Rhodium-Catalyzed Epoxide-Opening Cascades Toward Brevisin and Hemibrevetoxin B

by

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Thesis Supervisor

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Professor Stephen L. Buchwald _____ _____

to my wife, Holly, and my parents

Synthetic Studies Toward Strychnine; Rhodium-Catalyzed Epoxide-Opening Cascades

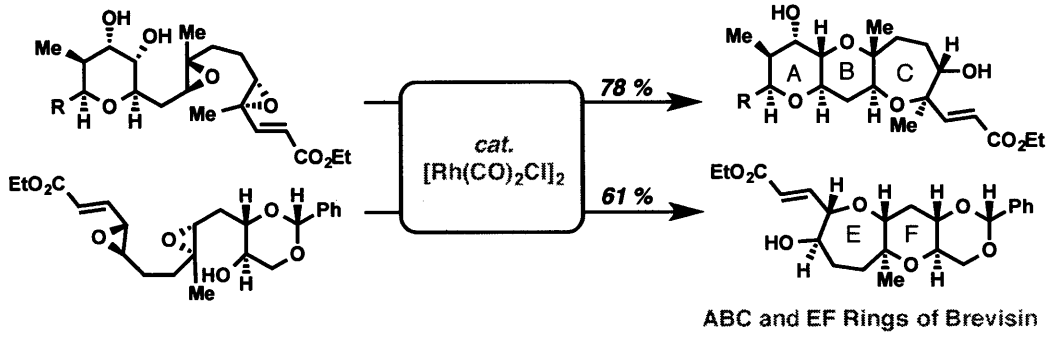
by

Kurt W. Armbrust

Submitted to the Department of Chemistry on August 20, 2014
in Partial Fulfillment of the Requirements for the Degree of Doctor of
Philosophy in Organic Chemistry

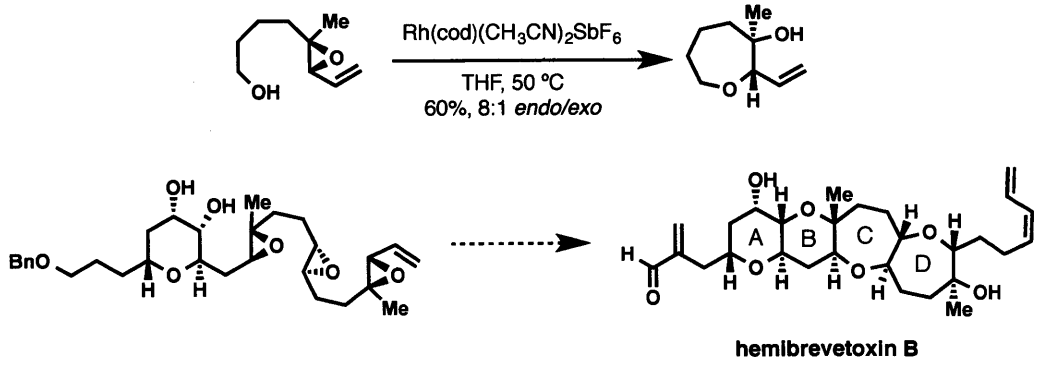
ABSTRACT

CHAPTER I. Rhodium-Catalyzed Epoxide-Opening Cascades: Formal Synthesis of (–)-Brevisin



$[Rh(CO)_2Cl]_2$ was found to be an effective catalyst for *endo*-selective cyclizations and cascades of epoxy-(*E*)-enoate alcohols, thus enabling the synthesis of oxepanes and oxepane-containing polyethers from di- and trisubstituted epoxides. Syntheses of the ABC and EF ring systems of (–)-brevisin via all *endo*-diepoxide-opening cascades using this method constitute a formal total synthesis and demonstrate the utility of this methodology in the context of the synthesis of marine ladder polyether natural products

CHAPTER II. Synthetic Studies Toward Hemibrevetoxin B



We report progress toward a biomimetic epoxide-opening cascade of the marine ladder polyether hemibrevetoxin B. Model studies demonstrate the ability of both $[Rh(CO)_2Cl]_2$ and cationic Rh(I) species to override the typical *exo*-directing of proximal methyl groups on in epoxy alcohol cyclizations for the synthesis of oxepanes. The synthesis of tri-epoxide cascade precursor and initial investigations toward an epoxide-opening cascade are described as well.

Thesis Supervisor: Timothy F. Jamison
Title: Professor of Chemistry

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I must first thank my research advisor, Professor Tim Jamison, for his continual guidance and support throughout my studies at MIT. From our initial interactions in tutorial and 5.511, to the years of challenging research projects, Tim's enthusiasm and vast knowledge of chemistry have provided guidance and inspiration. He encourages us to take full ownership of our projects, a hallmark of Tim's mentoring style, and this has enabled me to grow significantly as a scientist. Furthermore, Tim's ability to attract talented graduate students and post-docs has provided a rich environment where I've been able to develop as a chemist, mentor, and leader.

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With every new academic year, I've had the opportunity to mentor, learn from, and most importantly be inspired by the younger graduate students entering the Jamison group. To Pat Sittihan, Toma Halkina, and Beth Kelley, thank you for the never-ending helpful discussions regarding our common work toward the total synthesis of various marine ladder polyethers. I need to also thank Toma, Beth, and Sarah Tasker for their hours spent helping to improve my writing from appalling to readable. Eric Standley has been a great friend and colleague, and a great source of knowledge regarding transition metal chemistry. To the newest graduate students in the lab, Laurel Heckman, Andrew McTeague, and Charles Ocampo, thank you for continuing to make the lab a lighthearted and enjoyable place to work.

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I need to acknowledge two previous mentors who are largely reasonable for where I am today. To John Fischer, who first inspired me with the magic of chemistry at Ashwaubenon High School, thank you. To Professor Matt Zimmt, thank you for taking a bright-eyed, naïve undergraduate into your lab, teaching me the fundamentals of organic chemistry, and giving me the freedom to explore for three years at Brown University.

None of this would have been possible without the love and support from my family. To my parents, thank you for your understanding and support throughout the trials of graduate school. Finally, none of this would have been possible without the love and encouragement of my wife, Holly; thank you for standing by me through six long years. She is largely responsible for my sanity, keeping me grounded, and more importantly, challenging me to be the best version of myself.

Cambridge, MA
August 2014

TABLE OF CONTENTS

ABBREVIATIONS

9-BBN-H	9-Borabicyclo[3.3.1]nonane
Ac	acetyl
Bn	benzyl
Bu	butyl
CBz	carboxybenzyl
cod	cyclooctadiene
coe	cyclooctene
CSA	camphorsulfonic acid
d	day(s)
DART	direct analysis in real time
DCE	1,2-dichloroethane
DET	diethyl tartrate
DIBAL–H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMM	dimethoxymethane
DMSO	dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	diastereomer ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
ebi	ethylenebis(1-indenyl)
EDTA	ethylenediaminetetraacetic acid
er	enantiomer ratio
ESI	electron spray ionization
Et	ethyl
g	gram(s)
h	hour(s)
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HMDS	hexamethyldisilazide
HRMS	high-resolution mass spectometry
imid.	Imidazole
IR	infrared
LA	Lewis acid
LDA	lithium diisopropylamide
LLS	longest linear sequence
MAO	methylaluminoxane
*m*CPBA	*meta*-chloroperbenzoic acid
min	minute(s)
Me	methyl
mg	milligram(s)
MOM	methoxymethyl
MS	molecular sieves
nbd	norbornadiene
NMO	N-methyl morpholine oxide
NMR	nuclear magnetic resonance
Ph	phenyl
Phen	phenanthroline
pin	pinacol
PMP	*para*-methoxyphenyl

PPTS	pyridinium *para*-toluenesulfonic acid
Pr	propyl
pyr	pyridine
PT	phenyl-1*H*-tetrazole
rt	room temperature
rxn	reaction
t-Bu	*tert*-butyl
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydrogen peroxide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
TIPS	triisopropylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TMS	trimethylsilyl
t_R	retention time

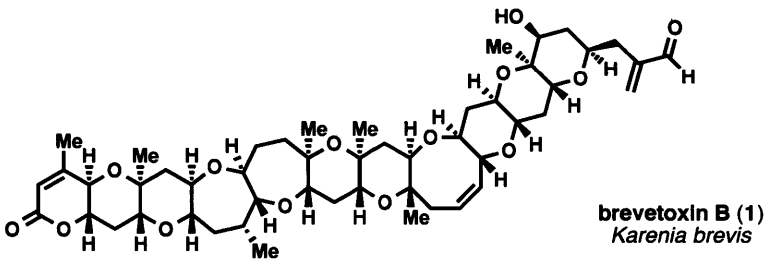
Chapter I

Rhodium-Catalyzed Epoxide-Opening Cascades: Formal Synthesis of (–)-Brevisin

A. Introduction to Ladder Polyether Natural Products

The marine ladder polyether family of natural products, isolated from marine dinoflagellates found in harmful algal blooms, is a fascinating class of potent toxins. Isolated from cultures of *Karenia brevis*, brevetoxin B (**1**) was the first structure fully elucidated for this class of molecules in 1981 (Figure 1).[1] The potent ichthyotoxicity (LC_{50} = 15 nM) and low natural abundance (5 mg/50 L cell culture) of brevetoxin B typify this class of natural products. The potent toxicity of the class results from their complex binding and interaction with voltage-gated ion channels. Upon binding, these molecules lower the activation voltage necessary for channel opening and inhibit inactivation of opened channels, resulting in persistent ion-channel activation.[2] The net result is an array of neurotoxic effects, including temperature sensitivity, muscle pain, and breathing difficulties. Conversely, a few molecules in the class have demonstrated desirable biological effects, such as antifungal (gambieric acid A)[3] and antitumor activity (gymnocin A).[4] Additionally, brevenal (**4**) has demonstrated antagonist activity to brevetoxins A (**2**) and B (**1**) for voltage gated sodium ion channels, sparking potential interest for treatment of brevetoxin poisoning in manatees.[5] Further, brevenal's ability to bind and modify the conformation of voltage-gated sodium ion-channels without additional toxic side effects has shown potential in sheep models for the treatment of cystic fibrosis.[6]

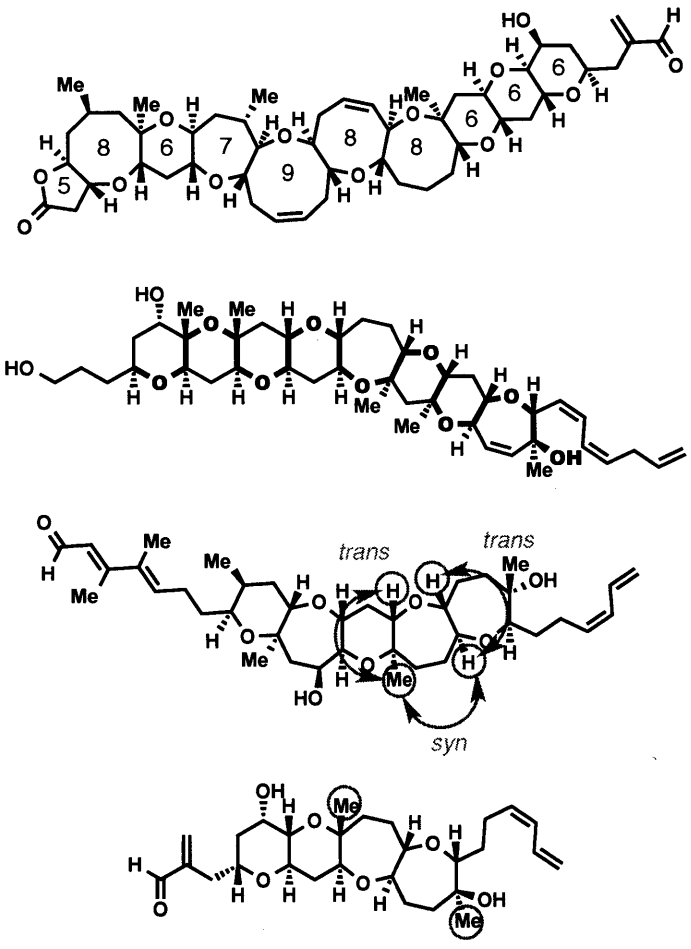
Figure 1. Structure of brevetoxin B (producing organism in italics)



[1] Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.
[2] Rein, K. S.; Lynn, B.; Gawley, R. E.; Baden, D. G. *J. Org. Chem.* **1994**, *59*, 2107.
[3] Nagai, H.; Murata, M.; Torigoe, K.; Satake, M.; Yasumoto, T. *J. Org. Chem.* **1992**, *57*, 5448.
[4] Satake, M.; Shoji, M.; Oshima, Y.; Naoki, H.; Fujita, T.; Yasumoto, T. *Tetrahedron Lett.* **2002**, *43*, 5829.
[5] Potera, C. *Science* **2007**, *316*, 1561.
[6] (a) Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, P. M.; Baden, D. G. *J. Nat. Prod.* **2005**, *68*, 2. (b) Abraham, W. M; Bourdelais, A. J.; Sabater, J. R.; Ahmed, A.; Lee, T. A.; Serebriakov, I.; Baden, D. G. *Am. J. Respir. Crit. Care Med.* **2005**, *171*, 26.

As a class, the ladder polyether natural products share a number of defining features (Figure 2). First, the molecules consist of fused oxygen heterocycles ranging from 5–9 membered sized rings, most commonly 6-membered tetrahydropyrans and 7-membered oxepanes. Second, the *trans-syn-trans* stereochemistry observed at ring junctions, in combination with the repeating C–C–O backbone give these molecules their "ladder-like" geometry. Third, the substitution at ring junctions is limited to hydrogen and methyl groups. Finally, as demonstrated with structurally modified variants of brevetoxin B, the positioning of 7-, 8-, and 9-membered rings at the ring junctions heavily influences the overall geometry and biological activity of these molecules.[2]

Figure 2. Selected examples of marine ladder polyether natural products with structural features common to the family highlighted



The limited natural abundance and potent biological activity of this class has inspired many innovative achievements in their total synthesis. Additionally, their unique structural features have provided the impetus for development of new methods to efficiently access these molecules.[7] Most method development for the synthesis of this class utilizes ingenious strategies to append rings one by one, with subsequent fragment coupling to complete the molecules. However, an alternative strategy to synthesize this class via epoxide-opening cascades, emulating the biosynthetic hypothesis, has long intrigued synthetic chemists. The biosynthetic hypothesis proposed by Nakanishi[8,9] invokes a three-step sequence shown in Scheme 1. After biosynthesis of polyene precursor (**6**), an enzymatic stereoselective epoxidation yields poly-epoxide **7**. Finally, an all-*endo* epoxide-opening cascade generates the desired ladder polyether framework (**1**). One limitation of this proposal is that formation of the larger ring, *endo*-product[10] via epoxide-opening is kinetically disfavored (vide infra), suggesting enzymatic assistance during the cascade to enforce high *endo*-selectivity. While only limited evidence for this pathway exists from feeding studies with labeled precursors,[11] support for the proposal can be found in *endo*-selective epoxide-opening enzymes that have been characterized from other organisms,[12] as well as the generation and theoretical studies of catalytic antibodies for *endo*-selective epoxy alcohol cyclizations by Janda, Lerner and Houk.[13]

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[7] Please see these reviews detailing method development and synthetic efforts towards the ladder polyether family of natural products: (a) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314. (b) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379. (c) Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7182.

[8] Nakanishi, K. *Toxicon* **1985**, *23*, 473.

[9] Nicolaou had put forth a similar biosynthetic hypothesis for a NIH grant application in 1982, revealed in a later research account: Nicolaou, K. C. *Angew. Chem., Int. Ed. Eng.* **1996**, *35*, 588.

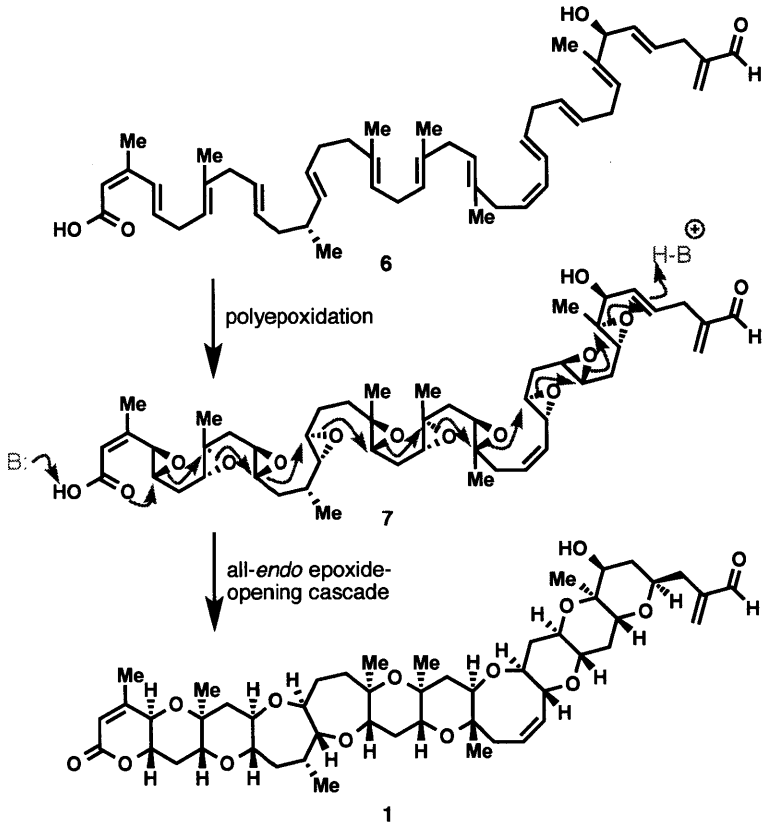
[10] Cyclizations of epoxy alcohols are not "*exo*" and "*endo*" in the traditional sense, as the C–O bond broken during the cyclization is outside the forming ring in both instances. Historically, Baldwin applied the nomenclature referenced in his work to intramolecular opening of epoxides, with terminology "*exo*" and "*endo*" referencing the smaller and larger ring products, respectively. See: Baldwin, J. E. *J. Chem. Soc., Chem. Comm.* **1976**, 734.

[11] (a) Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855. (b) Lee, M. S.; Qin, G.-W.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234. (c) Chou, H.-N.; Shimizu, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2184. (d) Yamazaki, M.; Izumikawa, M.; Tachibana, K.; Satake, M.; Itoh, Y.; Hashimoto, M. *J. Org. Chem.* **2012**, *77*, 4902.

[12] Hotta, K.; Chen, X.; Paton, R. S.; Minami, A.; Li, H.; Swaminathan, K.; Mathews, I. I.; Watanabe, K.; Oikawa, H.; Houk, K. N.; Kim, C.-Y. *Nature* **2012**, *483*, 355.

[13] (a) Janda, K.; Shevlin, C.; Lerner, R. *Science* **1993**, *259*, 490. (b) Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 2659. (c) Na, J.; Houk, K. N.; Shevlin, C. G.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 8453. (d) Na, J.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 9204.

Scheme 1. Proposed biosynthetic hypothesis for brevetoxin B (**1**)



Guided by the proposed biogenesis of these compounds, several groups, including ours, have investigated the feasibility of all-*endo* epoxide-opening cascades as a rapid and general approach to these and other polyethers.[14] Cascades proceeding in an entirely *endo*[10] selective fashion have been of particular interest to us, as they would allow direct access to the ladder polyether class. We are further motivated by the success of total syntheses utilizing biomimetic all–*exo* epoxide-opening cascades patterned after the related Cane–Celmer–Westley biosynthetic hypothesis for marine polyether ionophore natural products.[15,16] However, unlike the all-*exo* cascades, the proposed all-*endo* cascades present an ongoing challenge, as formation of the larger *endo* ring product is generally kinetically disfavored relative to the *exo* ring product.

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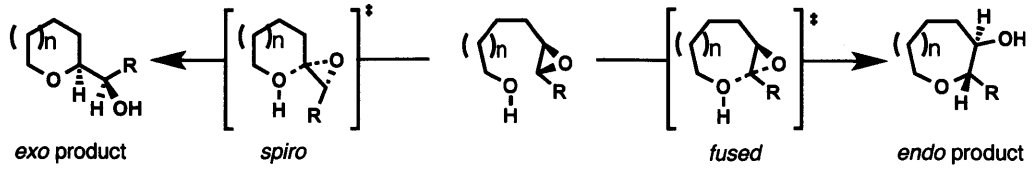
[14] Vilotijevic, I.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250.

[15] In addition to the discussion of biomimetic all-*exo* epoxide opening cascades in ref. 14, please see the following illustrative examples: (a) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9328. (b) Yang, P.; Li, P.-F.; Qu, J.; Tang, L.-F. *Org. Lett.* **2012**, *14*, 3932.

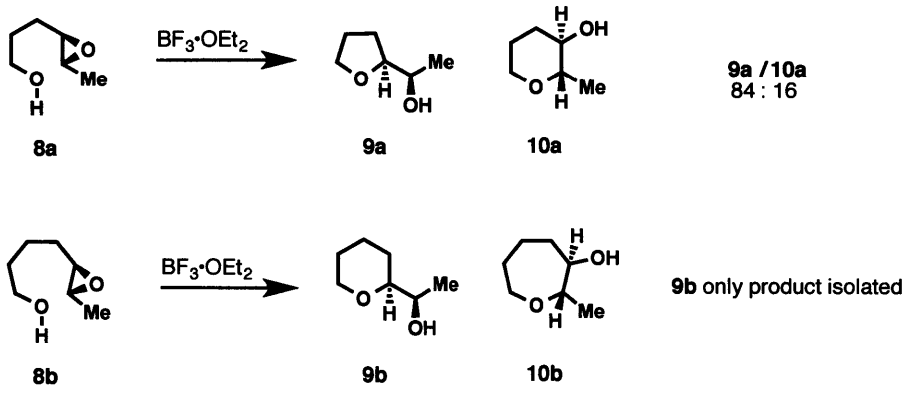
[16] Cane, D. E.; Celmer, W. D.; Westly, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594.

Scheme 2. Two possible transition states and products from epoxy alcohol cyclization



Cyclization of an epoxy-alcohol can proceed via two transition states shown in Scheme 2: the *spiro* transition state, leading to the *exo* product, and the *fused* transition state, leading to the *endo* product.[10] Experimentally, the *exo* product is favored in systems without electronic-bias present, as seen in Scheme 3. The reaction of epoxy alcohol **8a** produces two products: the smaller ring, 5-membered tetrahydrofuran **9a** (THF) via an *exo*-type closing, or the larger ring, 6-membered tetrahydropyran **10a** (THP) via an *endo*-type closing. Subjection of **8a** to BF_3•OEt_2 yields a 16:84 ratio of the *endo* product (**10a**) to the *exo* product (**9a**), demonstrating the strong kinetic[17] preference for the *exo* pathway.[18] Increasing the tether length by one methylene to epoxy alcohol **8b** yields two possible products: the *exo* product THP **9b**, and the *endo* product, oxepane **10b**. As seen with **8a**, cyclization of **8b** provides *exo* THP **9b** as the major product, with none of the *endo* oxepane **10b** observed.

Scheme 3. Product distribution from BF_3•OEt_2-promoted cyclization of epoxy alcohols **8a** and **8b**



[17] The THP product **9a** is actually lower in energy due to the lower ring strain in the THP relative to THF product **9a**. However, this reaction is irreversible under the reaction, conditions, yielding the THF as the primary product.

[18] Coxon, J.; Hartshorn, M.; Swallow, W. *Aust. J. Chem.* **1973**, *26*, 2521.

B. *Endo*-Selective Epoxide-Opening Cyclizations and Cascades

Methodology developed in the Jamison group has addressed the challenge of poor *endo*-selectivity through the use of template-guided, water-promoted cascades to enable rapid synthesis of poly-tetrahydropyran fragments.[19] This methodology is capable of promoting cyclizations of THP-templated epoxy alcohols (**11**) and poly-epoxy alcohols (**14**) with high *endo*-selectivity (Scheme 4, eq 1 and 2). Further work has demonstrated tolerance of methyl substitution on the epoxides without significant loss to yields and selectivity.[20] Most recently, modification of the THP-template to a 1,3-dioxane type template (**16**) has yielded cascade products amenable for use in synthesis of ladder polyethers, for example **17**, which can be further elaborated towards the FGH rings of gambierol (**3**) (Scheme 4, eq 3).[21]

Importantly, however, this methodology is not amenable to the synthesis of oxepanes, which represent an important structural motif present in nearly every ladder polyether natural product isolated to date.[22,23] Attempts to promote formation of an oxepane via an *endo*-selective epoxy alcohol cyclization utilizing this methodology have proven unsuccessful, providing only the *exo* THP product **20** (Scheme 4, eq 4).[24] Detailed mechanistic studies have revealed that the THP template and water disproportionately reduce the rate of *exo* cyclization relative to *endo* cyclization, leaving the 6-*endo* product **12** as both the thermodynamic and kinetic product.[24] With regard to the cyclization of **18**, the 6-*exo* THP product (**20**) is predicted to be the kinetic and thermodynamic product under most conditions, likely minimizing the impact of the THP template and water activation towards formation of the 7-*endo* oxepane **19**. To expand our synthetic efforts in this field, we have undertaken the goal of developing alternative methods for the synthesis of oxepanes utilizing epoxide-opening cascades.

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[19] (a) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189. (b) Morten, C. J.; Byers, J. A.; Van Dyke, A. R.; Vilotijevic, I.; Jamison, T. F. *Chem. Soc. Rev.* **2009**, *38*, 3175.

[20] Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678.

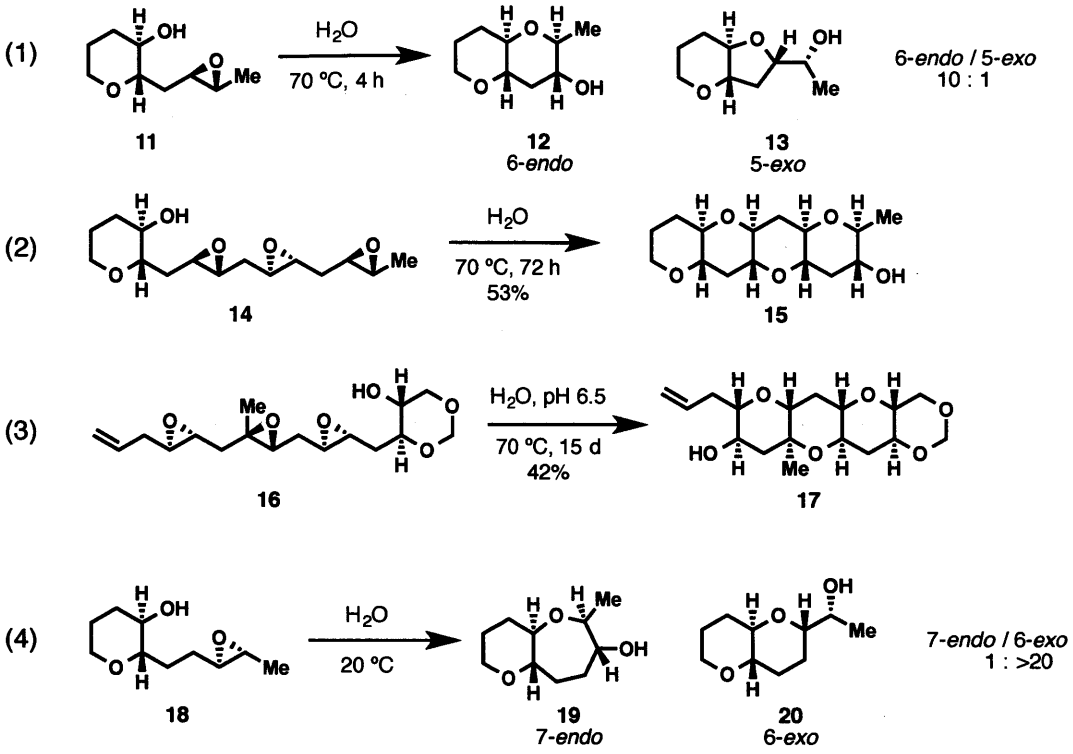
[21] (a) Van Dyke, A. R.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 4430. (b) Mousseau, J. J.; Morten, C. J.; Jamison, T. F. *Chem. Eur. J.* **2013**, *19*, 10004. (c) Morten, C. J. Ph.D. Dissertation. Massachusetts Institute of Technology, Cambridge, MA, 2011.

[22] A variety of alternative methods for the synthesis of oxepanes have been reported. Please see the following review for recent developments of alternative methods for the synthesis of oxepanes and medium-ring cyclic ethers: Kleinke, A. S.; Webb, D.; Jamison, T. F. *Tetrahedron* **2012**, *68*, 6999.

[23] Oxepanes, oxocanes, and oxonanes in ladder polyethers are often used as sites of fragment coupling for the convergent synthesis of these natural products.

[24] Byers, J. A.; Jamison, T. F. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 16724.

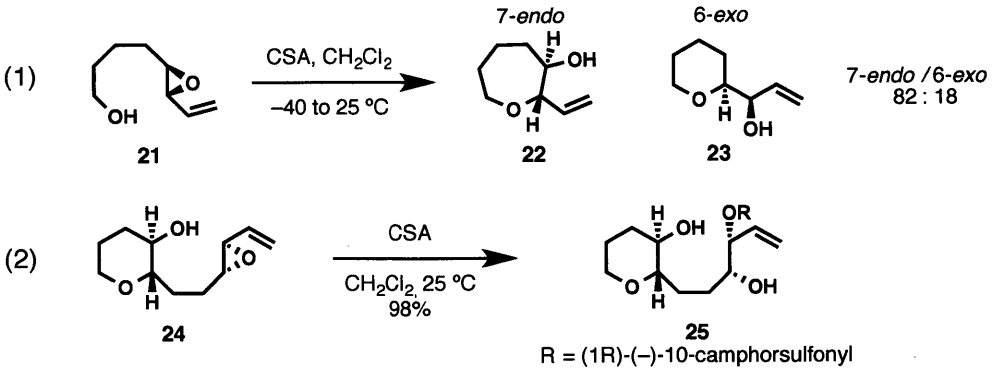
Scheme 4. THP-templated, water-promoted cyclizations of epoxy alcohols



Historically, alternative approaches to synthesizing oxepanes via epoxy alcohol cyclizations and cascades have utilized various directing groups. Nicolaou and coworkers investigated the ability of alkenyl epoxides to bias the cyclization toward the *endo* product, utilizing π-stabilization of the epoxonium intermediate to impart the desired selectivity. Cyclization of **21** under acid catalysis provided high *endo*-selectivity with vinyl substituents, providing oxepane **22** in good yield (Scheme 5, eq 1).[25] Unfortunately, this methodology appears to be limited to cyclization of substrates with primary alcohol trapping nucleophiles, as attempts to use secondary alcohol **24** with a preformed THP template led to trapping of the conjugate base during epoxide opening, yielding only **25** (Scheme 5, eq 2). While epoxide activation with CSA appears suitable for poly-THP formation,[25a] the higher activation barrier with respect to formation of oxepanes appears to limit use of weaker nucleophiles such as the secondary alcohols necessary for our goals.

[25] (a) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (b) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335.

Scheme 5. Brønsted acid catalyzed epoxy alcohol cyclizations towards oxepanes with vinyl directing groups



To circumvent the poor reactivity observed above, McDonald and coworkers have utilized a second epoxide as a trapping nucleophile, generating a highly reactive bicyclo[n.1.0] epoxonium. Subsequent trapping by a terminating nucleophile generates (poly-fused) oxygen heterocycles. McDonald and coworkers have reported all-*endo* epoxide-opening cascades utilizing this strategy in concert with suitable methyl-directing groups to successfully form oxepane (**27**) and poly-oxepane (**29a**) products under BF_3•OEt_2 promotion (Scheme 6, eq 1 and 2).[26] While the use of methyl-directing groups is necessary for successful *endo*-trapping of the pendant carbonate nucleophile (eq 4), substrate **28b** with a *trans*-disubstituted epoxide yields all-*endo* product **29b** (eq 3), demonstrating an alternative influence on regioselectivity for epoxonium trapping by a subsequent epoxide.[27]

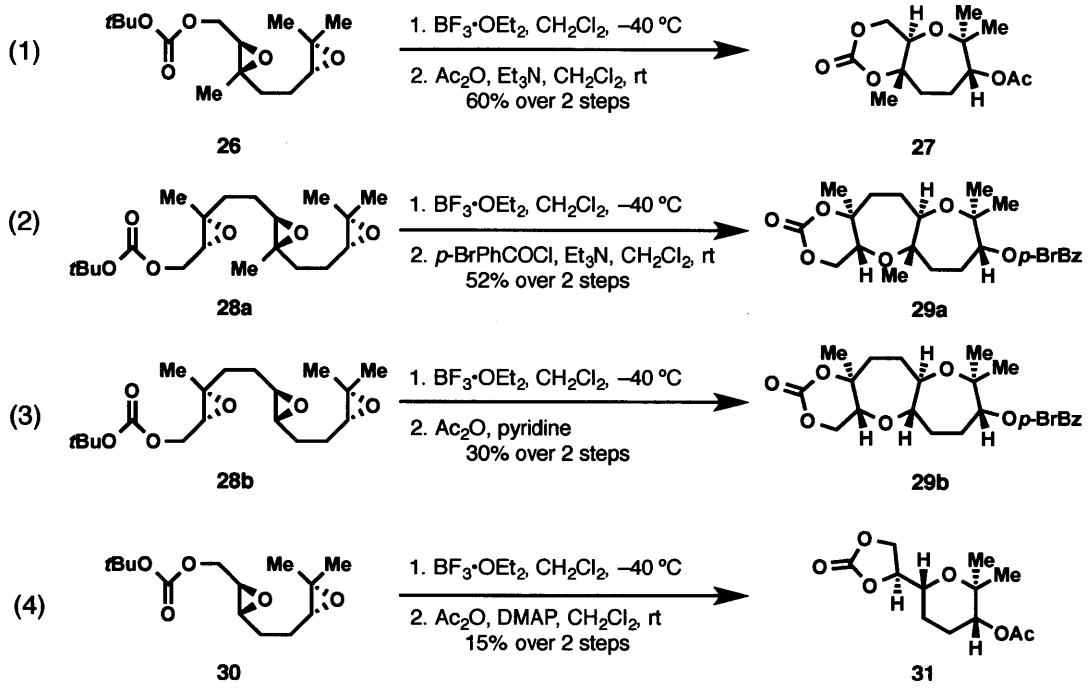
The proposed mechanism for these reactions requires activation of the epoxide furthest from the carbonate trapping nucleophile (**26** to **32**, Scheme 7), followed by *endo*-trapping of the next epoxide directed by the methyl group (**32** to **33a**). In addition to the electronic bias of the methyl substituent, the high *endo*-selectivity is thought to result from the difference in ring strain between *exo*-trapping, providing highly-strained bicyclo[3.1.0] epoxonium **33b**, versus the *endo*-trapping leading to a slightly less strained bicyclo[4.1.0] epoxonium **33a**. This difference in ring strain is thought to account for the successful cyclization of **28b**, which lacks a directing methyl on the central epoxide. Potential limitations of this methodology center on the non-selective activation method, as BF_3•OEt_2 is capable of activating any of the epoxides. This non-selective activation

[26] a) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917. (b) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodríguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515. (c) Bravo, F.; McDonald, F. E.; Neiwert, W. A; Hardcastle, K. I. *Org. Lett.* **2004**, *6*, 4487. (d) McDonald, F. E.; Tong, R.; Valentine, J. C.; Bravo, F. *Pure Appl. Chem.* **2007**, *79*, 281.

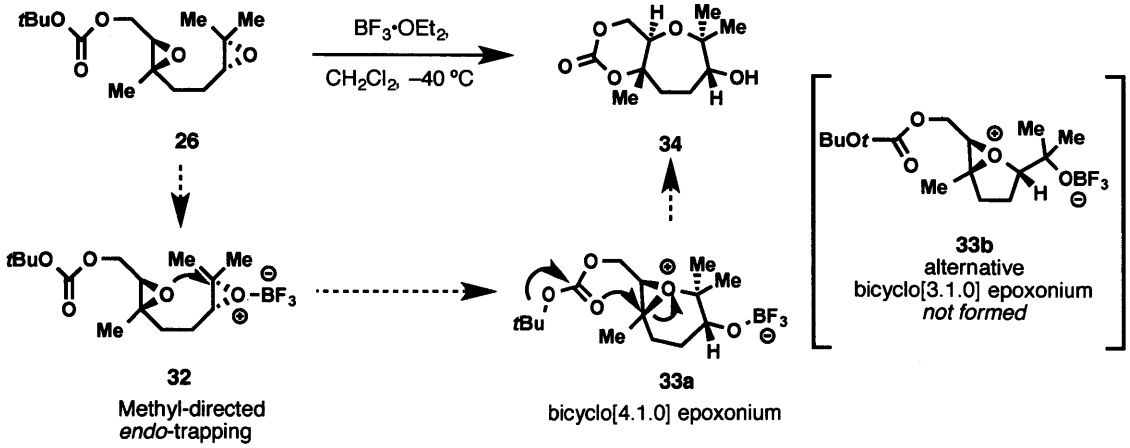
[27] Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586

could promote out-of-order cyclization, interrupting the desired cascade. The observed decrease in yield with additional epoxides is suggestive of such processes. Additionally, only weak nucleophiles such as esters and carbonates can be used as trapping nucleophiles, as the authors suggest primary alcohols are too nucleophilic, leading to undesired spontaneous epoxy alcohol cyclization outcompeting the desired pathway.

Scheme 6. Methyl-directed, Lewis acid promoted epoxide-opening cascades for the synthesis of oxepanes and poly-oxepanes



Scheme 7. Mechanistic hypothesis for *endo*-selective epoxide-opening cascades toward oxepanes



C. First Generation Approach Toward a Formal Synthesis of (–)-Brevisin

In line with the Jamison group's ongoing interest in synthesis of the ladder polyether natural products via epoxide-opening cascades, we undertook a formal synthesis of (–)-brevisin (**34**) (Scheme 8). Isolated from cell cultures (2.8 mg from 200 L), structural elucidation of **34** was reported in 2009 by Baden, Wright, and coworkers.[28] (–)-Brevisin was found to inhibit the binding of brevetoxin B (**1**) to voltage-gated sodium-ion channels at nearly 10 μM (ED_{50}), a level similar to that of brevenal (**2**). Structurally, **34** consists of two tricyclic fragments connected by a methylene bridge, representing a possible "interrupted" cascade product.

Tachibana and coworkers reported the first and only total synthesis of (–)-brevisin (**34**) in 2011, utilizing an aldol addition to couple the ABC and EF fragments **35** and **36**, while simultaneously forming the D-ring hydroxyl.[29] The ABC fragment was prepared via Suzuki coupling of the A and C rings (**37** and **38**), with a cyclization/methylation sequence resulting in synthesis of the B ring. The EF fragment was synthesized via an allyl-tin cyclization onto an aldehyde, providing the E-ring oxepane from **39**. The overall synthesis was achieved in 29 steps via the longest linear sequence (LLS), 57 total steps, and yielded over 70 mg of (–)-brevisin for further biological testing.

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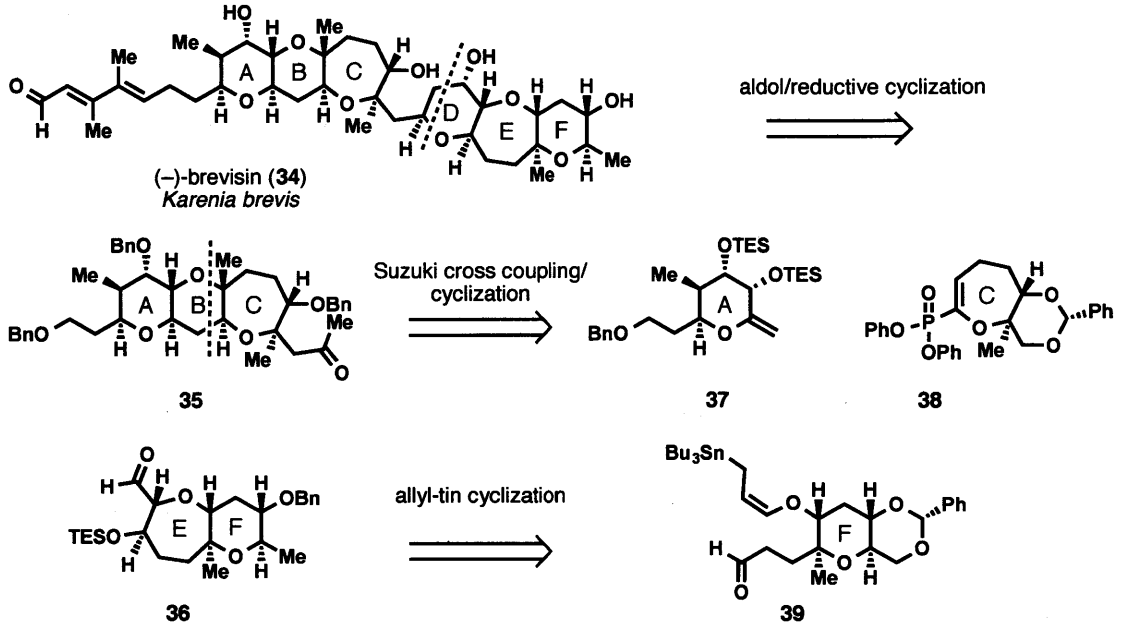
[28] (a) Satake, M.; Campbell, A.; Van Wagoner, R. M.; Bourdelais, A. J.; Jacocks, H.; Baden, D. G.; Wright, J. L. C. *J. Org. Chem.* **2009**, *74*, 989. (b) Van Wagoner, R. M.; Satake, M.; Bourdelais, A. J.; Baden, D. G.; Wright, J. L. C. *J. Nat. Prod.* **2010**, *73*, 1177.

[29] (a) Kuranaga, T.; Ohtani, N.; Tsutsumi, R.; Baden, D. G.; Wright, J. L. C.; Satake, M.; Tachibana, K. *Org. Lett.* **2011**, *13*, 696. For a discussion of fragment synthesis, see: (b) Kurenaga, T.; Satake, M.; Baden, D. G.; Wright, J. L.; Tachibana, K. *Tetrahedron Lett.* **2010**, *51*, 4673. (c) Ohtani, N.; Tsutsumi, R.; Kuranaga, T.; Shirai, T.; Wright, J. L.; Baden, D. G.; Satake, M.; Tachibana, K. *Heterocycles* **2010**, *80*, 825.

Scheme 8. Structure of (–)-brevisin and summary of first and only total synthesis by Tachibana and coworkers

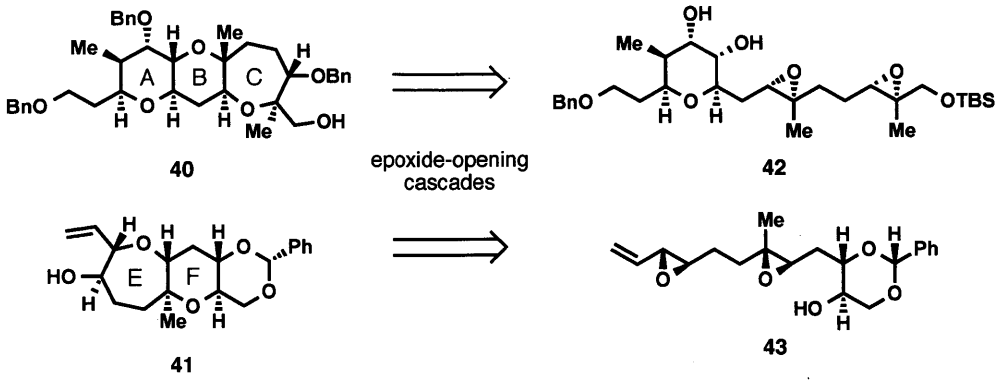


Toward our aim of developing a formal synthesis, we were inspired by two intermediates in the previously described synthesis, tricycles **40** and **41** (Scheme 9). Dr. Matthew Beaver, a postdoctoral fellow in the Jamison lab, initiated this project.[30] We envisioned intercepting two tricyclic fragments via Lewis acid promoted diepoxide cascades: ABC tricycle **40** from diepoxide **42** and EF-dioxane tricycle **41** from diepoxide **43**. While the use of alcohol trapping nucleophiles has limited precedence in Lewis acid promoted epoxide-opening cascades, we hoped the electronic deactivation from the neighboring oxygen atoms and decreased nucleophilicity of the secondary alcohol would slow the rate of epoxy alcohol cyclization relative to the desired epoxide trapping. Additionally, we were interested in exploring the electronic requirements for promoting selective activation of the epoxide furthest from the template, as McDonald had previously explored trisubstituted epoxides with either di-methyl or methyl-vinyl groups biasing openings in an *endo*-fashion. The cascades proposed in Scheme 9 rely on either a vinyl activating group (**43**), or a trisubstituted epoxide with an electronically deactivating OTBS group (**42**), which were untested prior to this work.[31]

[30] Dr. Matthew Beaver completed the EF-dioxane fragment and the first generation route toward the ABC fragment.

[31] Previous work in the epoxide-opening cascades toward poly-THP fragments had found oxygen substitution to be detrimental to *endo*-selectivity. See ref. 18c.

Scheme 9. First generation retrosynthetic analysis of ABC and EF-dioxane formal synthesis targets

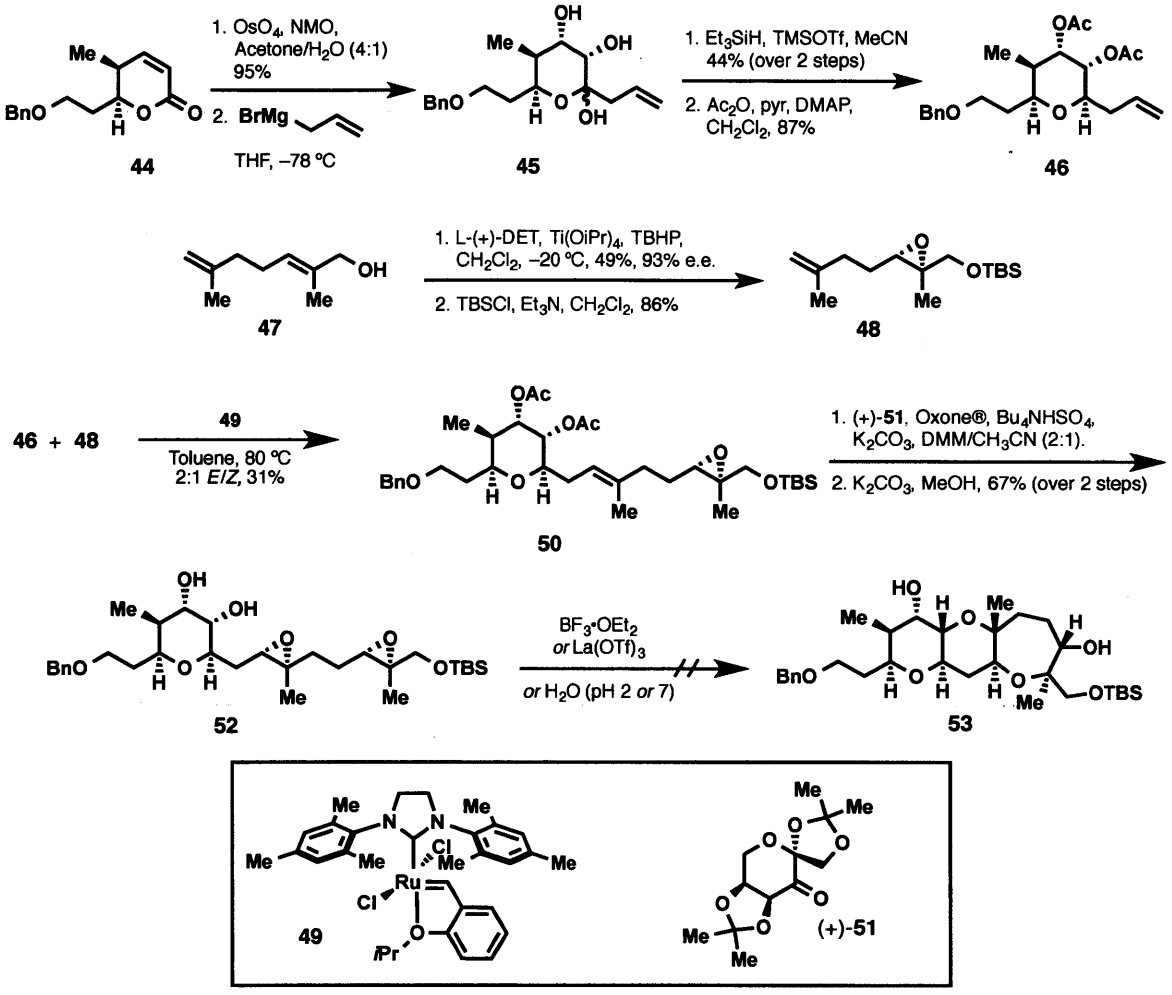


For the ABC fragment, synthesis of the A ring proceed via the previously reported route to lactone **44**[29c] in five steps from 1,3-propanediol (Scheme 10). This lactone was elaborated by diastereoselective dihydroxylation, and the incipient side chain was installed through allyl Grignard addition. Triethylsilane reduction of intermediate lactol **45**, and acetylation provided the fully elaborated A ring (**46**). Elaboration of the allyl group of **46** was accomplished via cross metathesis with **48**,[32] providing trisubstituted alkene **50**, albeit in low yield and stereoselectivity.[33] Subsequent asymmetric Shi epoxidation[34] and acetate removal by basic methanolysis provided the desired diepoxide **52**.

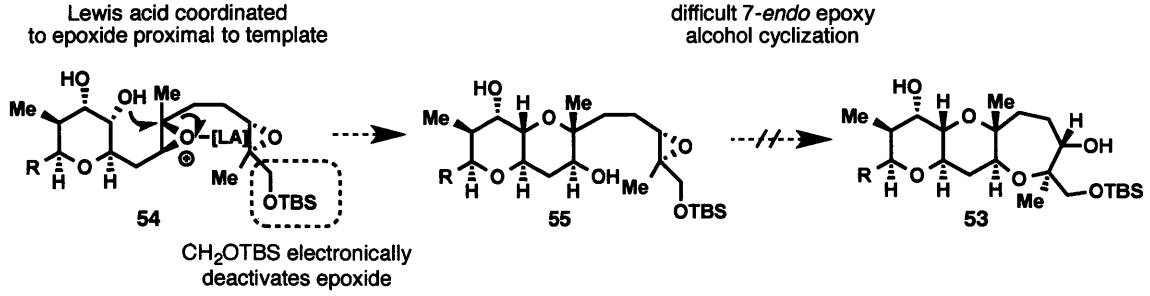
Subjecting **52** to Lewis acids (BF_3•OEt_2, $La(OTf)_3$) or aqueous conditions (pH 2 or pH 7) produced none of the desired all-*endo* ABC tricycle **53**. The lack of product formation was attributed to epoxide closest to the A ring cyclizing first to provide bis-THP **55** (Scheme 11). Our rationale is the electron-withdrawing CH_2OTBS deactivated the second epoxide toward activation and subsequent attack by the neighboring epoxide, allowing the template alcohol to react with the first epoxide (**54**). Formation of the desired ABC tricycle would necessitate a 7-*endo* cyclization of a secondary alcohol onto an electronically deactivated epoxide, generally disfavored under the conditions explored (*vide supra*). Ideally, an alternative biasing group and/or activation method could be applied to accelerate the desired bicyclo[4.1.0] epoxonium formation. However, given the difficulty of the cross metathesis and subsequent low material throughput, we decided to turn our attention toward the EF cascade.

[32] Yang, D.; Xu, M. *Org. Lett.* **2001**, *3*, 1785.
[33] Please see the second-generation synthesis for a discussion and optimization of the cross metathesis.
[34] Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. *Chem. Rev.* **2014**, *114*, DOI: 10.1021/cr500064w.

Scheme 10. First generation synthetic sequence toward ABC tricycle

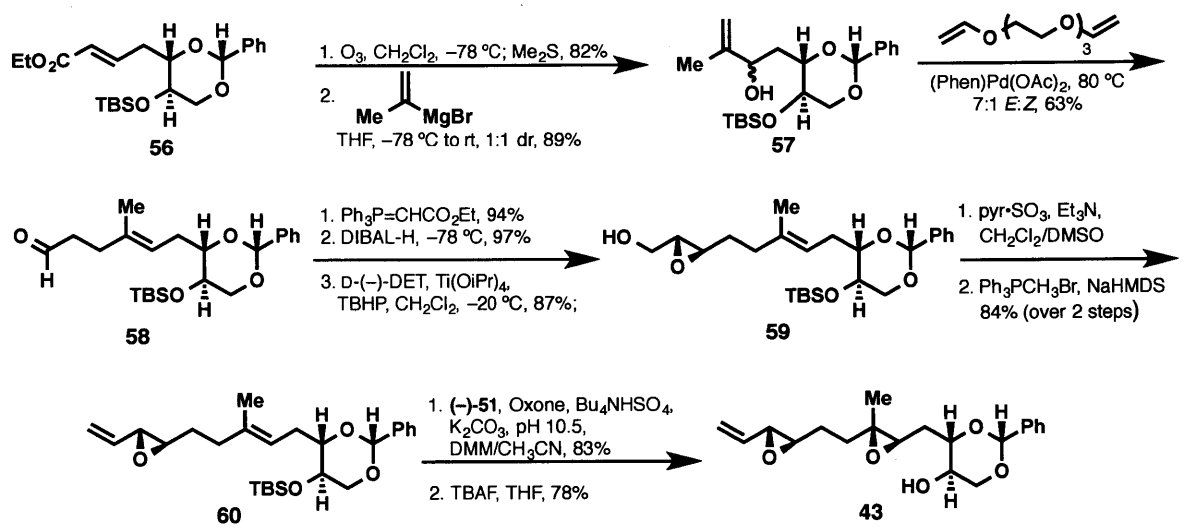


Scheme 11. Mechanistic hypothesis for unsuccessful cascade of diepoxide **52**



The route illustrated in Scheme 12 was pursued for synthesis of the EF diepoxy alcohol cascade precursor **43**. Ozonolysis of known enoate **56**,[35] subsequent nucleophilic addition of isopropenyl magnesium bromide, and a tandem vinylation–Claisen process[36] afforded aldehyde **58**. Stabilized-Wittig olefination, followed by reduction with DIBAL-H and Sharpless asymmetric epoxidation[37] provided epoxy alcohol **59**. Oxidation and Wittig methylenation installed the desired vinyl epoxide (**60**). Finally, asymmetric Shi epoxidation and TBAF desilylation provided the desired cascade precursor **43** in ten steps from **56**.

Scheme 12. Synthesis of EF diepoxide cascade precursor



Initial attempts to promote the desired all-*endo* diepoxide cascade with $BF_3{\bullet}OEt_2$ led to 23% isolated yield of the desired tricycle **41** (Table 1, entry 1). Attempts to improve the yield with alternative solvents, such as THF or MeCN, or alternative Lewis acids, such as $Eu(OTf)_3$ or $Yb(OTf)_3$, yielded similar results.[26c] The low yield of this process is ascribed to the sensitivity of the benzylidine acetal under the reaction conditions and the use of the alcohol trapping nucleophile, which could cyclize prior to bicyclo[4.1.0] epoxonium formation, similar to the ABC fragment (Scheme 11). CSA was found to provide similar yields, suggesting the choice of acid catalyst is inconsequential to the outcome of the reaction (entry 2). Attempts to limit benzylidine acetal

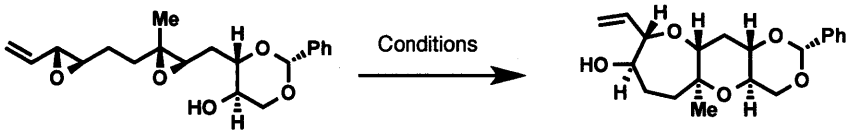
[35] Enoate **56** was prepared in three steps from commercially available 2-deoxy-D-ribose. See: Nicolaou, K. C.; Wallace, P. A.; Shi, S.; Ouellette, M. A.; Bunnage, M. E.; Gunzner, J. L.; Agrios, K. A.; Shi, G.; Gartner, P.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 618.

[36] Wei, X.; Lorenz, J. C.; Kapadia, S.; Saha, A.; Haddad, N.; Busacca, C. A.; Senanayake, C. H. *J. Org. Chem.* **2007**, *72*, 4250.

[37] Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

hydrolysis via silica gel promotion utilizing methodology developed by Dr. Aaron van Dyke for 6-*endo* selective cyclization of a similar epoxy alcohol provided only trace product (entry 3). Inspired by results from Inoue and coworkers (Scheme 15, eq 4),[38] $[Rh(CO)_2Cl]_2$ was found to also promote the desired transformation (entry 4). Although the yield was similar to previous conditions, the observation of a cleaner crude reaction mixture with less acetal hydrolysis, as well as 28% recovered diepoxide (**43**), suggested ample opportunity for reaction optimization.

Table 1. Investigation of epoxide-opening cascade of vinyl epoxide **43**



43 **41**

Entry	Catalyst	Solvent	Temp	Yield (%)[a]
1	$BF_3{\cdot}OEt_2$ (10 mol %)	CH_2Cl_2	–78 °C	23
2	CSA (10 mol %)	CH_2Cl_2	rt	22
3	SiO_2 (50 mg/mg)	CH_2Cl_2	rt	5
4	$[Rh(CO)_2Cl]_2$ (5 mol %)	THF	rt	21[b]

[a] isolated yield. [b] 28% of **43** was also recovered.

D. A New Approach to *Endo*-Selective Epoxide-Opening Cascades via $[Rh(CO)_2Cl]_2$ Catalysis

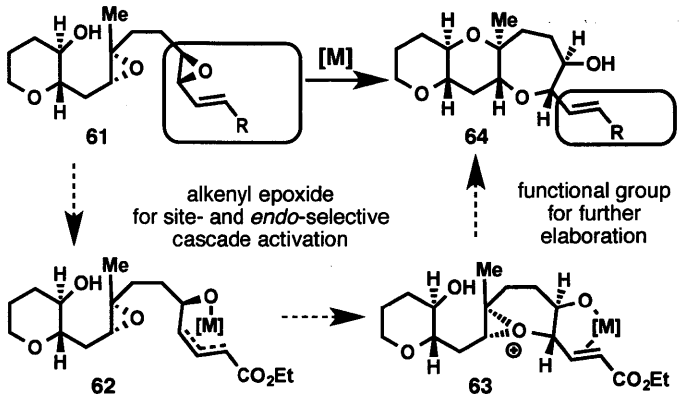
The initial results catalyzing an epoxide-opening cascade with $[Rh(CO)_2Cl]_2$ prompted us to rethink our approach to the diepoxide cascades. Rather than utilizing traditional Lewis acid catalysis, which does not readily discriminate between epoxides beyond minor differences in Lewis basicity, we sought to explore the potential of transition metal catalysis to selectively activate an alkenyl epoxide,[39] initiating the cascade in a site-selective fashion. Our design is depicted in Scheme 13 and can be summarized as follows: incorporation of an electronically tailored alkene at the distal epoxide would provide a specific site for complexation and activation by a transition metal (**61** to **62**). Activation would be selective for the C–O bond closest to the alkene, providing high *endo*-selectivity in the subsequent bicyclo[4.1.0] epoxonium formation (**63**). The remainder

[38] Inoue, M.; Saito, F.; Iwatsu, M.; Ishihara, Y.; Hirama, M. *Tetrahedron Lett.* **2007**, *48*, 2171.

[39] For a recent review on alkenyl epoxides in organic synthesis, see: He, J.; Ling, J.; Chiu, P. *Chem. Rev.* **2014**, *114*, DOI: 10.1021/cr400709j

of the cascade would be subject to previously observed *endo* versus *exo* selectivities in epoxide-opening cascades (**63** to **64**), as proposed by McDonald and further elaborated by Floreancig and Houk.[40]

Scheme 13. Substrate and promoter combination designed for selective initiation of all-*endo* epoxide-opening cascades.



The concept of site-selective initiation of cascades has rich precedence, such as in the synthesis of sterols in which epoxides and allylic alcohols are used as orthogonal initiators of polyene cyclizations.[41] Methods for site-selective epoxide-opening cascade initiation have been reported, resulting in cascades yielding oxepane-containing products. Floreancig and Houk reported oxidative generation of an oxocarbenium intermediate, which upon trapping of the nearest epoxide initiates the cascade (Scheme 14, eq 1).[40] The oxocarbenium ion is generated under neutral conditions via photochemical initiated electron transfer, limiting indiscriminate epoxide activation. By varying the number, spacing, substitution, and stereochemistry of the epoxides, Floreancig and Houk were able to compare selectivity and efficiency of epoxide-opening cascades. Computational modeling provided further insight into the regioselectivity observed in openings of bicyclo[4.1.0] epoxoniums, providing additional support for the desired *endo*-selectivity in trapping of our proposed epoxonium (**63** to **64**) for our proposed epoxide-opening cascades.

