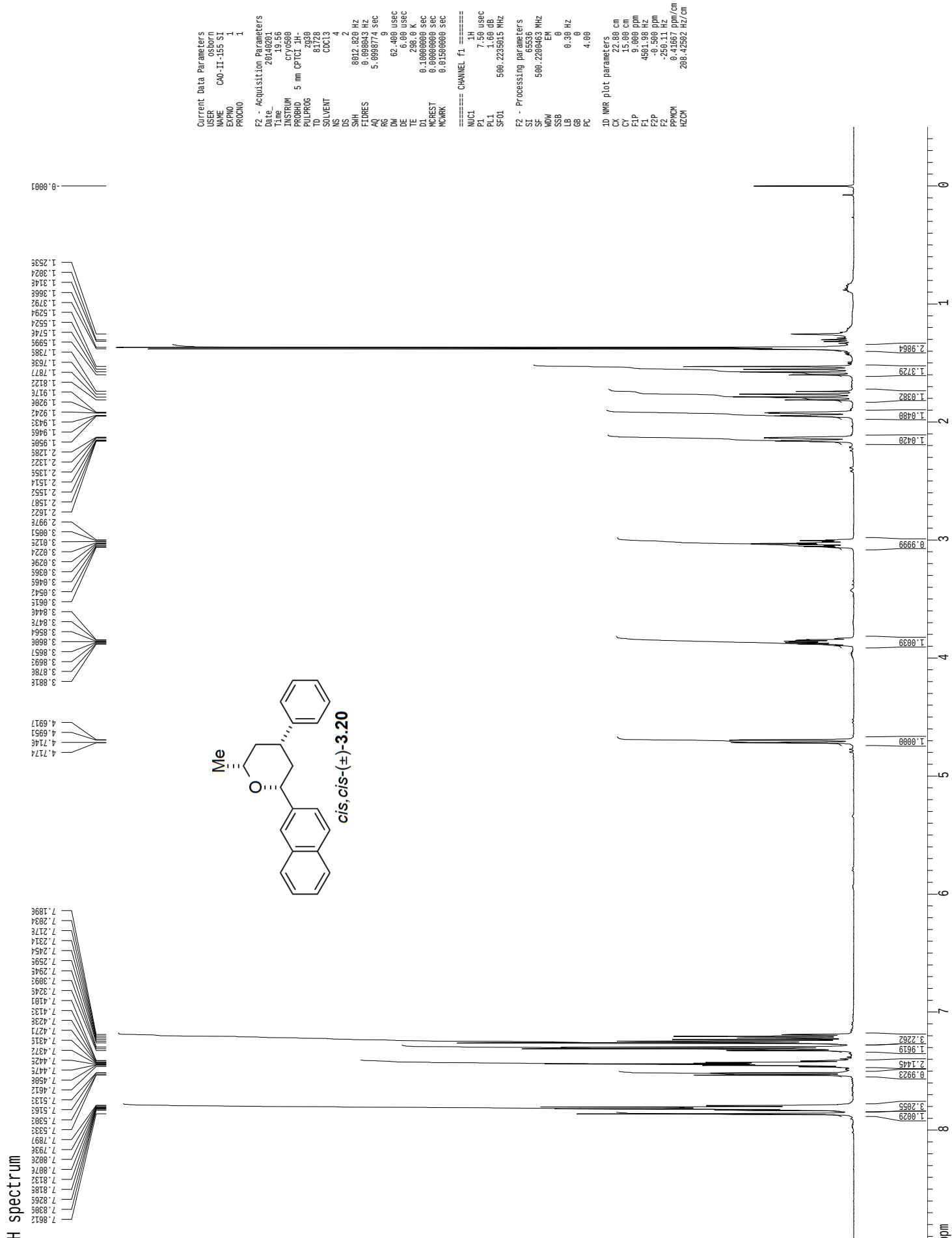
3.37

```
Current Data Parameters
USER              osborn
NAME          CAO-II-154C
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20131204
Time                13.56
INSTRUM           drx400
PROBHD   5 mm QNP H/F/P
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             6410.256 Hz
FIDRES          0.097813 Hz
AQ              5.1118579 sec
RG                    16
DW                78.000 usec
DE                 4.50 usec
TE                297.9 K
D1             0.10000000 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec

======= CHANNEL f1 =======
NUC1                  1H
P1                 12.00 usec
PL1                 0.00 dB
SFO1         400.1328009 MHz

F2 - Processing parameters
SI                 65536
SF           400.1301071 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  2.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.00 cm
F1P                9.000 ppm
F1               3601.17 Hz
F2P               -0.500 ppm
F2               -200.06 Hz
PPMCM           0.41667 ppm/cm
HZCM          166.72089 Hz/cm
```

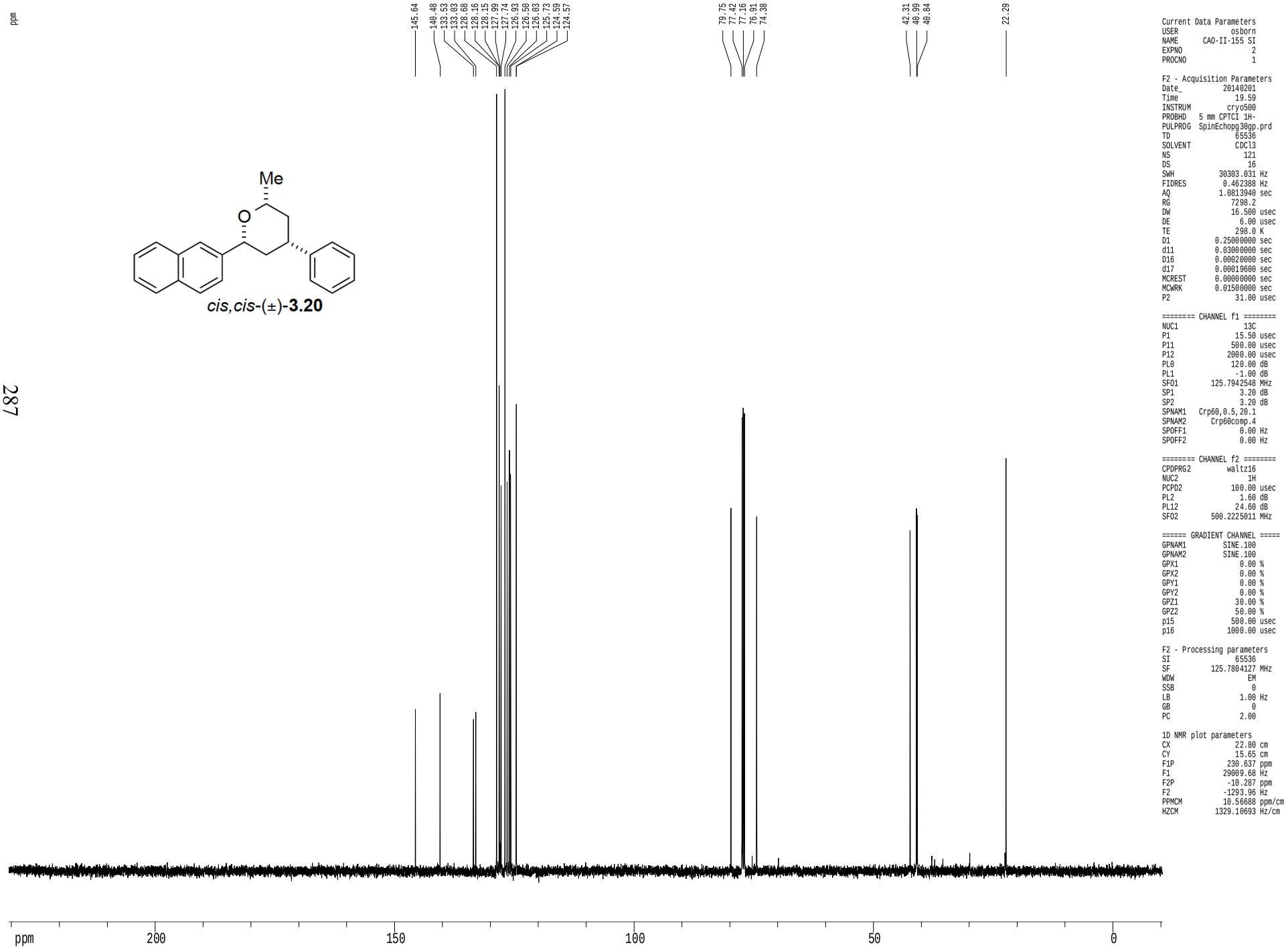
Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                 osborn
NAME      CAO-II-154C SI
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_             20140502
Time                 14.24
INSTRUM            cry0500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                    65536
SOLVENT               CDCl3
NS                      221
DS                       16
SWH               30303.031 Hz
FIDRES            0.462388 Hz
AQ                1.0813940 sec
RG                    3251
DW                  16.500 usec
DE                   6.00 usec
TE                  298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec
P2                  31.00 usec

======== CHANNEL f1 ========
NUC1                    13C
P1                   15.50 usec
P11                 500.00 usec
P12                2000.00 usec
PL0                 120.00 dB
PL1                  -1.00 dB
SFO1           125.7942548 MHz
SP1                  3.20 dB
SP2                  3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2       Crp60comp.4
SPOFF1                0.00 Hz
SPOFF2                0.00 Hz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2               100.00 usec
PL2                   1.60 dB
PL12                 24.60 dB
SFO2           500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPX1                  0.00 %
GPX2                  0.00 %
GPY1                  0.00 %
GPY2                  0.00 %
GPZ1                 30.00 %
GPZ2                 50.00 %
p15                 500.00 usec
p16                1000.00 usec

F2 - Processing parameters
SI                    65536
SF             125.7804164 MHz
WDW                      EM
SSB                       0
LB                    1.00 Hz
GB                        0
PC                    2.00

1D NMR plot parameters
CX                   22.80 cm
CY                   15.65 cm
F1P                230.637 ppm
F1                 29009.68 Hz
F2P                -10.287 ppm
F2                 -1293.96 Hz
PPMCM             10.56688 ppm/cm
HZCM           1329.10706 Hz/cm
```


1H spectrum
Current Data Parameters
USER osborn
NAME CAO-II-155 SI
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140201
Time 19.56
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 4
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0999774 sec
RG 9
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200463 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm
Me
O
cis,cis-(±)-3.20
ppm
Integral

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME CAO-II-155 SI
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20140201
Time 19.59
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 121
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 7298.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 31.00 usec

======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

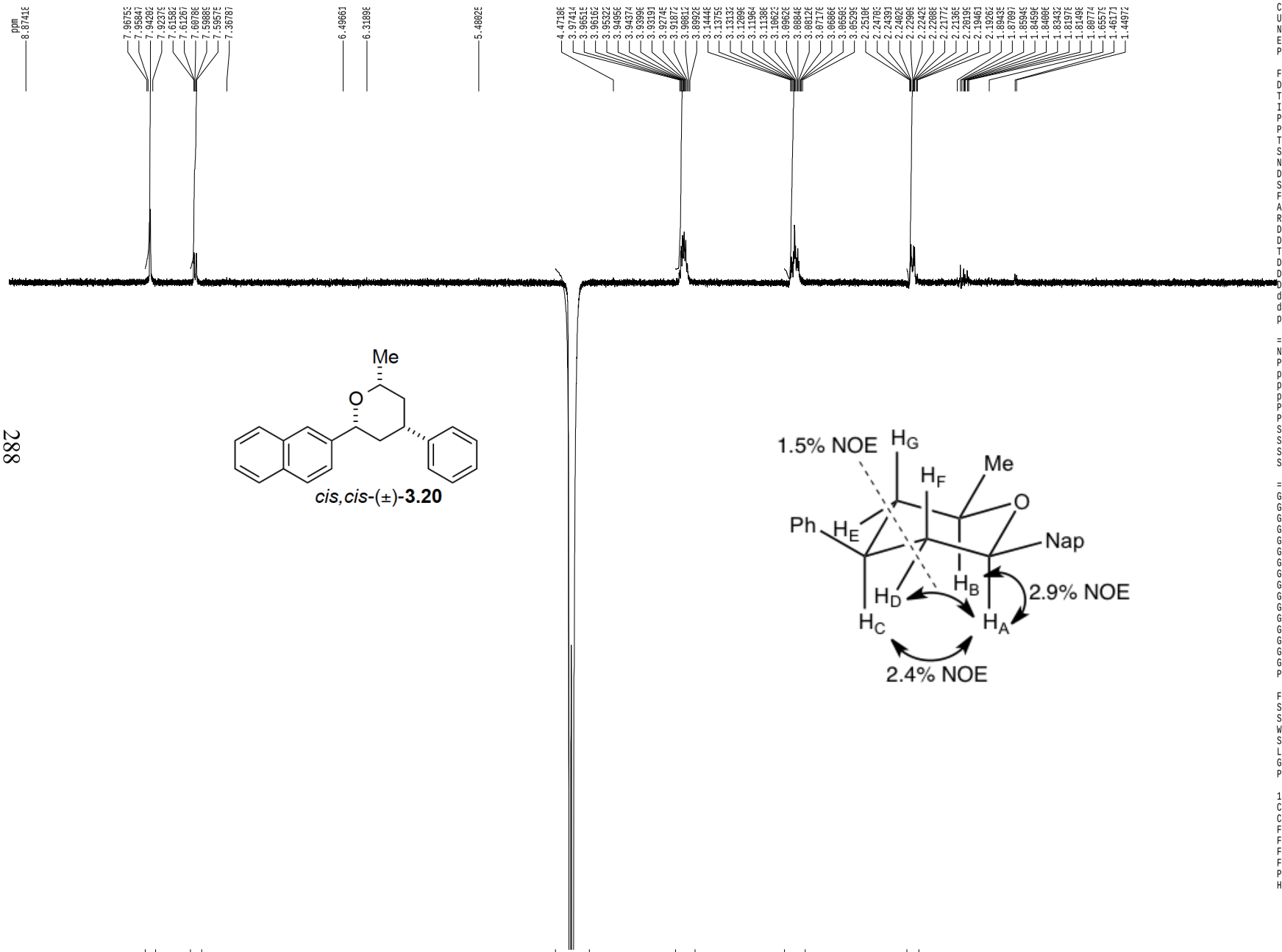
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 125.7804127 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

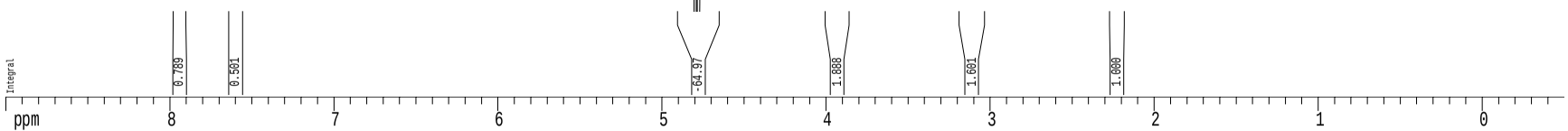
1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm

gnoe



288

cis,cis-(±)-**3.20**



Current Data Parameters
USER emilyt
NAME CAO-II-179-noe
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20140713
Time 1.37
INSTRUM gn500
PROBHD 5 mm broadband
PULPROG gnoe1cc.wu
TD 65536
SOLVENT CDCl3
NS 256
DS 8
SWH 5482.456 Hz
FIDRES 0.083656 Hz
AQ 5.9769330 sec
RG 4096
DW 91.200 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
D8 0.50000000 sec
D16 0.00020000 sec
d21 0.33374399 sec
d22 0.16399699 sec
p2 24.00 usec

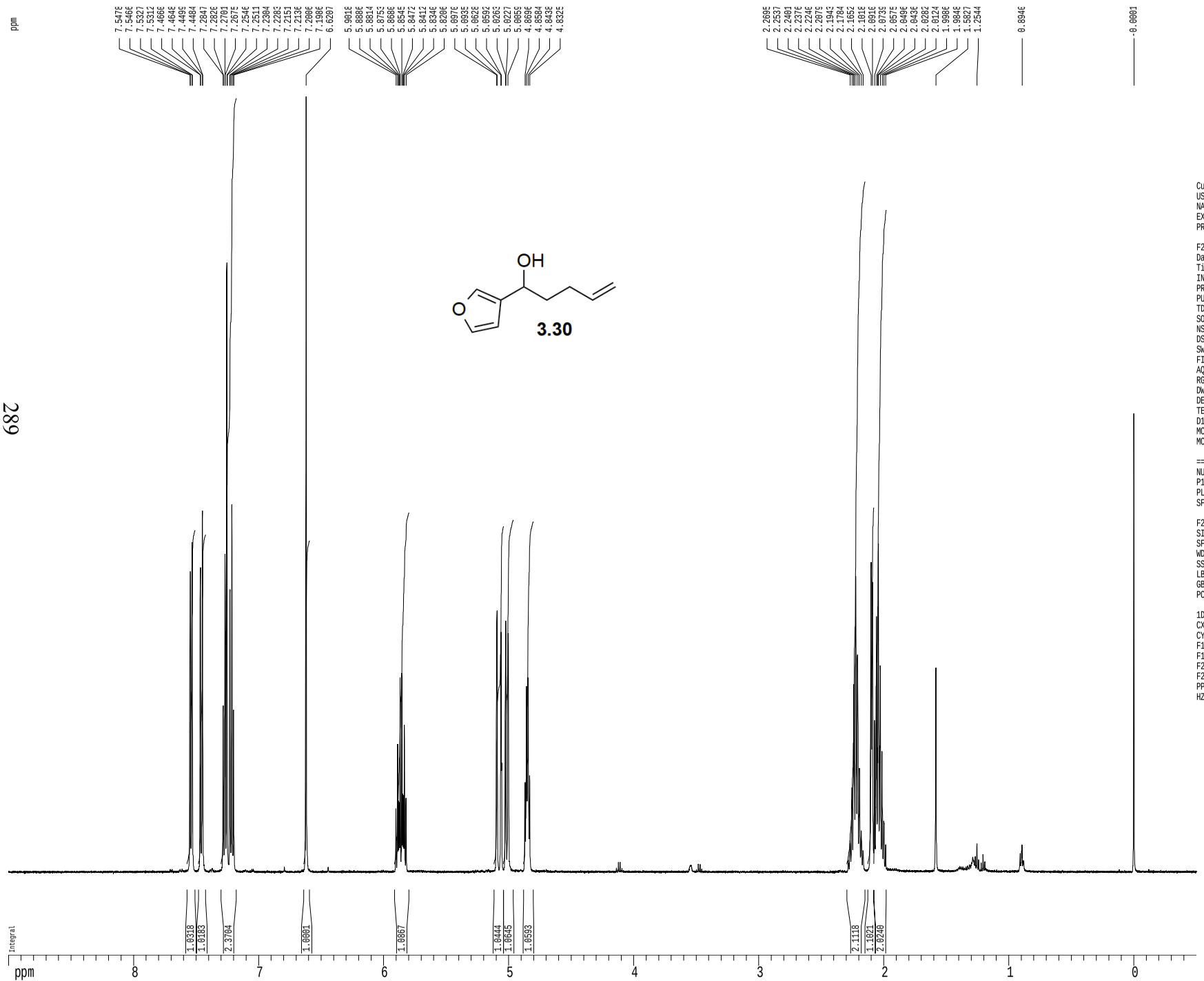
======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
p3 36.00 usec
p4 48.00 usec
p5 32.00 usec
P12 40000.00 usec
PL1 -5.80 dB
SFO1 499.2923899 MHz
SP1 53.60 dB
SPNAM1 gauss1.512
SPOFF1 0.00 Hz

===== GRADIENT CHANNEL =====
GPNAM1 sine.100
GPNAM2 sine.100
GPNAM3 sine.100
GPNAM4 sine.100
GPX1 0.00 %
GPX2 0.00 %
GPX3 0.00 %
GPX4 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPY3 0.00 %
GPY4 0.00 %
GPZ1 7.00 %
GPZ2 3.00 %
GPZ3 2.30 %
GPZ4 -2.30 %
P16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 499.2900000 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 22.80 cm
CY 50.00 cm
F1P 9.000 ppm
F1 4493.61 Hz
F2P -0.500 ppm
F2 -249.64 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.03751 Hz/cm

1H spectrum



Current Data Parameters
USER emilyt
NAME EJT-III-258
EXPNO 10
PROCNO 1

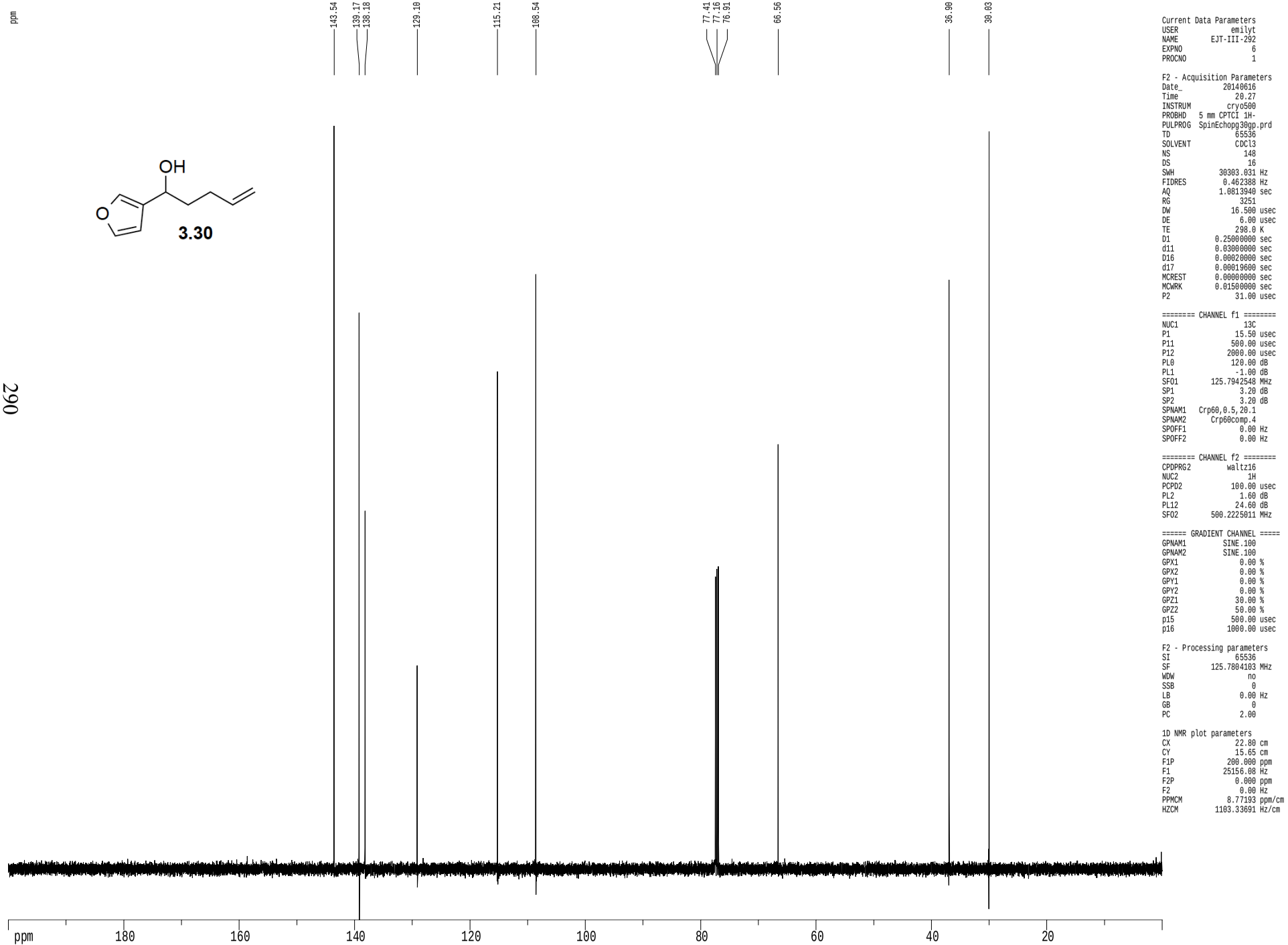
F2 - Acquisition Parameters
Date_ 20140616
Time 20.59
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 4.5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz

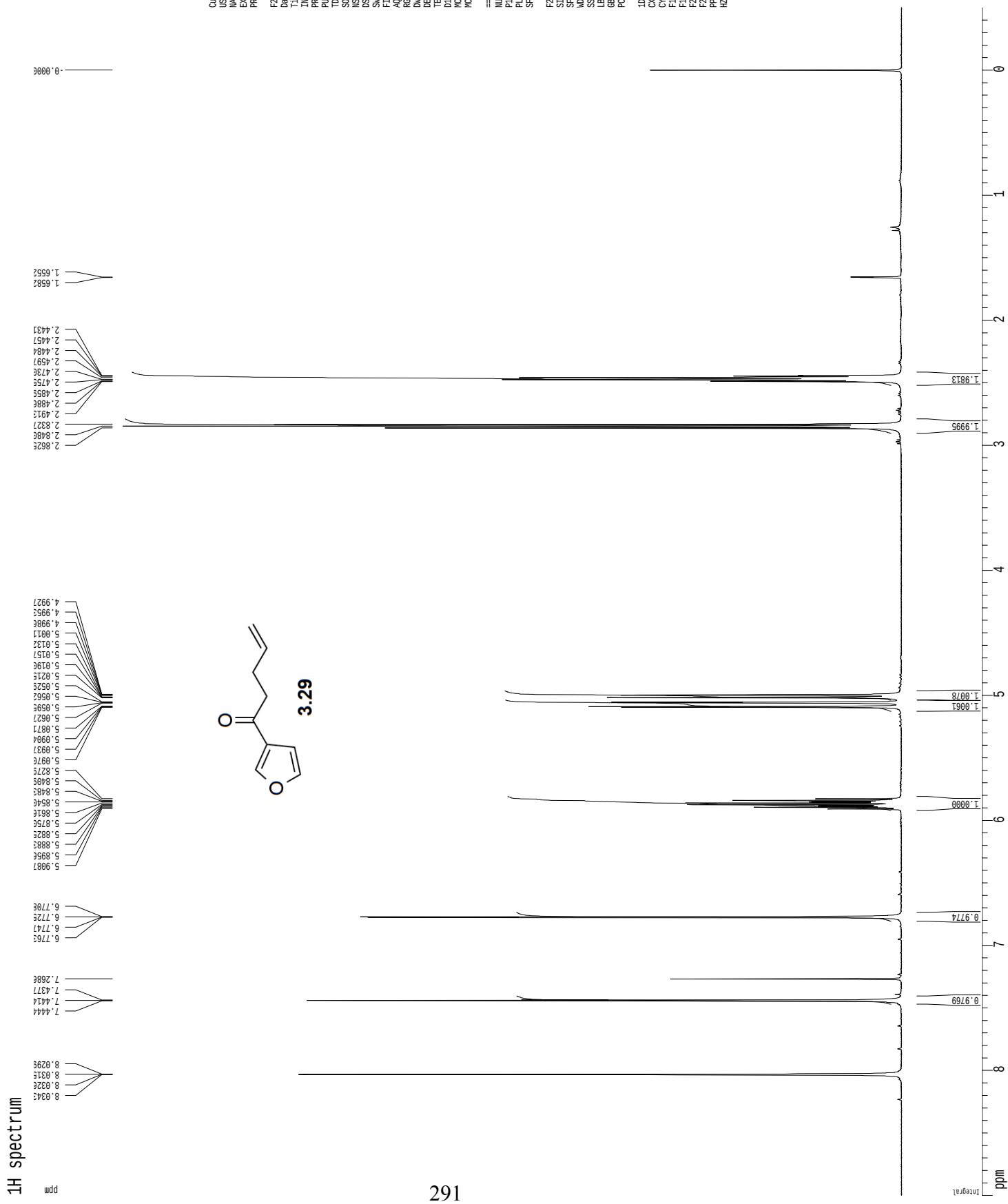
F2 - Processing parameters
SI 65536
SF 500.2200351 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm

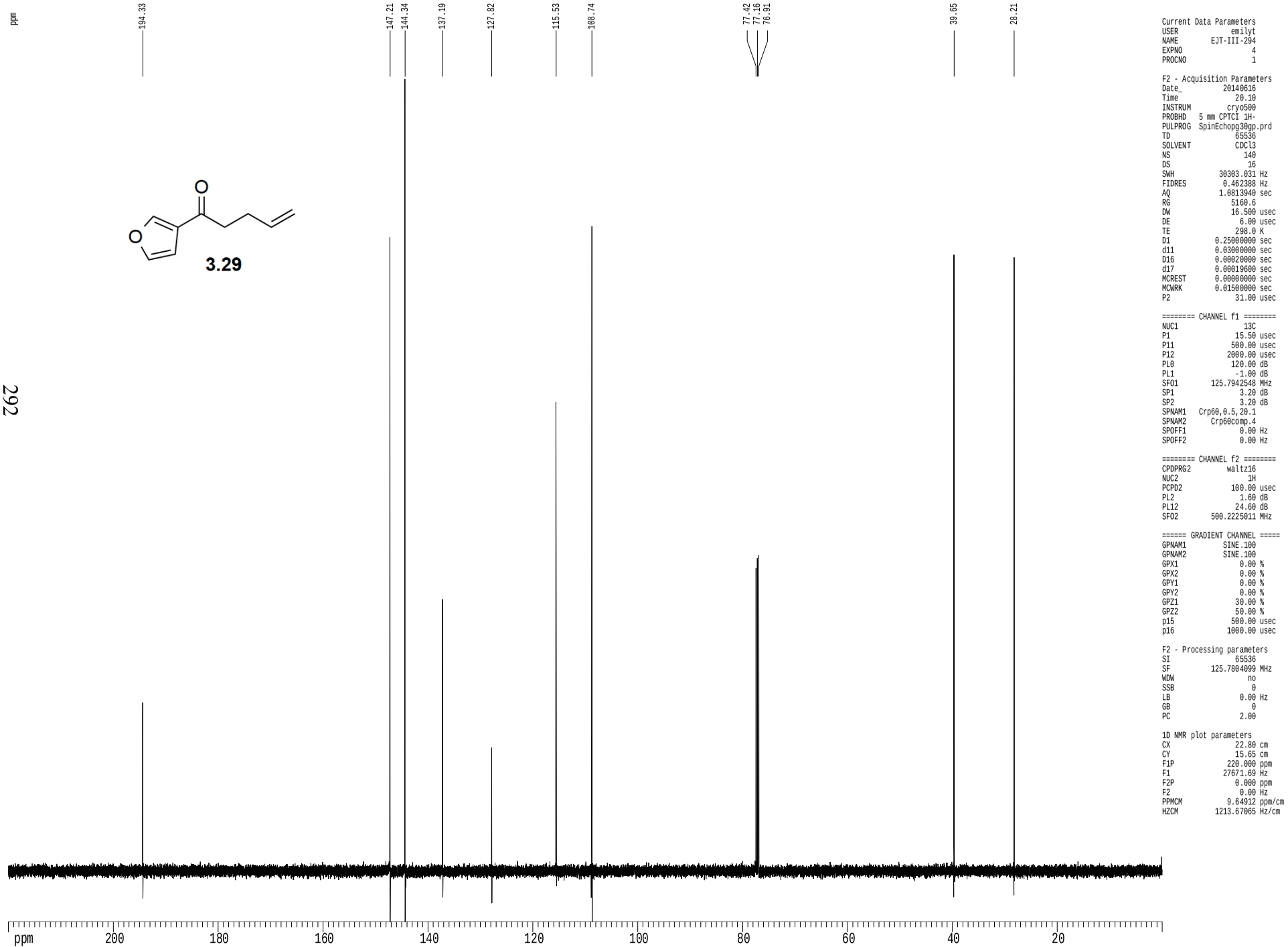
Z-restored spin-echo 13C spectrum with 1H decoupling



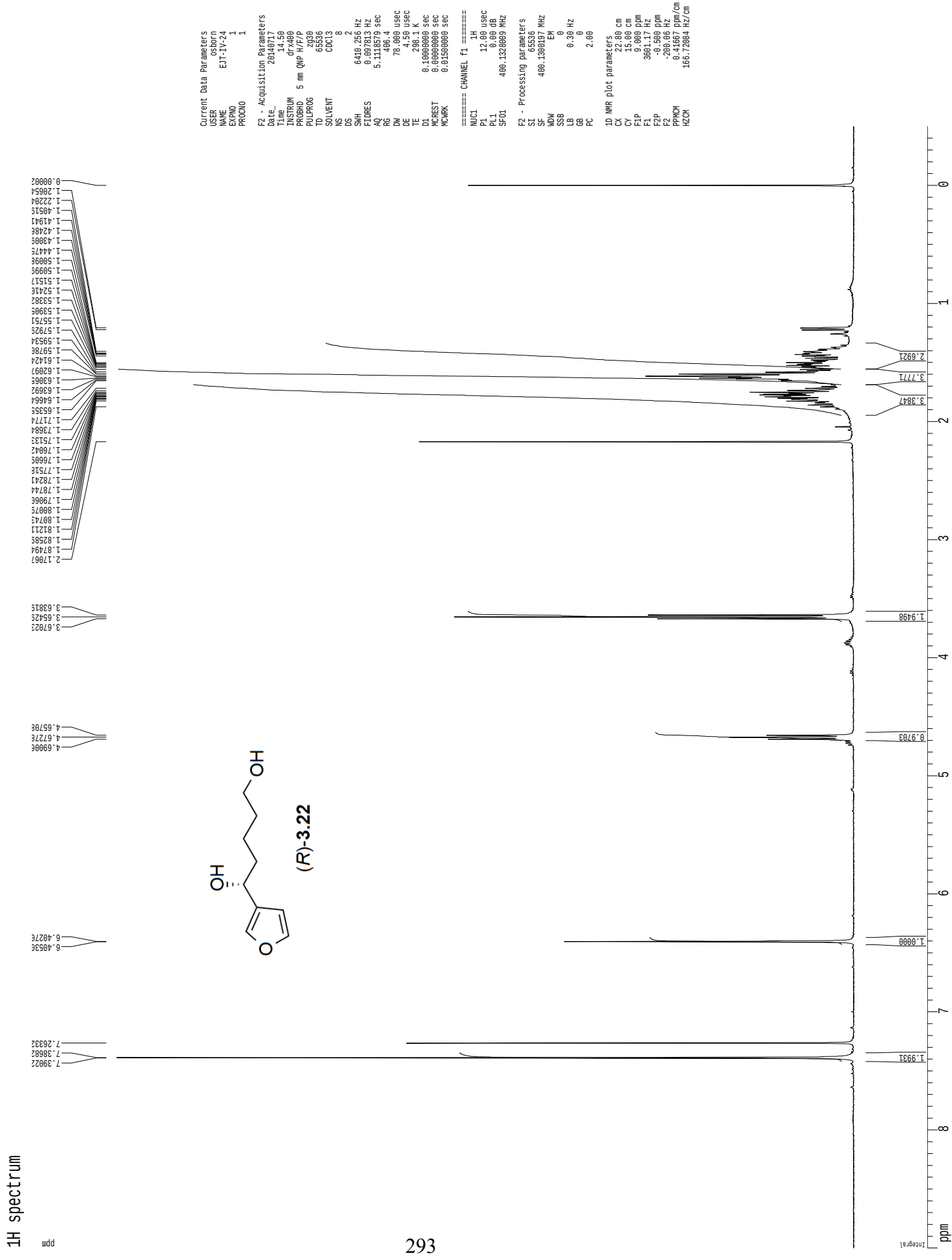

```
Current Data Parameters
USER                emilyt
NAME            EJT-III-292
EXPNO                     6
PROCNO                    1

F2 - Acquisition Parameters
Date_              20140616
Time                  20.27
INSTRUM             cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                    65536
SOLVENT               CDCl3
NS                      148
DS                       16
SWH               30303.031 Hz
FIDRES            0.462388 Hz
AQ                1.0813940 sec
RG                      3251
DW                  16.500 usec
DE                   6.00 usec
TE                   298.0 K
D1                0.25000000 sec
d11               0.03000000 sec
D16               0.00020000 sec
d17               0.00019600 sec
MCREST            0.00000000 sec
MCWRK             0.01500000 sec
P2                  31.00 usec

======== CHANNEL f1 ========
NUC1                    13C
P1                   15.50 usec
P11                 500.00 usec
P12                2000.00 usec
PL0                 120.00 dB
PL1                  -1.00 dB
SFO1            125.7942548 MHz
SP1                  3.20 dB
SP2                  3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1                0.00 Hz
SPOFF2                0.00 Hz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                    1H
PCPD2               100.00 usec
PL2                   1.60 dB
PL12                 24.60 dB
SFO2            500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1            SINE.100
GPNAM2            SINE.100
GPX1                  0.00 %
GPX2                  0.00 %
GPY1                  0.00 %
GPY2                  0.00 %
GPZ1                 30.00 %
GPZ2                 50.00 %
p15                 500.00 usec
p16                1000.00 usec

F2 - Processing parameters
SI                    65536
SF              125.7804183 MHz
WDW                      no
SSB                       0
LB                    0.00 Hz
GB                        0
PC                    2.00

1D NMR plot parameters
CX                   22.80 cm
CY                   15.65 cm
F1P                 200.000 ppm
F1                25156.08 Hz
F2P                   0.000 ppm
F2                    0.00 Hz
PPMCM              8.77193 ppm/cm
HZCM            1103.33691 Hz/cm
```


1H spectrum
Current Data Parameters
USER emilyt
NAME EJT-III-294
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140616
Time 20.06
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 4
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200280 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 4.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm
0.0006
1.6582
1.6562
2.4431
2.4457
2.4484
2.4597
2.4736
2.4756
2.4859
2.4886
2.4913
2.8327
2.8486
2.8626
4.9927
4.9963
4.9986
5.0013
5.0132
5.0157
5.0196
5.0216
5.0529
5.0562
5.0596
5.0627
5.0871
5.0904
5.0937
5.0976
5.8279
5.8409
5.8483
5.8546
5.8616
5.8756
5.8825
5.8883
5.8956
5.9087
6.7706
6.7726
6.7747
6.7763
7.2686
7.4377
7.4414
7.4444
8.0299
8.0315
8.0326
8.0343
3.29
1.9813
1.9995
1.0078
1.0061
1.0000
0.9774
0.9769
ppm
Integral

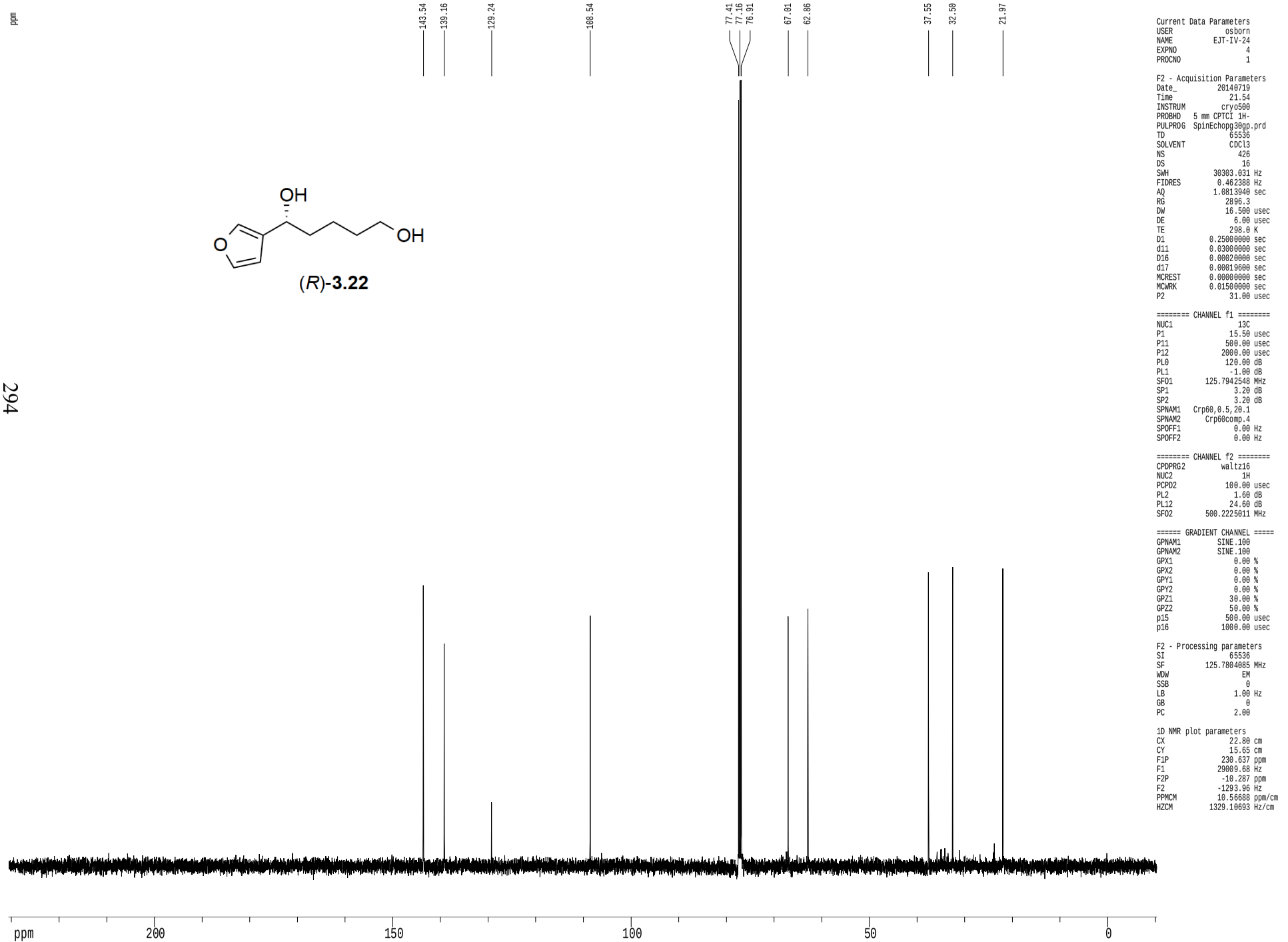
Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER              emilyt
NAME          EJT-III-294
EXPNO                   4
PROCNO                  1

F2 - Acquisition Parameters
Date_          20140616
Time              20.10
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                65536
SOLVENT           CDCl3
NS                  140
DS                   16
SWH           30303.031 Hz
FIDRES        0.462388 Hz
AQ            1.0813940 sec
RG               5160.6
DW               16.500 usec
DE                6.00 usec
TE                298.0 K
D1            0.25000000 sec
d11           0.03000000 sec
D16           0.00020000 sec
d17           0.00019600 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec
P2                31.00 usec

======== CHANNEL f1 ========
NUC1                13C
P1                15.50 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1               3.20 dB
SP2               3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                1H
PCPD2            100.00 usec
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15              500.00 usec
p16             1000.00 usec

F2 - Processing parameters
SI                 65536
SF          125.7804099 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  2.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.65 cm
F1P              220.000 ppm
F1              27671.69 Hz
F2P                0.000 ppm
F2                 0.00 Hz
PPMCM           9.64912 ppm/cm
HZCM         1213.67065 Hz/cm
```


1H spectrum
Current Data Parameters
USER osborn
NAME EJT-IV-24
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140717
Time 14.50
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 406.4
DW 78.000 usec
DE 4.50 usec
TE 298.1 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300197 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm
0.00002
1.20654
1.22204
1.40516
1.41941
1.42486
1.43006
1.44475
1.56098
1.56995
1.57517
1.52416
1.53382
1.53906
1.55751
1.57925
1.59534
1.59786
1.61424
1.62097
1.63065
1.63692
1.64664
1.65356
1.71774
1.73684
1.75133
1.76042
1.76609
1.77516
1.78241
1.78744
1.79066
1.80079
1.80743
1.81211
1.82586
1.87494
2.17067
3.63815
3.65425
3.67023
4.65706
4.67276
4.69006
6.40536
6.40276
7.26332
7.38682
7.39022
2.6921
3.7771
3.3847
1.9498
0.9703
1.0000
1.9931
OH
OH
O
(R)-3.22
ppm
Integral

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME EJT-IV-24
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20140719
Time 21.54
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 426
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 2896.3
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 31.00 usec