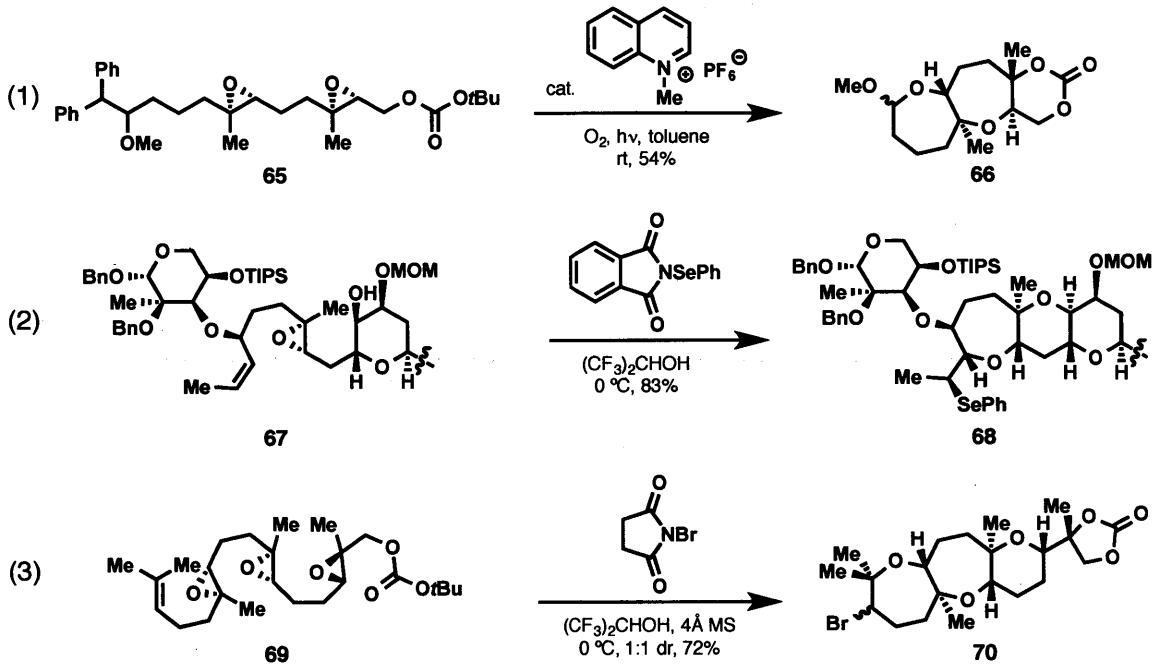
Selective activation of a distal alkene and subsequent intramolecular trapping of an epoxide has also seen success as a method for selective cascade initiation. For example, in Holton's synthesis of hemibrevetoxin B, a distal alkene was activated via an electrophilic selenium

[40] Wan, S.; Gunaydin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 7915.

[41] Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189. (b) Van Tamelen, E. E. *Acc. Chem. Res.* **1975**, *8*, 152. (c) Johnson, W. S.; Gravestock, M. B.; McCarry, B. E. *J. Am. Chem. Soc.* **1971**, *93*, 4332. (d) Gravestock, M. B.; Johnson, W. S.; McCarry, B. E.; Parry, R. J.; Ratcliffe, B. E. *J. Am. Chem. Soc.* **1978**, *100*, 4274. (e) Corey, E. J.; Luo, G.; Lin, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 9927.

reagent, initiating an epoxide-opening cascade in high yield (Scheme 14, eq 2).[42] An additional example of this strategy is the total synthesis of the bromotriterpene *ent*-dioxepandehydrothyrsiferol via a bromonium-initiated epoxide-opening cascade from our lab (Scheme 14, eq 3).[43] Utilizing *N*-bromosuccinimide to initiate the cascade, the tricyclic fragement **70** was rapidly formed from triepoxy-alkene precursor **69**, utilizing the inherent methyl directing groups to control epoxide-opening regioselectivity.

Scheme 14. Previous work demonstrating examples of site-selective initiation of epoxide-opening cascades



With the previous examples of site-selective activation as inspiration, we hoped to develop the combination of an alkenyl epoxide and a transition metal catalyst to develop further this area of research. Specifically, we planned to use a transition metal to selectively activate alkenyl epoxides for nucleophilic attack, as this concept has excellent and diverse precedents. Although Pd catalysis is the most well known,[44] we eschewed this path because of the limited examples of oxygen

[42] Zakarian, A.; Batch, A.; Holton, R. A. J. Am. Chem. Soc. 2003, 125, 7822.

[43] (a) Tanuwidjaja, J.; Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 12084. (b) Tanuwidjaja, J. Ph.D. Dissertation. Massachusetts Institute of Technology, Cambridge, MA, 2013. (c) Underwood, B. S.; Tanuwidjaja, J.; Ng, S.-S.; Jamison, T. F. *Tetrahedron* **2013**, *69*, 5205.

[44] Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575. (b) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. (c) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2931. (d) Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702. (e) Trost, B. M.; McEachern, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 8649. (f) Hirai, A.; Yu, X.-Q.; Tonooka, T.; Miyashita, M.

nucleophiles in this context and, more importantly, the likelihood that an undesired stereochemical outcome would be observed, i.e., net retention (double inversion) at the site of epoxide opening, rather than the necessary inversion of configuration.

In contrast, $[Rh(CO)_2Cl]_2$ has been shown to catalyze openings of alkenyl epoxides with inversion. Berchtold observed that highly activated arene oxides (**71**) with $[Rh(CO)_2Cl]_2$ in MeOH gave a moderate yield of **74**, corresponding to opening and net inversion by MeOH at the more electronically stabilized position (Scheme 15, eq 1).[45] Further work by Fangou and Lautens led to the development of $[Rh(CO)_2Cl]_2$ as a catalyst for regio- and stereo-selective intermolecular opening of *trans*-epoxides with alcohols and anilines, utilizing a variety of alkene stabilizing groups, such as styrenes, alkyl-substituted alkenes, and enoates, (eq 2).[46] $[Rh(CO)_2Cl]_2$ was shown to also be a competent catalyst for cyclizations of *trans*-disubstituted enoate epoxy-alcohols and carbamates (**78 a-e**) to provide five- and six-membered saturated heterocycles (**79 a-e**, eq 3) by Ha and coworkers.[47] Lastly, Inoue observed that $[Rh(CO)_2Cl]_2$ catalyzed the cyclization of epoxy alcohol **80** with limited acetal hydrolysis, whereas PPTS activation caused significant acetal cleavage (eq 4).[38] Prior to our investigations, however, no examples of oxepane formation via $[Rh(CO)_2Cl]_2$, activation of trisubstituted epoxides, or use in initiation of epoxide-opening cascades had been reported.

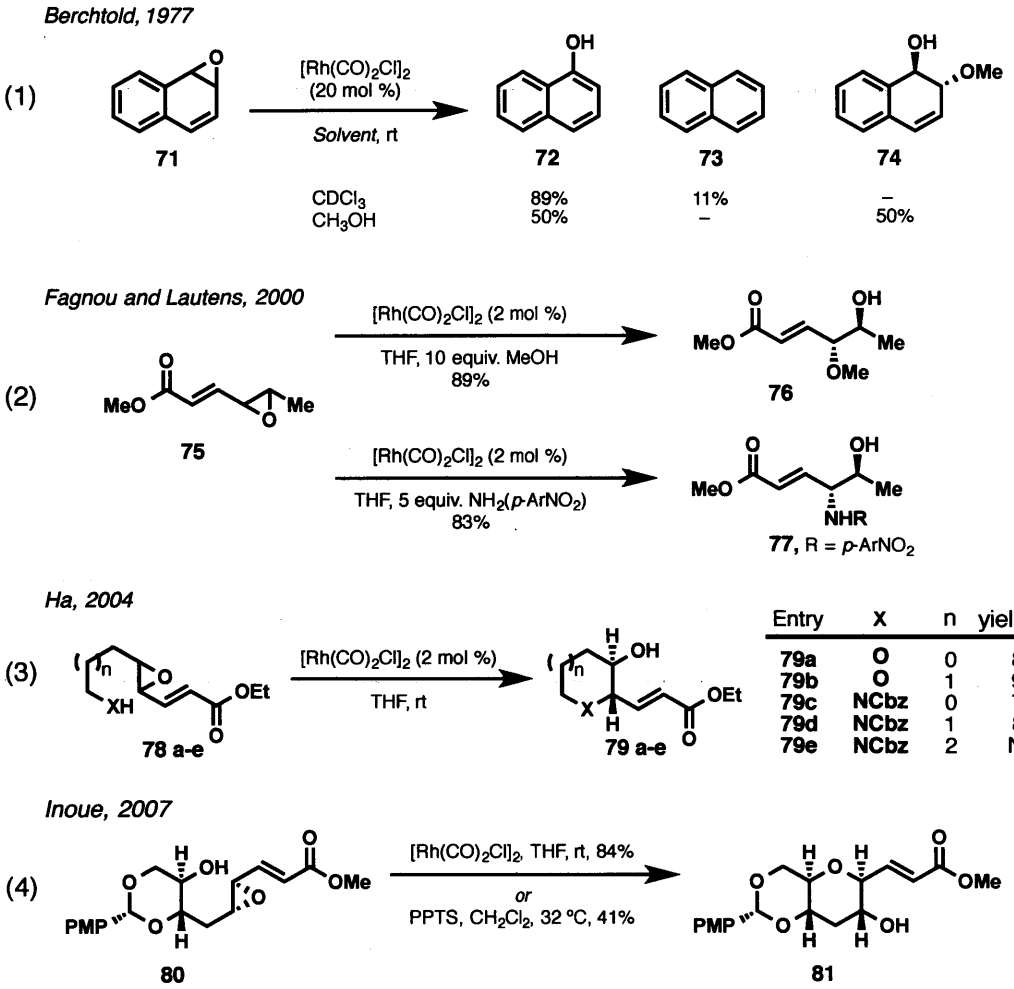
Chem. Commun. (Cambridge, U.K.). **2003**, 2482. (g) Yu, X.-Q.; Yoshimura, F.; Ito, F.; Sasaki, M.; Hirai, A.; Tanino, K.; Miyashita, M. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 750. (h) Arthuis, M.; Beaud, R.; Gandon, V.; Roulland, E. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 10510.

[45] Ashworth, R. W.; Berchtold, G. A. *Tetrahedron Lett.* **1977**, *18*, 343.

[46] Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319.

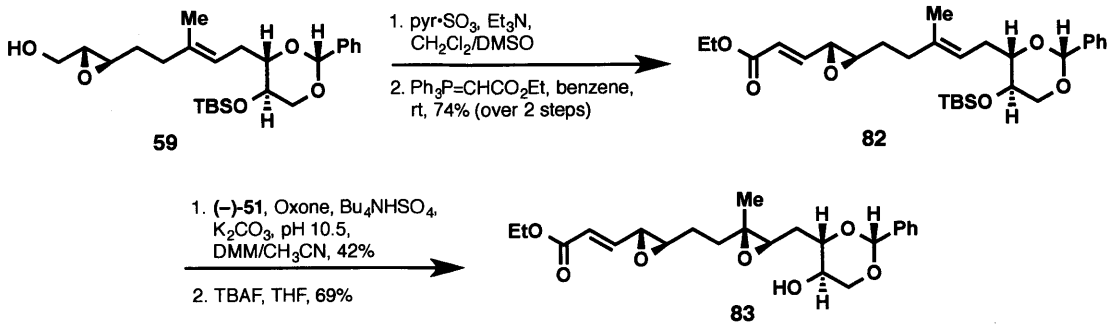
[47] Ha, J. D.; Shin, E. Y.; Kang, S. K.; Ahn, J. H.; Choi, J.-K. *Tetrahedron Lett.* **2004**, *45*, 4193.

Scheme 15. Previous work utilizing $[Rh(CO)_2Cl]_2$ as a site-selective activator for epoxide-opening with alcohols.



With these precedents in mind, we returned to the EF fragment of (–)-brevisin, investigating the use of an enoate as the activating group of the distal epoxide, used in both reports of epoxy alcohol cyclizations catalyzed by $[Rh(CO)_2Cl]_2$ (Scheme 16). From epoxy alcohol **59** in our previous synthetic route (Scheme 12), alcohol oxidation and stabilized-Wittig olefination installed the desired epoxy enoate functionality (**82**). Asymmetric Shi epoxidation and TBAF desilylation provided the desired cascade precursor **83**.

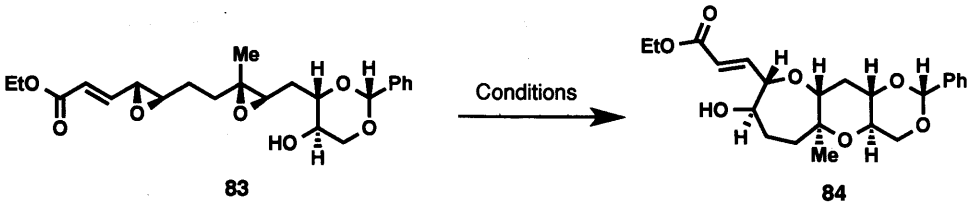
Scheme 16. Synthesis of EF diepoxy enoate cascade precursor



Investigation of cascade promoters for diepoxy alcohol **83** containing an (*E*)-enoate revealed $[Rh(CO)_2Cl]_2$ to be a highly chemo-, stereo-, and regioselective promoter. For example, $[Rh(CO)_2Cl]_2$ catalyzed the regioselective epoxide-opening cascade of (*E*)-enoate-diepoxy alcohol **83** to provide the desired product **84** in 38% isolated yield (Table 2, entry 1). Exploration of a variety of solvents found that CH_2Cl_2, toluene, and Et_2O provided similar yields as THF. TFE and HFIP provided complex mixtures, while acetonitrile and hexanes led to significant recovery of starting material. We were pleased to find use of 1,4-dioxane as the solvent and performing the reaction at elevated temperatures (65 °C) provided a slight increase to 45% yield (entry 3). A further improvement was observed by adding polymer-bound Ph_3P[48] at the end of the reaction to release the product from the residual Rh, boosting the isolated yield to 61% (entry 4), a three-fold increase relative to acid catalysis of vinyl diepoxide **43**. Subjection of **83** to Lewis or Brønsted acid activation, provided none of the desired **84**, again highlighting the selectivity of $[Rh(CO)_2Cl]_2$ catalysis with epoxy enoates (entries 5 and 6). The ester functional group appears to be critical to the success of the method. These results support the mechanistic hypothesis that Rh(I) activates alkenyl epoxides via π-coordination and oxidative addition of into the allylic C–O bond of the epoxide, which contrasts the generally non site-selective epoxide activation with Lewis acids. Importantly, these results represent the first examples of both a cascade process and a seven-membered ring formation using this method.

[48] See Section E, Table 3 for discussion of polymer-bound Ph_3P for improvement of product isolation.

Table 2. Investigation of epoxide-opening cascade of enoate epoxide **83**



Entry	Catalyst	Solvent	Temp	Yield (%)[a]
1	$[Rh(CO)_2Cl]_2$ (5 mol %)	THF	rt	38[c]
2	$[Rh(CO)_2Cl]_2$ (5 mol %)	THF	65 °C	39
3	$[Rh(CO)_2Cl]_2$ (5 mol %)	1,4-dioxane	65 °C	45
4[b]	$[Rh(CO)_2Cl]_2$ (5 mol %)	1,4-dioxane	65 °C	61[c]
5	$BF_3{\cdot}OEt_2$ (100 mol %)	CH_2Cl_2	–78 °C	–
6	CSA (100 mol %)	CH_2Cl_2	rt	–

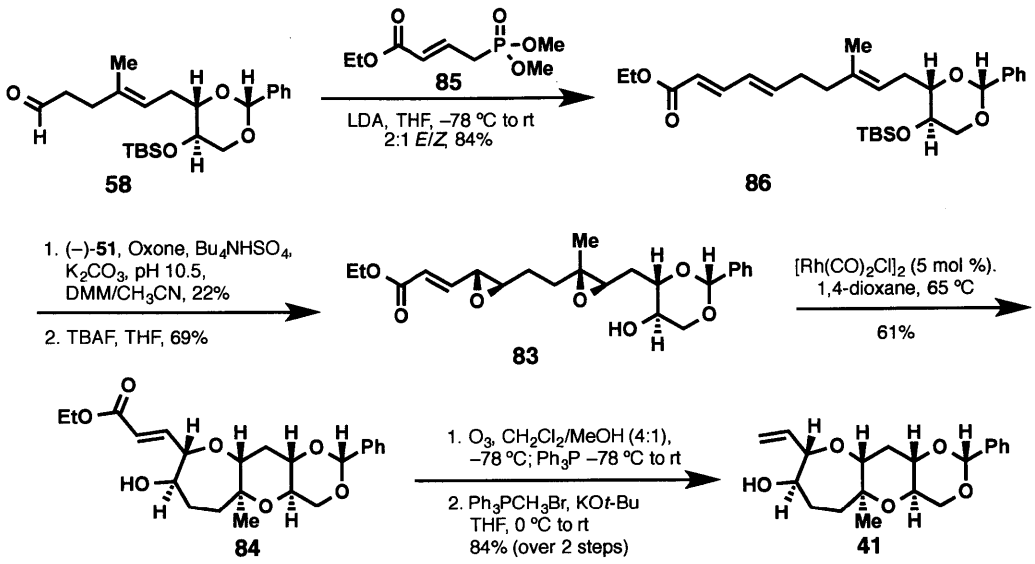
[a] Yields determined by ^1H NMR spectroscopy. [b] Ph_3P supported on polystyrene resin was added at the end of reaction. [c] Isolated yield.

Following identification of the enoate as the ideal activating group, a streamlined synthesis to **83** was developed (Scheme 17). Olefination of **58** with phosphonate **85**[49] provides triene **86**,[50] and subsequent asymmetric Shi epoxidation and TBAF desilylation provides cascade precursor **83**. The low yield of the epoxidation is due to the reduced reactivity of the dienoate, and is improved with resubjection of the crude reaction mixture to the standard conditions. Post-cyclization, the enoate was readily converted to a vinyl substituent via a two step sequence of ozonolysis and Wittig methylenation to provide **41**, intercepting the previously synthesized EF ring fragment of (–)-brevisin in 12 steps LLS, compared to 13 LLS in the Tachibana synthesis and 16 LLS for our previous route.

[49] The phosphonate ester was prepared in two steps by the literature method: Mitton-Fry, M. J.; Cullen, A. J.; Sammakia, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 1066.

[50] The 2:1 (*E*/*Z*) isomeric mixture could be carried forward to the next synthetic operation or subjected to literature conditions (I_2, $CHCl_3$) to improve the isomeric ratio to 5:1 (*E*/*Z*). See, for example: (a) Nazaré, M.; Waldmann, H. *Chem. Eur. J.* **2001**, *7*, 3363–3376. (b) Xu, J.; Caro-Diaz, E. J. E.; Trzoss, L.; Theodorakis, E. A. *J. Am. Chem. Soc.* **2012**, *134*, 5072–5075.

Scheme 17. Streamlined synthesis to EF-diepoxy alcohol **83** and completion of EF fragment synthesis

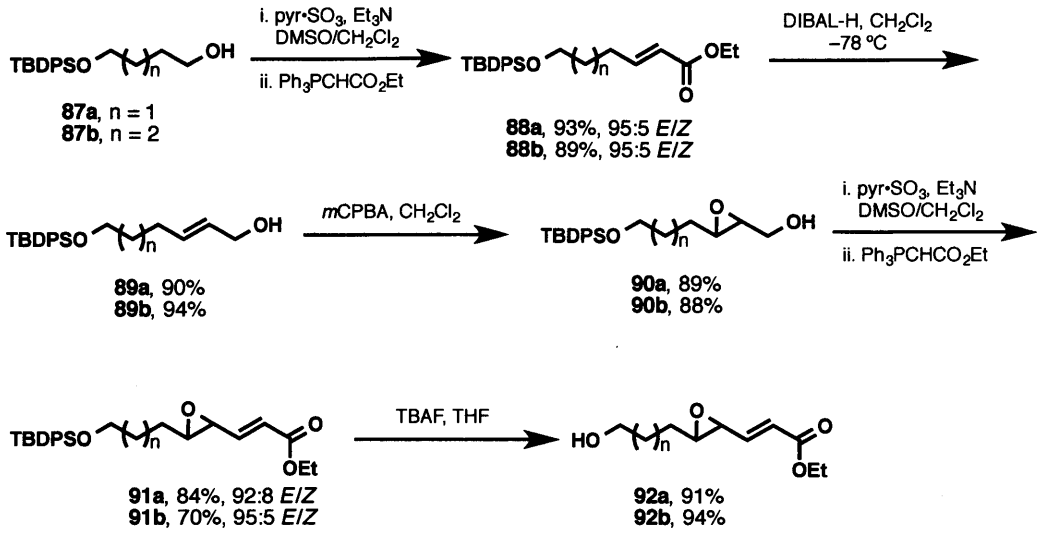


E. Model Studies of Epoxy Alcohol Cyclizations Catalyzed by $[Rh(CO)_2Cl]_2$

With the success of the epoxide-opening cascade toward the EF fragment, we sought to explore the limits of $[Rh(CO)_2Cl]_2$ catalysis for epoxy alcohol cyclization with respect to ring size and investigate the epoxide substitution patterns found in the proposed (–)-brevisin cascades. We were especially interested distal-methyl trisubstituted epoxides, as we hoped to use the $[Rh(CO)_2Cl]_2$ methodology in the synthesis of the ABC tricycle. The difficulty of oxepane synthesis via acid-catalyzed epoxy alcohol cyclization and the lack of any epoxy alcohol methodology towards oxocanes (8-membered oxygen heterocycles) also piqued our interest.

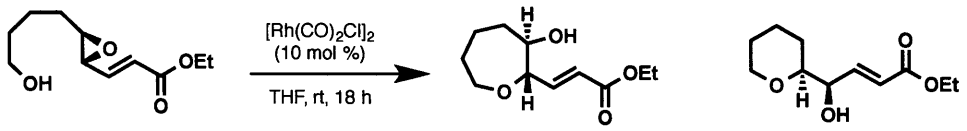
With these goals in mind, we undertook the synthesis of epoxy alcohol model systems **92a,b** (Scheme 18). Starting from mono-TBDPS protected diols **87a,b**, tandem alcohol oxidation and stabilized-Wittig olefination provided the desired *trans*-enoates **88a,b**. DIBAL-H reduction of the ester and *m*CPBA epoxidation provided epoxy alcohol **90a,b**. Finally, a second alcohol oxidation and in situ stabilized-Wittig olefination followed by TBAF desilylation affords the desired enoate-epoxy alcohols (**92a,b**) for our model studies. While this route requires two sequential homologation steps relative to the streamlined route utilized to afford the same substructure in Scheme 17, the products obtained in Scheme 18 are readily purified to >20:1 dr, free of *cis*-epoxide or *cis*-enoate by ^{1}H NMR spectroscopy, simplifying analysis during cyclization studies.

Scheme 18. Synthesis of *trans*-disubstituted epoxy-alcohol for cyclization model studies



Our first attempts to cyclize epoxy-alcohol **92b** to form oxepane **93b** proved successful; however, we were puzzled by a low mass recovery, as the reaction appeared to produce no side products (Table 1, entry 1). We thought the Rh might be interfering with analysis, so we attempted to remove the Rh post-reaction by filtering through a silica gel plug, eluting with EtOAc to obtain the product (entry 2). While this improved the resolution of the ^{1}H NMR, likely by removing Rh aggregates, the yield didn't significantly improve. Next we screened additives to coordinate to the Rh, attempting to displace any bound product. While Ph_3P did increase the recovery of the product, it also hampered analysis by overlapping with the key enoate signals in the ^{1}H NMR spectrum (entry 3). Switching to polymer-bound Ph_3P was the ideal solution, as seen in both the significant increase in product recovery and lack of other impurities in the ^{1}H NMR spectrum (entry 4). Other readily available additives, such as pyridine, polymer-bound pyridine, Na_4EDTA, or florisil were inferior (entries 5-8). The identification of Ph_3P resin to isolate clean product significantly streamlined reaction optimization, and greatly assisted in our studies.

Table 3. Exploration of additives to remove rhodium impurities and improve product recovery from the cyclization of **92b**



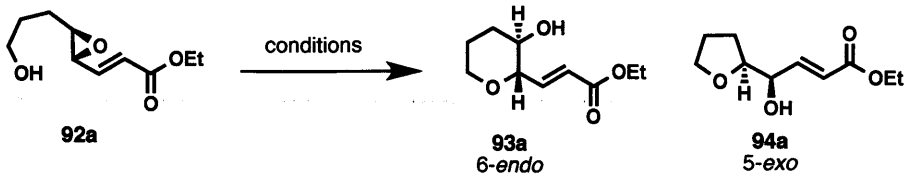
92b **93b** *7-endo* **94b** *6-exo*

Entry	Rh removal additive[a]	NMR yield **93b** (%)[b]	Notes
1	None, no SiO_2 plug	69	poor resolution in ^1H NMR
2	SiO_2 plug only	76	–
3	Ph_3P	83	significant Ph_3P overlap in ^1H NMR
4	Ph_3P polymer bound	91	–
5	pyridine	79	–
6	pyridine polymer bound	76	–
7	Na_4EDTA	62	–
8	florisil	66	–

[a] Added after complete consumption of SM, prior to filtering through SiO_2 plug with EtOAc.
[b] Yields determined by ^1H NMR spectroscopy.

Investigation of epoxy alcohol **92a** is shown in Table 4. We found similar results as Ha reported with this substrate,[47] observing near complete *endo* selectivity but with a slight increase in yield upon application of the Ph_3P resin (entries 1 and 2). Investigation of lower catalyst loading found that 1 mol % $[Rh(CO)_2Cl]_2$ produced full conversion, while 0.5 mol % only gave 60% conversion of **92a** after 18 h. Finally, to explore the selectivity of the enoate activating group under traditional acid catalysis, we subjected **92a** to CSA catalysis and observed a 1:1 *endo* to *exo* ratio, similar to the observations of Nicolaou with the methyl ester enoate.[25] It should be noted alternative stabilizing groups, such as vinyl, provide complete *endo* selectivity under CSA catalysis; rather the comparison of $[Rh(CO)_2Cl]_2$ to CSA catalysis is primarily to assess if $[Rh(CO)_2Cl]_2$ is acting as a traditional Lewis acid via direct activation of the epoxide at oxygen or interacting with the substrate in a more elaborate manor.

Table 4. Cyclization of epoxy alcohol **92a**



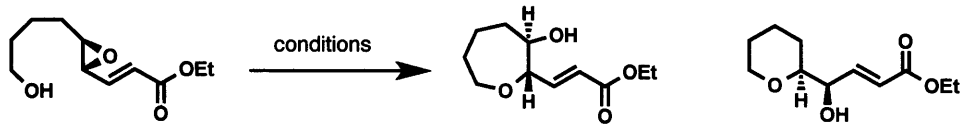
92a **93a** 6-*endo* **94a** 5-*exo*

entry	catalyst	solvent, temp	**93a/94a** *endo/exo*	yield **93a** (%)[a]
1[b]	$[Rh(CO)_2Cl]_2$ (2 mol %)	THF, rt	>20 : 1	90
2[c]	$[Rh(CO)_2Cl]_2$ (2.5 mol %)	THF, rt	>20 : 1	94
3	(±)-CSA (10 mol %)	CH_2Cl_2, rt	1 : 1	50

[a] Isolated yield. [b] Ref. 47. [c] Polymer-bound Ph_3P resin added at completion of reaction.

Returning to epoxy alcohol **92b** for the synthesis of oxepane **93b**, we found 5 mol % $[Rh(CO)_2Cl]_2$ loading to provide the desired product in high yield and selectivity (Table 5, entry 1). Attempts to lower the catalyst loading in THF or a variety of other solvents provided only partial conversion, attesting to the longer tether and ring strain for formation of oxepane **93b** versus THP **93a**. This is also seen in the results of CSA catalysis, which demonstrated lower regioselectivity and yields as compared to **92a** (entry 2). Of note, however, is constant high regioselectivity and yield afforded by $[Rh(CO)_2Cl]_2$ as compared to the further erosion in selectivity provided by traditional acid catalysis.

Table 5. Comparison of activation methods for cyclization of epoxy alcohol **92b**



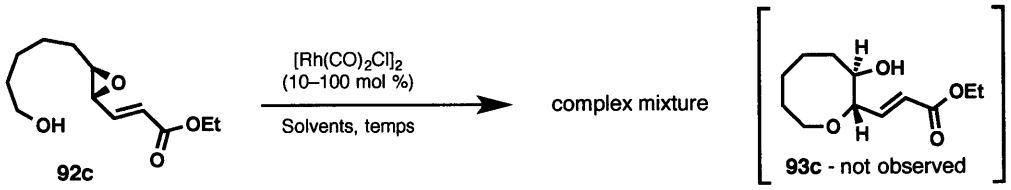
92b **93b** 7-*endo* **94b** 6-*exo*

entry	catalyst	solvent, temp	**93b/94b** *endo/exo*	yield **93b** (%)[a]
1	$[Rh(CO)_2Cl]_2$ (5 mol %)	THF, rt	>20 : 1	81
2	(±)-CSA (100 mol %)	CH_2Cl_2, rt	1 : 3	21

[a] Isolated yield.

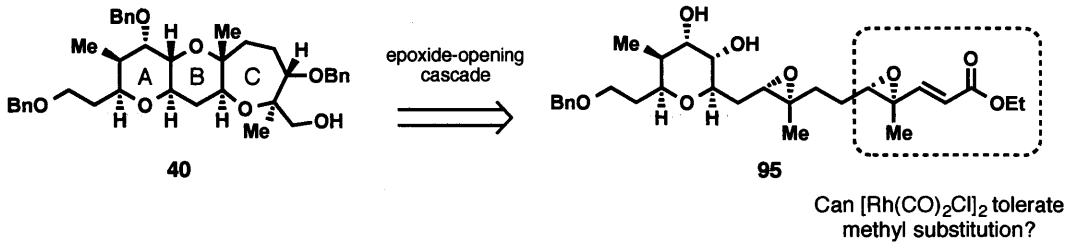
With successful synthesis of oxepanes with this methodology, we next attempted to form oxocanes, or 8-membered oxygen heterocycles, via epoxy-alcohol cyclizations. Unfortunately, all attempts to promote *endo*-selective cyclization of epoxy alcohol **92c** led to complex mixtures of more polar products (Scheme 19). Our attempts to improve the reaction by increasing the catalyst loading, cooling or heating the reaction mixture, use of alternative solvents, high dilution, or even slow reverse addition of substrate to catalyst failed to provide oxocane **93c**. Our hypothesis for the stark difference between the cyclization of **92b** and **92c** is the increase in the tether and ring strain of the oxocane product are reflected in a preference toward many alternative pathways, overwhelming the desired pathway. Oligomerization and epoxide rearrangements are likely the major products, although none could be isolated in pure form for structural elucidation.

Scheme 19. Attempted cyclization of epoxy alcohol **92c** for oxocane synthesis

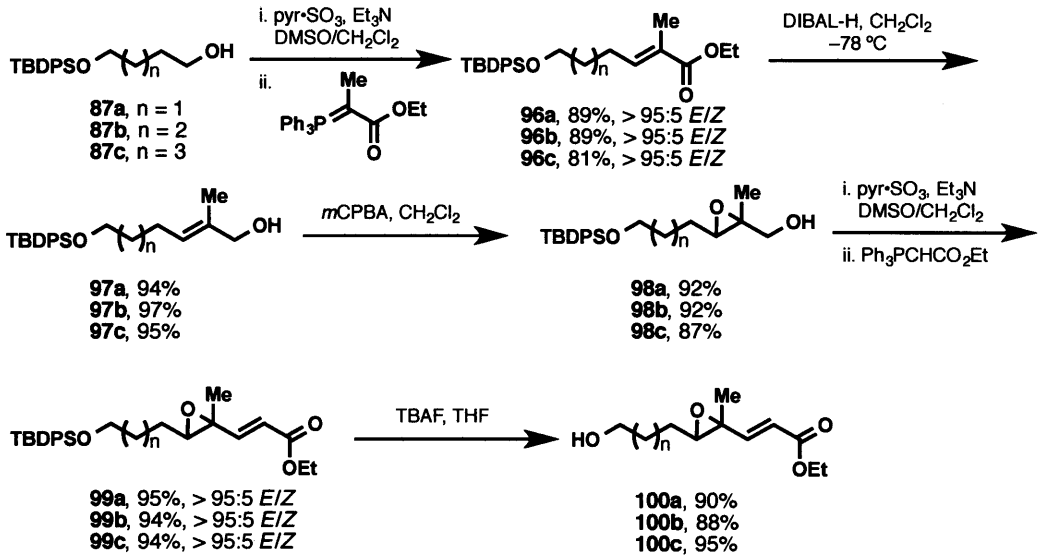


Following the successful formation of oxepanes from *endo*-selective epoxide opening cyclizations and cascades of *trans*-disubstituted epoxides, we next looked to the proposed ABC diepoxide opening cascade. We hoped the combination of the enoate directing group and $[Rh(CO)_2Cl]_2$ catalysis would provide site-selective initiation of the desired cascade (Scheme 20). However, given the lack of precedence for methyl substitution on the epoxide neighboring the enoate coupled with the complexity of the synthesis of **95**, we decided to pursue model studies to explore the ability and efficiency of $[Rh(CO)_2Cl]_2$ to promote *endo*-selective cyclization. Synthesis of the necessary substrates is shown in Scheme 21. Beyond utilizing an alternative phosphorane in the first homologation, substrate synthesis followed as described for the disubstituted-epoxide substrates.

Scheme 20. Proposed second-generation cascade toward ABC tricycle

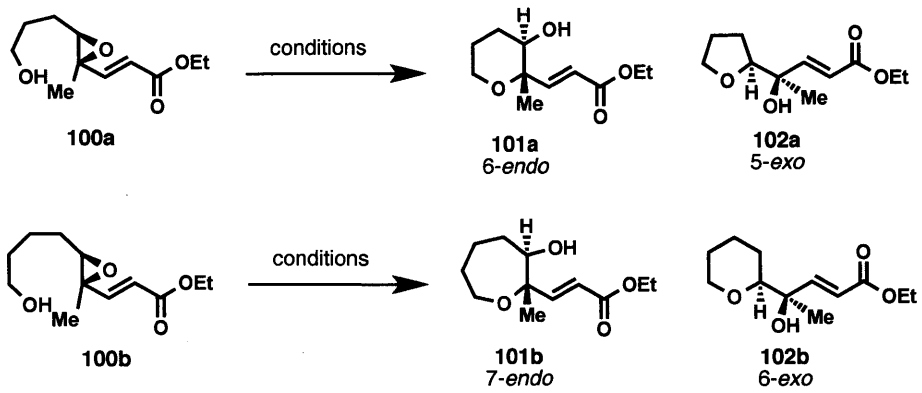


Scheme 21. Synthesis of distal-methyl (*E*)-trisubstituted epoxy-alcohol for model studies



Critical to the success of this method for the synthesis of the ABC tricycle of (–)-brevisin, distal methyl substitution was well tolerated under $[Rh(CO)_2Cl]_2$ promotion, providing complete *endo* selectivity for the synthesis of both tetrahydropyran (**101a**) and oxepane (**101b**) from epoxy alcohols **100a** and **100b** respectively (Table 6, entries 1 and 3). Of particular note, these substrates tolerated lower catalyst loadings than the disubstituted epoxide substrates, suggesting the addition of the distal methyl group might be beneficial. In comparison, promotion with (±)-CSA yielded a mixture of *endo*- and *exo*-products, albeit with a slight improvement in regioselectivity compared to disubstituted epoxides **92a** and **92b** (entries 2 and 4).

Table 6. Comparison of activation methods for cyclization of trisubstituted epoxy alcohols **100a** and **100b**



entry	substrate	catalyst	solvent, temp	**101** / **102** *endo* : *exo*	yield **101** (%)[a]
1	**100a**	$[Rh(CO)_2Cl]_2$ (1 mol %)	THF, rt	>20 : 1	93
2	**100a**	(±)-CSA (10 mol %)	CH_2Cl_2, rt	3.4 : 1	69
3	**100b**	$[Rh(CO)_2Cl]_2$ (2.5 mol %)	THF, rt	>20 : 1	88
4	**100b**	(±)-CSA (100 mol %)	CH_2Cl_2, rt	1: 1.8	43

[a] Isolated yield.

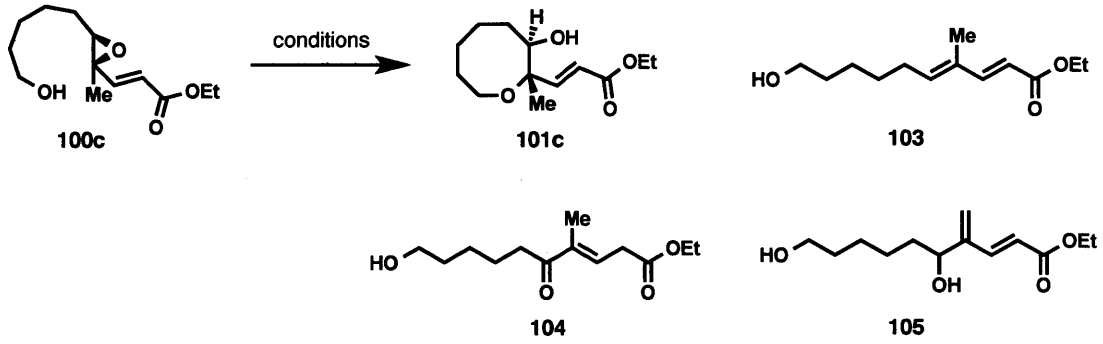
Following the successful *endo*-selective cyclizations of the distal-methyl epoxides **100a** and **100b**, we investigated the synthesis of oxocanes utilizing the trisubstituted-epoxides, subjecting epoxy alcohol **100c** to $[Rh(CO)_2Cl]_2$ catalysis (Table 7). The crude reaction mixtures obtained were not as pristine as for the smaller ring products, but we were able to isolate small quantities of oxocane **101c**, along with diene **103**, ketone **104**, and diene-diol **105**.[51] Preforming the reaction at elevated or reduced temperatures did not improve the yield significantly, but did impact side product formation. Attempts to use either CH_2Cl_2 or 1,4-dioxane as the reaction solvent did not yield any of the desired oxocane (**101c**). Running the reaction at a lower concentration or utilizing a reverse addition procedure resulted in decreased conversion and lower yields. In comparison, activation with CSA provided diene-diol **105** as the exclusive product. Although limited examples of benzo-oxocane synthesis by *endo*-selective epoxy alcohol cyclization are known,[52] to the best of our knowledge this work represents the first isolated oxocane synthesized via an *endo*-selective epoxy alcohol cyclization. Additionally, these results are

[51] Formation of side products by net deoxygenation (**103**) or 1,2 hydride shifts (**104**) have been reported previous by Berchtold (see ref 41.)

[52] (a) Arnone, A.; Bernardi, R.; Bravo, P.; Frigerio, M. *Gazz. Chim. Ital.* **1989**, *119*, 87. (b) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807.

especially intriguing for possible application towards the synthesis of oxocanes found in marine ladder polyethers, such as brevetoxin A (**2**).

Table 7. Oxocane formation and product distribution from cyclization attempts of epoxy alcohol **100c**.



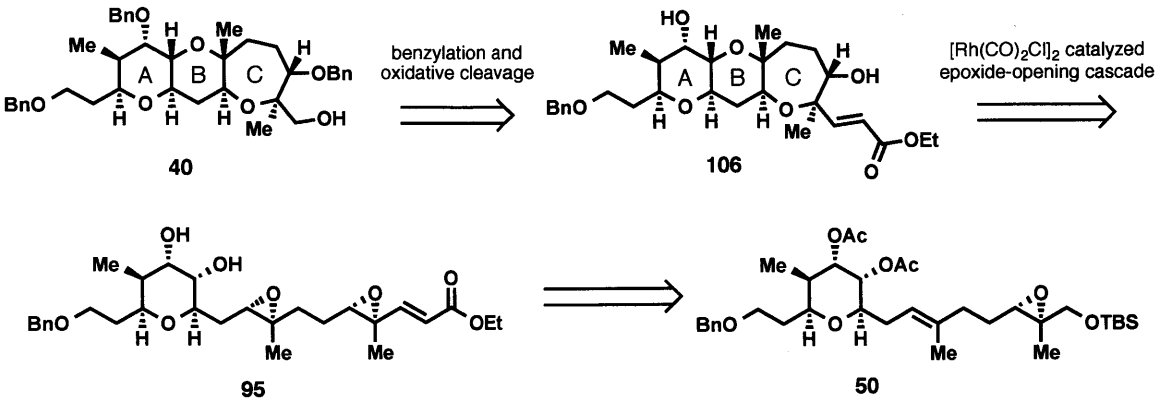
entry	catalyst	solvent, temp	yield (%)[a] 101c	103	104	105
1	$[Rh(CO)_2Cl]_2$ (10 mol %)	THF, rt	17	17	4	4
2	$[Rh(CO)_2Cl]_2$ (20 mol %)	THF, 4 °C	19	21	–	6
3	(±)-CSA (100 mol %)	CH_2Cl_2, rt	–	–	–	62

[a] Isolated yield.

F. Synthesis of the (–)-Brevisin ABC tricycle

Following the success of the model studies, we resumed efforts towards a formal synthesis of the ABC tricycle of (–)-brevisin (**40**). Our revised retrosynthetic analysis is shown in Scheme 22. We planned to use the combination of $[Rh(CO)_2Cl]_2$ catalysis and an enoate directing group as described previously in Scheme 20 to effect the desired all-*endo* epoxide-opening cascade of diepoxide **95**, key to our formal synthesis. Revisiting our previous efforts (Scheme 10), we wanted to improve the low yield and stereoselectivity of the cross metathesis to synthesize alkene **50** to ensure sufficient material throughput to explore the cascade.

Scheme 22. Revised retrosynthetic analysis of ABC tricycle **40**



Synthesis of trisubstituted alkenes via cross metathesis of α-olefins and geminal disubstituted alkenes has seen limited success in comparison to cross metathesis to generate 1,2 disubstituted alkenes. Grubbs demonstrated the ability of Ru alkylidene **49** to promote cross metathesis of simple α -olefins with geminal disubstituted alkenes.[53] From our attempts to couple **46** and **48**, we observed full conversion of **46**, leading us to suspect our low yields were from significant non-productive cross metathesis events such as homo-dimerization of **46** (Table 8, entries 1–3). Further work by Grubbs suggested modification to the NHC ligand could reduce non-productive metathesis events by utilizing catalyst **108**.[54] However, application of **108** did not lead to improvement in yield (entry 4).

Motivated by reports of higher yields in cross metathesis of allyl groups with increased steric hindrance,[55] alkene **107** was prepared from **46** via cross metathesis with 2-methyl-2-butene (Scheme 23).[53b] Metathesis of **48** and trisubstituted alkene **107** provided a significantly higher yield, particularly when performed in the absence of additional solvent (Table 8, entries 5-8). The significant improvement in yield is thought to result from a decrease of non-productive cross metathesis events, such as homo-dimerization and methylene exchange, by increasing the steric match of the alkylidene and incoming metathesis partner.[56] Despite the modest stereoselectivity, the 2:1 *E*/*Z* mixture of alkene isomers could be enriched to 10:1 *E*/*Z* by repeated careful column chromatography.

---

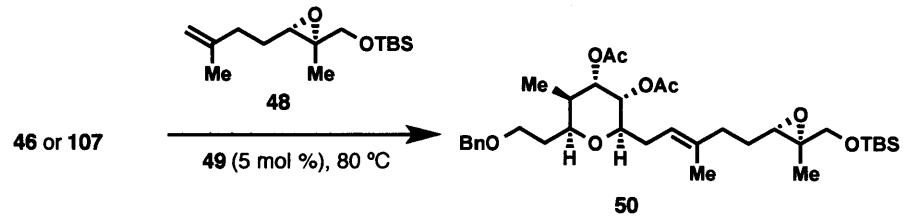
[53] (a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751. (b) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939.

[54] Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441.

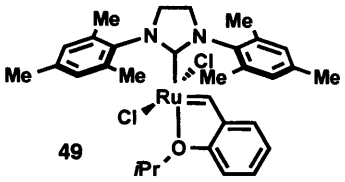
[55] Netscher, T. *J. Organomet. Chem.* **2006**, *691*, 5155.

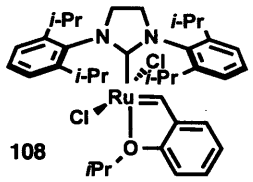
[56] Concurrent with our studies, a similar report was published with mechanistic experiments to support these hypotheses: Z. J.; Jackson, W. R.; Robinson, A. J. *Org. Lett.* **2013**, *15*, 3006.

Table 8. Optimization of cross metathesis to synthesize trisubstituted alkene **50**



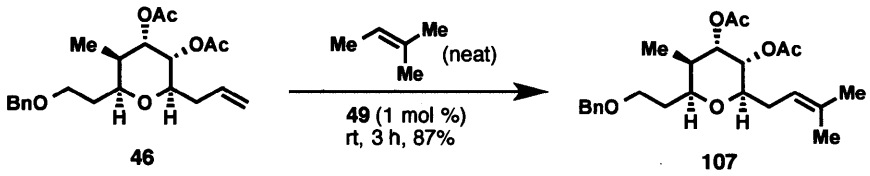
Entry	Substrate	Eq. **48**	Solvent	Yield **50** (%)[a]	*E*/*Z*	rsm (%)[a]
1	**46**	1	toluene	22	nd	–
2	**46**	3	"	29	nd	–
3	**46**	1.2	"	34	nd	–
4[b]	**46**	1.5	DCE	31	nd	–
5	**107**	2	toluene	54	2:1	39
6	**107**	2	neat	90[c]	2:1	9[c]
7[d]	**107**	2	neat	89[c]	2:1	8[c]
8	**107**	2	neat	78	2:1	7





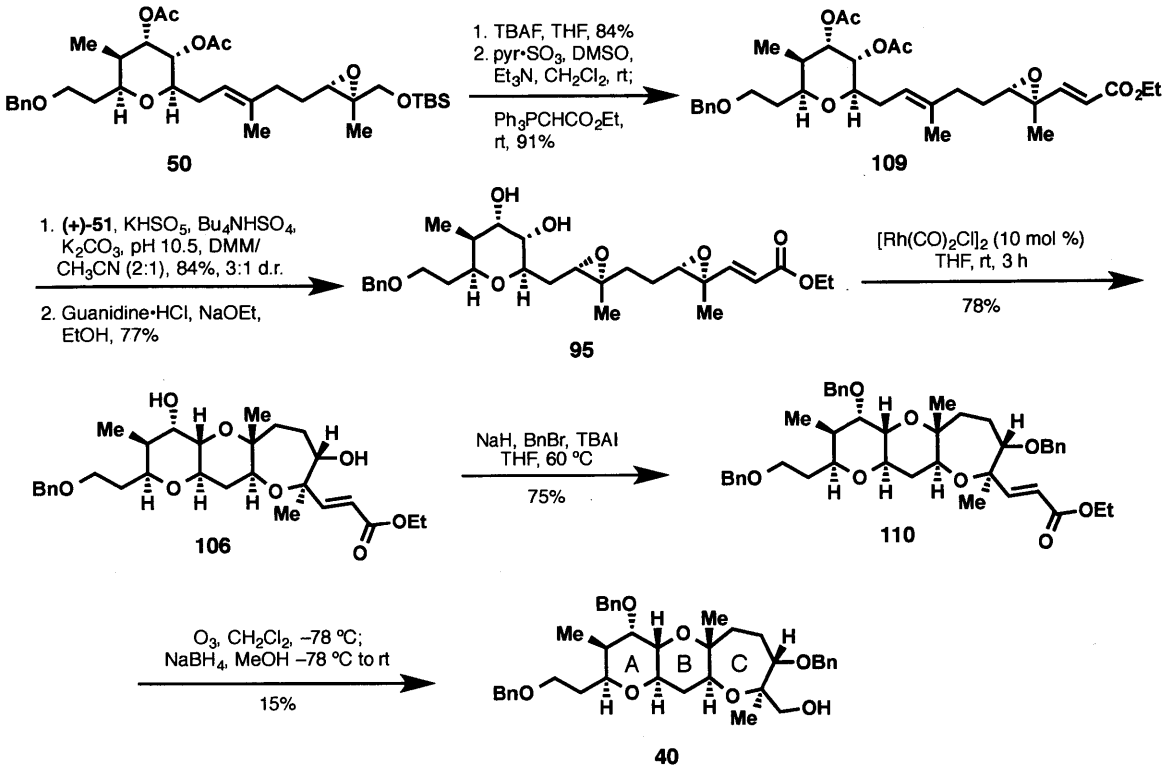
[a] Isolated yield. [b] Reaction run with catalyst **108**. [c] Yields determined by ^{1}H NMR spectroscopy. [d] Reaction run under static vacuum of 30 torr.

Scheme 23. Synthesis of trisubstituted alkene **107**



The enoate directing group was installed by desilylation of **50**, alcohol oxidation, and in situ stabilized-Wittig olefination (**109**, Scheme 24). Asymmetric Shi epoxidation, followed by acetate ethanolysis provided the diepoxide cascade precursor **95**. We utilized a guanidine-based buffer made in-situ from NaOEt and the guanidine•HCl, as attempts with K_2CO_3 in ethanol yielded significant amounts of product representing spontaneous cyclization of the first epoxide.

Scheme 24. Completion of the ABC tricycle synthesis

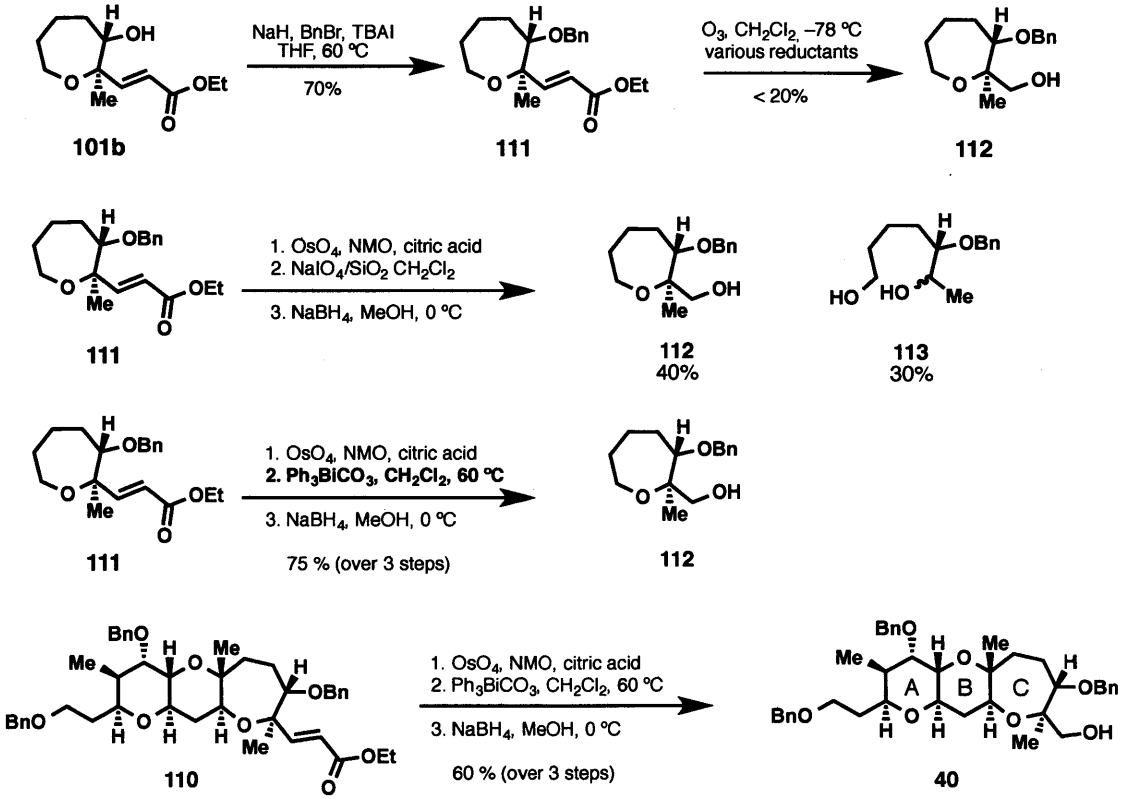


Exposure of diepoxide **95** to catalytic $[Rh(CO)_2Cl]_2$ at ambient temperature in THF led to full conversion and 78% yield of the desired ABC tricycle (**106**). Efforts directed toward lowering the catalyst loading (5 or 2 mol %) led to inferior yields. Unlike the monocyclic products from the model studies, the product of the cascade is a fused tricycle, locking the enoate and pendant alcohol into pseudo-equatorial conformations. We presume this conformation to have a higher affinity for the active rhodium species, slowing turnover. Additionally, we observed Brønsted acid promotion with (±)-CSA did not provide any desired product, further differentiating $[Rh(CO)_2Cl]_2$ from acid promoted conditions.

Following the success of the cascade, completion of formal synthesis of (–)-brevisin required protection of the A- and C-ring hydroxyls as benzyl ethers and cleavage of the enoate to provide the desired methylene alcohol functional group. Bis-benzylation of **106** under gentle heating proceeded smoothly to provide **110**. Our first attempts to oxidatively cleave enoate **110** via ozonolysis with subsequent reductive quenching with $NaBH_4$ yielded only small amounts of the desired formal synthesis intermediate (**40**), with what appeared to be significant amounts of oxidation of benzyloxy to benzoate groups. With limited quantities of **110**, we synthesized **111** for model studies to allow rapid screening of oxidation conditions (Scheme 25).

Attempts to limit undesired benzyl oxidation by reverse addition of a saturated O_3 solution in CH_2Cl_2, or use of Ph_3P to first provide an aldehyde saw no improvement in product yield. The combination of low yields and difficulty obtaining high purity product prompted us to explore an alternative sequence of dihydroxylation, oxidative diol cleavage, and reduction. Dihydroxylation of **111**, followed by periodate cleavage and subsequent reduction with $NaBH_4$ provided the desired alcohol (**112**). In addition to the moderate yield of **112,** a significant side product was observed: diol **113**. We reasoned the acidic nature of $NaIO_4$ was resulting in opening the oxepane, with subsequent oxidative cleavage yielding a ketone and ultimately producing diol **113**. Use of a neutral diol oxidative cleavage reagent, Ph_3BiCO_3, provided the desired **112** in 75% yield.[57] Application of this three-step sequence to tricycle **110** provided **40** in high purity and 60% yield over three steps.

Scheme 25. Model studies of enoate oxidative cleavage and application of improved sequence to the synthesis of ABC tricycle



[57] Barton, D. H. R.; Kitchin, J. P.; Lester, D. J.; Motherwell, W. B.; Papoula, M. T. B. *Tetrahedron* **1981**, *37*, 73.

In summary, the synthesis of the ABC tricycle intercept **40** was completed in 18 steps LLS compared to the previously reported 17 steps LLS by Tachibana and coworkers. Our synthesis features a highly selective epoxide opening cascade to synthesize the fully elaborated B and C rings in a single step. Additionally, the improvement of the fragment coupling via cross metathesis of a trisubstituted alkene streamlined the synthesis, allowing rapid access to the cascade precursor.

G. Conclusion

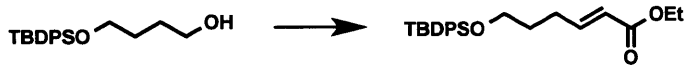
In conclusion, we have completed a formal synthesis of (–)-brevisin (**34**) utilizing $[Rh(CO)_2Cl]_2$ catalysis to selectively initiate diepoxide cascades as the key step in each fragment. During the course of this study, we have shown the combination of an enoate group and $[Rh(CO)_2Cl]_2$ catalysis is effective not only for the synthesis of 6-, 7, and 8-membered oxygen heterocycles from epoxy alcohols bearing a variety of substitution patterns (Tables 4–7), but also cascades of diepoxides where control of the sequence of epoxide opening events is tantamount to success (Table 3; Scheme 24). In comparison to the first generation approach utilizing Lewis acid catalysis, the high yield, stereospecificity, functional group compatibility, and *endo*-selectivity make this approach particularly well suited for target-directed synthesis, as highlighted by the synthesis of the ABC and EF fragments of (–)-brevisin.

H. General Experimental

All reactions were performed under an atmosphere of argon under anhydrous conditions, unless otherwise noted. Dichloromethane, tetrahydrofuran (THF), Et_2O, benzene, dioxane and triethylamine were purified via an SG Water USA solvent column system. Unless otherwise noted, all reagents were commercially obtained and used without further purification. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates, visualizing with a UV lamp (254 nm), $KMnO_4$, *p*-anisaldehyde, or CAM. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Silicycle silica gel (230–400 mesh) or Biotage® Isolera flash purification system on SNAP HP-SIL columns.

^1H NMR and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded at ambient temperature at 600 MHz and 150 MHz, respectively, using a Bruker AVANCE-600 spectrometer or 500 MHz and 125 MHz, respectively, using a Varian Inova-500 spectrometer. The ^1H NMR data are reported as follows: chemical shift in parts per million (ppm) from an internal standard of residual $CHCl_3$ in $CDCl_3$ (7.27 ppm) on the d scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz (Hz), and integration (H). Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.2 ppm).

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR or an Agilent Cary 630 FTIR Spectrometer. High-resolution mass spectra (HR-MS) were acquired on a Bruker Daltronics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer at the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured using a Jasco Model 1010 digital polarimeter at 589 nm and calculated using the formula: $[a]_D = a_{obs}/(l(c/1000))$, where c = (g of substrate/100 mL of solvent) and l = 1 dm.



87a **88a**

Enoate 88a: To a solution of TBDPS-protected alcohol **87a**[58] (2.0 g, 6.09 mmol) in CH_2Cl_2 (61 mL) was added DMSO (6.1 mL, 85.9 mmol) and Et_3N (4.3 mL, 30.5 mmol), cooled to 0 °C, and Pyr•SO_3 (1.94 g, 12.2 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (4.25 g, 12.2 mmol) was added as a solid at room temperature and stirred for 30 min. The reaction was quenched by addition of H_2O (35 mL) and diluted with CH_2Cl_2 (35 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (20 mL each). The combined organics were washed with H_2O (20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude enoate **88a** as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford **88a** as a colorless oil (2.24 g, 5.67 mmol, 93%, 95:5 *E*/*Z*). The product could be purified further by MPLC (Biotage Ultra Column) with a gradient of solvents (100% hexanes to 6% EtOAc in hexanes) to afford **88a** as only the *E* alkene (1.98 g, 82%).

Data were consistent with those reported by Beauchemin and coworkers.[59]

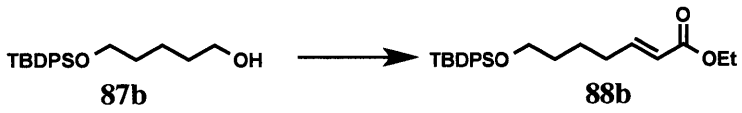
[58] Zhu, G.; Negishi, E. *Org. Lett.* **2007**, *9*, 2771.
[59] Clavette, C.; Rocan, J.-F. V.; Beauchemin, A. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12705.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.45-7.39 (m, 6H), 7.00 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.84 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.70 (t, *J* = 6.1 Hz, 2H), 2.39-2.31 (m, 2H), 1.78-1.69 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.07 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 149.1, 135.7, 134.0, 129.8, 127.8, 121.7, 63.1, 60.3, 31.1, 28.8, 27.0, 19.4, 14.5.

IR (thin film): 3069, 2933, 2858, 1718, 1654, 1472, 1427, 1265, 1203, 1105, 1041 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{24}H_{32}O_3Si$ $(M+NH_4)^+$: 414.2459, found 414.2460.



87b **88b**

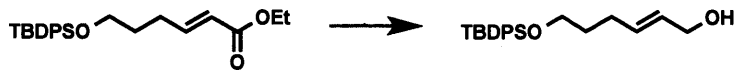
Enoate 88b: To a solution of TBDPS-protected alcohol **87b**[58] (2.50 g, 7.30 mmol) in CH_2Cl_2 (73 mL) was added DMSO (7.3 mL, 0.10 mol) and Et_3N (5.1 mL, 36.5 mmol), cooled to 0 °C, and Pyr•SO_3 (2.32 g, 14.6 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3h. At this point, (carbethoxymethylene)triphenylphosphorane (5.1 g, 14.6 mmol) was added as a solid at room temperature and stirred for 30 min. The reaction was quenched by addition of H_2O (50 mL) and diluted with CH_2Cl_2 (50 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (30 mL each). The combined organics were washed with H_2O (50 mL), sat. $NaCl_{(aq)}$ (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude enoate **88b** as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford **88b** as a colorless oil (2.68 g, 6.53 mmol, 89%, 95:5 *E*/*Z*). The product was purified further by flash chromatography with a gradient of solvents (100% hexanes to 3% EtOAc in hexanes) to afford **88b** enriched to 98:2 *E*/Z (1.20 g, 40%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.45-7.38 (m, 6H), 6.97 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.81 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.68 (t, *J* = 5.9 Hz, 2H), 2.20 (qd, *J* = 7.1, 1.3 Hz, 2H), 1.63-1.55 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 149.4, 135.7, 134.1, 129.7, 127.8, 121.5, 63.6, 60.3, 32.11, 32.05, 27.0, 24.5, 19.4, 14.5.