======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

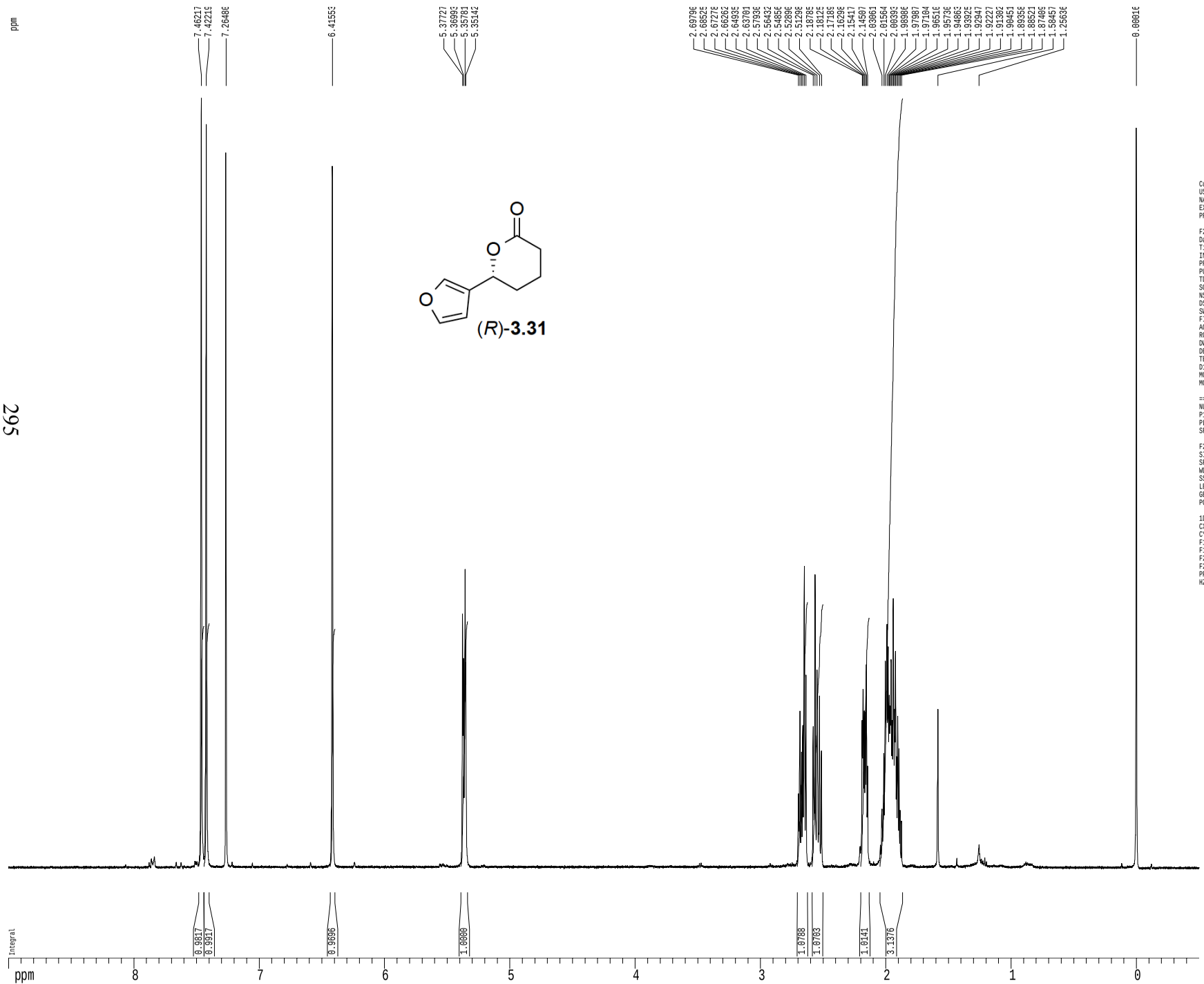
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 125.7804085 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm

1H spectrum



Current Data Parameters
USER emilyt
NAME EJT-III-200-characterization
EXPNO 2
PROCNO 1

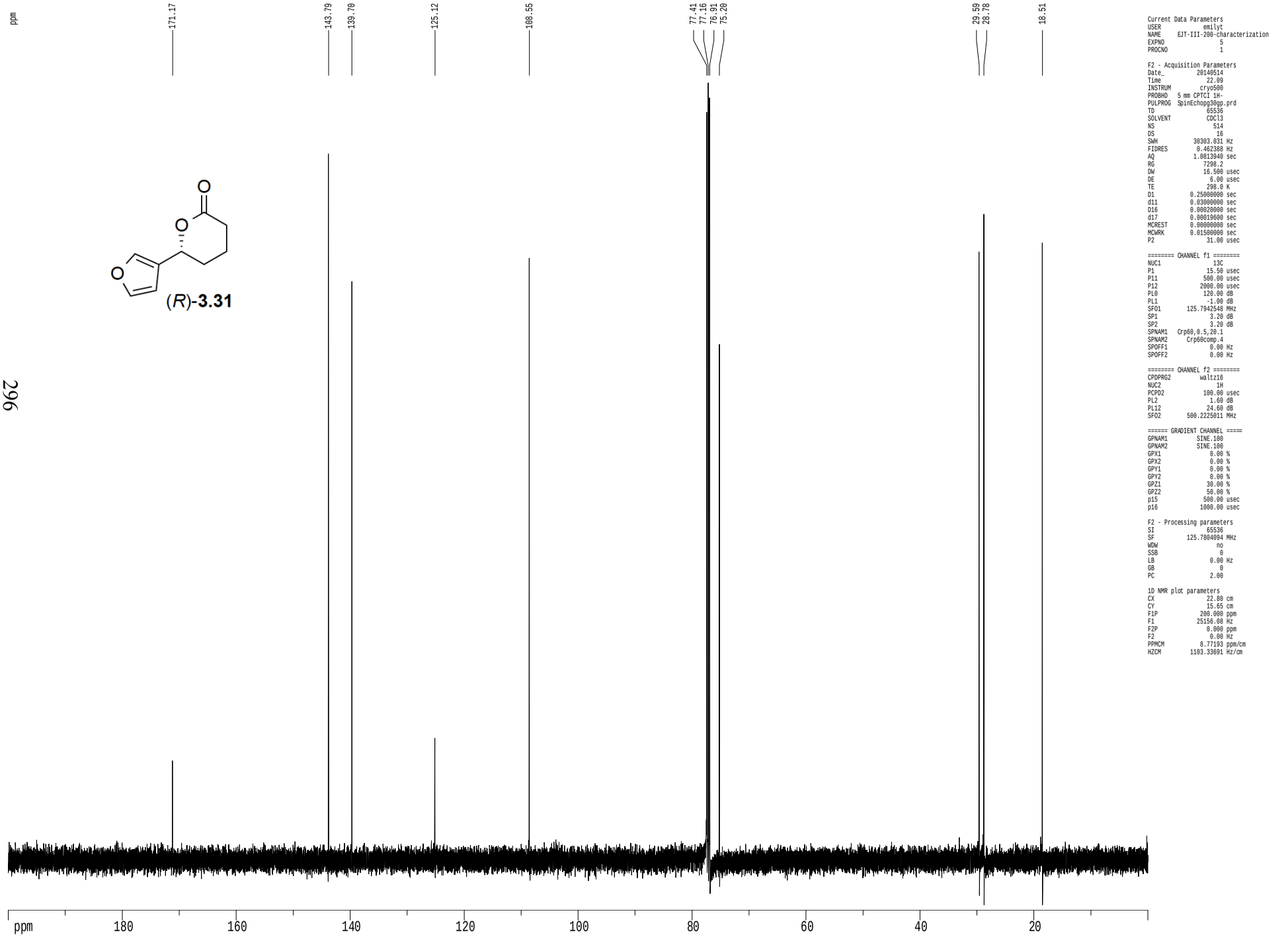
F2 - Acquisition Parameters
Date_ 20140514
Time 21.49
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 8
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz

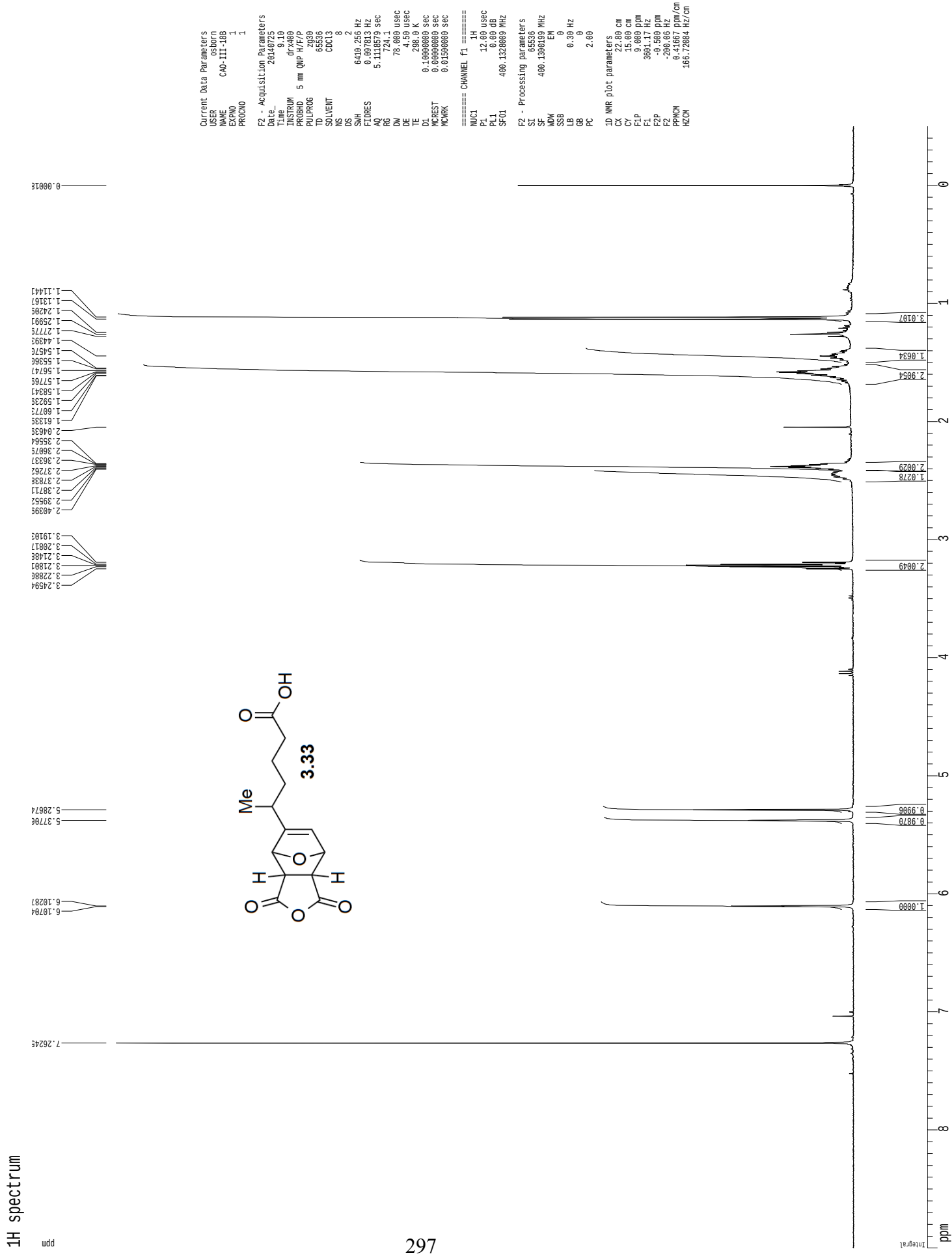
F2 - Processing parameters
SI 65536
SF 500.2200299 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm

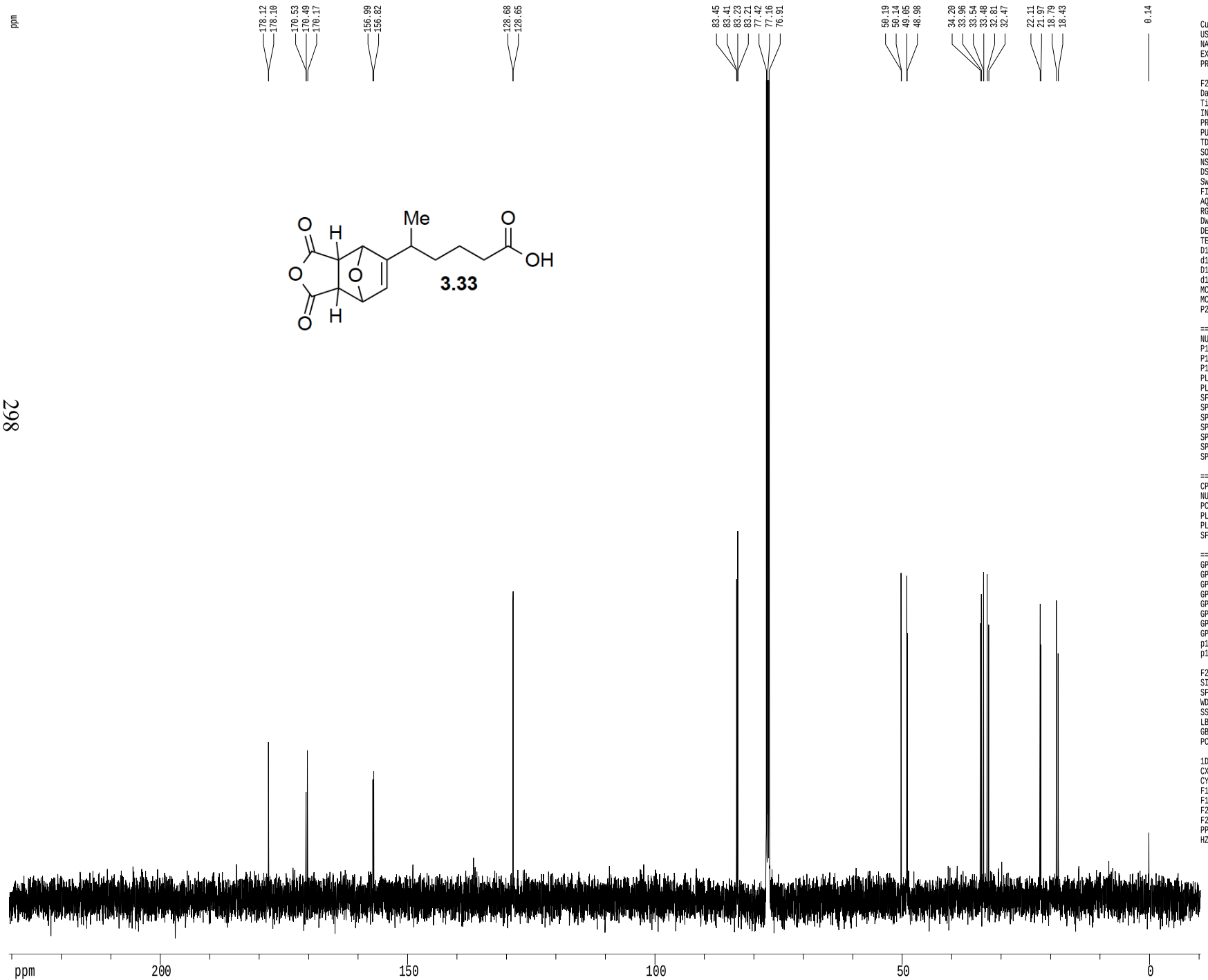
Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER              emilyt
NAME      EJT-III-200-characterization
EXPNO                5
PROCNO               1

F2 - Acquisition Parameters
Date_          20140514
Time             22.09
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD               65536
SOLVENT          CDCl3
NS                 514
DS                  16
SWH          30303.031 Hz
FIDRES        0.462388 Hz
AQ           1.0813940 sec
RG              7298.2
DW             16.500 usec
DE              6.00 usec
TE               298.0 K
D1           0.25000000 sec
d11          0.03000000 sec
D16          0.00020000 sec
d17          0.00019600 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec
P2                31.00 usec

======== CHANNEL f1 ========
NUC1                13C
P1                15.50 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1               3.20 dB
SP2               3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1              0.00 Hz
SPOFF2              0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                1H
PCPD2            100.00 usec
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL ====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15              500.00 usec
p16             1000.00 usec

F2 - Processing parameters
SI                 65536
SF          125.7804094 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  2.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.65 cm
F1P               200.000 ppm
F1              25156.08 Hz
F2P                0.000 ppm
F2                 0.00 Hz
PPMCM           8.77193 ppm/cm
HZCM         1103.33691 Hz/cm
```


Current Data Parameters
USER osborn
NAME CAO-III-18B
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140725
Time_ 9.10
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 724.1
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300199 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm
7.26245
6.10704
6.10287
5.37706
5.28674
3.24594
3.22886
3.21801
3.20817
3.21486
3.19103
2.40396
2.39552
2.38711
2.37836
2.37262
2.36337
2.36075
2.35564
2.04636
1.61336
1.60773
1.59236
1.58341
1.57766
1.56747
1.55366
1.54576
1.44393
1.27779
1.25991
1.24206
1.13167
1.11441
0.00018
3.33
Me
O
OH
H
H
O
O
O
O
3.0107
1.0634
2.9054
2.0029
1.0278
2.0049
0.9906
0.9870
1.0000
Integral
ppm
1H spectrum
ppm

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME CAO-III-18B
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20140725
Time 11.24
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 1024
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 7298.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 31.00 usec

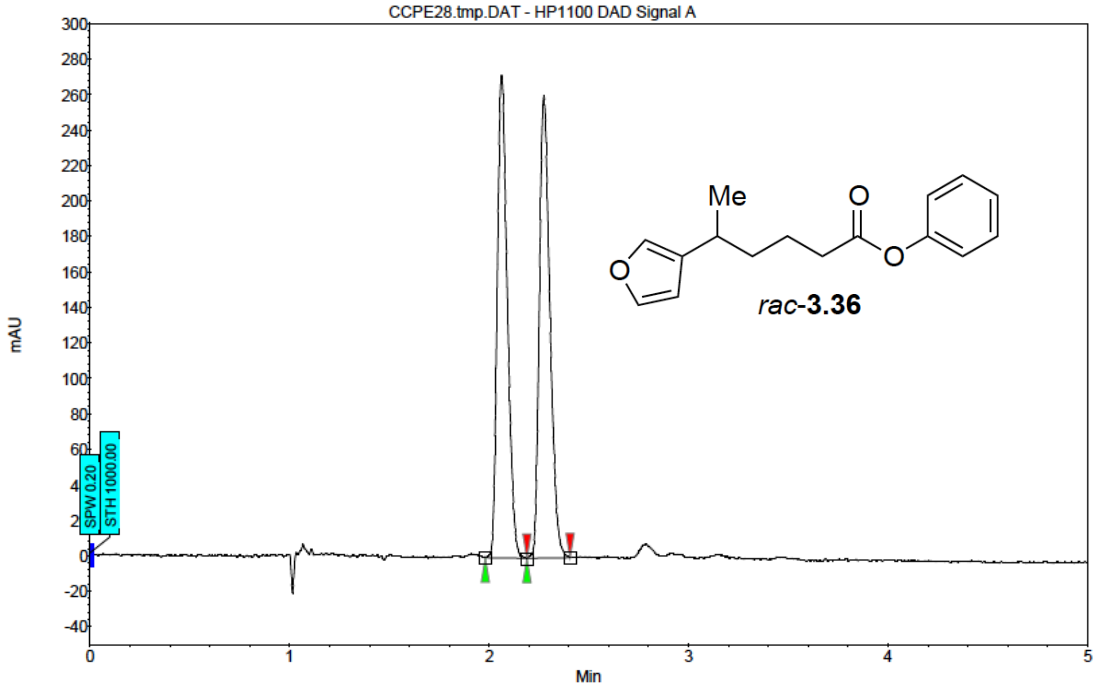
======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz

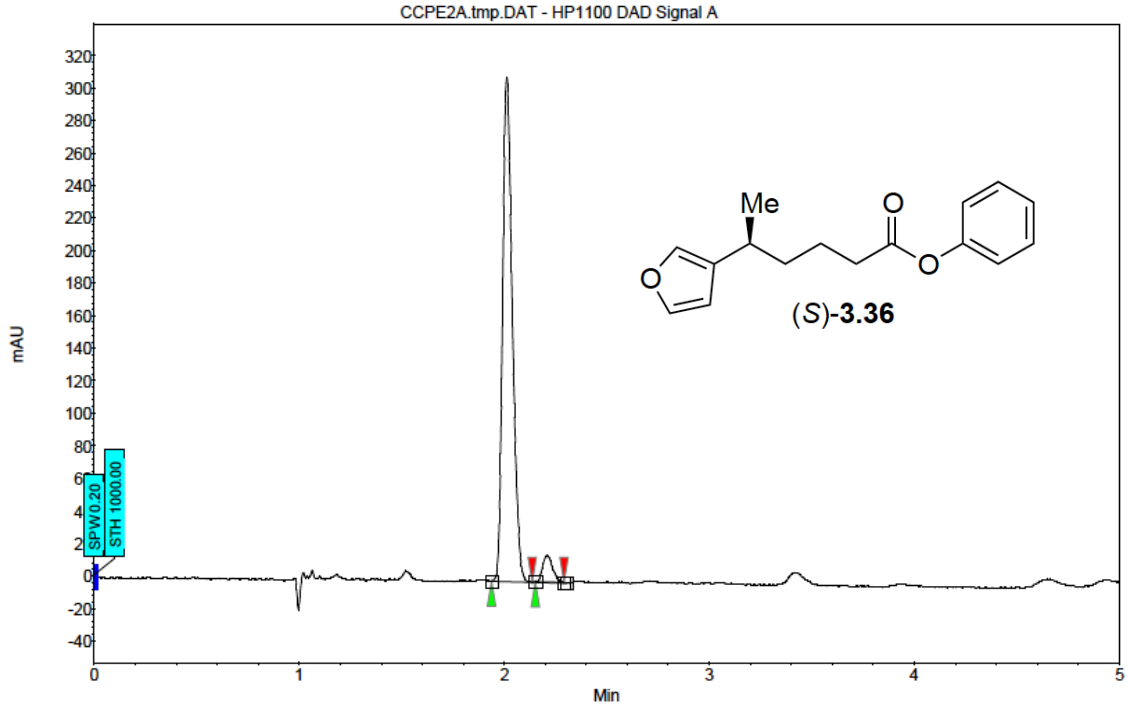
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 125.7804071 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

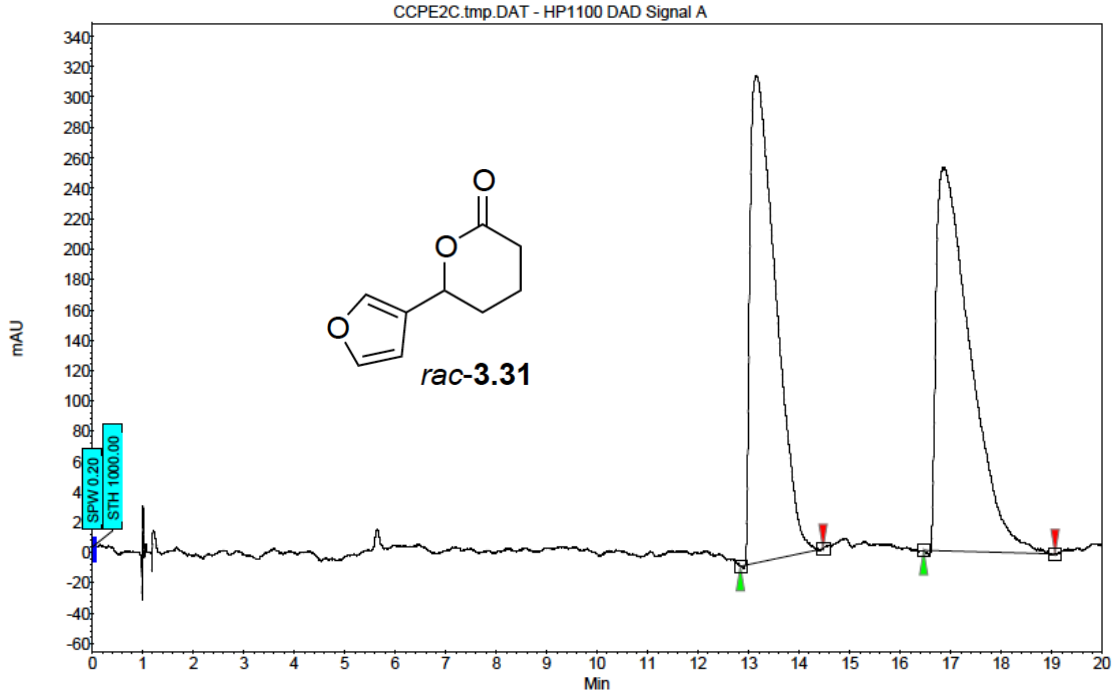
1D NMR plot parameters
CX 22.80 cm
CY 90.00 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm



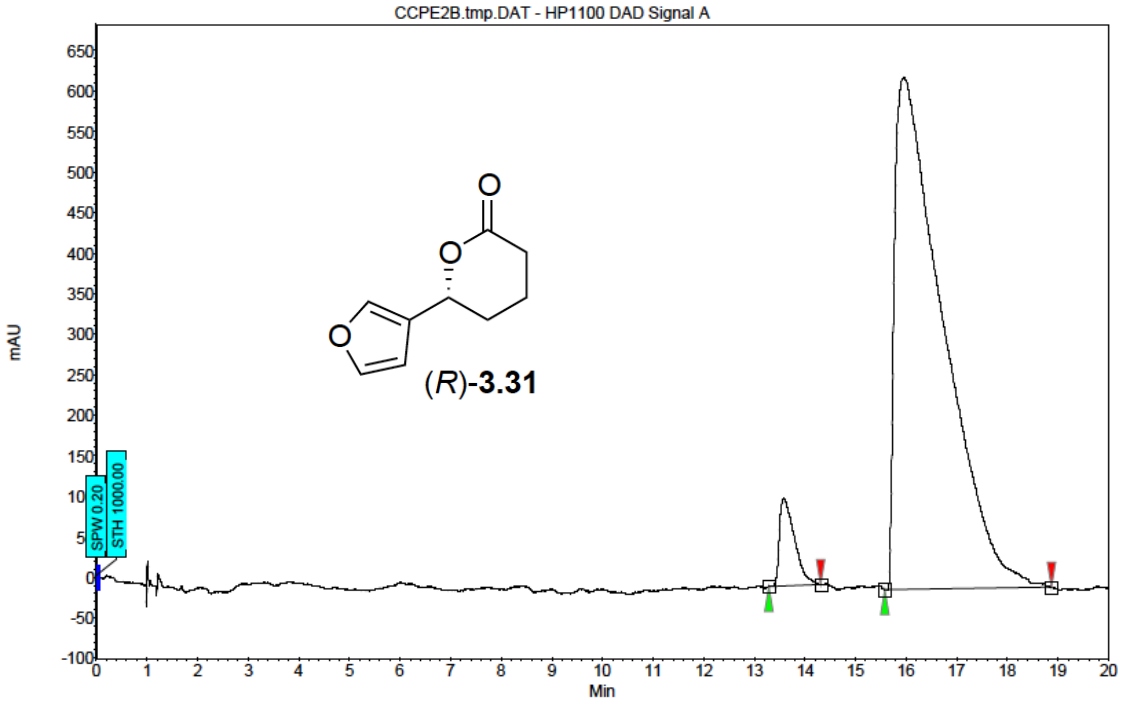
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	1.98	2.06	2.19	0.00	49.94	272.4	16.0	49.939
2	UNKNOWN	2.19	2.27	2.41	0.00	50.06	260.6	16.0	50.061
Total						100.00	533.0	32.0	100.000



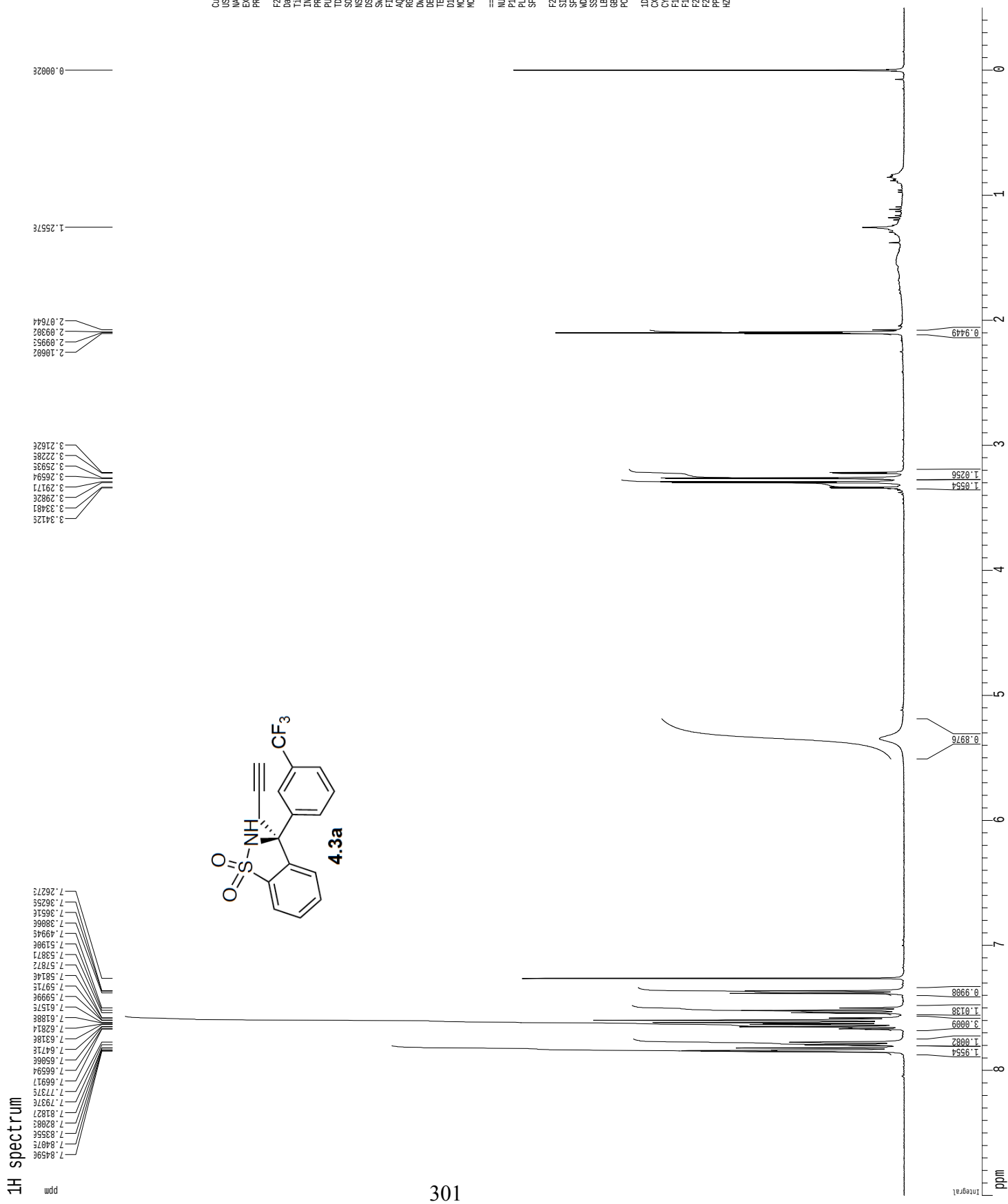
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	1.94	2.01	2.14	0.00	94.95	310.4	17.0	94.946
2	UNKNOWN	2.15	2.21	2.29	0.00	5.05	16.5	0.9	5.054
Total						100.00	326.9	17.9	100.000



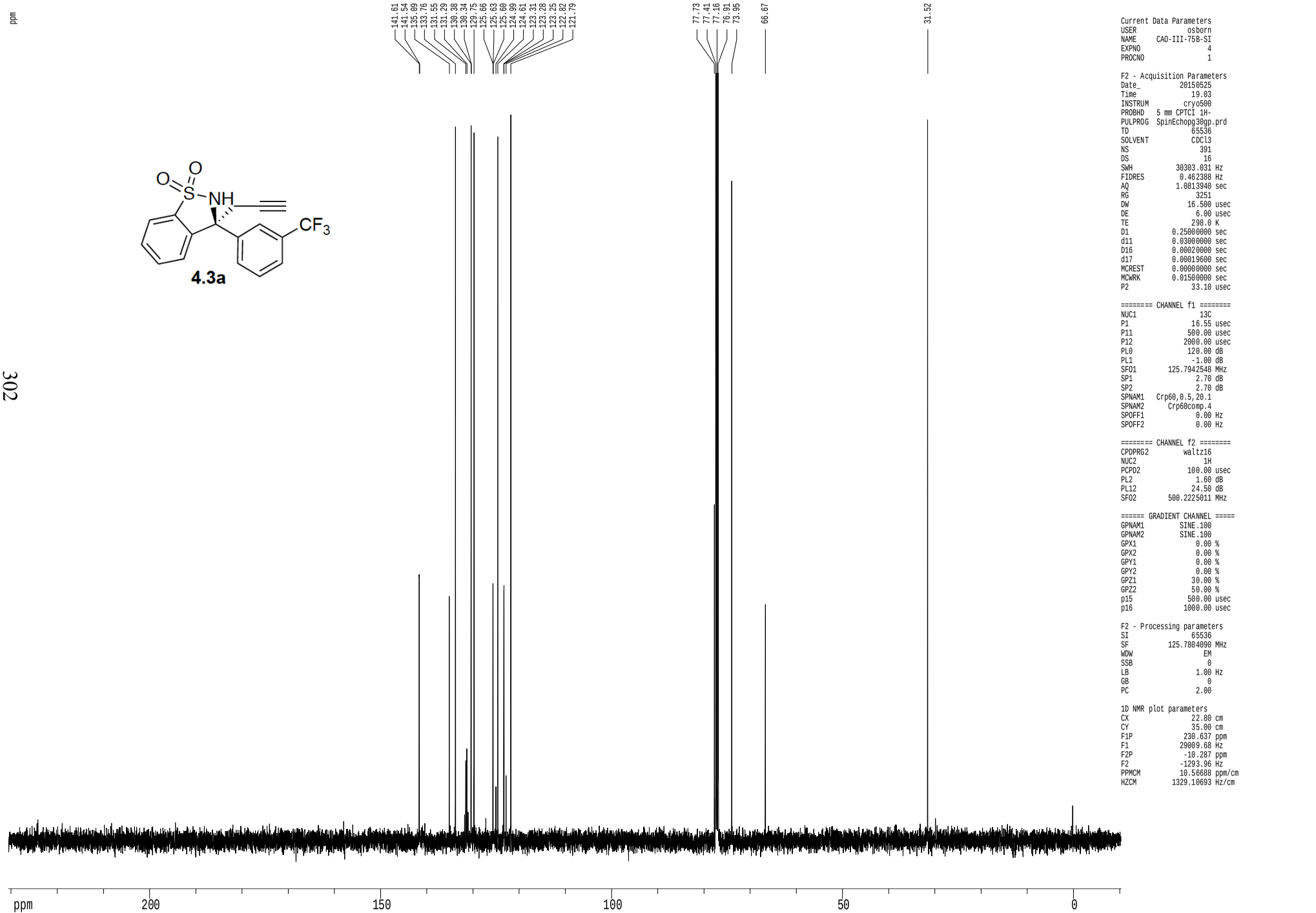
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	12.83	13.15	14.48	0.00	48.70	321.1	187.4	48.704
2	UNKNOWN	16.46	16.88	19.07	0.00	51.30	252.7	197.4	51.296
Total						100.00	573.8	384.8	100.000



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
2	UNKNOWN	13.29	13.58	14.31	0.00	5.09	108.4	37.3	5.089
1	UNKNOWN	15.58	15.96	18.87	0.00	94.91	632.1	694.8	94.911
Total						100.00	740.5	732.0	100.000


1H spectrum
Current Data Parameters
USER osborn
NAME CAO-III-75B-SI
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150526
Time 14.35
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 362
DW 78.000 usec
DE 4.50 usec
TE 295.8 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300197 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 7.50 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm
0.00026
1.25578
2.07644
2.09302
2.09953
2.10602
3.21626
3.22286
3.25936
3.26594
3.29171
3.29826
3.33481
3.34126
7.26273
7.36259
7.36516
7.38066
7.49946
7.51906
7.53871
7.57872
7.58146
7.59716
7.59996
7.61576
7.61886
7.62814
7.63186
7.64716
7.65066
7.66594
7.66917
7.77376
7.79376
7.81827
7.82083
7.83566
7.84076
7.84596
0.9449
1.0256
1.0554
0.8976
0.9908
1.0138
3.0009
1.0082
1.9554
CF3
NH
O
S
O
4.3a
ppm
Integral

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME CAO-III-75B-SI
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150525
Time 19.03
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 391
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 3251
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 33.10 usec

======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

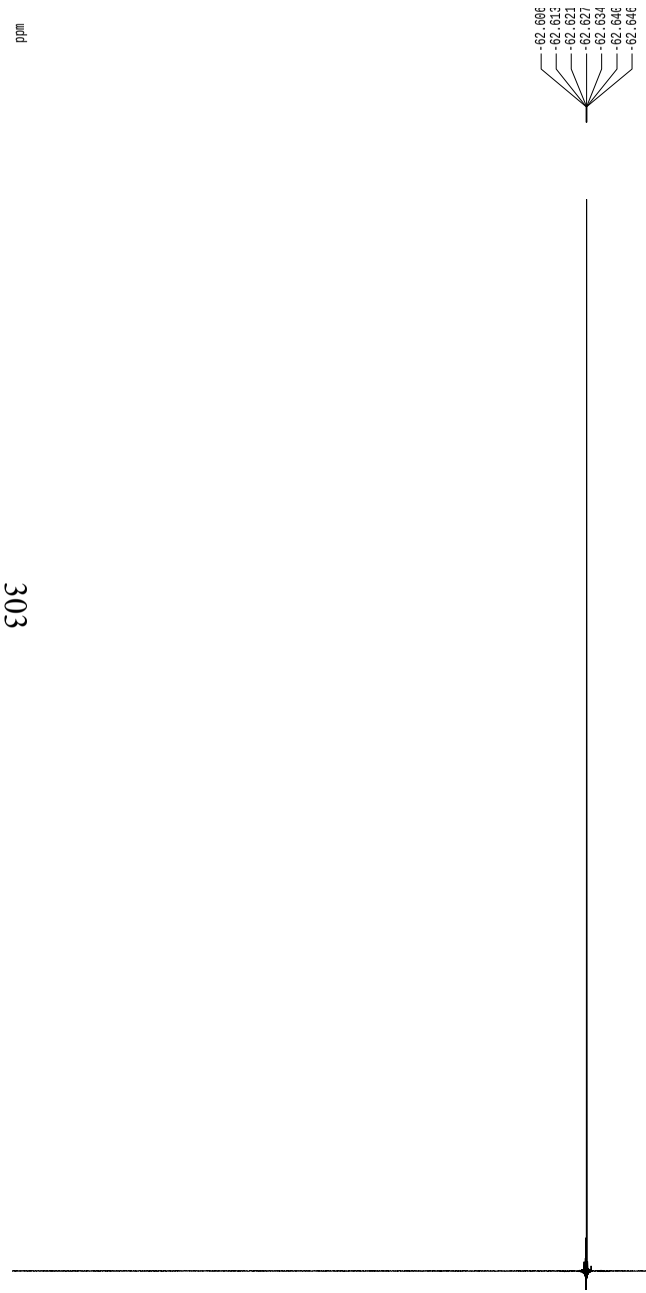
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz

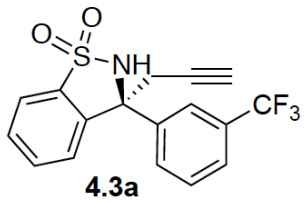
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 125.7804090 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 35.00 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm

19F spectrum with 1H decoupling

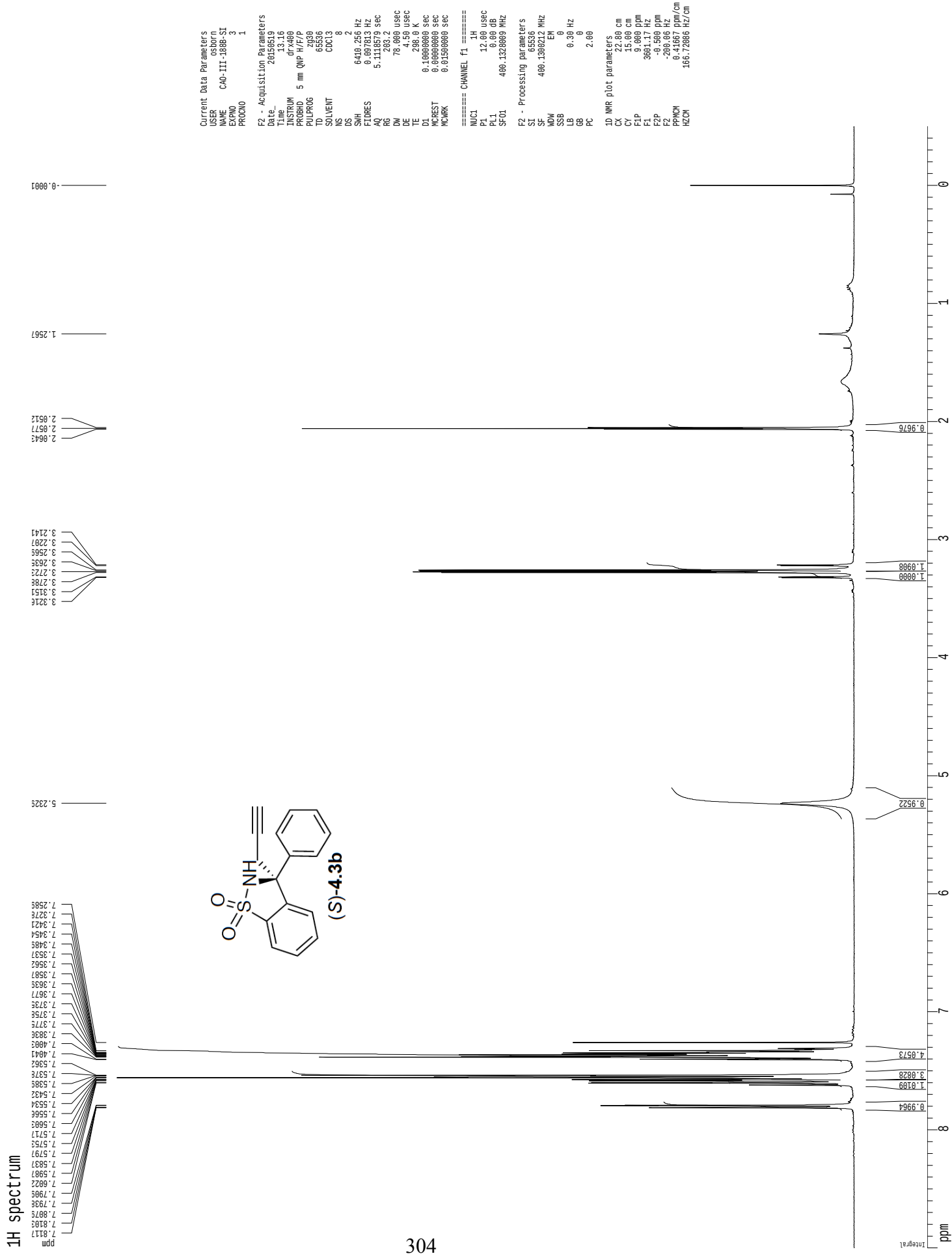




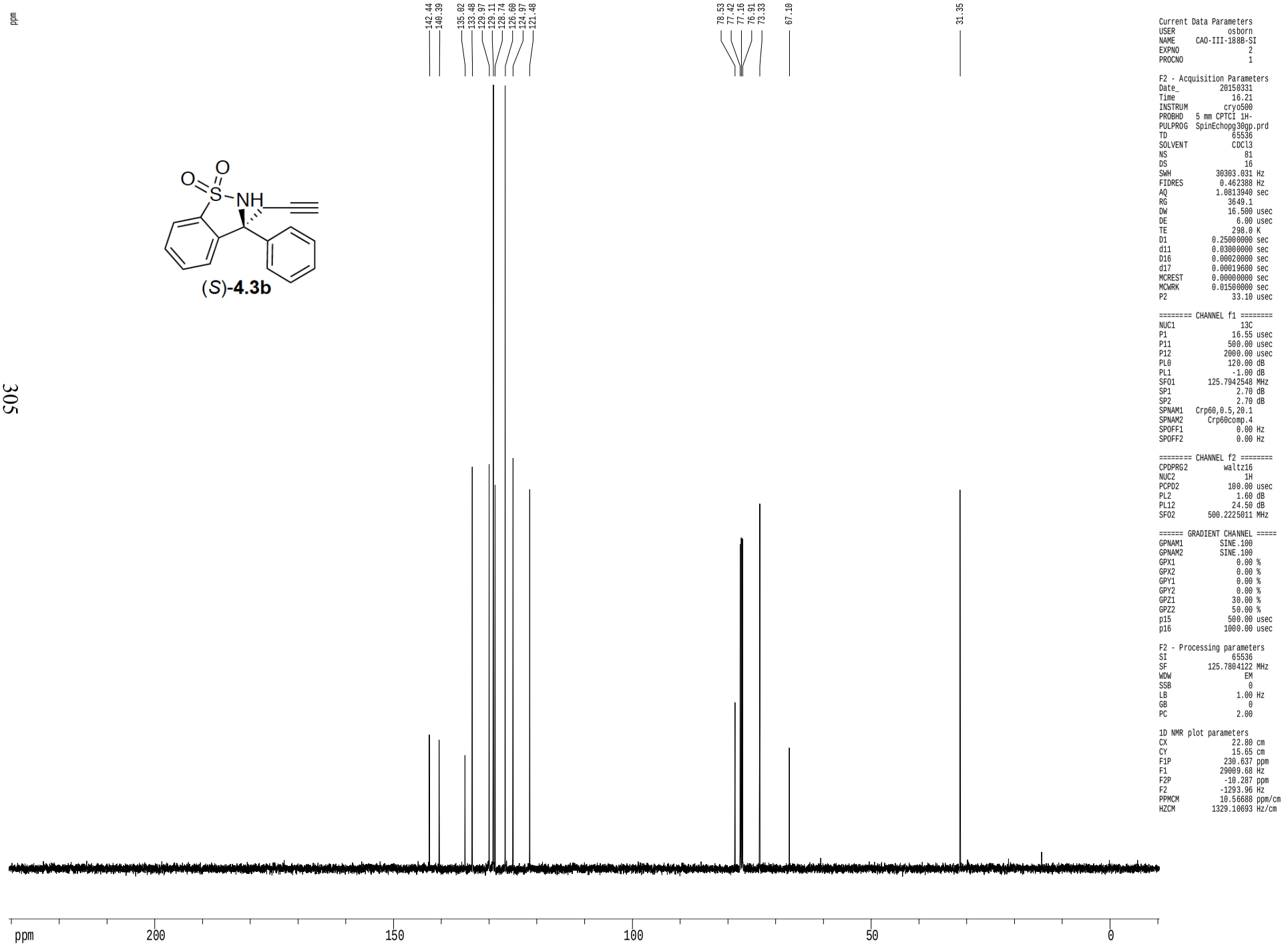
4.3a

303