IR (thin film): 3069, 2932, 2858, 1719, 1653, 1473, 1428, 1265, 1195, 1159, 1108, 1043 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{25}H_{34}O_3Si$ $(M+NH_4)^+$: 428.2615, found 428.2617.



88a **89a**

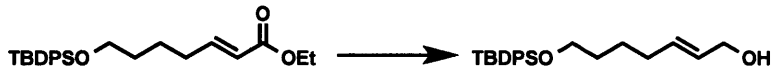
Alcohol 89a: To a solution of enoate **88a** (1.97 g, 4.97 mmol) in CH_2Cl_2 (20 mL) at –78 °C was added DIBAL–H (1.0 M in CH_2Cl_2, 17.4 mL, 17.4 mmol) dropwise over three min. The reaction was stirred for 20 min, and then quenched by slow addition of MeOH (5 mL) at –78 °C. The reaction mixture was then poured into an Erlenmeyer flask containing sat. aq. Rochelle's salt (150 mL) and stirred vigorously for 2 h at room temperature. The aqueous layer was separated and extracted with CH_2Cl_2 (2x20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford crude alcohol **89a** as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 35% EtOAc in hexanes) to afford **89a** as a colorless oil (1.59 g, 4.48 mmol, 90%).

^{1}H NMR (500 MHz, $CDCl_3$): δ7.71-7.70 (m, 4H), 7.47-7.39 (m, 6H), 5.72-5.62 (m, 2H), 4.09-4.07 (br, 2H), 3.71 (t, J = 6.3 Hz, 2H), 2.18 (q, J = 6.9 Hz, 2H), 1.69 (quint, J = 7.1 Hz, 2H), 1.48-1.44 (br, 1H), 1.09 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.7, 134.1, 132.9, 129.7, 129.4, 127.8, 63.9, 63.3, 32.1, 28.6, 27.0, 19.4.

IR (thin film): 3325, 3068, 2932, 2857, 1670, 1589, 1472, 1728, 1389, 1361, 1105, 998, 967 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{22}H_{30}O_2Si$ $(M+NH_4)^+$: 372.2353, found 372.2346.



88b **89b**

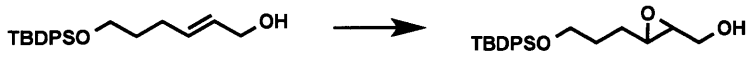
Alcohol 89b: To a solution of enoate **88b** (1.20 g, 2.92 mmol) in CH_2Cl_2 (12 mL) at –78 °C was added DIBAL–H (1.0 M in CH_2Cl_2, 10.5 mL, 10.5 mmol) dropwise over three min. The reaction was stirred for 25 min, and then quenched by slow addition of MeOH (3 mL) at –78 °C. The reaction mixture was then poured into an Erlenmeyer flask containing sat. aq. Rochelle's salt (100 mL) and stirred vigorously for 2 h at room temperature. The aqueous layer was separated and extracted with CH_2Cl_2 (2x20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford crude alcohol **89b** as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 35% EtOAc in hexanes) to afford **89b** as a colorless oil (1.02 g, 2.77 mmol, 94%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70-7.68 (m, 4H), 7.46-7.38 (m, 6H), 5.72-5.60 (m, 2H), 4.10 (br, 2H), 3.68 (t, J = 6.4 Hz, 2H), 2.06 (q, J = 6.9 Hz, 2H), 1.59 (dq, J = 8.7, 6.1 Hz, 2H), 1.51-1.45 (m, 2H), 1.35 (br, 1H), 1.07 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.7, 134.2, 133.4, 129.7, 129.2, 127.8 63.98, 63.89, 32.20, 32.08, 27.0, 25.5, 19.4.

IR (thin film): 3324, 3057, 2931, 2859, 1669, 1590, 1472, 1428, 1389, 1105 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{23}H_{32}O_2Si$ $(M+NH_4)^+$: 386.2510, found 386.2520



89a **90a**

Epoxide 90a: To a solution of alcohol **89a** (1.57 g, 4.43 mmol) in CH_2Cl_2 (44 mL) at 0 °C was added *m*CPBA (≤ 77 wt %, 1.49 g, 6.64 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 2 h, and then quenched by addition of 10% $Na_2CO_{3(aq)}$ (60 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (30 mL each). The combined organic layer was washed with sat. $NaHSO_{3(aq)}$ (30 mL), and 10% $Na_2CO_{3(aq)}$ (30 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude alcohol **90a** as a colorless oil. The crude product was purified by flash chromatography (15% EtOAc in hexanes to 45% EtOAc in hexanes) to afford **90a** as a colorless oil (1.47 g, 3.94 mmol, 89%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.66 (m, 4H), 7.44-7.38 (m, 6H), 3.88 (dd, J = 12.6, 2.5 Hz, 1H), 3.73-3.71 (m, 2H), 3.59 (dd, J = 12.6, 4.4 Hz, 1H), 2.98-2.96 (m, 1H), 2.91 (ddd, J = 4.5, 2.3, 2.3 Hz, 1H), 1.90-1.80 (br, 1H), 1.75-1.66 (m, 4H), 1.07 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.7, 133.98, 133.97, 129.8, 127.8, 63.4, 61.8, 58.6, 55.9, 29.0, 28.2, 27.0, 19.4.

IR (thin film): 3407, 2932, 2858, 1472, 1428, 1389, 1361, 1307, 1105 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{22}H_{30}O_3Si$ $(M+NH_4)^+$: 388.2302, found 388.2292.

89b **90b**

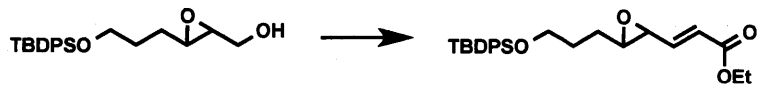
Epoxide 90b: To a solution of alcohol **89b** (0.97 g, 2.63 mmol) in CH_2Cl_2 (26 mL) at 0 °C was added *m*CPBA (≤ 77 wt %, 0.88 g, 3.95 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 2 h, and then quenched by addition of 10% $Na_2CO_{3(aq)}$ (30 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (20 mL each). The combined organic layer was washed with sat. $NaHSO_{3(aq)}$ (20 mL), and 10% $Na_2CO_{3(aq)}$ (20 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude alcohol **90b** as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 40% EtOAc in hexanes) to afford **90b** as a colorless oil (0.89 g, 2.31 mmol, 88%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68-7.67 (m, 4H), 7.45-7.38 (m, 6H), 3.93-3.90 (m, 1H), 3.68 (t, J = 6.1 Hz, 2H), 3.65-3.61 (m, 1H), 2.96-2.94 (m, 1H), 2.91 (dt, J = 4.4, 2.3 Hz, 1H), 1.74 (t, J = 5.8 Hz, 1H), 1.65-1.50 (m, 6H), 1.06 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.7, 134.1, 129.7, 127.8, 63.7, 61.8, 58.5, 56.0, 32.4, 31.4, 27.0, 22.5, 19.4.

IR (thin film): 3420, 3069, 2931, 2858, 1589, 1472, 1428, 1389, 1361, 1188, 1105 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{23}H_{32}O_3Si$ $(M+NH_4)^+$: 402.2459, found 402.2443.



90a **91a**

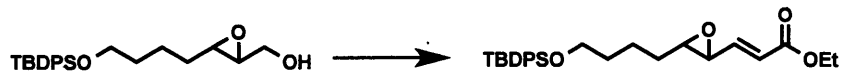
Epoxy Enoate 91a : To a solution of epoxy alcohol **90a** (1.40 g, 3.78 mmol) in CH_2Cl_2 (38 mL) was added DMSO (3.8 mL, 53.5 mmol) and Et_3N (2.6 mL, 19 mmol), cooled to 0 °C, and Pyr•SO_3 (1.20 g, 7.56 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (2.63 g, 7.56 mmol) was added as a solid at room temperature and stirred for 30 min. The reaction was quenched by addition of H_2O (25 mL) and diluted with CH_2Cl_2 (25 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (20 mL each). The combined organics were washed with H_2O (20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude enoate **91a** as a yellow oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes) to afford **91a** as a colorless oil (1.39 g, 3.17 mmol, 84%, 92:8 *E/Z*). The product was purified further by MPLC (Biotage Ultra Column) with a gradient of solvents (100% hexanes to 8% EtOAc in hexanes) to afford **91a** as only the (*E*)-alkene (1.07 g, 65%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68-7.66 (m, 4H), 7.46-7.38 (m, 6H), 6.65 (dd, *J* = 15.7, 7.2 Hz, 1H), 6.11 (dd, *J* = 15.7, 0.7 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.71 (t, *J* = 5.4 Hz, 2H), 3.20 (ddd, *J* = 7.2, 1.9, 0.5 Hz, 1H), 2.89 (td, *J* = 5.1, 2.0 Hz, 1H), 1.76-1.69 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 144.9, 135.7, 133.92, 133.89, 129.8, 127.84, 127.83, 123.8, 63.2, 61.3, 60.7, 56.5, 28.8, 28.6, 27.0, 19.4, 14.4.

IR (thin film): 3067, 2933, 2858, 1719, 1655, 1589, 1472, 1428, 1390, 1368, 1302, 1258, 1182, 1106 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{26}H_{34}O_4Si$ $(M+NH_4)^+$: 456.2565, found 456.2557.



90b **91b**

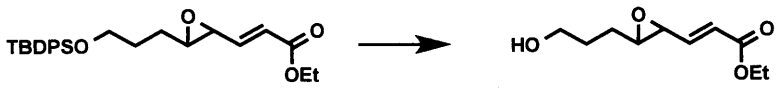
Epoxy Enoate 91b: To a solution of epoxy alcohol **90b** (0.83 g, 2.16 mmol) in CH_2Cl_2 (21 mL) was added DMSO (2.2 mL, 31 mmol) and Et_3N (1.5 mL, 10.8 mmol), cooled to 0 °C, and Pyr•SO_3 (0.69 g, 4.3 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (1.5 g, 4.3 mmol) was added as a solid at room temperature and stirred for 30 min. The reaction was quenched by addition of H_2O (25 mL) and diluted with CH_2Cl_2 (25 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (20 mL each). The combined organics were washed with H_2O (20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude enoate **91b** as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford **91b** as a colorless oil (0.69 g, 1.52 mmol, 70%, 95:5 *E/Z*). The product was purified further by MPLC (Biotage Ultra Column) with a gradient of solvents (100% hexanes to 6% EtOAc in hexanes) to afford **91b** as only the (*E*)-alkene (0.38 g, 38%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68-7.66 (m, 4H), 7.45-7.37 (m, 6H), 6.68 (dd, *J* = 15.7, 7.1 Hz, 1H), 6.12 (dd, *J* = 15.7, 0.6 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.68 (t, *J* = 5.9 Hz, 2H), 3.19 (ddd, *J* = 7.1, 2.0, 0.6 Hz, 1H), 2.89-2.86 (m, 1H), 1.62-1.52 (m, 6H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 144.9, 135.7, 134.1, 129.7, 127.8, 123.7, 63.7, 61.5, 60.7, 56.4, 32.3, 31.8, 27.0, 22.4, 19.4, 14.4.

IR (thin film): 3067, 2933, 2858, 1719, 1655, 1589, 1473, 1428, 1390, 1368, 1302, 1256, 1180, 1093, 1041 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{27}H_{36}O_4Si$ $(M+NH_4)^+$: 470.2721, found 470.2703.



91a **92a**

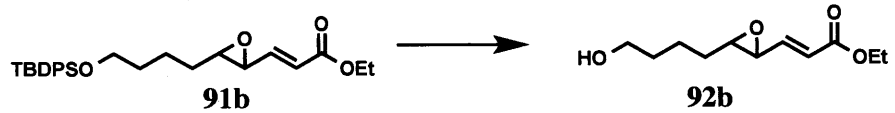
Epoxy Alcohol 92a: To a solution of enoate **91a** (0.60 g, 1.37 mmol) in THF (2.7 mL) at 0 °C was added TBAF (1.0 M in THF, 2.7 mL, 2.7 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 2 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et_3N in 50% EtOAc in hexanes, then 50% EtOAc in hexanes to 60% EtOAc in hexanes) to afford **92a** as a colorless oil (0.25 g, 1.25 mmol, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.67 (dd, *J* = 15.7, 7.1 Hz, 1H), 6.12 (d, *J* = 15.7 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.69 (t, *J* = 5.9 Hz, 2H), 3.25 (dd, *J* = 7.1, 1.5 Hz, 1H), 2.94 (td, *J* = 5.4, 1.8 Hz, 1H), 1.84-1.61 (m, 5H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 144.6, 123.9, 62.3, 61.3, 60.8, 56.6, 29.0, 28.6, 14.4.

IR (thin film): 3414, 2983, 2934, 2875, 1715, 1654, 1446, 1369, 1303, 1259, 1182, 1142, 1033 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{10}H_{16}O_4$ $(M+NH_4)^+$: 218.1387, found 218.1391.



91b **92b**

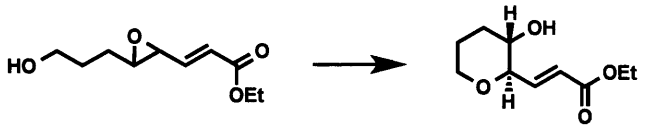
Epoxy Alcohol 92b: To a solution of enoate **91b** (0.38 g, 0.84 mmol) in THF (1.7 mL) at 0 °C was added TBAF (1.0 M in THF, 1.7 mL, 1.7 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 2 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et_3N in 50% EtOAc in hexanes, then 50% EtOAc in hexanes to 60% EtOAc in hexanes) to afford **92b** as a colorless oil (0.17 g, 0.79 mmol, 94%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.64 (dd, *J* = 15.7, 7.1 Hz, 1H), 6.10 (d, *J* = 15.7 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.62 (t, *J* = 6.2 Hz, 2H), 3.21 (dd, *J* = 7.1, 1.7 Hz, 1H), 2.90-2.87 (m, 1H), 1.91 (br, 1H), 1.65-1.50 (m, 6H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 144.8, 123.8, 62.5, 61.4, 60.7, 56.4, 32.3, 31.7, 22.3, 14.3.

IR (thin film): 3423, 2978, 2936, 2865, 1716, 1655, 1446, 1369, 1303, 1258, 1180, 1141, 1033 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{11}H_{18}O_4$ $(M+NH_4)^+$: 232.1543, found 232.1541.



92a **93a**

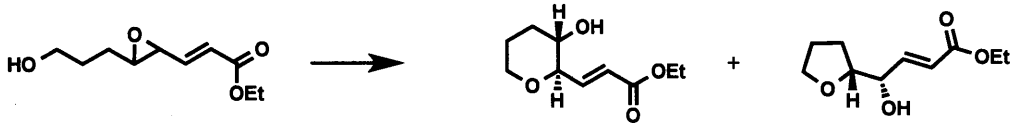
[Rh(CO)$_2$Cl]$_2$ promoted cyclization of epoxy alcohol 92a: To a 20 ml vial equipped with a magnetic stir bar was added epoxide **92a** (57 mg, 0.28 mmol), THF (1.4 mL), and a solution of [Rh(CO)$_2$Cl]$_2$ in THF (2.8 mg, 7 μmol, in 1.4 mL THF) and stirred at room temperature. After consumption of the starting material (1 h, as determined by TLC analysis), 40 mg of polymer-bound triphenylphosphine resin was added and stirred for 30 min. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified mixture indicated a 97.5:1.5 [*endo*(**93a**)/*exo*(**94a**)] ratio of products. The resultant pale yellow film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford **93a** as a colorless oil (53.2 mg, 0.27 mmol, 94%).

Characterization Data for 93a:
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (dd, *J* = 15.8, 4.9 Hz, 1H), 6.09 (dd, *J* = 15.8, 1.5 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.95 (d, *J* = 12.1 Hz, 1H), 3.67 (ddd, *J* = 9.0, 4.9, 1.4 Hz, 1H), 3.41-3.34 (m, 2H), 2.54-2.50 (br, 1H), 2.16-2.13 (m, 1H), 1.72-1.67 (m, 2H), 1.52-1.44 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ. 166.7, 145.4, 122.2, 81.3, 70.0, 67.5, 60.7, 32.7, 25.4, 14.4.

IR (thin film): 3422, 2940, 2857, 1700, 1658, 1445, 1368, 1303, 1265, 1174, 1077, 1041, 982 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{10}H_{16}O_4$ $(M+NH_4)^+$: 218.1387, found 218.1385.



92a **93a** **94a**

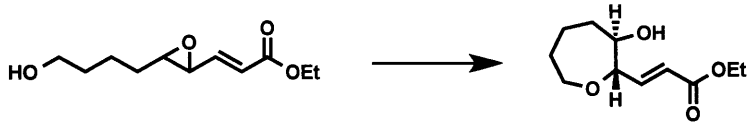
(±)-CSA Promoted cyclization of epoxy alcohol 92a: To a 20 ml vial equipped with a magnetic stir bar was added epoxide **92a** (60 mg, 0.30 mmol) in CH_2Cl_2 (15 mL) and (±)-CSA (7.0 mg, 0.03 mmol) and stirred at room temperature. After consumption of the starting material (15 h, as determined by TLC analysis), the clear solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified mixture indicated a 1:1 [*endo*(**93a**)/*exo*(**94a**)] ratio of products. The resultant clear film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford **93a** as a colorless oil (25.9 mg, 0.13 mmol, 43%) and **94a** as a colorless oil (30.3 mg, 0.15 mmol, 50%).

Characterization Data for 94a:
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (dd, J = 15.7, 4.3 Hz, 1H), 6.15 (dd, J = 15.7, 2.0 Hz, 1H), 4.53 (td, J = 3.9, 1.9 Hz, 1H), 4.21 (q, J = 7.1Hz, 2H), 3.98 (td, J = 7.3, 3.7 Hz, 1H), 3.92 (dt, J = 8.2, 6.6 Hz, 1H), 3.80 (dt, J = 8.2, 6.8 Hz, 1H), 2.45-2.38 (br, 1H), 1.92-1.87 (m, 2H), 1.81-1.77 (m, 2H), 1.30 (t, J = 7.1 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5, 145.4, 121.8, 81.0, 71.9, 69.3, 60.6, 26.3, 25.2, 14.4.

IR (thin film): 3426, 2977, 2932, 2872, 1717, 1659, 1464, 1447, 1368, 1302, 1267, 1175, 1067, 1039 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{10}H_{16}O_4$ $(M+NH_4)^+$: 218.1387, found 218.1380.



92b **93b**

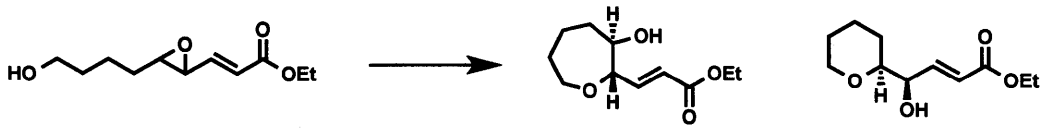
[Rh(CO)$_2$Cl]$_2$ promoted cyclization of epoxy alcohol 92b: To a 20 ml vial equipped with a magnetic stir bar was added epoxide **92b** (54 mg, 0.25 mmol), THF (1.25 mL), and a solution of [Rh(CO)$_2$Cl]$_2$ in THF (4.9 mg, 13 μmol, in 1.25 mL THF) and stirred at room temperature. After consumption of the starting material (9 h, as determined by TLC analysis), 45 mg of polymer-bound triphenylphosphine resin was added and stirred for 30 min. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified mixture indicated a 99:1 [*endo*(**93b**)/*exo*(**94b**)] ratio of products. The resultant pale yellow film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford **93b** as a colorless oil (43.6 mg, 0.20 mmol, 81%).

Characterization Data for 93b:
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (dd, J = 15.7, 4.4 Hz, 1H), 6.10 (dd, J = 15.7, 1.8 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.94 (dt, J = 12.2, 5.3 Hz, 1H), 3.88 (ddd, J = 8.5, 4.4, 1.8 Hz, 1H), 3.70-3.60 (m, 2H), 2.13 (br, 1H), 2.01-1.97 (m, 1H), 1.80-1.67 (m, 4H), 1.61-1.55 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 147.2, 121.1, 83.4, 74.7, 70.8, 60.6, 36.1, 30.7, 21.0, 14.4.

IR (thin film): 3425, 2932, 2864, 1700, 1656, 1446, 1368, 1300, 1270, 1172, 1135, 1102, 1038 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{11}H_{18}O_4$ $(M+NH_4)^+$: 232.1543, found 232.1543.



92b 93b 94b

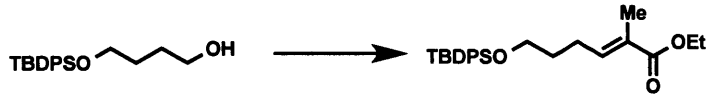
(±)-CSA Promoted cyclization of epoxy alcohol 92b: To a 20 ml vial equipped with a magnetic stir bar was added epoxide **92b** (54 mg, 0.25 mmol) in CH_2Cl_2 (12 mL) and (±)-CSA (58 mg, 0.25 mmol) and stirred at room temperature. After consumption of the starting material (7 h, as determined by TLC analysis), the clear solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. ^1H NMR spectroscopic analysis of the unpurified mixture indicated a 1:3 [*endo*(**93b**)/*exo*(**94b**)] ratio of products. The resultant clear film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford **94b** as a colorless oil (35.8 mg, 0.167 mmol, 67%) and **93b** as a colorless oil (11.4 mg, 0.053 mmol, 21%).

Characterization Data for 94b:
^1H NMR (500 MHz, $CDCl_3$): δ 6.93 (dd, J = 15.7, 4.7 Hz, 1H), 6.12 (dd, J = 15.7, 1.9 Hz, 1H), 4.33 (br, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.02 (ddt, J = 11.4, 4.1, 2.0 Hz, 1H), 3.50-3.43 (m, 2H), 2.56 (br, 1H), 1.89-1.86 (m, 1H), 1.58-1.42 (m, 5H), 1.29 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.5, 145.8, 122.1, 79.7, 73.4, 69.0, 60.6, 26.0, 25.7, 23.1, 14.4.

IR (thin film): 3429, 2936, 2851, 1717, 1659, 1443, 1368, 1306, 1270, 1175, 1092, 1043 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{11}H_{18}O_4$ $(M+NH_4)^+$: 232.1543, found 232.1539.



87a 96a

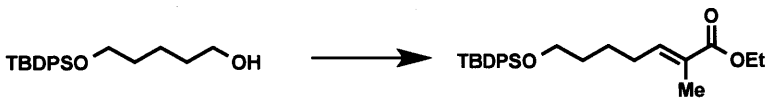
Enoate 96a: To a solution of TBDPS-protected alcohol **87a**[58] (3.33 g, 10.1 mmol) in CH_2Cl_2 (100 mL) was added DMSO (10 mL, 0.14 mol) and Et_3N (7.0 mL, 50 mmol), cooled to 0 °C, and Pyr•SO_3 (3.22 g, 20.2 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (Carbethoxyethylidene)triphenylphosphorane (7.32 g, 20.2 mmol) was added as a solid at room temperature and stirred for 12 h. The reaction was quenched by addition of H_2O (75 mL) and diluted with CH_2Cl_2 (25 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (30 mL each). The combined organics were washed with H_2O (50 mL), sat. $NaCl_{(aq)}$ (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude enoate **96a** as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford **96a** as a colorless oil (2.92 g, 6.88 mmol, 89%, 96:4 *E*/*Z*). The product was purified further by flash chromatography with a gradient of solvents (2% EtOAc in hexanes to 4% EtOAc in hexanes) to afford **96a** enriched to >99:1 *E*/Z (1.27 g, 39%).

^1H NMR (500 MHz, $CDCl_3$): δ 7.69-7.66 (m, 4H), 7.46-7.38 (m, 6H), 6.77 (tq, J = 7.5, 1.4 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.69 (t, J = 6.1 Hz, 2H), 2.30 (q, J = 7.4 Hz, 2H), 1.85 (d, J = 1.3 Hz, 3H), 1.73-1.67 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.07 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 142.0, 135.7, 134.0, 129.8, 128.2, 127.8, 63.4, 60.6, 31.6, 27.0, 25.3, 19.4, 14.5, 12.5.

IR (thin film): 3073, 2933, 2858, 1708, 1651, 1590, 1473, 1428, 1389, 1366, 1261, 1234, 1190, 1106, 1030 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{25}H_{34}O_3Si$ $(M+NH_4)^+$: 428.2615, found 428.2635.



87b **96b**

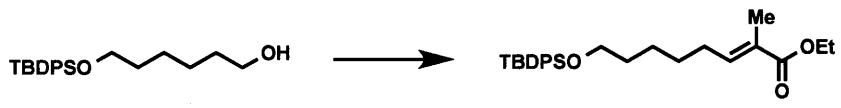
Enoate 96b: To a solution of TBDPS-protected alcohol **87b**[58] (2.64 g, 7.7 mmol) in CH_2Cl_2 (77 mL) was added DMSO (7.7 mL, 0.11 mol) and Et_3N (5.4 mL, 39 mmol), cooled to 0 °C, and Pyr•SO_3 (2.45 g, 15.4 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3h. At this point, (Carbethoxyethylidene)triphenylphosphorane (5.60 g, 15.4 mmol) was added as a solid at room temperature and stirred for 12 h. The reaction was quenched by addition of H_2O (75 mL) and diluted with CH_2Cl_2 (25 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (30 mL each). The combined organics were washed with H_2O (50 mL), sat. $NaCl_{(aq)}$ (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude enoate **96b** as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford **96b** as a colorless oil (2.92 g, 6.88 mmol, 89%, 96:4 *E/Z*). The product was purified further by flash chromatography with a gradient of solvents (2% EtOAc in hexanes to 4% EtOAc in hexanes) to afford **96b** enriched to >99:1 *E/Z* (1.27 g, 39%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.68 (m, 4H), 7.46-7.38 (m, 6H), 6.77 (d, J = 7.4 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.69 (t, J = 5.9 Hz, 2H), 2.18 (q, J = 7.2 Hz, 2H), 1.83 (s, 3H), 1.63-1.53 (m, 4H), 1.32 (t, J = 7.1 Hz, 3H), 1.07 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 142.3, 135.7, 134.1, 129.7, 128.0, 127.8, 63.7, 60.6, 32.4, 28.5, 27.0, 25.1, 19.4, 14.5, 12.5.

IR (thin film): 3055, 2932, 2858, 1708, 1651, 1590, 1472, 1428, 1389, 1365, 1254, 1223, 1185, 1104 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{26}H_{36}O_3Si$ $(M+NH_4)^+$: 442.2772, found 442.2772.



87c **96c**

Enoate 96c: To a solution of TBDPS-protected alcohol **87c**[60] (2.23 g, 6.26 mmol) in CH_2Cl_2 (62 mL) was added DMSO (6.3 mL, 88 mmol) and Et_3N (4.4 mL, 31 mmol), cooled to 0 °C, and Pyr•SO_3 (2.00 g, 12.5 mmol) added as a solid. The reaction was allowed to warm to room

[60] Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 251.

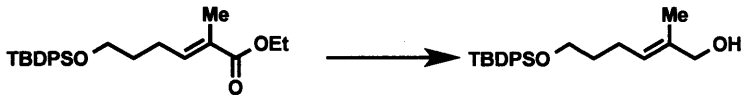
temperature and stirred for 3h. At this point, (Carbethoxyethylidene)triphenylphosphorane (4.5 g, 12.5 mmol) was added as a solid at room temperature and stirred for 12 h. The reaction was quenched by addition of H_2O (75 mL) and diluted with CH_2Cl_2 (25 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (30 mL each). The combined organics were washed with H_2O (50 mL), sat. $NaCl_{(aq)}$ (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude enoate **96c** as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford **96c** as a colorless oil (2.22 g, 5.06 mmol, 81%, 96:4 *E*/*Z*). The product was purified further by flash chromatography with a gradient of solvents (2% EtOAc in hexanes to 4% EtOAc in hexanes) to afford **96c** enriched to >99:1 *E*/*Z* (1.44 g, 52%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71-7.69 (m, 4H), 7.46-7.39 (m, 6H), 6.78 (tq, *J* = 7.5, 1.4 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.69 (t, *J* = 6.4 Hz, 2H), 2.18 (q, *J* = 6.8 Hz, 2H), 1.86 (d, *J* = 1.1 Hz, 3H), 1.60 (quint, *J* = 6.9 Hz, 2H), 1.47-1.41 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.08 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 168.4, 142.4, 135.7, 134.2, 129.7, 127.86, 127.74, 63.9, 60.5, 32.5, 28.8, 28.5, 27.0, 25.7, 19.4, 14.5, 12.5.

IR (thin film): 2932, 2858, 1708, 1651, 1589, 1473, 1428, 1389, 1365, 1259, 1175, 1129, 1092, 1036 cm^{-1}.

HR-MS (DART) *m*/*z* calcd for $C_{27}H_{38}O_3Si$ $(M+NH_4)^+$: 456.2928, found 456.2939.



96a **97a**

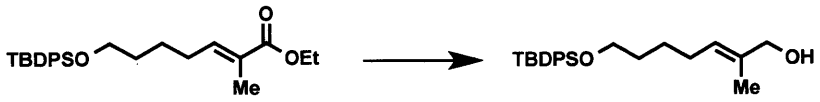
Alcohol 97a: To a solution of enoate **96a** (2.37 g, 5.77 mmol) in CH_2Cl_2 (25 mL) at –78 °C was added DIBAL–H (1.0 M in CH_2Cl_2, 20 mL, 20 mmol) dropwise over three min. The reaction was stirred for 2.5 h, and then quenched by slow addition of MeOH (6 mL) at –78 °C. The reaction mixture was then poured into an Erlenmeyer flask containing sat. aq. Rochelle's salt (150 mL) and stirred vigorously for 2 h at room temperature. The aqueous layer was separated and extracted with CH_2Cl_2 (2x30 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford crude alcohol **97a** as a colorless oil. The crude product was purified by flash chromatography (15% EtOAc in hexanes to 20% EtOAc in hexanes) to afford **97a** as a colorless oil (1.98 g, 5.43 mmol, 94%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.68 (m, 4H), 7.45-7.38 (m, 6H), 5.38 (tq, *J* = 7.2, 1.3 Hz, 1H), 3.99 (d, *J* = 5.0 Hz, 2H), 3.68 (t, *J* = 6.3 Hz, 2H), 2.14 (q, *J* = 7.3 Hz, 2H), 1.67 (d, *J* = 0.4 Hz, 3H), 1.65-1.61 (m, 2H), 1.26 (t, *J* = 5.9 Hz, 1H), 1.07 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 135.7, 135.2, 134.2, 129.7, 127.8, 126.1, 69.2, 63.5, 32.5, 27.0, 24.0, 19.4, 13.8.

IR (thin film): 3300, 2931, 2858, 1472, 1428, 1388, 1109, 1007 cm^{-1}.

HR-MS (DART) *m*/*z* calcd for $C_{23}H_{32}O_2Si$ $(M+NH_4)^+$: 386.2510, found 386.2492.



96b **97b**

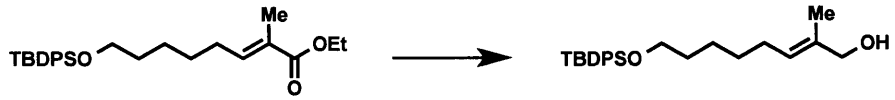
Alcohol 97b: To a solution of enoate **96b** (1.21 g, 2.85 mmol) in CH_2Cl_2 (12 mL) at –78 °C was added DIBAL–H (1.0 M in CH_2Cl_2, 10 mL, 10 mmol) dropwise over three min. The reaction was stirred for 2.5 h, and then quenched by slow addition of MeOH (3 mL) at –78 °C. The reaction mixture was then poured into an Erlenmeyer flask containing sat. aq. Rochelle's salt (100 mL) and stirred vigorously for 5 h at room temperature. The aqueous layer was separated and extracted with CH_2Cl_2 (2x20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford crude alcohol **97b** as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 30% EtOAc in hexanes) to afford **97b** as a colorless oil (1.06 g, 2.77 mmol, 97%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (m, 4H), 7.45-7.37 (m, 6H), 5.40 (tq, J = 7.1, 1.2 Hz, 1H), 4.01 (s, 2H), 3.67 (t, J = 6.4 Hz, 2H), 2.04 (q, J = 7.3 Hz, 2H), 1.65 (s, 3H), 1.61-1.56 (m, 2H), 1.48-1.42 (m, 2H), 1.39 (br, 1H), 1.06 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 135.0, 134.3, 129.7, 127.8, 126.6, 69.2, 64.0, 32.4, 27.5, 27.1, 25.9, 19.4, 13.9.

IR (thin film): 3321, 3069, 2931, 2857, 1472, 1428, 1389, 1361, 1189, 1109, 1007 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{24}H_{34}O_2Si$ $(M+NH_4)^+$: 400.2666, found 400.2669.



96c **97c**

Alcohol 97c: To a solution of enoate **96c** (1.42 g, 3.24 mmol) in CH_2Cl_2 (13 mL) at –78 °C was added DIBAL–H (1.0 M in CH_2Cl_2, 11.3 mL, 11.3 mmol) dropwise over three min. The reaction was stirred for 1 h, and then quenched by slow addition of MeOH (3 mL) at –78 °C. The reaction mixture was then poured into an Erlenmeyer flask containing sat. aq. Rochelle's salt (100 mL) and stirred vigorously for 4 h at room temperature. The aqueous layer was separated and extracted with CH_2Cl_2 (2x20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford crude alcohol **97c** as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 20% EtOAc in hexanes) to afford **97c** as a colorless oil (1.21 g, 2.76 mmol, 95%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.69-7.68 (m, 4H), 7.45-7.38 (m, 6H), 5.41 (tq, J = 7.2, 1.2 Hz, 1H), 4.01 (s, 2H), 3.67 (t, J = 6.5 Hz, 2H), 2.03 (q, J = 6.8 Hz, 2H), 1.67 (s, 3H), 1.58 (quint, J = 7.0 Hz, 2H), 1.42 (br, 1H), 1.39-1.36 (m, 4H), 1.06 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 135.7, 134.8, 134.2, 129.7, 127.7, 126.7, 69.2, 64.1, 32.6, 29.4, 27.7, 27.0, 25.6, 19.4, 13.9.

IR (thin film): 3320, 3076, 2930, 2857, 1590, 1472, 1426, 1388, 1361, 1262, 1189, 1109, 1007 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{25}H_{36}O_2Si$ $(M+NH_4)^+$: 414.2823, found 414.2808.

97a **98a**

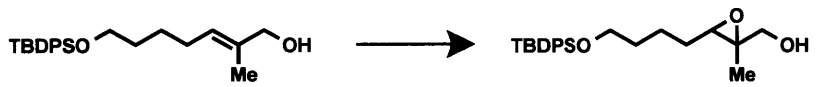
Epoxide 98a: To a solution of alcohol **97a** (1.94 g, 5.32 mmol) in CH_2Cl_2 (53 mL) at 0 °C was added *m*CPBA (≤ 77 wt %, 1.78 g, 8.00 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 2 h, and then quenched by addition of 10% $Na_2CO_{3(aq)}$ (60 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (30 mL each). The combined organic layer was washed with sat. $NaHSO_{3(aq)}$ (30 mL), and 10% $Na_2CO_{3(aq)}$ (30 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude alcohol **98a** as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 40% EtOAc in hexanes) to afford **98a** as a colorless oil (1.87 g, 4.91 mmol, 92%).

^1H NMR (500 MHz, $CDCl_3$): δ 7.68-7.66 (m, 4H), 7.44-7.37 (m, 6H), 3.75-3.70 (m, 2H), 3.67 (dd, *J* = 12.1, 4.4 Hz, 1H), 3.56 (dd, *J* = 12.2, 8.7 Hz, 1H), 3.04 (t, *J* = 6.0 Hz, 1H), 1.78-1.67 (m, 4H), 1.60 (dd, *J* = 8.7, 4.4 Hz, 1H), 1.27 (s, 3H), 1.06 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 135.73, 135.72, 134.0, 129.8, 127.8, 65.4, 63.5, 61.0, 60.0, 29.5, 27.0, 24.9, 19.4, 14.3.

IR (thin film): 3400, 2931, 2858, 1472, 1428, 1387, 1258, 1191, 1106, 1039 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{23}H_{32}O_3Si$ $(M+NH_4)^+$: 402.2459, found 402.2450.



97b **98b**

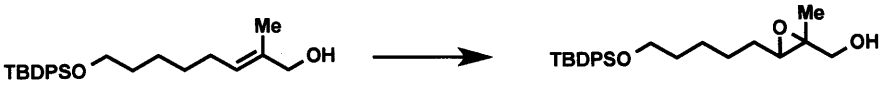
Epoxide 98b: To a solution of alcohol **97b** (1.02 g, 2.67 mmol) in CH_2Cl_2 (27 mL) at 0 °C was added *m*CPBA (≤ 77 wt %, 0.90 g, 4.0 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 2 h, and then quenched by addition of 10% $Na_2CO_{3(aq)}$ (30 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (20 mL each). The combined organic layer was washed with sat. $NaHSO_{3(aq)}$ (20 mL), and 10% $Na_2CO_{3(aq)}$ (20 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude alcohol **98b** as a colorless oil. The crude product was purified by flash chromatography (20% EtOAc in hexanes to 40% EtOAc in hexanes) to afford **98b** as a colorless oil (0.98 g, 2.46 mmol, 92%).

^1H NMR (500 MHz, $CDCl_3$): δ 7.70-7.67 (m, 4H), 7.45-7.38 (m, 6H), 3.71-3.68 (m, 3H), 3.58 (dd, *J* = 12.1, 8.1 Hz, 1H), 3.04 (t, *J* = 5.8 Hz, 1H), 1.87 (dd, *J* = 8.0, 4.3 Hz, 1H), 1.66-1.52 (m, 6H), 1.28 (s, 3H), 1.07 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.7, 134.1, 129.7, 127.8, 65.5, 63.7, 61.0, 60.3, 32.5, 28.1, 27.0, 23.0, 19.4, 14.4.

IR (thin film): 3424, 3069, 2931, 2859, 1589, 1472, 1428, 1388, 1260, 1188, 1105, 1039 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{24}H_{34}O_3Si$ $(M+NH_4)^+$: 416.2615, found 416.2593.



97c **98c**

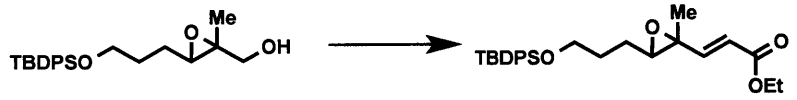
Epoxide 98c: To a solution of alcohol **97c** (1.20 g, 3.03 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added *m*CPBA (≤ 77 wt %, 1.02 g, 4.54 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 1 h, and then quenched by addition of 10% $Na_2CO_{3(aq)}$ (30 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (20 mL each). The combined organic layer was washed with sat. $NaHSO_{3(aq)}$ (20 mL), and 10% $Na_2CO_{3(aq)}$ (20 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude alcohol **98c** as a colorless oil. The crude product was purified by flash chromatography (20% EtOAc in hexanes to 30% EtOAc in hexanes) to afford **98c** as a colorless oil (1.08 g, 2.62 mmol, 87%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.45-7.38 (m, 6H), 3.70-3.66 (m, 3H), 3.58 (dd, J = 12.2, 8.6 Hz, 1H), 3.03 (t, J = 6.2 Hz, 1H), 1.75 (dd, J = 8.6, 4.4 Hz, 1H), 1.62-1.39 (m, 8H), 1.28 (s, 3H), 1.06 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 135.7, 134.2, 129.7, 127.8, 65.4, 63.9, 61.0, 60.2, 32.6, 28.3, 27.0, 26.4, 25.9, 19.4, 14.4.

IR (thin film): 3431, 3069, 2931, 2858, 1590, 1472, 1428, 1388, 1305, 1258, 1187, 1106, 1039 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{25}H_{36}O_3Si$ $(M+NH_4)^+$: 430.2772, found 430.2768.



98a **99a**

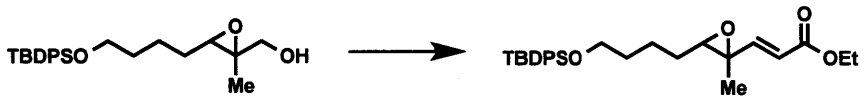
Epoxy Enoate 99a: To a solution of epoxy alcohol **98a** (1.82 g, 4.78 mmol) in CH_2Cl_2 (48 mL) was added DMSO (4.8 mL, 67.6 mmol) and Et_3N (3.4 mL, 24 mmol), cooled to 0 °C, and Pyr•SO_3 (1.53 g, 9.6 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (3.34 g, 9.6 mmol) was added as a solid at room temperature and stirred for 30 min. The reaction was quenched by addition of H_2O (50 mL) and diluted with CH_2Cl_2 (25 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (25 mL each). The combined organics were washed with H_2O (30 mL), sat. $NaCl_{(aq)}$ (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude enoate **99a** as a yellow oil. The crude product was purified by flash chromatography (7% EtOAc in hexanes to 10% EtOAc in hexanes) to afford **99a** as a colorless oil (2.06 g, 4.55 mmol, 95%, 95:5 *E*/*Z*).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (m, 4H), 7.45-7.38 (m, 6H), 6.73 (d, J = 15.7 Hz, 1H), 6.00 (d, J = 15.7 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.73-3.67 (m, 2H), 2.85 (t, J = 5.7 Hz, 1H), 1.76-1.65 (m, 4H), 1.42 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.05 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 166.3, 150.1, 135.7, 133.89, 133.87, 129.8, 127.8, 121.7, 65.8, 63.3, 60.7, 58.7, 29.3, 27.0, 25.3, 19.4, 15.2, 14.4.

IR (thin film): 2932, 2858, 1719, 1654, 1473, 1428, 1389, 1366, 1304, 1270, 1175, 1111, 1035 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{27}H_{36}O_4Si$ $(M+NH_4)^+$: 470.2721, found 470.2717.



98b **99b**

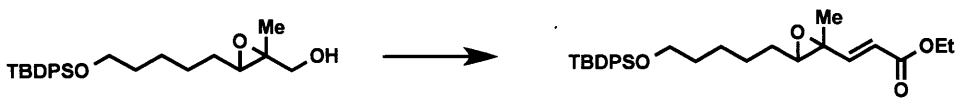
Epoxy Enoate 99b: To a solution of epoxy alcohol **98b** (0.94 g, 2.36 mmol) in CH_2Cl_2 (24 mL) was added DMSO (2.4 mL, 34 mmol) and Et_3N (1.6 mL, 12 mmol), cooled to 0 °C, and Pyr•SO_3 (0.94 g, 5.9 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (1.64 g, 4.7 mmol) was added as a solid at room temperature and stirred for 30 min. The reaction was quenched by addition of H_2O (30 mL) and diluted with CH_2Cl_2 (15 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (15 mL each). The combined organics were washed with H_2O (20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude enoate **99b** as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford **99b** as a colorless oil (1.04 g, 2.23 mmol, 94%, 95:5 *E*/*Z*). The product was purified further by MPLC (Biotage Ultra Column) with a gradient of solvents (2% EtOAc in hexanes to 10% EtOAc in hexanes) to afford **99b** as only the (*E*)-alkene (0.50 g, 45%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.45-7.38 (m, 6H), 6.77 (d, J = 15.8 Hz, 1H), 6.03 (d, J = 15.8 Hz, 1H), 4.22 (q, J = 7.1, 2H), 3.69 (t, J = 6.0 Hz, 2H), 2.84 (t, J = 5.7 Hz, 1H), 1.66-1.53 (m, 6H), 1.42 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.07 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 150.1, 135.7, 134.1, 129.7, 127.8, 121.6, 66.0, 63.6, 60.7, 58.5, 32.4, 28.4, 27.0, 22.9, 19.4, 15.3, 14.4.

IR (thin film): 2933, 2858, 1718, 1654, 1472, 1428, 1388, 1366, 1303, 1262, 1210, 1166, 1105, 1033 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{28}H_{38}O_4Si$ $(M+NH_4)^+$: 484.2878, found 484.2858.



98c **99c**

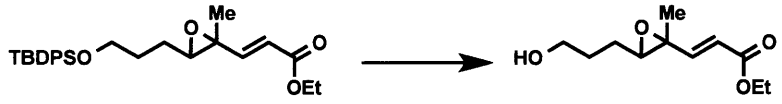
Epoxy Enoate 99c: To a solution of epoxy alcohol **98c** (1.08 g, 2.62 mmol) in CH_2Cl_2 (26 mL) was added DMSO (2.6 mL, 36.6 mmol) and Et_3N (1.8 mL, 13 mmol), cooled to 0 °C, and Pyr•SO_3 (1.24 g, 6.55 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (1.83 g, 5.24 mmol) was added as a solid at room temperature and stirred for 12 h. The reaction was quenched by addition of H_2O (30 mL) and diluted with CH_2Cl_2 (15 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (15 mL each). The combined organics were washed with H_2O (20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude enoate **99c** as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford **99c** as a colorless oil (1.19 g, 2.48 mmol, 94%, 95:5 *E*/*Z*).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.68-7.67 (m, 4H), 7.45-7.38 (m, 6H), 6.76 (d, *J* = 15.8 Hz, 1H), 6.02 (d, *J* = 15.8 Hz, 1H), 4.21 (q, *J* = 7.1, 2H), 3.67 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 6.2 Hz, 1H), 1.65-1.42 (m, 8H), 1.43 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 166.3, 150.2, 135.7, 134.1, 129.7, 127.8, 121.6, 66.0, 63.8, 60.7, 58.6, 32.5, 28.7, 27.0, 26.2, 25.8, 19.4, 15.3, 14.4.

IR (thin film): 3069, 2933, 2858, 1718, 1654, 1463, 1428, 1388, 1366, 1303, 1262, 1165, 1105, 1034 cm^{-1}.

HR-MS (DART) *m*/*z* calcd for $C_{29}H_{40}O_4Si$ $(M+NH_4)^+$: 498.3034, found 498.3027.



99a **100a**

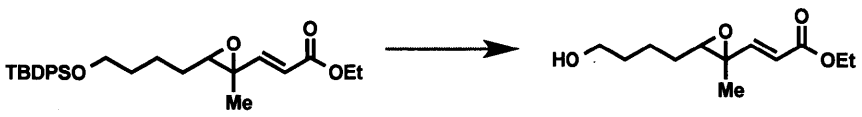
Epoxy Alcohol 100a: To a solution of enoate **99a** (0.42 g, 0.93 mmol) in THF (1.9 mL) at 0 °C was added TBAF (1.0 M in THF, 1.9 mL, 1.9 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 1.5 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et_3N in 50% EtOAc in hexanes, then 50% EtOAc in hexanes to 60% EtOAc in hexanes) to afford **100a** as a colorless oil (0.18 g, 0.84 mmol, 90%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.73 (d, *J* = 15.7 Hz, 1H), 6.00 (d, *J* = 15.7 Hz, 1H), 4.19-4.16 (m, 2H), 3.69 (br, 2H), 2.89-2.87 (m, 1H), 2.01 (br, 1H), 1.77-1.63 (m, 4H), 1.43 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 166.3, 149.8, 121.7, 65.8, 62.2, 60.7, 58.9, 29.4, 25.2, 15.3, 14.3.

IR (thin film): 3453, 2938, 2885, 1716, 1654, 1456, 1368, 1304, 1264, 1174, 1032 cm^{-1}.

HR-MS (DART) *m*/*z* calcd for $C_{11}H_{18}O_4$ $(M+H)^+$: 215.1278, found 215.1290.



99b **100b**

Epoxy Alcohol 100b: To a solution of enoate **99b** (0.53 g, 1.14 mmol) in THF (2.3 mL) at 0 °C was added TBAF (1.0 M in THF, 2.3 mL, 2.3 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 1.5 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et_3N in 50% EtOAc in hexanes, then 50% EtOAc in hexanes to 60% EtOAc in hexanes) to afford **100b** as a colorless oil (0.21 g, 0.92 mmol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (d, J = 15.8 Hz, 1H), 5.98 (d, J = 15.8 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.63 (t, J = 6.1 Hz, 2H), 2.83 (t, J = 5.9 Hz, 1H), 1.92 (br, 1H), 1.65-1.49 (m, 6H), 1.41 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 150.0, 121.6, 65.9, 62.6, 60.7, 58.6, 32.4, 28.4, 22.8, 15.3, 14.3.

IR (thin film): 3400, 2933, 2870, 1716, 1654, 1457, 1388, 1368, 1305, 1264, 1175, 1031 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+NH_4)^+$: 246.1700, found 246.1699.

99c **100c**

Epoxy Alcohol 100c: To a solution of enoate **99c** (0.48 g, 1.00 mmol) in THF (2.0 mL) at 0 °C was added TBAF (1.0 M in THF, 2.0 mL, 2.0 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 1.5 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et_3N in 50% EtOAc in hexanes, then 50% EtOAc in hexanes to 60% EtOAc in hexanes) to afford **100c** as a colorless oil (0.23 g, 0.95 mmol, 95%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.72 (d, J = 15.8 Hz, 1H), 5.98 (d, J = 15.8 Hz, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.61 (t, J = 6.5 Hz, 2H), 2.82 (t, J = 6.1 Hz, 1H), 1.94 (br, 1H), 1.60-1.42 (m, 8H), 1.40 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 150.1, 121.6, 66.0, 62.8, 60.7, 58.6, 32.7, 28.6, 26.3, 25.7, 15.3, 14.4.

IR (thin film): 3451, 2934, 2862, 1717, 1654, 1457, 1388, 1368, 1304, 1264, 1175, 1032 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+NH_4)^+$: 260.1856, found 260.1852.

100a **101a**

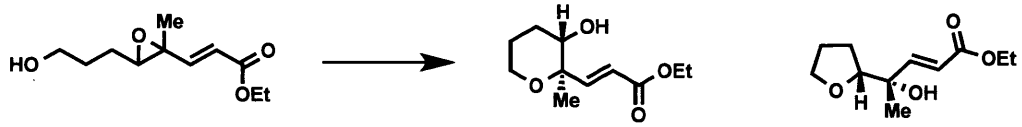
$[Rh(CO)_2Cl]_2$ promoted cyclization of epoxy alcohol 100a: To a 20 ml vial equipped with a magnetic stir bar was added epoxide **100a** (60 mg, 0.28 mmol), THF (2.3 mL), and a solution of $[Rh(CO)_2Cl]_2$ in THF (1.1 mg, 3 μmol, in 0.5 mL THF) and stirred at room temperature. After consumption of the starting material (3 h, as determined by TLC analysis), 11 mg of polymer-bound triphenylphosphine resin was added and stirred for 30 min. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. ^1H NMR spectroscopic analysis of the unpurified mixture indicated only *endo*-**101a** present and no *exo*-**102a** was observed. The resultant pale yellow film was purified by flash chromatography (15–35% EtOAc/hexanes) to afford **101a** as a colorless oil (56 mg, 0.26 mmol, 93%).

Characterization Data for 101a:
^1H NMR (600 MHz, $CDCl_3$): δ 7.05 (d, J = 16.0 Hz, 1H), 6.04 (d, J = 16.0 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.72 (ddd, J = 11.5, 6.7, 4.5 Hz, 1H), 3.67 (ddd, J = 11.6, 7.4, 3.8 Hz, 1H), 3.62-3.59 (m, 1H), 1.92 (d, J = 6.7 Hz, 1H), 1.86-1.71 (m, 3H), 1.56-1.50 (m, 1H), 1.31 (s, 3H) 1.30 (t, J = 7.1 Hz, 6H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 166.8, 151.4, 120.8, 77.07, 70.9, 61.8, 60.7, 27.7, 22.6, 19.8, 14.4.

IR (thin film): 3452, 2979, 2940, 2870, 1700, 1654, 1445, 1368, 1302, 1268, 1230, 1178, 1117, 1083, 1056 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{11}H_{18}O_4$ $(M+H)^+$: 215.1278, found 215.1278.



100a **101a** **102a**

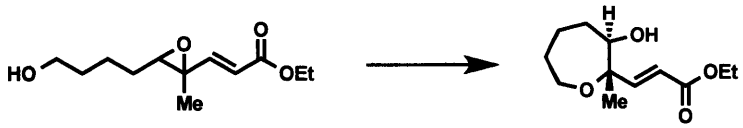
(±)-CSA Promoted cyclization of epoxy alcohol 100a: To a 20 ml vial equipped with a magnetic stir bar was added epoxide **100a** (54 mg, 0.25 mmol) in CH_2Cl_2 (12 mL) and (±)-CSA (6 mg, 0.025 mmol) and stirred at room temperature. After consumption of the starting material (2 h, as determined by TLC analysis), the clear solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. ^1H NMR spectroscopic analysis of the unpurified mixture indicated a 3.4:1 [*endo*(**101a**)/*exo*(**102a**)] ratio of products. The resultant clear film was purified by flash chromatography (10–30% EtOAc/hexanes) to afford **102a** as a colorless oil (10.5 mg, 0.049 mmol, 20%) and **101a** as a colorless oil (37 mg, 0.17 mmol, 69%).

^1H NMR (500 MHz, $CDCl_3$): δ 6.90 (d, J = 15.6 Hz, 1H), 6.12 (d, J = 15.6 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.88-3.79 (m, 3H), 2.39 (br, 1H), 1.91-1.79 (m, 3H), 1.72 (dq, J = 12.2, 8.2 Hz, 1H), 1.36 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 149.8, 120.5, 84.4, 74.2, 69.3, 60.6, 26.60, 26.51, 25.6, 14.4.

IR (thin film): 3481, 2979, 2933, 2874, 1716, 1657, 1456, 1368, 1304, 1256, 1178, 1072, 1034 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{11}H_{18}O_4$ $(M+NH_4)^+$: 232.1543, found 232.1533.



100b **101b**

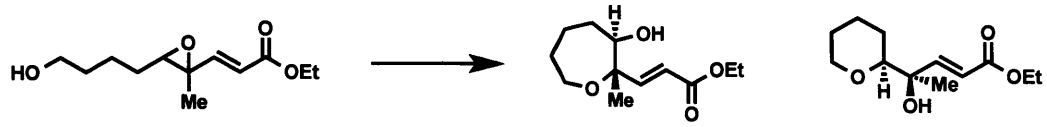
[Rh(CO)$_2$Cl]$_2$ promoted cyclization of epoxy alcohol 100b: To a 20 ml vial equipped with a magnetic stir bar was added epoxide **100b** (60 mg, 0.26 mmol), THF (2.0 mL), and a solution of [Rh(CO)$_2$Cl]$_2$ in THF (2.5 mg, 7 μmol, in 0.6 mL THF) and stirred at room temperature. After consumption of the starting material (5 h, as determined by TLC analysis), 25 mg of polymer-bound triphenylphosphine resin was added and stirred for 30 min. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified mixture indicated only *endo*-**101b** present and no *exo*-**102b** was observed. The resultant pale yellow film was purified by flash chromatography (10–35% EtOAc/hexanes) to afford **101b** as a colorless oil (53 mg, 0.23 mmol, 88%).

Characterization Data for 101b:
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (d, *J* = 15.8 Hz, 1H), 6.05 (d, *J* = 15.8 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.85 (dd, *J* = 9.7, 1.0 Hz, 1H), 3.77 (dtd, *J* = 12.5, 3.9, 0.9 Hz, 1H), 3.44 (ddd, *J* = 12.7, 7.0, 5.5 Hz, 1H), 2.02 (dddd, *J* = 13.6, 11.1, 9.7, 2.5 Hz, 1H), 1.95 (br, 1H), 1.83-1.80 (m, 1H), 1.69-1.59 (m, 3H), 1.45-1.37 (m, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.25 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 152.2, 119.4, 80.2, 76.0, 64.7, 60.7, 32.5, 30.8, 24.6, 21.2, 14.4.

IR (thin film): 3452, 2981, 2934, 1699, 1653, 1446, 1368, 1299, 1271, 1175, 1118, 1096, 1072, 1045 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+NH_4)^+$: 246.1700, found 246.1694.



100b **101b** **102b**

(±)-CSA Promoted cyclization of epoxy alcohol 100b: To a 20 ml vial equipped with a magnetic stir bar was added epoxide **100b** (54 mg, 0.24 mmol) in CH_2Cl_2 (12 mL) and (±)-CSA (55 mg, 0.24 mmol) and stirred at room temperature. After consumption of the starting material (4 h, as

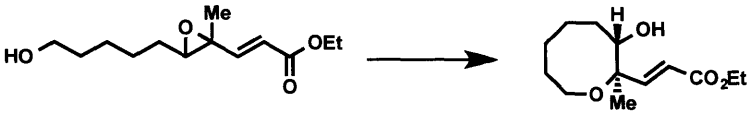
determined by TLC analysis), the clear solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. ^1H NMR spectroscopic analysis of the unpurified mixture indicated a 1:1.8 [*endo*(**101b**)/*exo*(**102b**)] ratio of products. The resultant clear film was purified by flash chromatography (15–35% EtOAc/hexanes) to afford **102b** as a colorless oil (23.1 mg, 0.10 mmol, 43%) and **101b** as a colorless oil (13.3 mg, 0.058 mmol, 25%).

Characterization Data for 102b:
^1H NMR (500 MHz, $CDCl_3$): δ 6.97 (d, J = 15.6 Hz, 1H), 6.10 (d, J = 15.6 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.03 (dt, J = 11.1, 2.1 Hz, 1H), 3.44 (td, J = 11.5, 2.7 Hz, 1H), 3.22 (dd, J = 11.3, 1.9 Hz, 1H), 2.87 (br, 1H), 1.89-1.86 (m, 1H), 1.59-1.33 (m, 5H), 1.29 (t, J = 7.1 Hz, 3H), 1.28 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 150.6, 120.4, 83.6, 74.5, 69.2, 60.5, 26.2, 25.9, 24.2, 23.4, 14.4

IR (thin film): 3487, 2936, 2854, 1715, 1655, 1443, 1367, 1302, 1283, 1265, 1174, 1089, 1034 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+NH_4)^+$: 246.1700, found 246.1694.



100c **101c**

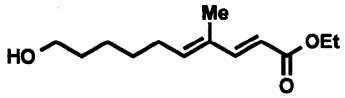
$[Rh(CO)_2Cl]_2$ promoted cyclization of epoxy alcohol 100c: To a 20 ml vial equipped with a magnetic stir bar was added epoxide **100c** (70 mg, 0.29 mmol), THF (4.8 mL), and a solution of $[Rh(CO)_2Cl]_2$ in THF (11.3 mg, 0.03 mmol, in 1.0 mL THF) and stirred at 4 °C. After 30 h, an additional portion of $[Rh(CO)_2Cl]_2$ in THF (11.3 mg, 0.03 mmol, in 1.0 mL THF) and stirred at 4 °C until consumption of the starting material (43 h, as determined by TLC analysis). 180 mg of polymer-bound triphenylphosphine resin was added and stirred for 2 h. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. The resultant yellow film was purified by flash chromatography (20–100% EtOAc/hexanes) to afford **101c** as a colorless oil (13.1 mg, 0.054 mmol, 19%), **103** as colorless film (13.4 mg, 0.06 mmol, 21%), and **105** as a colorless film (4.5 mg, 0.019 mmol, 6%).

Characterization Data for 101c:
^1H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 16.0 Hz, 1H), 6.07 (d, J = 16.0 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.13-4.10 (m, 1H), 3.82 (dt, J = 12.3, 3.7 Hz, 1H), 3.53 (td, J = 12.0, 2.7 Hz, 1H), 1.89-1.65 (m, 6H), 1.50 (ddq, J = 14.5, 5.7, 2.9 Hz, 1H), 1.46-1.40 (m, 1H), 1.38 (d, J = 5.9 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.28 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0, 151.5, 120.8, 80.0, 70.1, 64.8, 60.7, 34.4, 30.7, 25.3, 24.4, 20.3, 14.5.

IR (thin film): 3447, 2983, 2929, 2863, 1717, 1700, 1650, 1452, 1368, 1301, 1276, 1183, 1117, 1090, 1063, 1037 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+NH_4)^+$: 260.1856, found 260.1840.

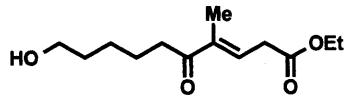


Characterization Data for 103:
IR (thin film): 3418, 2977, 2931, 2859, 1708, 1620, 1447, 1394, 1367, 1303, 1266, 1166, 1035 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ 7.32 (d, J = 15.7 Hz, 1H), 5.90 (t, J = 7.4 Hz, 1H), 5.79 (d, J = 15.7 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.66 (t, J = 6.4 Hz, 2H), 2.22 (q, J = 7.3 Hz, 2H), 1.77 (s, 3H), 1.61-1.56 (m, 2H), 1.49-1.44 (m, 2H), 1.42-1.36 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.26 (br, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 149.8, 142.1, 133.1, 115.7, 63.0, 60.3, 32.8, 29.03, 28.91, 25.6, 14.5, 12.3.

HR-MS (DART) *m/z* calcd for $C_{13}H_{22}O_3$ $(M+NH_4)^+$: 244.1907, found 244.1906.