```
Current Data Parameters
USER              osborn
NAME      CAO-III-75B-SI
EXPNO                  7
PROCNO                 1

F2 - Acquisition Parameters
Date_          20150526
Time              20.53
INSTRUM          drx400
PROBHD   5 mm QNP H/F/P
PULPROG      zgfhigqn30
TD                65536
SOLVENT           CDCl3
NS                   31
DS                    4
SWH           75187.969 Hz
FIDRES         1.147277 Hz
AQ             0.4358644 sec
RG                3649.1
DW                6.650 usec
DE                9.46 usec
TE                298.0 K
D1           2.00000000 sec
d11          0.03000000 sec
d12          0.00002000 sec

======== CHANNEL f1 ========
NUC1                 19F
P1                22.50 usec
PL1               -6.00 dB
SFO1        376.4646491 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             90.00 usec
PL2              120.00 dB
PL12              17.70 dB
SFO2        400.1320007 MHz

F2 - Processing parameters
SI                65536
SF          376.4983852 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                22.80 cm
CY                15.00 cm
F1P               1.000 ppm
F1              376.50 Hz
F2P            -190.000 ppm
F2           -71534.70 Hz
PPMCM          8.37719 ppm/cm
HZCM        3153.99976 Hz/cm
```

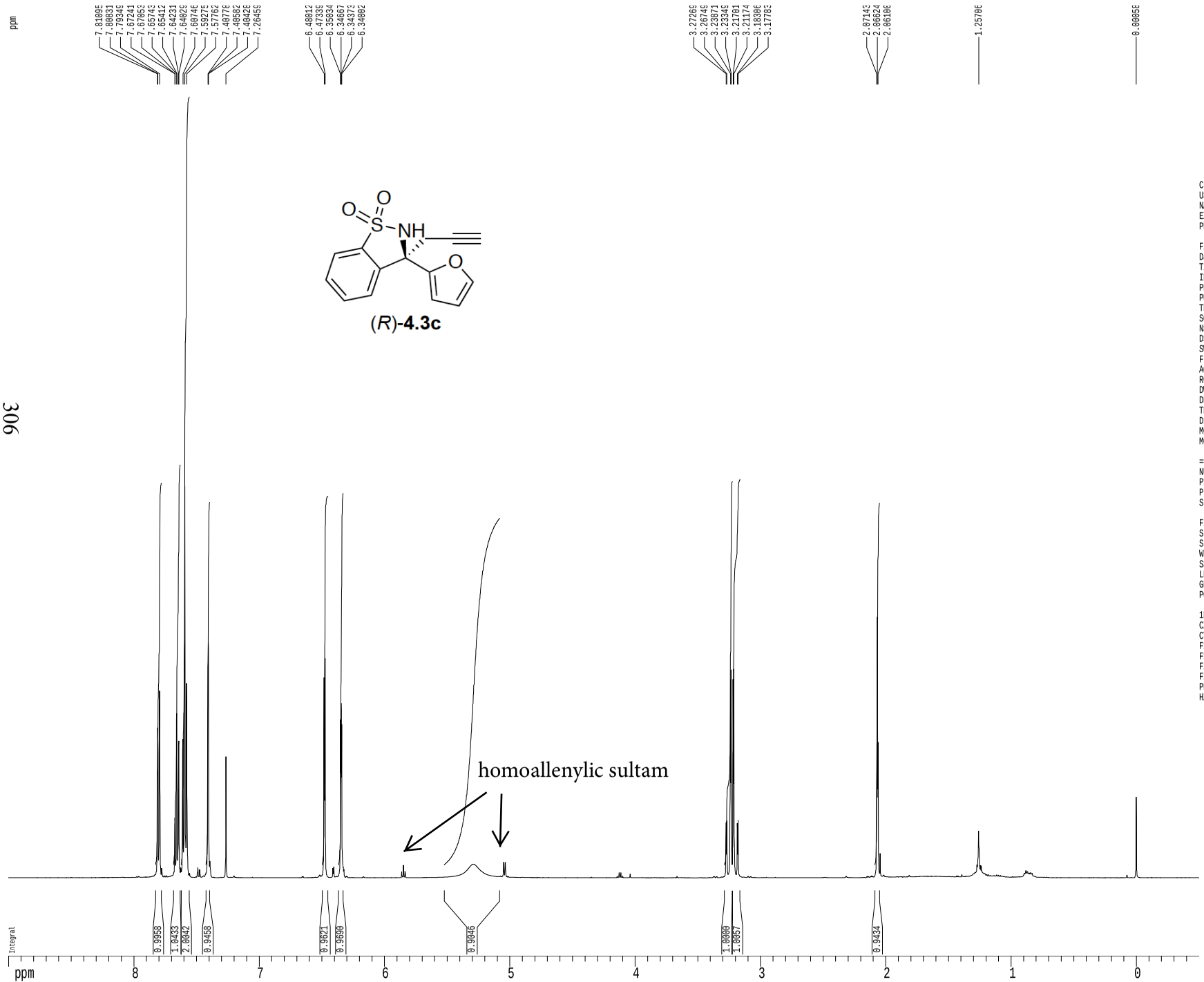

1H spectrum
(S)-4.3b
Current Data Parameters
USER osborn
NAME CAO-III-188B-SI
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150519
Time 13.16
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 203.2
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300212 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72086 Hz/cm
0.0001
1.2567
2.0643
2.0577
2.0512
3.2141
3.2287
3.2569
3.2636
3.2723
3.2786
3.3151
3.3216
5.3229
7.2589
7.3227
7.3423
7.3454
7.3489
7.3537
7.3562
7.3587
7.3639
7.3677
7.3736
7.3758
7.3775
7.3836
7.4003
7.4041
7.5362
7.5376
7.5389
7.5432
7.5534
7.5566
7.5603
7.5717
7.5753
7.5797
7.5837
7.5987
7.6022
7.7906
7.7936
7.8079
7.8103
7.8117
ppm
0.9676
1.0908
1.0000
0.9522
4.0573
3.0828
1.0109
0.9964
Integral
ppm

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME      CAO-III-188B-SI
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_             20150331
Time                 16.21
INSTRUM            cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                   65536
SOLVENT              CDCl3
NS                      81
DS                      16
SWH              30303.031 Hz
FIDRES           0.462388 Hz
AQ               1.0813940 sec
RG                 3649.1
DW                 16.500 usec
DE                  6.00 usec
TE                 298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec
P2                  33.10 usec

======== CHANNEL f1 ========
NUC1                   13C
P1                  16.55 usec
P11                500.00 usec
P12               2000.00 usec
PL0                120.00 dB
PL1                 -1.00 dB
SFO1          125.7942548 MHz
SP1                  2.70 dB
SP2                  2.70 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2       Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2             100.00 usec
PL2                 1.60 dB
PL12               24.50 dB
SFO2          500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPX1                 0.00 %
GPX2                 0.00 %
GPY1                 0.00 %
GPY2                 0.00 %
GPZ1                30.00 %
GPZ2                50.00 %
p15                500.00 usec
p16               1000.00 usec

F2 - Processing parameters
SI                   65536
SF            125.7804122 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   2.00

1D NMR plot parameters
CX                  22.80 cm
CY                  15.65 cm
F1P               230.637 ppm
F1                29009.68 Hz
F2P               -10.287 ppm
F2                -1293.96 Hz
PPMCM             10.56688 ppm/cm
HZCM           1329.10693 Hz/cm
```

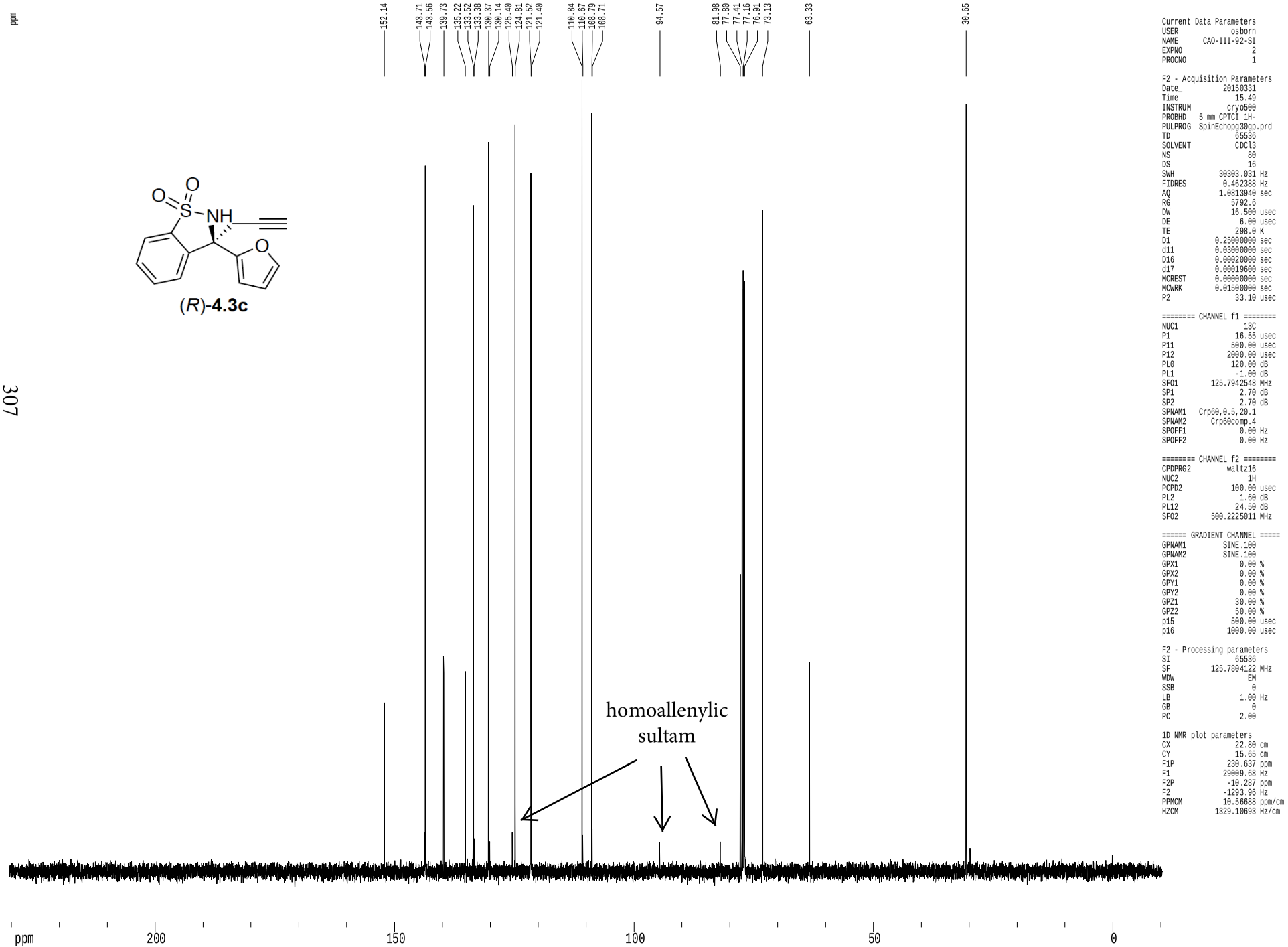
1H spectrum



306

```
Current Data Parameters
USER                osborn
NAME       CAO-III-92-SI
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20150331
Time               15.47
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG              zg30
TD                  81728
SOLVENT             CDCl3
NS                      8
DS                      2
SWH              8012.820 Hz
FIDRES           0.098043 Hz
AQ               5.0998774 sec
RG                      5
DW                 62.400 usec
DE                  6.00 usec
TE                298.0 K
D1              0.10000000 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 =======
NUC1                   1H
P1                  7.50 usec
PL1                 1.60 dB
SFO1          500.2235015 MHz

F2 - Processing parameters
SI                  65536
SF            500.2200287 MHz
WDW                    EM
SSB                     0
LB                  0.30 Hz
GB                      0
PC                  4.00

1D NMR plot parameters
CX                 22.80 cm
CY                  7.50 cm
F1P                9.000 ppm
F1               4501.98 Hz
F2P               -0.500 ppm
F2               -250.11 Hz
PPMCM            0.41667 ppm/cm
HZCM           208.42502 Hz/cm
```

Z-restored spin-echo 13C spectrum with 1H decoupling



307

Current Data Parameters
USER osborn
NAME CAO-III-92-SI
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150331
Time 15.49
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 80
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 5792.6
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 33.10 usec

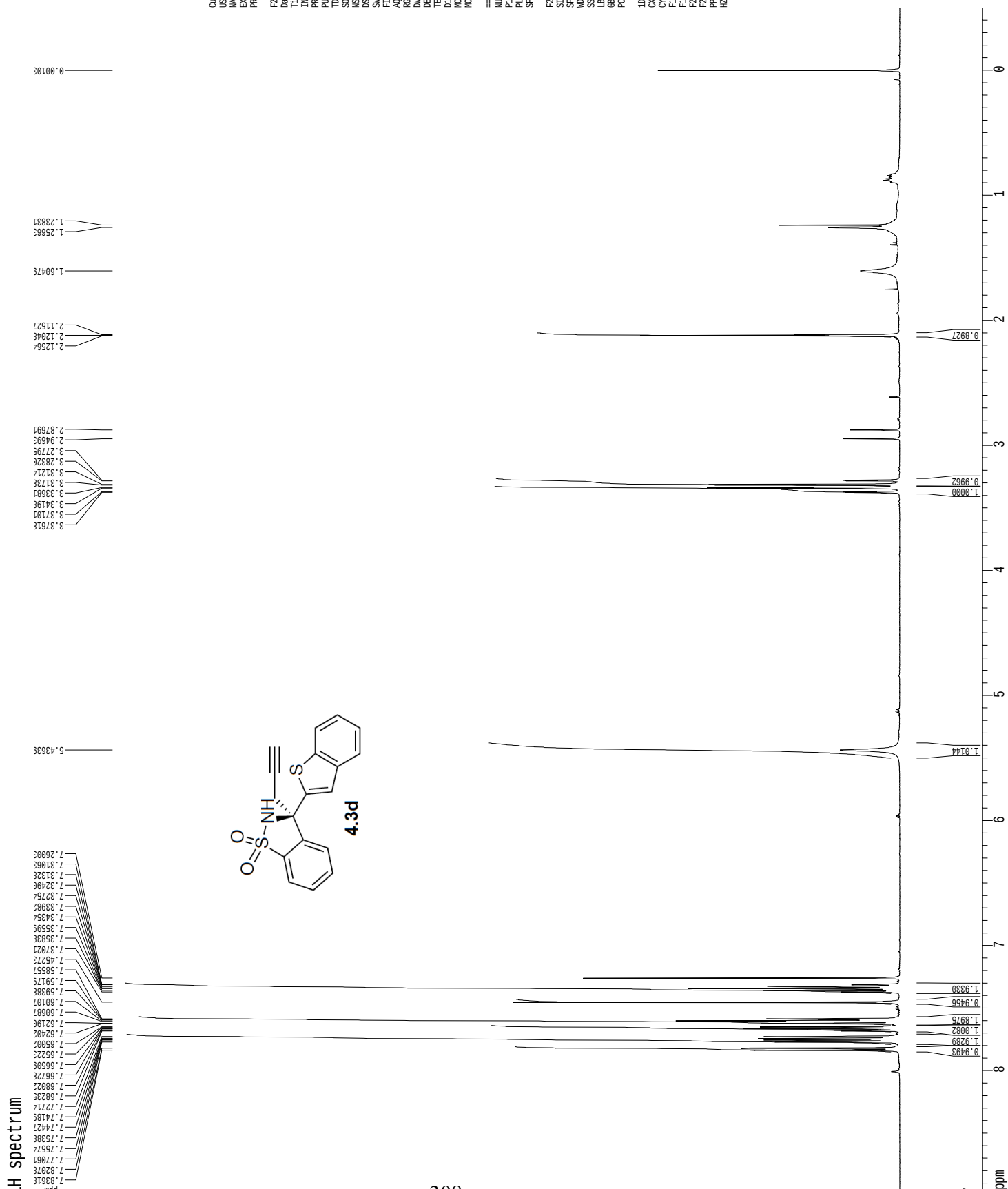
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz

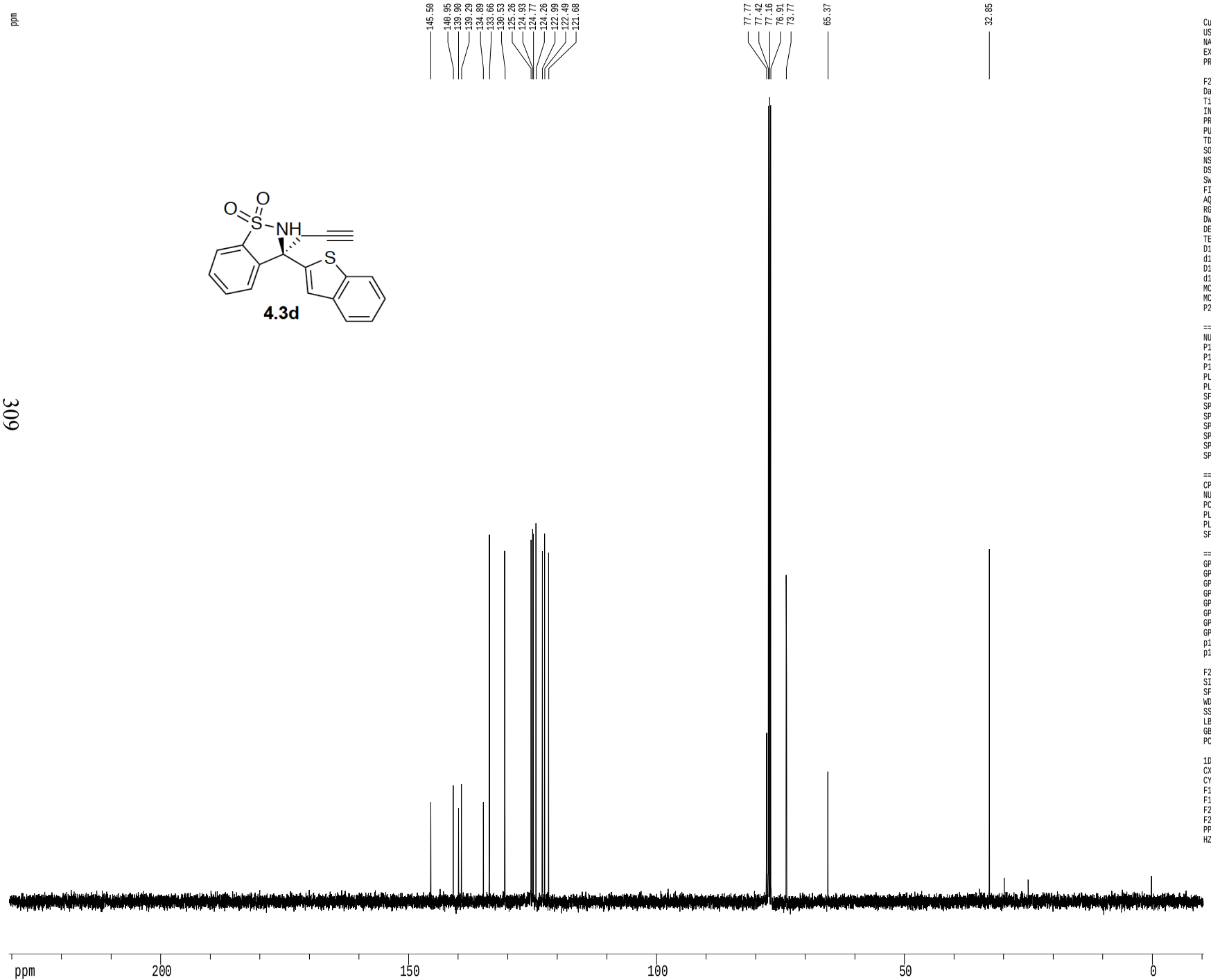
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 125.7804122 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm


1H spectrum
4.3d
Current Data Parameters
USER osborn
NAME CAO-III-196-SI
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150515
Time 19.16
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0999774 sec
RG 3.6
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200313 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
1D NMR plot parameters
CX 22.80 cm
CY 7.50 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm
0.00103
1.23831
1.25663
1.60479
2.11527
2.12048
2.12564
2.87691
2.94693
3.27796
3.28326
3.31214
3.31736
3.33681
3.34198
3.37101
3.37618
5.43639
7.26003
7.31063
7.31326
7.32496
7.32754
7.33982
7.34354
7.35599
7.35838
7.37021
7.45273
7.58557
7.59175
7.59386
7.60107
7.60687
7.62196
7.62402
7.65002
7.65223
7.66509
7.66726
7.68022
7.68236
7.72174
7.74185
7.74427
7.75386
7.75574
7.77061
7.82076
7.83618
0.8927
0.9962
1.0000
1.0144
1.9330
0.9456
1.8975
1.0082
1.9289
0.9493
ppm
Integral

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME CAO-III-196-SI
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150515
Time 19.19
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 215
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 7298.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 33.10 usec

======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

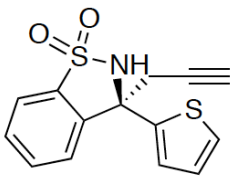
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

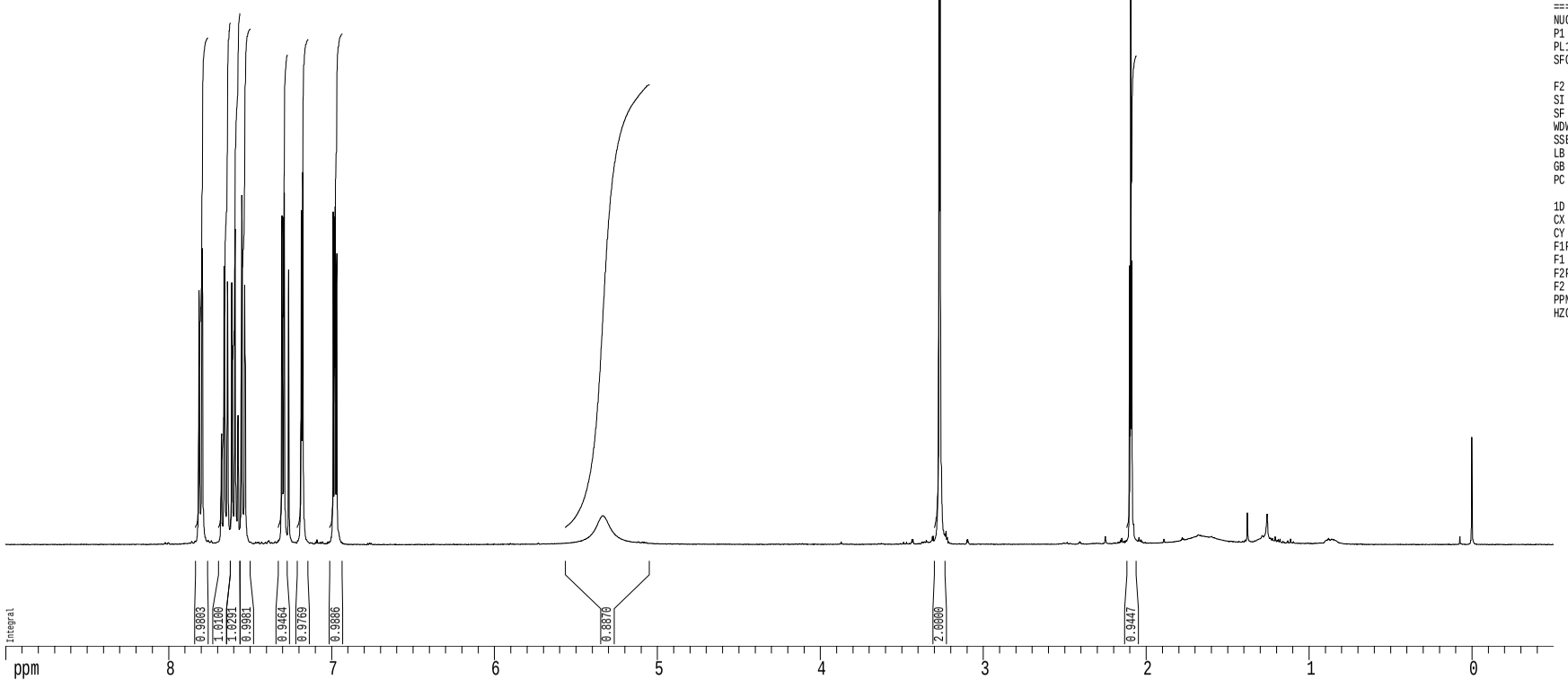
F2 - Processing parameters
SI 65536
SF 125.7804094 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm

1H spectrum



(R)-**4.3e**



Current Data Parameters
USER osborn
NAME CAO-III-81B-SI
EXPNO 2
PROCNO 1

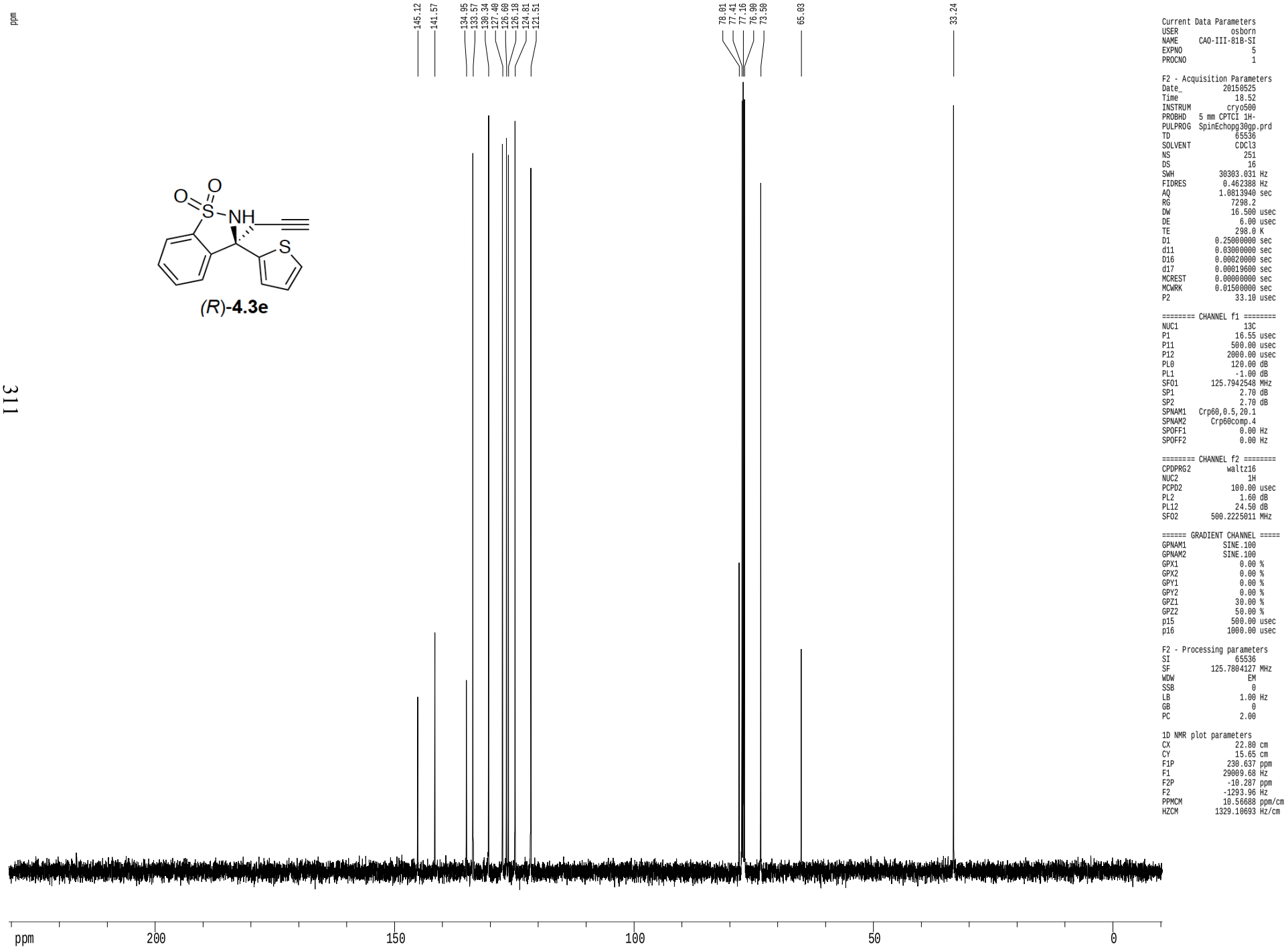
F2 - Acquisition Parameters
Date_ 20150525
Time 18.04
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 228.1
DW 78.000 usec
DE 4.50 usec
TE 295.8 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz

F2 - Processing parameters
SI 65536
SF 400.1300198 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME CAO-III-81B-SI
EXPNO 5
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150525
Time 18.52
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 251
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 7298.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 33.10 usec

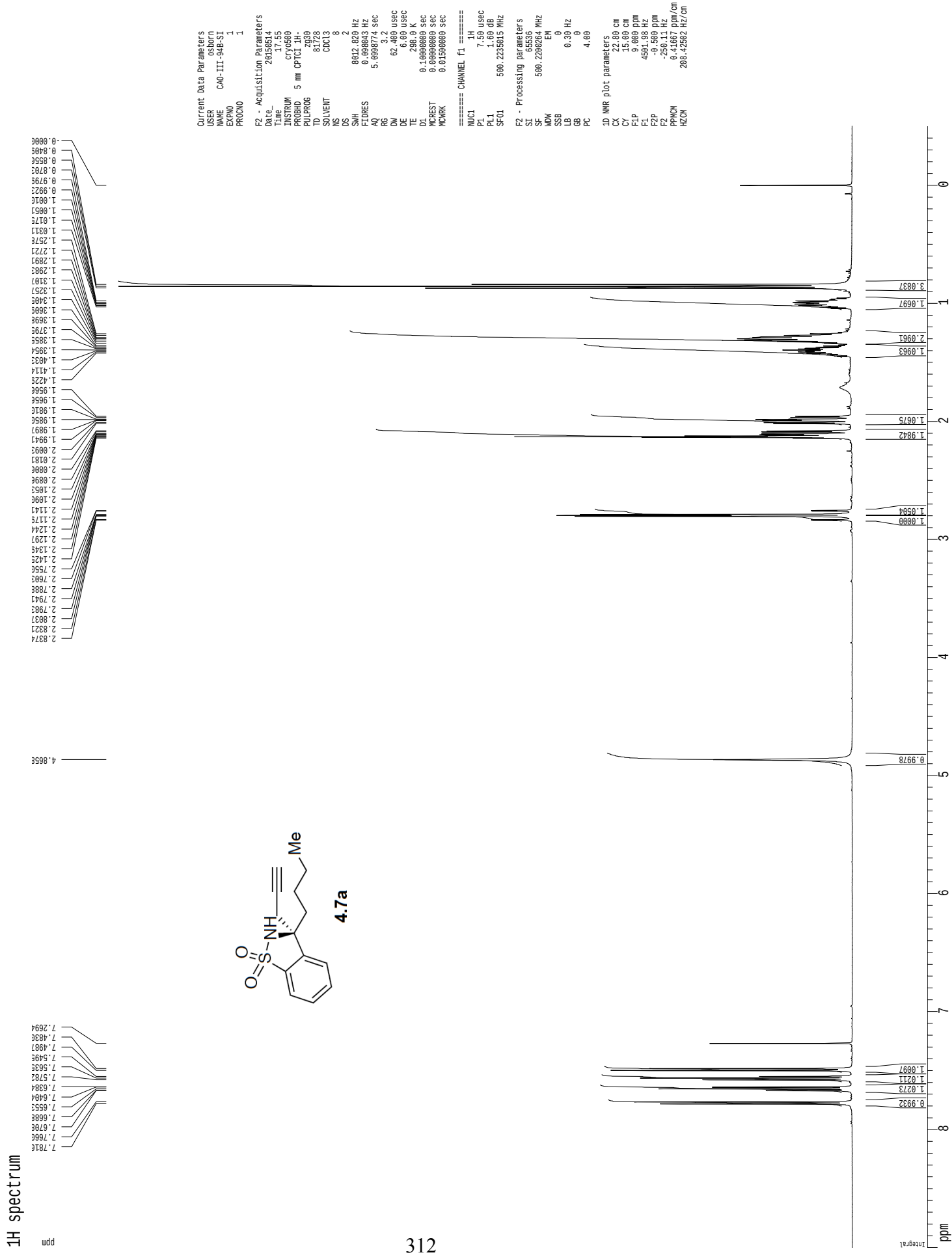
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz

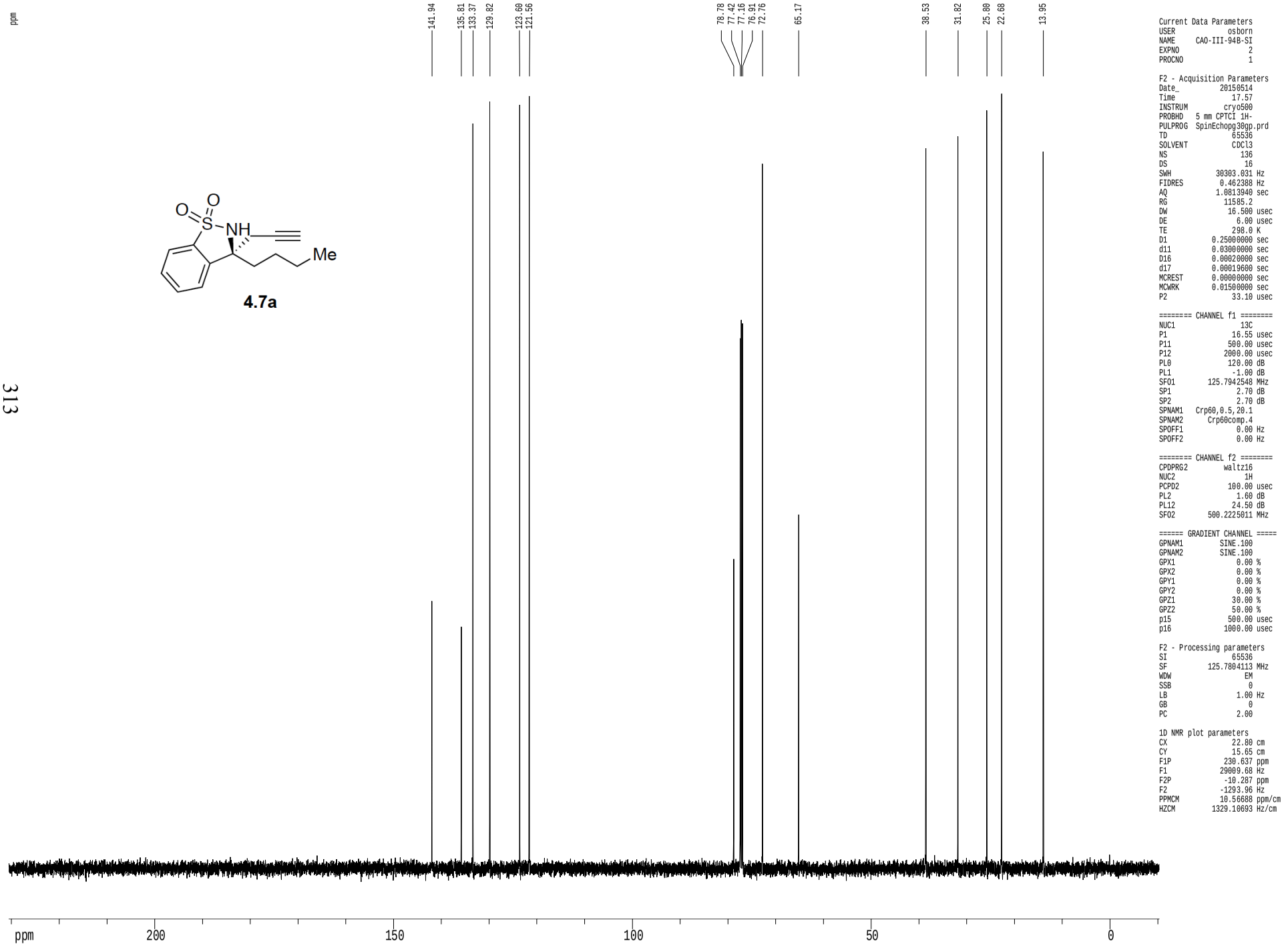
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 125.7804127 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm


1H spectrum
Current Data Parameters
USER osborn
NAME CAO-III-94B-SI
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150514
Time 17.55
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 3.2
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200264 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F2P -0.500 ppm
F1 4501.98 Hz
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm
Me
NH
O
O
S
4.7a
ppm
Integral

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME CAO-III-94B-SI
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150514
Time 17.57
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 136
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 11585.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 33.10 usec

======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

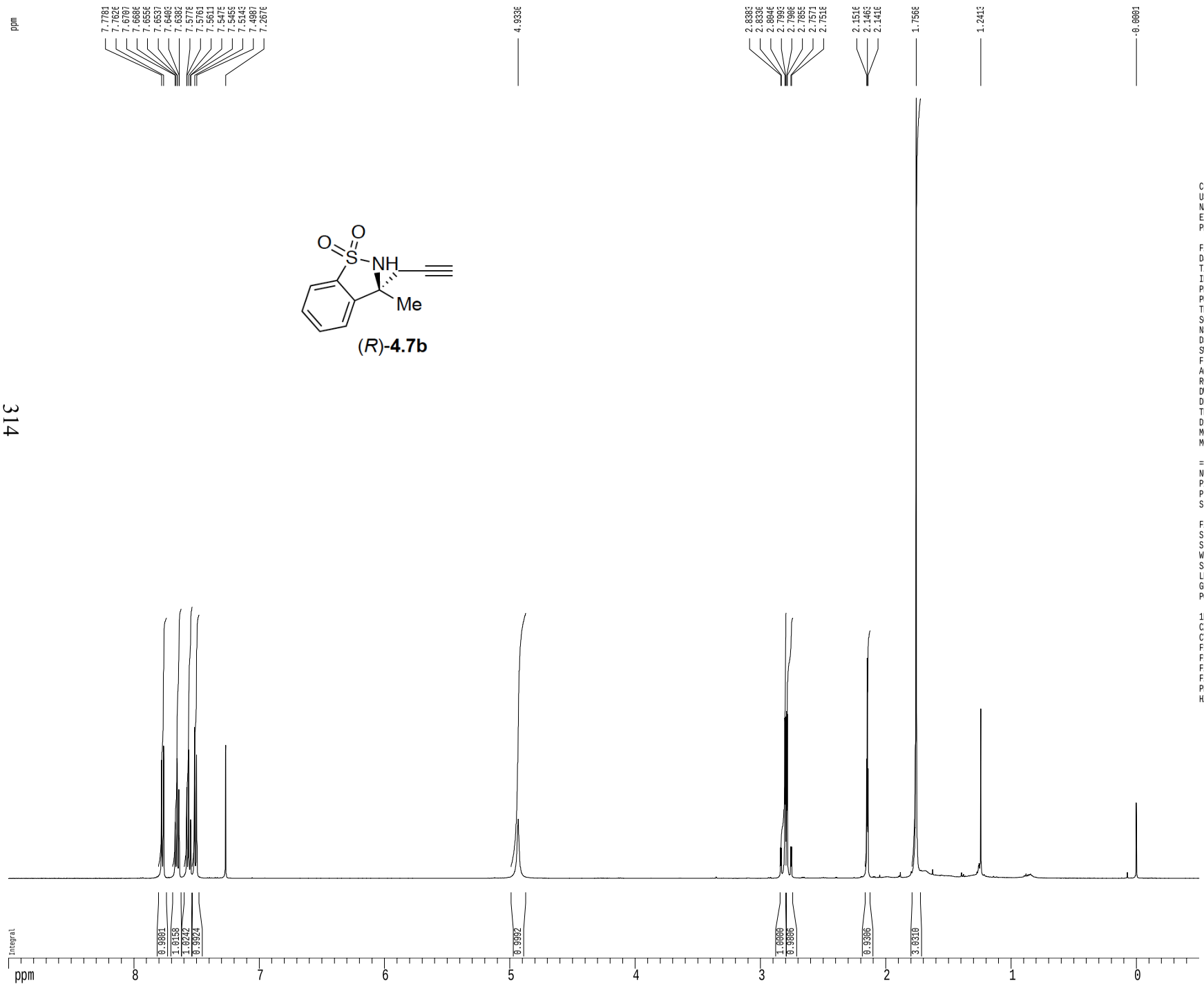
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 125.7804113 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm

1H spectrum



Current Data Parameters
USER osborn
NAME CAO-III-124B-SI
EXPNO 3
PROCNO 1

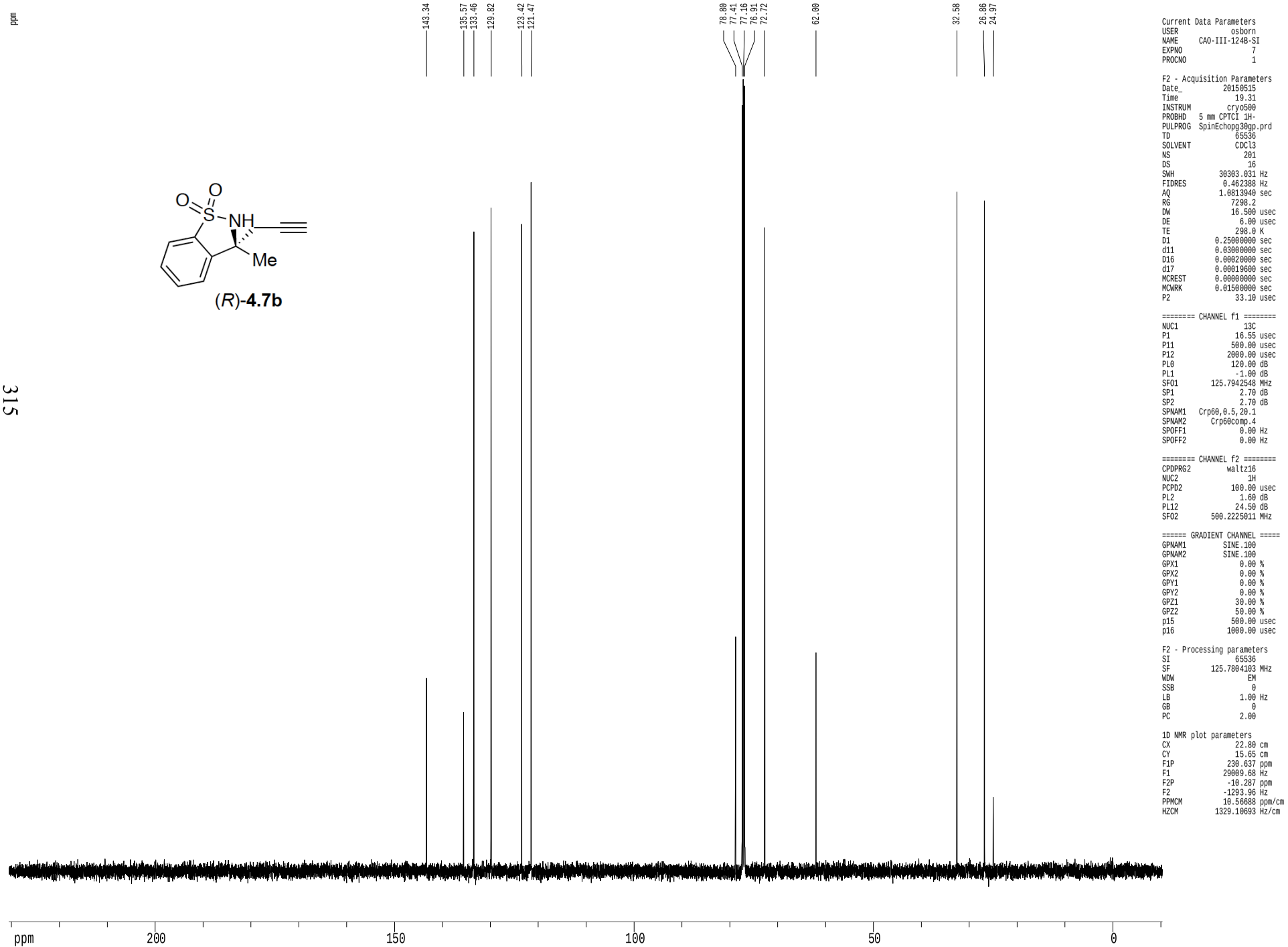
F2 - Acquisition Parameters
Date_ 20150515
Time 16.42
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

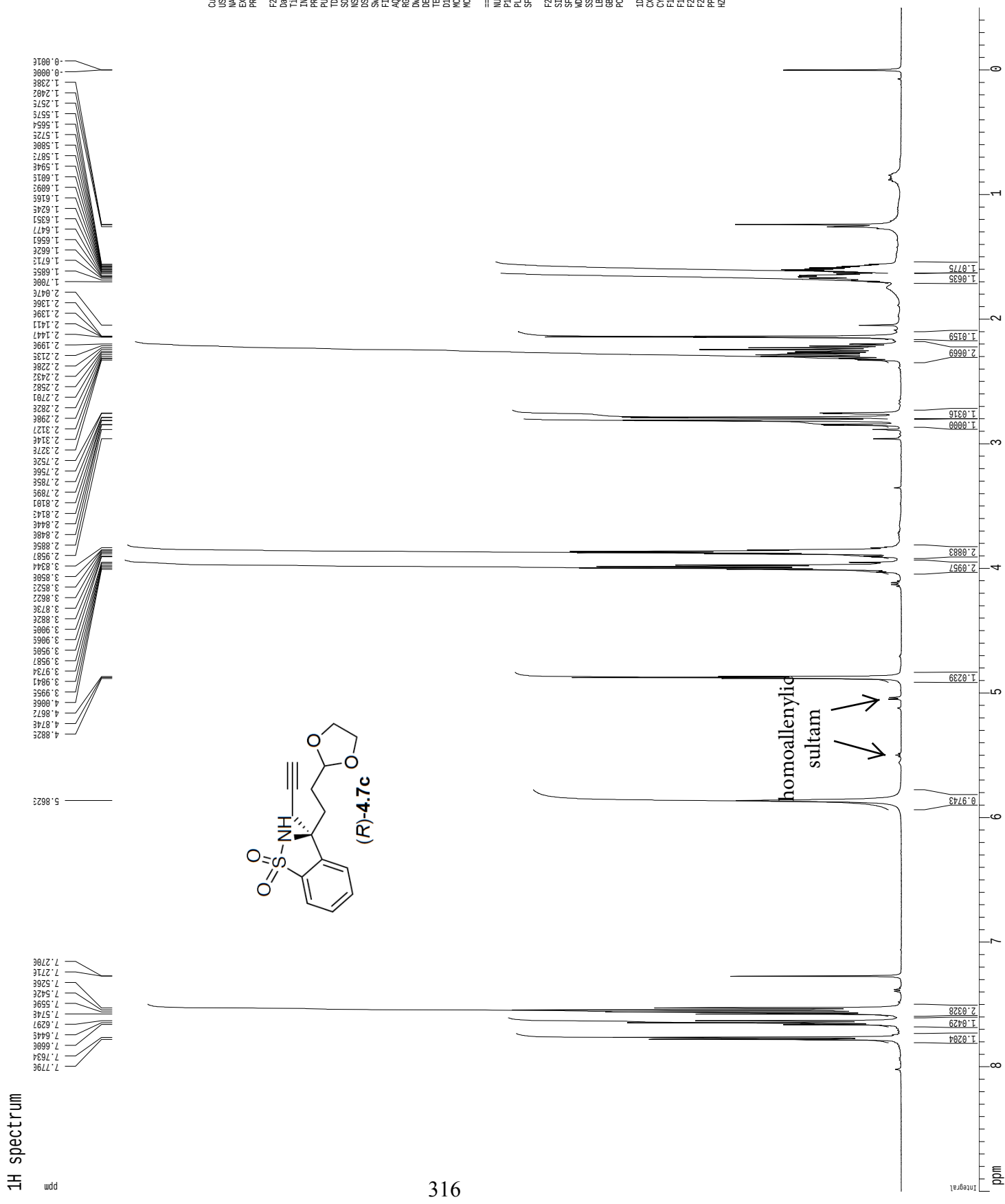
======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz

F2 - Processing parameters
SI 65536
SF 500.2200275 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

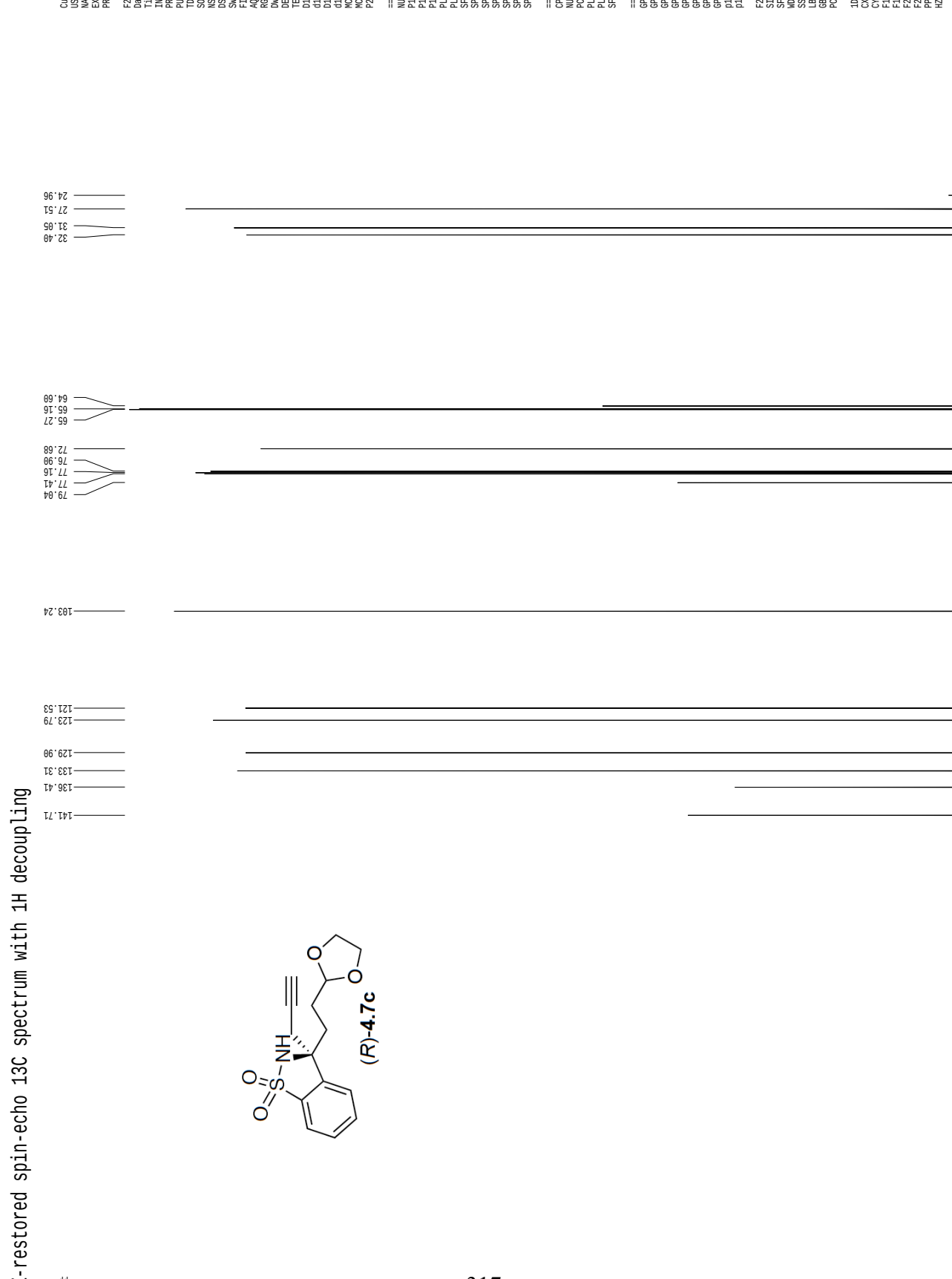
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm

Z-restored spin-echo 13C spectrum with 1H decoupling

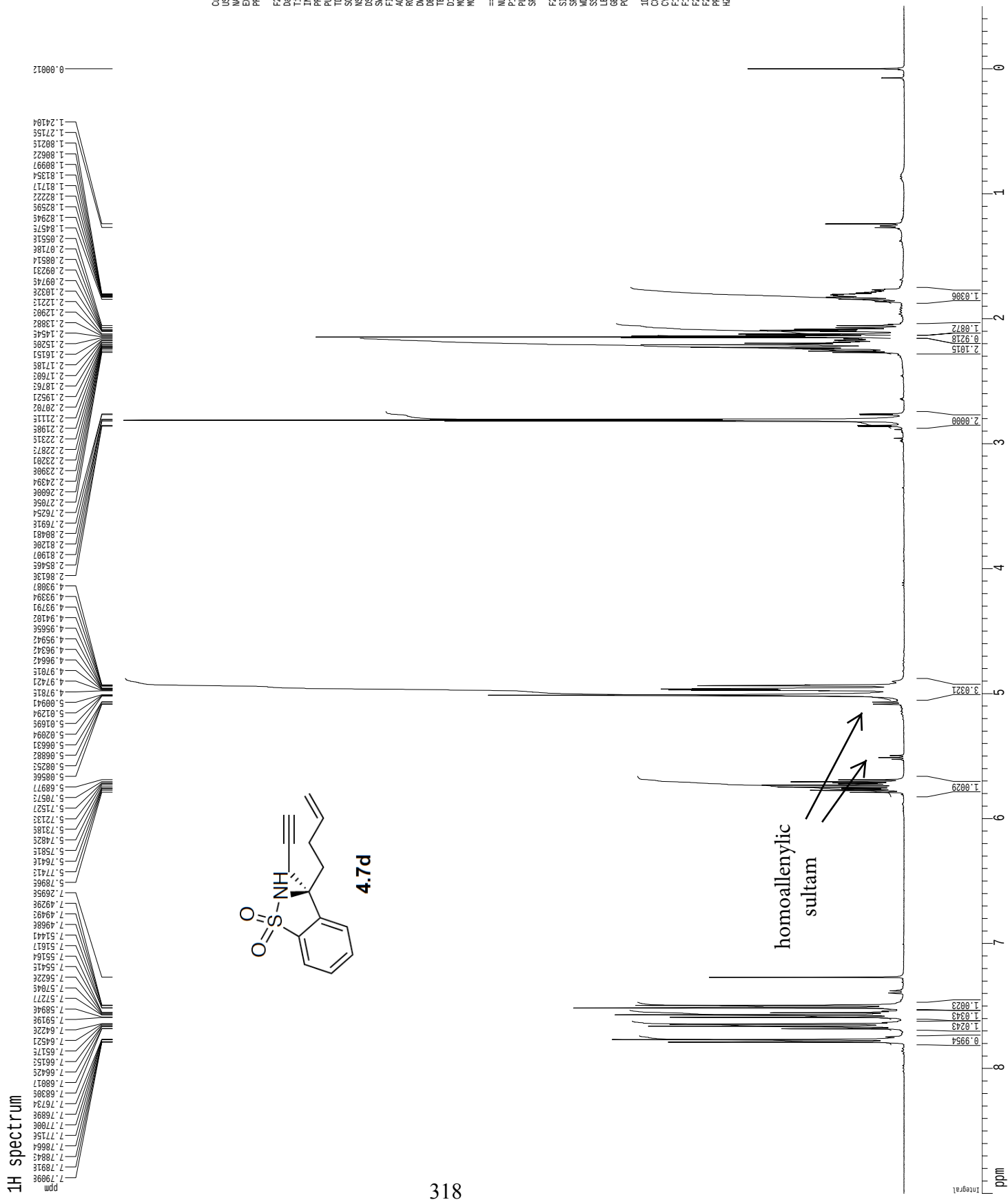



1H spectrum
Current Data Parameters
USER osborn
NAME CAO-III-123B-SI
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150331
Time 16.06
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0999774 sec
RG 4.5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200253 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
1D NMR plot parameters
CX 22.80 cm
CY 7.50 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm
homoallenylic sultam
(R)-4.7c
ppm
Integral

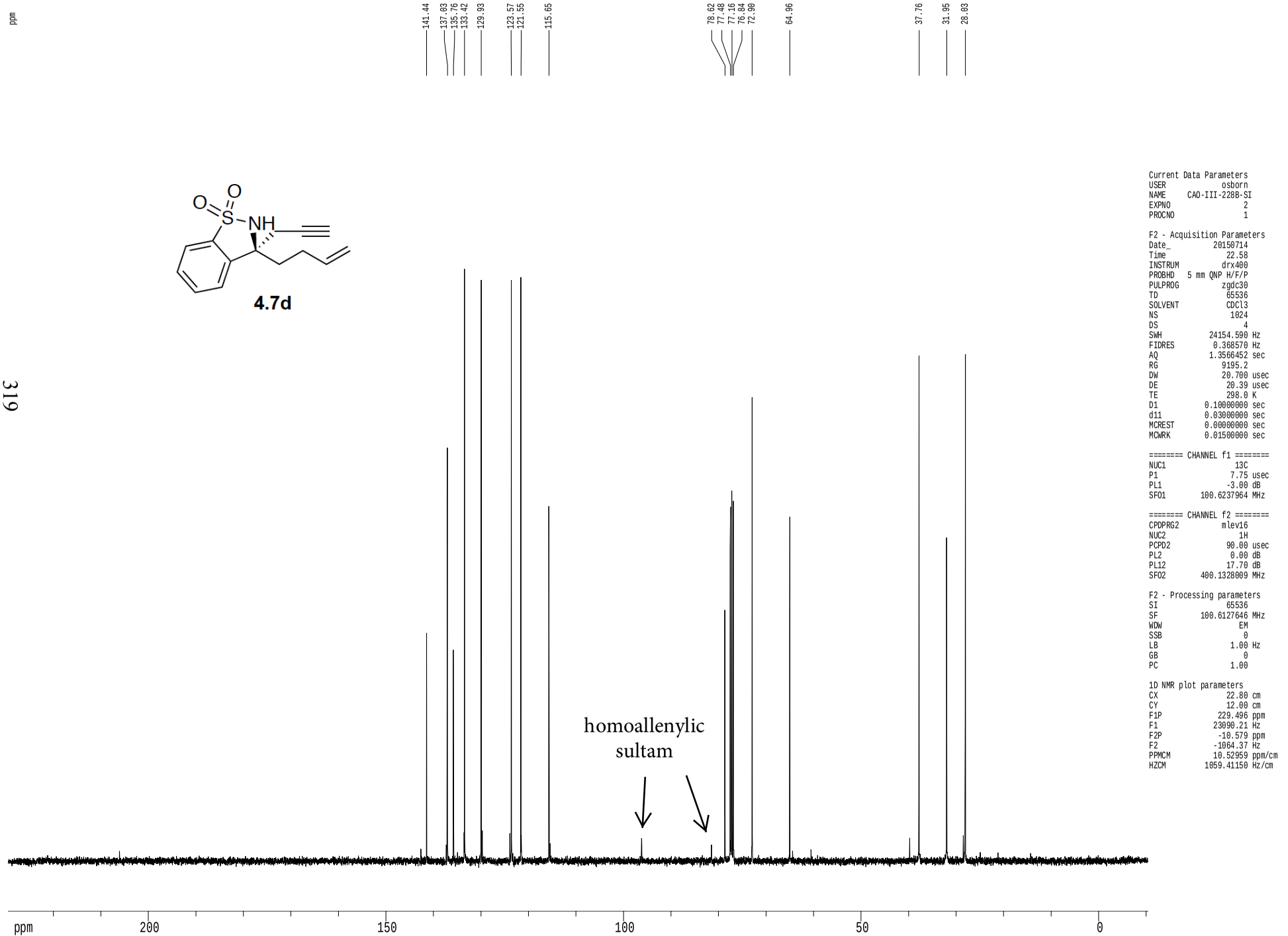
Z-restored spin-echo 13C spectrum with 1H decoupling



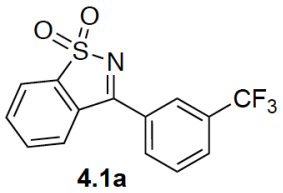
(*R*)-**4.7c**


1H spectrum
Current Data Parameters
USER osborn
NAME CAO-III-228B-SI
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150715
Time 9.17
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 128
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300178 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm
4.7d
homoallenylic
sultam
ppm
Integral

z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



4.1a

320

Current Data Parameters
USER osborn
NAME CAO-III-26-pure
EXPNO 1
PROCNO 1

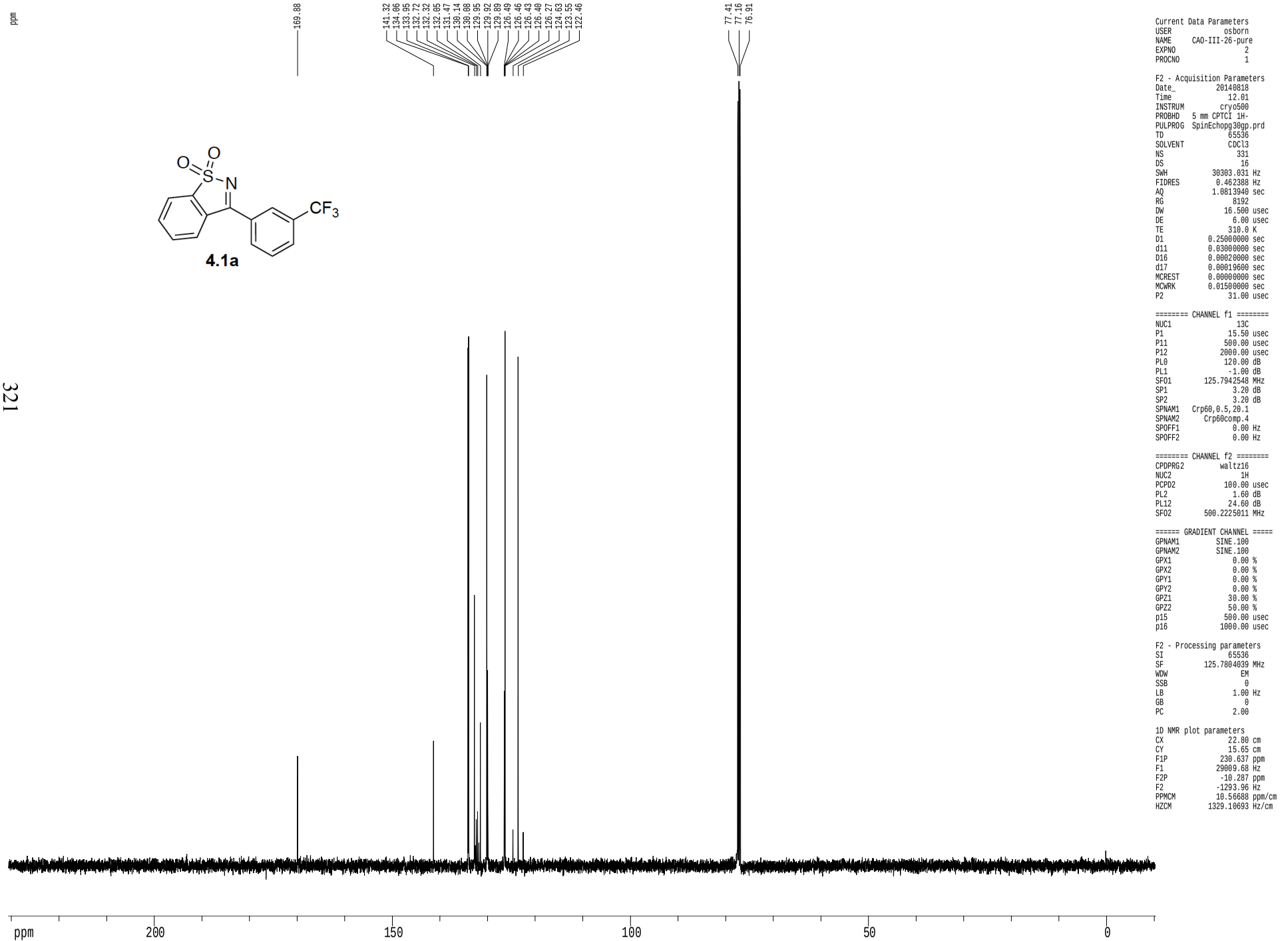
F2 - Acquisition Parameters
Date_ 20140818
Time 11.59
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 6.3
DW 62.400 usec
DE 6.00 usec
TE 310.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz

F2 - Processing parameters
SI 65536
SF 500.2200319 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

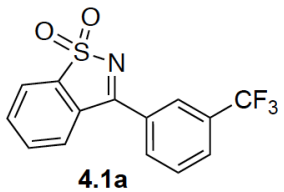
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME      CAO-III-26-pure
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_           20140818
Time               12.01
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                 65536
SOLVENT            CDCl3
NS                   331
DS                    16
SWH            30303.031 Hz
FIDRES         0.462388 Hz
AQ             1.0813940 sec
RG                  8192
DW                16.500 usec
DE                 6.00 usec
TE                310.0 K
D1             0.25000000 sec
d11            0.03000000 sec
D16            0.00020000 sec
d17            0.00019600 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec
P2                31.00 usec

======== CHANNEL f1 ========
NUC1                 13C
P1                15.50 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1                3.20 dB
SP2                3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7804039 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   2.00

1D NMR plot parameters
CX                  22.80 cm
CY                  15.65 cm
F1P              230.637 ppm
F1              29009.68 Hz
F2P              -10.287 ppm
F2              -1293.96 Hz
PPMCM            10.56688 ppm/cm
HZCM          1329.10693 Hz/cm
```

19F spectrum with 1H decoupling

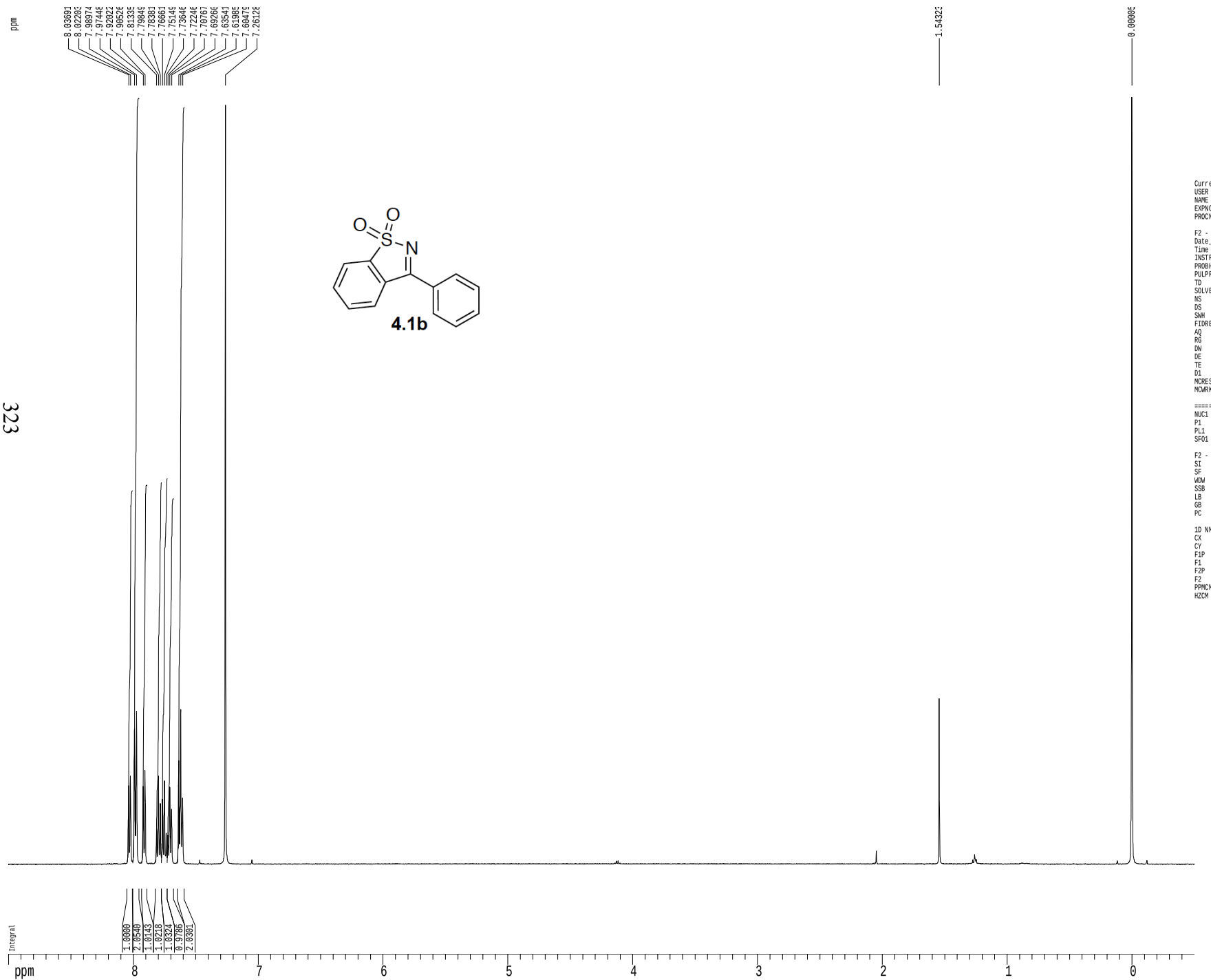


4.1a

322


```
Current Data Parameters
USER             osborn
NAME       CAO-III-26-SI
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20150530
Time              19.49
INSTRUM           drx400
PROBHD   5 mm QNP H/F/P
PULPROG       zgfhigqn30
TD                65536
SOLVENT           CDCl3
NS                   31
DS                    4
SWH           75187.969 Hz
FIDRES         1.147277 Hz
AQ             0.4358644 sec
RG                3649.1
DW                6.650 usec
DE                9.46 usec
TE                298.0 K
D1            2.00000000 sec
d11           0.03000000 sec
d12           0.00002000 sec

======== CHANNEL f1 ========
NUC1                 19F
P1                22.50 usec
PL1               -6.00 dB
SFO1         376.4646491 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             90.00 usec
PL2              120.00 dB
PL12              17.70 dB
SFO2         400.1320007 MHz

F2 - Processing parameters
SI                65536
SF           376.4983851 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX                22.80 cm
CY                15.00 cm
F1P               1.000 ppm
F1               376.50 Hz
F2P            -190.000 ppm
F2           -71534.70 Hz
PPMCM          8.37719 ppm/cm
HZCM         3153.99976 Hz/cm
```

1H spectrum

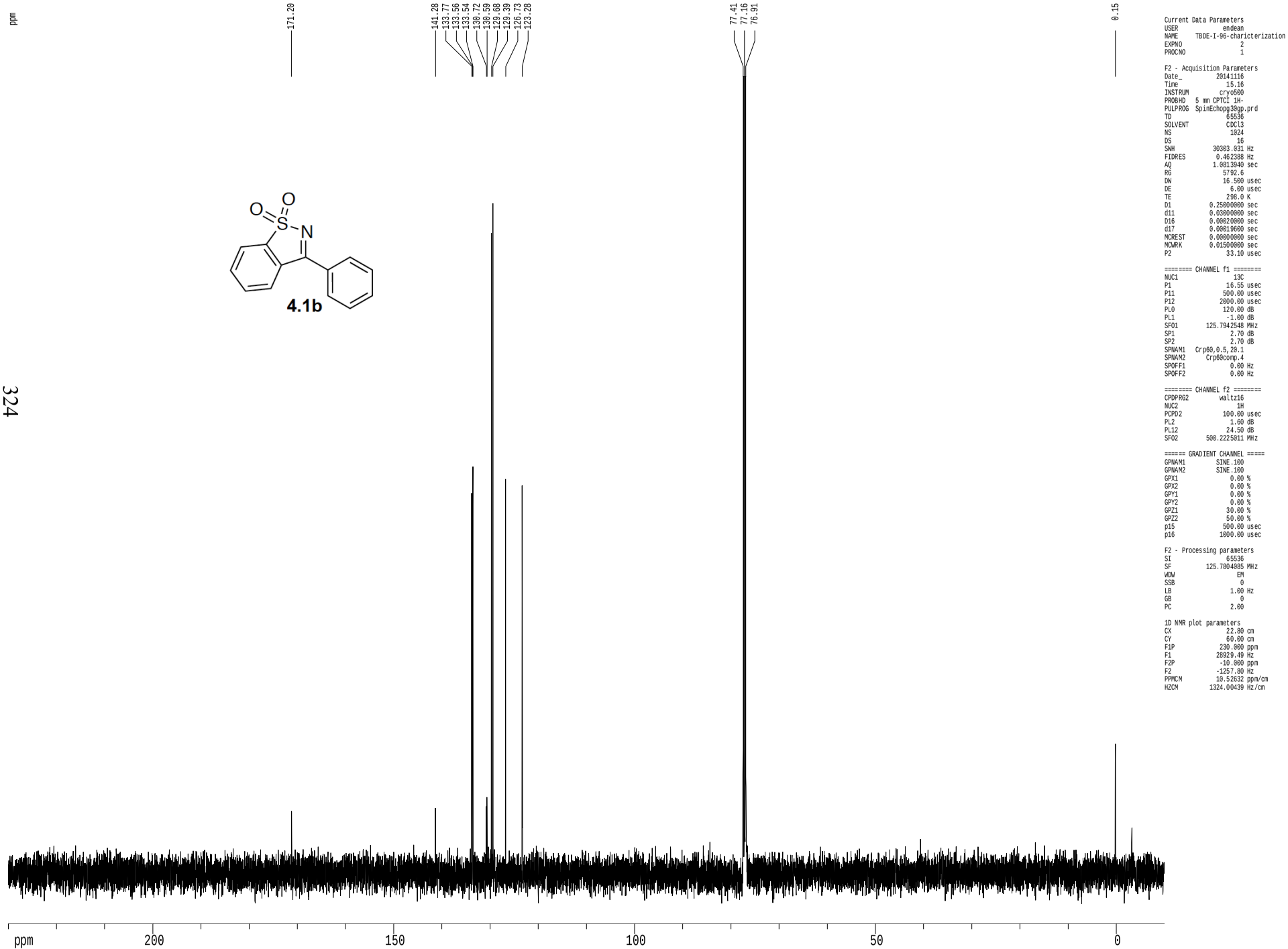


4.1b

323

```
Current Data Parameters
USER              endean
NAME      TBDE-I-96-charicterization
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_          20141116
Time              15.12
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                81728
SOLVENT           CDCl3
NS                    8
DS                    2
SWH            8012.820 Hz
FIDRES         0.098043 Hz
AQ             5.0998774 sec
RG                  5.7
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1           0.10000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                1H
P1                 7.50 usec
PL1                1.60 dB
SFO1         500.2235015 MHz

F2 - Processing parameters
SI                65536
SF           500.2200327 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 4.00

1D NMR plot parameters
CX                22.80 cm
CY                15.00 cm
F1P               9.000 ppm
F1              4501.98 Hz
F2P              -0.500 ppm
F2              -250.11 Hz
PPMCM          0.41667 ppm/cm
HZCM         208.42502 Hz/cm
```

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER endean
NAME TBDE-I-96-charicterization
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20141116
Time 15.16
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 1024
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 5792.6
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 33.10 usec

======= CHANNEL f1 =======
NUC1 13C
P1 16.55 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

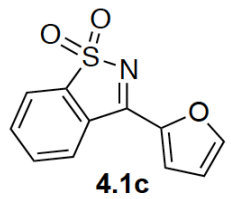
======== CHANNEL f2 =======
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz

====== GRADIENT CHANNEL ====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 125.7804085 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 60.00 cm
F1P 230.000 ppm
F1 28929.49 Hz
F2P -10.000 ppm
F2 -1257.80 Hz
PPMCM 10.52632 ppm/cm
HZCM 1324.00439 Hz/cm

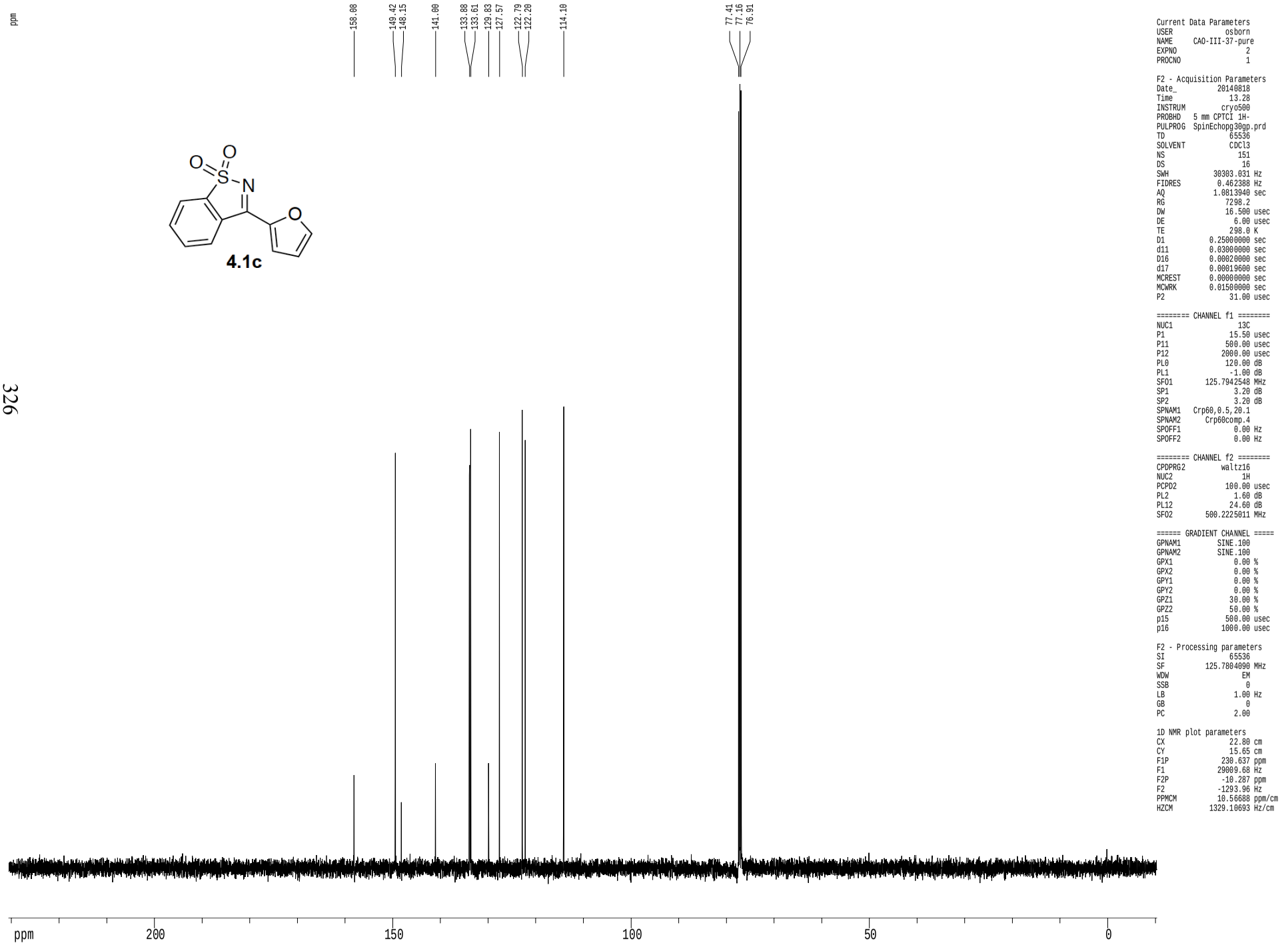
1H spectrum



4.1c

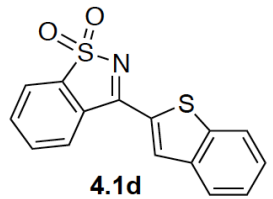

```
Current Data Parameters
USER                osborn
NAME      CAO-III-37-pure
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_            20140818
Time                13.26
INSTRUM           cryo500
PROBHD    5 mm CPTCI 1H-
PULPROG               zg30
TD                   81728
SOLVENT              CDCl3
NS                       8
DS                       2
SWH              8012.820 Hz
FIDRES           0.098043 Hz
AQ               5.0998774 sec
RG                     6.3
DW                62.400 usec
DE                 6.00 usec
TE                 298.0 K
D1              0.10000000 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 =======
NUC1                    1H
P1                   7.50 usec
PL1                  1.60 dB
SFO1          500.2235015 MHz

F2 - Processing parameters
SI                   65536
SF            500.2200292 MHz
WDW                     EM
SSB                      0
LB                   0.30 Hz
GB                       0
PC                   4.00

1D NMR plot parameters
CX                   22.80 cm
CY                   15.00 cm
F1P                  9.000 ppm
F1                 4501.98 Hz
F2P                 -0.500 ppm
F2                 -250.11 Hz
PPMCM             0.41667 ppm/cm
HZCM            208.42502 Hz/cm
```

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME      CAO-III-37-pure
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_            20140818
Time                13.28
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                  65536
SOLVENT             CDCl3
NS                    151
DS                     16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.0813940 sec
RG                 7298.2
DW                16.500 usec
DE                 6.00 usec
TE                 298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec
P2                 31.00 usec

======== CHANNEL f1 ========
NUC1                  13C
P1                 15.50 usec
P11               500.00 usec
P12              2000.00 usec
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MHz
SP1                3.20 dB
SP2                3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12               24.60 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7804090 MHz
WDW                    EM
SSB                     0
LB                 1.00 Hz
GB                      0
PC                 2.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.65 cm
F1P              230.637 ppm
F1               29009.68 Hz
F2P              -10.287 ppm
F2               -1293.96 Hz
PPMCM            10.56688 ppm/cm
HZCM          1329.10693 Hz/cm
```

1H spectrum



Current Data Parameters
USER osborn
NAME CAO-III-184-SI
EXPNO 3
PROCNO 1

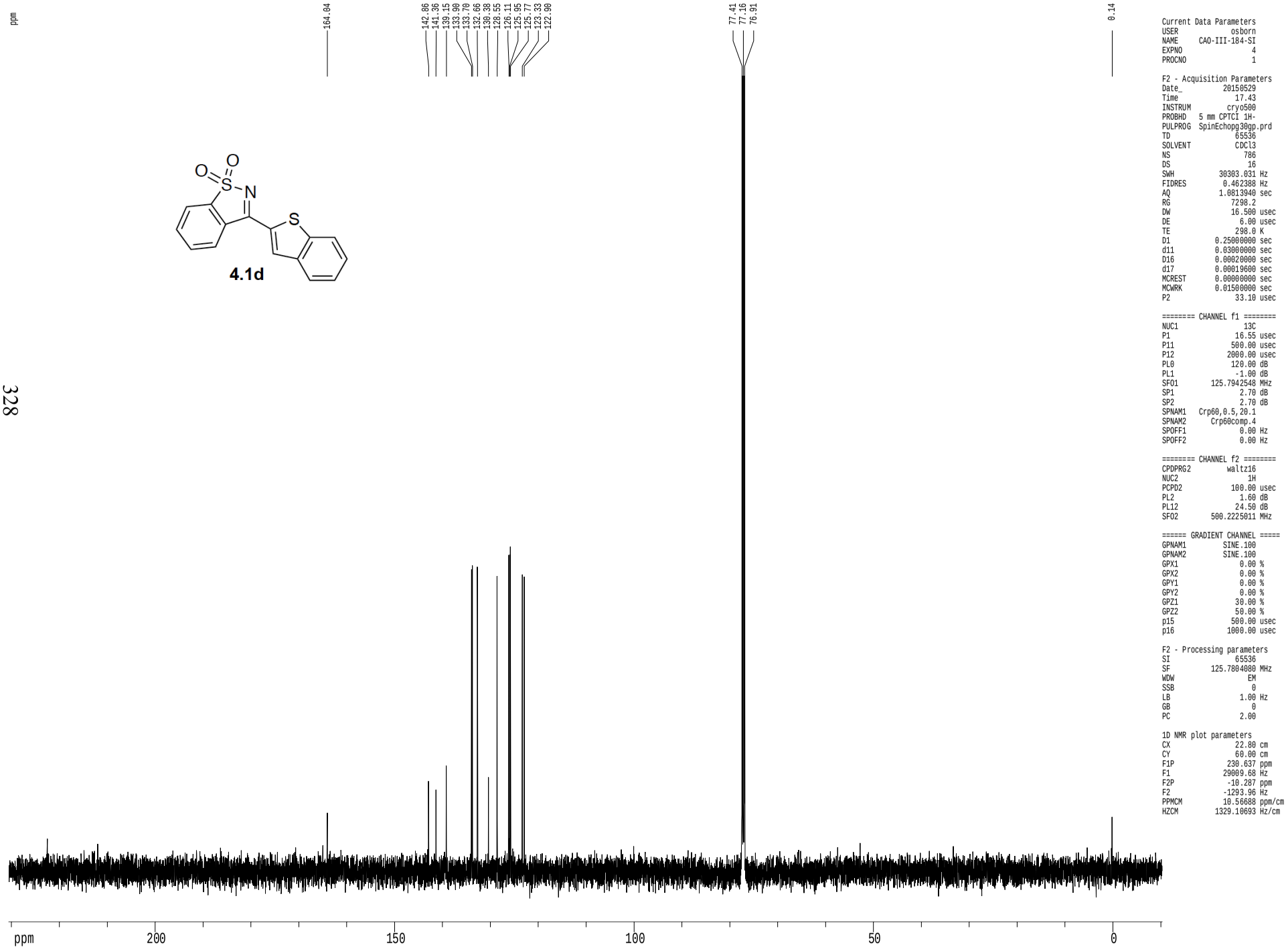
F2 - Acquisition Parameters
Date_ 20150529
Time 17.41
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 6.3
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz

F2 - Processing parameters
SI 65536
SF 500.2200309 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

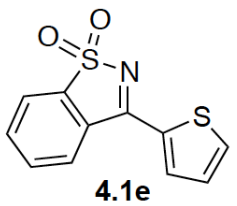
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME      CAO-III-184-SI
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
Date_           20150529
Time              17.43
INSTRUM          cry0500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                65536
SOLVENT           CDCl3
NS                  786
DS                   16
SWH           30303.031 Hz
FIDRES         0.462388 Hz
AQ             1.0813940 sec
RG                7298.2
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1             0.25000000 sec
d11            0.03000000 sec
D16            0.00020000 sec
d17            0.00019600 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec
P2                33.10 usec