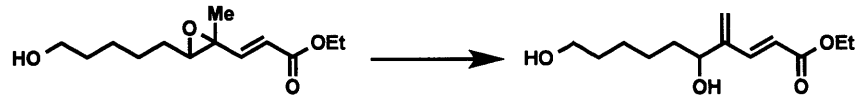


Characterization Data for 104:
^1H NMR (600 MHz, $CDCl_3$): δ 6.82 (tq, J = 6.8, 1.4 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.67 (t, J = 6.4 Hz, 2H), 3.29 (dd, J = 6.8, 0.9 Hz, 2H), 2.73 (t, J = 7.4 Hz, 2H), 1.80 (d, J = 1.0 Hz, 3H), 1.66 (quint, J = 7.6 Hz, 2H), 1.62-1.59 (m, 2H), 1.42-1.37 (m, 2H), 1.32-1.29 (br, 1H), 1.30 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 201.7, 170.8, 139.6, 133.0, 62.9, 61.4, 37.3, 34.6, 32.7, 25.6, 24.5, 14.4, 12.0.

IR (thin film): 3441, 2927, 2863, 1734, 1668, 1391, 1369, 1305, 1261, 1180, 1050, 1026 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{13}H_{22}O_4$ $(M+NH_4)^+$: 260.1856, found 260.1865.



100c **105**

(±)-CSA Promoted cyclization of epoxy alcohol 100c: To a 20 ml vial equipped with a magnetic stir bar was added epoxide **100c** (65 mg, 0.27 mmol) in CH_2Cl_2 (13 mL) and (±)-CSA (124 mg, 0.54 mmol) and stirred at room temperature. After consumption of the starting material (4 h, as determined by TLC analysis), the clear solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. The resultant clear film was purified by flash chromatography (40–100% EtOAc/hexanes) to afford **105** as a colorless oil (40 mg, 0.17 mmol, 62%).

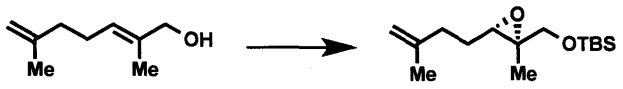
Characterization Data for 105:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (dd, J = 16.2, 0.6 Hz, 1H), 6.03 (d, J = 16.2 Hz, 1H), 5.59 (s, 1H), 5.49 (s, 1H), 4.43 (dd, J = 7.8, 4.4 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.64 (t, J = 6.5 Hz, 2H), 1.98 (br, 1H), 1.71-1.65 (m, 1H), 1.60-1.55 (m, 4H), 1.49-1.47 (m, 1H), 1.44-1.37 (m, 3H), 1.31 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 147.6, 143.9, 121.5, 119.0, 71.6, 63.0, 60.7, 36.4, 32.8, 25.72, 25.60, 14.4.

IR (thin film): 3372, 2935, 2860, 1700, 1632, 1464, 1393, 1368, 1310, 1278, 1181, 1038 cm^{-1}.

HR-MS (DART) m/z calcd for $C_{13}H_{22}O_4$ $(M+H)^+$: 243.1591, found 243.1591.



47 **48**

Epoxide 48: To a cooled (–40 °C) solution of 3Å molecular sieves (180 mg) in CH_2Cl_2 (42 mL) was added (+)-diethyl tartrate (0.10 mL, 0.55 mmol), Ti(iOPr)$_4$ (0.13 mL, 0.42 mmol), then a solution of **47**[61] (0.60 g, 4.24 mmol) in CH_2Cl_2 (5 mL). The solution was stirred for 20 min and then a solution of tBuOOH in decane (1.16 mL, 5.5 M, 6.36 mmol) was added dropwise over 5 min. The reaction mixture was stirred at –20 °C for 18 h and then diluted with EtOAc (75 mL) and allowed to warm to room temperature. The organic layer was washed with sat. $Na_2SO_{4(aq)}$ and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant yellow oil was purified by flash chromatography (20–50% EtOAc/hexanes) to an epoxy alcohol, which was used directly in the next step.

To a solution of the epoxy alcohol in CH_2Cl_2 (22 mL) cooled to 0 °C was added Et_3N (0.93 mL, 6.7 mmol) and TBSCl (0.40 g, 2.68 mmol), and then warmed to room temperature. After 24 h, the reaction was quenched by the addition of sat. $NH_4Cl_{(aq)}$ (25 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resultant yellow oil was purified by flash chromatography (5–20% EtOAc/hexanes) to yield **48** as a colorless oil (0.53g, 1.96 mmol, 46% over two steps). The ee of **48** was determined to be 93%. Determination of the ee of **48** was accomplished by formation of the benozoate ester of the intermediate epoxy alcohol, and comparison to the racemic epoxy benzoate on chiral analytical HPLC analysis (Chiracel OJ–H; 0.5% iPrOH in hexanes, 1.00 mL/min; t_R(major) = 13.0 min, t_R(minor) = 14.2 min.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.75 (s, 1H), 4.72 (s, 1H), 3.58 (s, 2H), 2.88 (t, J = 6.3 Hz, 1H), 2.20 (dt, J = 14.9, 7.5 Hz, 1H), 2.13 (dt, J = 14.9, 7.6 Hz, 1H), 1.75 (s, 3H), 1.70 (m, 2H), 1.29 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

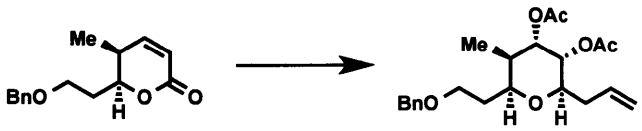
^{13}C NMR (150 MHz, $CDCl_3$): δ 145.0, 110.6, 68.0, 61.2, 60.8, 34.7, 26.7, 26.0, 22.7, 18.5, 14.3, –5.2.

IR (thin film): 3076, 2957, 2930, 2858, 1651, 1473, 1463, 1376, 1253, 1135, 1098, 1007 cm^{-1}.

HR-MS (ESI) m/z calcd for $C_{15}H_{30}O_2Si$ $(M+Na)^+$: 293.1907, found 293.1907.

$[\alpha]^{24}_D = -2.5$ (c = 0.51, $CHCl_3$).

[61] For the synthesis of **47**, please see: Yang, D.; Xu, M. *Org. Lett.* **2001**, *3*, 1785.



44 **46**

Alkene 46: To a solution of **44**[62] (3.42 g, 13.9 mmol) and NMO (50 wt% in H_2O, 4.3 mL, 20.8 mmol) in acetone/H_2O (4:1, 139 mL) cooled to 0 °C was added OsO_4 (2.5 wt% in *t*-BuOH, 8.7 mL, 0.70 mmol). After 10 min at 0 °C, the reaction was allowed to warm to room temperature. After 5 h, the reaction was diluted with EtOAc (250 mL), mixed with H_2O (50 mL), and the two layers separated. The aqueous layer was extracted with EtOAc (3 x 100 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant brown oil was purified via by flash chromatography (70% EtOAc in hexanes to 100% EtOAc) to yield a colorless oil that was used directly in the next reaction.

The previously obtained oil was diluted in THF (700 mL), cooled –78 °C, and allylmagnesium bromide in Et_2O (97 mL, 1.0 M, 97 mmol) was added dropwise over 1 h. After an additional 2.5 h at –78 °C, the reaction was warmed to 0 °C and quenched by dropwise addition of sat. $NH_4Cl_{(aq)}$ (50 mL). The reaction mixture was extracted with EtOAc (3 x 100 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provided a yellow-brown oil that was carried forward into the next reaction.

To the previously obtained oil diluted in CH_3CN (139 mL) was added Et_3SiH (4.0 mL, 25.0 mmol), cooled to 0 °C, and then TMSOTf (0.50 mL, 2.8 mmol) was added dropwise over 1 min. After an addition 10 min the reaction was quenched by the addition of sat. $NaHCO_{3(aq)}$ (50 mL) and extracted EtOAc (3 x 50 mL). The combined organic layers were washed with sat. $NaCl_{(aq)}$, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant brown oil was purified by flash chromatography (40–60% EtOAc in hexanes) to yield a colorless oil that was used directly in the next reaction.

To the previously obtained oil diluted in CH_2Cl_2 (60 mL) was added DMAP (12 mg, 0.1 mmol), pyridine (4.4 mL, 55 mmol), and Ac_2O (3.4 mL, 36.4 mmol). The reaction was heated to 30 °C for 18 h, then concentrated *in vacuo*. The resultant yellow oil was purified by flash chromatography (15–30% EtOAc in hexanes) to yield **46** as a colorless oil (2.02 g, 6.1 mmol, 37% over 4 steps)

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36-7.29 (m, 5H), 5.83 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.20 (t, *J* = 3.0 Hz, 1H), 5.07-5.03 (m, 2H), 4.80 (dd, *J* = 10.2, 3.1 Hz, 1H), 4.55-4.49 (m, 2H), 4.01 (dt, *J* = 9.5, 2.9 Hz, 1H), 3.74 (ddd, *J* = 10.5, 7.9, 2.9 Hz, 1H), 3.62-3.54 (m, 2H), 2.31-2.27 (m, 1H), 2.17-2.13 (m, 1H), 2.12 (s, 3H), 2.00 (s, 3H), 1.89-1.83 (m, 1H), 1.80 (ddd, *J* = 14.4, 9.6, 4.9 Hz, 1H), 1.64-1.58 (m, 1H), 1.06 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 170.4, 170.1, 138.6, 134.3, 128.6, 127.83, 127.77, 117.0, 73.9, 73.2, 72.6, 71.3, 68.8, 67.1, 38.1, 36.4, 32.4, 21.3, 21.1, 10.6.

IR (thin film): 2965, 2919, 2860, 1743, 1454, 1370, 1242, 1219, 1102, 1054 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{22}H_{30}O_6$ $(M+H)^+$: 391.2115, found 391.2114.

$[\alpha]^{24}_D = +0.86$ (*c* = 0.40, $CHCl_3$).

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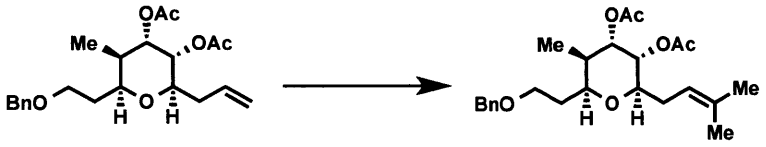
[62] Ohtani, N.; Tsutsumi, R.; Kuranaga, T.; Shirai, T.; Wright, J. L.; Baden, D. G.; Satake, M.; Tachibana, K. *Heterocycles* **2010**, *80*, 825.



46 **107**

Trisubstituted Alkene 107: To a solution of **46** (417 mg, 1.07 mmol) in 2-methyl-2-butene (3.4 mL, 31.6 mmol) was added benzoquinone (17 mg, 0.16 mmol) and Hoveyda-Grubbs 2nd Generation Catalyst (**49**, 15 mg, 0.024 mmol) and stirred at room temperature. After consumption of **46** (1 h, determined by ^{1}H NMR of aliquot of reaction mixture), the reaction mixture was concentrated *in vacuo*. The resultant green oil was purified by flash chromatography (10–25% EtOAc/hexanes) to afford **107** as a pale green oil (387 mg, 0.93 mmol, 87%).

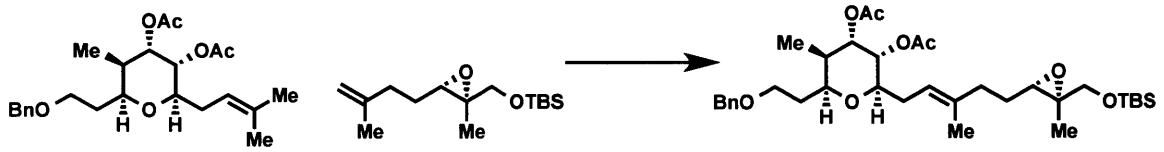
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.28 (m, 5H), 5.21-5.17 (m, 2H), 4.80 (dd, J = 10.2, 3.1 Hz, 1H), 4.55-4.50 (m, 2H), 4.00 (ddd, J = 9.5, 3.6, 2.5 Hz, 1H), 3.68 (ddd, J = 10.5, 7.4, 3.3 Hz, 1H), 3.62-3.54 (m, 2H), 2.25-2.20 (m, 1H), 2.13-2.08 (m, 1H), 2.11 (s, 3H), 2.00 (s, 3H), 1.87-1.77 (m, 2H), 1.69 (s, 3H), 1.63-1.60 (m, 1H), 1.57 (s, 3H), 1.06 (d, J = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 170.1, 138.7, 133.8, 128.6, 127.80, 127.77, 119.6, 74.5, 73.3, 72.8, 71.3, 69.0, 67.2, 38.2, 32.5, 30.8, 26.0, 21.3, 21.1, 18.1, 10.6.

IR (thin film): 2965, 2919, 2860, 1743, 1454, 1370, 1242, 1219, 1102, 1054 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{24}H_{34}O_6$ $(M+Na)^+$: 441.2248, found 441.2260.

$[\alpha]^{24}_D = -2.1$ (c = 1.51, CH_2Cl_2).



107 **48** **50**

Trisubstituted Alkene 50: To a 10 mL Schlenk tube containing **107** (350 mg, 0.86 mmol), **48** (465 mg, 1.72 mmol), and benzoquinone (10 mg, 0.09 mmol) was added Hoveyda-Grubbs 2nd Generation Catalyst (**49**, 27 mg, 0.043 mmol) and flushed Ar. This mixture was heated with stirring on an oil bath at 80 °C. After 18 h, the reaction mixture was transferred out of the Schlenk tube with CH_2Cl_2 (3x5 mL) and the reaction mixture was concentrated *in vacuo*. The resultant green oil was purified by flash chromatography (5–20% EtOAc/hexanes) to afford **50** as a pale green oil (423 mg, 0.67 mmol, 78%, 2:1 *E*/*Z*). Enrichment to >9:1 *E*/*Z* of **50** could be achieved through three rounds of flash chromatography (10–20% EtOAc/hexanes), utilizing ^{1}H NMR to assay individual fractions for enrichment.

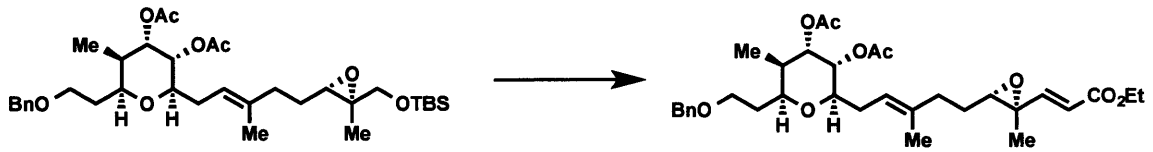
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.29 (m, 5H), 5.27-5.24 (m, 1H), 5.20 (t, J = 3.1 Hz, 1H), 4.79 (dd, J = 10.2, 3.1 Hz, 1H), 4.54-4.48 (m, 2H), 4.00 (ddd, J = 9.4, 3.6, 2.5 Hz, 1H), 3.70 (ddd, J = 10.4, 7.5, 3.1 Hz, 1H), 3.60-3.55 (m, 4H), 2.85 (t, J = 6.3 Hz, 1H), 2.24-2.21 (m, 1H), 2.18-2.05 (m, 3H), 2.11 (s, 3H), 2.00 (s, 3H), 1.87-1.78 (m, 2H), 1.67-1.62 (m, 3H), 1.58 (s, 3H), 1.27 (s, 3H), 1.05 (d, J = 7.3 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 170.1, 138.7, 136.6, 128.6, 127.8, 120.0, 74.4, 73.2, 72.7, 71.4, 68.9, 68.0, 67.3, 61.2, 60.8, 38.1, 36.5, 32.5, 30.6, 27.3, 26.1, 21.3, 21.1, 18.5, 16.5, 14.3, 10.6, –5.2.

IR (thin film): 2958, 2930, 2850, 1748, 1455, 1371, 1245, 1223, 1101, 1057 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{35}H_{56}O_8Si$ $(M+Na)^+$: 655.3637, found 655.3644.

$[\alpha]^{24}_D = -8.0$ (c = 0.92, CH_2Cl_2).



Enoate 109: To a solution of **50** (57 mg, 0.09 mmol) in THF (0.9 mL) at 0 °C was added TBAF (1.0 M in THF, 0.11 mL, 0.11 mmol). The reaction was stirred for 30 min, and quenched with H_2O (2 mL). The reaction was extracted with Et_2O (3x5 mL), and the combined organic layers were washed with sat. $NaCl_{(aq)}$ (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide a crude alcohol. The crude alcohol was purified by flash chromatography (30% EtOAc in hexanes to 70% EtOAc in hexanes) to provide an alcohol intermediate as a colorless oil (39 mg).

To a solution of the alcohol intermediate in CH_2Cl_2 (0.7 mL) was added DMSO (0.15 mL, 2 mmol) and Et_3N (0.10 mL, 0.73 mmol), cooled to 0 °C, and Pyr•SO_3 (35 mg, 0.22 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 4 h. At this point, (carbethoxymethylene)triphenylphosphorane (77 mg, 0.22 mmol) was added as a solid at room temperature and stirred for 1 h. The reaction was quenched by addition of H_2O (5 mL) and diluted with CH_2Cl_2 (5 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (5 mL each). The combined organics were washed with H_2O (3 mL), sat. $NaCl_{(aq)}$ (3 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude enoate **109** as a yellow oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 40% EtOAc in hexanes) to afford **109** as a colorless oil (39 mg, 0.066 mmol, 91%, 95:5 *E*/*Z*).

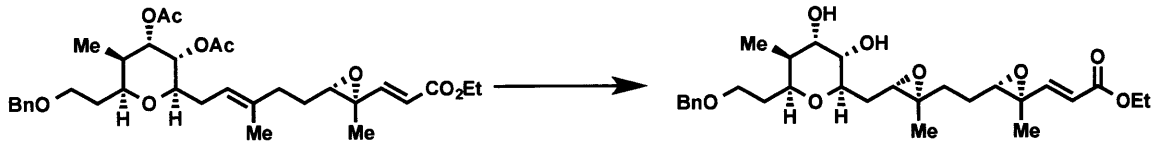
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37-7.29 (m, 5H), 6.74 (d, J = 15.8 Hz, 1H), 6.01 (d, J = 15.7 Hz, 1H), 5.25 (t, J = 6.4 Hz, 1H), 5.19 (t, J = 3.0 Hz, 1H), 4.79 (dd, J = 10.2, 3.1 Hz, 1H), 4.54-4.49 (m, 2H), 4.22-4.18 (m, 2H), 4.01-3.99 (m, 1H), 3.70 (ddd, J = 10.4, 7.5, 3.1 Hz, 1H), 3.60-3.53 (m, 2H), 2.84 (t, J = 6.2 Hz, 1H), 2.25-2.21 (m, 1H), 2.18-2.08 (m, 3H), 2.11 (s, 3H), 2.00 (s, 3H), 1.87-1.77 (m, 2H), 1.72-1.68 (m, 2H), 1.63-1.59 (m, 1H), 1.58 (s, 3H), 1.42 (s, 3H), 1.30-1.27 (m, 3H), 1.04 (d, J = 7.3 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 170.4, 170.1, 166.3, 150.1, 138.6, 136.2, 128.6, 127.78, 127.74, 121.7, 120.4, 74.3, 73.2, 72.6, 71.3, 68.8, 67.2, 65.6, 60.7, 58.7, 38.1, 36.3, 32.4, 30.5, 27.4, 21.3, 21.1, 16.4, 15.3, 14.4, 10.6.

IR (thin film): 2963, 2928, 2862, 1744, 1718, 1654, 1454, 1368, 1304, 1242, 1221, 1175, 1101, 1054, 1031 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{33}H_{46}O_9$ $(M+Na)^+$: 609.3034, found 609.3029.

$[\alpha]^{24}_D = -3.2$ (c = 1.95, CH_2Cl_2).



109 **95**

Diol 95: To a solution of **109** (36 mg, 0.06 mmol) and chiral ketone (+)-**51**[63] (16 mg, 0.061 mmol) in DMM/MeCN (2:1, 2.8 mL) was added a solution of 0.05 M $Na_2B_4O_7 \cdot 10H_2O$ in 4 x 10^{-4} Na_2EDTA (1.85 mL) and nBu_4HSO_4 (4 mg, 0.01 mmol), and the mixture was cooled to –10 °C. To this vigorously stirred reaction mixture was added, simultaneously over 1 h via syringe pump, a 0.212 M solution of Oxone® in 4 x 10^{-4} Na_2EDTA (0.86 mL) and a 0.89 M solution of K_2CO_3 in H_2O (0.86 mL). Upon completion of syringe pump addition, the reaction mixture was diluted with Et_2O/H_2O (1:1, 10 mL) and warmed to room temperature. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were washed with sat. $NaCl_{(aq)}$ (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude diepoxide was purified by flash chromatography (20% EtOAc in hexanes to 40% EtOAc in hexanes) to provide a diepoxide intermediate as a colorless oil (31 mg).

To the previous diepoxide in EtOH (0.9 mL) at 0 °C was added a premixed solution of EtOH (0.25 mL) containing guanidinium•HCl (0.7 mg, 7 μmol) and NaOEt (0.4 mg, 6 μmol). After 2 h, the reaction was allowed to warm to room temperature. After 6 h, the reaction was concentrated *in vacuo*, and directly purified by flash chromatography (50% EtOAc in hexanes to 100% EtOAc) to provide **95** as a colorless film (19.1 mg, 0.037 mmol, 72%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5H), 6.74 (d, J = 15.7 Hz, 1H), 6.01 (d, J = 15.7 Hz, 1H), 4.53-4.48 (m, 2H), 4.20 (q, J = 7.1 Hz, 2H), 4.03 (ddd, J = 9.3, 3.7, 2.4 Hz, 1H), 3.89 (br, 1H), 3.69-3.65 (m, 2H), 3.57 (dd, J = 7.3, 5.8 Hz, 2H), 3.01 (dd, J = 7.3, 4.5 Hz, 1H), 2.84 (t, J = 5.8 Hz, 1H), 2.57 (d, J = 6.0 Hz, 1H), 2.45 (br, 1H), 2.01-1.96 (m, 1H), 1.93-1.87 (m, 1H), 1.84-1.77 (m, 2H), 1.75-1.68 (m, 3H), 1.68-1.60 (m, 2H), 1.43 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.28 (s, 3H), 0.96 (d, J = 7.3 Hz, 3H).

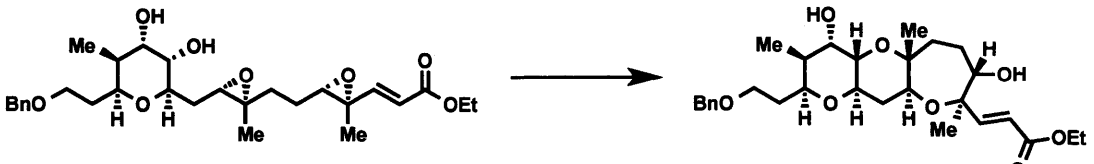
^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 149.8, 138.7, 128.5, 127.75, 127.70, 121.8, 74.5, 73.6, 73.1, 71.0, 68.1, 67.6, 65.5, 60.8, 60.4, 59.8, 58.8, 39.7, 35.2, 32.5, 31.6, 24.4, 16.9, 15.3, 14.4, 10.8.

IR (thin film): 3434, 2965, 2927, 2866, 2362, 1717, 1659, 1456, 1387, 1368, 1307, 1266, 1210, 1177, 1104, 1071, 1038 cm^{-1}.

HR-MS (DART) m/z calcd for $C_{29}H_{42}O_8$ $(M+H)^+$: 519.2925, found 519.2937.

$[\alpha]^{24}_D = -16.0$ (c = 0.40, CH_2Cl_2).

[63] Jamison, T. F.; Ikeuchi, Y. Epoxidation Catalysts. U.S. Patent 8,680,303 B2, Mar. 25, 2014



95 106

$[Rh(CO)_2Cl]_2$ promoted cyclization of 95: To a 2 dram vial equipped with a magnetic stir bar was added **95** (7.8 mg, 0.015 mmol), THF (0.5 mL), and a solution of $[Rh(CO)_2Cl]_2$ in THF (0.6 mg, 1.5 μmol, in 0.25 mL THF) and stirred at room temperature. After consumption of the starting material (3 h, as determined by TLC analysis), 10 mg of polymer-bound triphenylphosphine resin was added and stirred for 30 min. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. The resultant pale yellow film was purified by flash chromatography (40–70% EtOAc/hexanes) to afford **106** as a colorless oil (6.1 mg, 0.011 mmol, 78%).

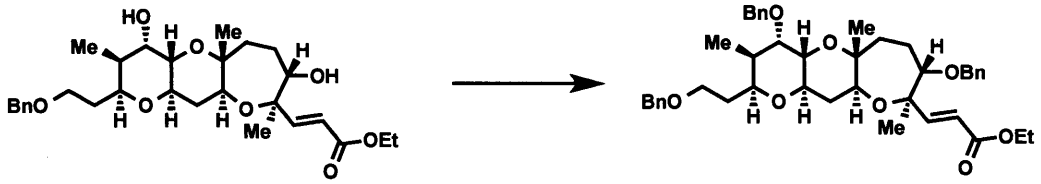
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.28 (m, 5H), 6.72 (d, J = 15.4 Hz, 1H), 6.08 (d, J = 15.4 Hz, 1H), 4.55-4.47 (m, 2H), 4.25-4.16 (m, 2H), 4.02 (td, J = 6.1, 3.3 Hz, 1H), 3.98 (d, J = 6.8 Hz, 1H), 3.89 (dd, J = 11.9, 4.8 Hz, 1H), 3.80 (t, J = 2.6 Hz, 1H), 3.57 (dd, J = 7.4, 5.8 Hz, 2H), 3.48 (ddd, J = 11.9, 9.9, 4.2 Hz, 1H), 3.36 (dd, J = 9.8, 2.8 Hz, 1H), 1.99-1.88 (m, 4H), 1.86-1.74 (m, 3H), 1.68-1.61 (m, 2H), 1.57 (q, J = 11.9 Hz, 1H), 1.50 (ddd, J = 13.3, 5.0, 2.3 Hz, 1H), 1.36 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.26 (s, 3H), 0.98 (d, J = 7.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0, 151.9, 138.8, 128.5, 127.82, 127.64, 120.3, 80.5, 78.5, 74.0, 73.0, 72.10, 71.99, 71.6, 71.0, 69.3, 67.6, 60.7, 39.0, 34.22, 34.03, 32.6, 24.9, 20.7, 16.4, 14.4, 11.2.

IR (thin film): 3427, 2929, 2871, 1715, 1655, 1455, 1367, 1292, 1224, 1179, 1088, 1075, 1029 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{29}H_{42}O_8$ $(M+H)^+$: 519.2925, found 519.2953.

$[\alpha]^{24}_D = -50.5$ (c = 0.30, CH_2Cl_2).



106 110

Enoate 110: To a solution of **106** (5.0 mg, 9.6 μmol) in THF (0.96 mL) was added NaH (95%, 9 mg, 0.38 mmol), TBAI (7 mg, 0.02 mmol), and BnBr (45 μL, 0.38 mmol). The reaction was heated in an oil bath at 40 °C for 3 h, then at 60 °C for an additional 2 h. After cooling to room temperature, the reaction was quenched by the careful addition of sat. $NH_4Cl_{(aq)}$ (2 mL) and extracted with EtOAc (3 x 3mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resultant colorless film was purified by flash chromatography (5–40% EtOAc/hexanes) to afford **110** as a colorless oil (5.0 mg, 7 μmol, 75%).

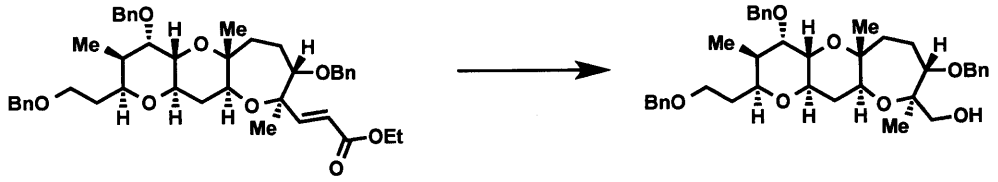
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.29 (m, 10H), 7.27-7.23 (m, 5H), 6.68 (d, *J* = 15.4 Hz, 1H), 6.08 (d, *J* = 15.4 Hz, 1H), 4.86 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 11.9 Hz, 1H), 4.25-4.15 (m, 2H), 4.02 (dt, *J* = 9.1, 3.1 Hz, 1H), 3.96 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.64 (ddd, *J* = 11.8, 10.0, 4.5 Hz, 1H), 3.60-3.52 (m, 4H), 3.45 (dd, *J* = 9.9, 2.5 Hz, 1H), 1.96-1.77 (m, 5H), 1.60-1.55 (m, 4H), 1.34 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.25 (s, 3H), 0.96 (d, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 152.4, 139.9, 138.8, 138.2, 128.63, 128.48, 128.32, 127.88, 127.74, 127.62, 127.53, 127.3, 120.1, 81.1, 80.7, 79.6, 76.9, 73.10, 73.07, 71.92, 71.79, 71.69, 71.4, 70.4, 67.7, 60.7, 39.3, 34.9, 34.1, 32.7, 21.32, 21.22, 16.0, 14.5, 11.8.

IR (thin film): 3065, 3032, 2926, 2863, 1717, 1660, 1497, 1454, 1365, 1291, 1241, 1179, 1096, 1064, 1028 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{43}H_{54}O_8$ $(M+Na)^+$: 721.3711, found 721.3725.

$[\alpha]^{24}_D = -17.5$ (*c* = 0.18, CH_2Cl_2).



110 **40**

Alcohol 40: To a solution of **110** (4.0 mg, 5.7 μmol) in *t*-BuOH/H_2O (2:1, 0.42 mL) was added citric acid monohydrate (2.4 mg, 0.012 mmol), NMO (as solid, 2.0 mg, 0.017 mmol), and $K_2OsO_2(OH)_4 \cdot 2H_2O$ (0.4 mg, 12 μmol), and the green reaction mixture was stirred at room temperature. After 16 h, the colorless reaction was quenched by addition of 1M $HCl_{(aq)}$ (0.2 mL), then extracted EtOAc (3 x 2 mL). The combined organic layers were washed sat. $Na_2CO_{3(aq)}$ (1 x 2.5 mL), sat. $NaCl_{(aq)}$ (1 x 2.5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude diol as a pale green oil, which was used without further purification.

To a solution of the crude diol in CH_2Cl_2 (0.3 mL) was added Ph_3BiCO_3 (17 mg, 0.034 mmol) and heated to 60 °C in an oil bath. After 2 h, the reaction was removed from the oil bath, filtered through Celite (washed CH_2Cl_2 3 x 1 mL), and concentrated *in vacuo*. The crude beige gel was purified by flash chromatography (10%–30% EtOAc/hexanes) to afford an aldehyde that was used immediately in the next step.

To a solution of aldehyde in MeOH (0.3 mL) at 0 °C was added $NaBH_4$ (1.6 mg, 0.04 mmol). The reaction was quenched after 5 min by the addition of 1M $HCl_{(aq)}$ (0.1 mL), EtOAc (1 mL), and H_2O (0.2 mL). The reaction mixture was extracted with EtOAc (3 x 2 mL), and the combined organic layers were washed with sat. $NaCl_{(aq)}$ (2 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The colorless film was purified by flash chromatography (20%–50% EtOAc/hexanes) to yield **40** as a colorless film (2.1 mg, 3.3 μmol, 60% over 3 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.28 (m, 10H), 7.27-7.22 (m, 5H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.64-4.56 (m, 2H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.30 (d, *J* = 11.8 Hz, 1H), 4.04-4.00 (m, 1H), 3.80 (dd, *J* = 12.1, 4.7 Hz, 1H), 3.66-3.61 (m, 1H), 3.59 (t, *J* = 2.6 Hz, 1H), 3.56-3.52 (m, 2H), 3.45-3.42 (m, 2H), 3.38 (d, *J* = 10.7 Hz, 1H), 3.24 (d, *J* = 10.7 Hz, 1H), 2.02-

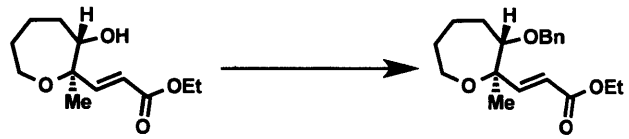
1.93 (m, 3H), 1.89 (dt, J = 11.7, 4.7 Hz, 1H), 1.80-1.77 (m, 1H), 1.72-1.67 (m, 1H), 1.60-1.58 (m, 1H), 1.57-1.53 (m, 1H), 1.52-1.49 (m, 1H), 1.29 (s, 3H), 1.21 (s, 3H), 0.95 (d, J = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 139.8, 138.74, 138.57, 128.56, 128.49, 128.32, 127.88, 127.70, 127.64, 127.58, 127.54, 127.3, 81.1, 80.4, 79.6, 77.4, 73.11, 73.08, 72.08, 71.95, 71.51, 71.34, 70.4, 69.3, 67.6, 39.3, 35.1, 34.0, 32.7, 22.8, 17.5, 15.7, 11.8.

IR (thin film): 3427, 3030, 2925, 2858, 1718, 1670, 1605, 1496, 1453, 1361, 1260, 1215, 1156, 1089, 1062, 1027 cm^{-1}.

HR-MS (DART) m/z calcd for $C_{39}H_{50}O_7$ $(M+H)^+$: 631.3629, found 631.3629.

$[\alpha]^{24}_D = -17.5$ (c = 0.105, $CHCl_3$).[64]



101b **111**

Enoate 111: To a solution of **101b** (190 mg, 0.83 mmol) in THF (8.3 mL) was added NaH (95%, 40 mg, 1.66 mmol), TBAI (30 mg, 0.08 mmol), and BnBr (217 μL, 1.83 mmol). The reaction was stirred at room temperature for 17 h then quenched by the careful addition of sat. $NH_4Cl_{(aq)}$ (5 mL) and extracted with EtOAc (3 x 10mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resultant colorless film was purified by flash chromatography (5–20% EtOAc/hexanes) to afford **110** as a colorless oil (160 mg, 0.5 mmol, 60%).

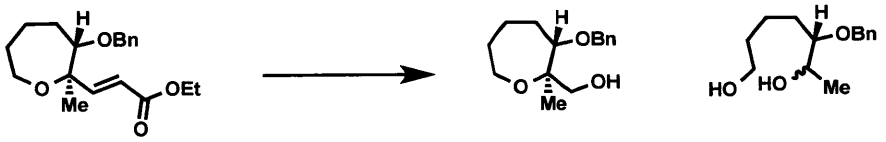
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H), 7.02 (d, J = 15.7 Hz, 1H), 6.04 (d, J = 15.7 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.41 (d, J = 11.7 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.83-3.78 (m, 1H), 3.51 (d, J = 9.1 Hz, 1H), 3.44 (ddd, J = 12.4, 8.2, 3.8 Hz, 1H), 1.95-1.89 (m, 1H), 1.86-1.79 (m, 2H), 1.67-1.60 (m, 2H), 1.40-1.35 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.29 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 152.4, 138.4, 128.5, 127.78, 127.72, 119.3, 83.4, 80.3, 71.8, 64.7, 60.5, 31.1, 26.8, 24.6, 21.8, 14.4.

IR (thin film): 2980, 2934, 2875, 1715, 1654, 1497, 1453, 1366, 1298, 1272, 1214, 1173, 1115, 1096, 10671 1029 cm^{-1}.

HR-MS (DART) m/z calcd for $C_{19}H_{26}O_4$ $(M+H)^+$: 319.1904, found 319.1912.

[64] Characterization data for **40** matches except the optical rotation data differs by a factor of 10 (reported: $[\alpha]^{27}_D = -168$ (c = 0.111, $CHCl_3$)) as reported in Kuranaga, T.; Ohtani, N.; Tsutsumi, R.; Baden, D. G.; Wright, J. L. C.; Satake, M.; Tachibana, K. *Org. Lett.* **2011**, *13*, 696. Attempts to contact the corresponding author were unsuccessful.



111 112 113

Alcohol 112: To a solution of **111** (8.9 mg, 0.028 mmol) in *t*-BuOH/H_2O (1:1, 0.56 mL) was added citric acid monohydrate (6 mg, 0.028 mmol), NMO (as solid, 7 mg, 0.056 mmol), and $K_2OsO_2(OH)_4 \cdot 2H_2O$ (0.5 mg, 1.4 μmol), and the green reaction mixture was stirred at room temperature. After 8 h, the colorless reaction was quenched by addition of 1M $HCl_{(aq)}$ (0.2 mL), then extracted EtOAc (3 x 2 mL). The combined organic layers were washed sat. $Na_2CO_{3(aq)}$ (1 x 2.5 mL), sat. $NaCl_{(aq)}$ (1 x 2.5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude diol as a pale green oil, which was used without further purification.

To a solution of the crude diol in CH_2Cl_2 (0.55 mL) was added $NaIO_4/SiO_2$ (1.2 g/mmol, 100 mg, 0.084 mmol) and stirred at room temperature. After 30 min, the reaction was filtered through a cotton plug and washed CH_2Cl_2 (1 x 1 mL), then Et_2O (2 x 1 mL), and concentrated *in vacuo*. The crude aldehyde was used directly without purification.

To a solution of crude aldehyde in MeOH (0.3 mL) at 0 °C was added $NaBH_4$ (6 mg, 0.15 mmol). The reaction was quenched after 10 min by the addition of 1M $HCl_{(aq)}$ (0.3 mL), EtOAc (2 mL), and H_2O (0.4 mL). The reaction mixture was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with sat. $NaCl_{(aq)}$ (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resultant colorless film was purified by flash chromatography (20–60% EtOAc/hexanes) to afford **112** as a colorless oil (4.2 mg, 0.017 mmol, 60%) and **113** as a colorless film (1.5:1 d.r., 3 mg, 0.012 mmol, 43%).

Characterization Data For 112:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 4.63 (d, J = 11.7 Hz, 1H), 4.35 (d, J = 11.7 Hz, 1H), 3.73 (ddd, J = 12.6, 6.2, 3.6 Hz, 1H), 3.60 (ddd, J = 12.6, 7.3, 3.6 Hz, 1H), 3.52 (d, J = 10.9 Hz, 1H), 3.47-3.43 (m, 2H), 1.94-1.87 (m, 2H), 1.83-1.79 (m, 1H), 1.67-1.61 (m, 2H), 1.44-1.39 (m, 1H), 1.24 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6, 128.5, 127.77, 127.74, 82.3, 79.9, 71.5, 68.6, 63.8, 31.2, 27.6, 23.3, 17.3.

IR (thin film): 3415, 2930, 2873, 1718, 1606, 1497, 1453, 1400, 1367, 1267, 1206, 1062, 1027 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{15}H_{22}O_3$ $(M+H)^+$: 251.1642, found 251.1653.

Characterization Data For 113 (major diastereomer):

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.30 (m, 5H), 4.67 (d, J = 11.3 Hz, 1H), 4.53 (d, J = 11.3 Hz, 1H), 3.77 (quintet, J = 6.4 Hz, 1H), 3.66 (t, J = 6.4 Hz, 2H), 3.25 (q, J = 5.4 Hz, 1H), 1.67-1.48 (m, 6H), 1.20 (d, J = 6.4 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.5, 128.7, 128.03, 127.95, 84.1, 72.8, 69.1, 63.0, 33.2, 30.2, 21.3, 19.3.

IR (thin film): 3359, 2925, 2859, 1717, 1497, 1454, 1371, 1276, 1208, 1068 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{14}H_{22}O_3$ $(M+Na)^+$: 261.1461, found 261.1467.

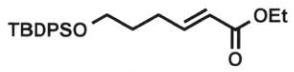
111 **112**

Alcohol 112: To a solution of **111** (27 mg, 0.085 mmol) in *t*-BuOH/H_2O (1:1, 0.86 mL) was added citric acid monohydrate (18 mg, 0.085 mmol), NMO (as solid, 20 mg, 0.17 mmol), and $K_2OsO_2(OH)_4 \bullet 2H_2O$ (1.5 mg, 4 μmol), and the green reaction mixture was stirred at room temperature. After 14 h, the colorless reaction was quenched by addition of 1M $HCl_{(aq)}$ (0.4 mL), then extracted EtOAc (3 x 3 mL). The combined organic layers were washed sat. $Na_2CO_{3(aq)}$ (1 x 5 mL), sat. $NaCl_{(aq)}$ (1 x 5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude diol as a pale green oil, which was used without further purification.

To a solution of the crude diol in CH_2Cl_2 (1 mL) was added Ph_3BiCO_3 (85 mg, 0.17 mmol) and heated to 50 °C in an oil bath. After 3 h, the reaction was removed from the oil bath, filtered through Celite (washed CH_2Cl_2 3 x 1 mL), and concentrated *in vacuo*. The crude gel was purified by flash chromatography (100% hexanes–6% EtOAc/hexanes) to afford an aldehyde that was used immediately in the next step.

To a solution of aldehyde in MeOH (2 mL) at 0 °C was added $NaBH_4$ (12 mg, 0.31 mmol). The reaction was quenched after 5 min by the addition of 1M $HCl_{(aq)}$ (0.4 mL), EtOAc (2 mL), and H_2O (0.4 mL). The reaction mixture was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with sat. $NaCl_{(aq)}$ (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield **112** as a colorless film (16 mg, 0.064 mmol, 75% over 3 steps).

I. ^{1}H and ^{13}C NMR Spectra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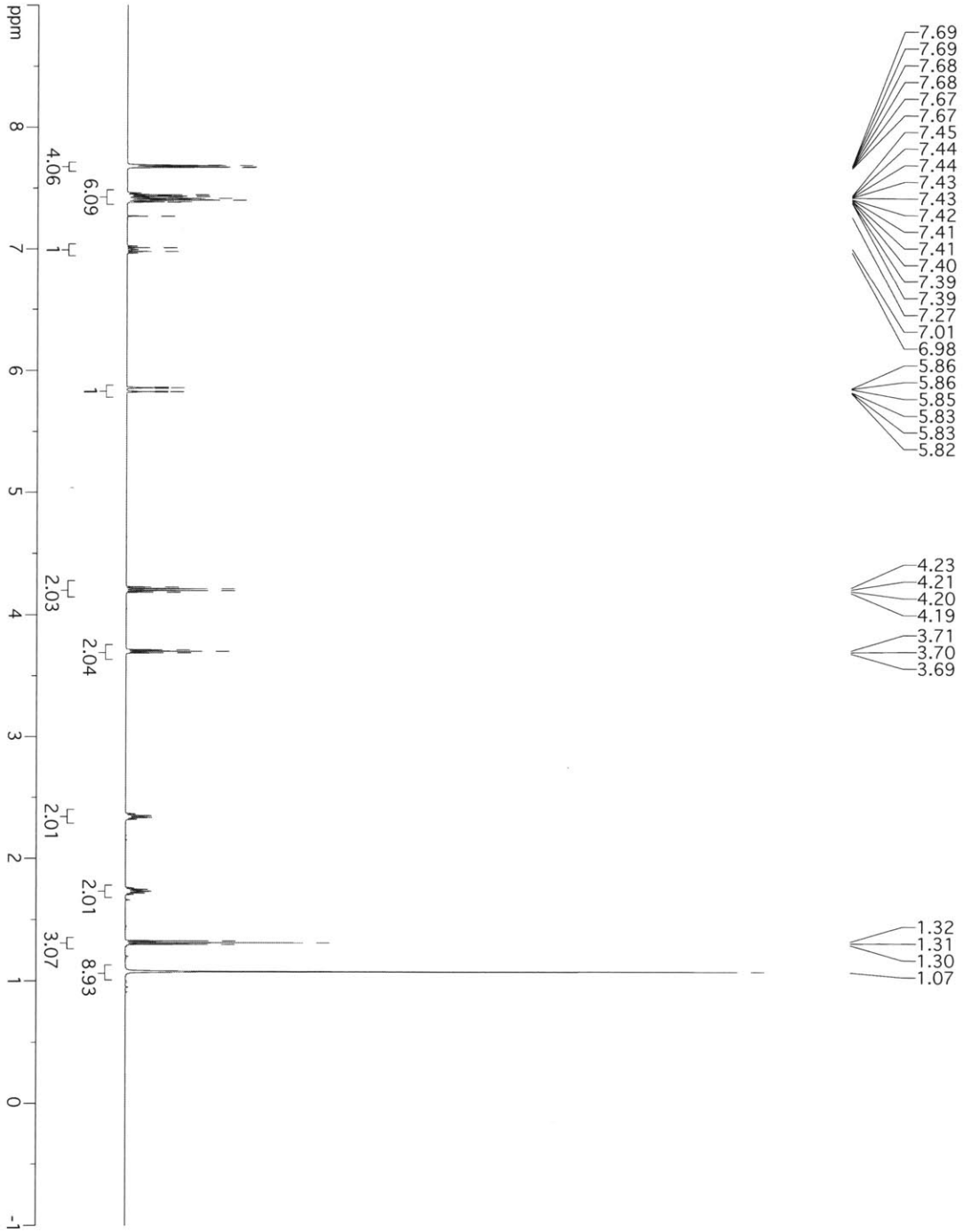
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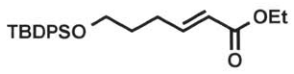
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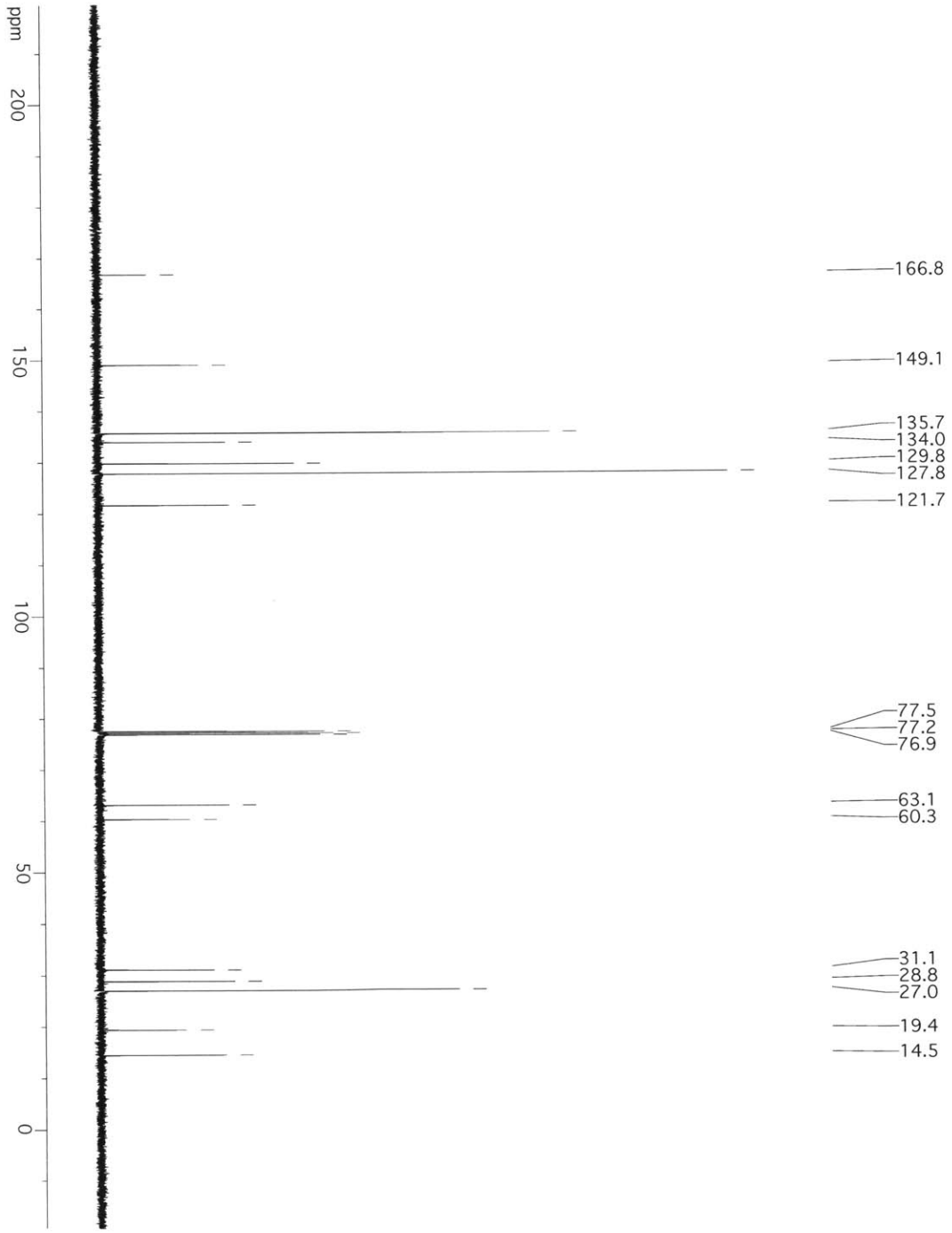
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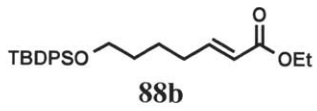
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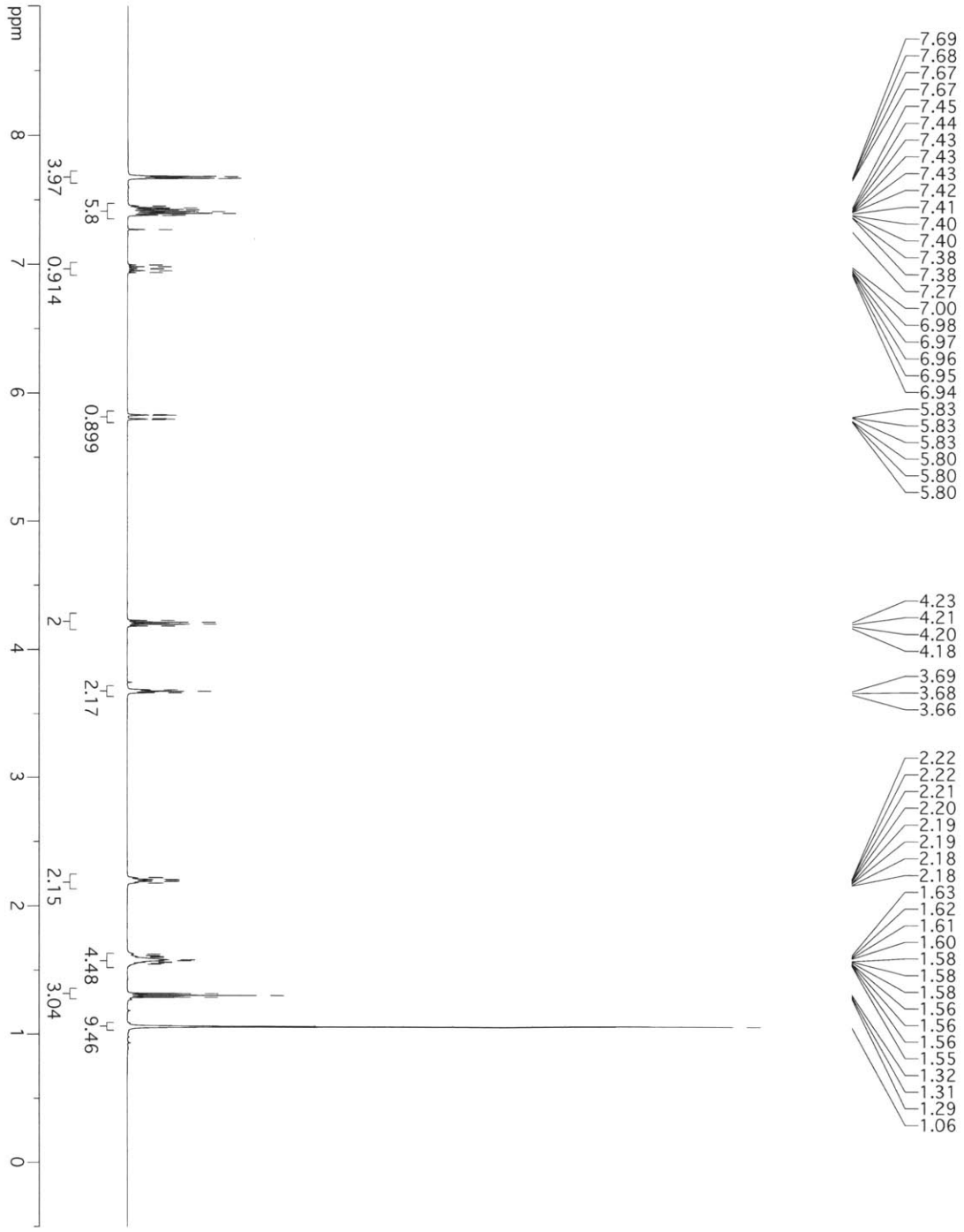
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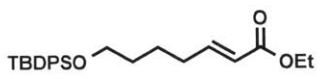
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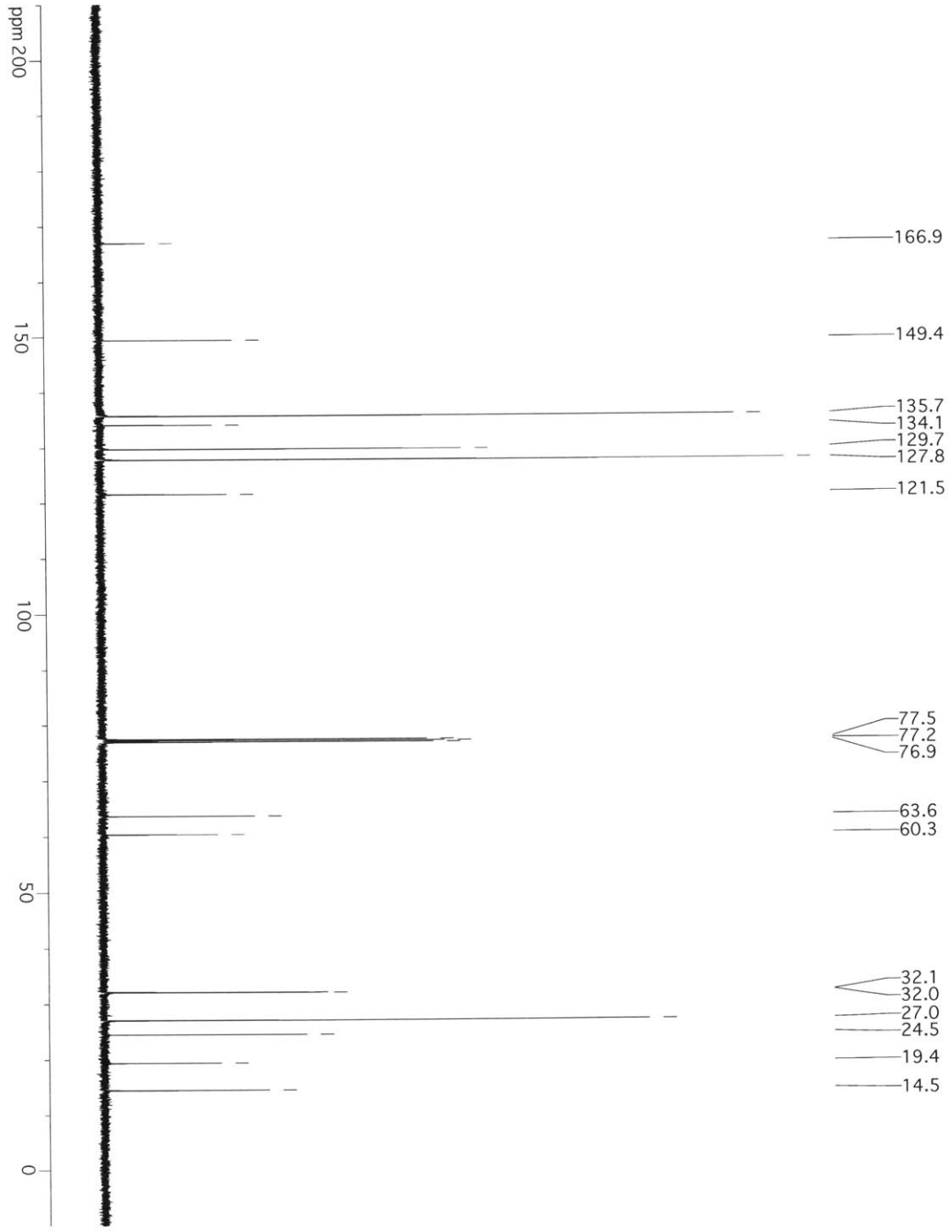
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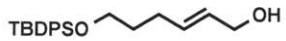
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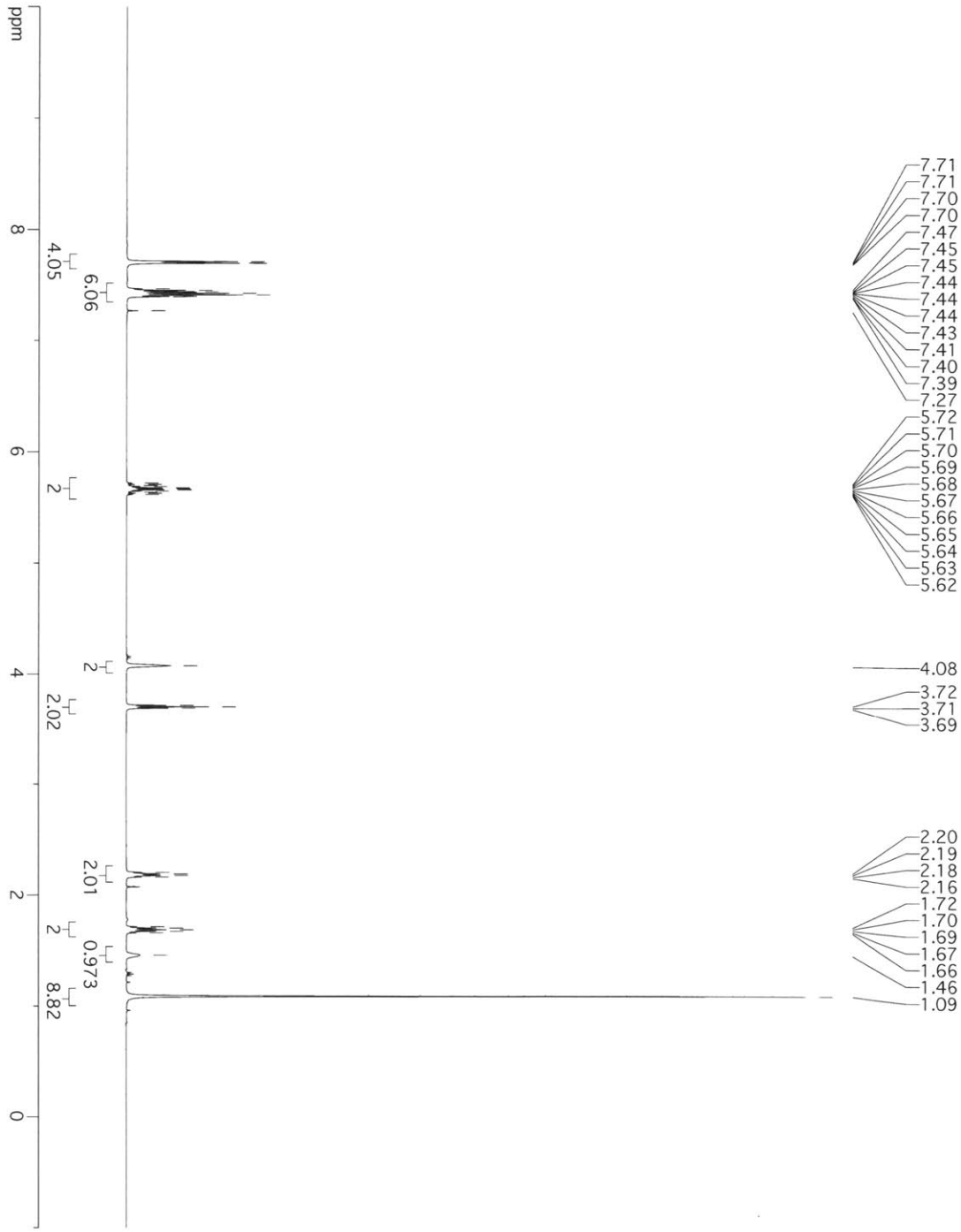
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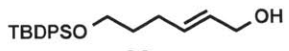
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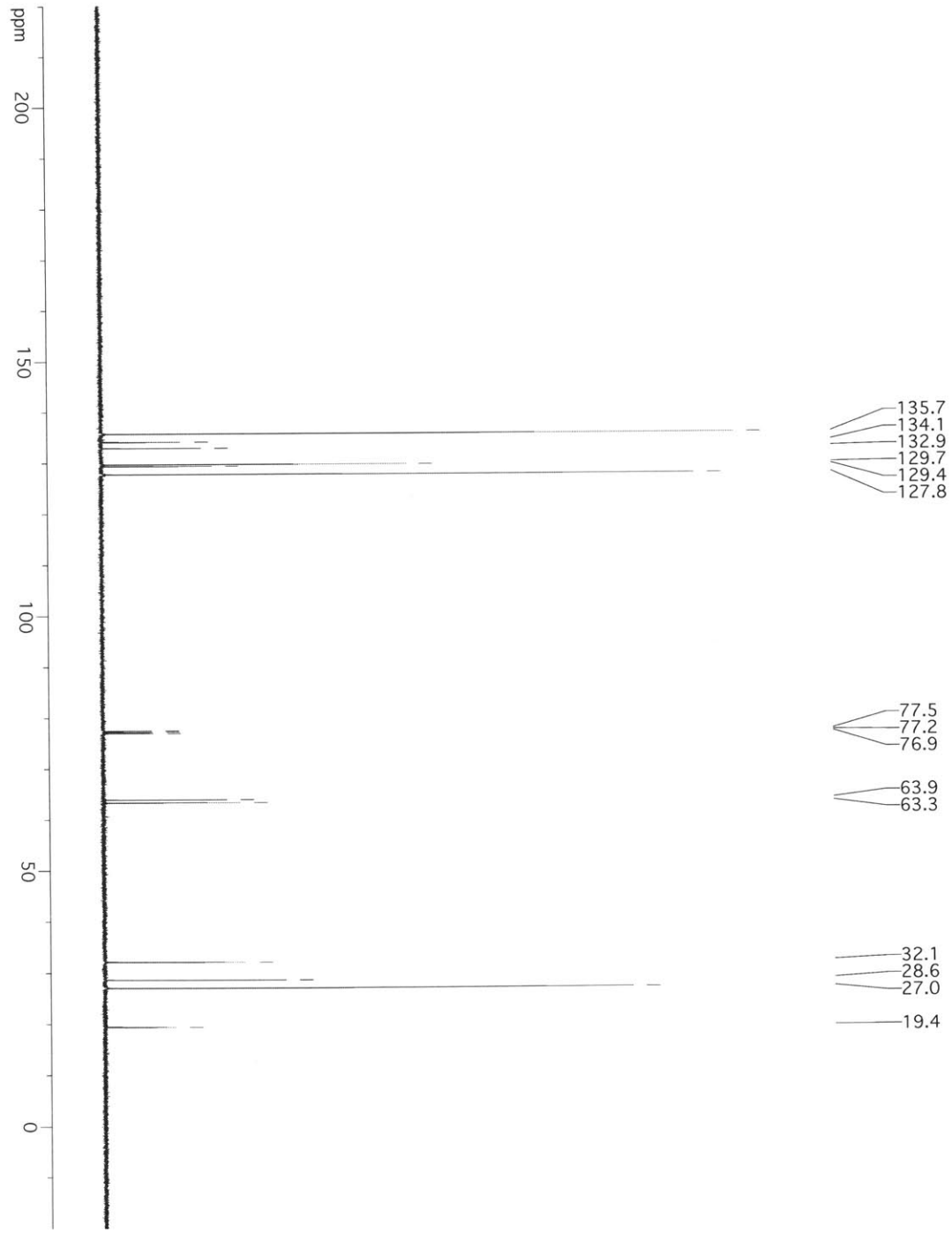
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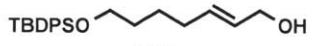
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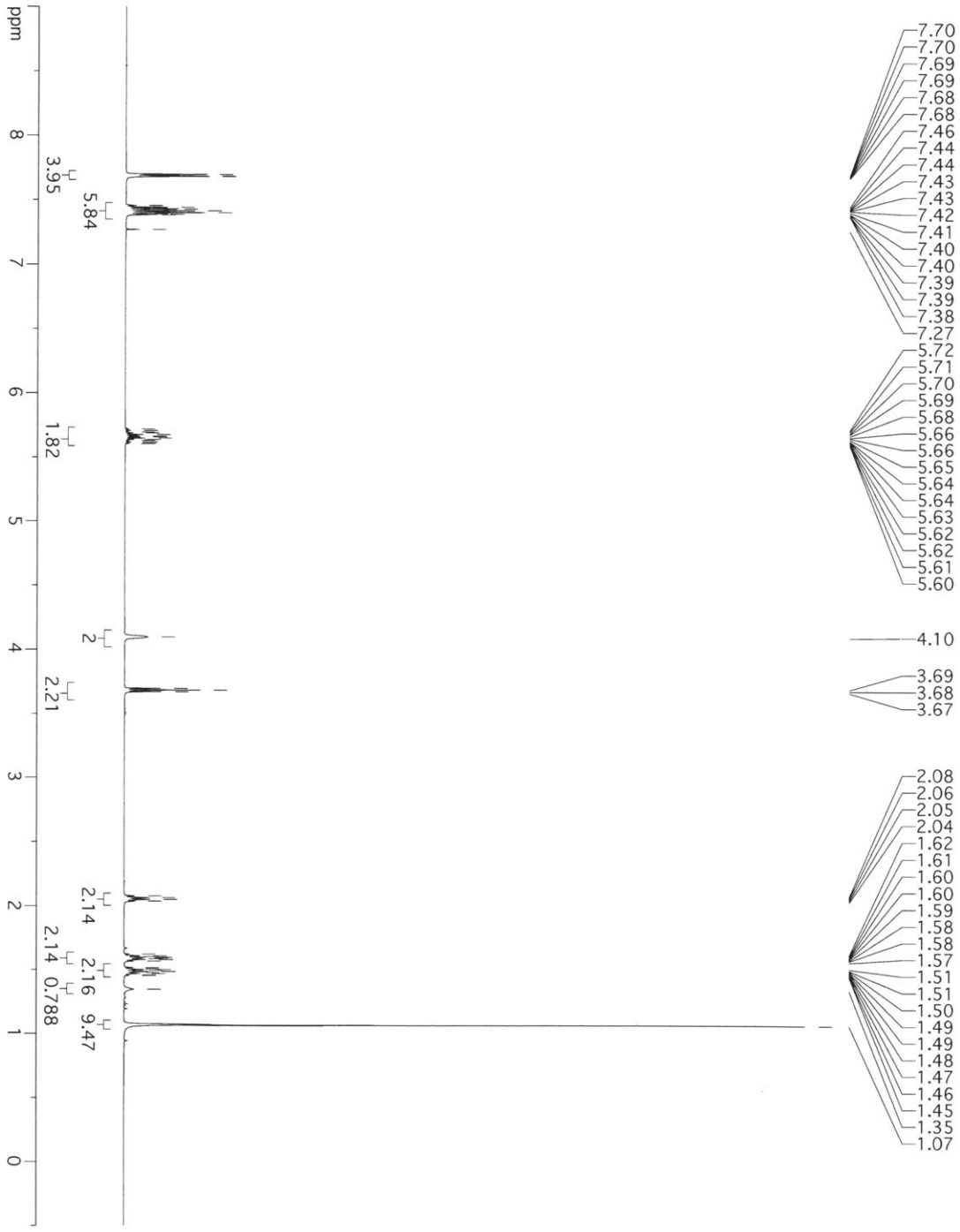
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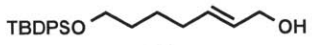
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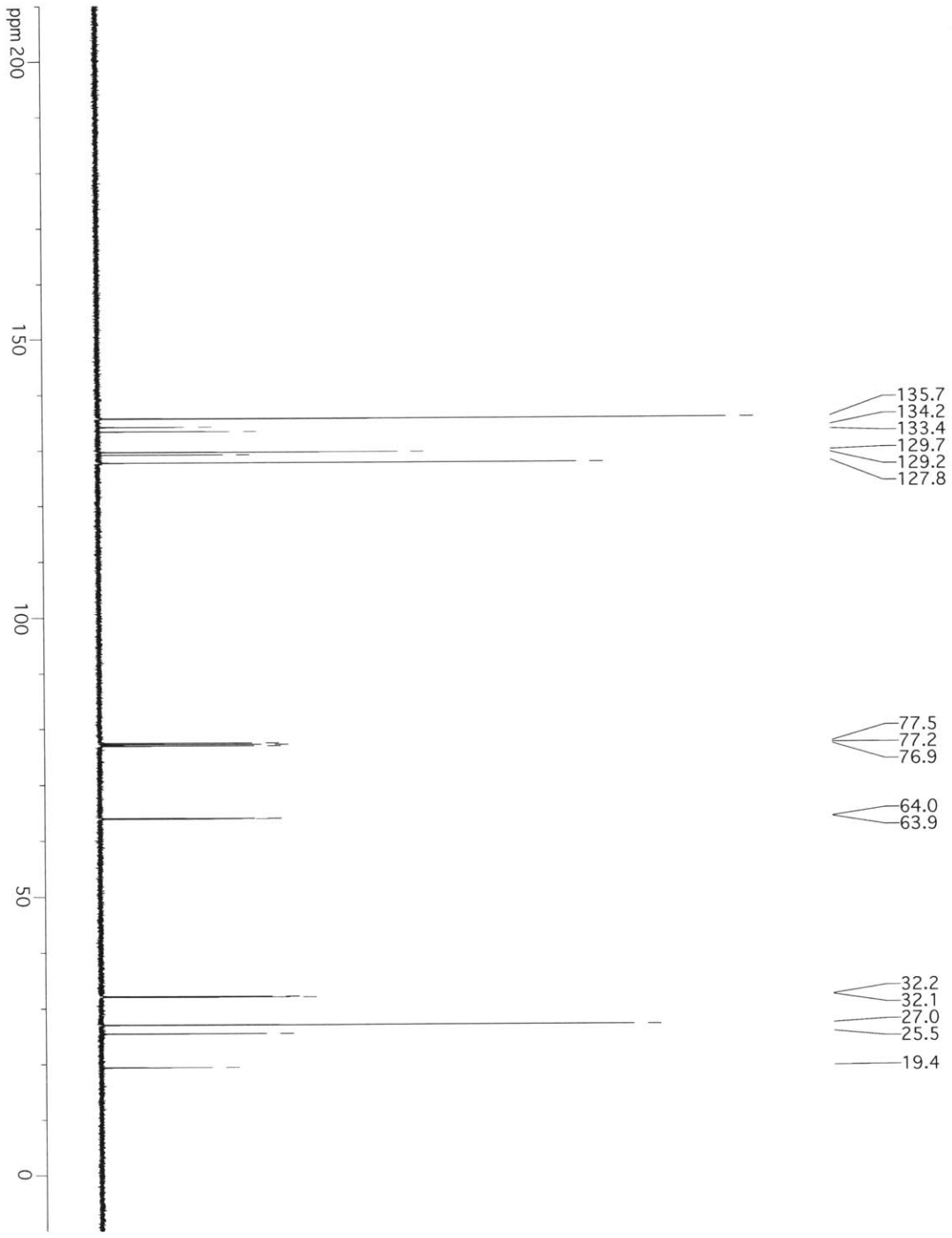
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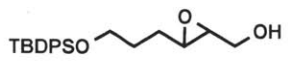
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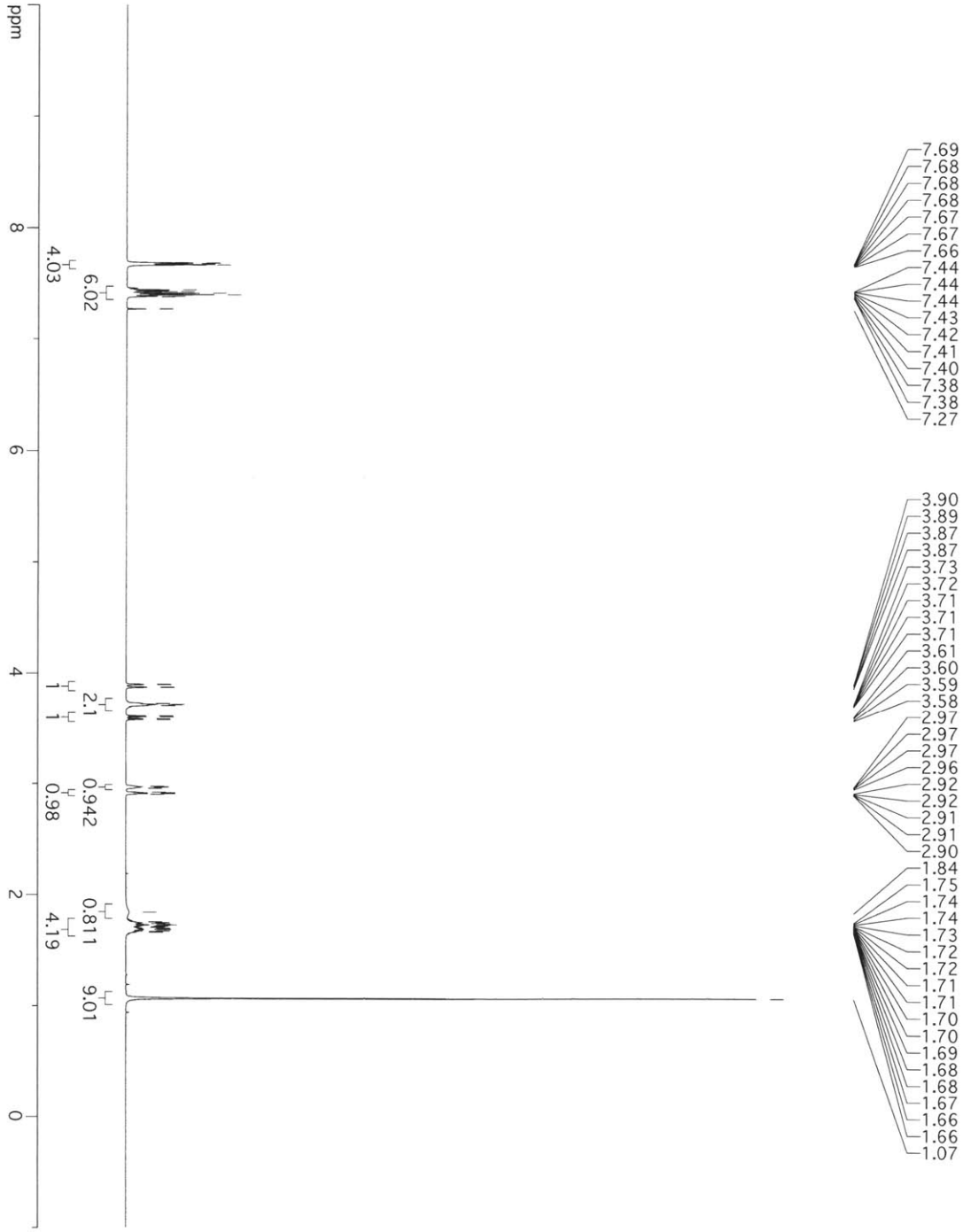
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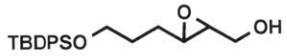
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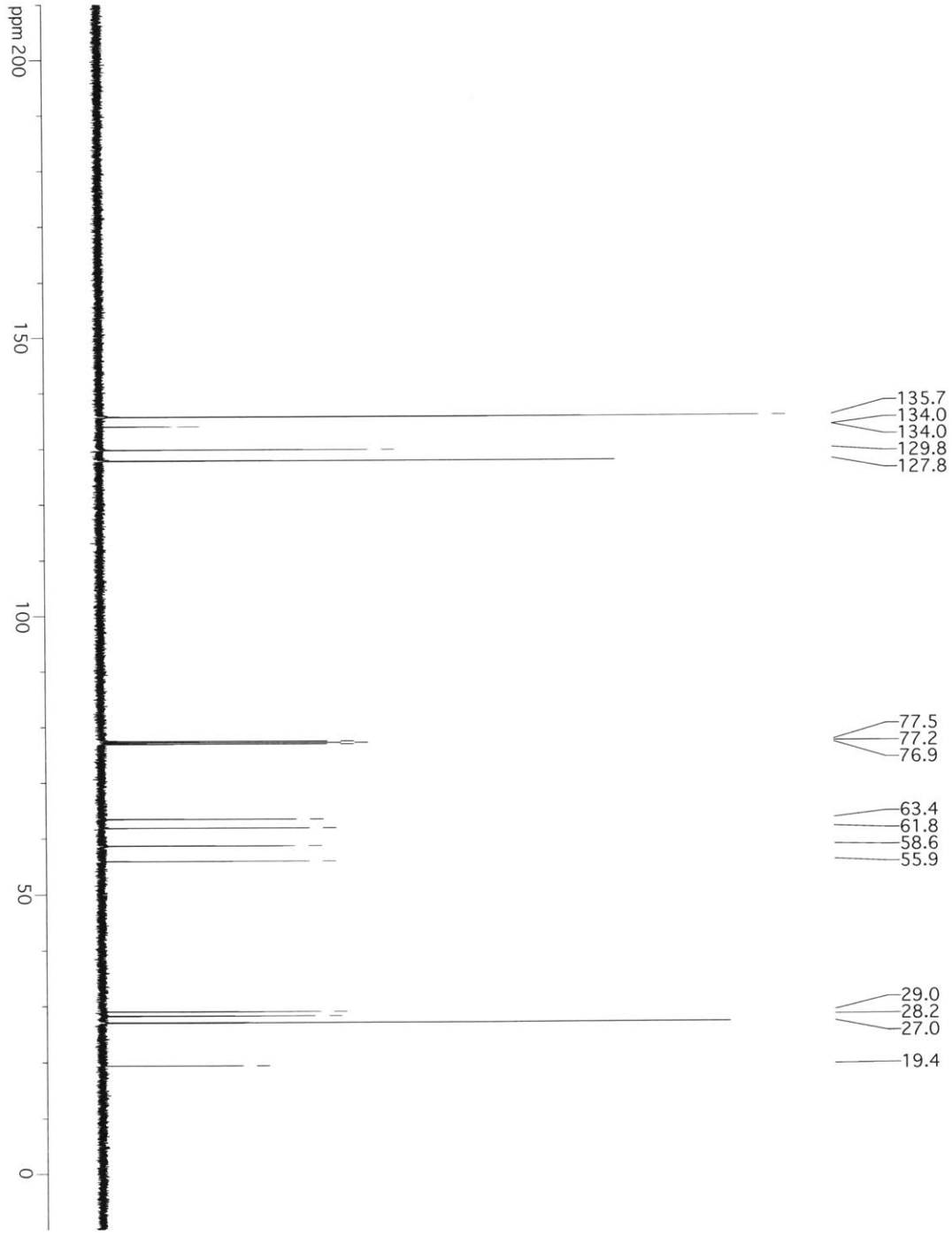
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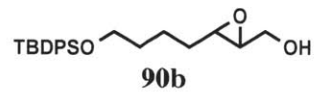
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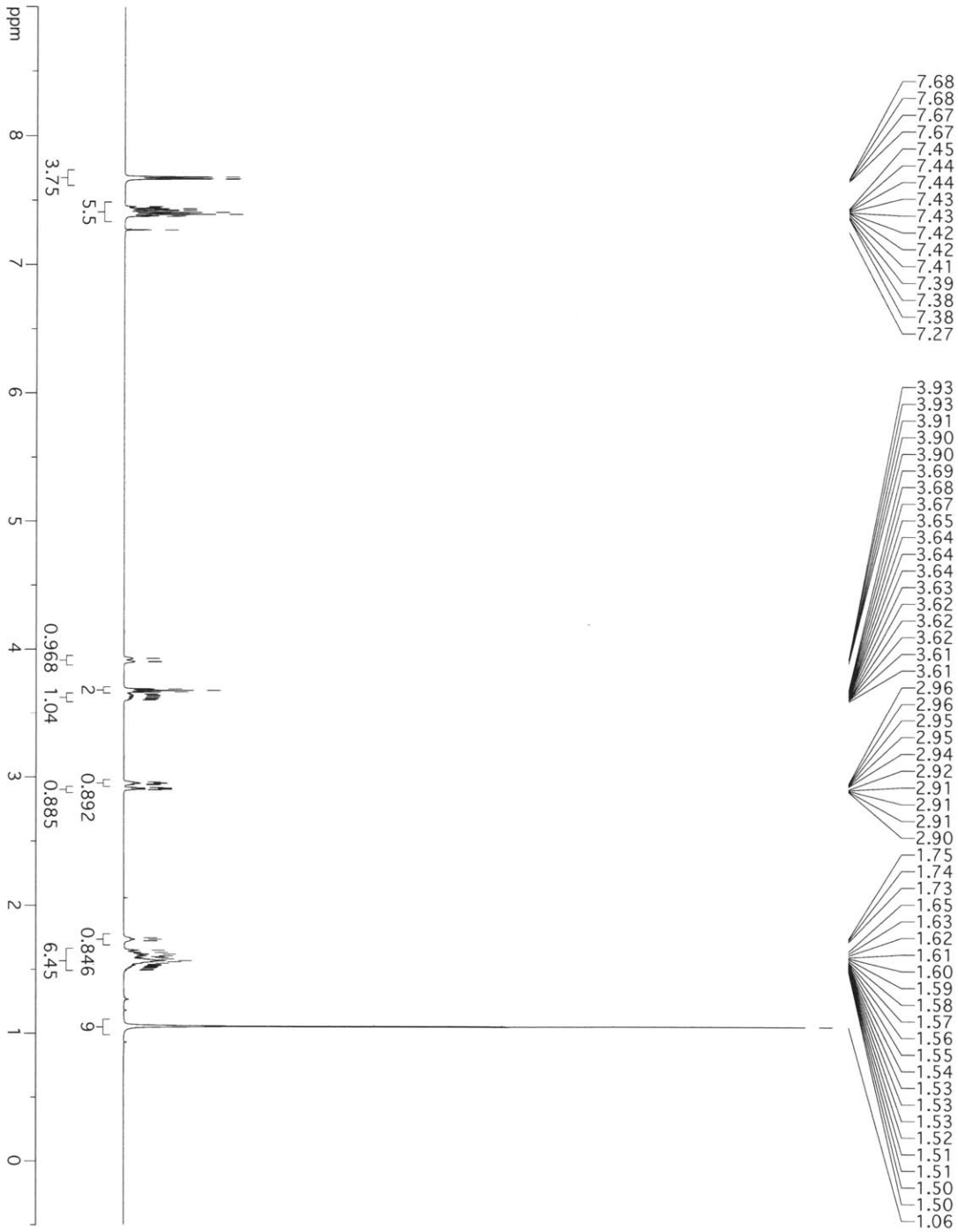
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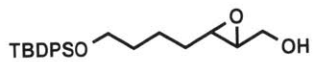
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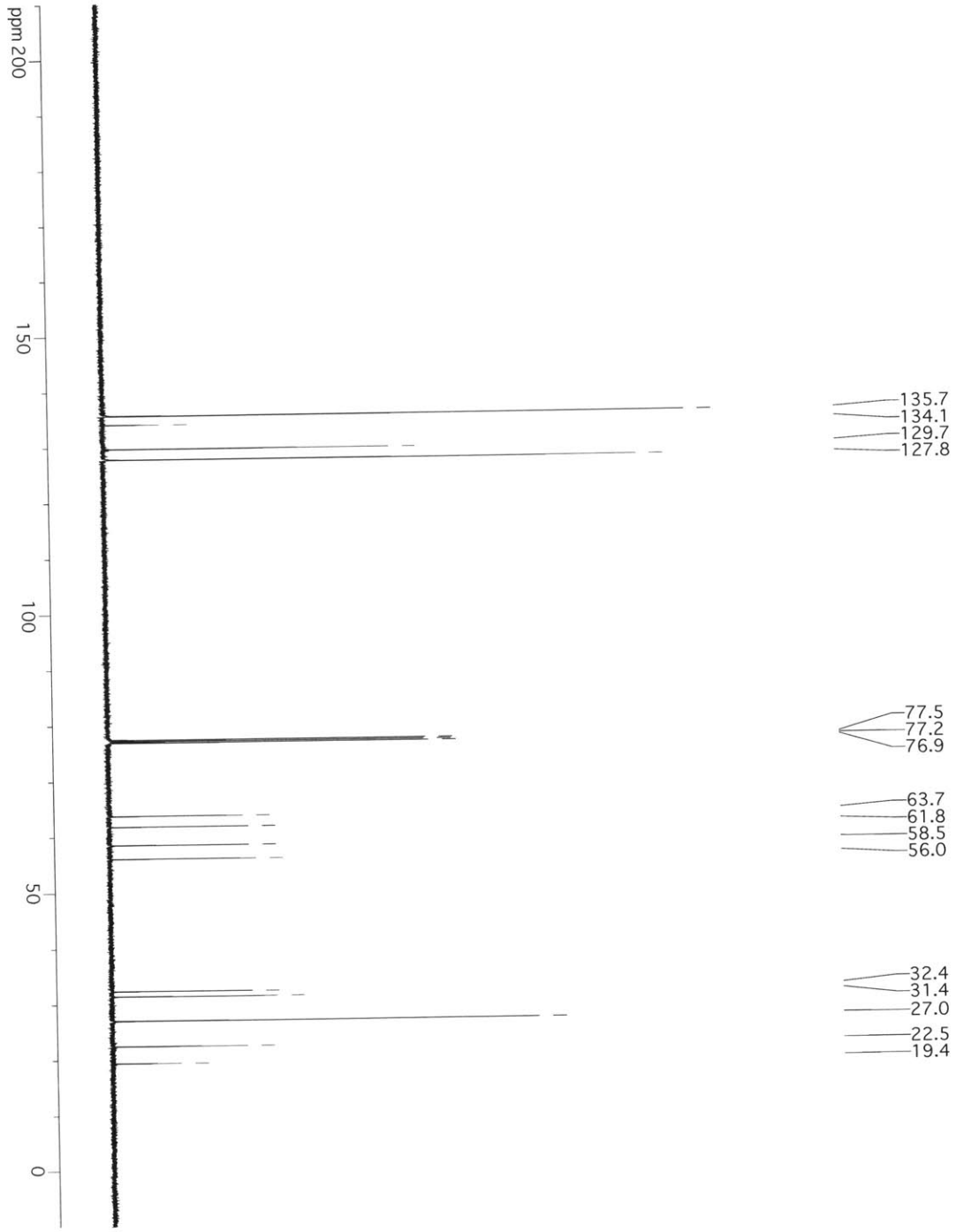
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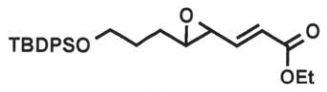
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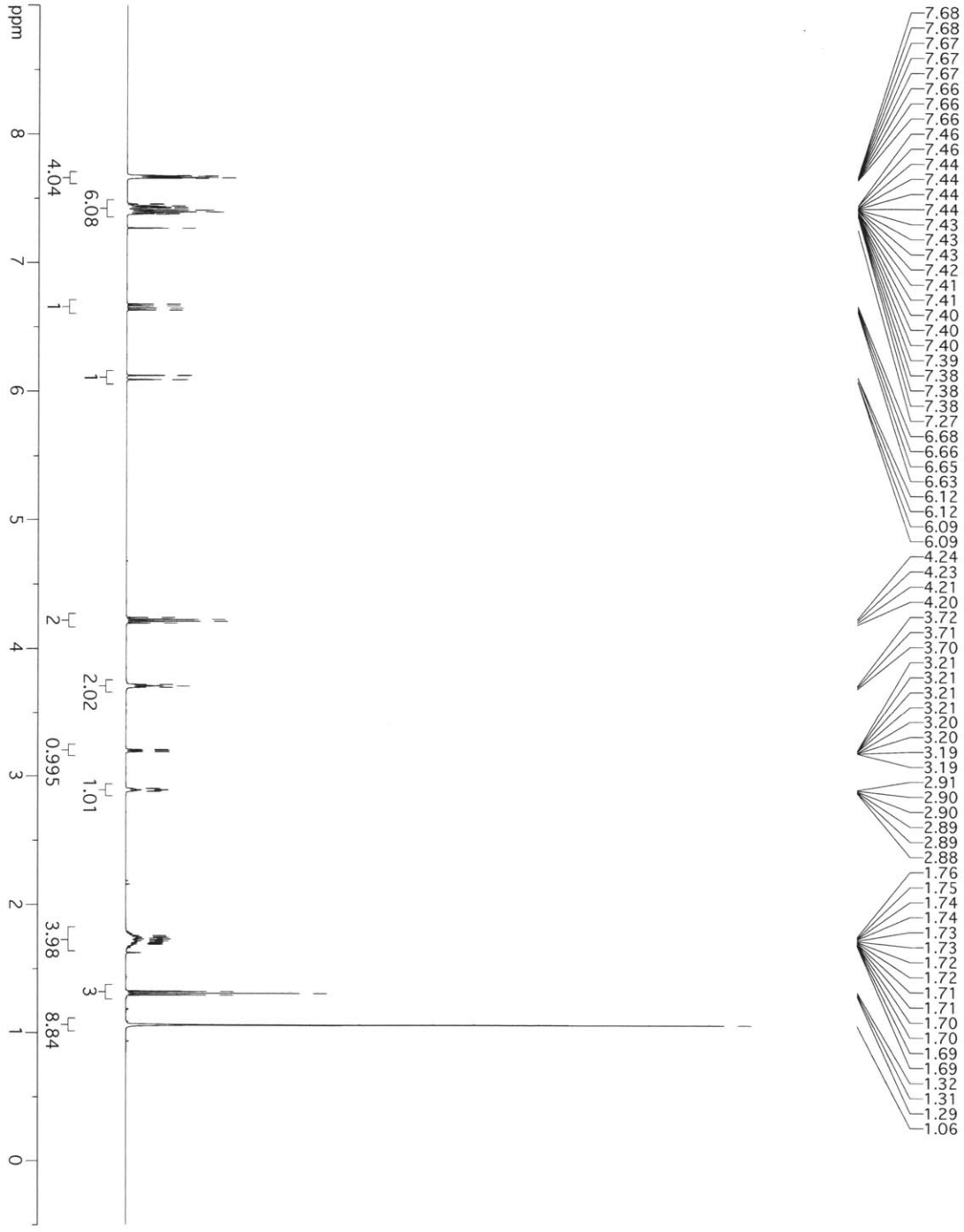
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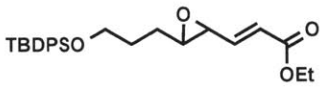
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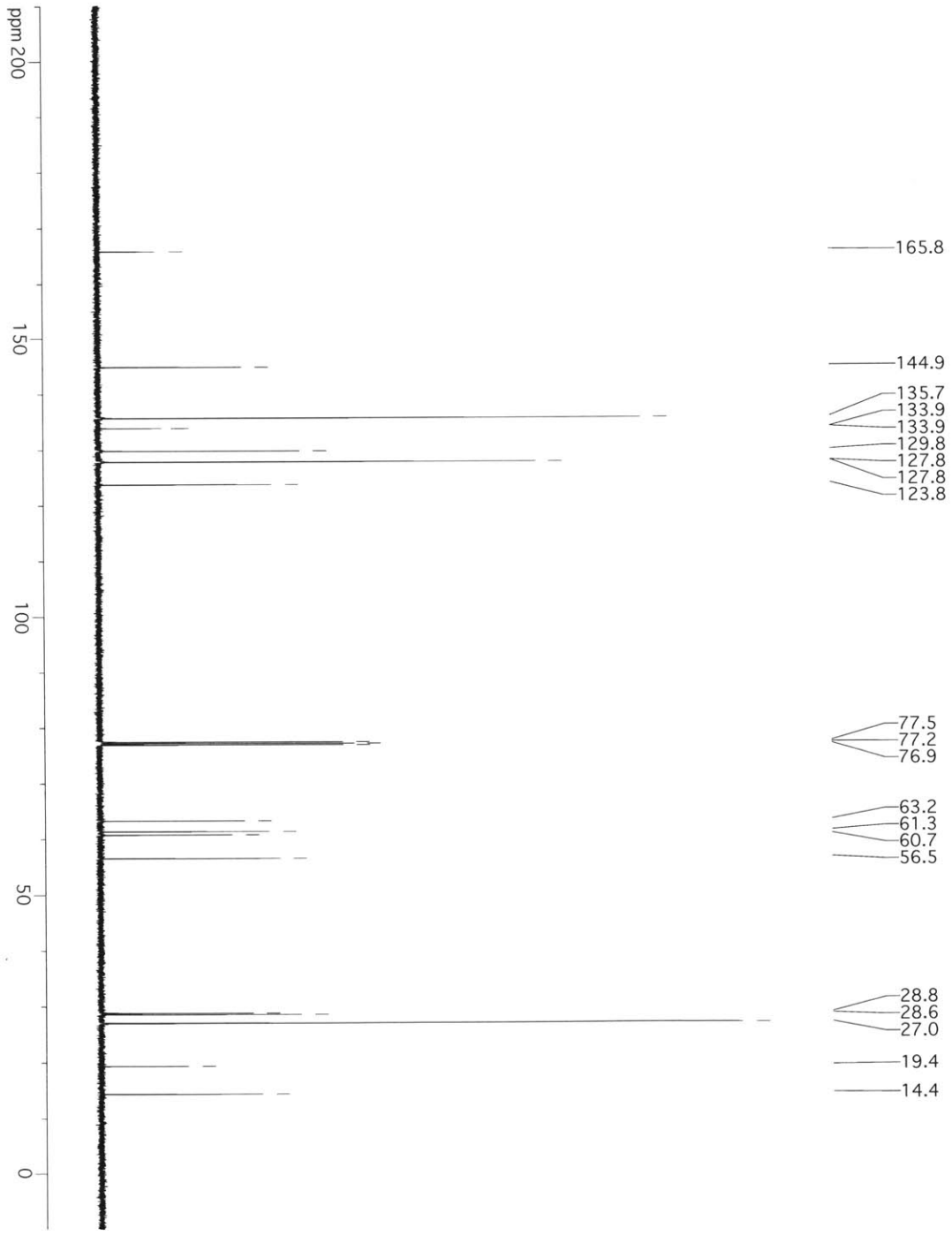
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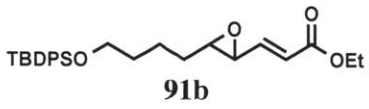
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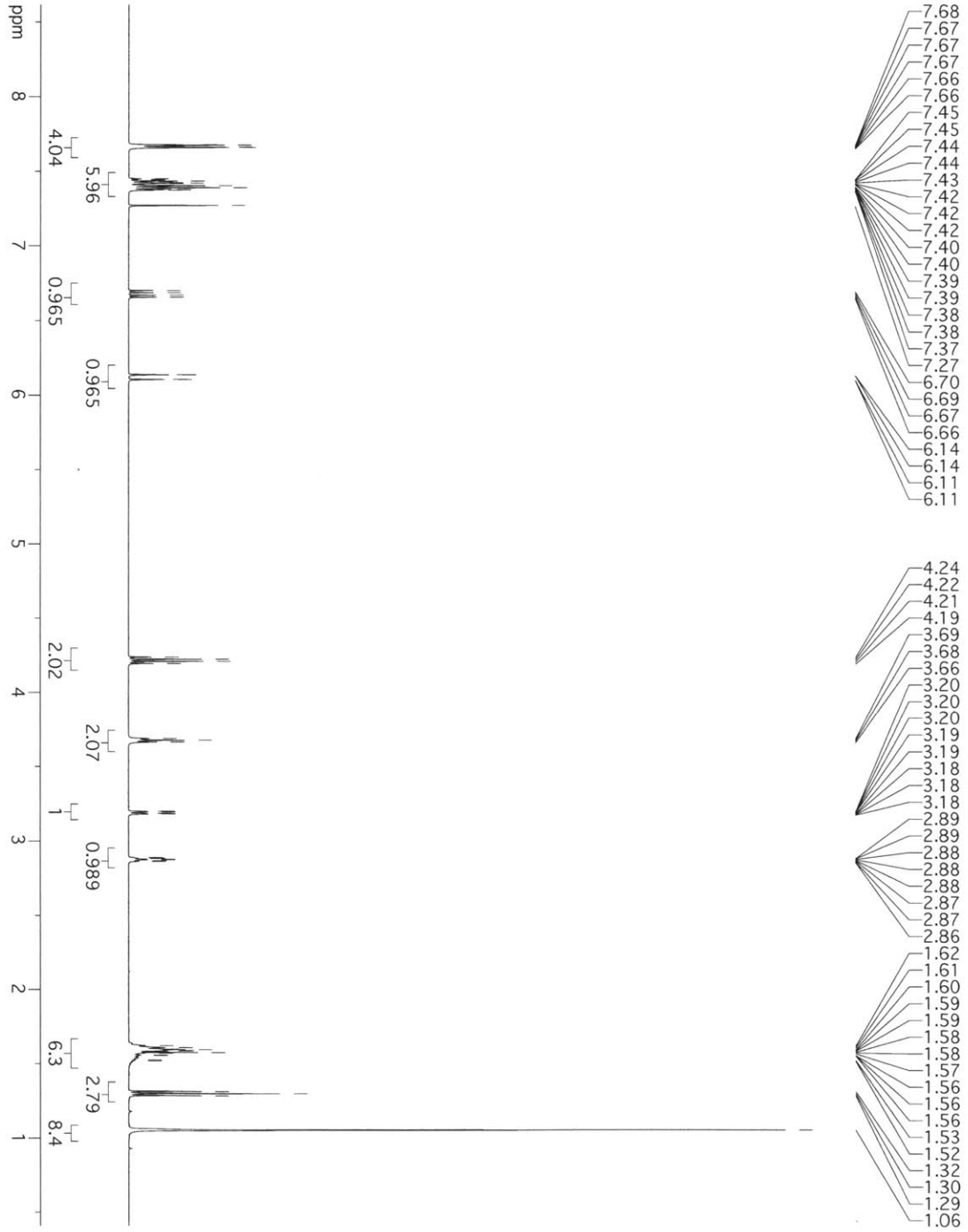
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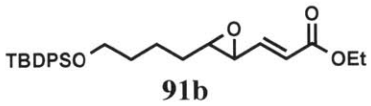
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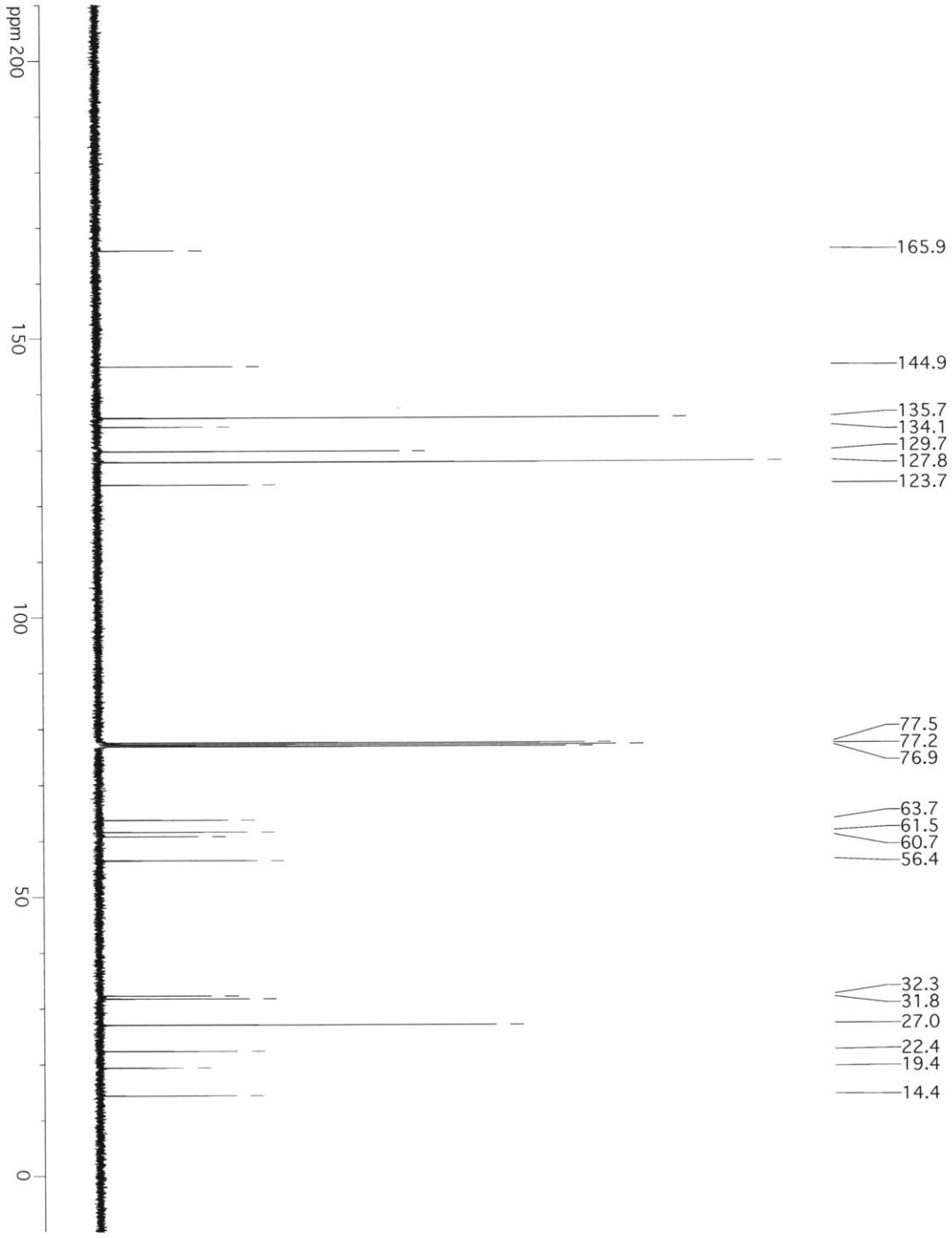
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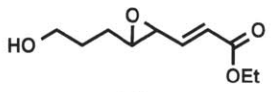
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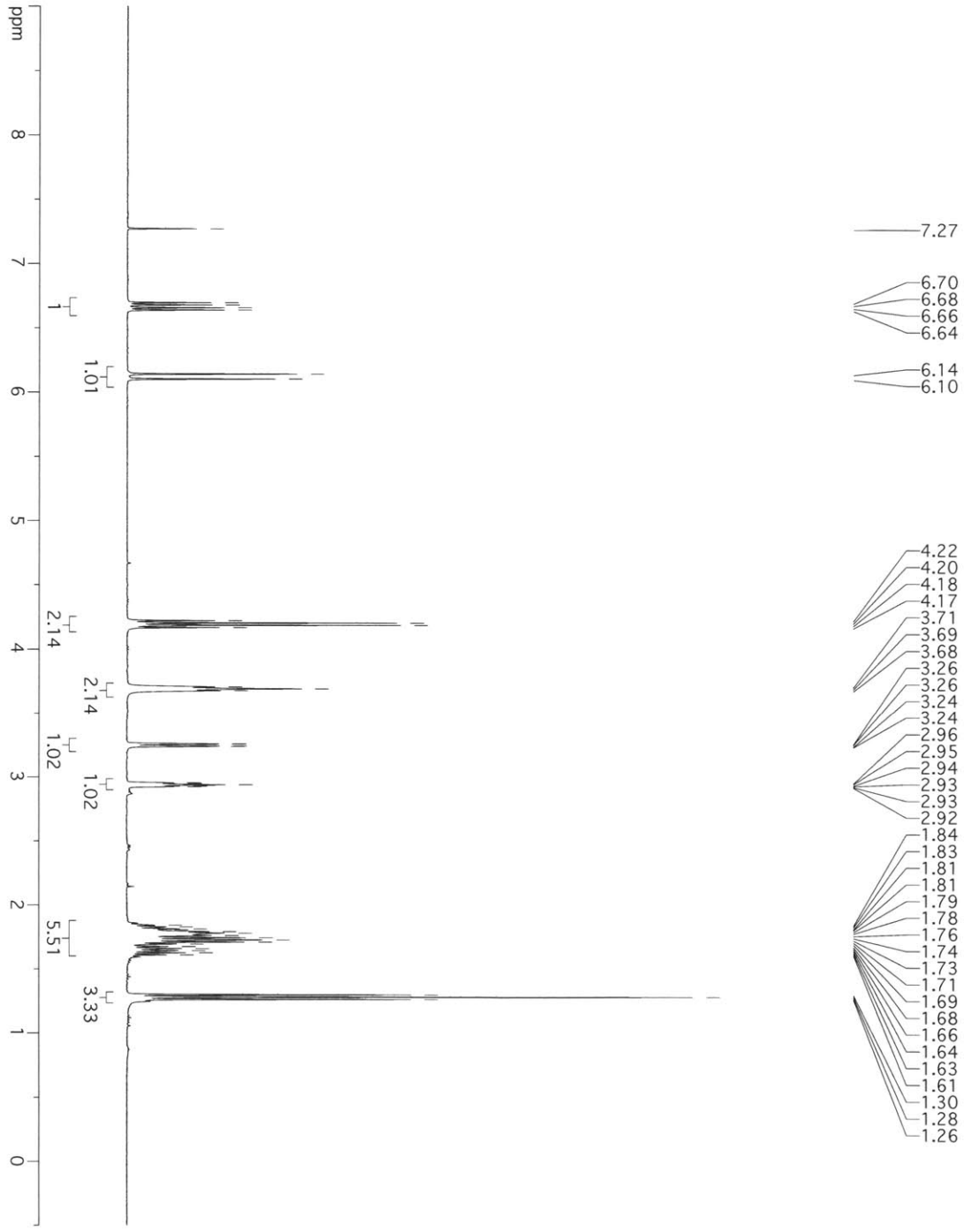
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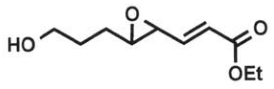
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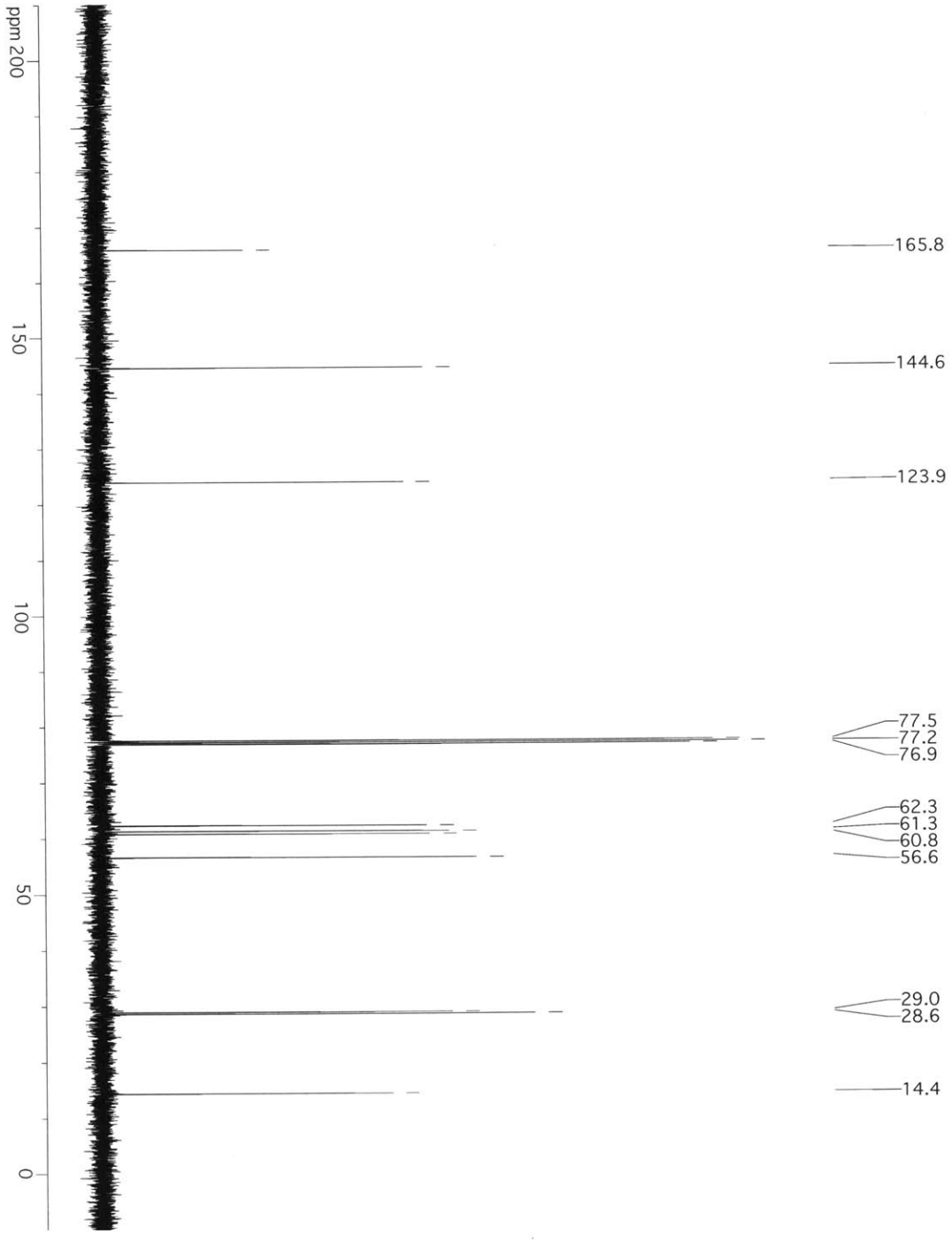
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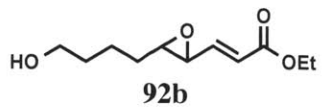
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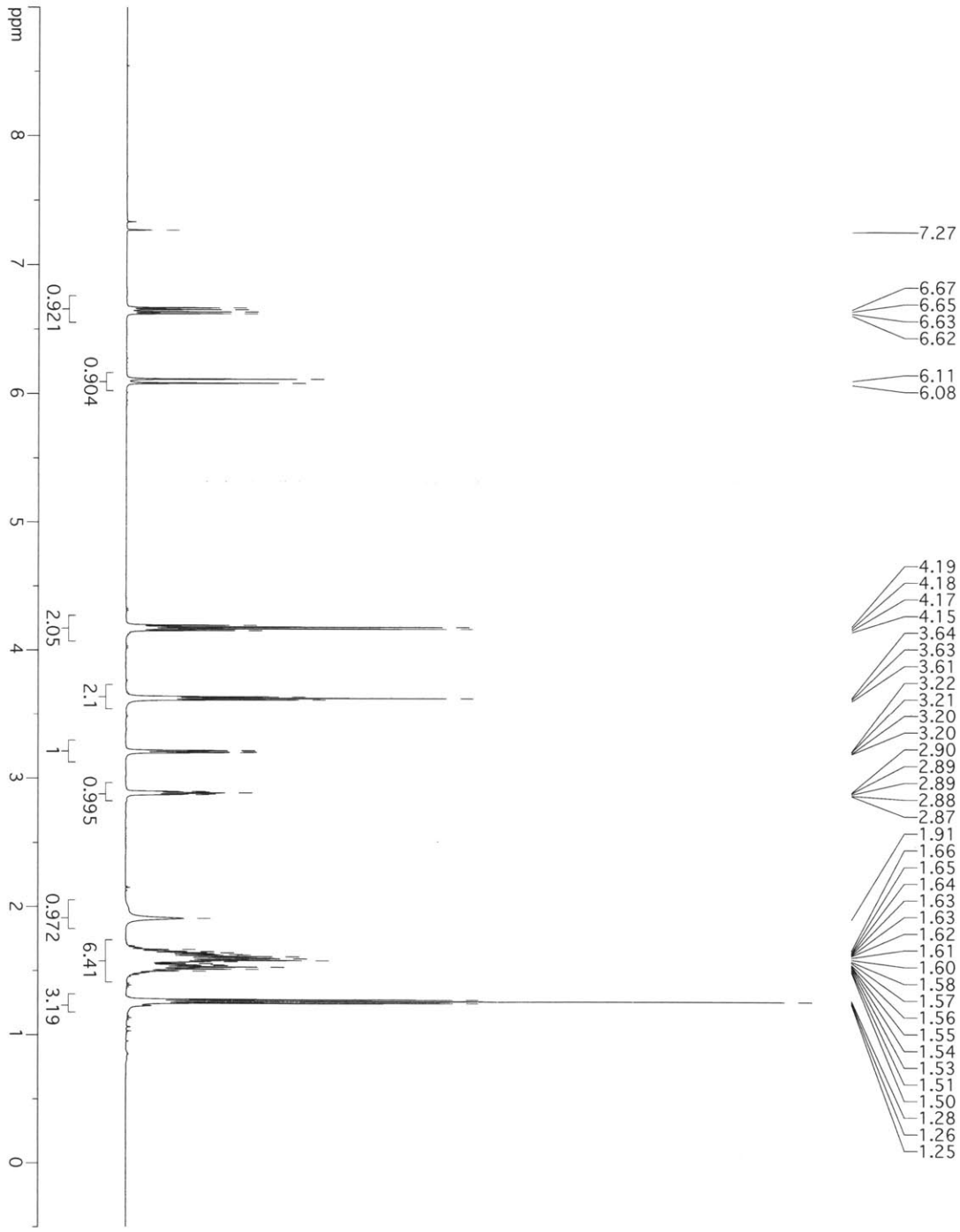
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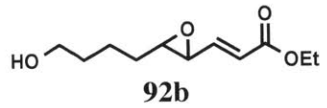
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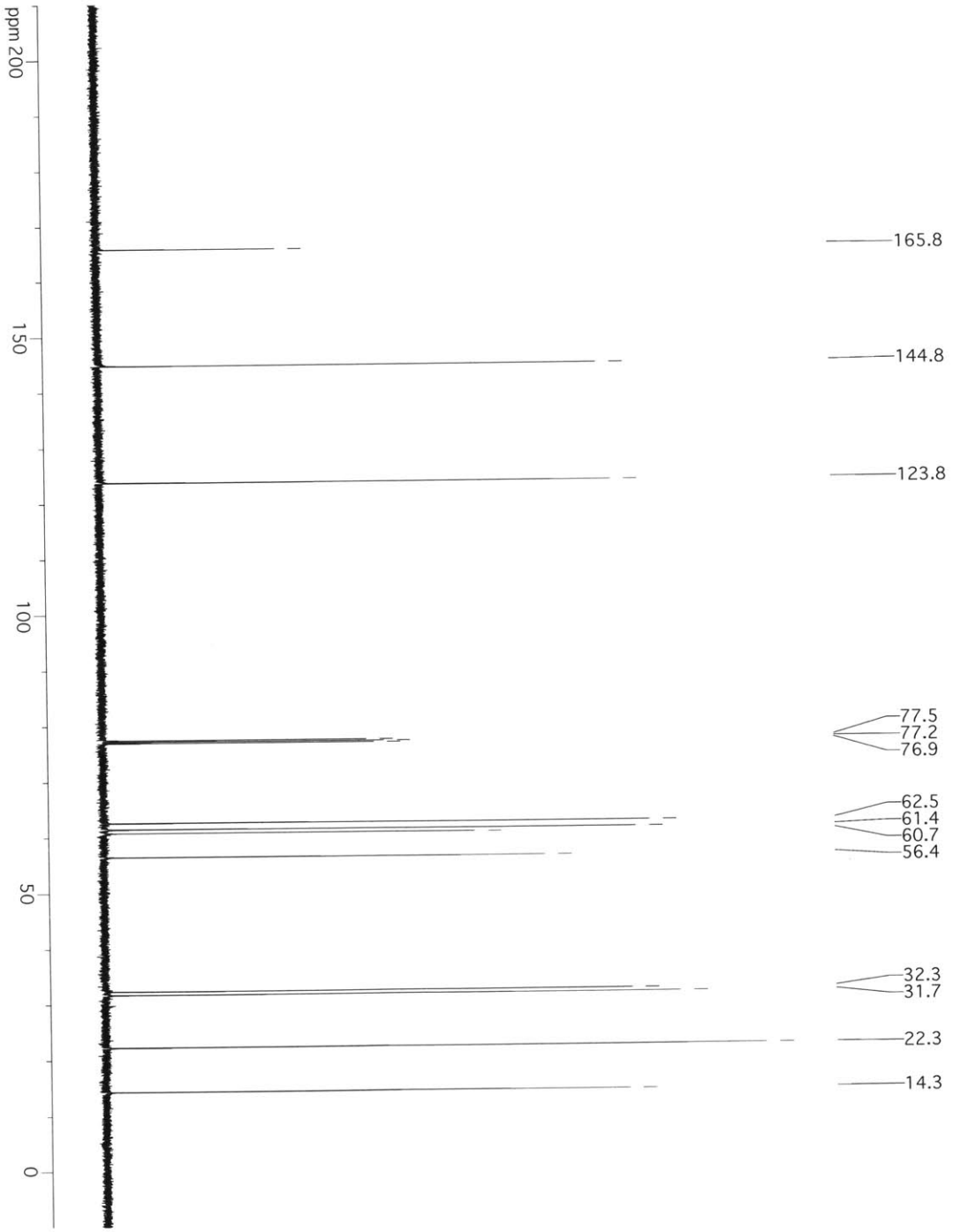
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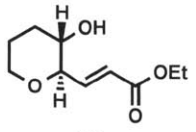
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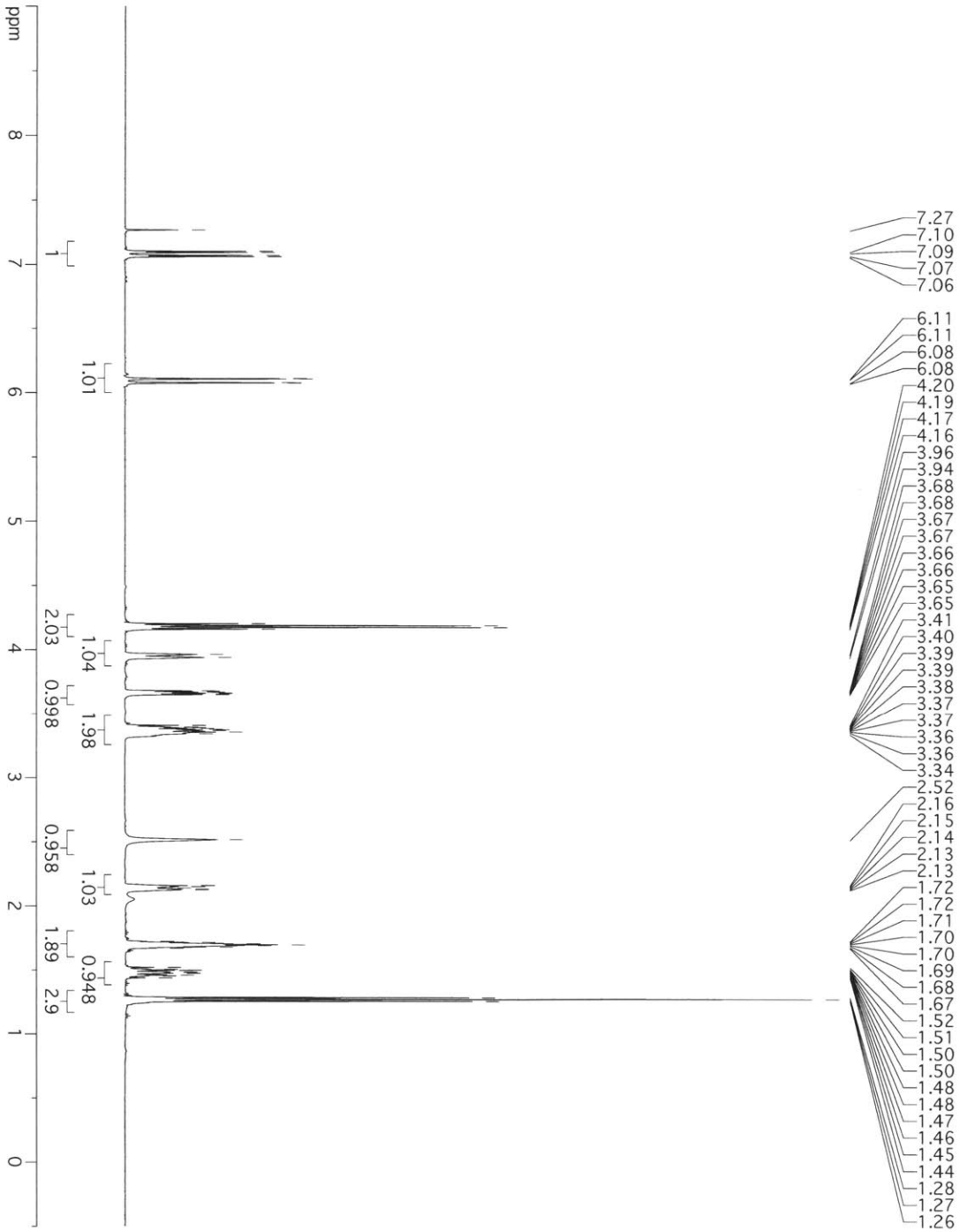
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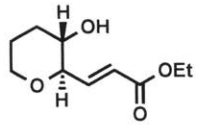
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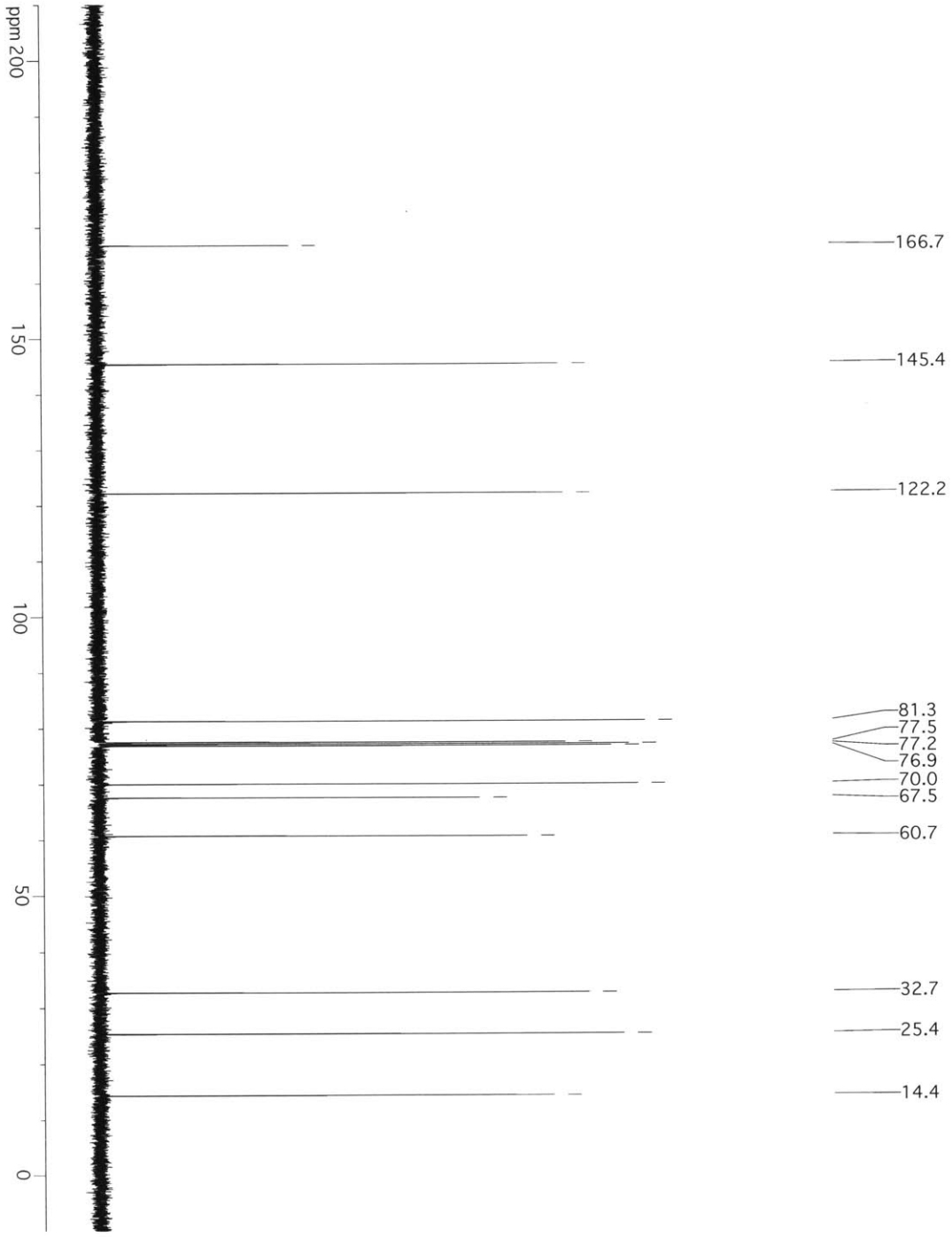
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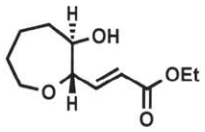
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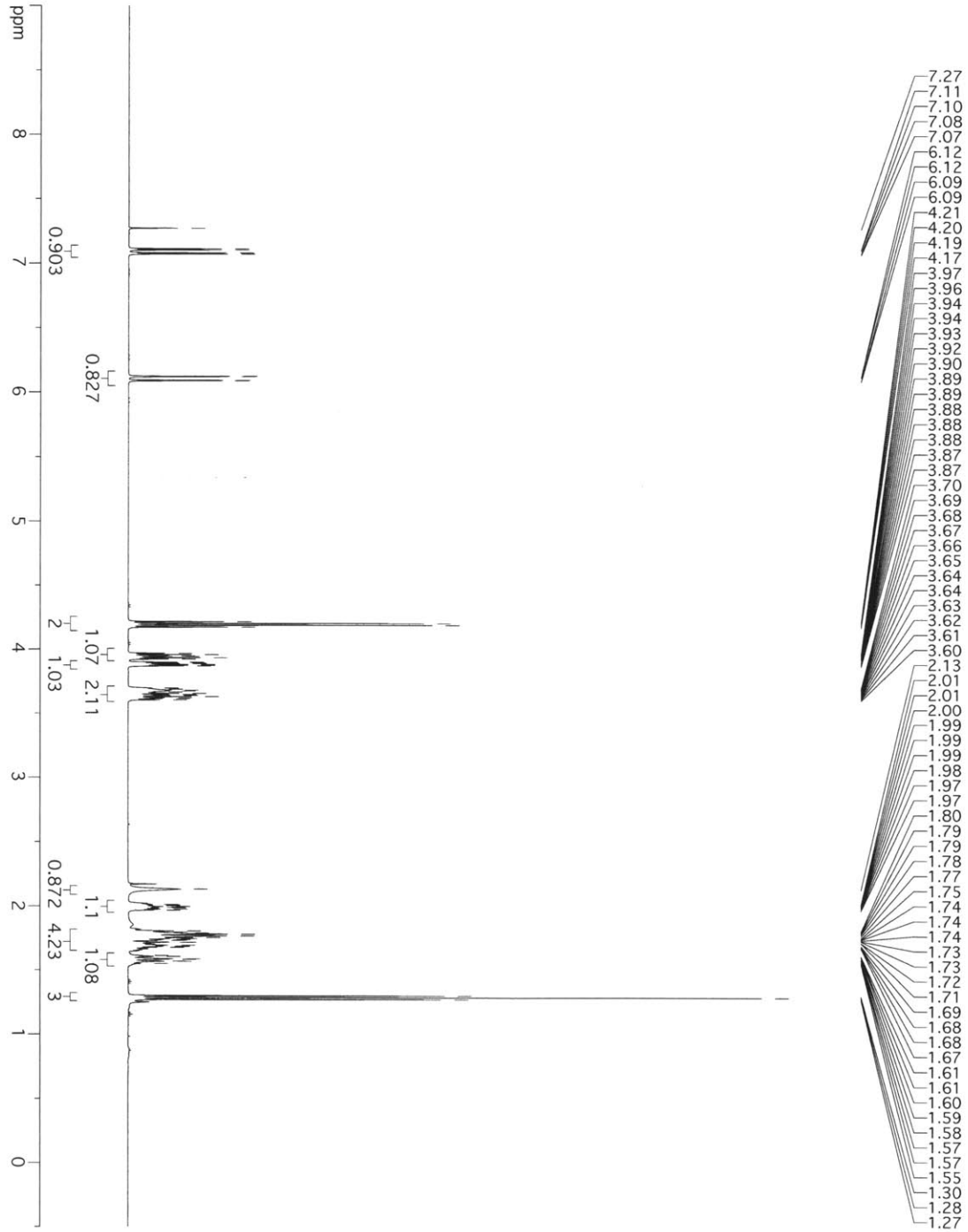
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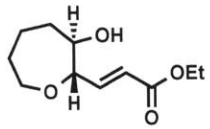
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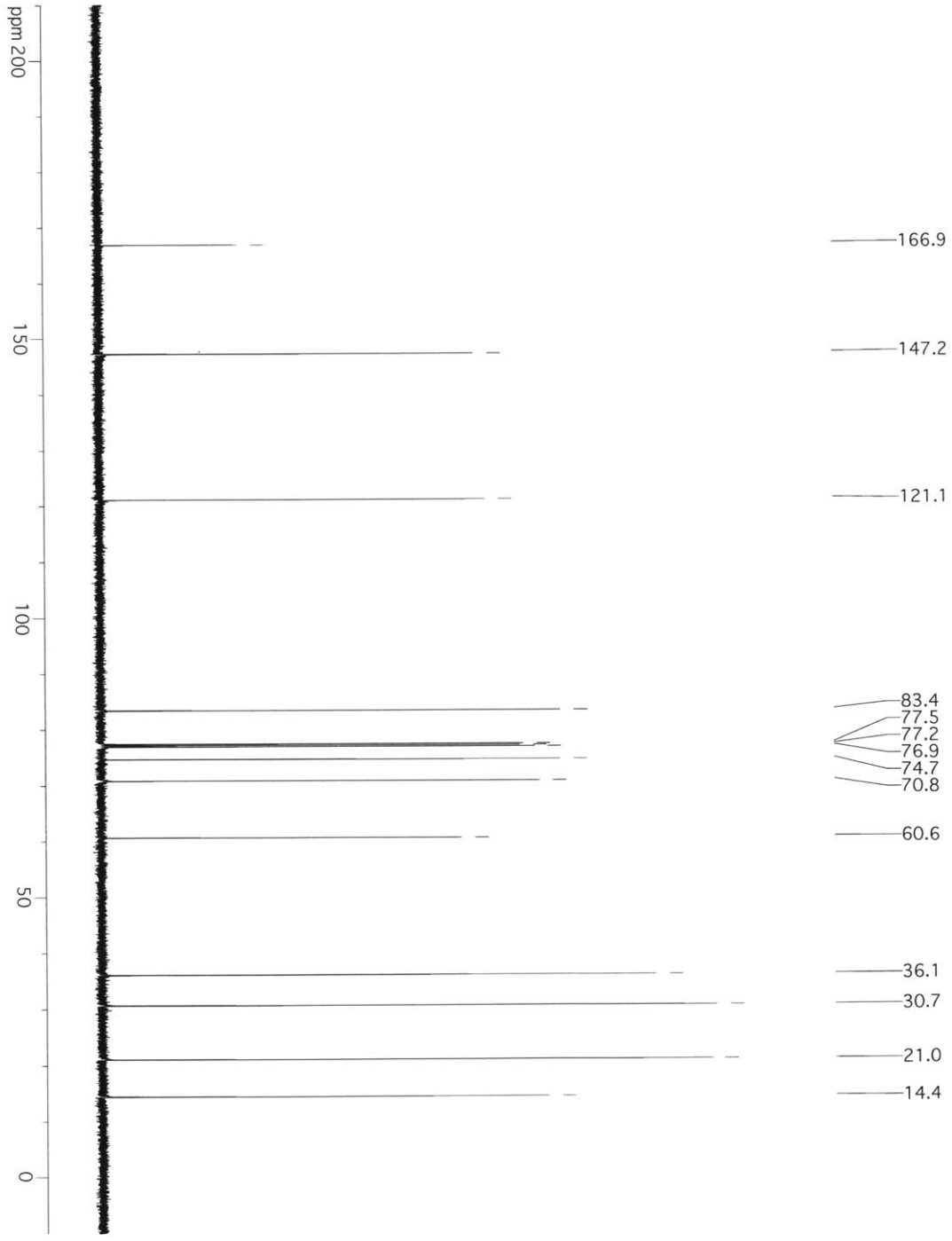
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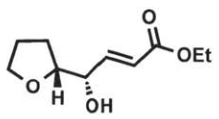
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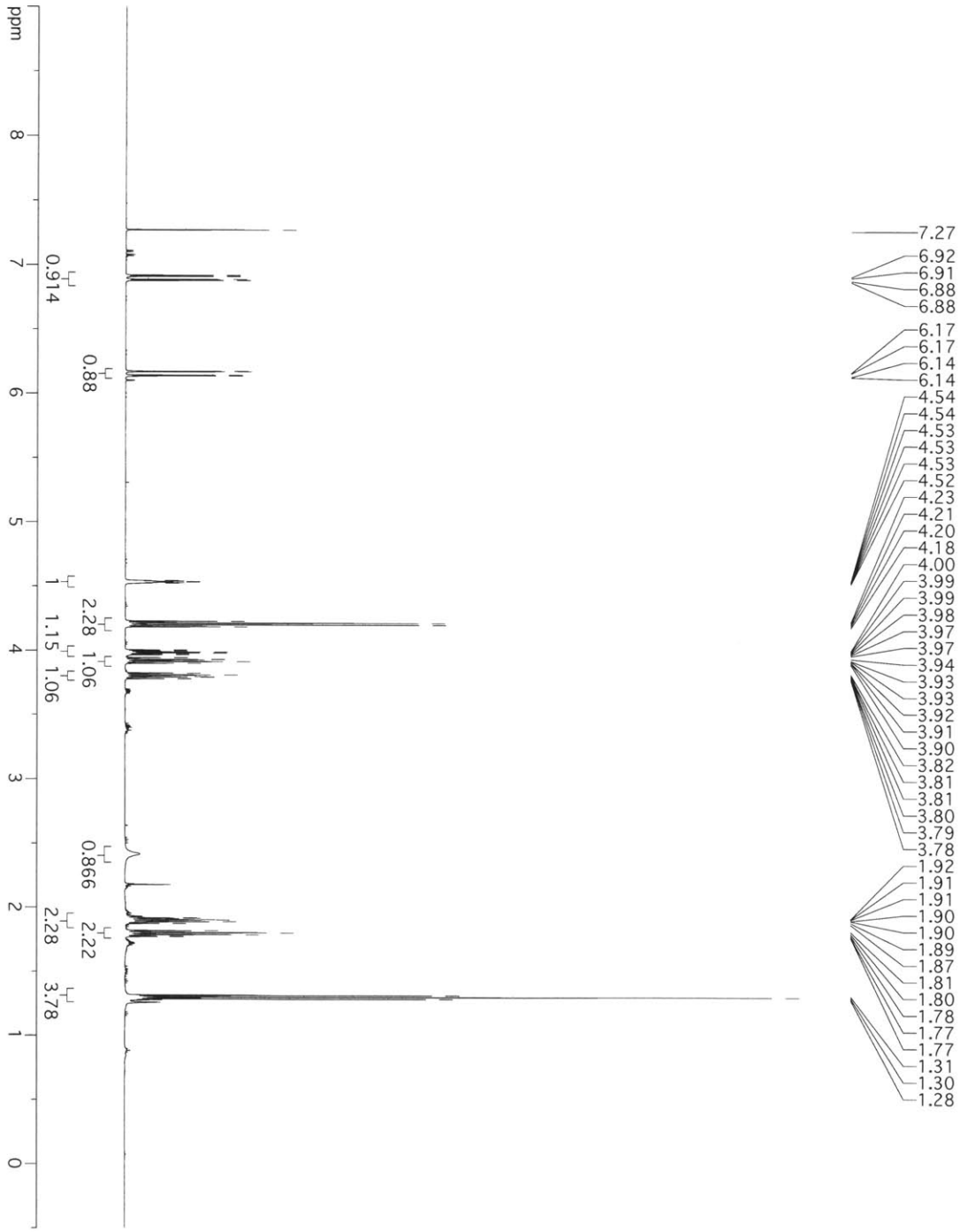
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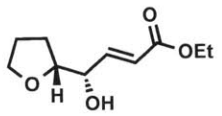
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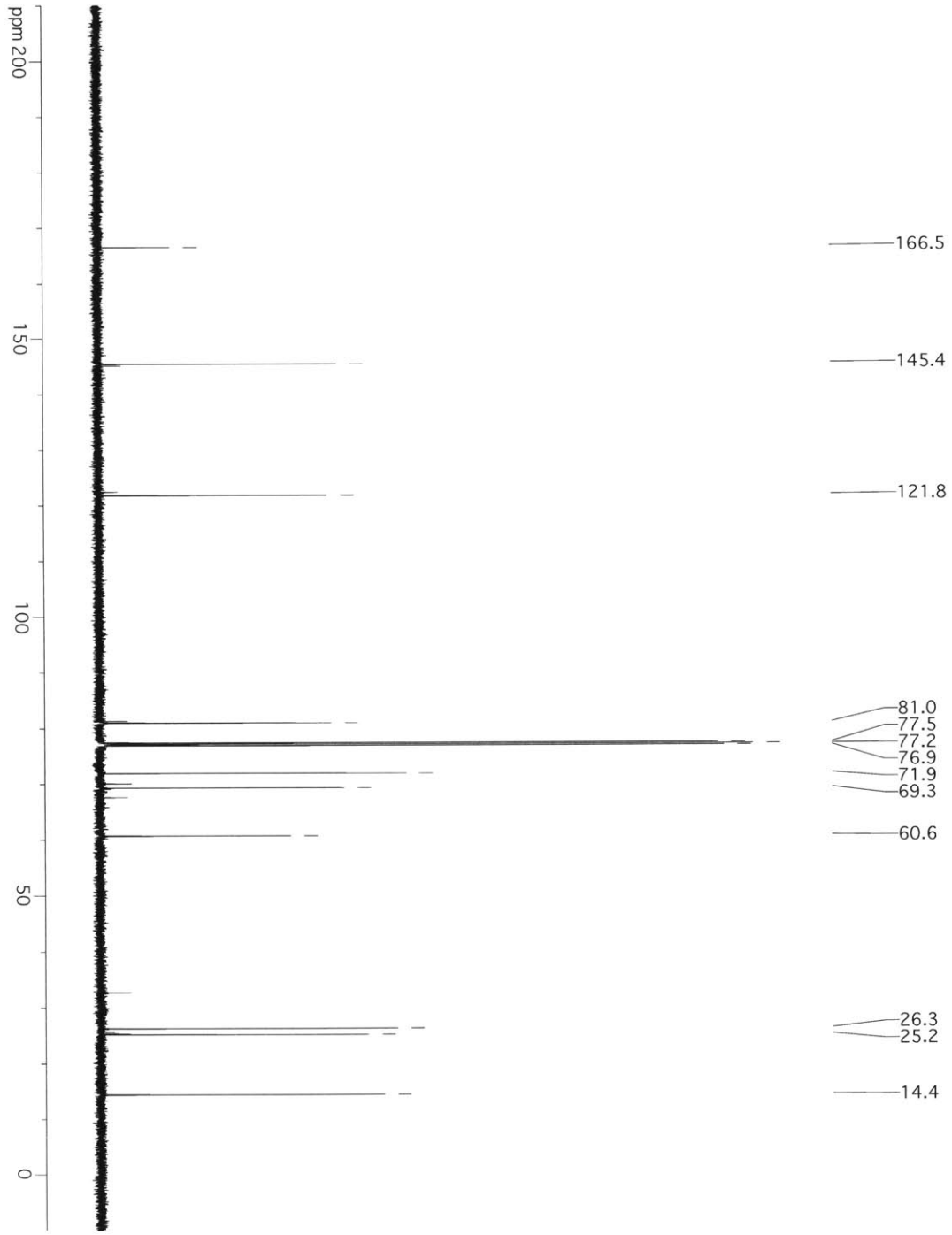
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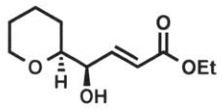
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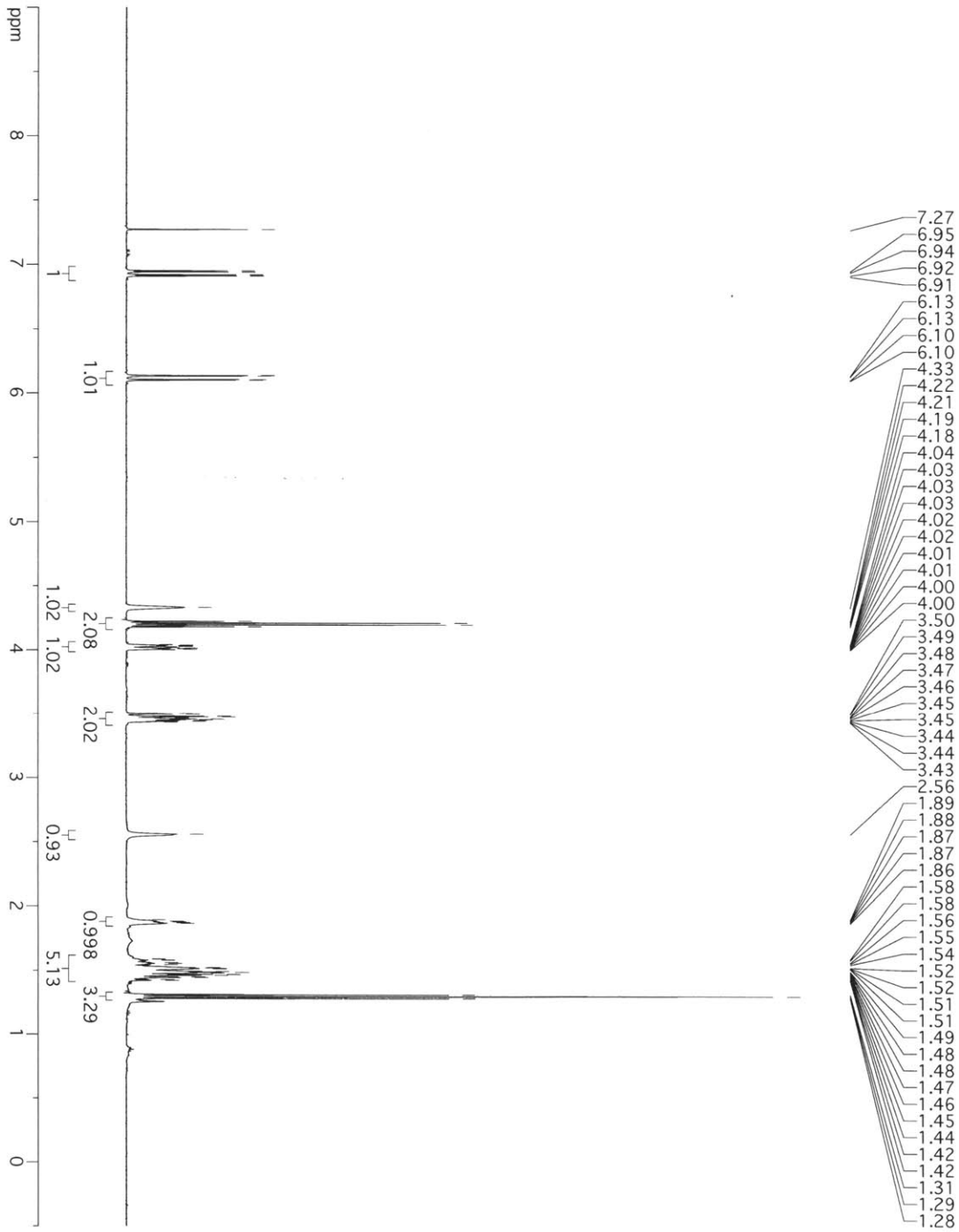
OH