======== CHANNEL f1 ========
NUC1                 13C
P1                16.55 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1                2.70 dB
SP2                2.70 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15              500.00 usec
p16             1000.00 usec

F2 - Processing parameters
SI                 65536
SF           125.7804080 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  2.00

1D NMR plot parameters
CX                 22.80 cm
CY                 60.00 cm
F1P              230.637 ppm
F1               29009.68 Hz
F2P              -10.287 ppm
F2               -1293.96 Hz
PPMCM            10.56688 ppm/cm
HZCM          1329.10693 Hz/cm
```

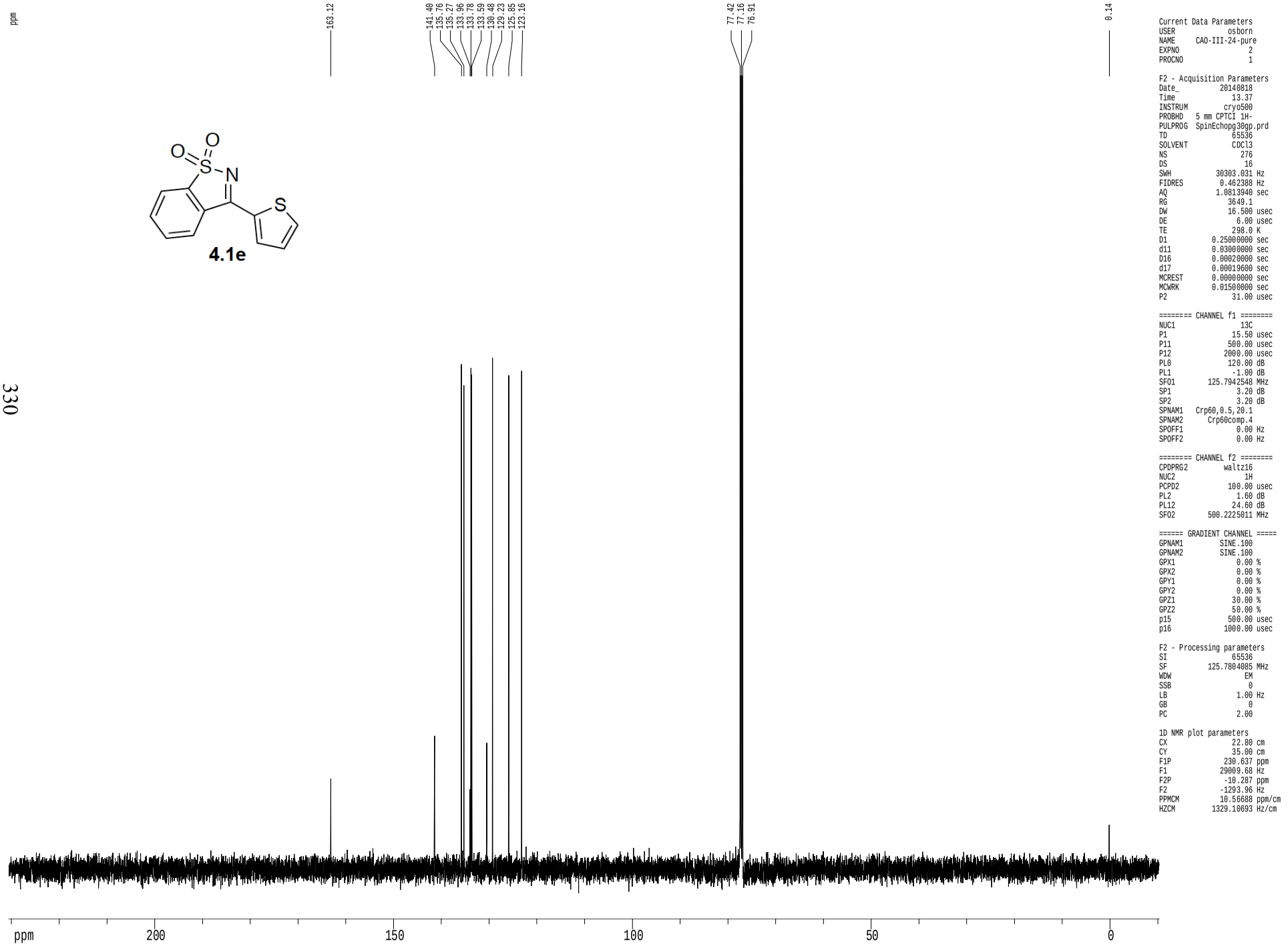
1H spectrum



4.1e

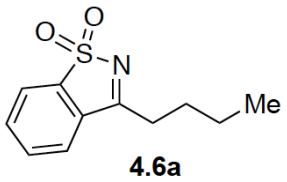

```
Current Data Parameters
USER                osborn
NAME      CAO-III-24-pure
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_            20140818
Time                13.35
INSTRUM          cryo500
PROBHD    5 mm CPTCI 1H-
PULPROG               zg30
TD                   81728
SOLVENT              CDCl3
NS                       8
DS                       2
SWH              8012.820 Hz
FIDRES           0.098043 Hz
AQ               5.0998774 sec
RG                       8
DW                 62.400 usec
DE                  6.00 usec
TE                 298.0 K
D1              0.10000000 sec
MCREST          0.00000000 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 =======
NUC1                    1H
P1                   7.50 usec
PL1                  1.60 dB
SFO1          500.2235015 MHz

F2 - Processing parameters
SI                   65536
SF            500.2200296 MHz
WDW                     EM
SSB                      0
LB                   0.30 Hz
GB                       0
PC                   4.00

1D NMR plot parameters
CX                   22.80 cm
CY                   15.00 cm
F1P                   9.000 ppm
F1                 4501.98 Hz
F2P                 -0.500 ppm
F2                 -250.11 Hz
PPMCM             0.41667 ppm/cm
HZCM            208.42502 Hz/cm
```

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME      CAO-III-24-pure
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_           20140818
Time                13.37
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                  65536
SOLVENT             CDCl3
NS                    276
DS                     16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.0813940 sec
RG                 3649.1
DW                 16.500 usec
DE                  6.00 usec
TE                298.0 K
D1             0.25000000 sec
d11            0.03000000 sec
D16            0.00020000 sec
d17            0.00019600 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec
P2                 31.00 usec

======== CHANNEL f1 ========
NUC1                 13C
P1                 15.50 usec
P11               500.00 usec
P12              2000.00 usec
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MHz
SP1                3.20 dB
SP2                3.20 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.60 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7804085 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   2.00

1D NMR plot parameters
CX                  22.80 cm
CY                  35.00 cm
F1P              230.637 ppm
F1              29009.68 Hz
F2P              -10.287 ppm
F2              -1293.96 Hz
PPMCM            10.56688 ppm/cm
HZCM          1329.10693 Hz/cm
```

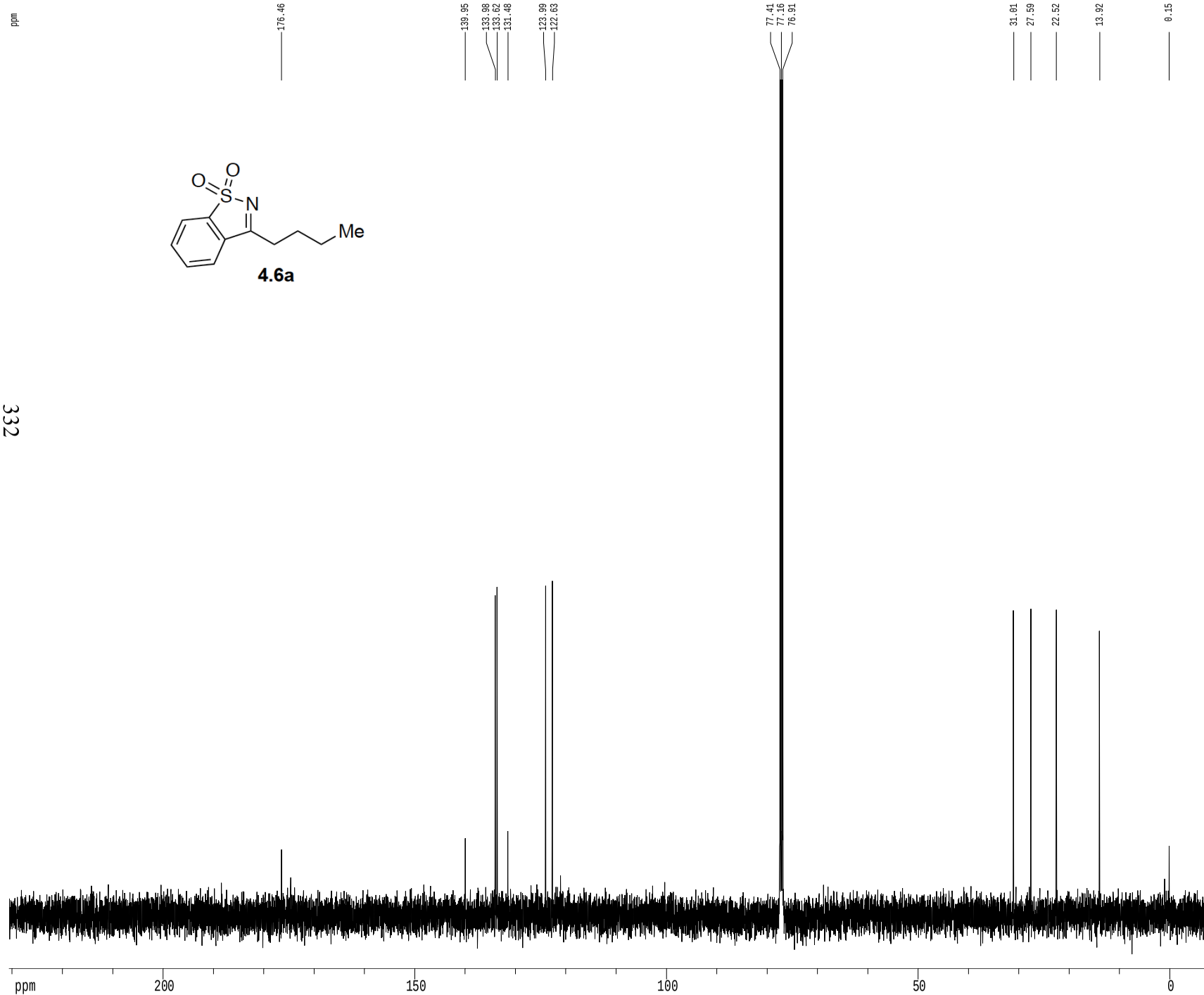
1H spectrum



4.6a

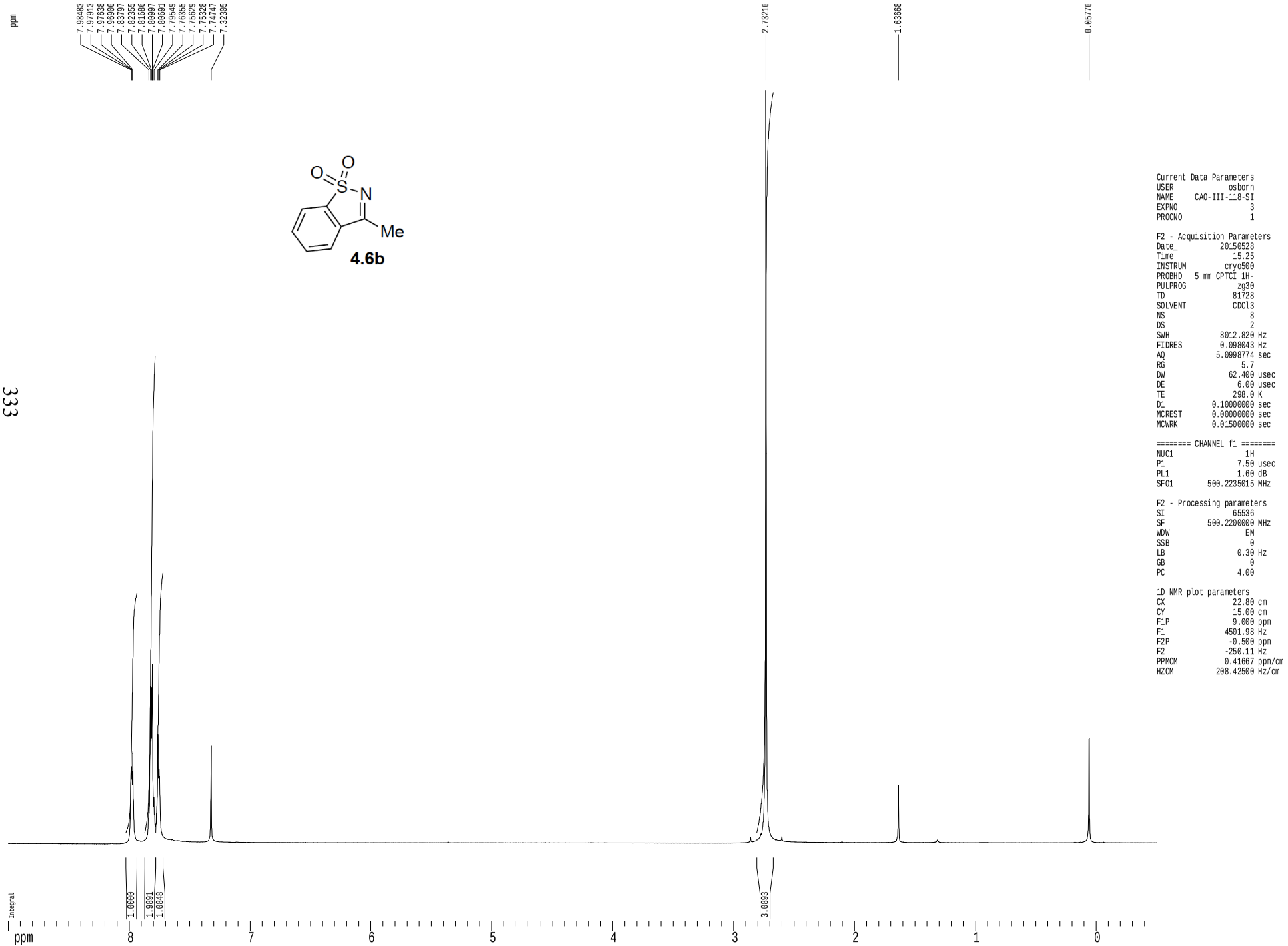

```
Current Data Parameters
USER              osborn
NAME      CAO-III-45B-xtal
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_          20140917
Time              11.17
INSTRUM         drx400
PROBHD   5 mm QNP H/F/P
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                   8
DS                   2
SWH           6410.256 Hz
FIDRES        0.097813 Hz
AQ            5.1118579 sec
RG               456.1
DW              78.000 usec
DE               4.50 usec
TE               298.0 K
D1          0.10000000 sec
MCREST      0.00000000 sec
MCWRK       0.01500000 sec

======= CHANNEL f1 =======
NUC1                 1H
P1              12.00 usec
PL1              0.00 dB
SFO1        400.1328009 MHz

F2 - Processing parameters
SI                65536
SF          400.1300196 MHz
WDW                  EM
SSB                  0
LB               0.30 Hz
GB                   0
PC               2.00

1D NMR plot parameters
CX              22.80 cm
CY              10.00 cm
F1P              9.000 ppm
F1            3601.17 Hz
F2P             -0.500 ppm
F2            -200.06 Hz
PPMCM         0.41667 ppm/cm
HZCM        166.72084 Hz/cm
```

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER              osborn
NAME      CAO-III-61P-SI
EXPNO                4
PROCNO               1

F2 - Acquisition Parameters
Date_          20150529
Time             18.23
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD               65536
SOLVENT          CDCl3
NS                 401
DS                  16
SWH          30303.031 Hz
FIDRES        0.462388 Hz
AQ           1.0813940 sec
RG              7298.2
DW             16.500 usec
DE              6.00 usec
TE             298.0 K
D1          0.25000000 sec
d11         0.03000000 sec
D16         0.00020000 sec
d17         0.00019600 sec
MCREST      0.00000000 sec
MCWRK       0.01500000 sec
P2             33.10 usec

======== CHANNEL f1 ========
NUC1               13C
P1              16.55 usec
P11            500.00 usec
P12           2000.00 usec
PL0            120.00 dB
PL1             -1.00 dB
SFO1       125.7942548 MHz
SP1             2.70 dB
SP2             2.70 dB
SPNAM1   Crp60,0.5,20.1
SPNAM2     Crp60comp.4
SPOFF1             0.00 Hz
SPOFF2             0.00 Hz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2               1H
PCPD2          100.00 usec
PL2              1.60 dB
PL12            24.50 dB
SFO2       500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1         SINE.100
GPNAM2         SINE.100
GPX1              0.00 %
GPX2              0.00 %
GPY1              0.00 %
GPY2              0.00 %
GPZ1             30.00 %
GPZ2             50.00 %
p15            500.00 usec
p16           1000.00 usec

F2 - Processing parameters
SI                65536
SF         125.7804080 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 2.00

1D NMR plot parameters
CX               22.80 cm
CY               60.00 cm
F1P            230.637 ppm
F1           29009.68 Hz
F2P            -10.287 ppm
F2           -1293.96 Hz
PPMCM         10.56688 ppm/cm
HZCM        1329.10693 Hz/cm
```

1H spectrum



Current Data Parameters
USER osborn
NAME CAO-III-118-SI
EXPNO 3
PROCNO 1

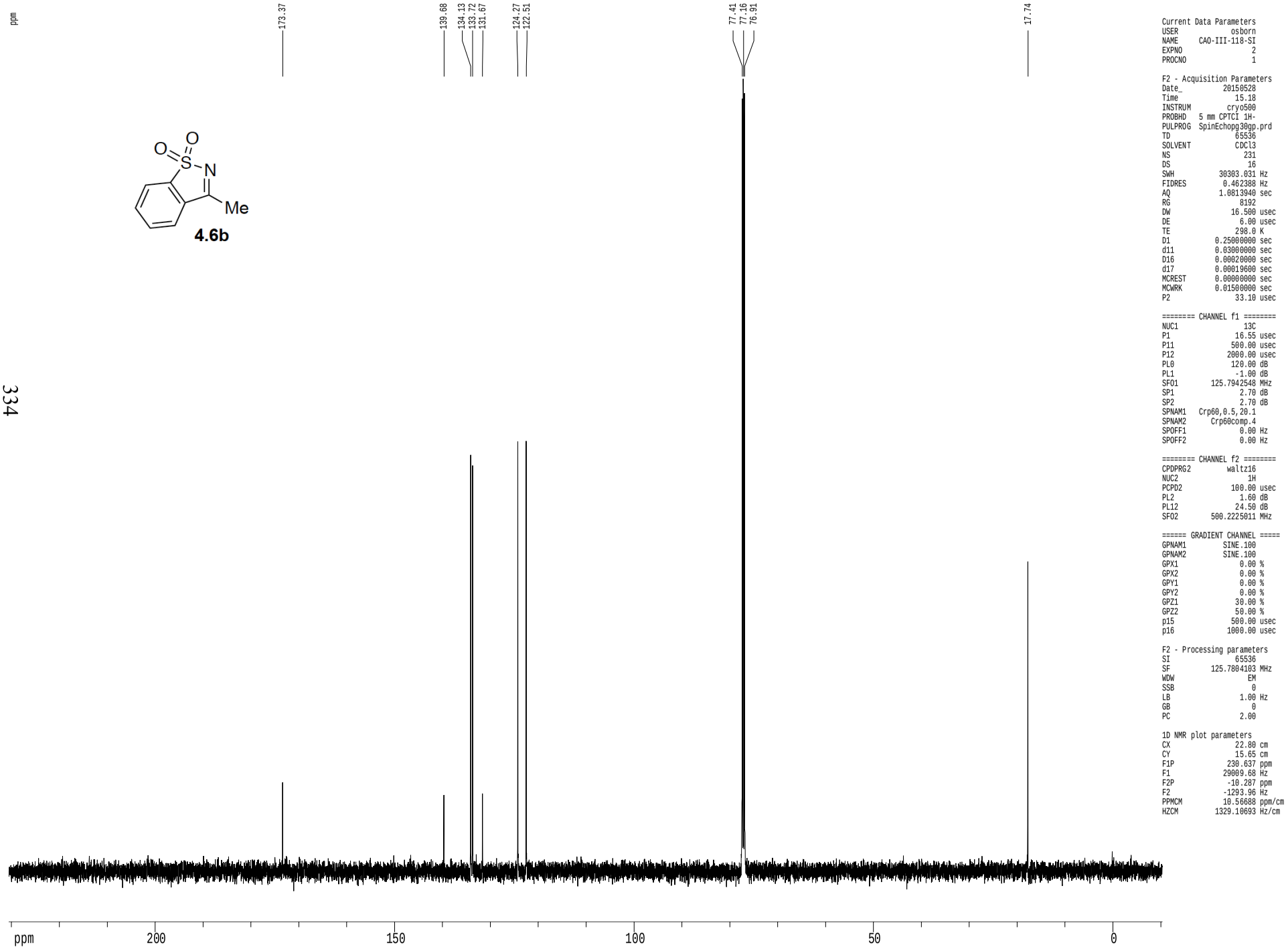
F2 - Acquisition Parameters
Date_ 20150528
Time 15.25
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 5.7
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz

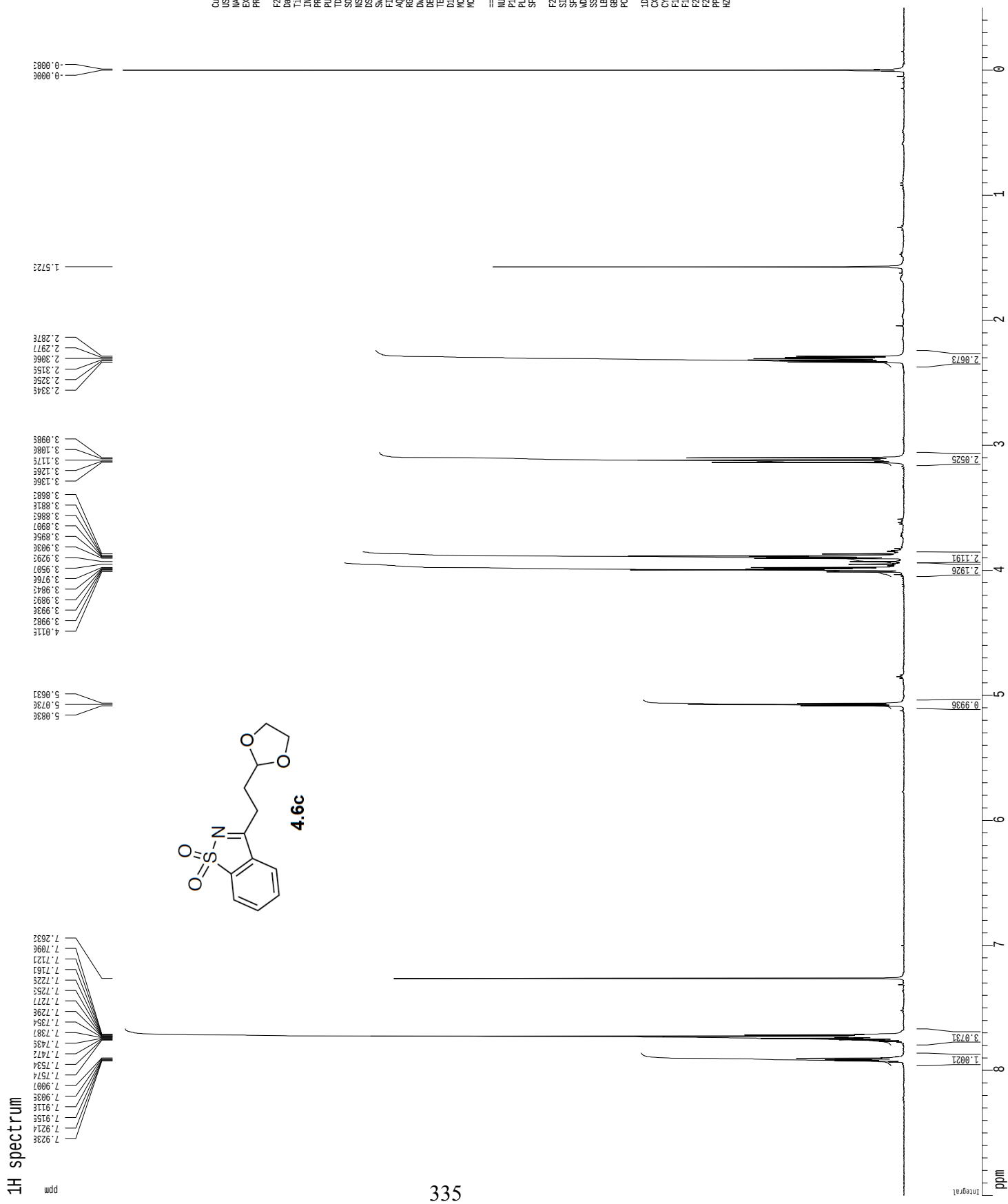
F2 - Processing parameters
SI 65536
SF 500.2200000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42500 Hz/cm

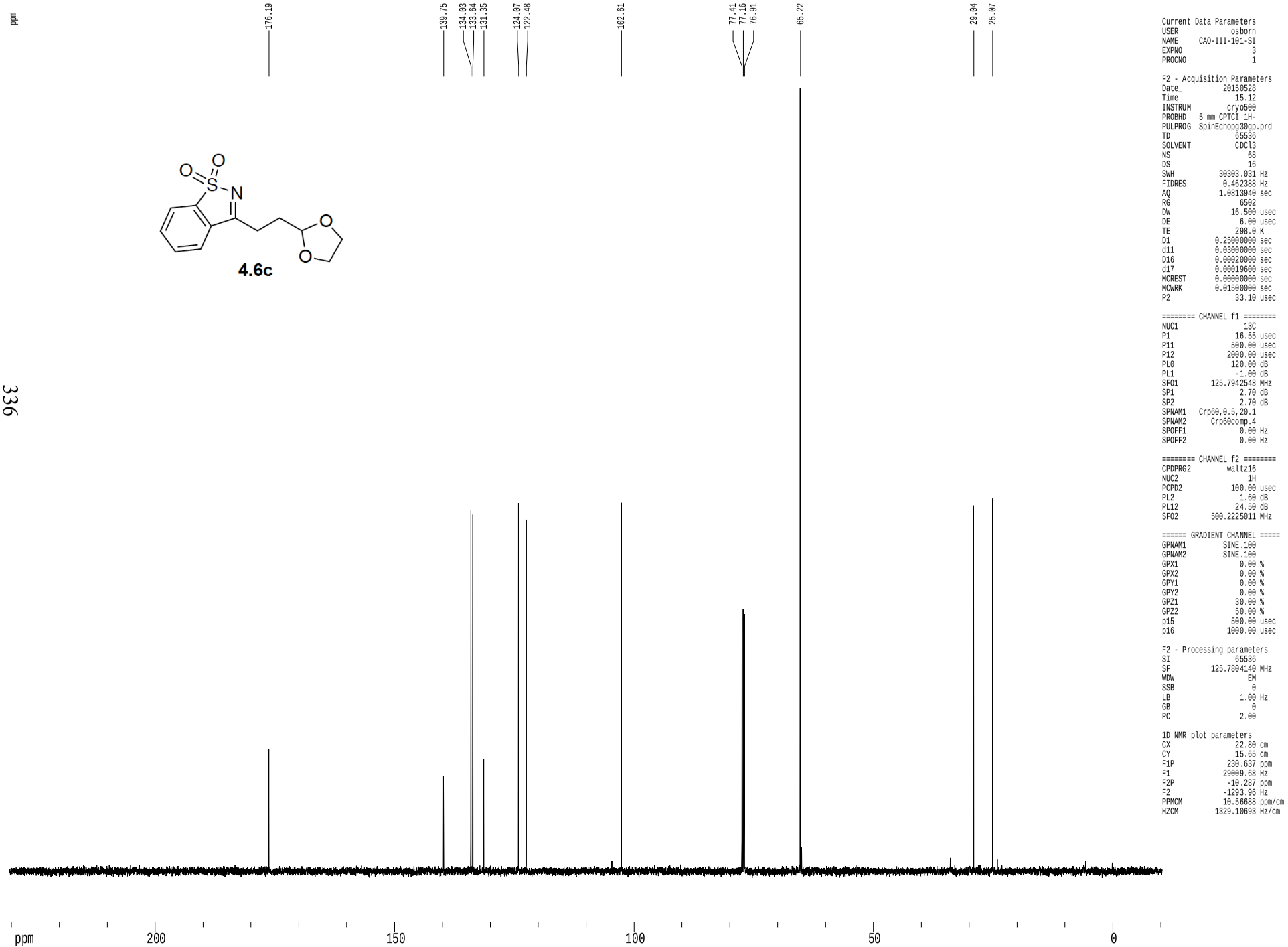
Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
USER                osborn
NAME      CAO-III-118-SI
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20150528
Time               15.18
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                 65536
SOLVENT            CDCl3
NS                   231
DS                    16
SWH            30303.031 Hz
FIDRES         0.462388 Hz
AQ             1.0813940 sec
RG                  8192
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1            0.25000000 sec
d11           0.03000000 sec
D16           0.00020000 sec
d17           0.00019600 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec
P2                33.10 usec

======== CHANNEL f1 ========
NUC1                 13C
P1                16.55 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1                2.70 dB
SP2                2.70 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                1.60 dB
PL12              24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15              500.00 usec
p16             1000.00 usec

F2 - Processing parameters
SI                 65536
SF           125.7804183 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  2.00

1D NMR plot parameters
CX                 22.80 cm
CY                 15.65 cm
F1P              230.637 ppm
F1             29009.68 Hz
F2P              -10.287 ppm
F2             -1293.96 Hz
PPMCM           10.56688 ppm/cm
HZCM          1329.10693 Hz/cm
```


1H spectrum
4.6c
Current Data Parameters
USER osborn
NAME CAO-III-101-pure
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20141121
Time 12.17
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 456.1
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300196 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 15.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm
ppm
Integral

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME CAO-III-101-SI
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150528
Time 15.12
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 68
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 6502
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 33.10 usec

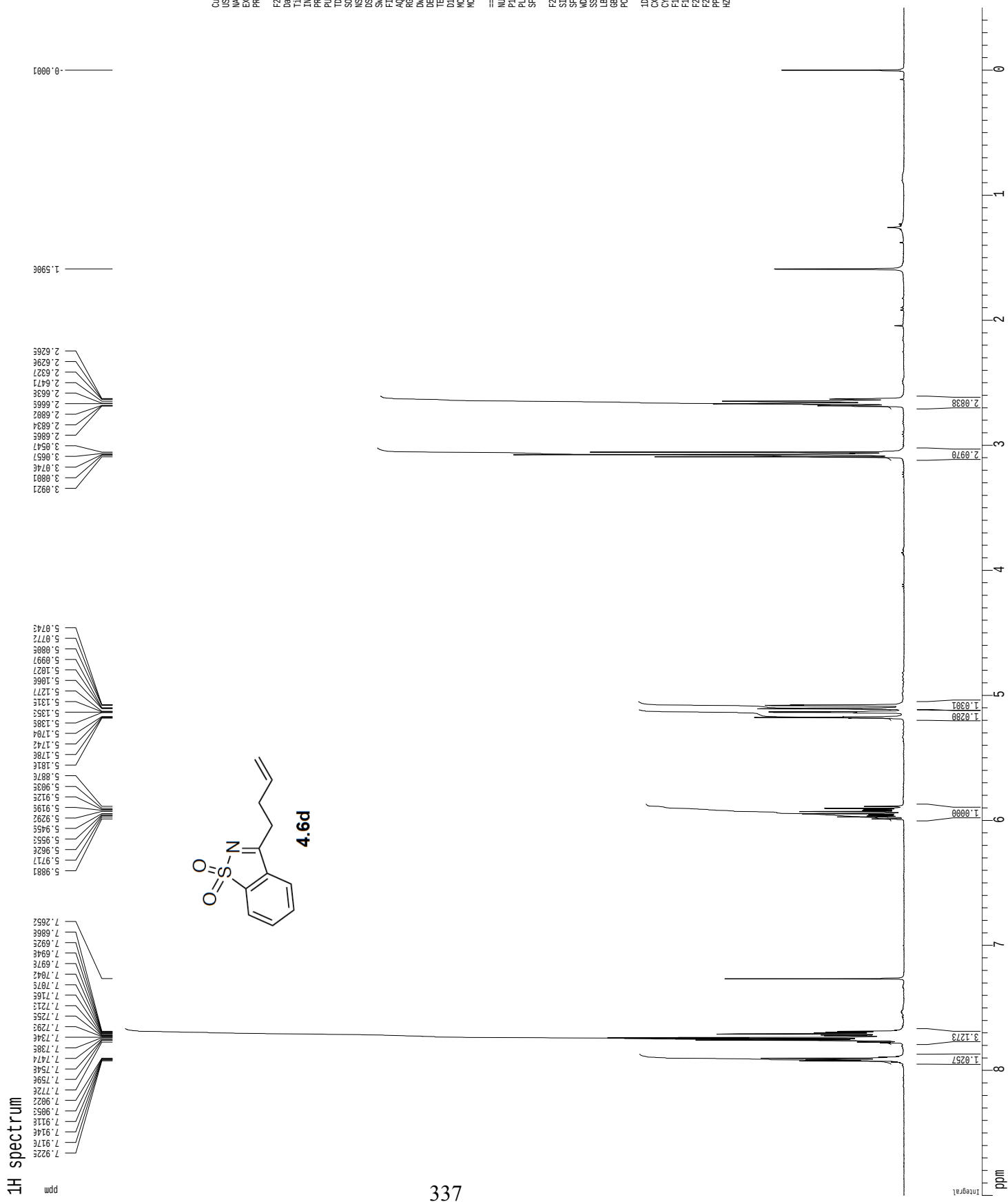
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz

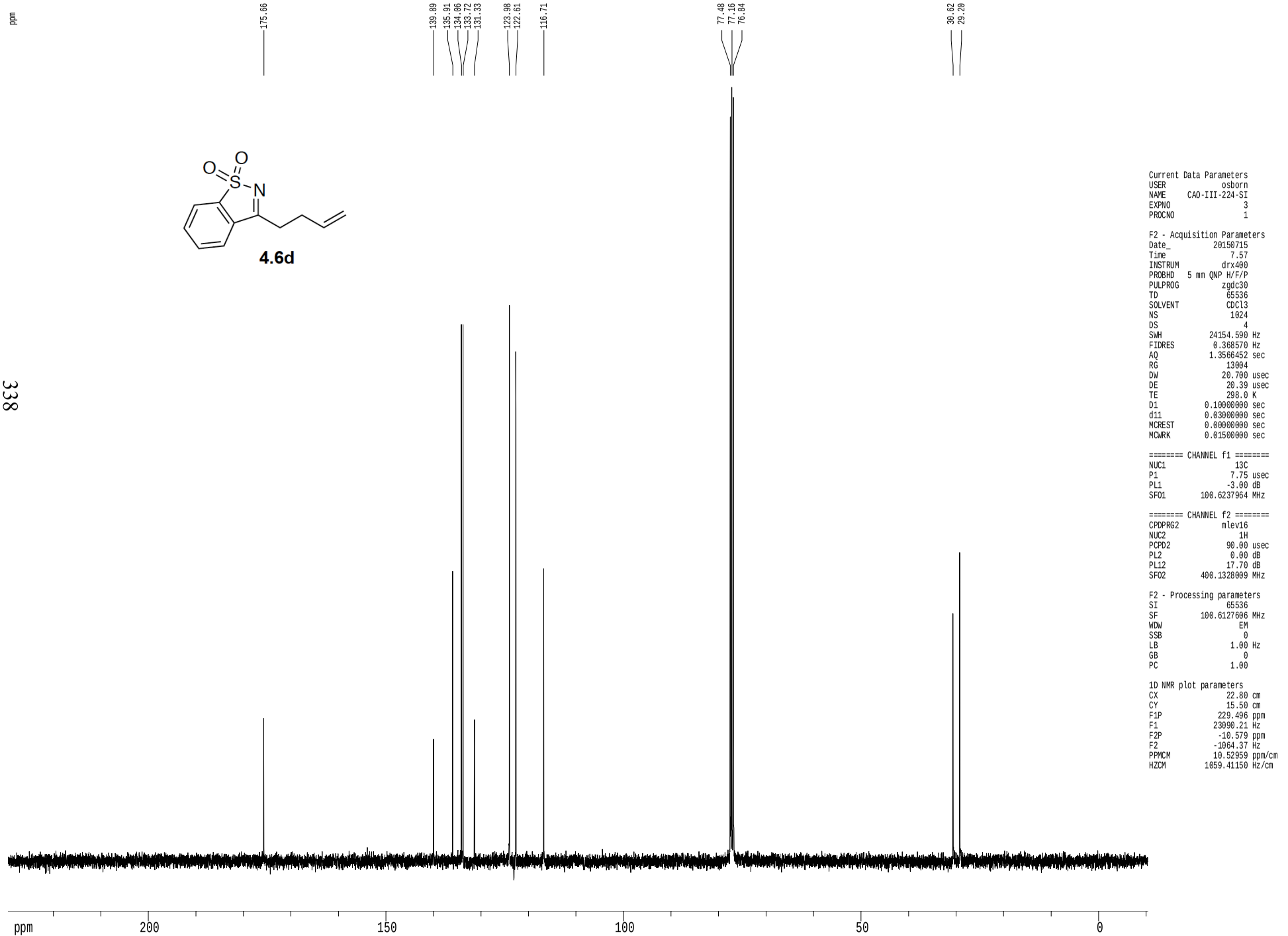
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

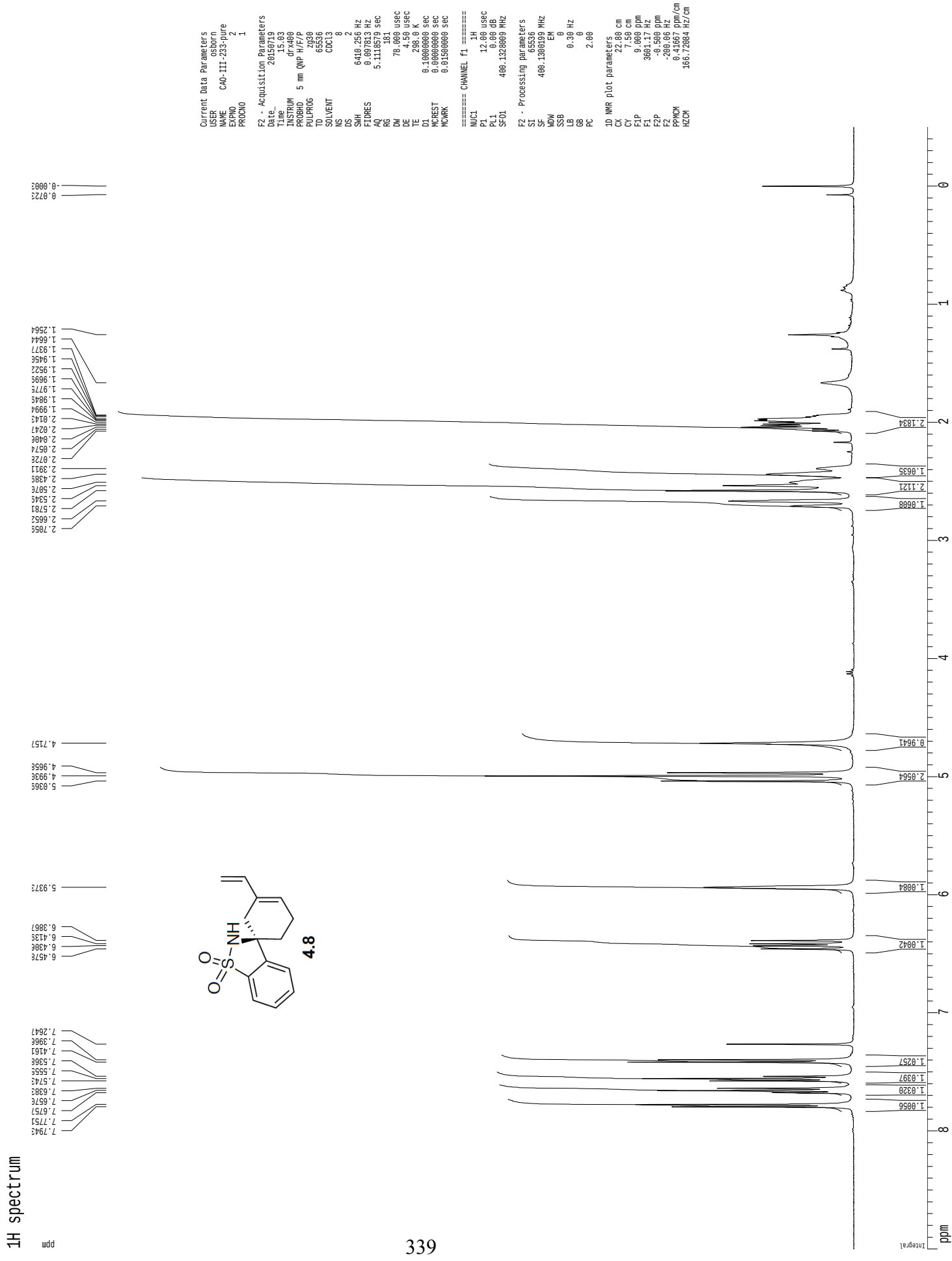
F2 - Processing parameters
SI 65536
SF 125.7804140 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

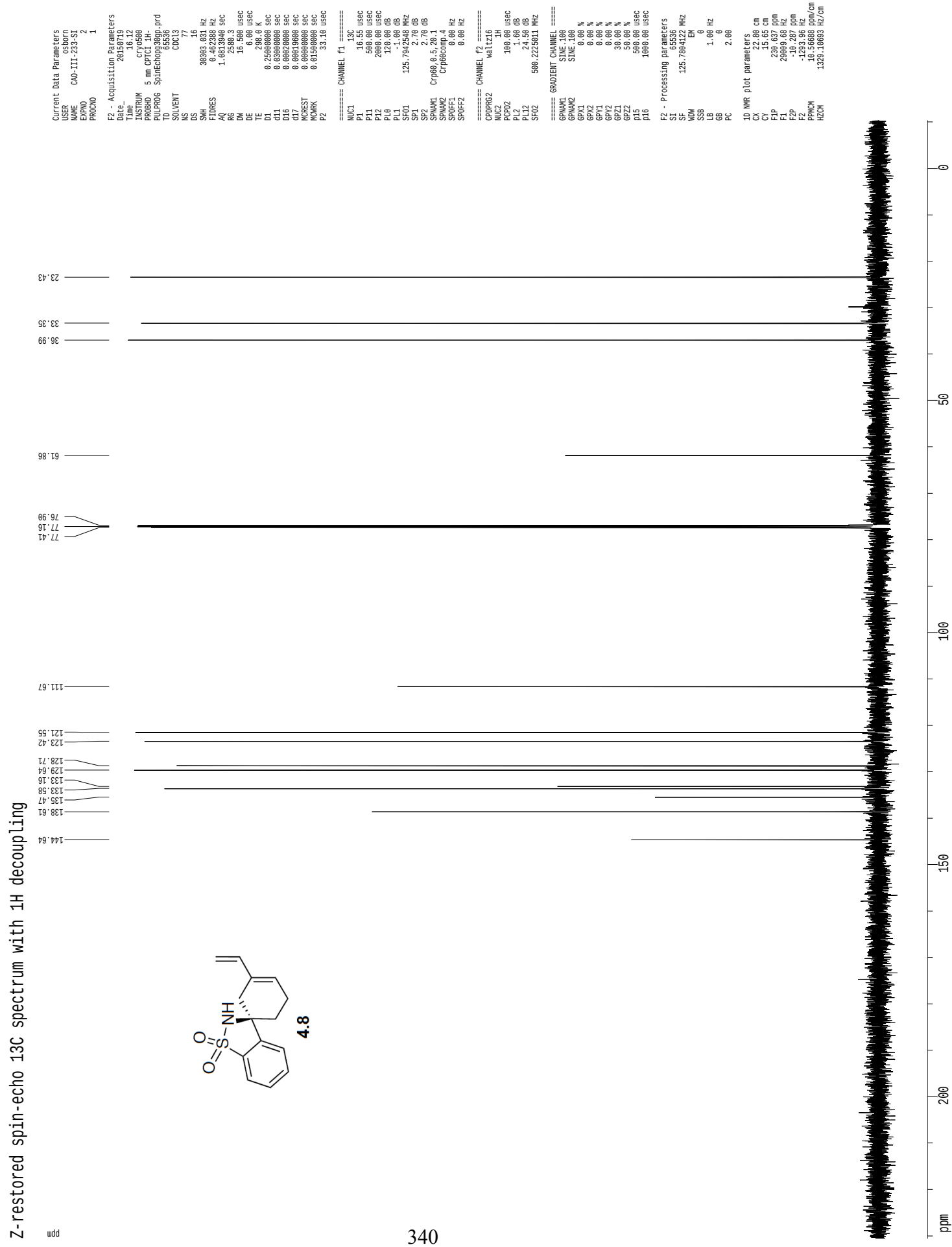
1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm


1H spectrum
4.6d
Current Data Parameters
USER osborn
NAME CAO-III-224-SI
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150715
Time_ 7.49
INSTRUM dr'400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 287.4
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300196 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 7.50 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm
7.9225
7.9176
7.9146
7.9118
7.9053
7.9022
7.7726
7.7596
7.7548
7.7474
7.7386
7.7293
7.7256
7.7213
7.7165
7.7079
7.7042
7.6976
7.6948
7.6926
7.6866
7.2652
5.9881
5.9717
5.9626
5.9553
5.9459
5.9292
5.9199
5.9125
5.9036
5.8876
5.1816
5.1786
5.1742
5.1704
5.1386
5.1353
5.1316
5.1277
5.1066
5.1027
5.0997
5.0806
5.0772
5.0743
3.0921
3.0801
3.0746
3.0657
3.0547
2.6866
2.6834
2.6802
2.6666
2.6636
2.6471
2.6327
2.6296
2.6265
1.5906
0.0001
2.0838
2.0970
1.0381
1.0280
1.0000
3.1273
1.0257
Integral
ppm
0
1
2
3
4
5
6
7
8

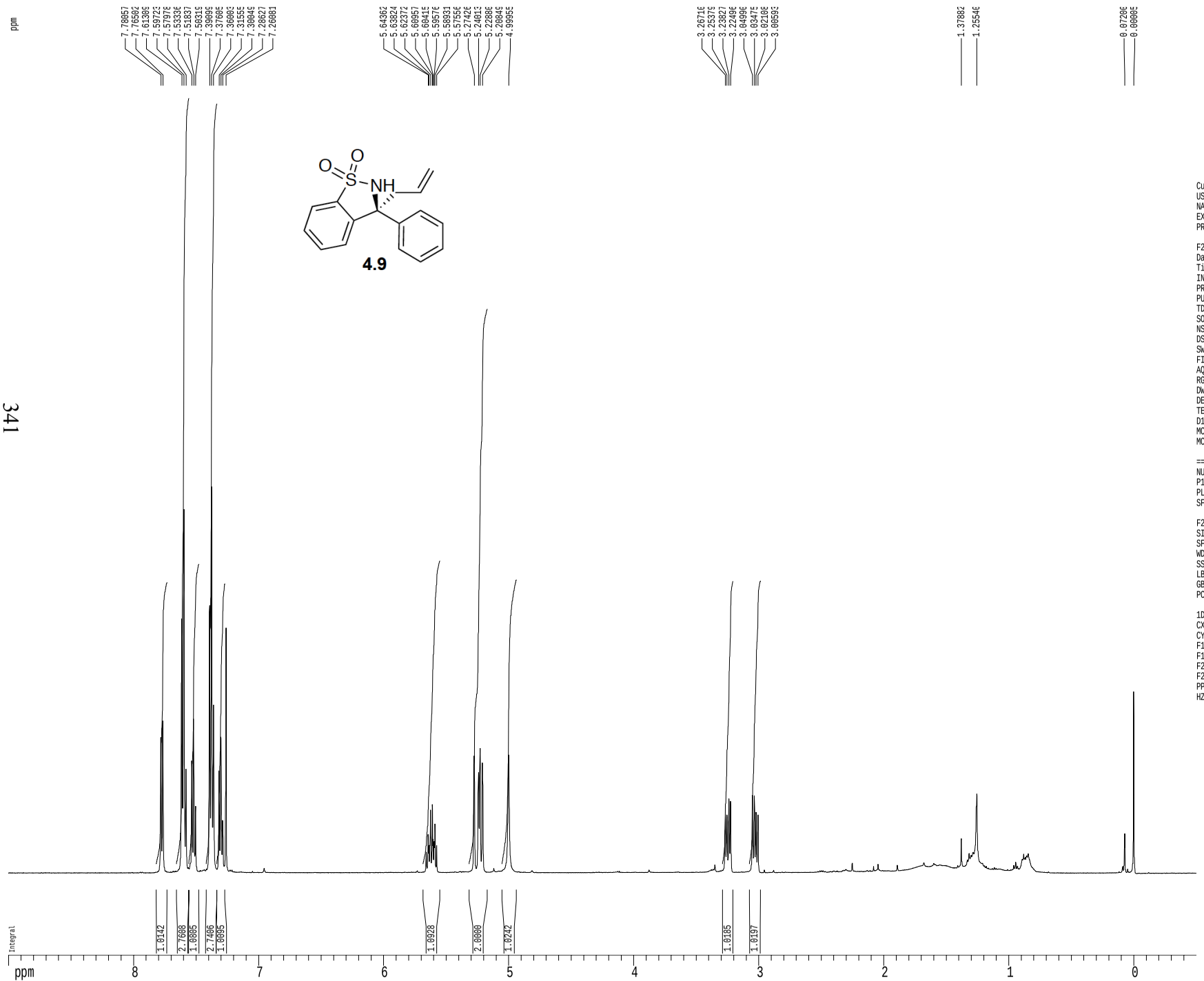
13C spectrum with 1H decoupling




1H spectrum
Current Data Parameters
USER osborn
NAME CAO-III-233-pure
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150719
Time_ 15.03
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 181
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300199 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 7.50 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm
0.0003
0.0723
1.2564
1.6644
1.9377
1.9456
1.9522
1.9695
1.9775
1.9845
1.9994
2.0143
2.0247
2.0406
2.0574
2.0728
2.3913
2.4389
2.5076
2.5345
2.5781
2.6652
2.7059
4.7157
4.9656
4.9936
5.0369
5.9373
6.3867
6.4139
6.4306
6.4578
7.2647
7.3966
7.4461
7.5366
7.5556
7.5743
7.6383
7.6576
7.6757
7.7751
7.7943
2.1834
1.0635
2.1121
1.0808
0.9641
2.0564
1.0084
1.0042
1.0257
1.0397
1.0320
1.0056
4.8
ppm
Integral


Z-restored spin-echo 13C spectrum with 1H decoupling
Current Data Parameters
USER osborn
NAME CAO-III-233-SI
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150719
Time 16.12
INSTRUM cryo600
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 77
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 2580.3
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 33.10 usec
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz
===== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7884122 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.00 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.08 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm
23.43
33.35
36.99
61.86
76.90
77.16
77.41
111.67
121.55
123.42
128.71
129.64
133.16
133.58
135.47
138.61
144.64
ppm
0
50
100
150
200
4.8

1H spectrum



Current Data Parameters
USER osborn
NAME CAO-III-248C-SI
EXPNO 1
PROCNO 1

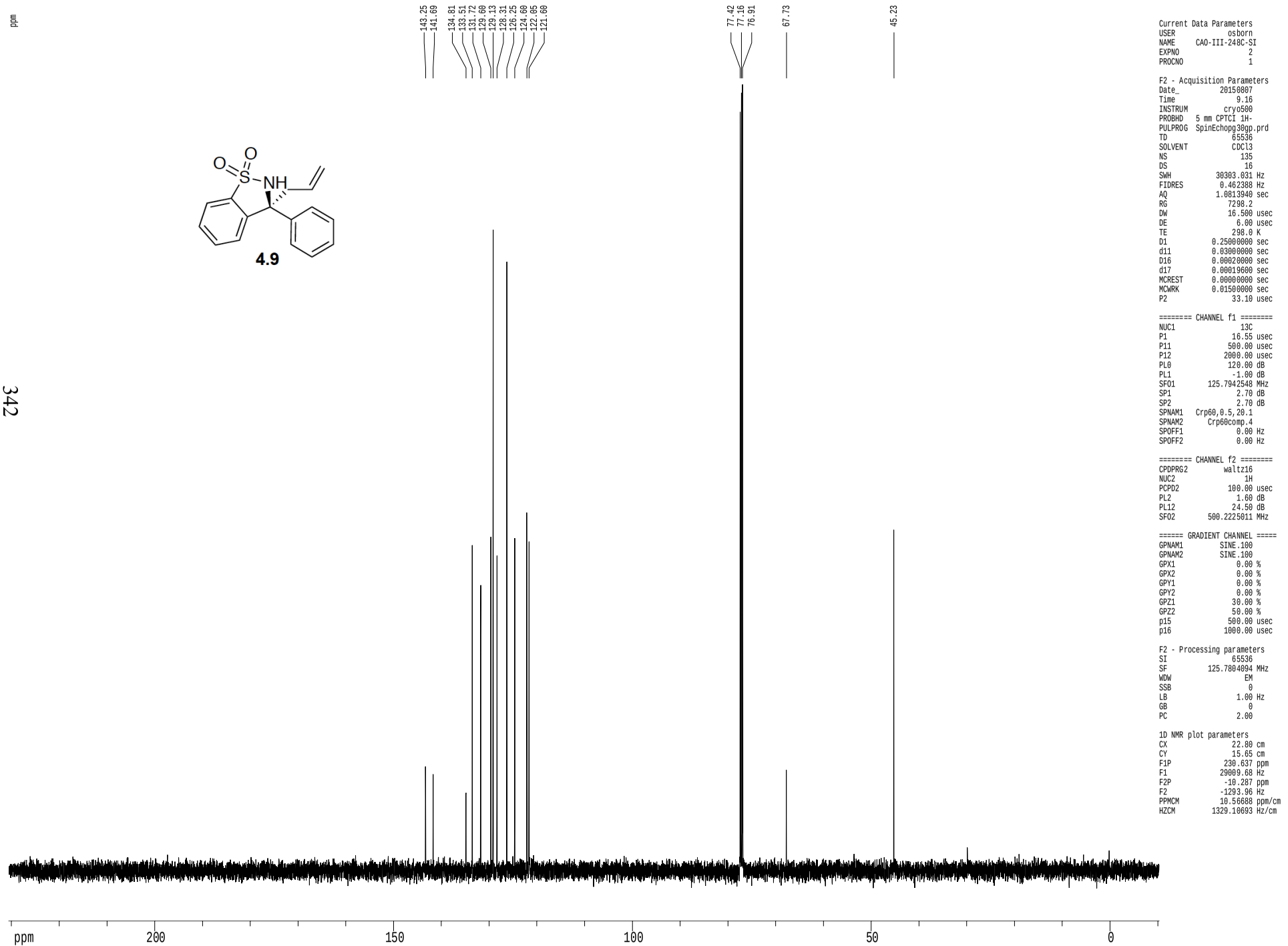
F2 - Acquisition Parameters
Date_ 20150807
Time 9.15
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998774 sec
RG 4
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz

F2 - Processing parameters
SI 65536
SF 500.2200310 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00

1D NMR plot parameters
CX 22.80 cm
CY 7.50 cm
F1P 9.000 ppm
F1 4501.98 Hz
F2P -0.500 ppm
F2 -250.11 Hz
PPMCM 0.41667 ppm/cm
HZCM 208.42502 Hz/cm

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME CAO-III-248C-SI
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20150807
Time 9.16
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 135
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 7298.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 33.10 usec

======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

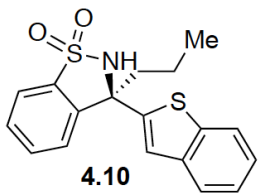
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 125.7804094 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10693 Hz/cm

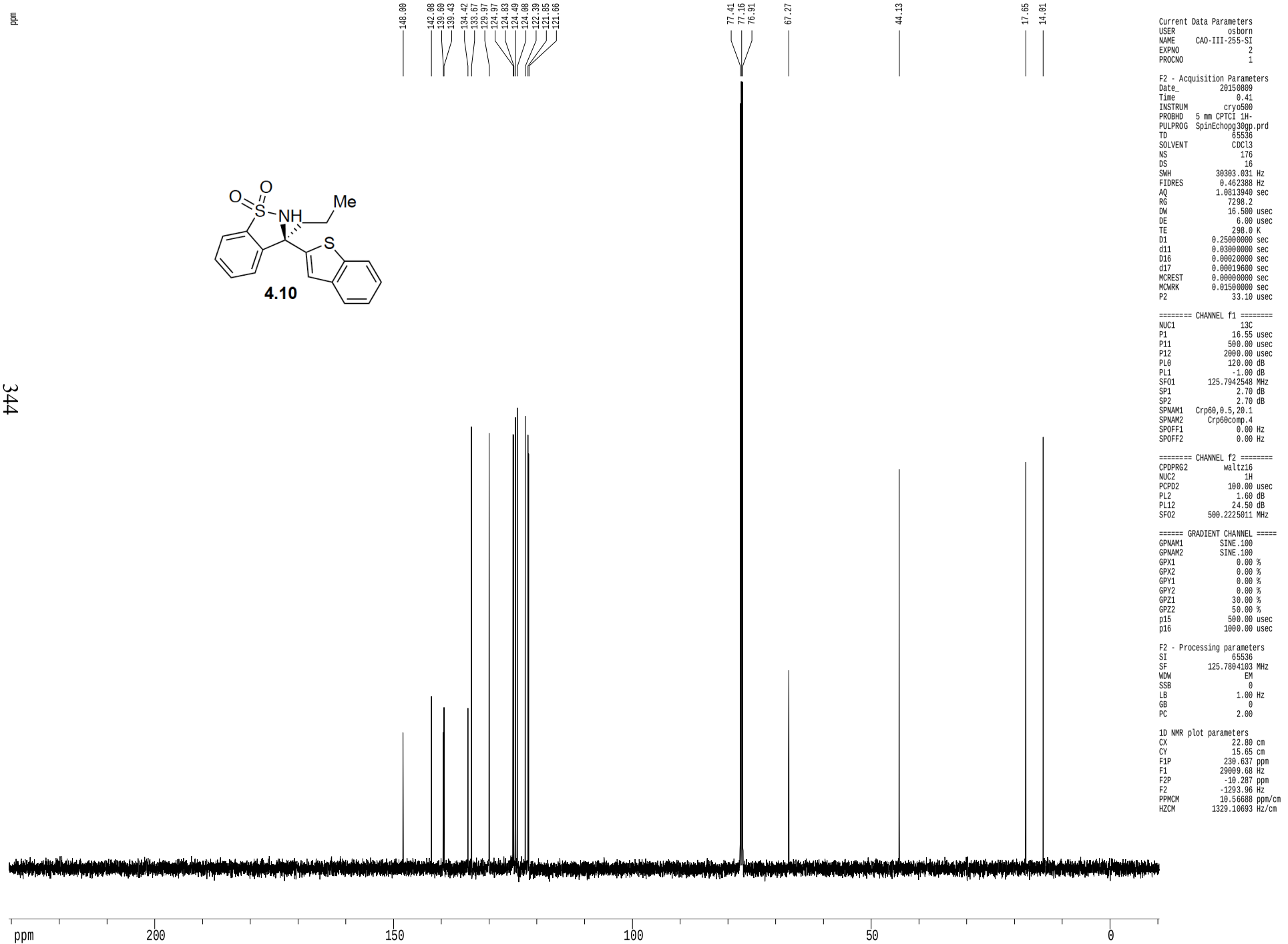
1H spectrum



4.10

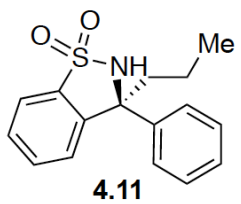

```
Current Data Parameters
USER              osborn
NAME      CAO-III-255-SI
EXPNO                3
PROCNO               1

F2 - Acquisition Parameters
Date_          20150809
Time              15.44
INSTRUM          drx400
PROBHD   5 mm QNP H/F/P
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                   8
DS                   2
SWH           6410.256 Hz
FIDRES        0.097813 Hz
AQ            5.1118579 sec
RG                 362
DW              78.000 usec
DE               4.50 usec
TE               298.0 K
D1          0.10000000 sec
MCREST      0.00000000 sec
MCWRK       0.01500000 sec

======= CHANNEL f1 =======
NUC1                 1H
P1               12.00 usec
PL1               0.00 dB
SFO1        400.1328009 MHz

F2 - Processing parameters
SI                65536
SF          400.1300229 MHz
WDW                  EM
SSB                  0
LB                0.30 Hz
GB                   0
PC                2.00

1D NMR plot parameters
CX               22.80 cm
CY               15.00 cm
F1P               9.000 ppm
F1             3601.17 Hz
F2P              -0.500 ppm
F2             -200.06 Hz
PPMCM          0.41667 ppm/cm
HZCM         166.72086 Hz/cm
```

Z-restored spin-echo 13C spectrum with 1H decoupling



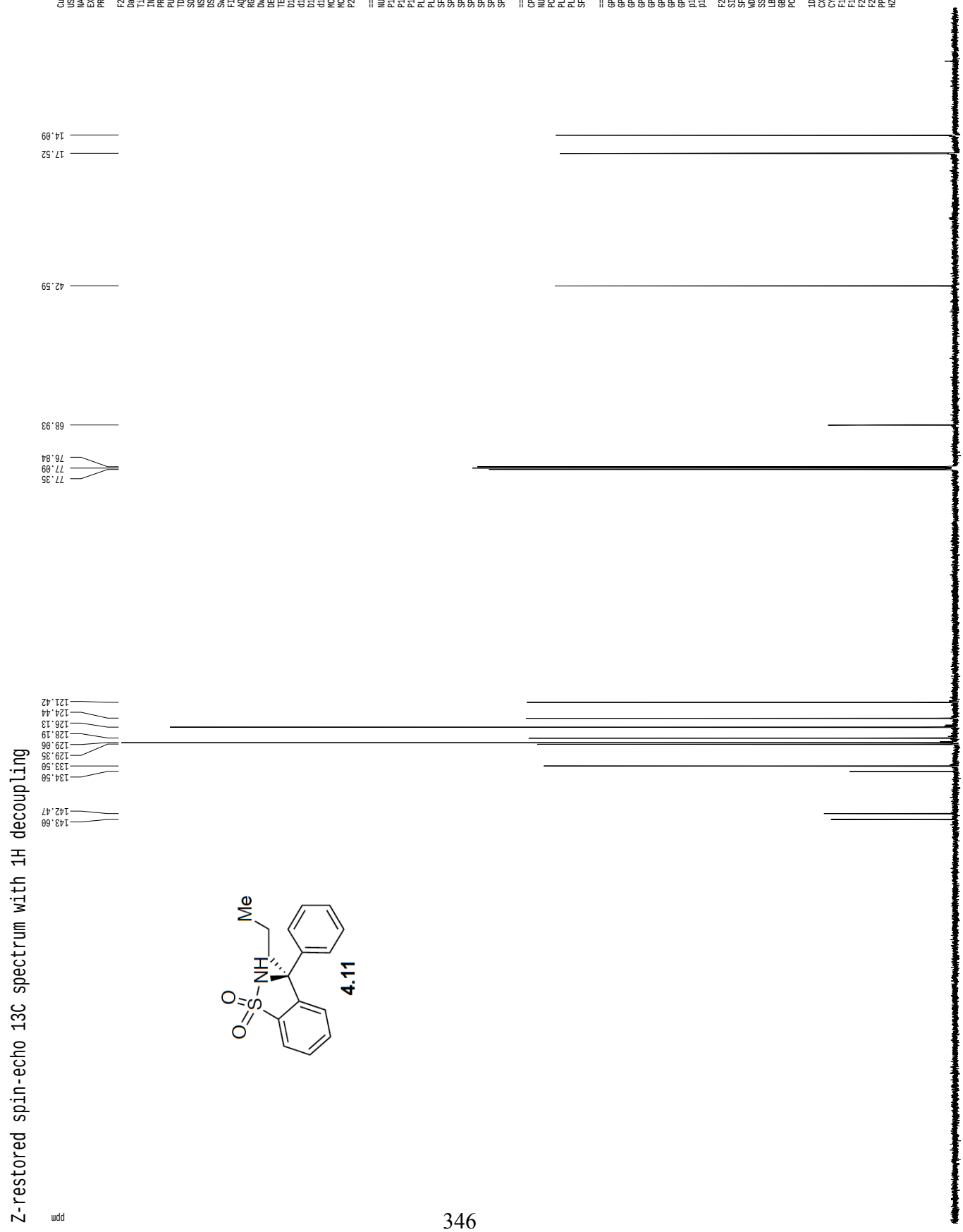

```
Current Data Parameters
USER                osborn
NAME      CAO-III-255-SI
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20150809
Time                0.41
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                 65536
SOLVENT            CDCl3
NS                   176
DS                    16
SWH            30303.031 Hz
FIDRES         0.462388 Hz
AQ             1.0813940 sec
RG                7298.2
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1             0.25000000 sec
d11            0.03000000 sec
D16            0.00020000 sec
d17            0.00019600 sec
MCREST         0.00000000 sec
MCWRK          0.01500000 sec
P2                33.10 usec

======== CHANNEL f1 ========
NUC1                 13C
P1                16.55 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1                2.70 dB
SP2                2.70 dB
SPNAM1    Crp60,0.5,20.1
SPNAM2      Crp60comp.4
SPOFF1               0.00 Hz
SPOFF2               0.00 Hz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPX1                0.00 %
GPX2                0.00 %
GPY1                0.00 %
GPY2                0.00 %
GPZ1               30.00 %
GPZ2               50.00 %
p15              500.00 usec
p16             1000.00 usec

F2 - Processing parameters
SI                 65536
SF           125.7804183 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 2.00

1D NMR plot parameters
CX                22.80 cm
CY                15.65 cm
F1P             230.637 ppm
F1              29009.68 Hz
F2P             -10.287 ppm
F2              -1293.96 Hz
PPMCM           10.56688 ppm/cm
HZCM          1329.10693 Hz/cm
```

1H spectrum

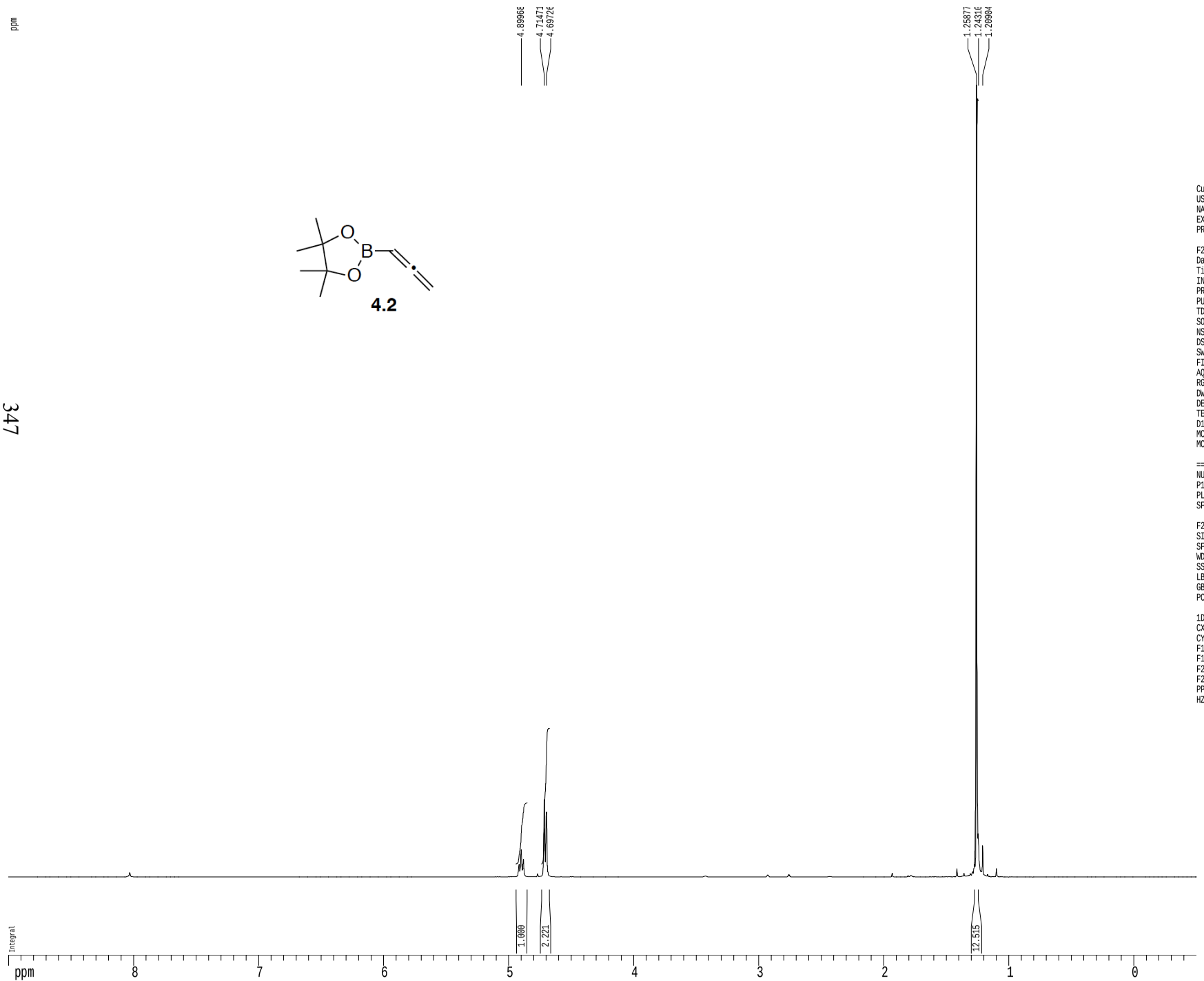


4.11


```
Current Data Parameters
USER                endean
NAME      CAO-III-253-SI
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20150811
Time              17.33
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                81728
SOLVENT           CDCl3
NS                    8
DS                    2
SWH            8012.820 Hz
FIDRES         0.098043 Hz
AQ             5.0998774 sec
RG                  6.3
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1           0.10000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 =======
NUC1                1H
P1                7.50 usec
PL1               1.60 dB
SFO1        500.2235015 MHz

F2 - Processing parameters
SI                65536
SF           500.2200309 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                4.00

1D NMR plot parameters
CX                22.80 cm
CY                15.00 cm
F1P               9.000 ppm
F1              4501.98 Hz
F2P              -0.500 ppm
F2             -250.11 Hz
PPMCM          0.41667 ppm/cm
HZCM         208.42502 Hz/cm
```


Z-restored spin-echo 13C spectrum with 1H decoupling
Current Data Parameters
USER endean
NAME CAO-III-253-SI
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150911
Time 17.38
INSTRUM cryo600
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 608
DS 16
SWH 30303.031 Hz
FIDRES 0.462308 Hz
AQ 1.0813940 sec
RG 2896.3
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 33.10 usec
======== CHANNEL f1 ========
NUC1 13C
P1 16.55 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 2.70 dB
SP2 2.70 dB
SPNAM1 Crp80,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.50 dB
SFO2 500.2225011 MHz
===== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec
F2 - Processing parameters
SI 65536
SF 125.7804190 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.00 cm
CY 15.65 cm
F1P 220.000 ppm
F1 27671.09 Hz
F2P -10.000 ppm
F2 -1257.80 Hz
PPMCM 10.03772 ppm/cm
HZCM 1288.83765 Hz/cm
14.09
17.52
42.59
68.93
76.84
77.09
77.35
121.42
124.44
126.13
128.19
129.06
129.35
133.60
134.60
142.47
143.60
Me
NH
O
O
S
4.11
ppm
0
50
100
150
200

1H spectrum



4.2

Current Data Parameters
USER osborn
NAME CAO-III-162A
EXPNO 3
PROCNO 1

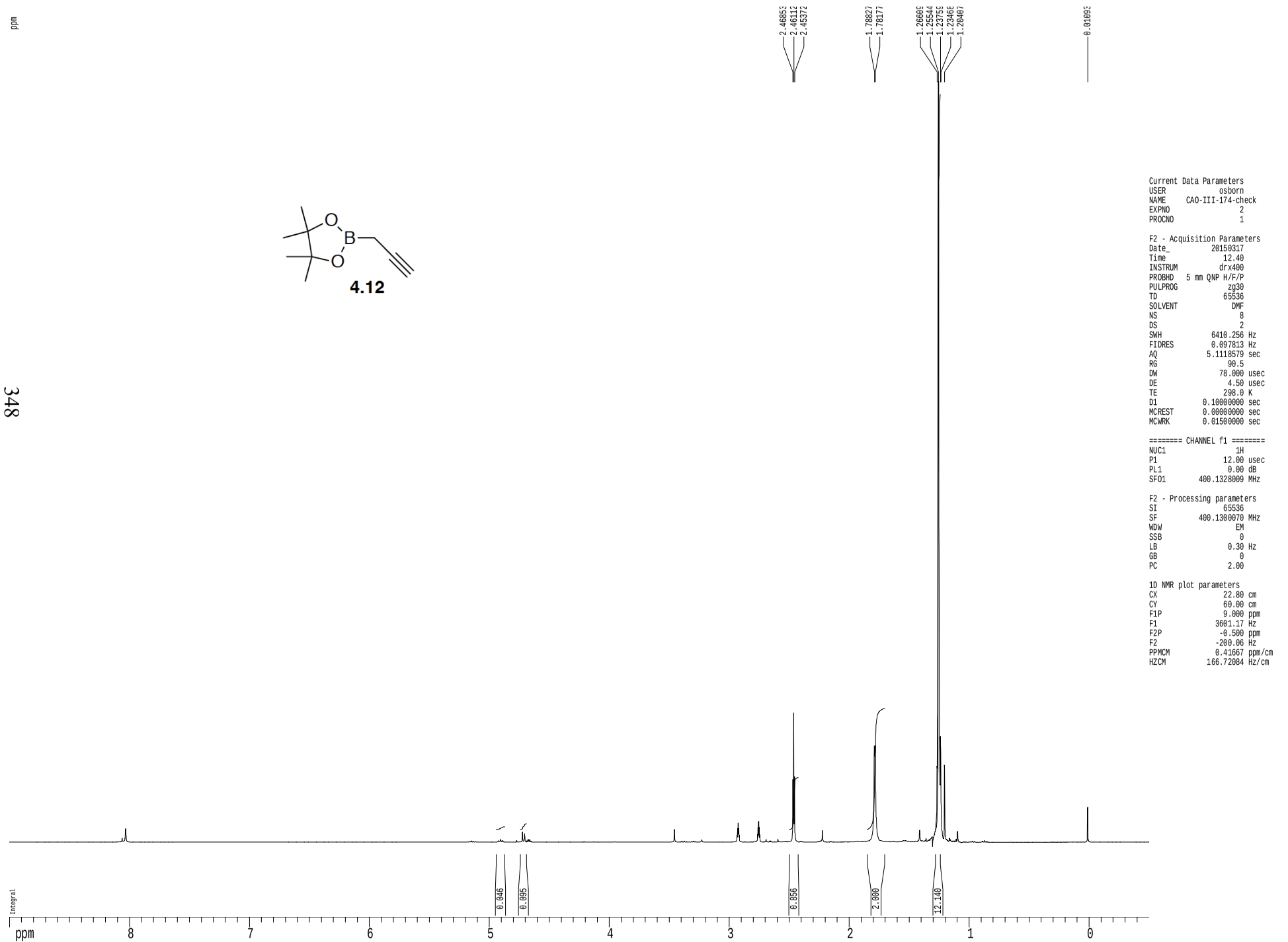
F2 - Acquisition Parameters
Date_ 20150205
Time 11.26
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT DMF
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 32
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======= CHANNEL f1 =======
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz

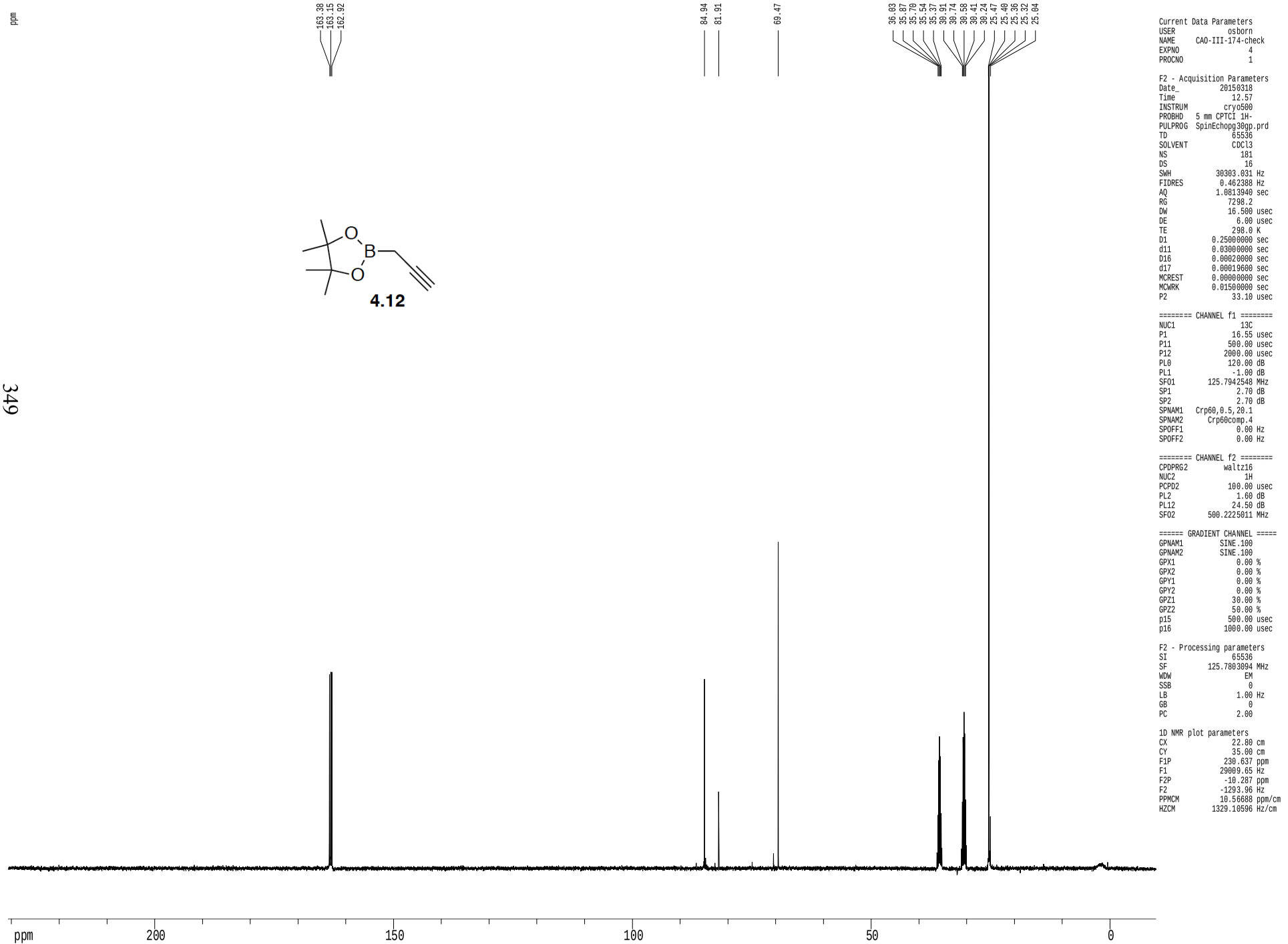
F2 - Processing parameters
SI 65536
SF 400.1300059 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00

1D NMR plot parameters
CX 22.80 cm
CY 30.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm

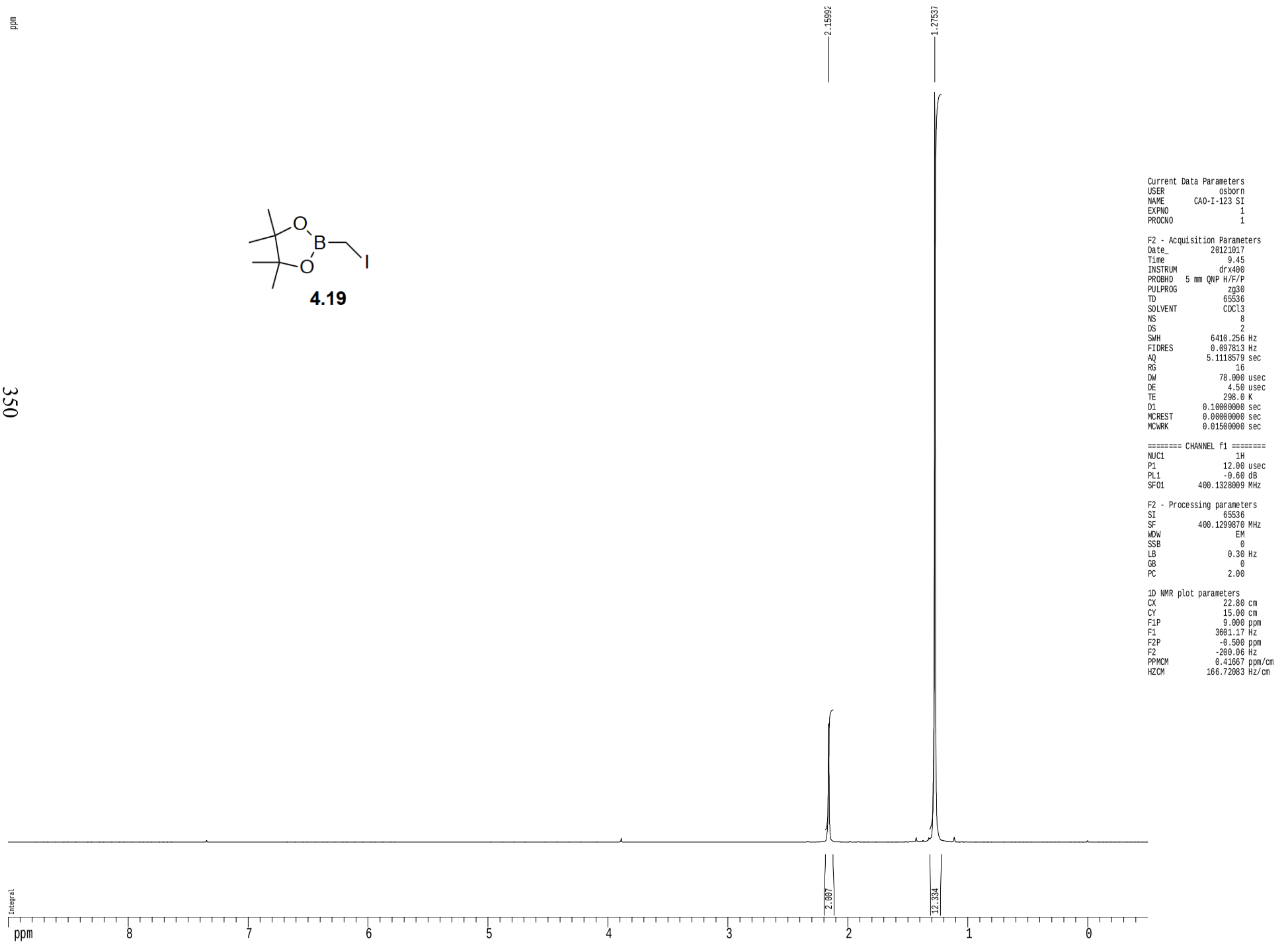
1H spectrum


ppm
2.46853
2.46112
2.45372
1.78827
1.78177
1.26609
1.25544
1.23759
1.23468
1.20407
0.01093
O
B
O
4.12
Current Data Parameters
USER osborn
NAME CAO-III-174-check
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150317
Time 12.40
INSTRUM drx400
PROBHD 5 mm QNP H/F/P
PULPROG zg30
TD 65536
SOLVENT DMF
NS 8
DS 2
SWH 6410.256 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 90.5
DW 78.000 usec
DE 4.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 0.00 dB
SFO1 400.1328009 MHz
F2 - Processing parameters
SI 65536
SF 400.1300070 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 2.00
1D NMR plot parameters
CX 22.80 cm
CY 60.00 cm
F1P 9.000 ppm
F1 3601.17 Hz
F2P -0.500 ppm
F2 -200.06 Hz
PPMCM 0.41667 ppm/cm
HZCM 166.72084 Hz/cm
Integral
0.046
0.095
0.856
2.000
12.140
ppm
8
7
6
5
4
3
2
1
0

Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum

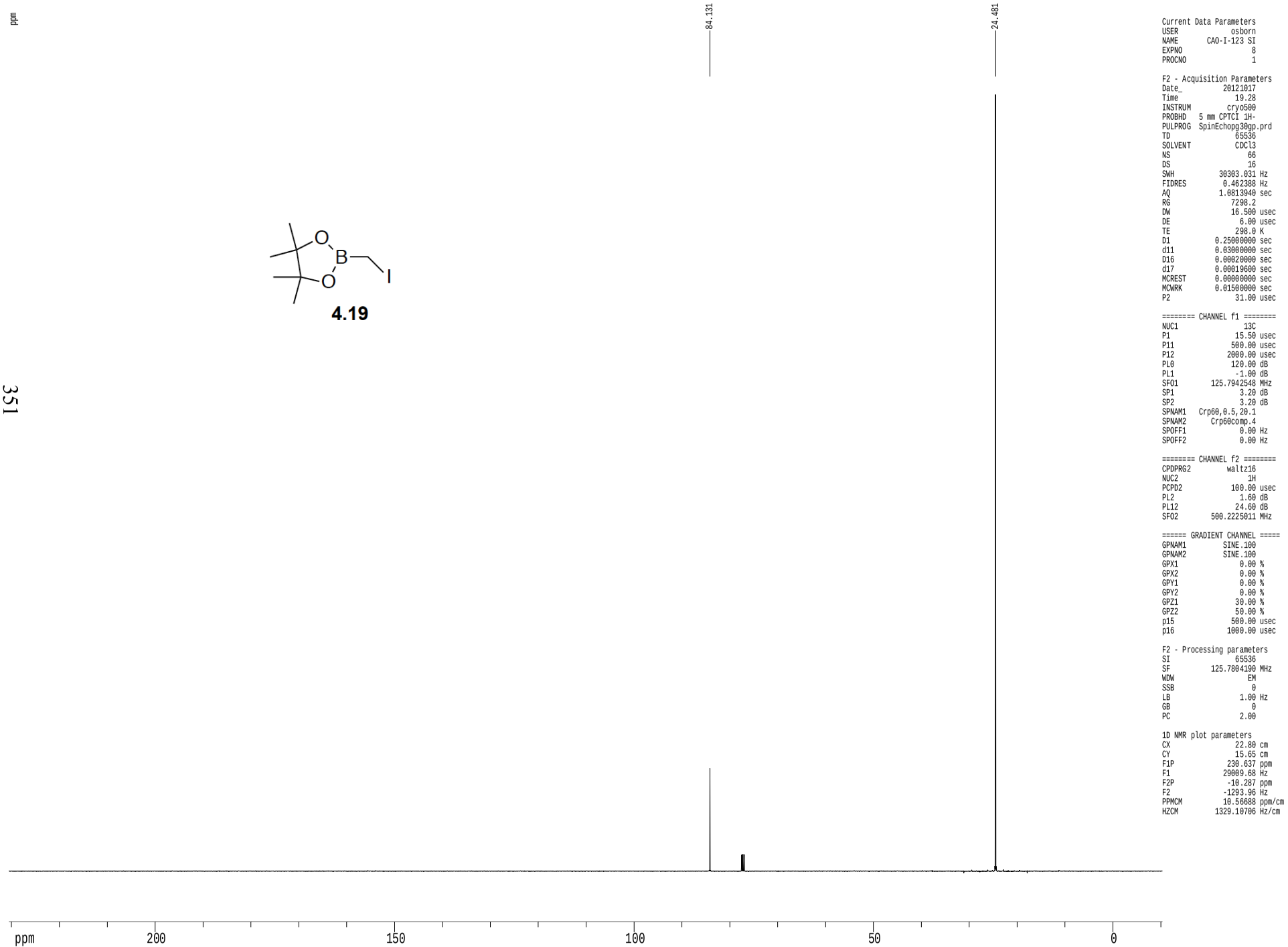


4.19

350

```
Current Data Parameters
USER             osborn
NAME        CAO-I-123 SI
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20121017
Time               9.45
INSTRUM          drx400
PROBHD   5 mm QNP H/F/P
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                    8
DS                    2
SWH           6410.256 Hz
FIDRES        0.097813 Hz
AQ            5.1118579 sec
RG                   16
DW               78.000 usec
DE                4.50 usec
TE                298.0 K
D1           0.10000000 sec
MCREST       0.00000000 sec
MCWRK        0.01500000 sec

======= CHANNEL f1 =======
NUC1                 1H
P1               12.00 usec
PL1               -0.60 dB
SFO1        400.1328009 MHz

F2 - Processing parameters
SI                65536
SF          400.1299870 MHz
WDW                  EM
SSB                   0
LB                0.30 Hz
GB                    0
PC                2.00

1D NMR plot parameters
CX               22.80 cm
CY               15.00 cm
F1P               9.000 ppm
F1             3601.17 Hz
F2P              -0.500 ppm
F2             -200.06 Hz
PPMCM          0.41667 ppm/cm
HZCM         166.72083 Hz/cm
```