94b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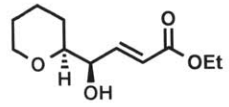
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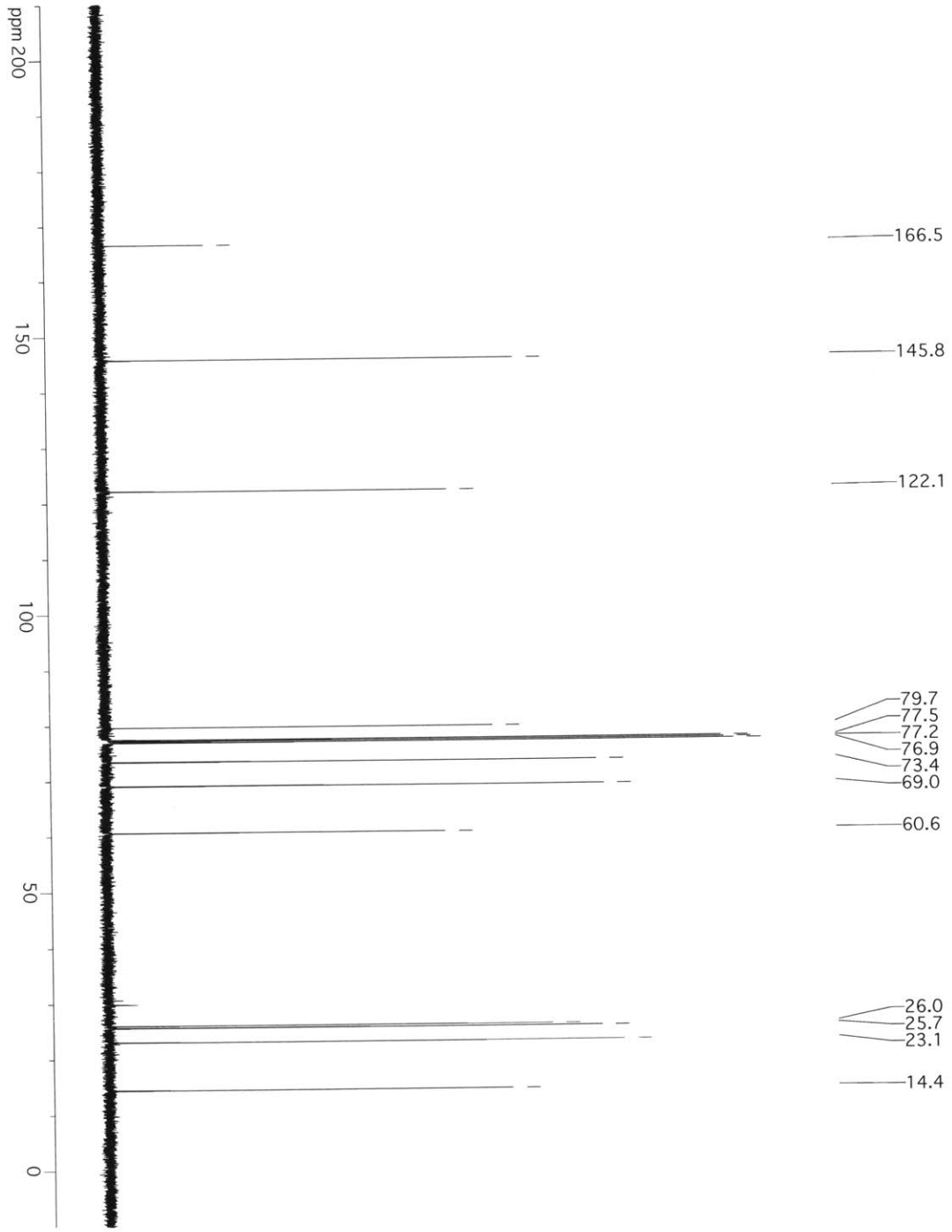
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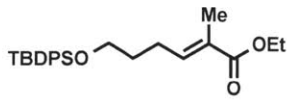
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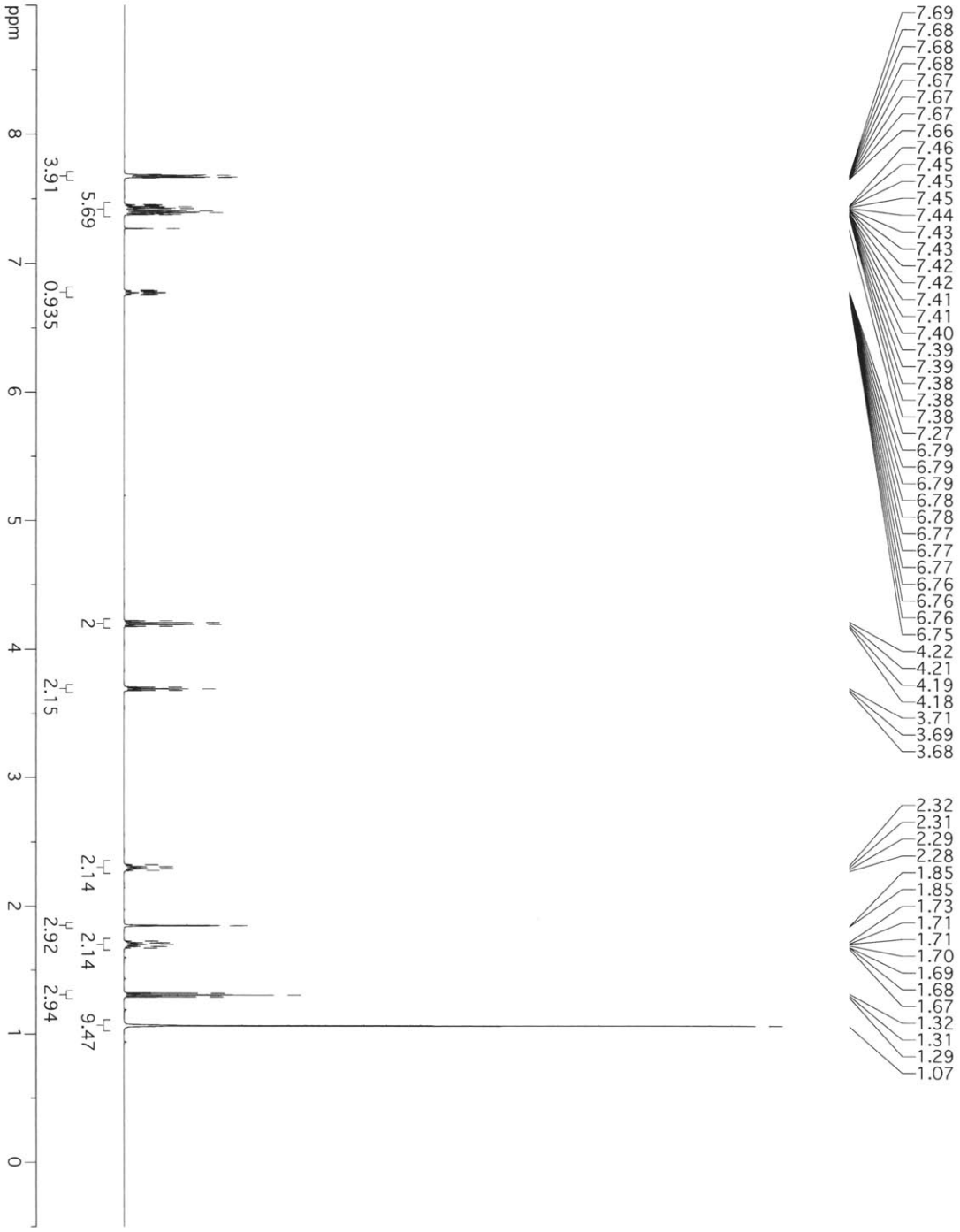
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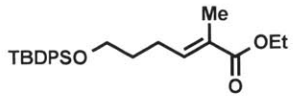
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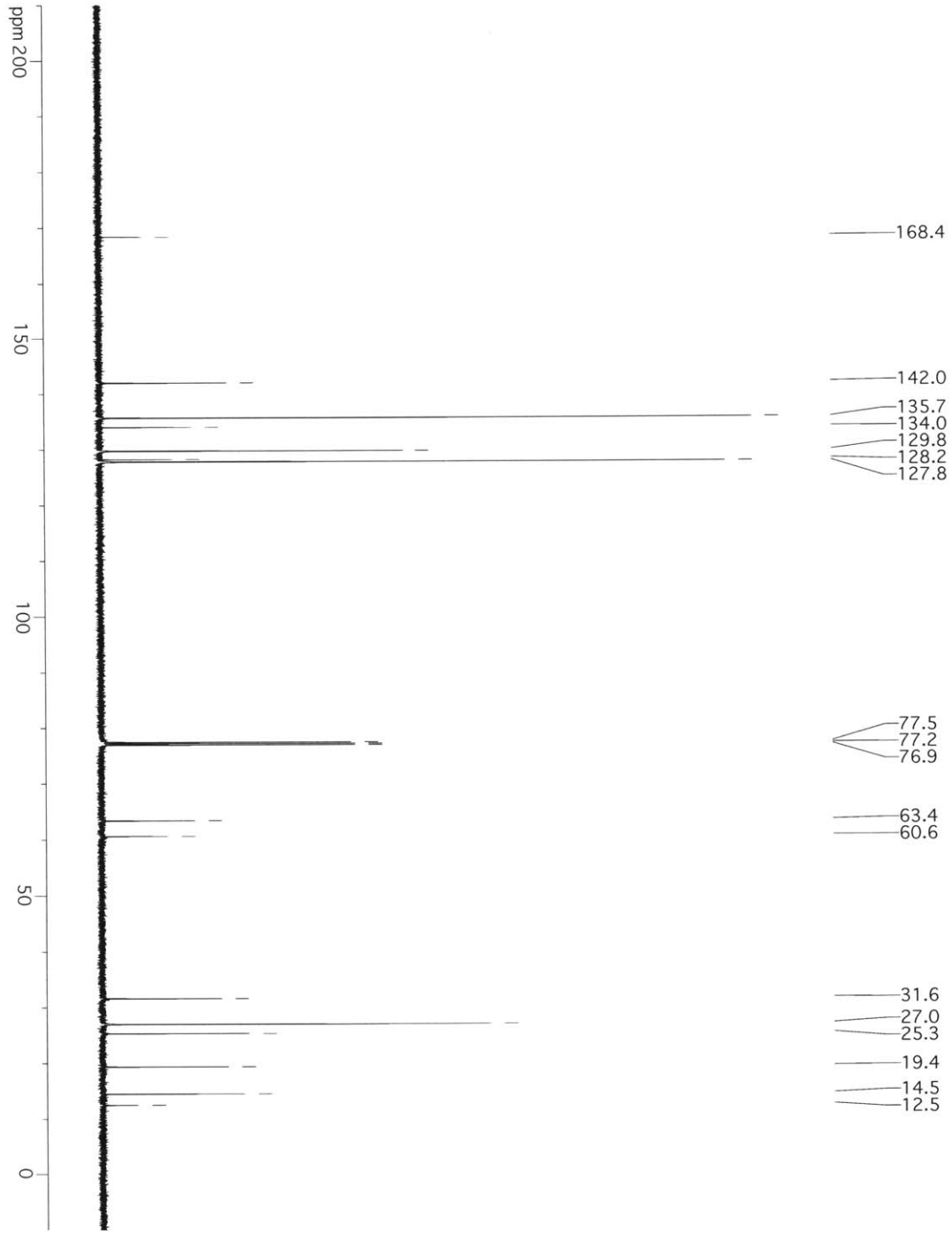
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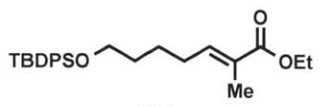
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Me