Z-restored spin-echo 13C spectrum with 1H decoupling



Current Data Parameters
USER osborn
NAME CAO-I-123 SI
EXPNO 8
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121017
Time 19.28
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD 65536
SOLVENT CDCl3
NS 66
DS 16
SWH 30303.031 Hz
FIDRES 0.462388 Hz
AQ 1.0813940 sec
RG 7298.2
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 0.25000000 sec
d11 0.03000000 sec
D16 0.00020000 sec
d17 0.00019600 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
P2 31.00 usec

======== CHANNEL f1 ========
NUC1 13C
P1 15.50 usec
P11 500.00 usec
P12 2000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 125.7942548 MHz
SP1 3.20 dB
SP2 3.20 dB
SPNAM1 Crp60,0.5,20.1
SPNAM2 Crp60comp.4
SPOFF1 0.00 Hz
SPOFF2 0.00 Hz

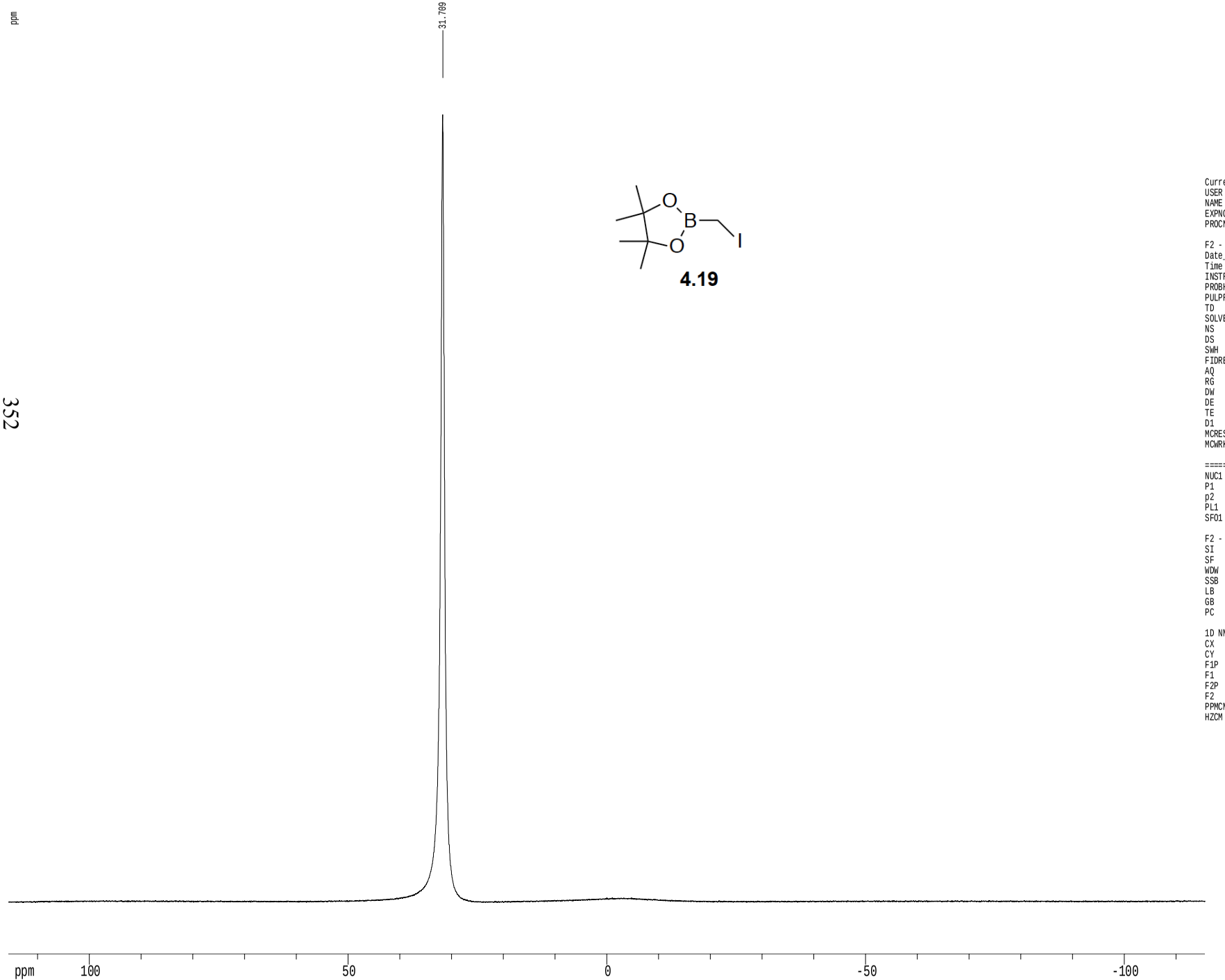
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 1.60 dB
PL12 24.60 dB
SFO2 500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPY1 0.00 %
GPY2 0.00 %
GPZ1 30.00 %
GPZ2 50.00 %
p15 500.00 usec
p16 1000.00 usec

F2 - Processing parameters
SI 65536
SF 125.7804190 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 2.00

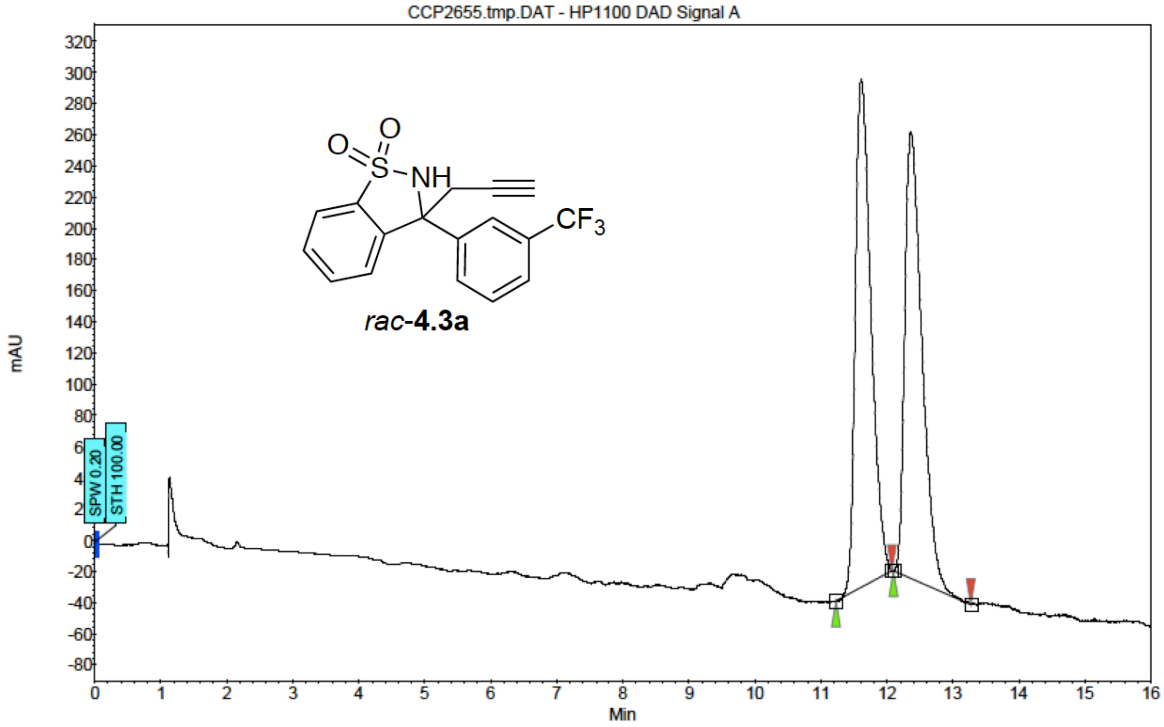
1D NMR plot parameters
CX 22.80 cm
CY 15.65 cm
F1P 230.637 ppm
F1 29009.68 Hz
F2P -10.287 ppm
F2 -1293.96 Hz
PPMCM 10.56688 ppm/cm
HZCM 1329.10706 Hz/cm

11B spectrum with 1H decoupling with background suppression

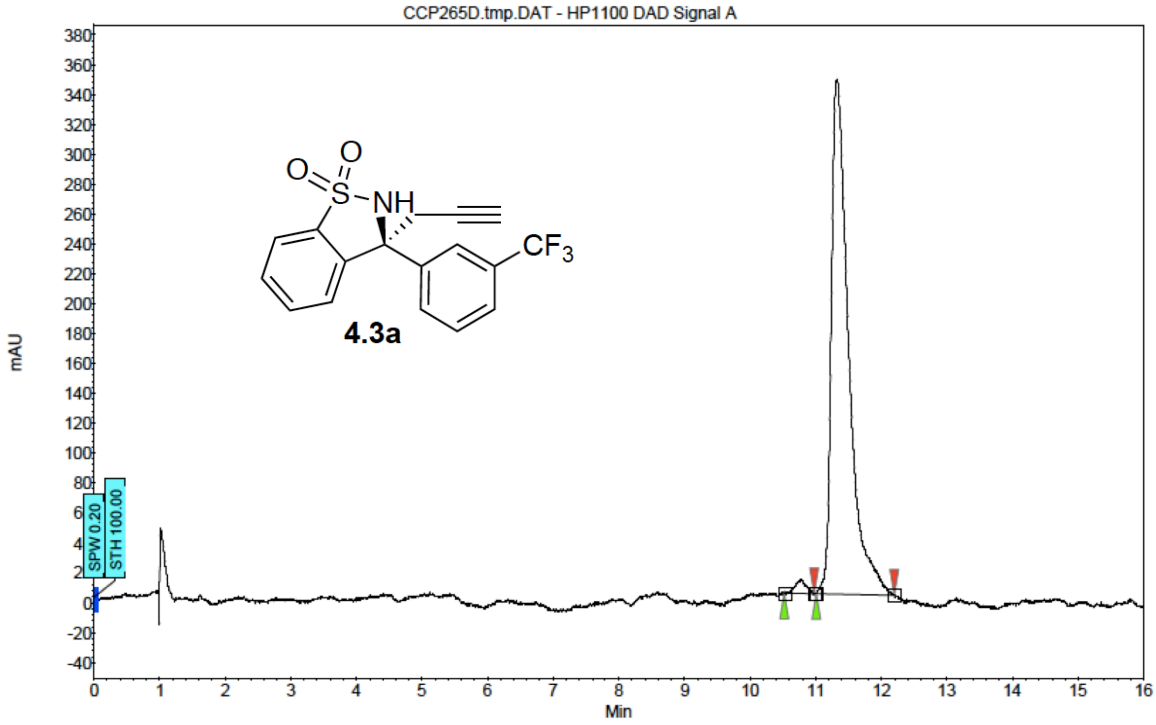


4.19

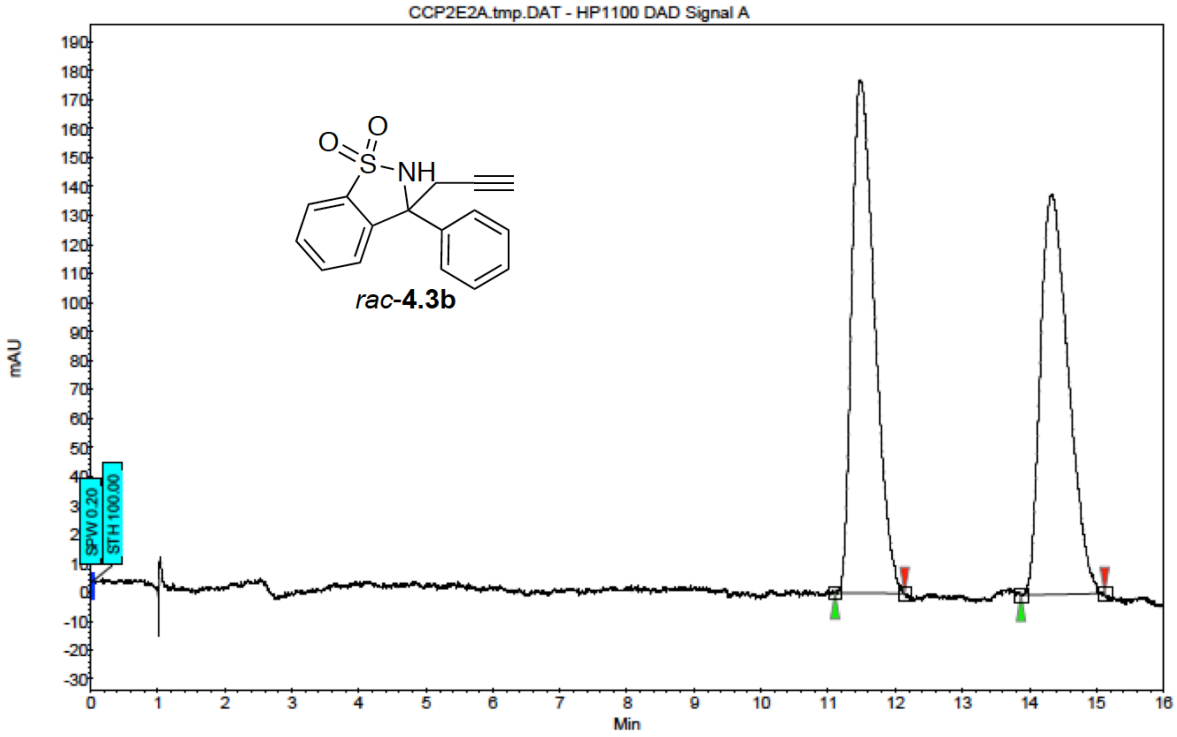
```
Current Data Parameters
USER             osborn
NAME       CAO-I-123 SI
EXPNO                 5
PROCNO                1

F2 - Acquisition Parameters
Date_          20121017
Time              10.21
INSTRUM           gn500
PROBHD   5 mm broadband
PULPROG            zgbs
TD                65536
SOLVENT           CDCl3
NS                   64
DS                    4
SWH           37037.035 Hz
FIDRES         0.565140 Hz
AQ             0.8847860 sec
RG                 90.5
DW                13.500 usec
DE                 6.00 usec
TE                298.0 K
D1            1.00000000 sec
MCREST        0.00000000 sec
MCWRK         0.01500000 sec

======= CHANNEL f1 =======
NUC1                11B
P1                 8.65 usec
p2                17.30 usec
PL1               -3.00 dB
SFO1         160.2273660 MHz

F2 - Processing parameters
SI                 65536
SF           160.2273621 MHz
WDW                   EM
SSB                    0
LB                 2.00 Hz
GB                     0
PC                 2.00

1D NMR plot parameters
CX                22.80 cm
CY                15.00 cm
F1P             115.601 ppm
F1             18522.36 Hz
F2P            -115.552 ppm
F2            -18514.67 Hz
PPMCM          10.13829 ppm/cm
HZCM         1624.43140 Hz/cm
```



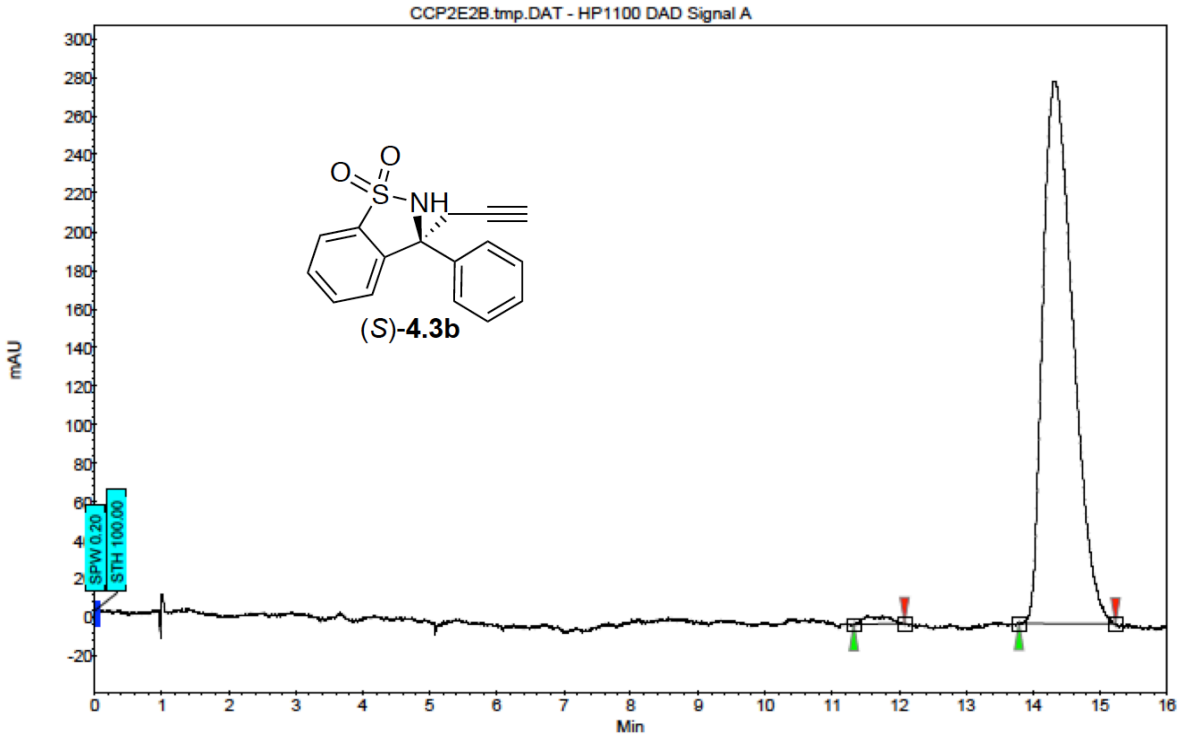
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	11.23	11.61	12.07	0.00	50.60	325.9	88.7	50.596
2	UNKNOWN	12.10	12.37	13.27	0.00	49.40	286.1	86.6	49.404
Total						100.00	612.0	175.4	100.000



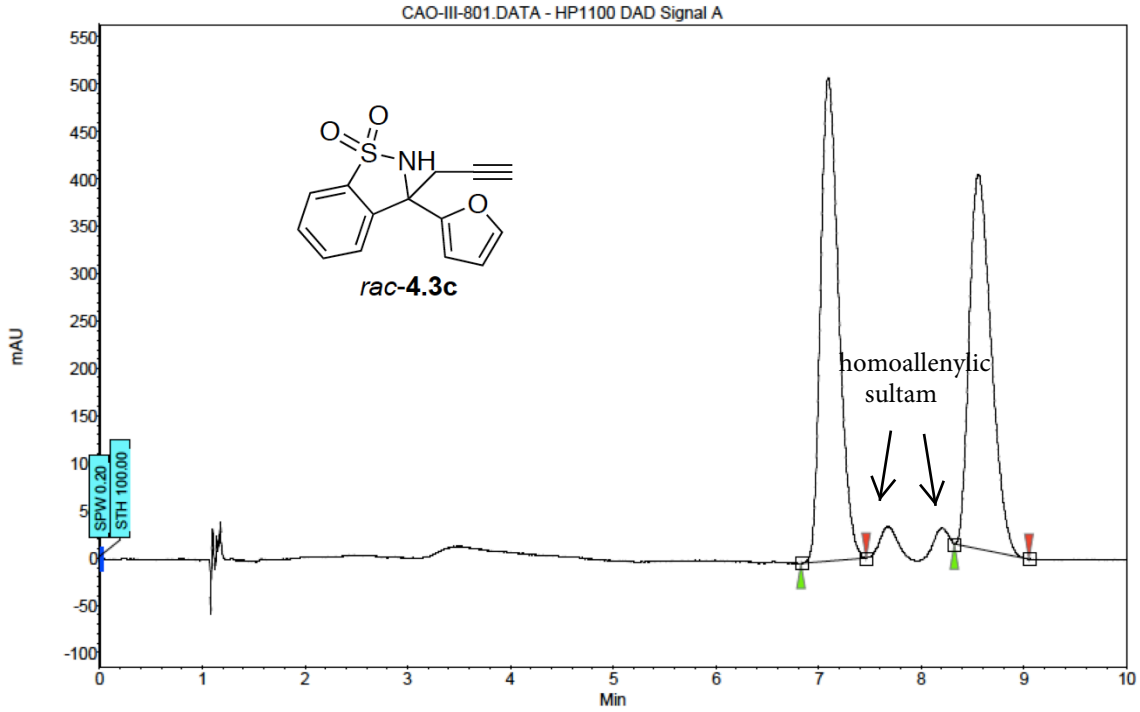
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	10.53	10.77	10.98	0.00	1.61	9.2	1.7	1.611
2	UNKNOWN	11.01	11.33	12.20	0.00	98.39	344.7	105.1	98.389
Total						100.00	353.9	106.8	100.000



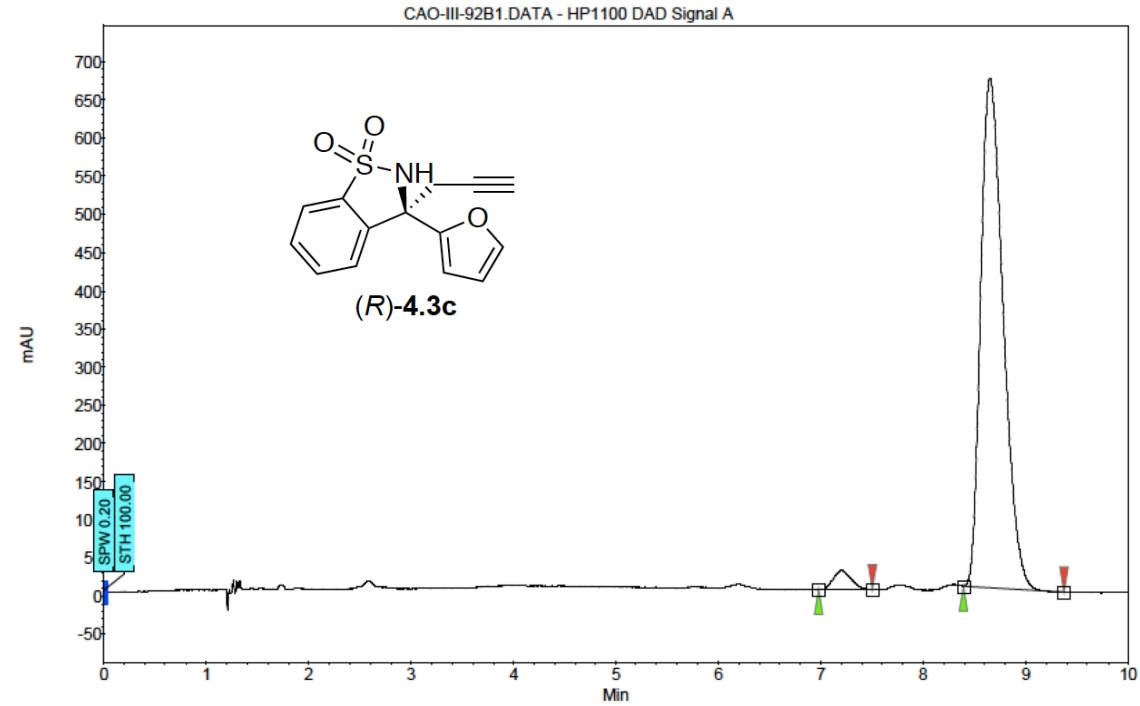
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	11.10	11.48	12.14	0.00	51.26	177.2	70.1	51.263
2	UNKNOWN	13.87	14.33	15.12	0.00	48.74	138.2	66.6	48.737



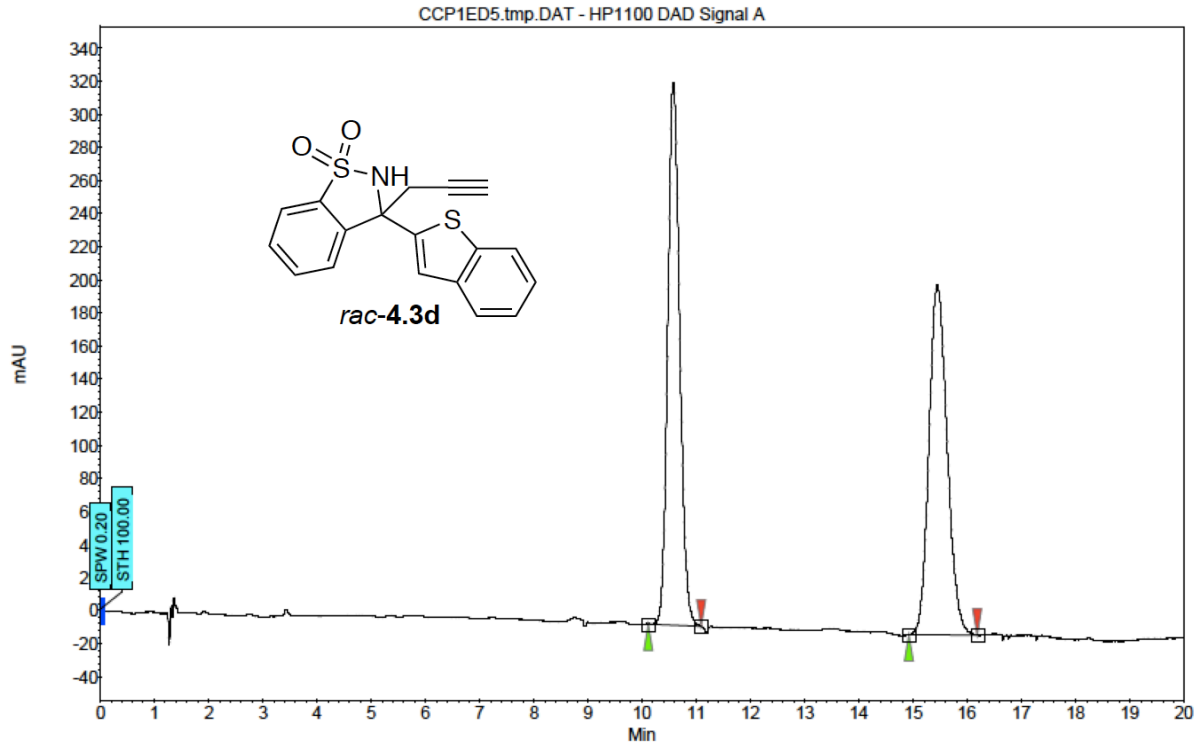
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	11.33	11.54	12.08	0.00	1.19	4.6	1.8	1.190
2	UNKNOWN	13.79	14.32	15.23	0.00	98.81	281.6	146.1	98.810
Total						100.00	286.2	147.9	100.000



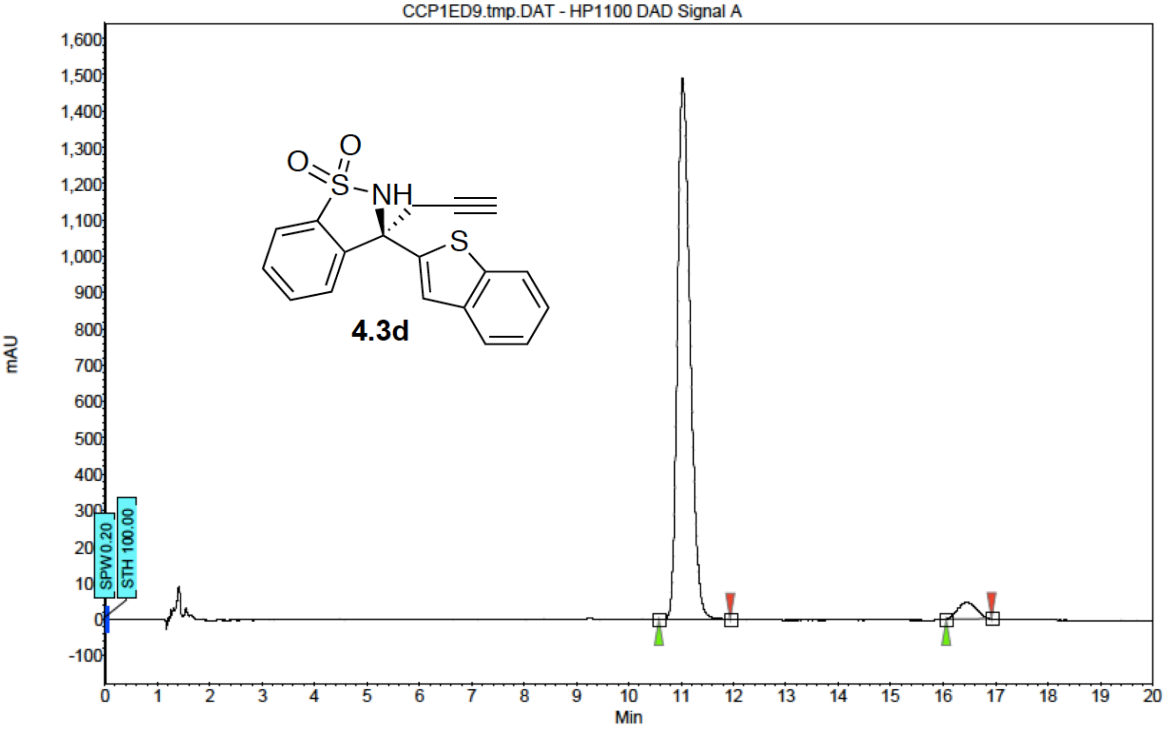
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	6.83	7.09	7.46	0.00	51.48	510.0	104.0	51.480
2	UNKNOWN	8.32	8.55	9.05	0.00	48.52	395.3	98.0	48.520
Total						100.00	905.3	202.0	100.000



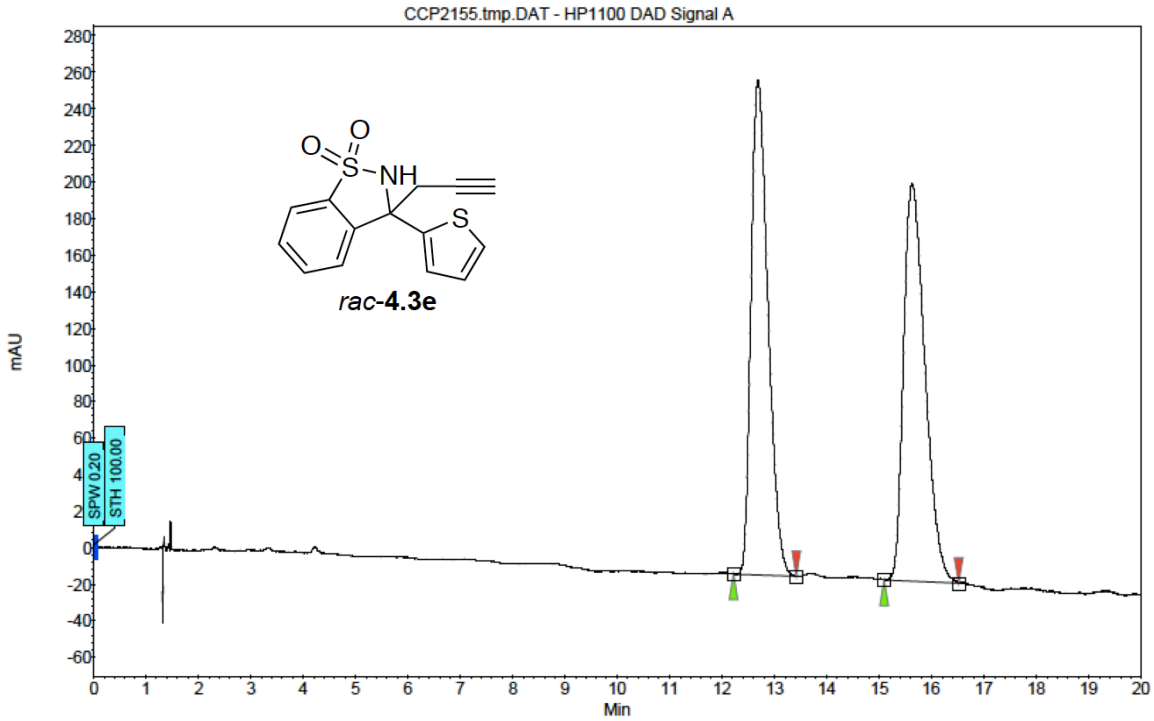
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	6.98	7.20	7.50	0.00	2.78	24.7	4.9	2.778
2	UNKNOWN	8.39	8.65	9.37	0.00	97.22	667.3	170.0	97.222
Total						100.00	692.0	174.8	100.000



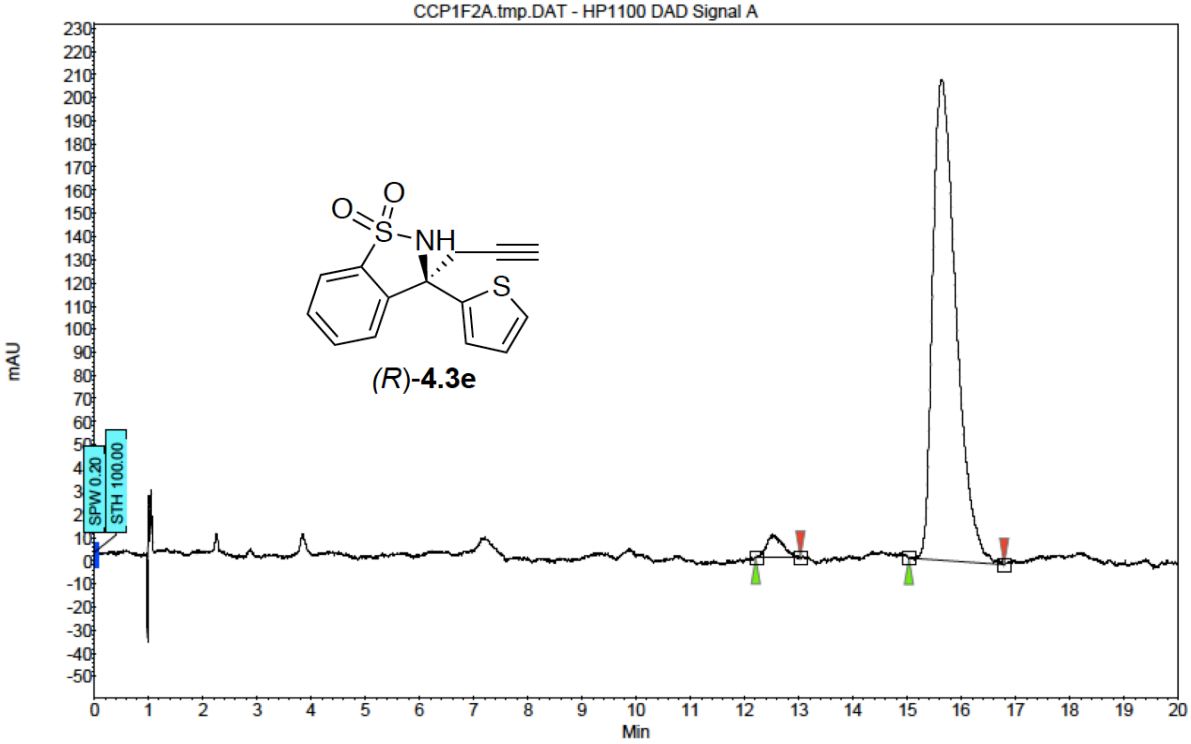
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	10.12	10.58	11.09	0.00	50.44	328.0	83.7	50.437
2	UNKNOWN	14.92	15.45	16.18	0.00	49.56	211.6	82.3	49.563
Total						100.00	539.6	166.0	100.000



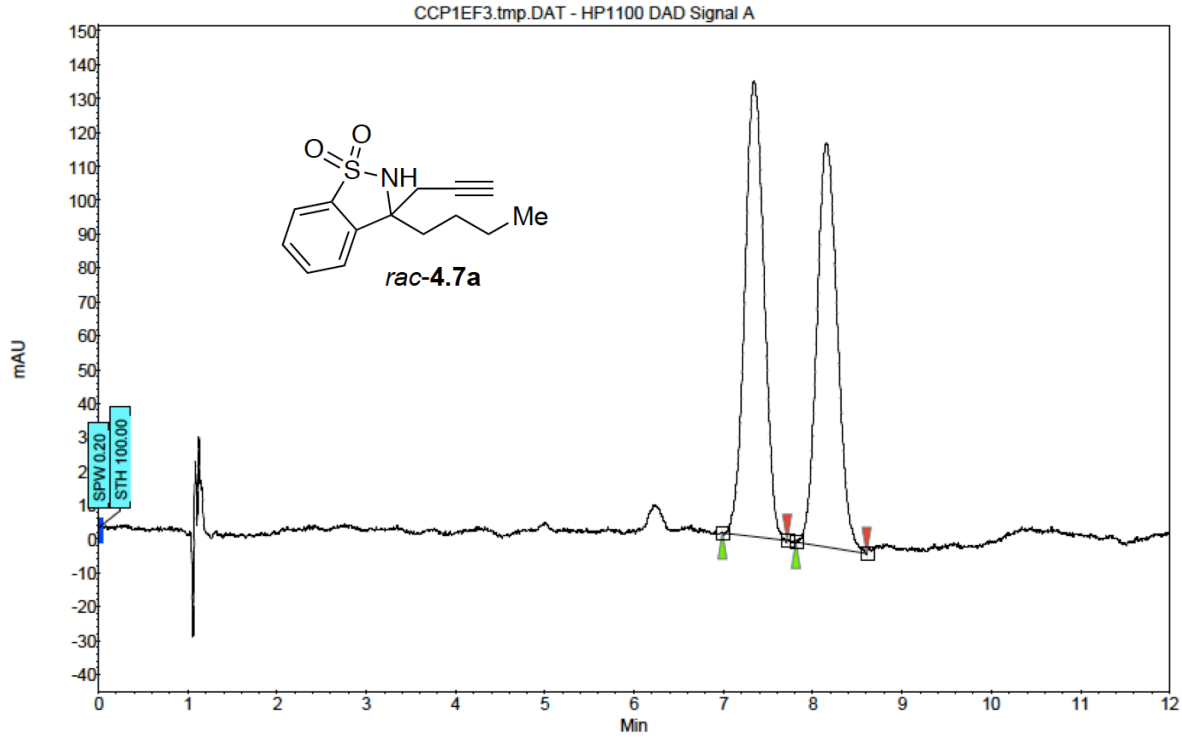
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	10.57	11.03	11.94	0.00	95.62	1491.4	417.1	95.617
2	UNKNOWN	16.05	16.46	16.92	0.00	4.38	46.7	19.1	4.383
Total						100.00	1538.0	436.3	100.000



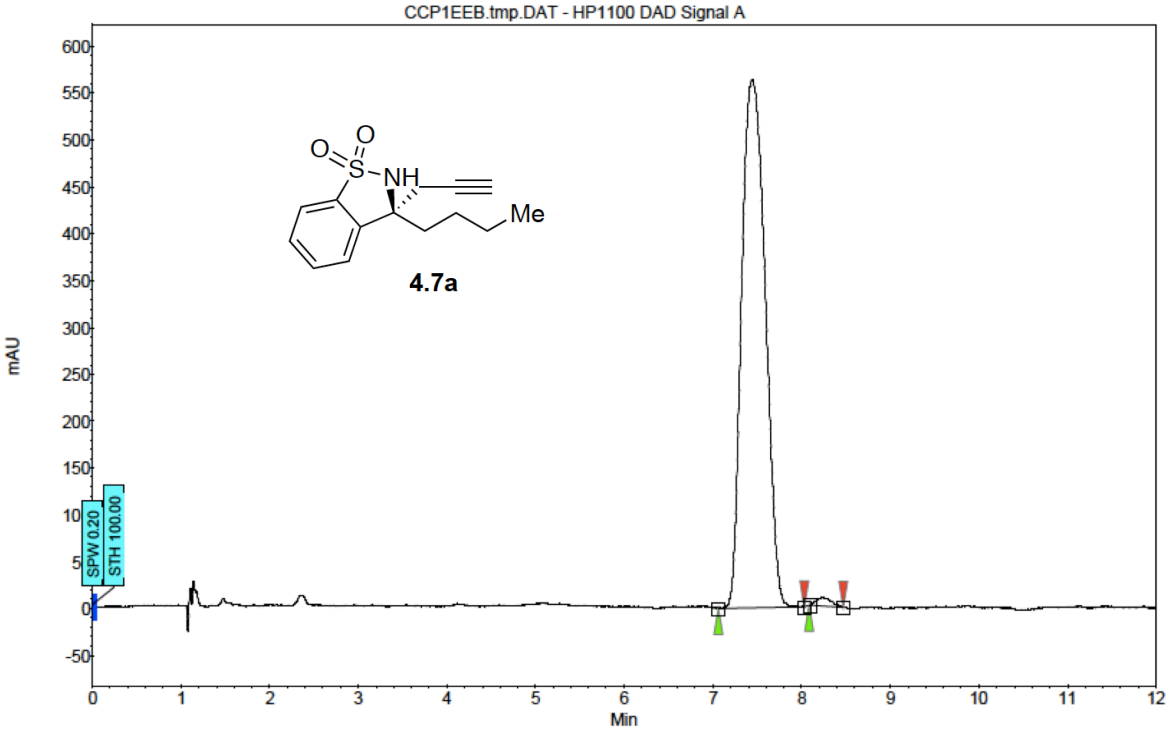
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	12.22	12.68	13.42	0.00	49.78	270.8	101.5	49.777
2	UNKNOWN	15.09	15.63	16.51	0.00	50.22	217.6	102.4	50.223
Total						100.00	488.4	203.9	100.000



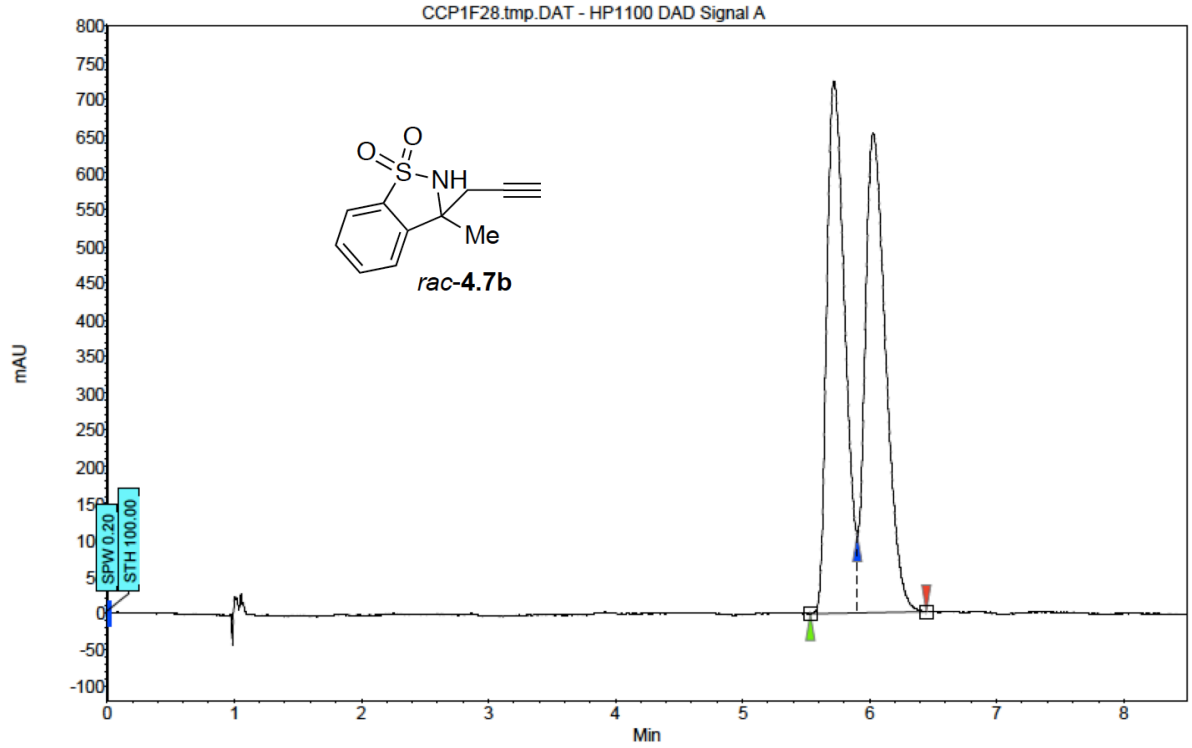
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	12.21	12.52	13.03	0.00	3.10	9.8	3.3	3.102
2	UNKNOWN	15.03	15.65	16.79	0.00	96.90	207.5	103.4	96.898
Total						100.00	217.4	106.7	100.000