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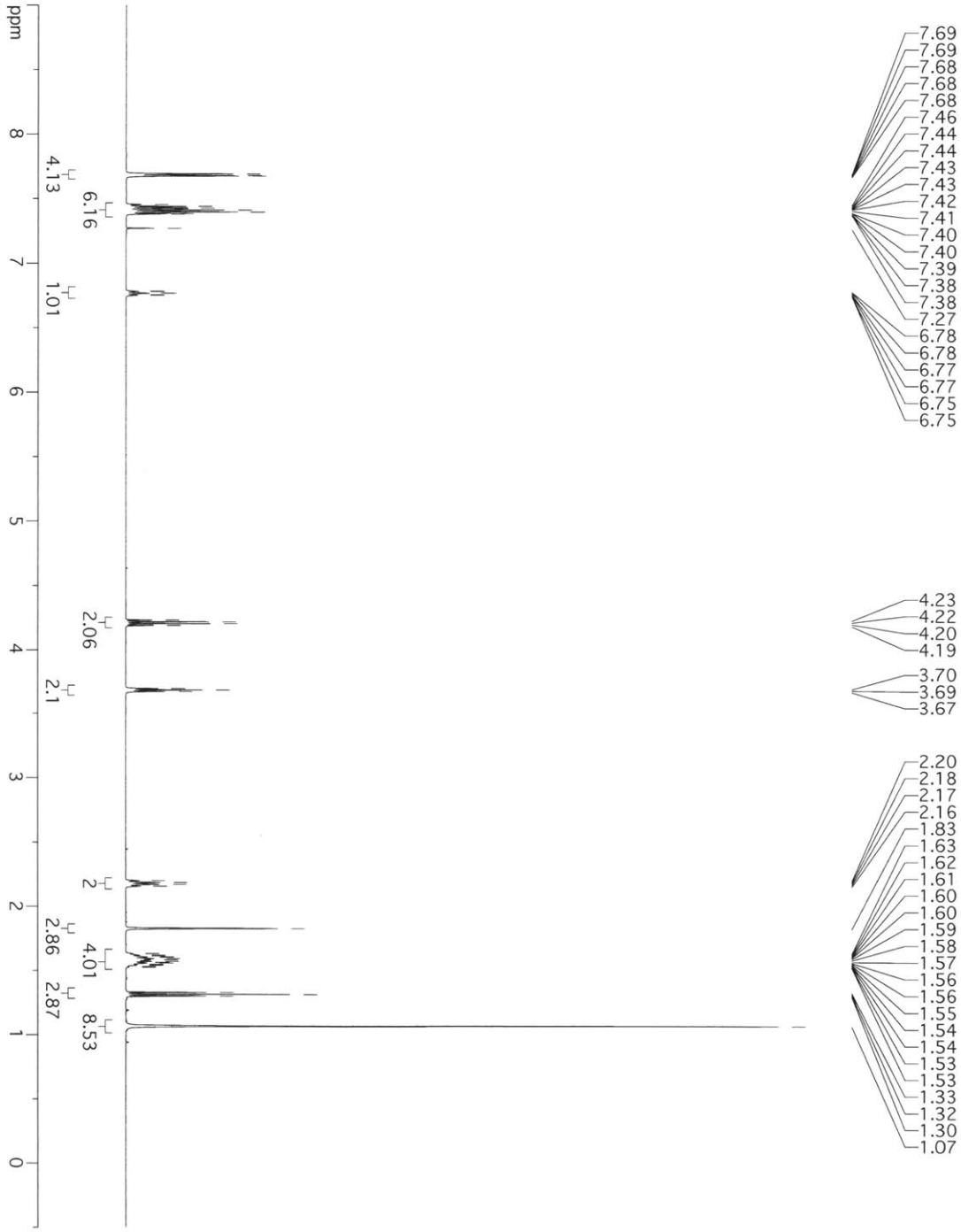
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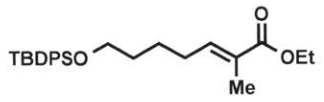
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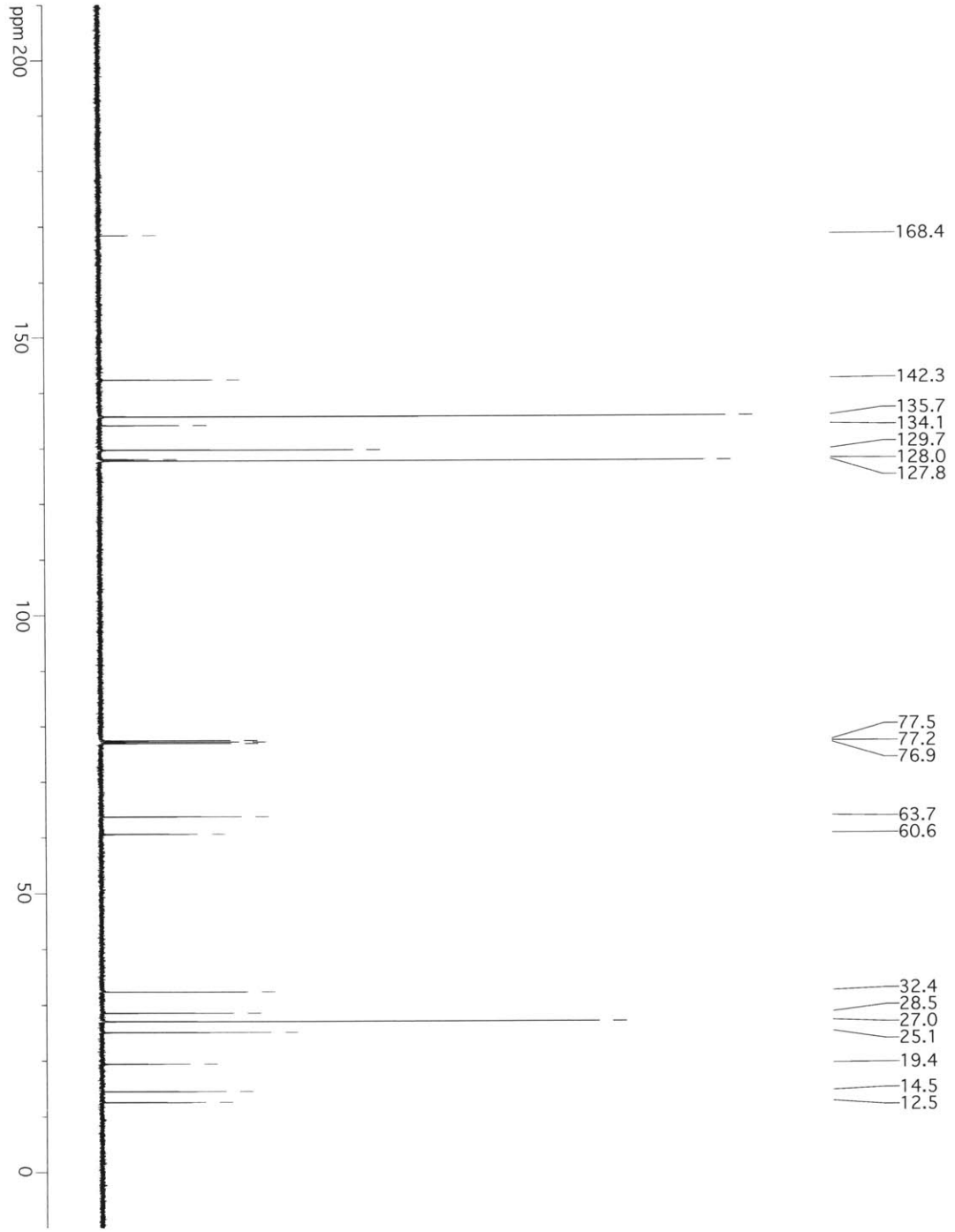
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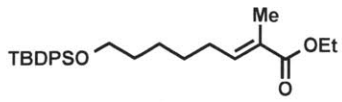
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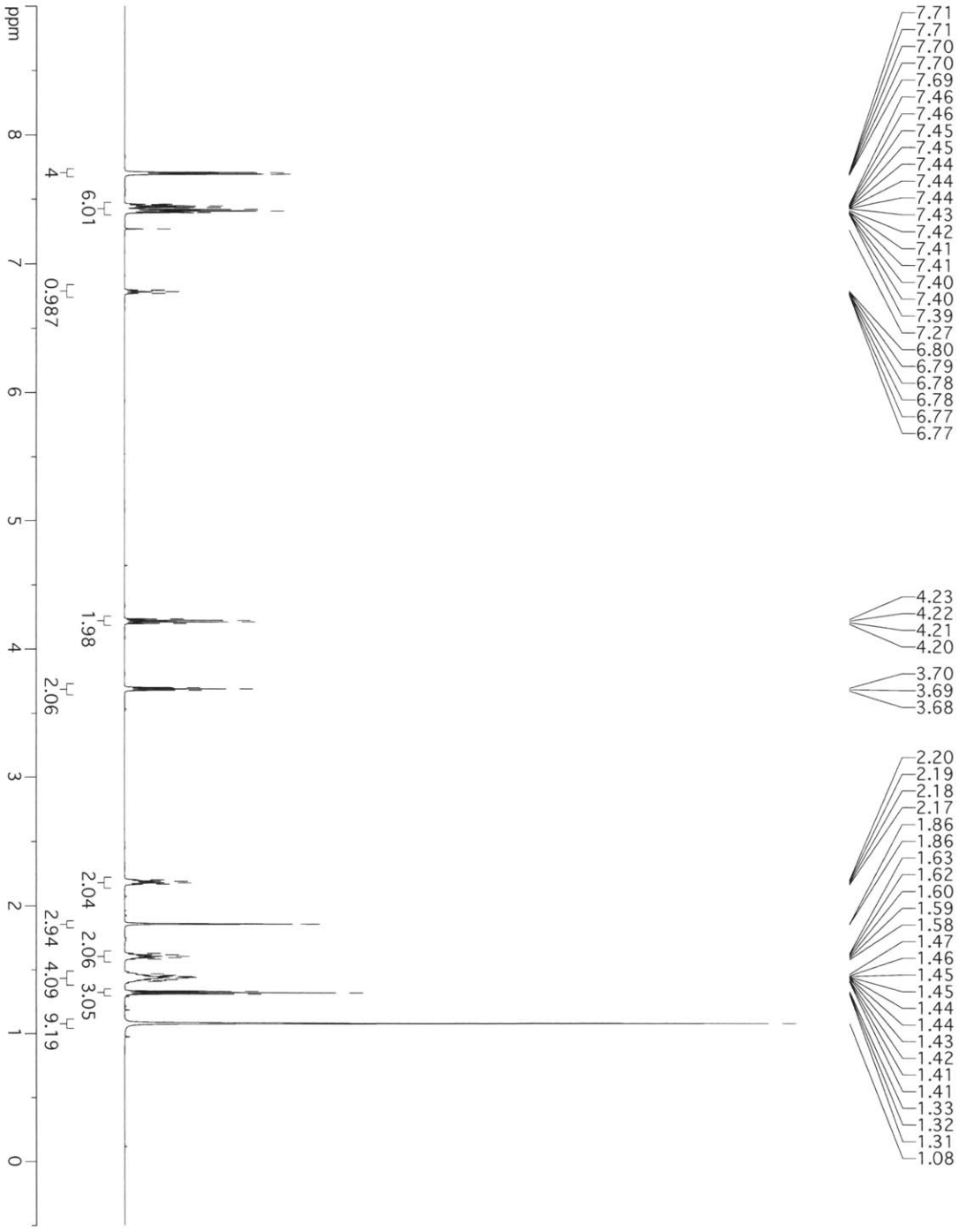
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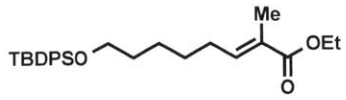
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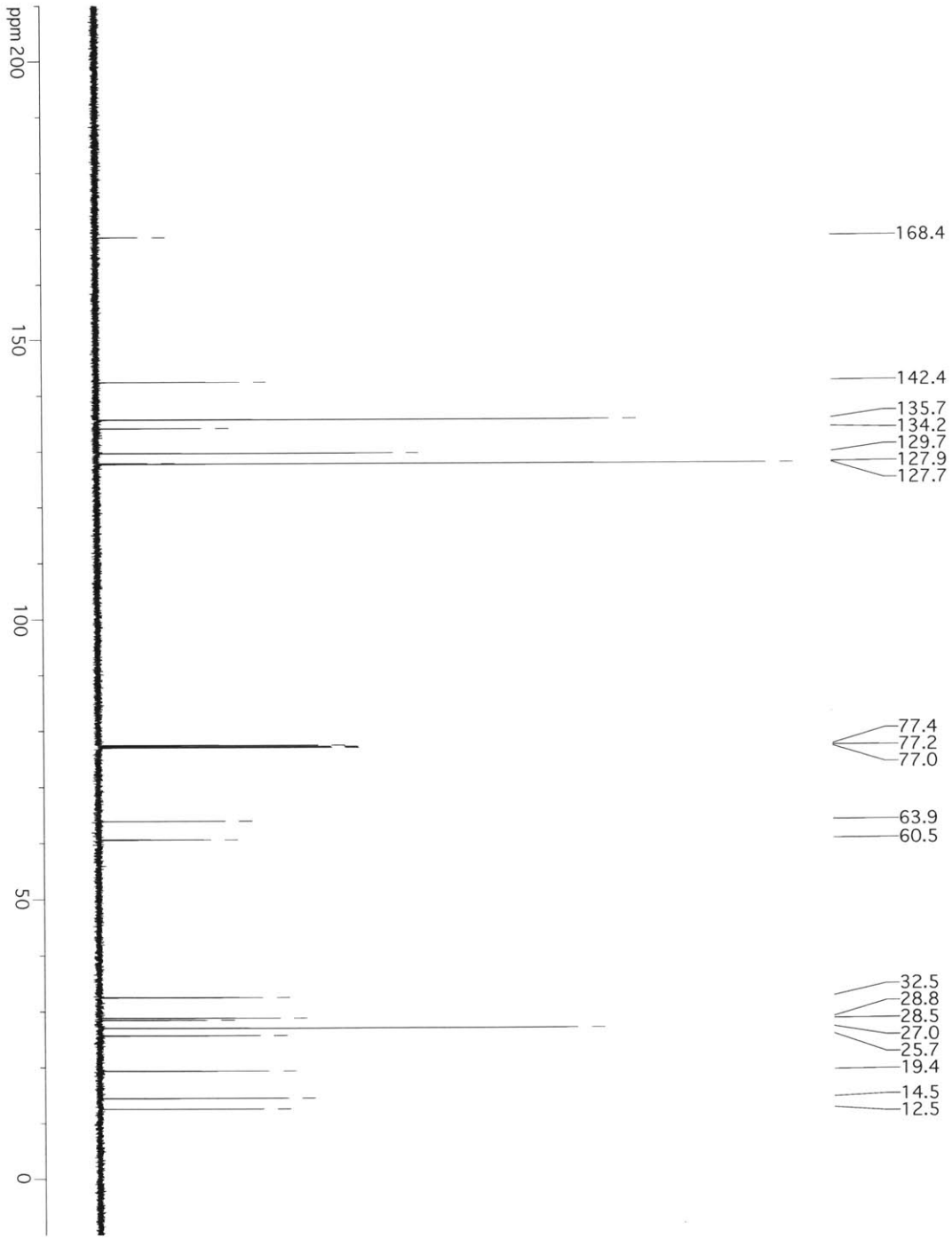
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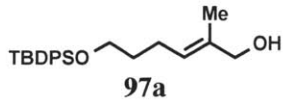
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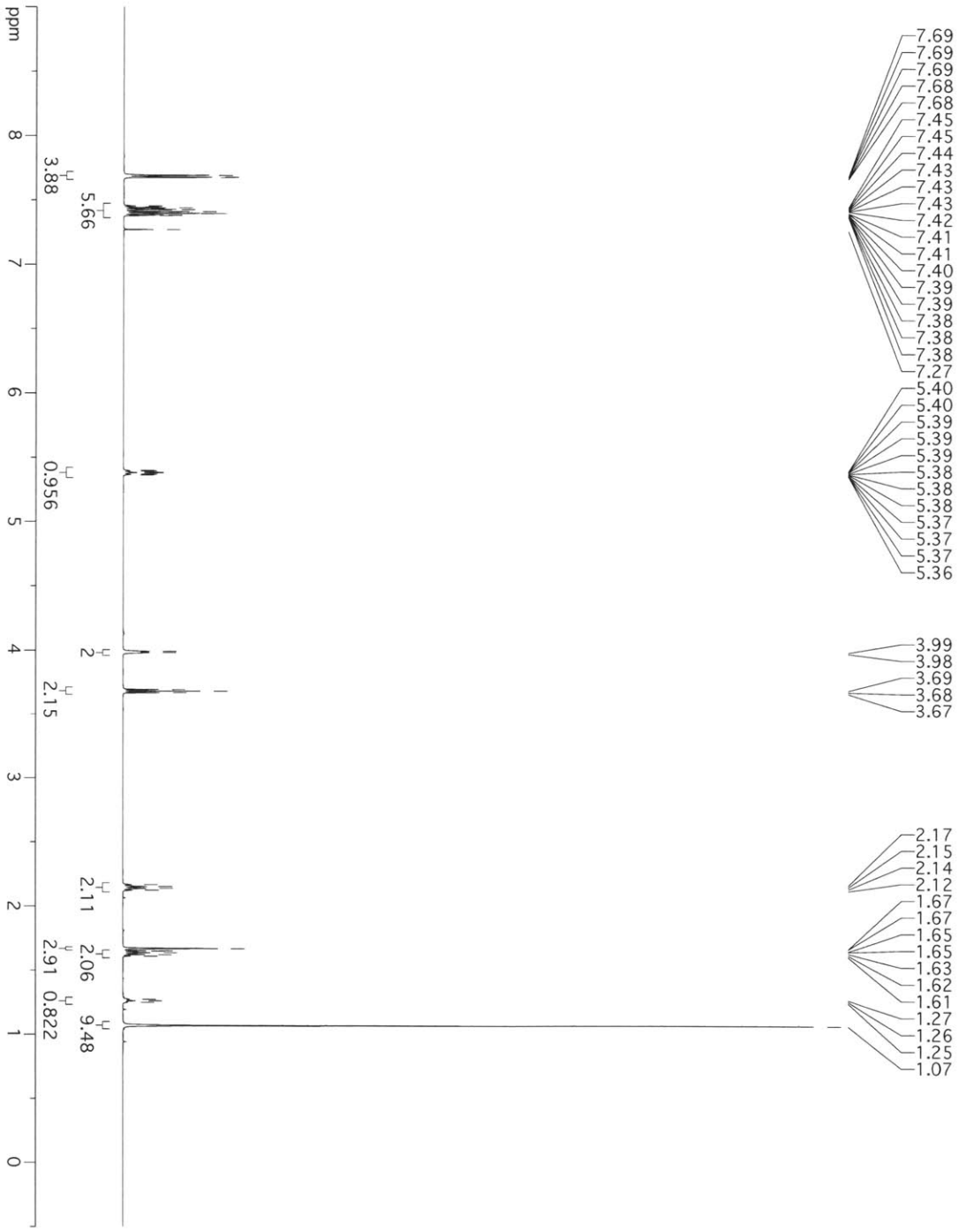
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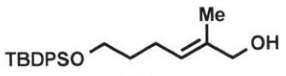
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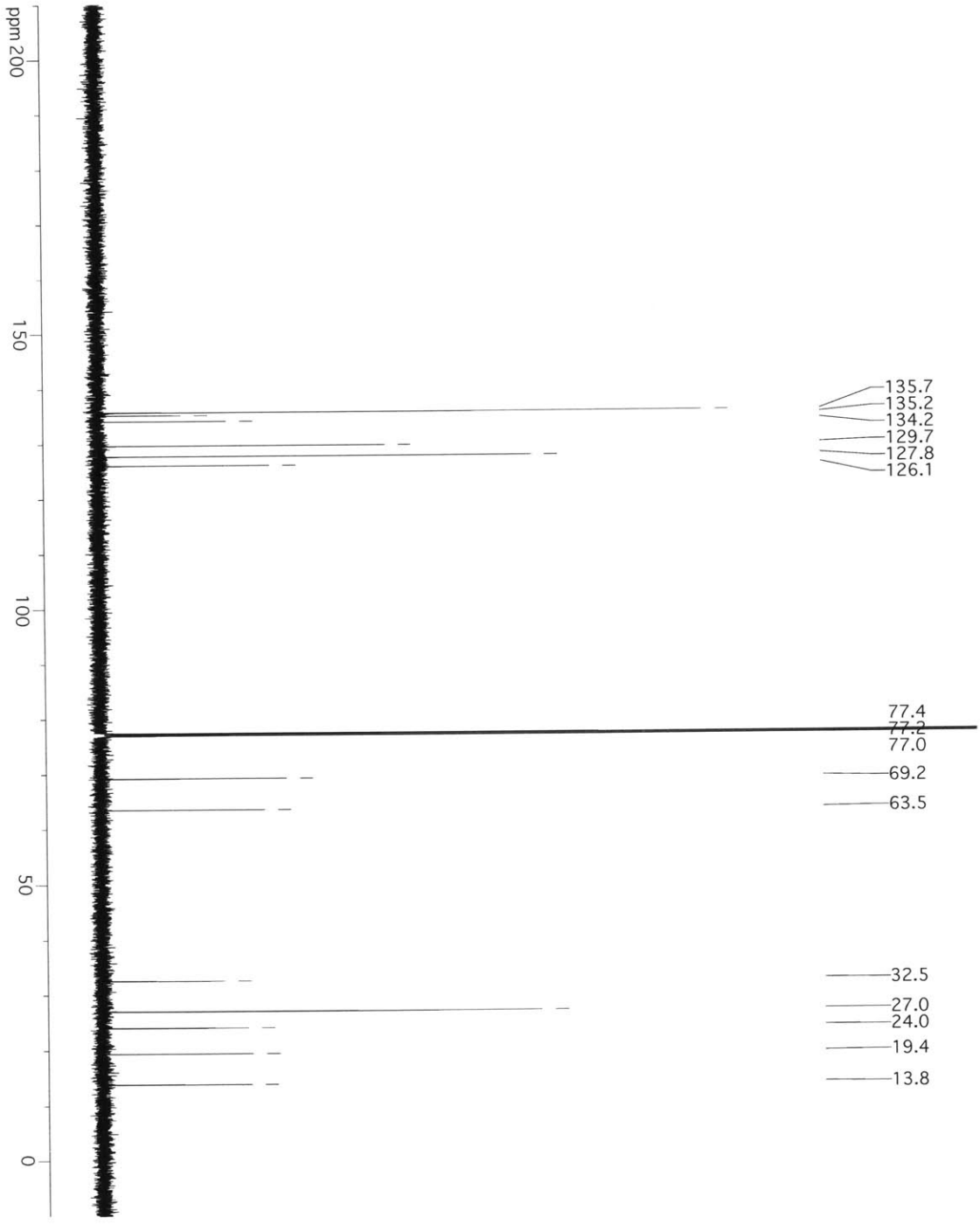
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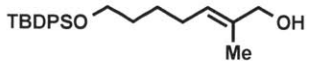
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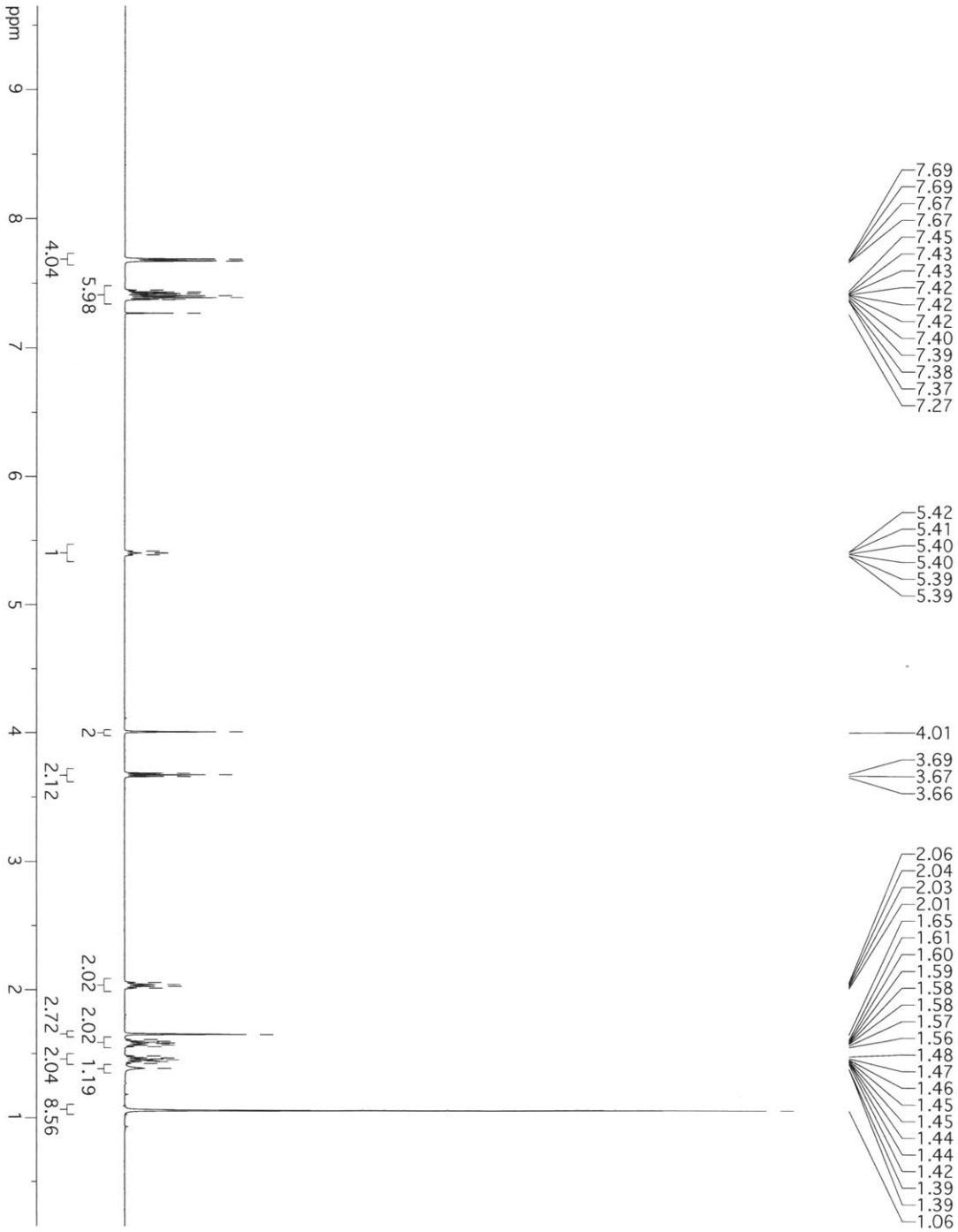
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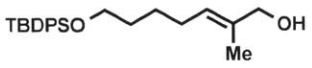
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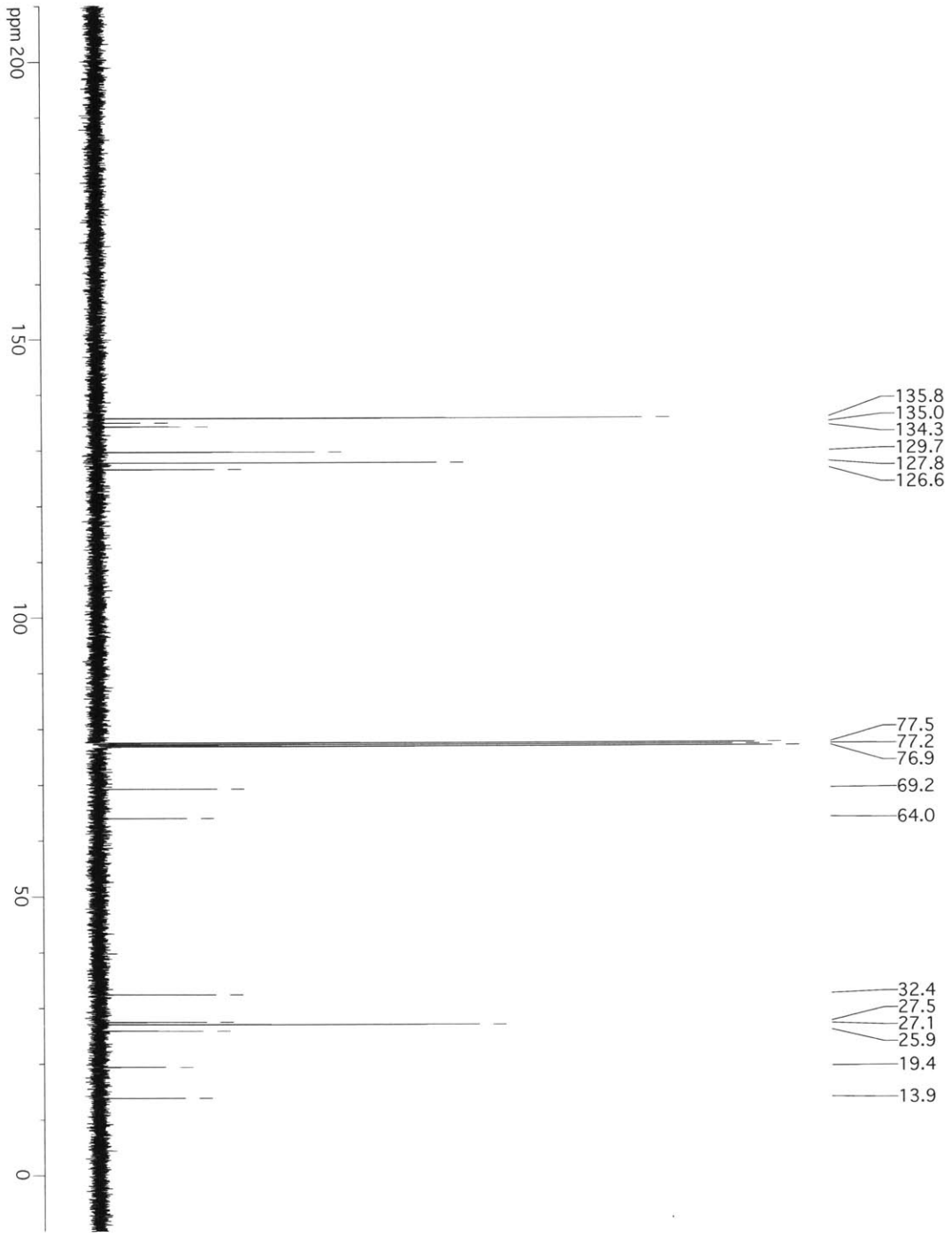
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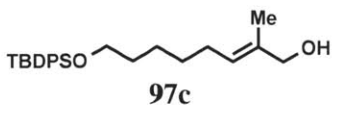
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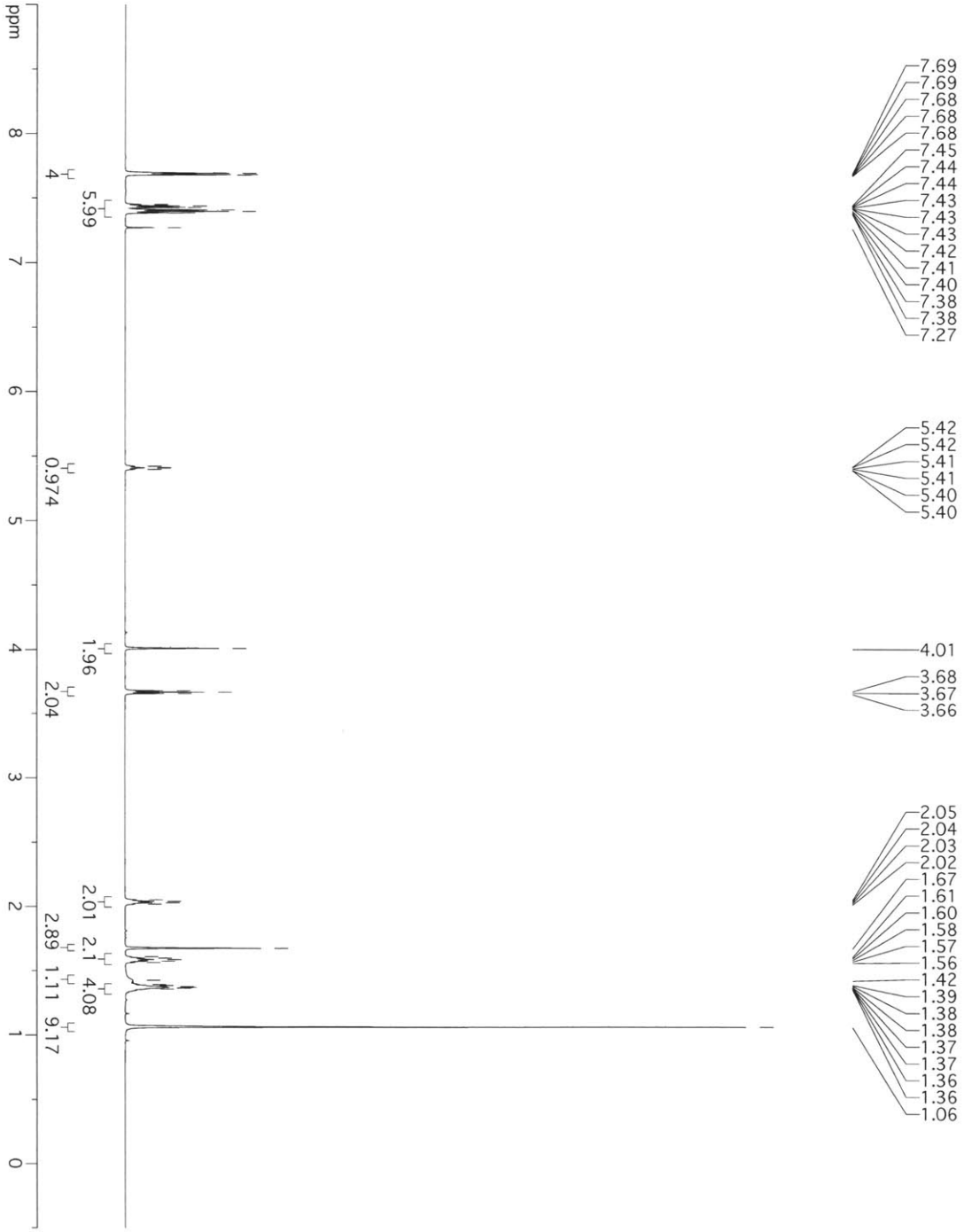
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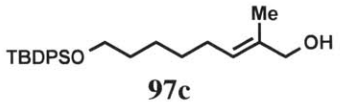
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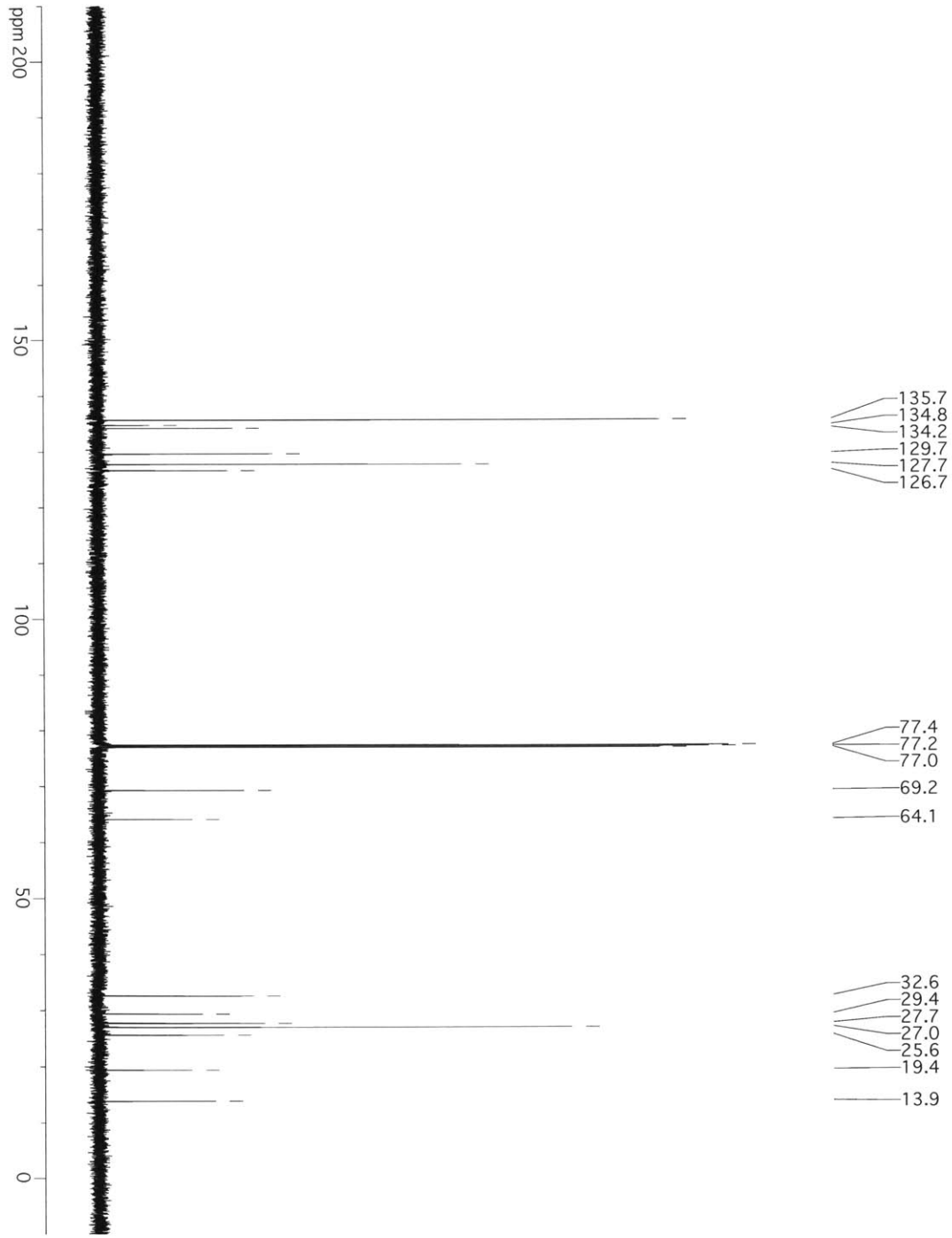
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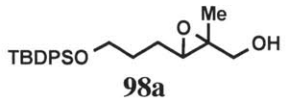
13.9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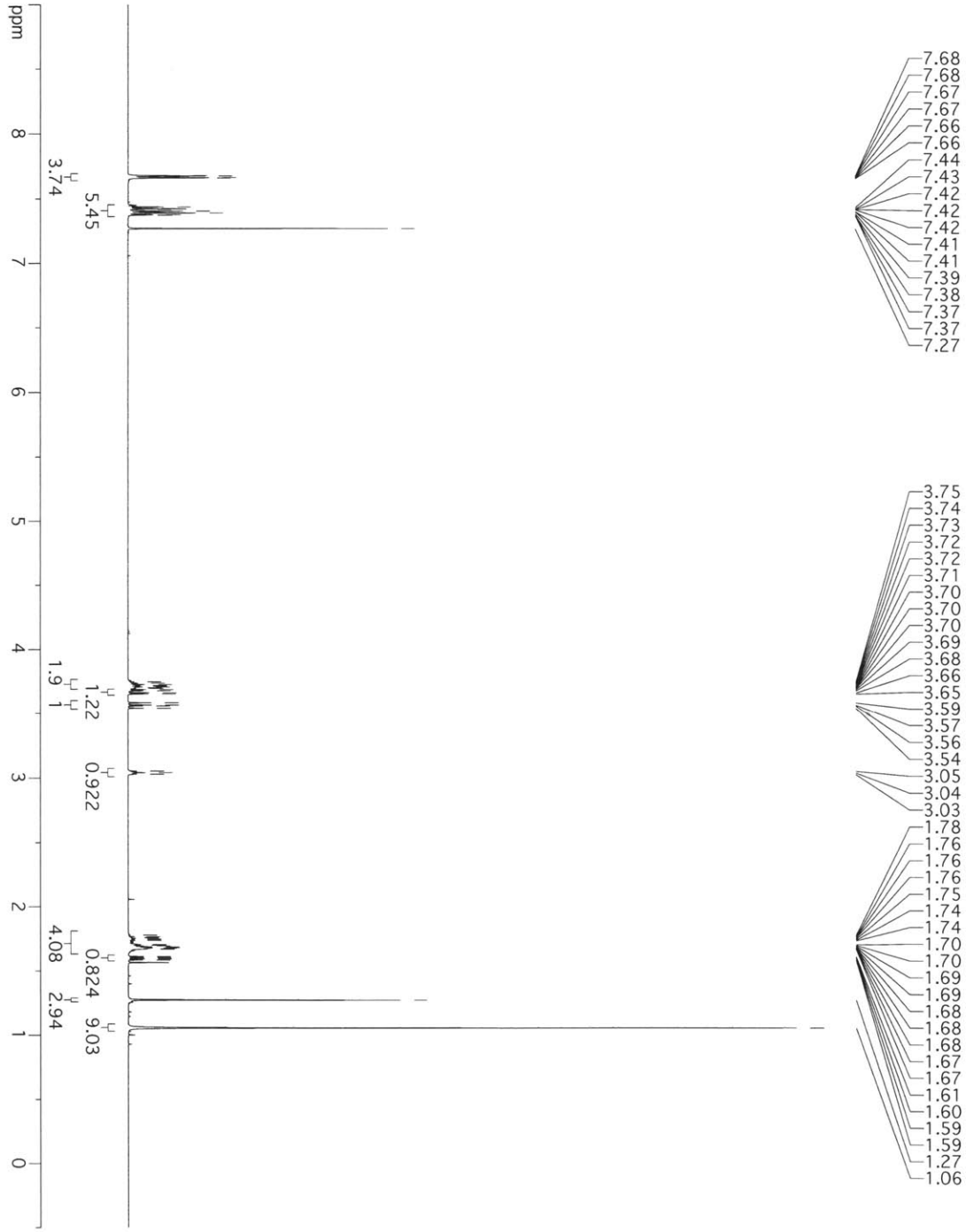
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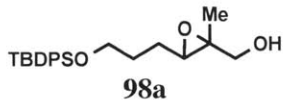
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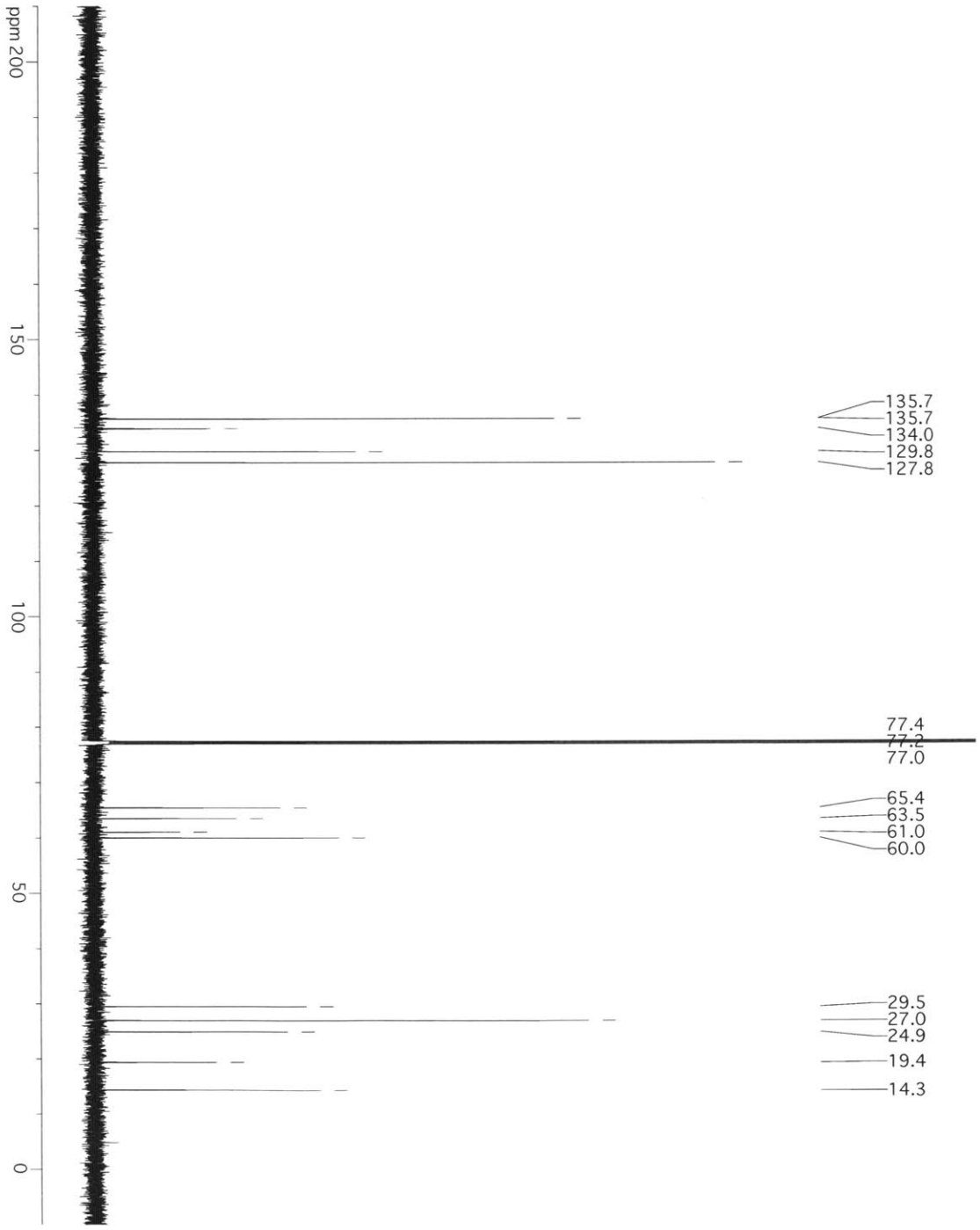
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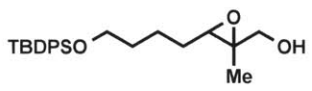
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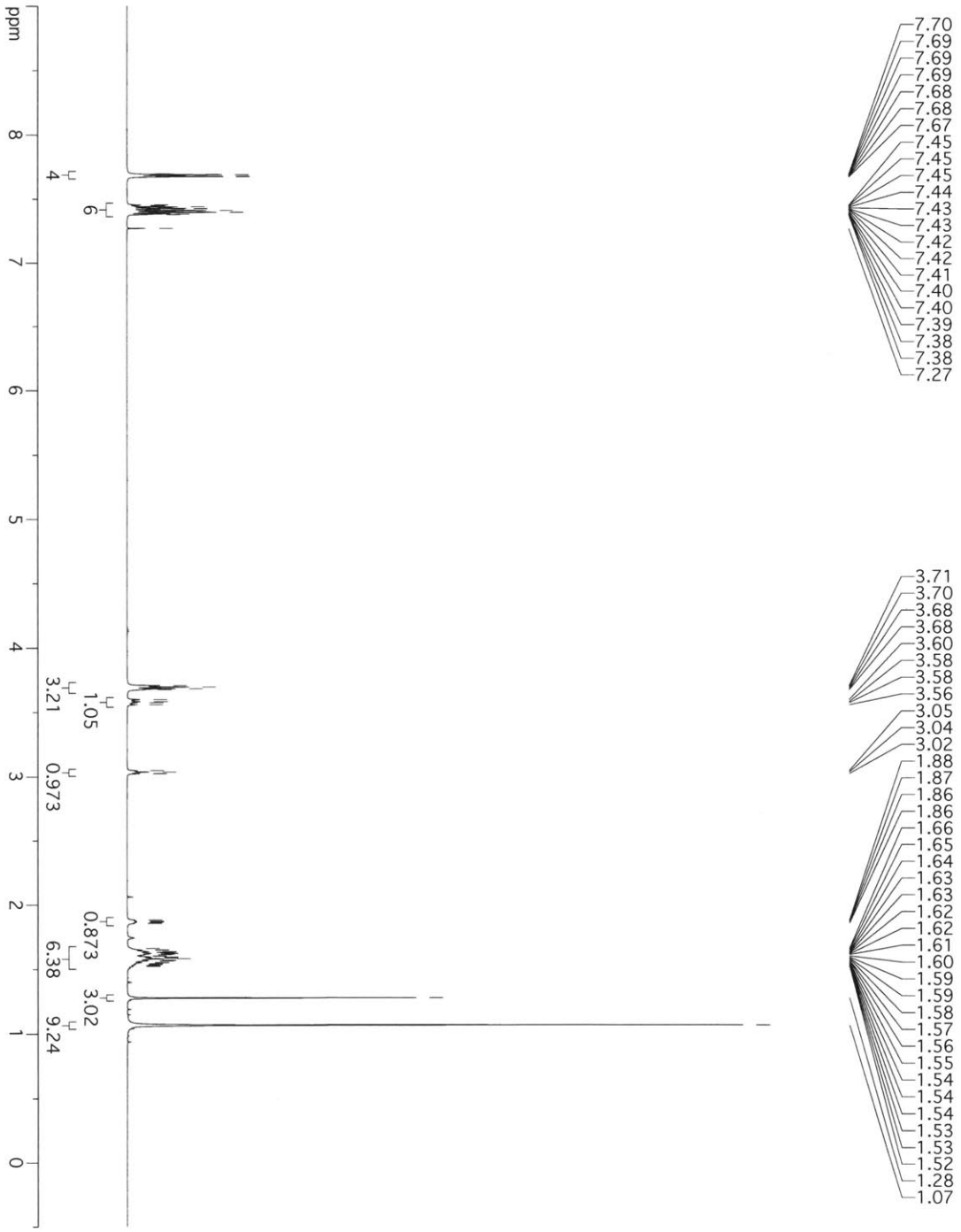
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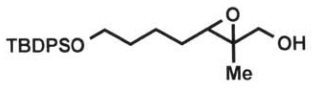
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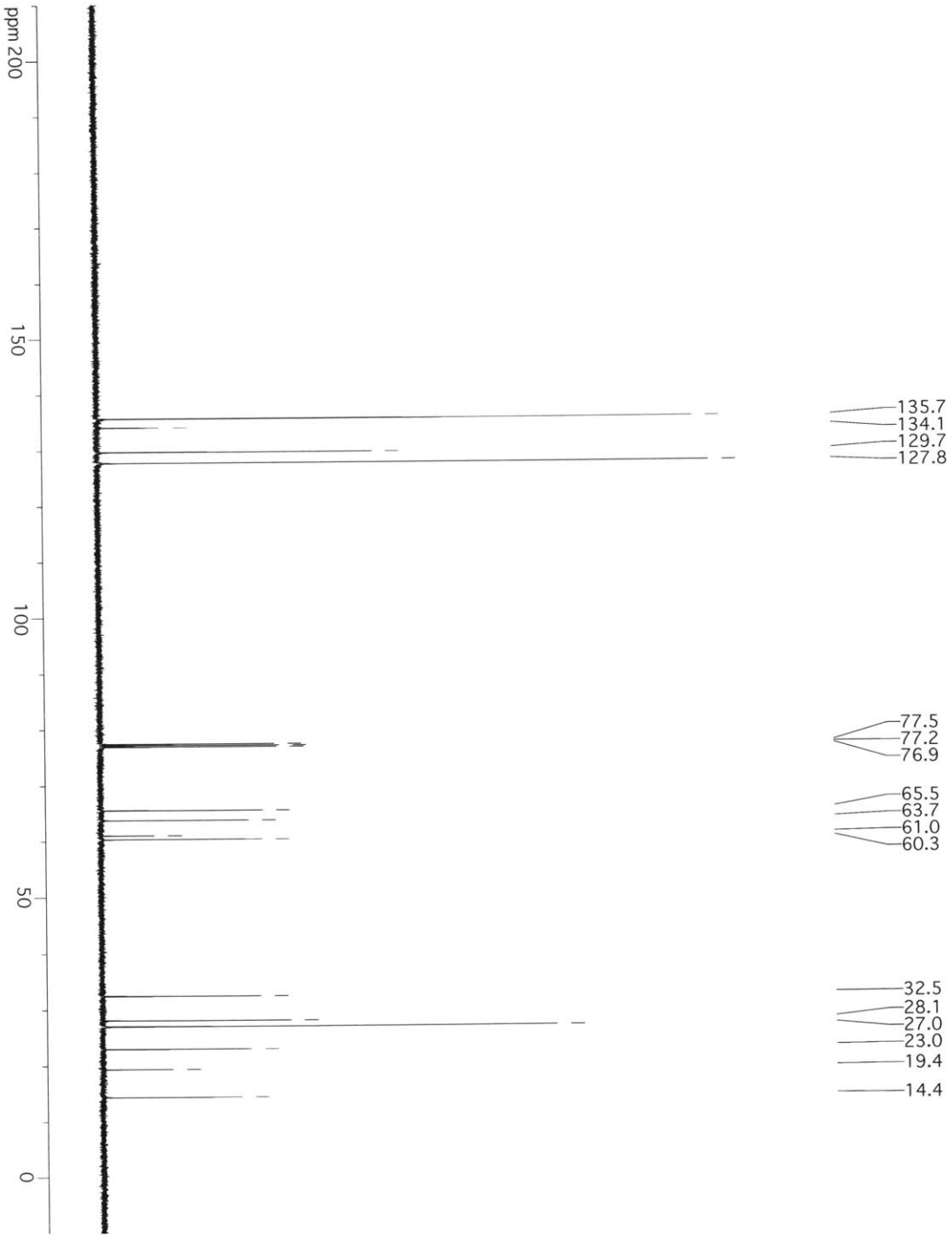
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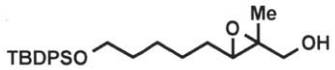
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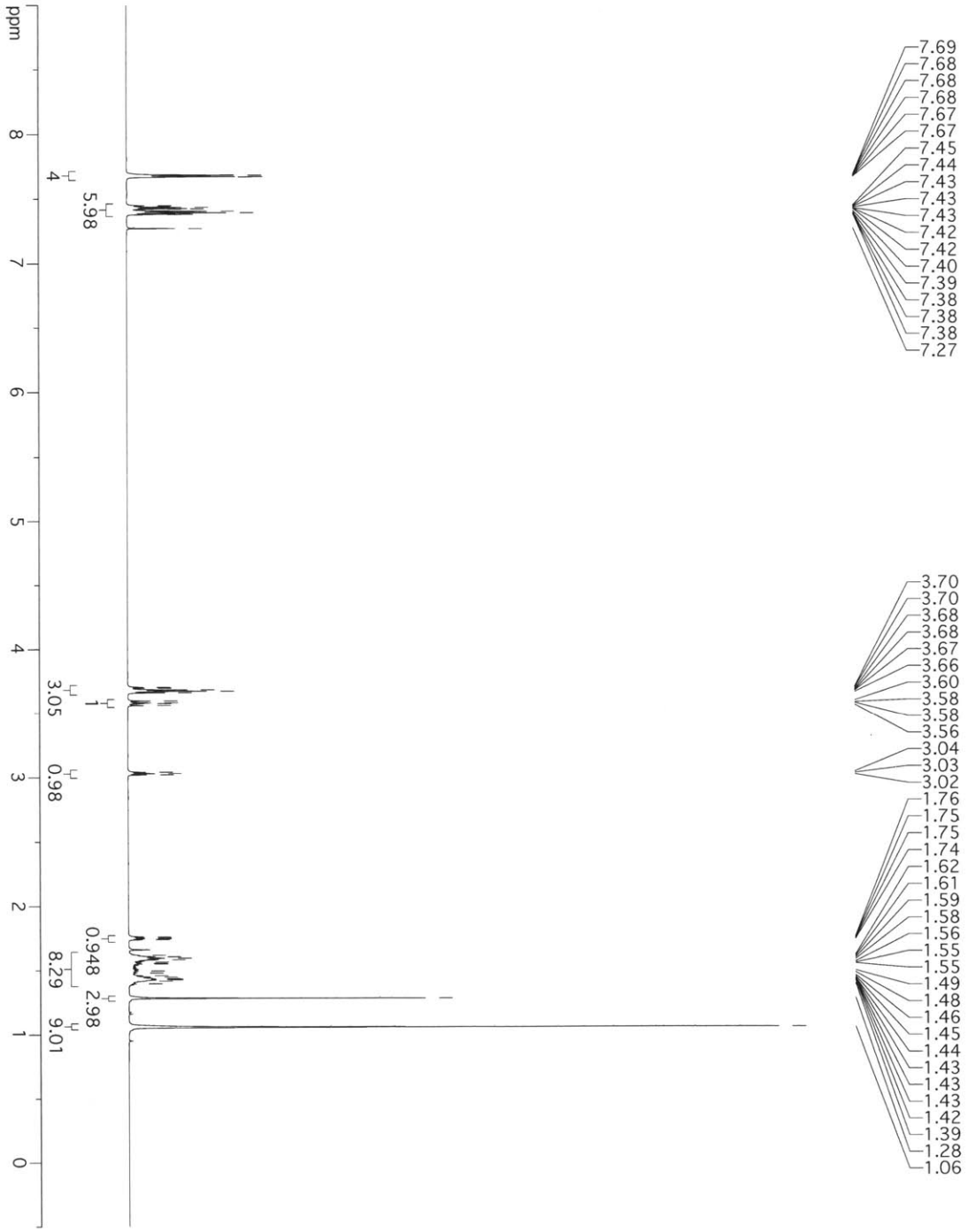
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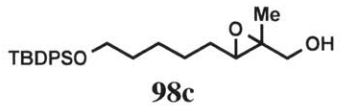
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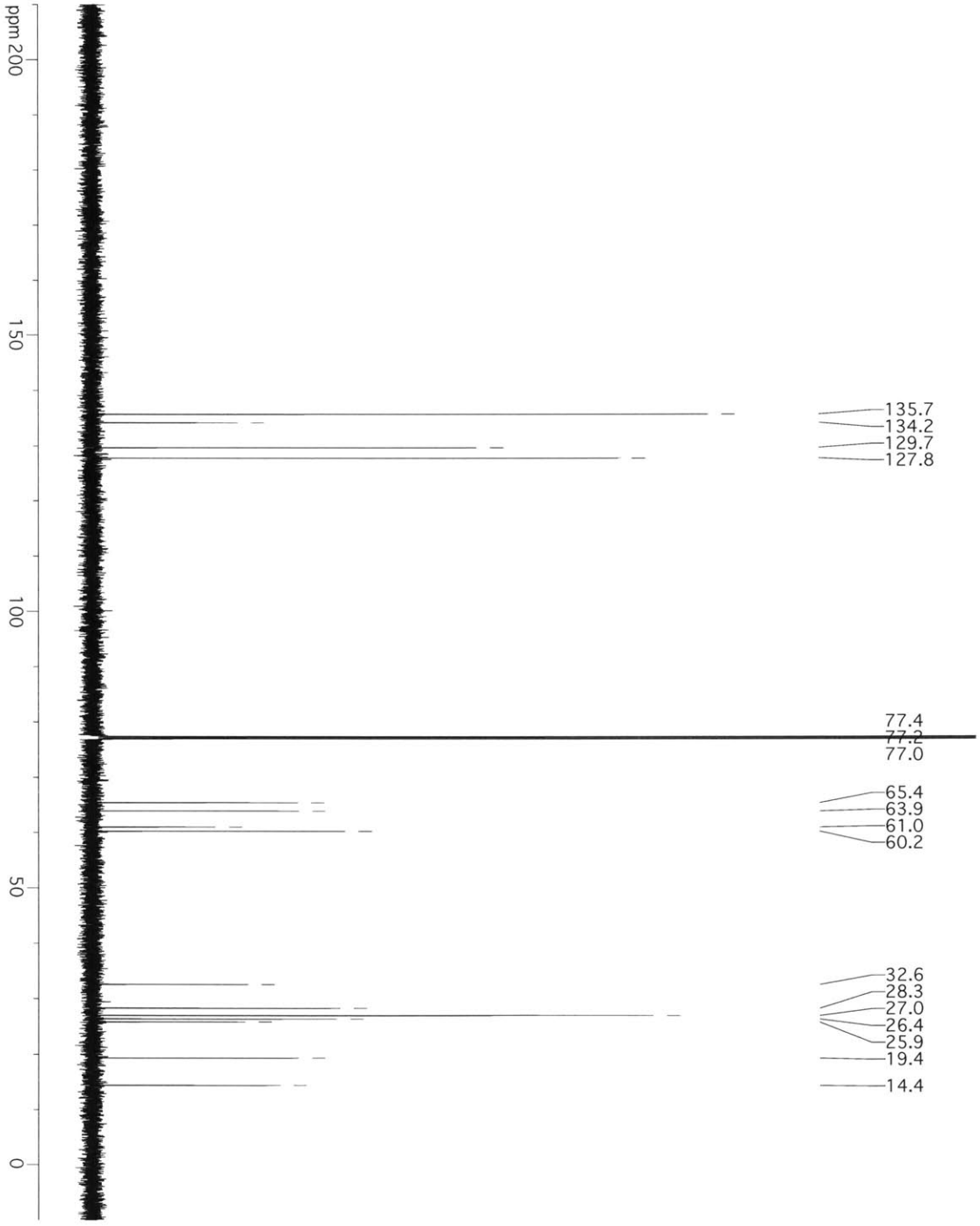
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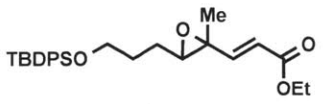
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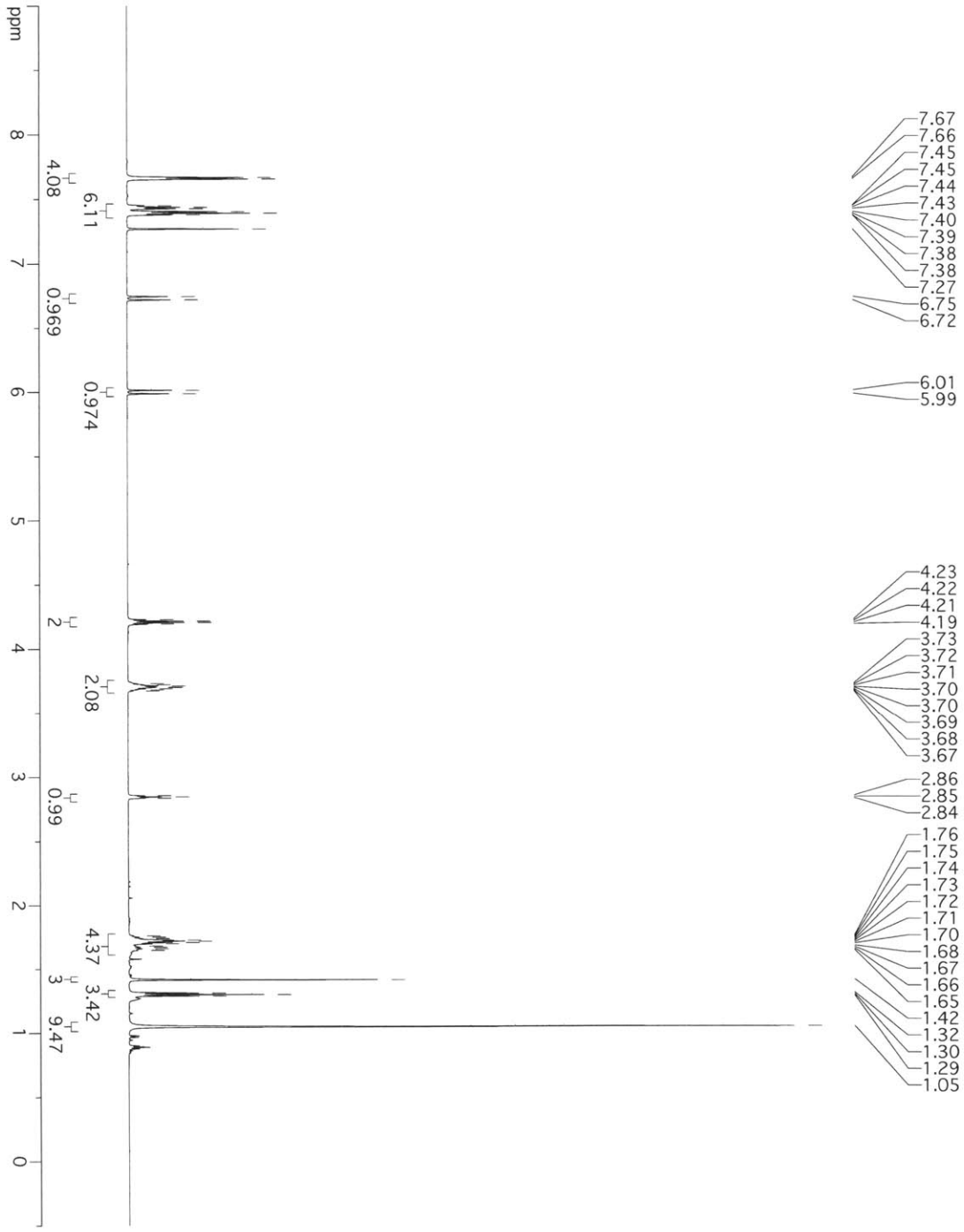
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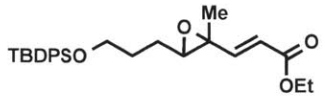
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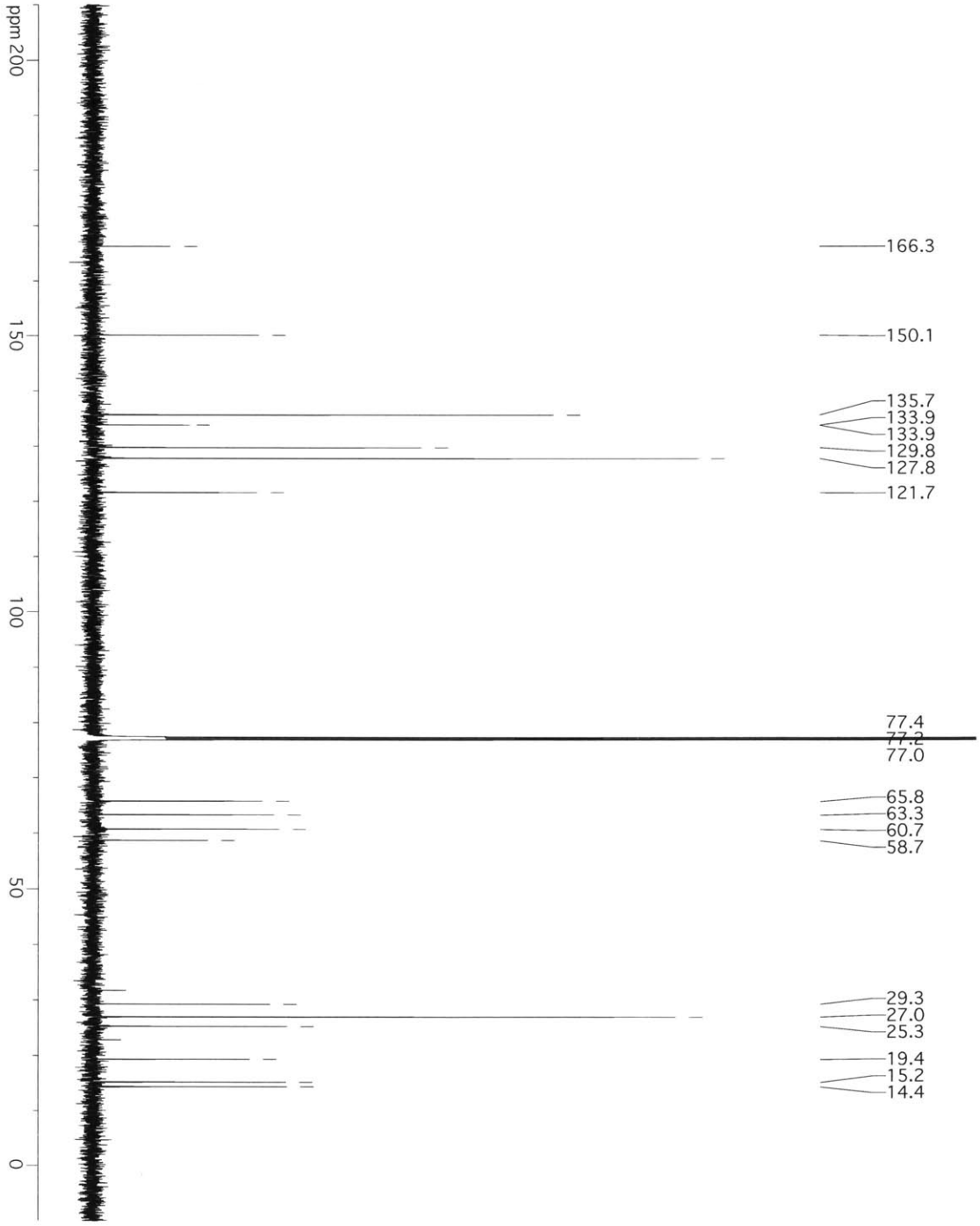
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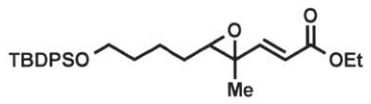
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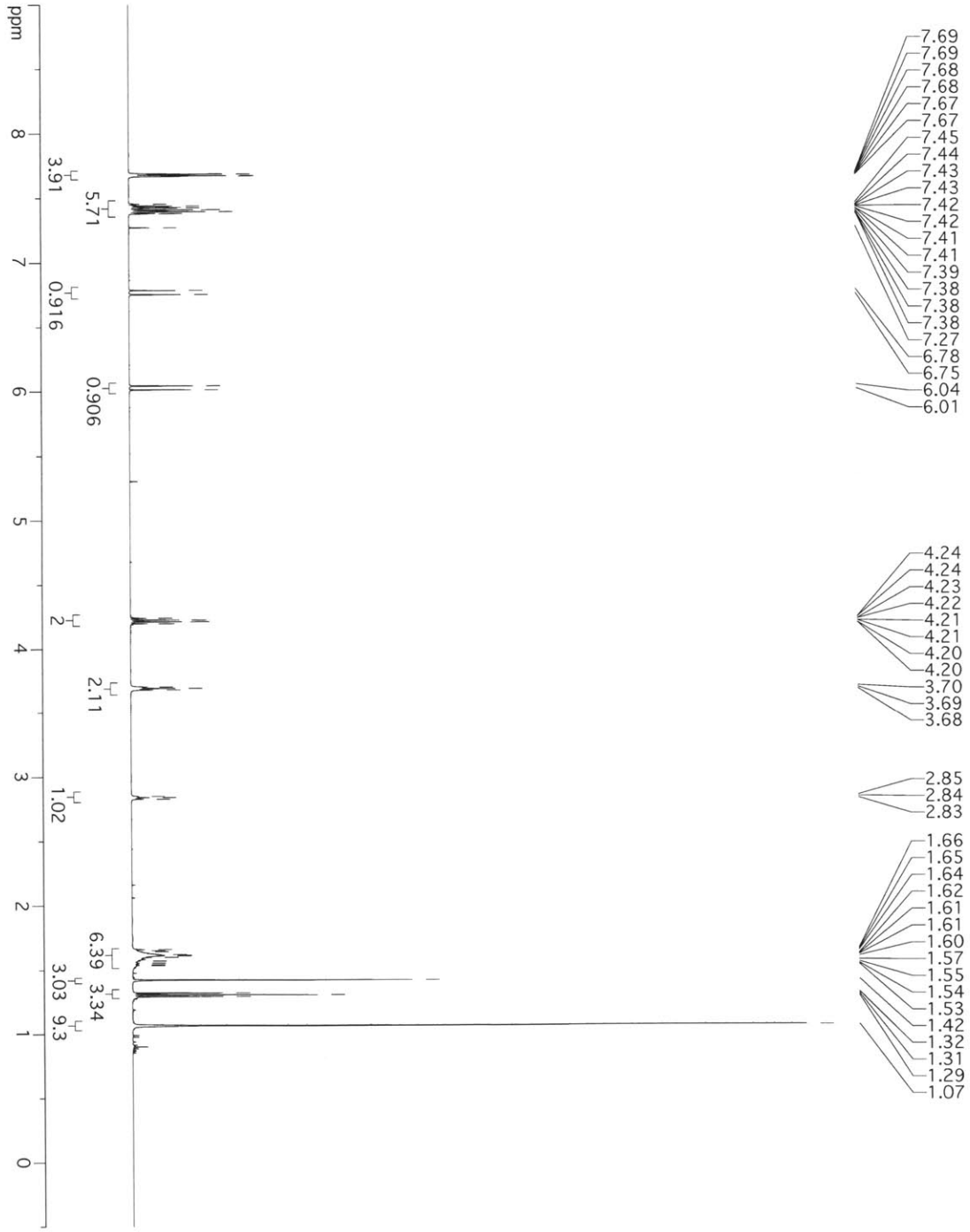
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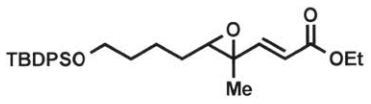
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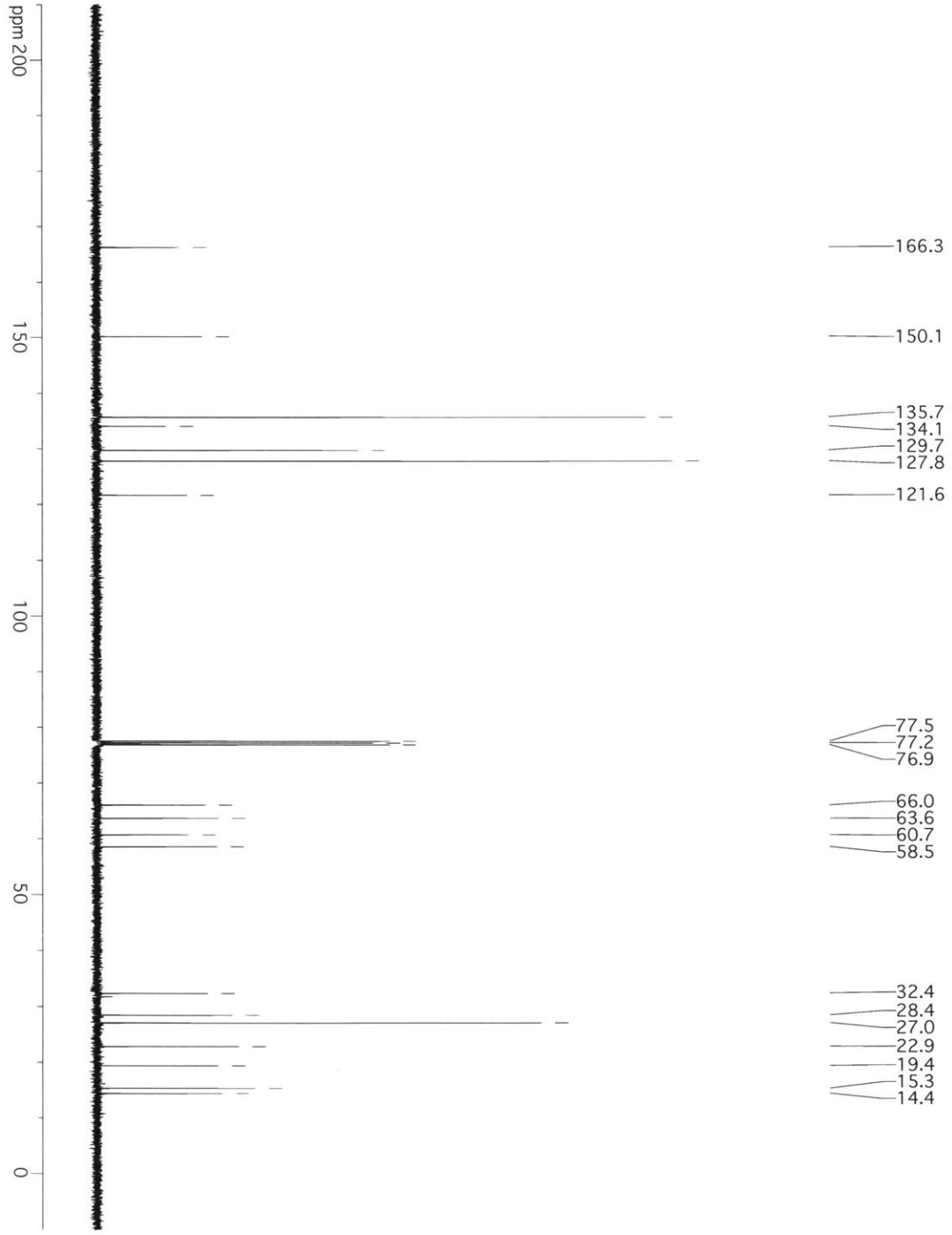
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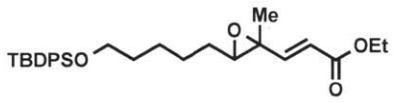
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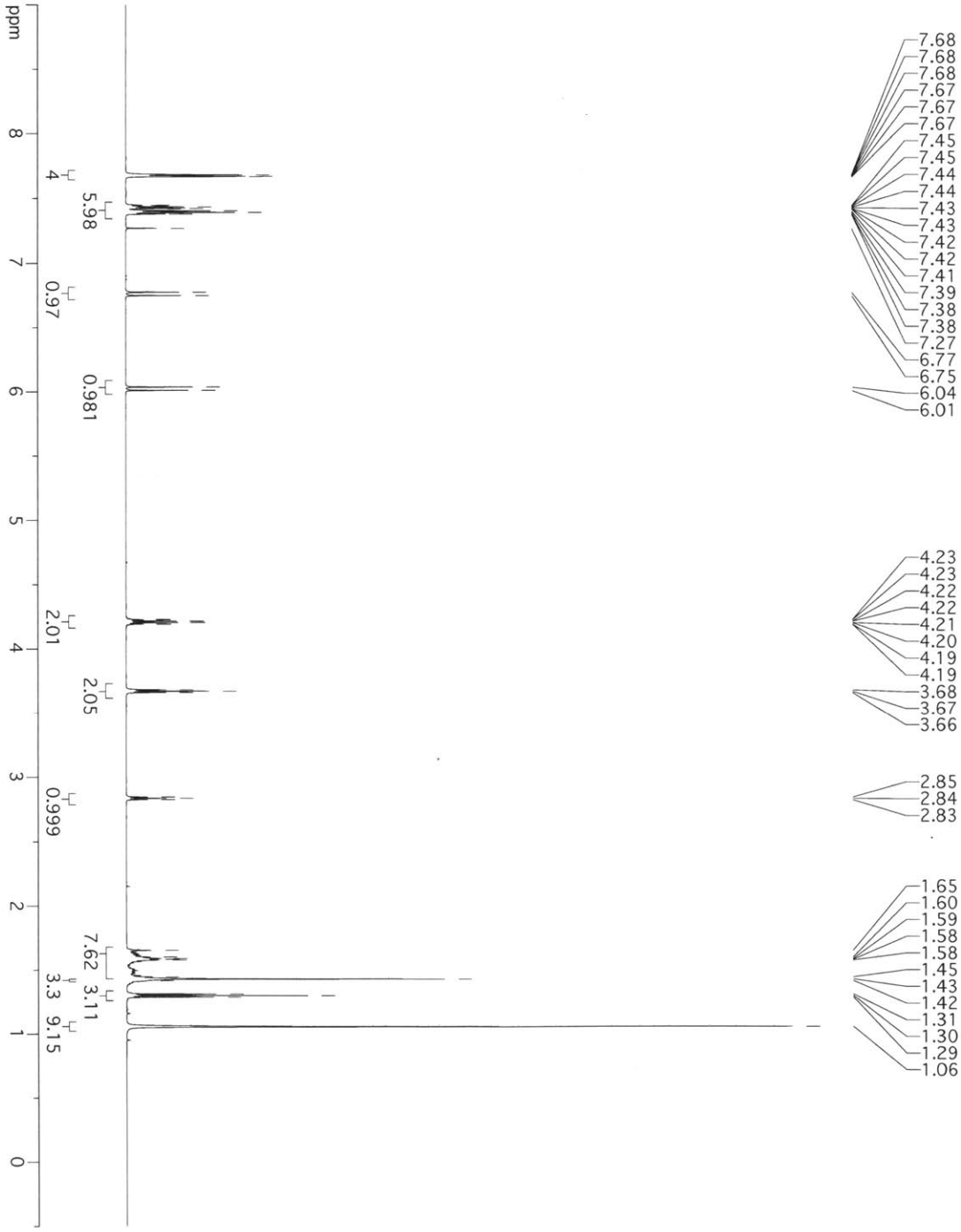
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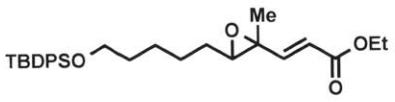
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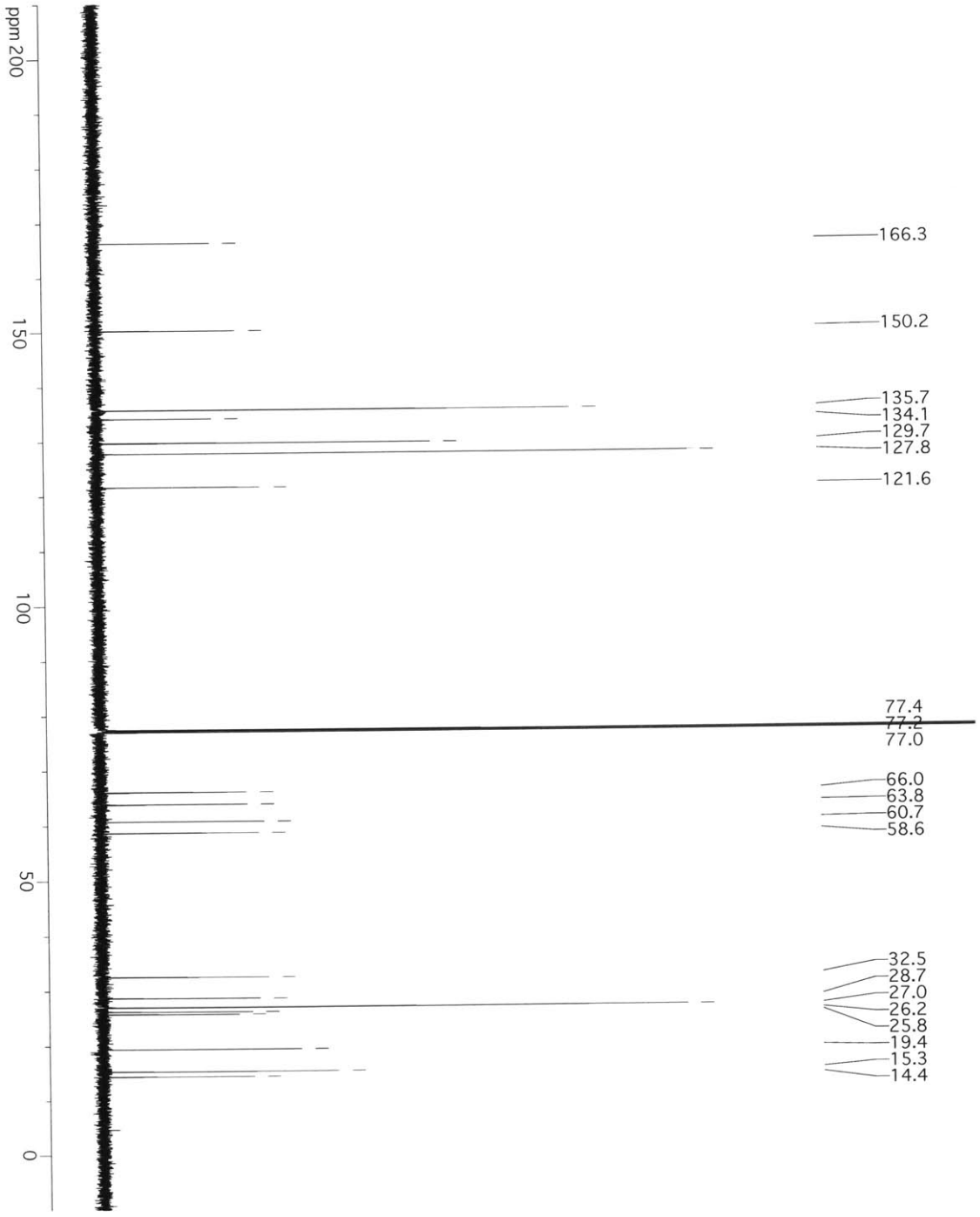
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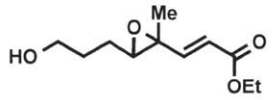
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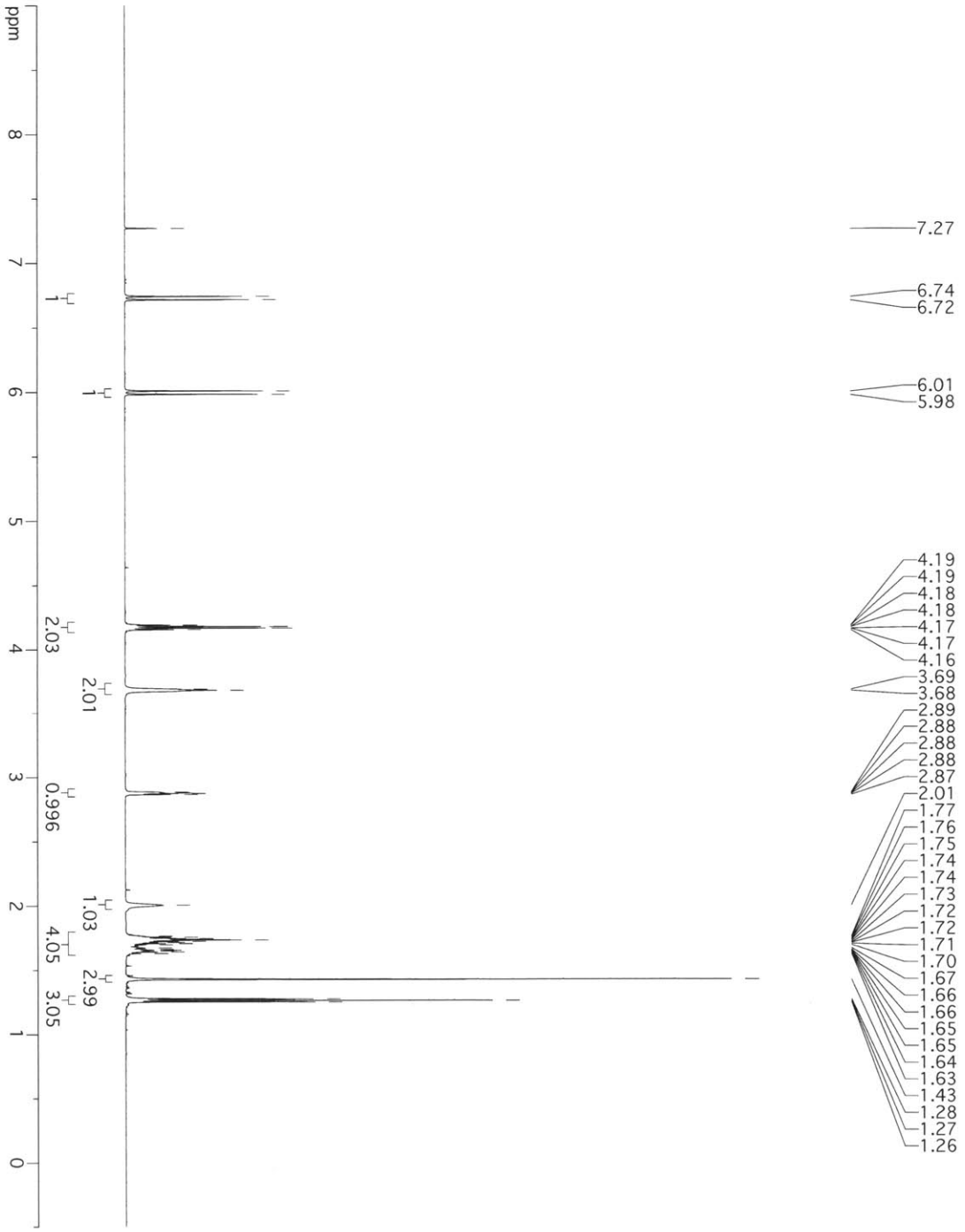
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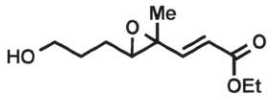
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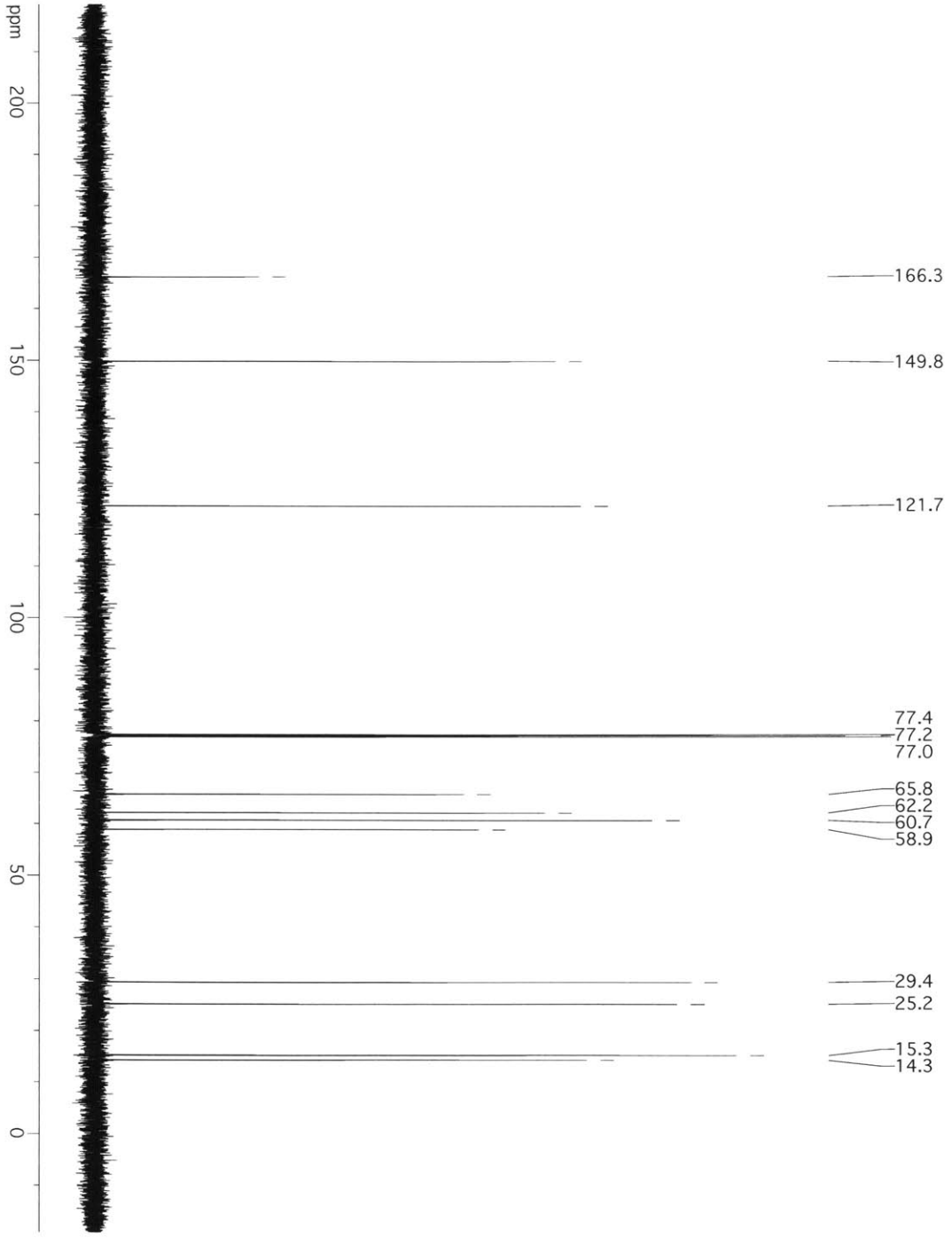
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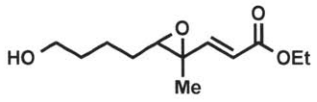
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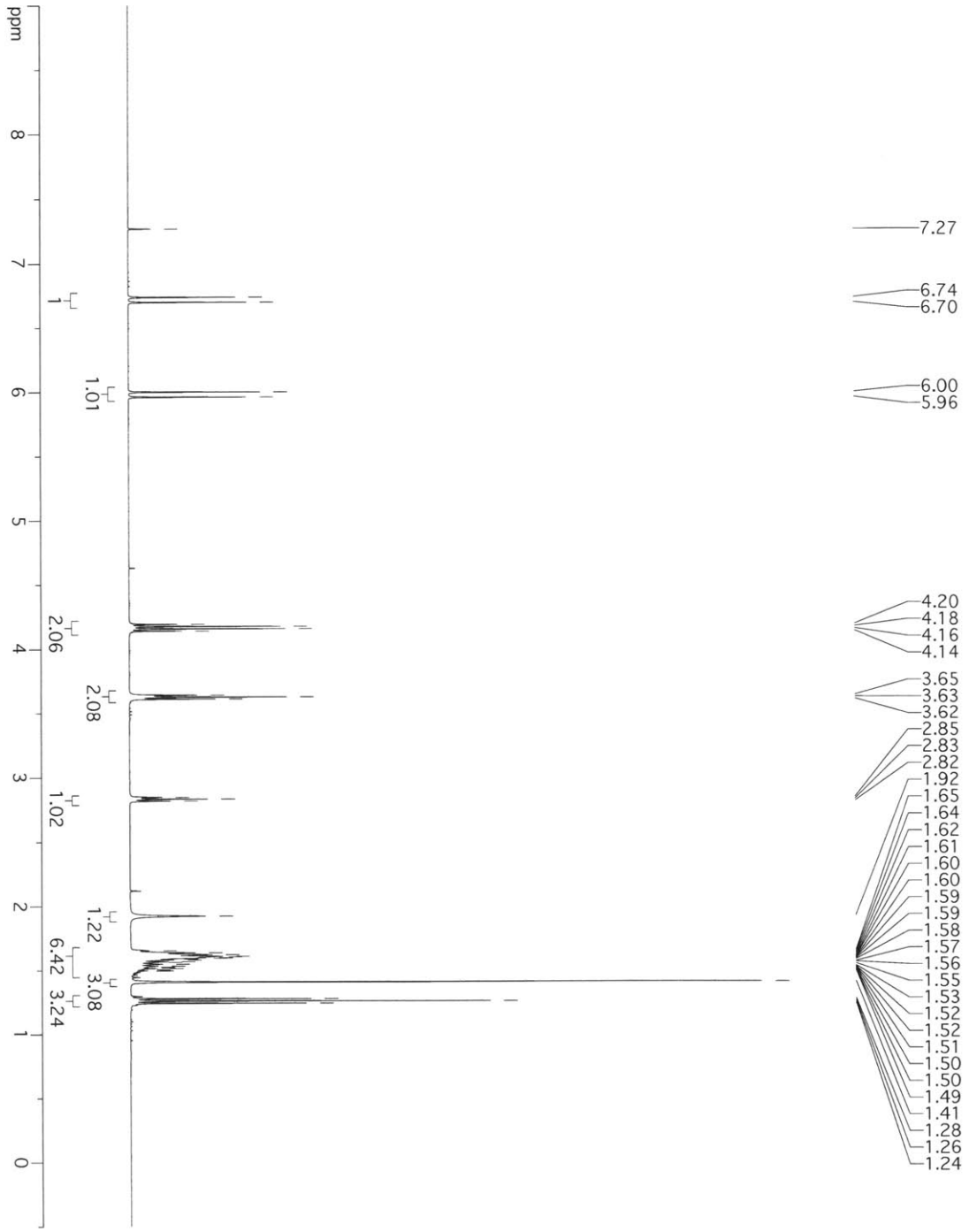
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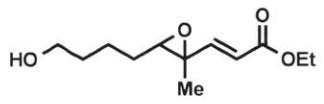
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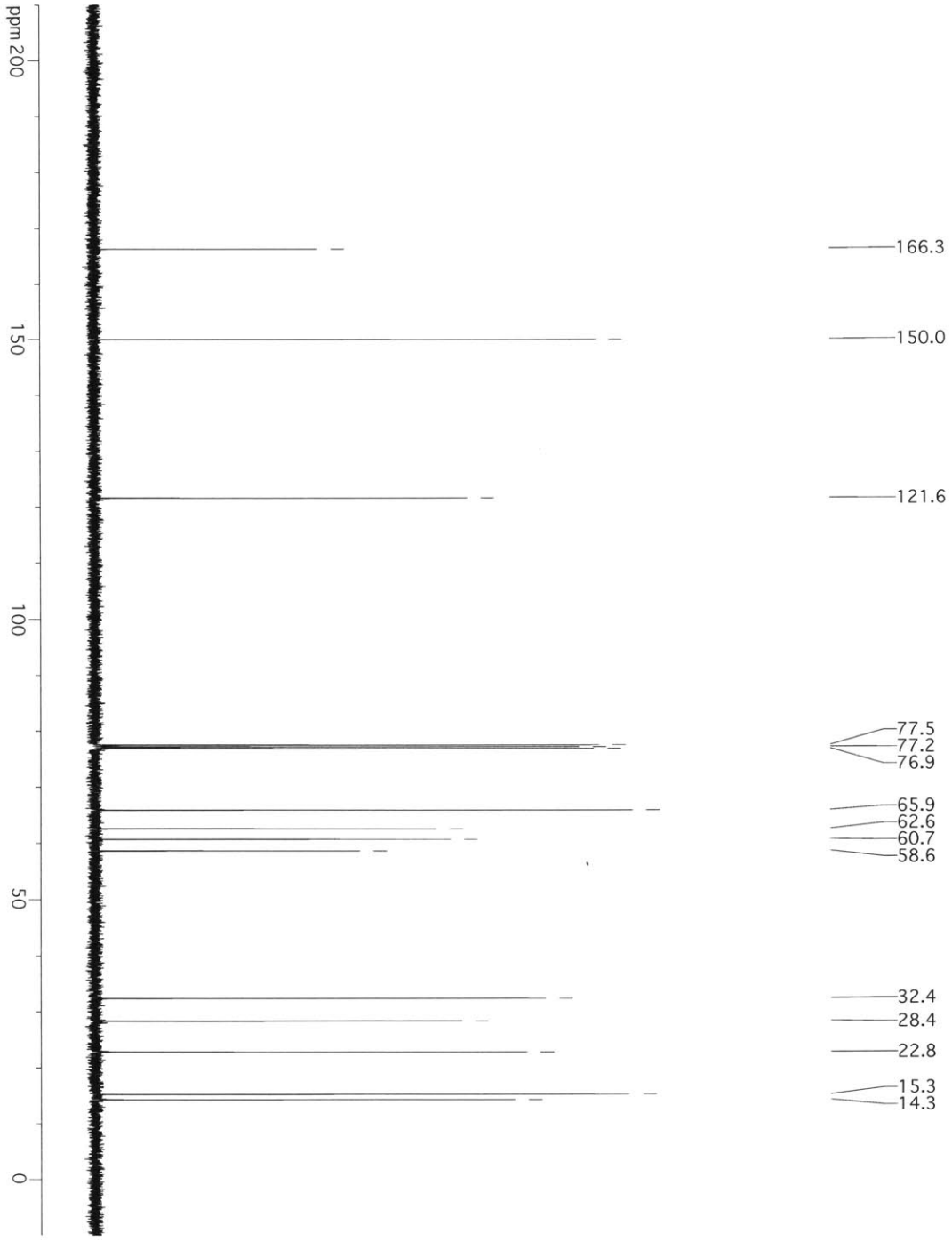
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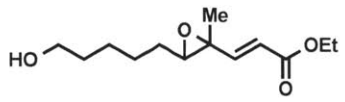
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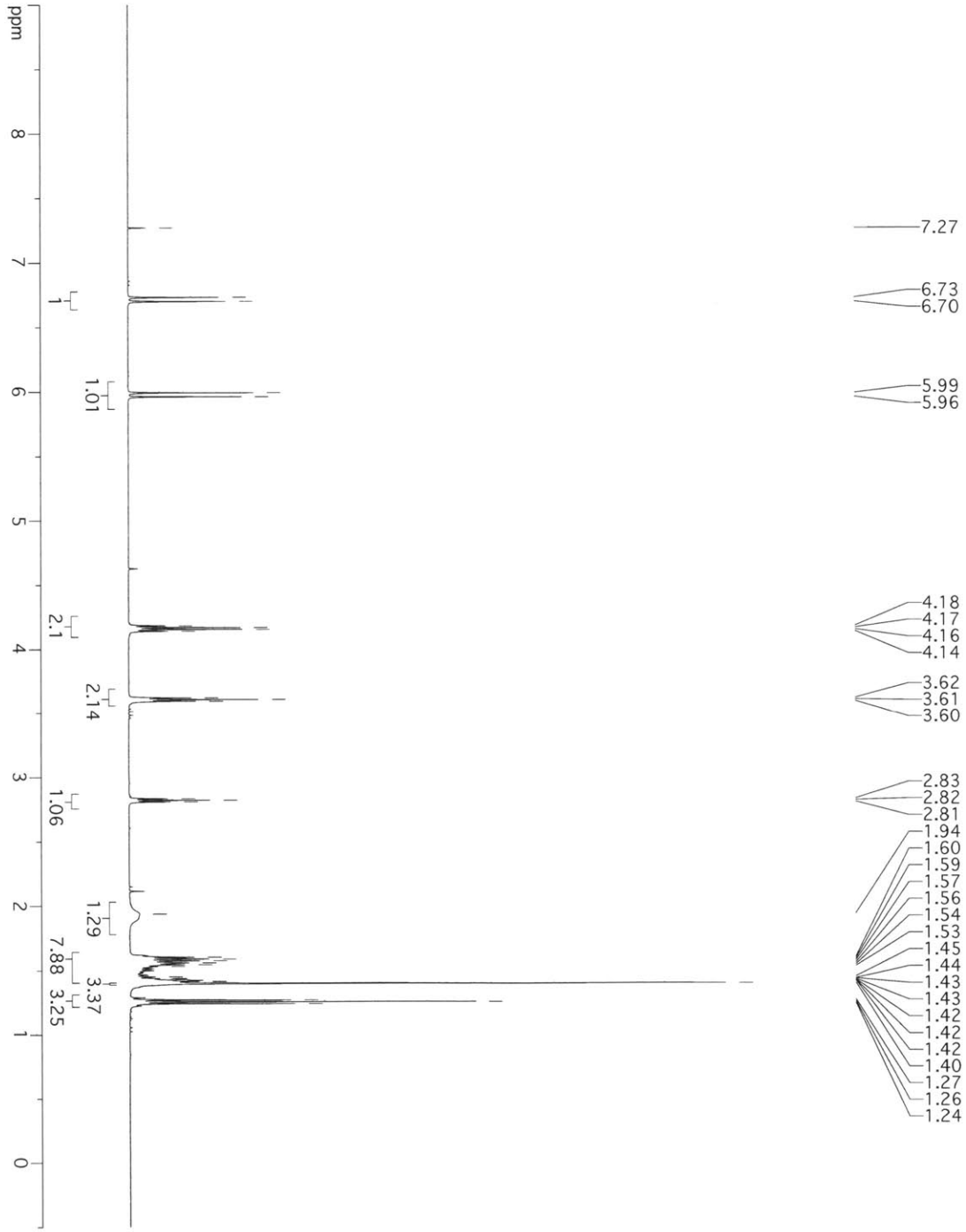
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1.54
1.53
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1.43
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1.42
1.42
1.42
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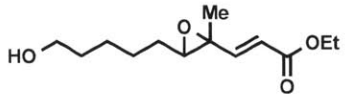
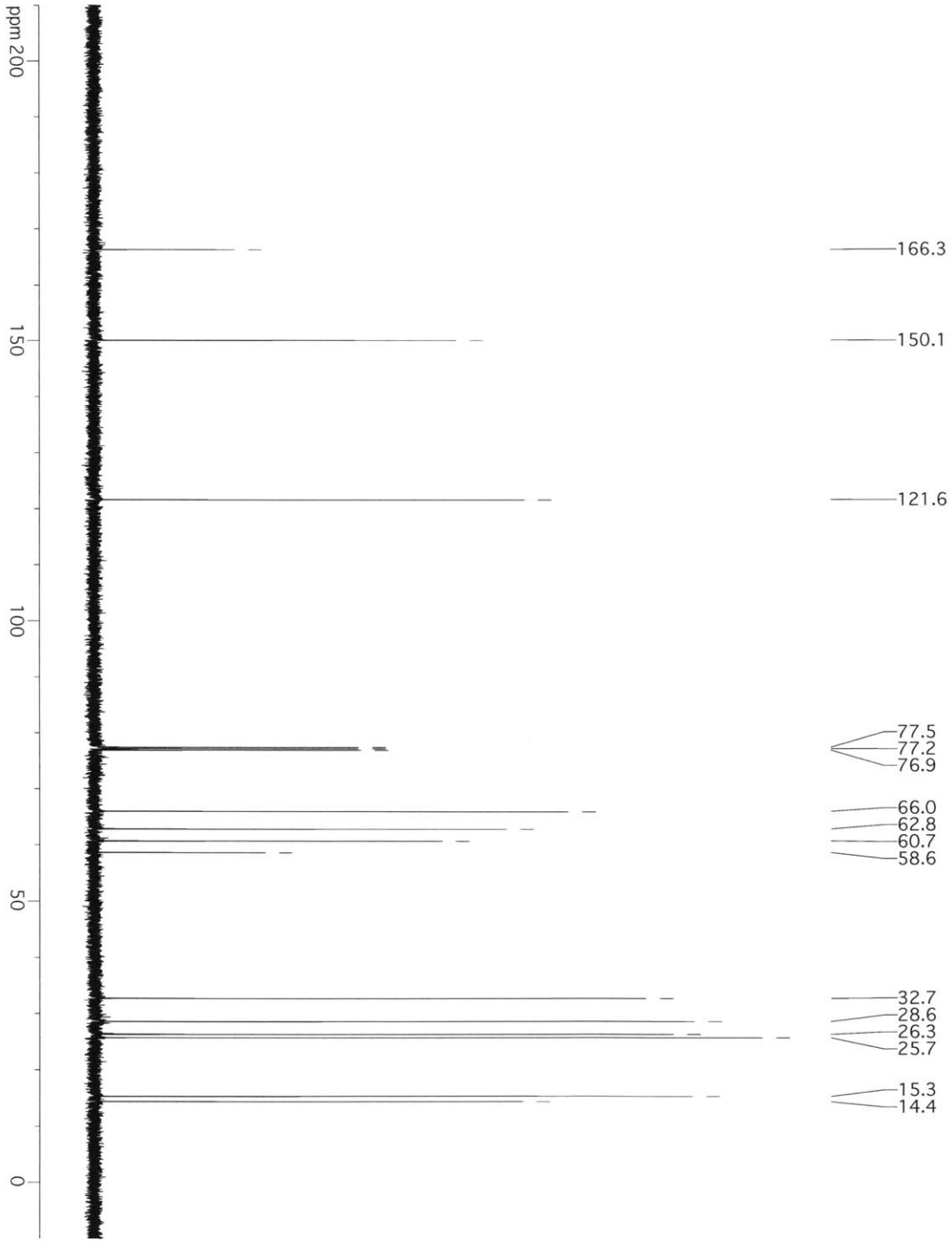
1.26
1.24