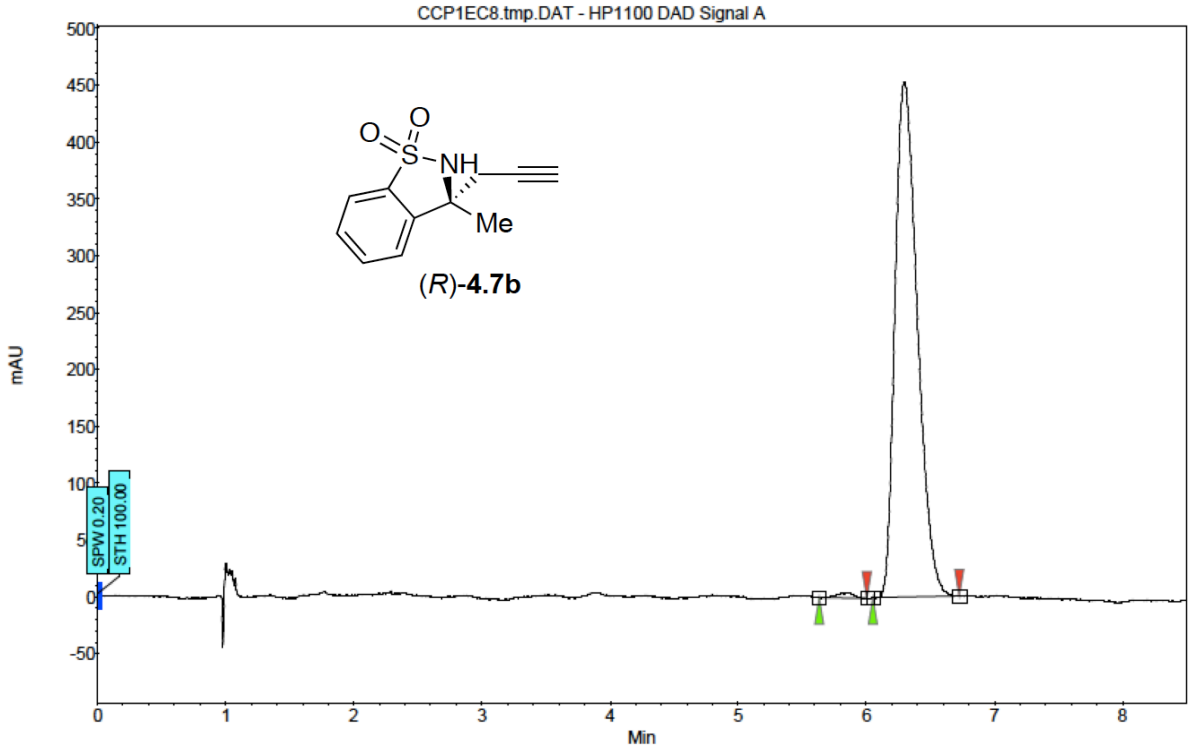
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	6.99	7.34	7.72	0.00	51.18	134.7	33.3	51.180
2	UNKNOWN	7.81	8.15	8.61	0.00	48.82	119.6	31.7	48.820
Total						100.00	254.3	65.0	100.000



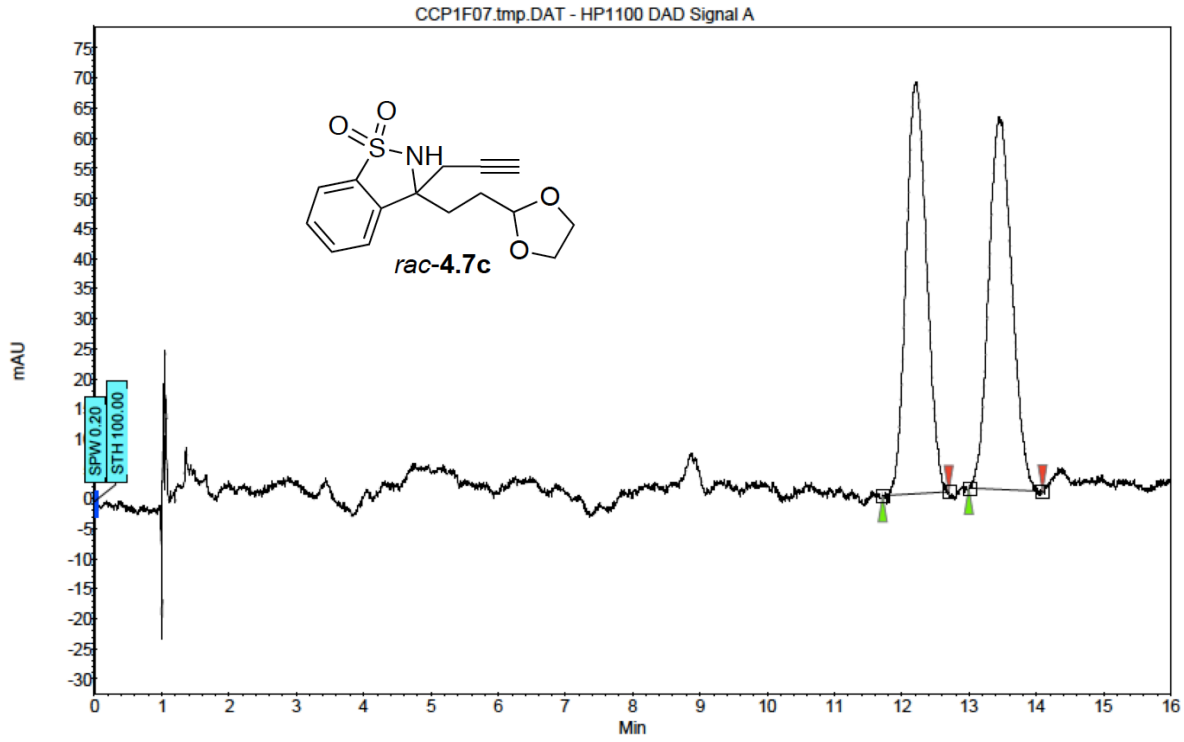
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	7.06	7.45	8.03	0.00	98.96	563.5	172.9	98.965
2	UNKNOWN	8.09	8.26	8.47	0.00	1.04	9.5	1.8	1.035
Total						100.00	573.0	174.7	100.000



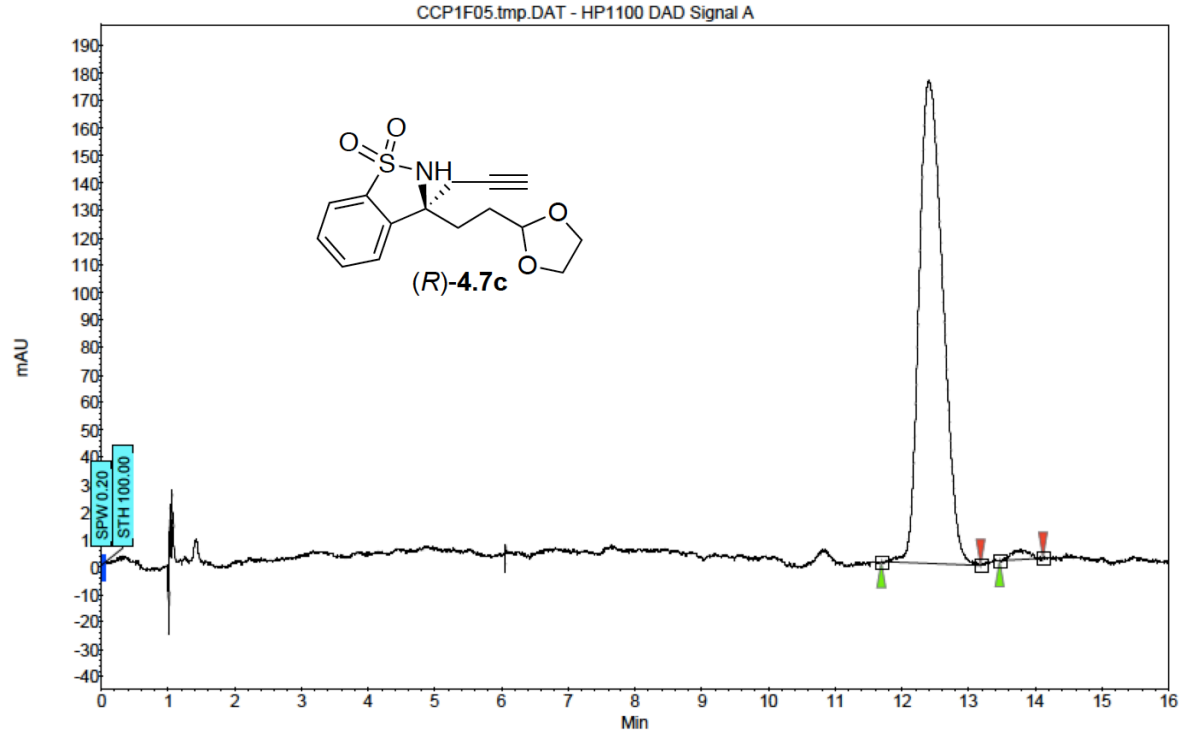
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	5.54	5.72	5.90	0.00	49.03	724.8	118.8	49.029
2	UNKNOWN	5.90	6.03	6.45	0.00	50.97	652.4	123.5	50.971
Total						100.00	1377.2	242.4	100.000



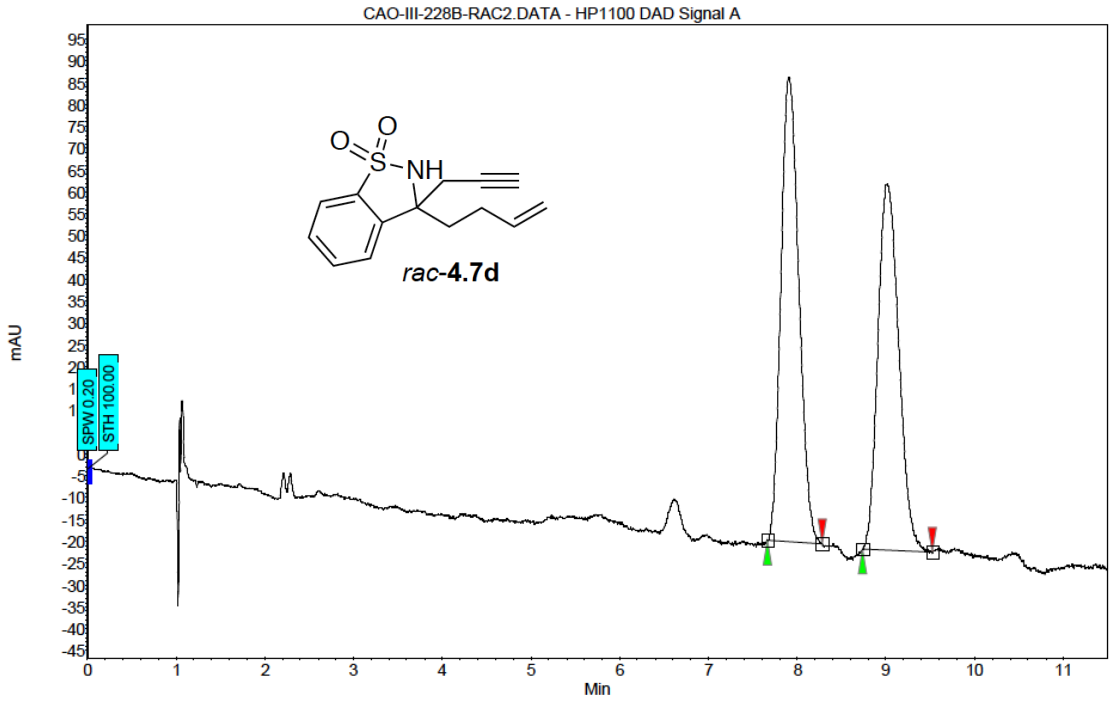
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	5.63	5.81	6.00	0.00	0.78	4.6	0.7	0.781
2	UNKNOWN	6.05	6.30	6.72	0.00	99.22	453.1	91.3	99.219
Total						100.00	457.6	92.0	100.000



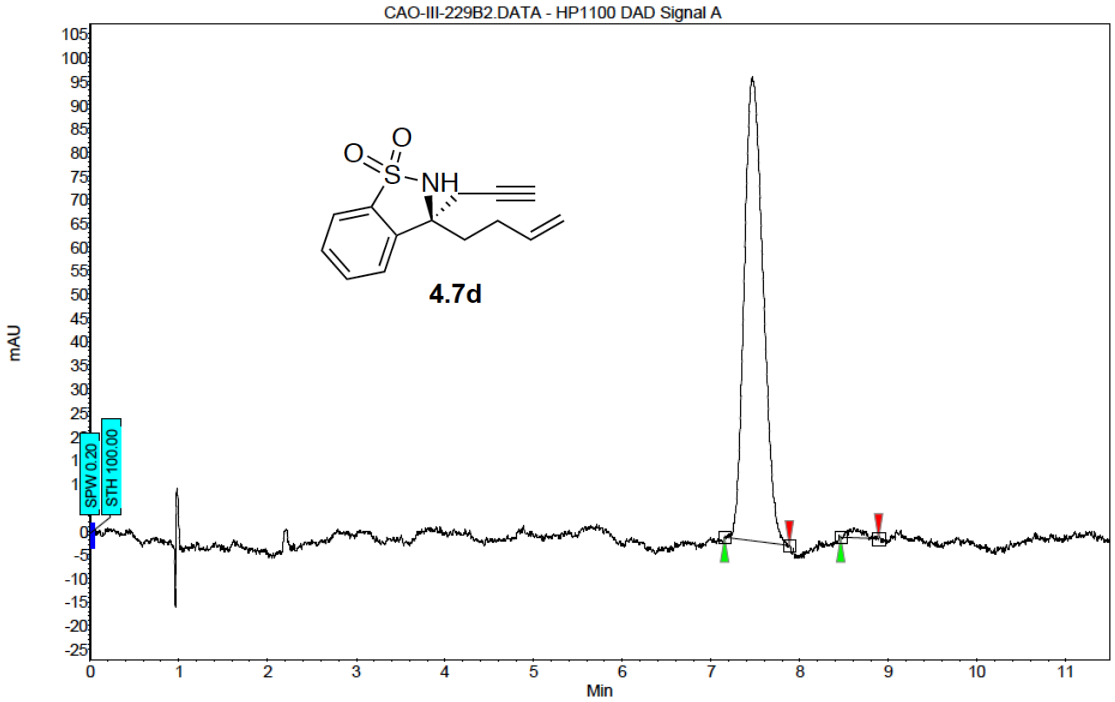
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	11.72	12.21	12.69	0.00	49.61	68.6	24.2	49.609
2	UNKNOWN	13.00	13.45	14.09	0.00	50.39	62.0	24.6	50.391
Total						100.00	130.5	48.9	100.000



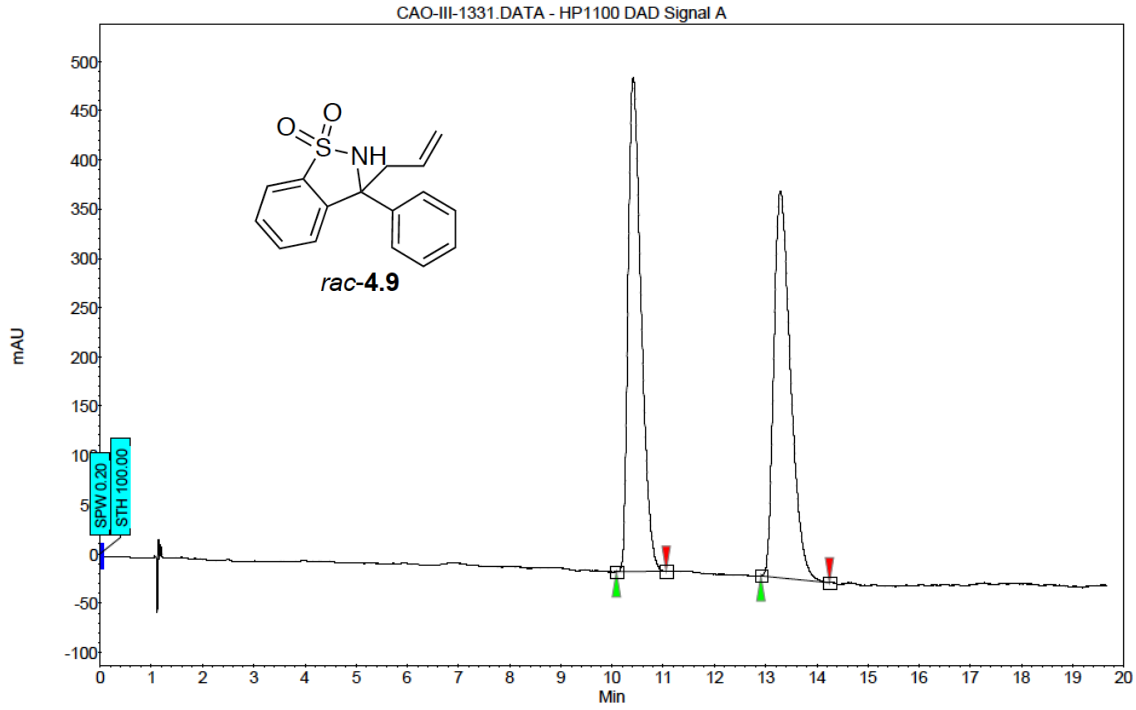
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	11.69	12.41	13.18	0.00	98.62	176.3	72.6	98.615
2	UNKNOWN	13.47	13.78	14.11	0.00	1.38	3.5	1.0	1.385
Total						100.00	179.8	73.6	100.000



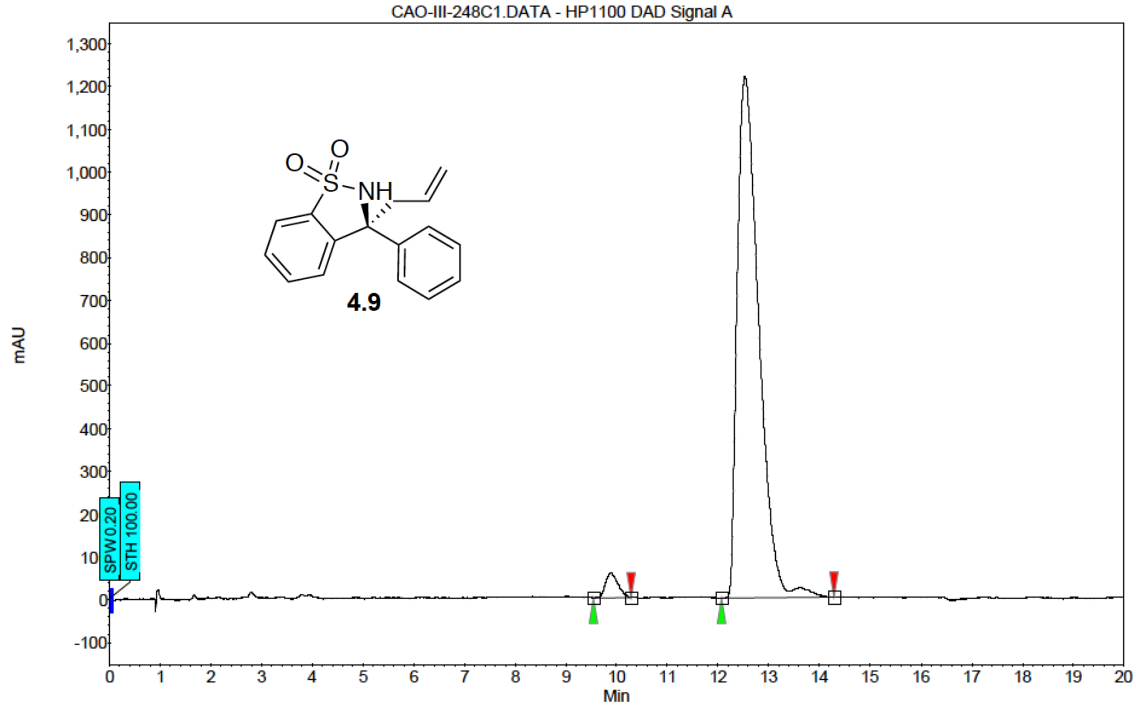
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	7.66	7.91	8.28	0.00	52.12	106.2	24.9	52.119
2	UNKNOWN	8.73	9.02	9.52	0.00	47.88	84.0	22.9	47.881
Total						100.00	190.2	47.8	100.000



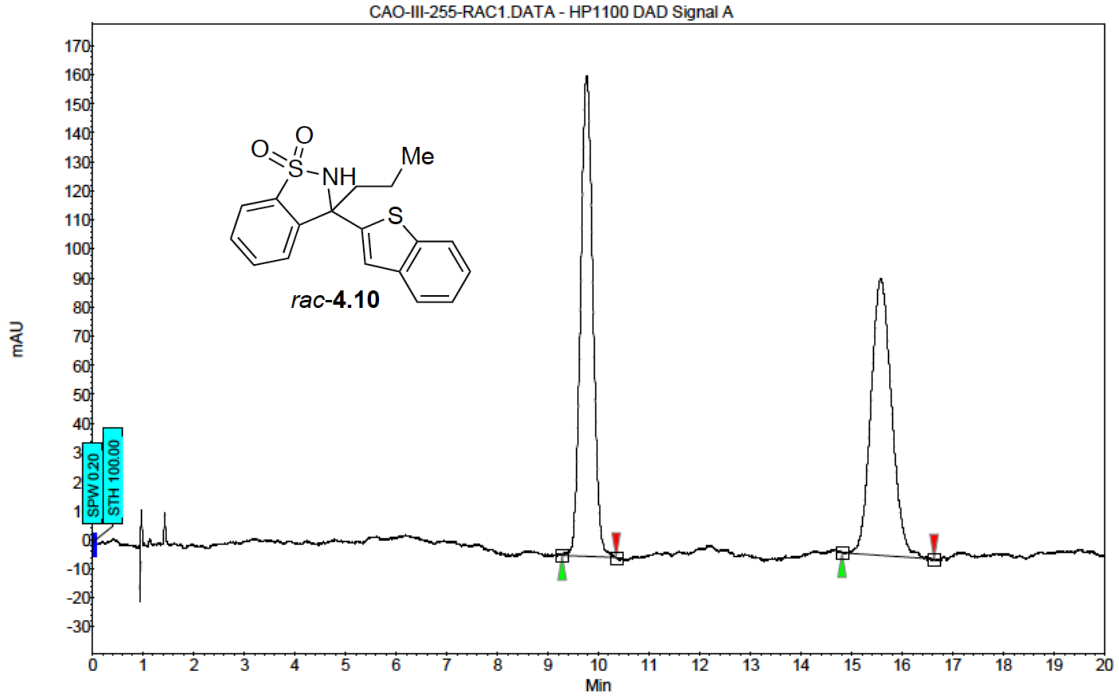
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	7.15	7.46	7.88	0.00	98.46	98.0	24.1	98.463
2	UNKNOWN	8.46	8.62	8.89	0.00	1.54	2.3	0.4	1.537
Total						100.00	100.2	24.5	100.000



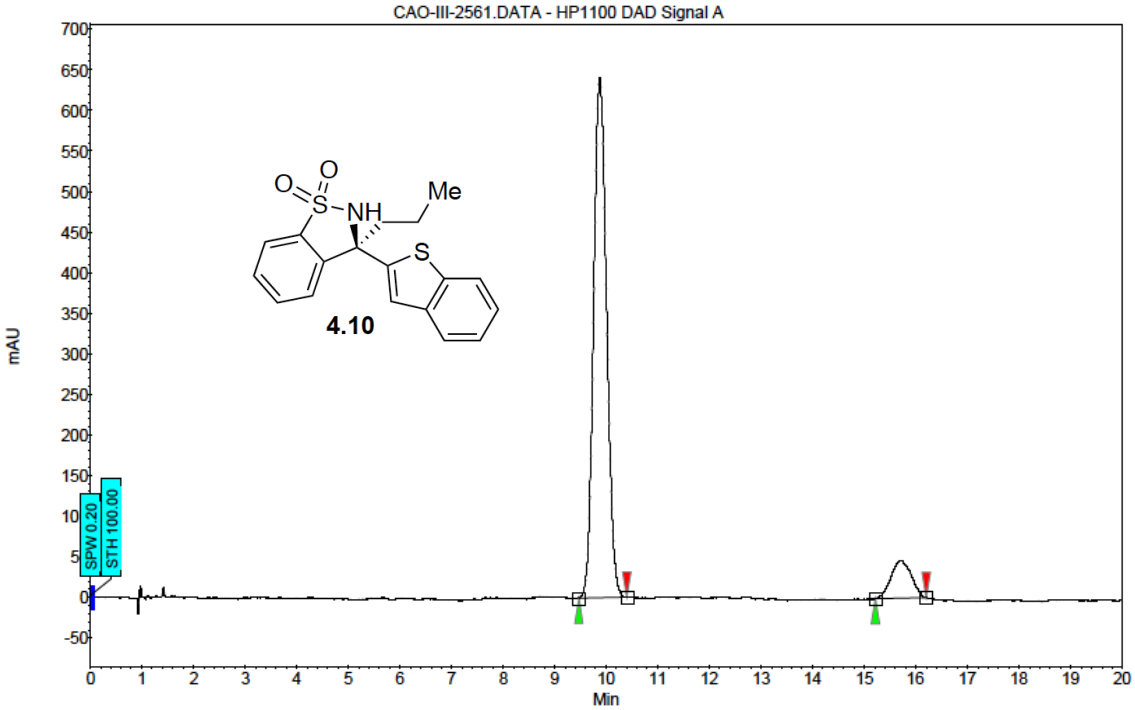
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	10.10	10.42	11.06	0.00	49.87	501.6	148.2	49.871
2	UNKNOWN	12.91	13.30	14.25	0.00	50.13	392.5	148.9	50.129
Total						100.00	894.1	297.1	100.000



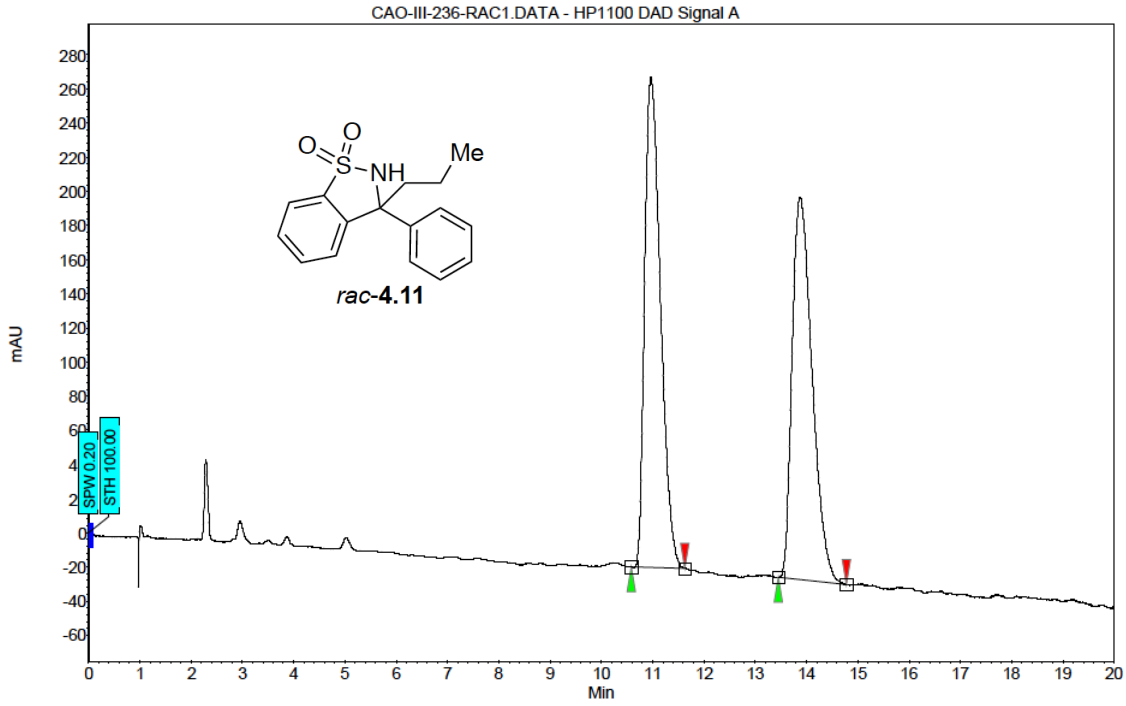
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	9.54	9.89	10.29	0.00	2.69	58.5	16.5	2.686
2	UNKNOWN	12.07	12.54	14.29	0.00	97.31	1217.8	598.1	97.314
Total						100.00	1276.3	614.6	100.000



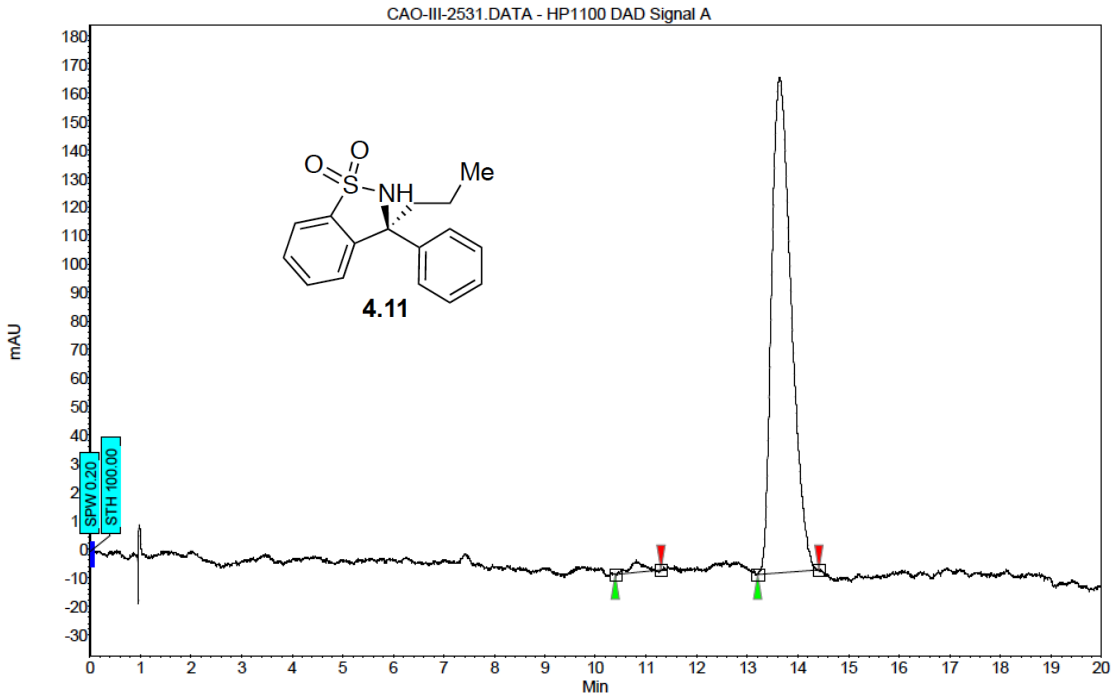
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	9.27	9.77	10.35	0.00	50.78	165.4	46.4	50.780
2	UNKNOWN	14.81	15.58	16.63	0.00	49.22	95.4	44.9	49.220
Total						100.00	260.8	91.3	100.000



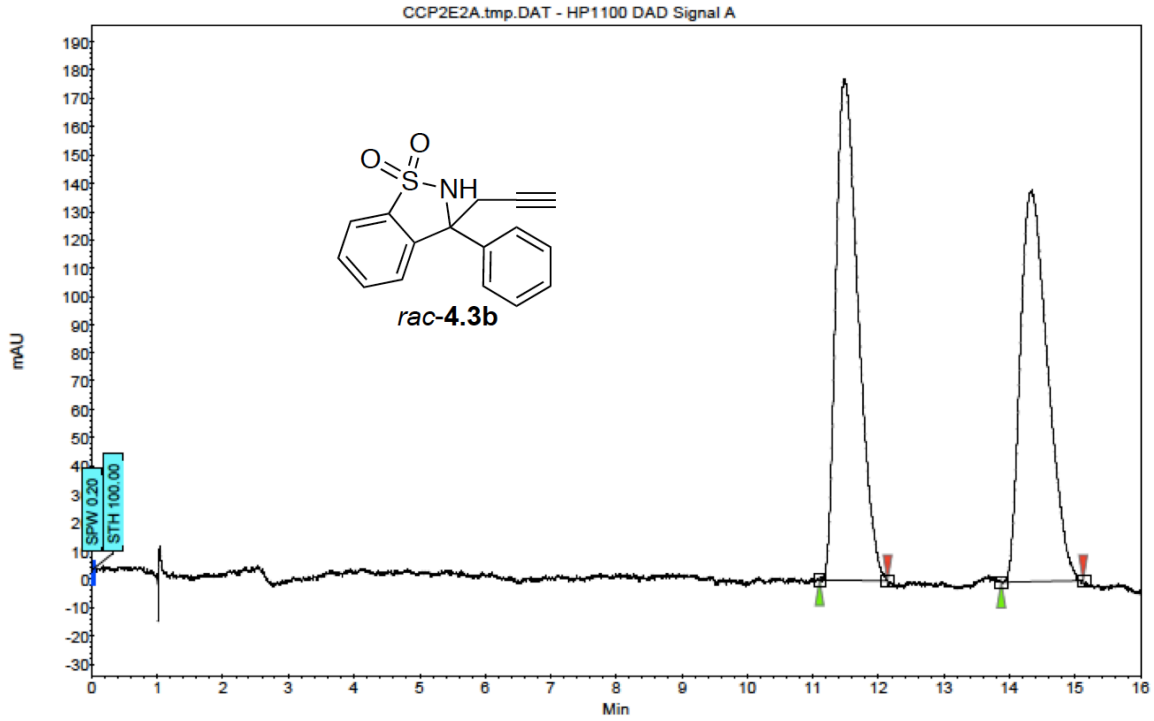
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	9.47	9.88	10.40	0.00	89.76	640.8	185.6	89.762
2	UNKNOWN	15.22	15.71	16.20	0.00	10.24	46.3	21.2	10.238
Total						100.00	687.1	206.7	100.000



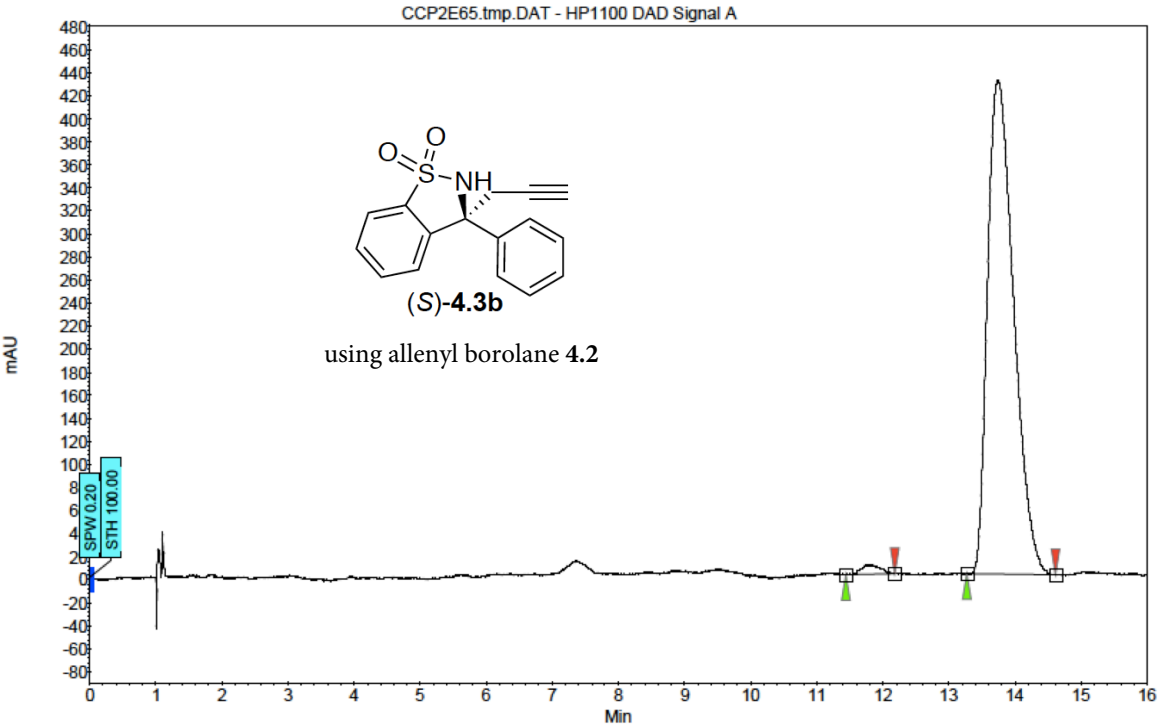
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	10.59	10.97	11.63	0.00	50.35	287.2	102.7	50.353
2	UNKNOWN	13.46	13.88	14.78	0.00	49.65	224.0	101.3	49.647
Total						100.00	511.2	204.0	100.000



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	10.39	10.81	11.29	0.00	1.46	4.4	1.2	1.464
2	UNKNOWN	13.20	13.63	14.41	0.00	98.54	173.5	77.9	98.536
Total						100.00	177.9	79.1	100.000

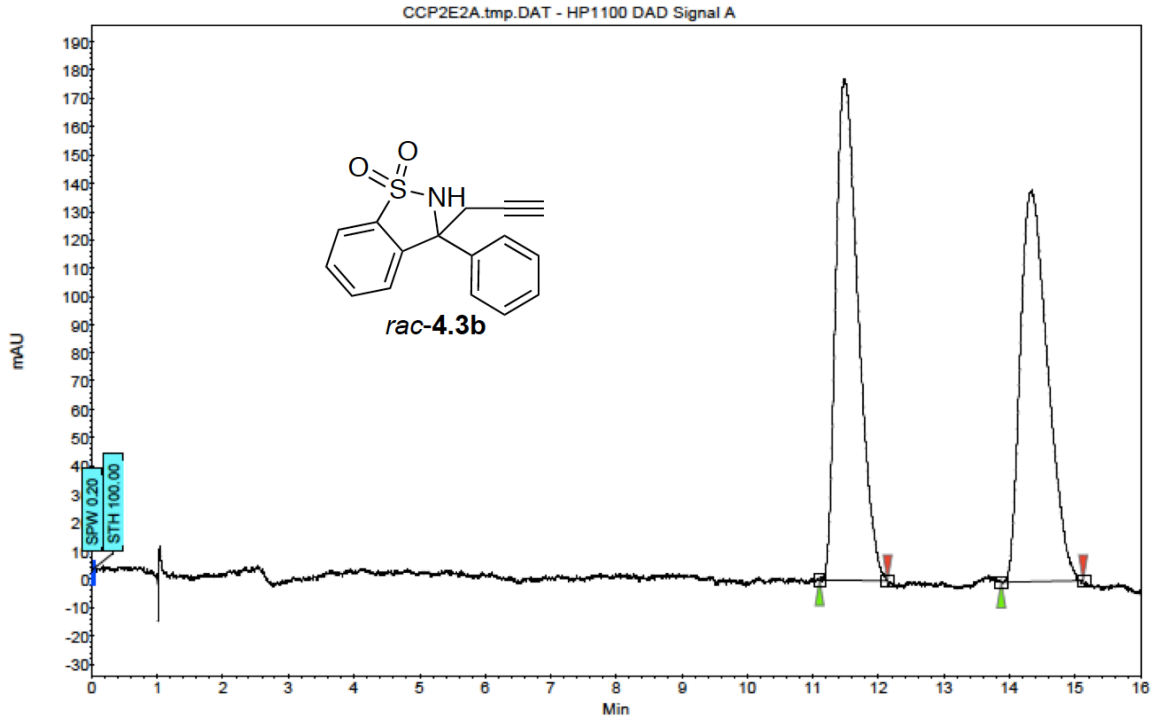


Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	11.10	11.48	12.14	0.00	51.26	177.2	70.1	51.263
2	UNKNOWN	13.87	14.33	15.12	0.00	48.74	138.2	66.6	48.737
Total						100.00	315.3	136.7	100.000

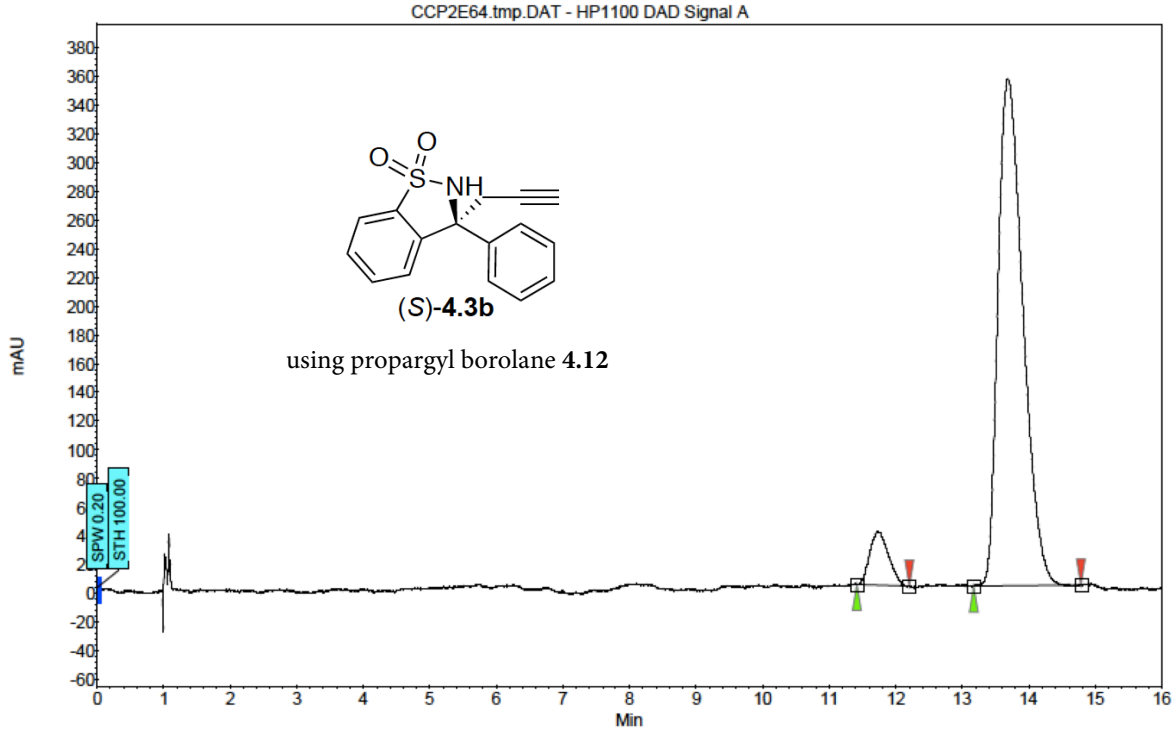


using allenyl borolane **4.2**

Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	11.44	11.78	12.18	0.00	1.38	8.5	2.7	1.379
2	UNKNOWN	13.27	13.73	14.61	0.00	98.62	428.9	196.4	98.621
Total						100.00	437.3	199.2	100.000



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	11.10	11.48	12.14	0.00	51.26	177.2	70.1	51.263
2	UNKNOWN	13.87	14.33	15.12	0.00	48.74	138.2	66.6	48.737
Total						100.00	315.3	136.7	100.000



using propargyl borolane **4.12**

Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	11.42	11.74	12.21	0.00	7.32	36.9	12.1	7.325
2	UNKNOWN	13.18	13.68	14.78	0.00	92.68	353.1	153.2	92.675
Total						100.00	390.0	165.3	100.000