Me
O
HO
OEt
O

100c


ppm 200
150
100
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0
166.3
150.1
121.6
77.5
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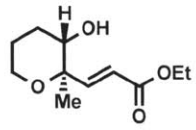
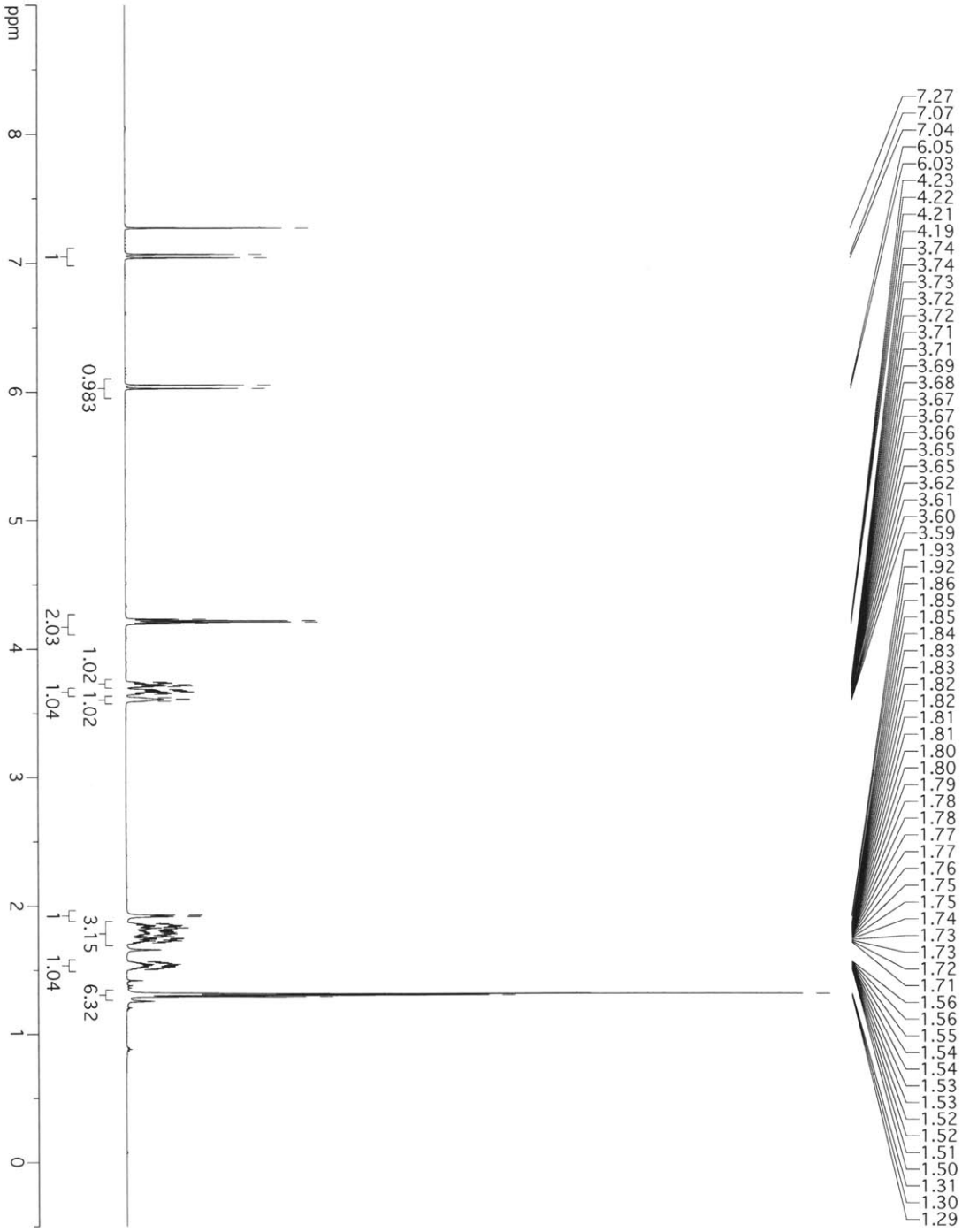
76.9
66.0
62.8
60.7
58.6
32.7
28.6
26.3
25.7
15.3
14.4


H
OH
OEt
O
Me
O

101a


ppm
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7
6
5
4
3
2
1
0
1
0.983
2.03
1.02
1.02
1.04
3.15
6.32
1
1.04
7.27
7.07
7.04
6.05
6.03
4.23
4.22
4.21
4.19
3.74
3.74
3.73
3.72
3.72
3.71
3.71
3.69
3.68
3.67
3.67
3.66
3.65
3.65
3.62
3.61
3.60
3.59
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1.83
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1.82
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1.56
1.56
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1.52
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1.51
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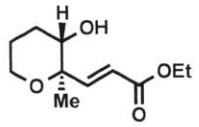
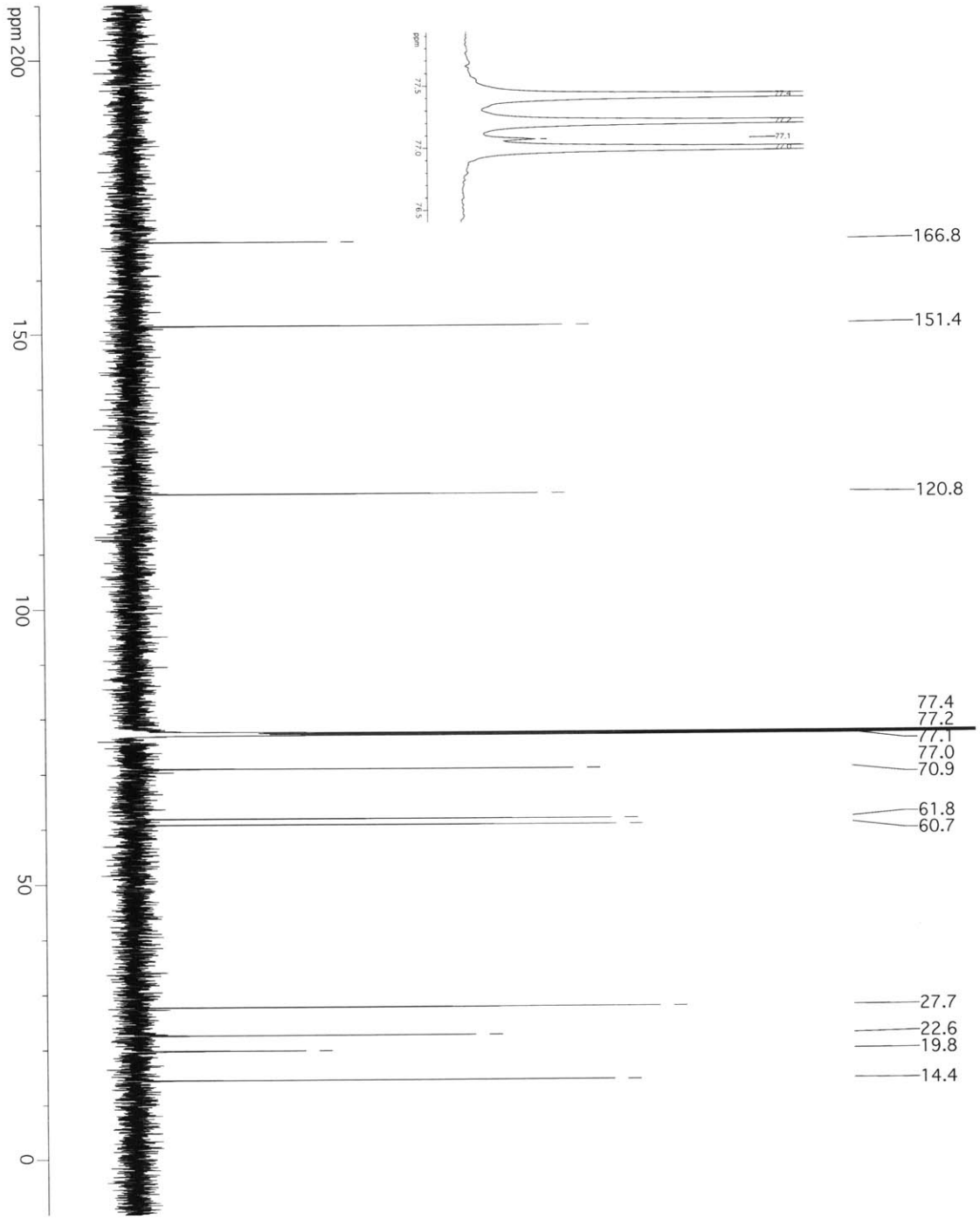
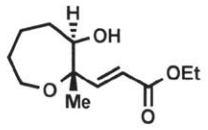
1.30
1.29

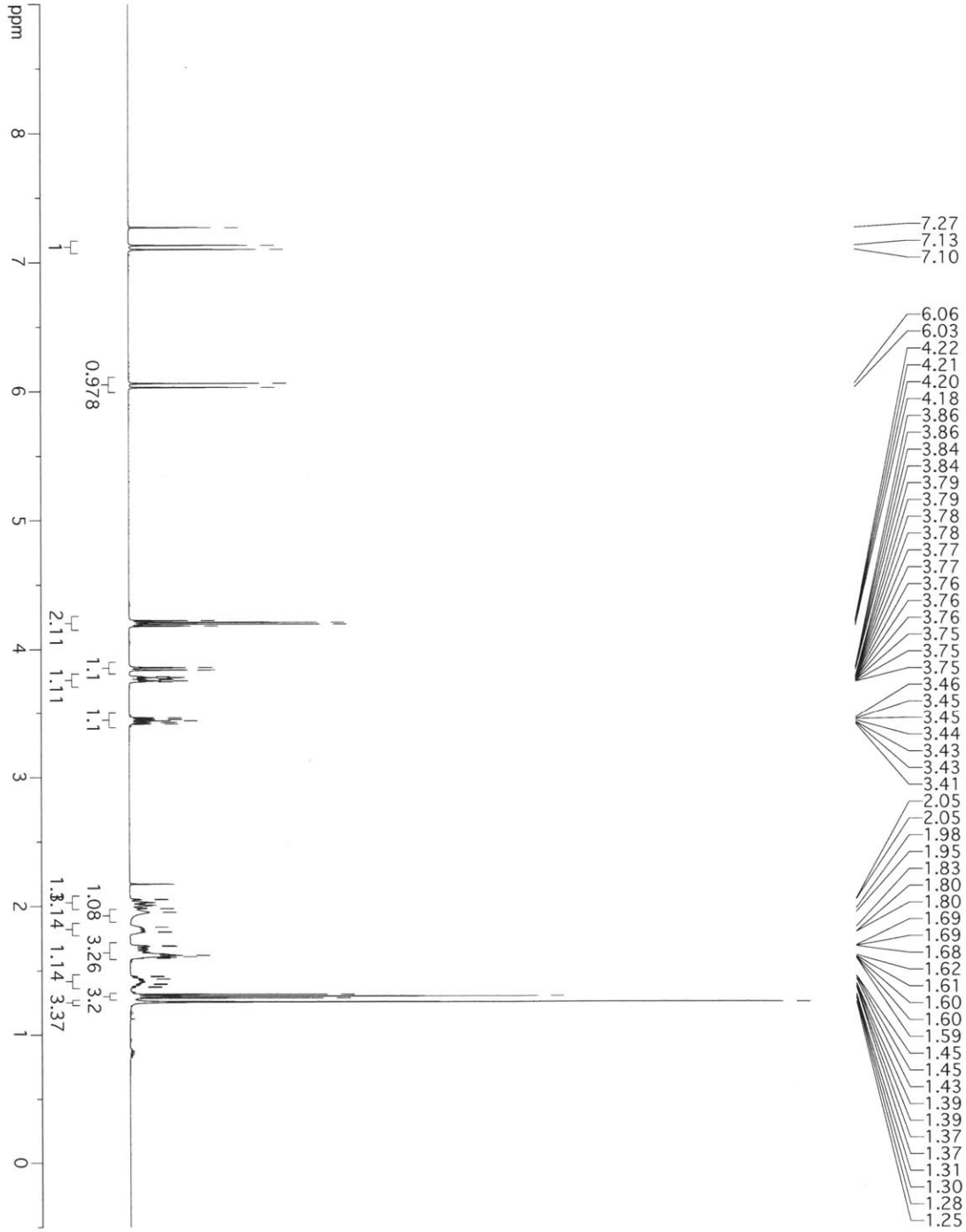

H
OH
OEt
O
Me
O

101a


ppm
200
150
100
50
0
166.8
151.4
120.8
77.4
77.2
77.1
77.0
70.9
61.8
60.7
27.7
22.6
19.8
14.4


H
OH
OEt
O
Me
O

101b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6
5
4
3
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1
0
1
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2.11
1.11
1.1
1.1
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3.26
3.2
1.14
1.14
3.37
7.27
7.13
7.10
6.06
6.03
4.22
4.21
4.20
4.18
3.86
3.86
3.84
3.84
3.79
3.79
3.78
3.78
3.77
3.77
3.76
3.76
3.76
3.75
3.75
3.75
3.46
3.45
3.45
3.44
3.43
3.43
3.41
2.05
2.05
1.98
1.95
1.83
1.80
1.80
1.69
1.69
1.68
1.62
1.61
1.60
1.60
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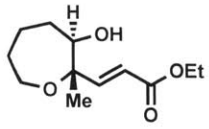
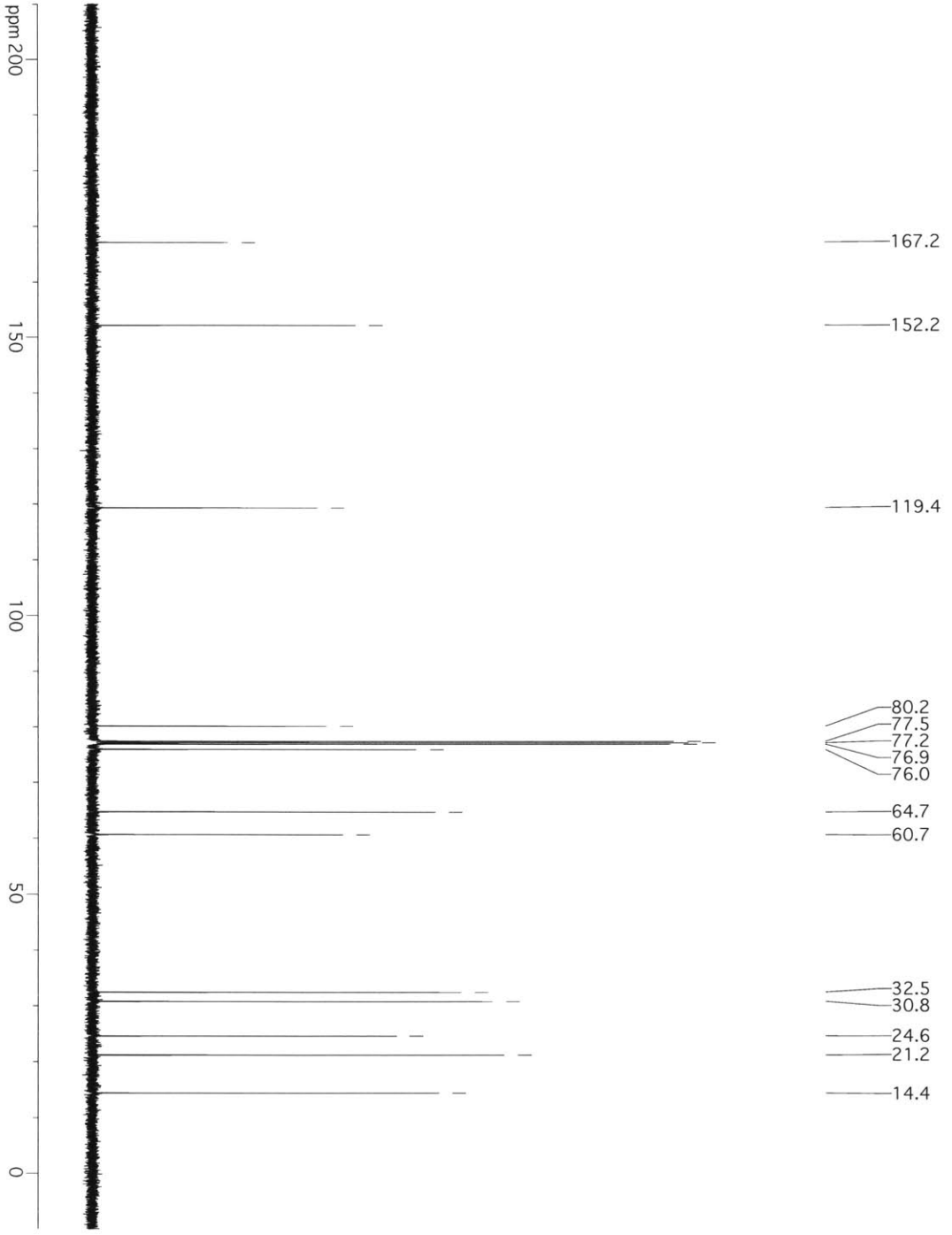
1.37
1.37
1.31
1.30
1.28
1.25


H
OH
OEt
O
Me
O

101b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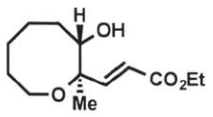
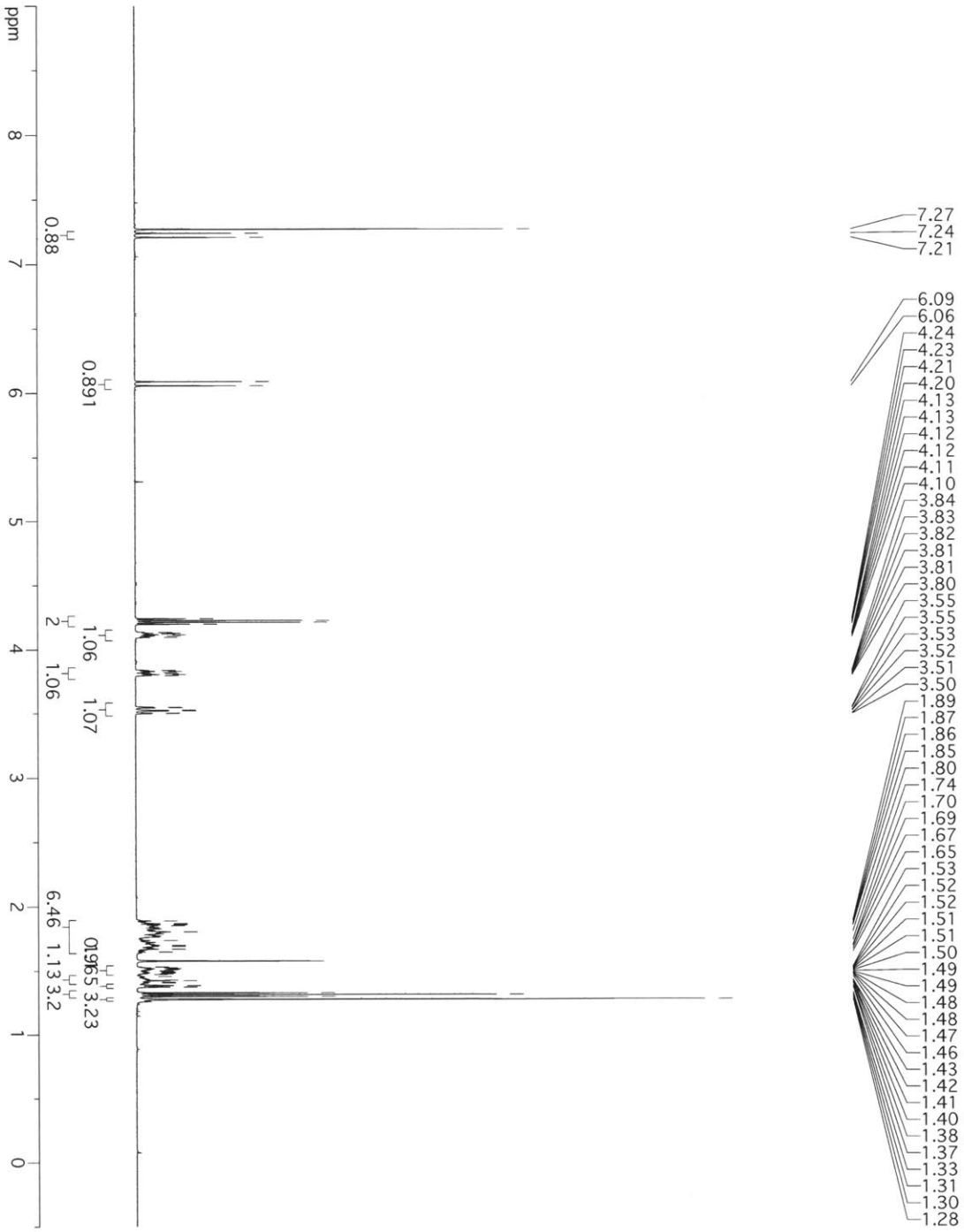
100
50
0
167.2
152.2
119.4
80.2
77.5
77.2
76.9
76.0
64.7
60.7
32.5
30.8
24.6
21.2
14.4


H
OH
CO2Et
O
Me

101c


ppm
8
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6
5
4
3
2
1
0
0.88
0.891
2
1.06
1.06
1.07
6.46
1.13
3.2
3.23
7.27
7.24
7.21
6.09
6.06
4.24
4.23
4.21
4.20
4.13
4.13
4.12
4.12
4.11
4.10
3.84
3.83
3.82
3.81
3.81
3.80
3.55
3.55
3.53
3.52
3.51
3.50
1.89
1.87
1.86
1.85
1.80
1.74
1.70
1.69
1.67
1.65
1.53
1.52
1.52
1.51
1.51
1.50
1.49
1.49
1.48
1.48
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1.46
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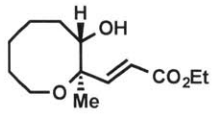
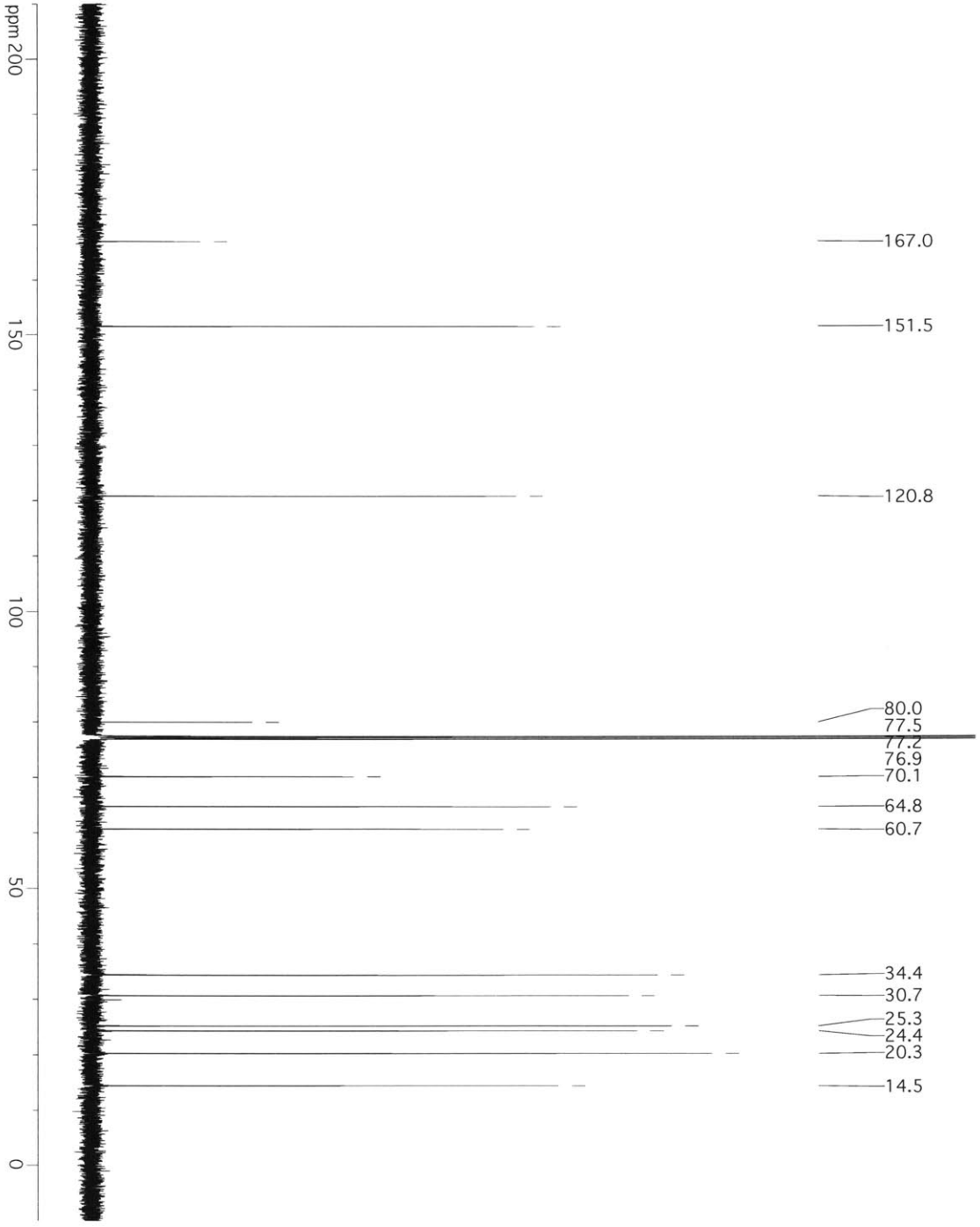
1.38
1.37
1.33
1.31
1.30
1.28


H
OH
CO2Et
O
Me

101c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100
50
0
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151.5
120.8
80.0
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77.2
76.9
70.1
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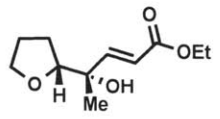
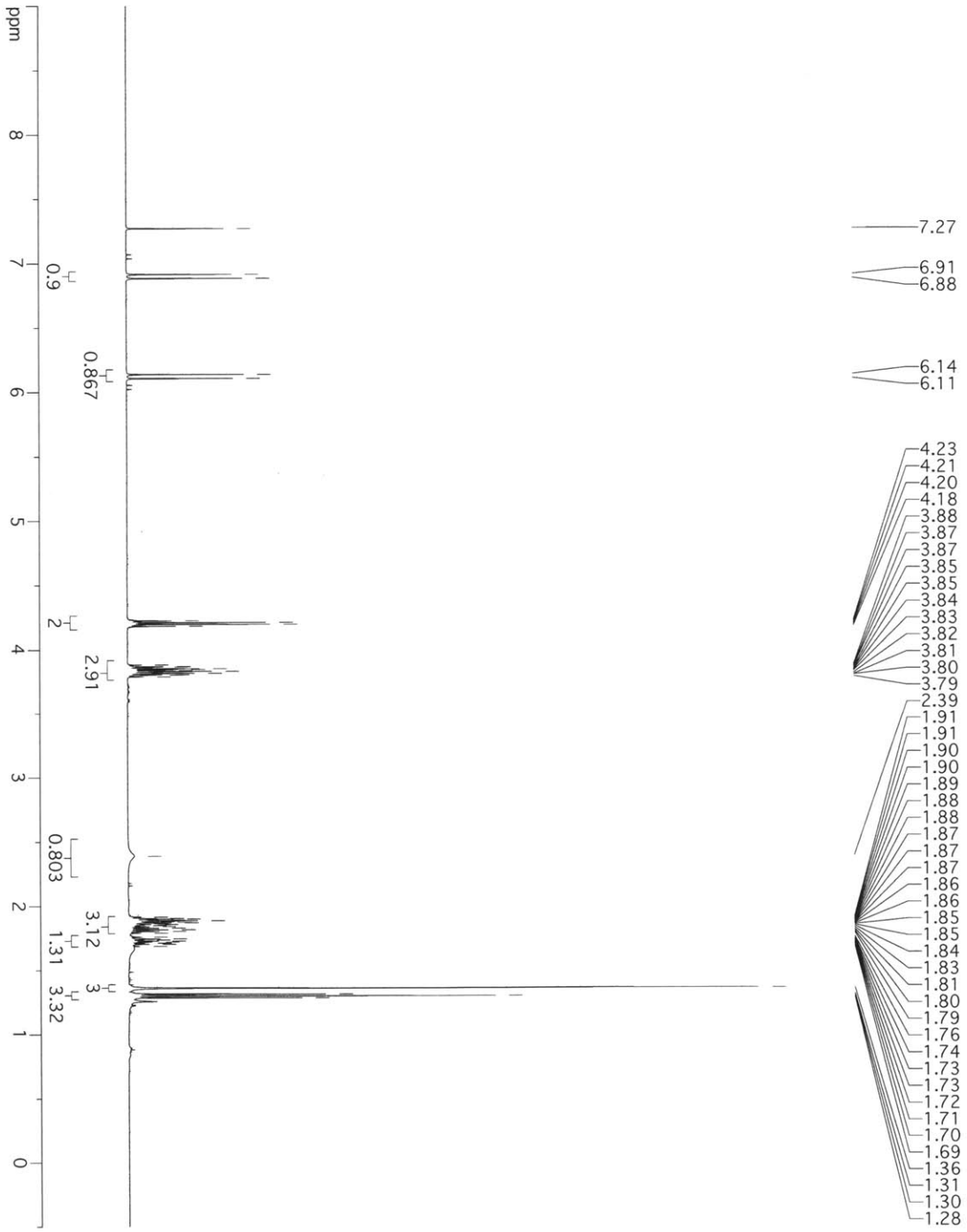
34.4
30.7
25.3
24.4
20.3
14.5


O
OEt
O
H
OH
Me

102a


ppm
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7
6
5
4
3
2
1
0
0.9
0.867
2
2.91
0.803
3.12
1.31
3
3.32
7.27
6.91
6.88
6.14
6.11
4.23
4.21
4.20
4.18
3.88
3.87
3.87
3.85
3.85
3.84
3.83
3.82
3.81
3.80
3.79
2.39
1.91
1.91
1.90
1.90
1.89
1.88
1.88
1.87
1.87
1.87
1.86
1.86
1.85
1.85
1.84
1.83
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1.70
1.69
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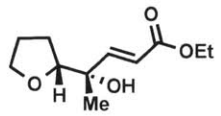
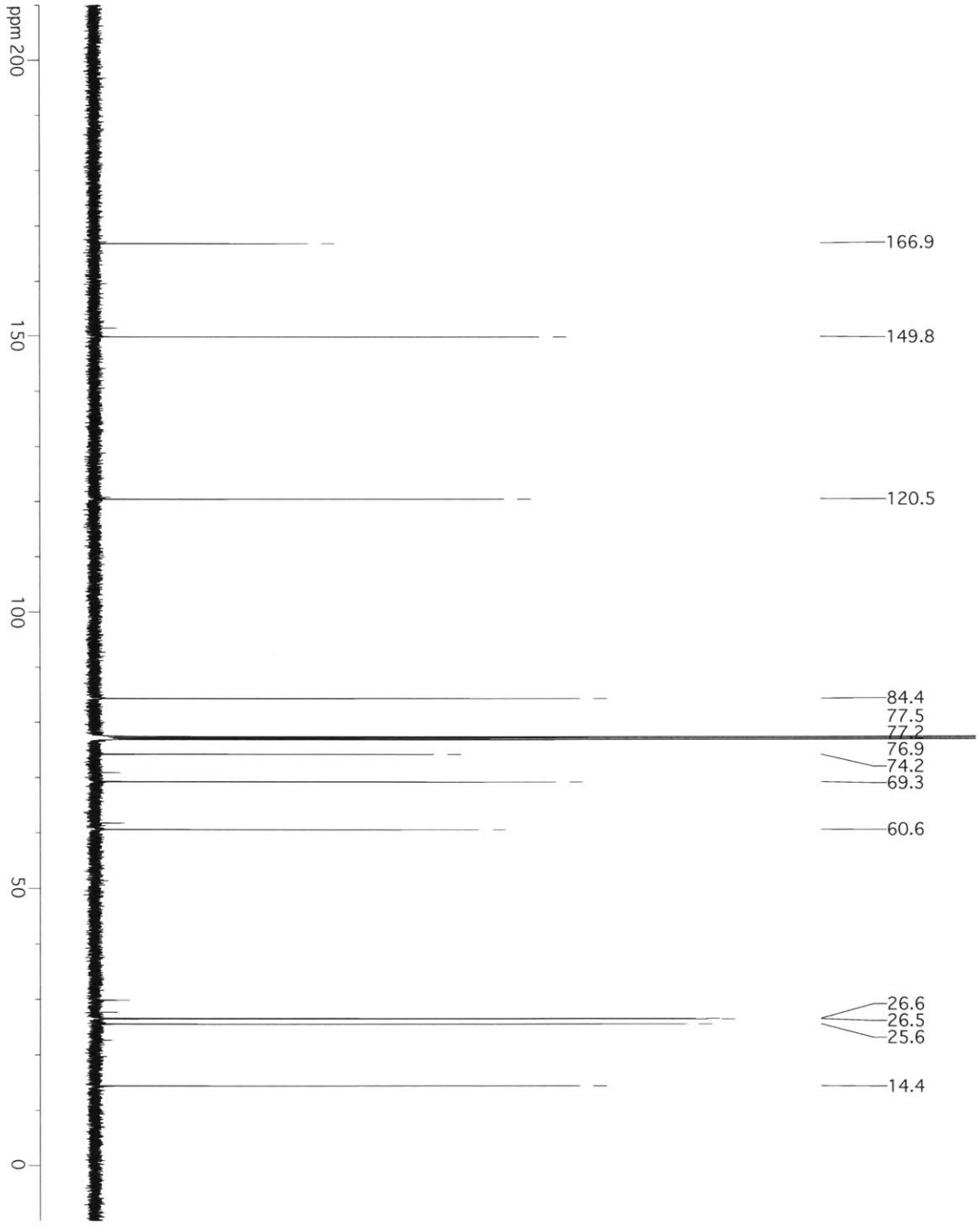
1.30
1.28


O
OEt
O
H
OH
Me

102a


ppm
200
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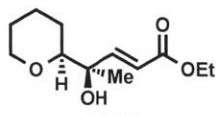
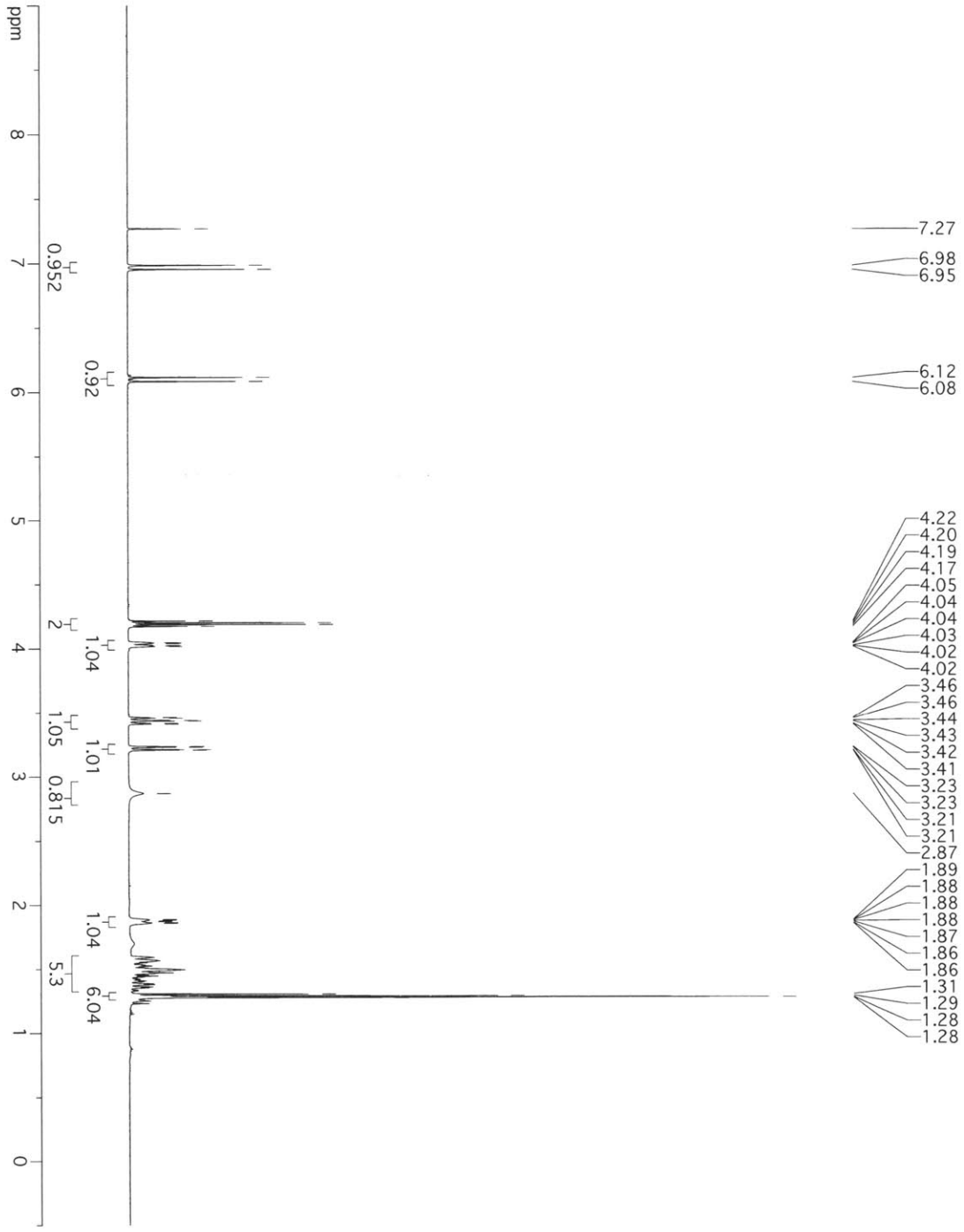
100
50
0
166.9
149.8
120.5
84.4
77.5
77.2
76.9
74.2
69.3
60.6
26.6
26.5
25.6
14.4


O
OEt
Me
H
OH

102b


ppm
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7
6
5
4
3
2
1
0
0.952
0.92
2
1.04
1.05
1.01
0.815
1.04
5.3
6.04
7.27
6.98
6.95
6.12
6.08
4.22
4.20
4.19
4.17
4.05
4.04
4.04
4.03
4.02
4.02
3.46
3.46
3.44
3.43
3.42
3.41
3.23
3.23
3.21
3.21
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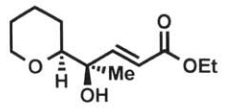
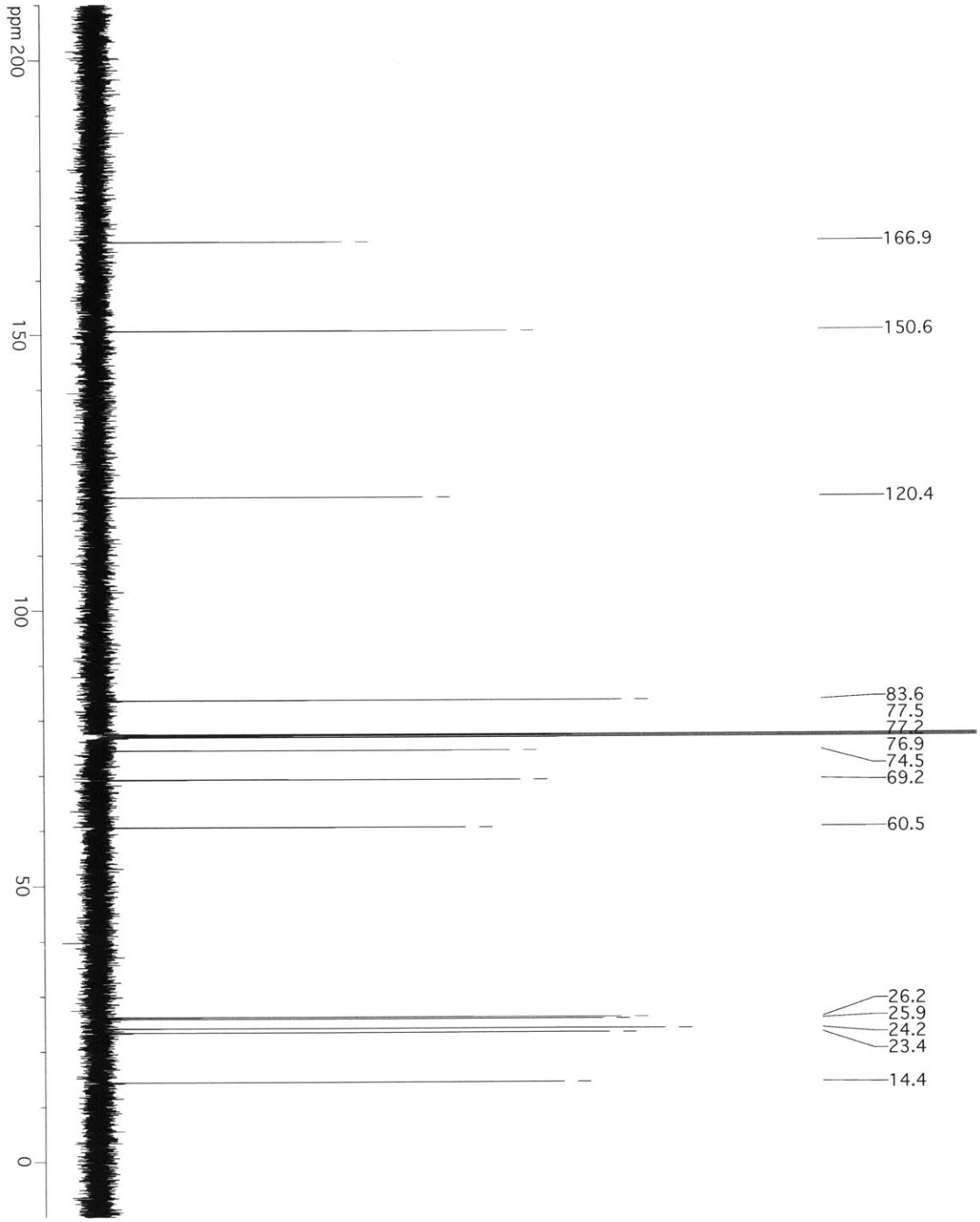
1.89
1.88
1.88
1.88
1.87
1.86
1.86
1.31
1.29
1.28
1.28


O
H
Me
OH
OEt

102b


ppm
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100
50
0
166.9
150.6
120.4
83.6
77.5
77.2
76.9
74.5
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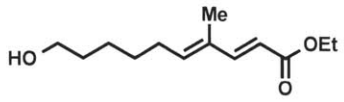
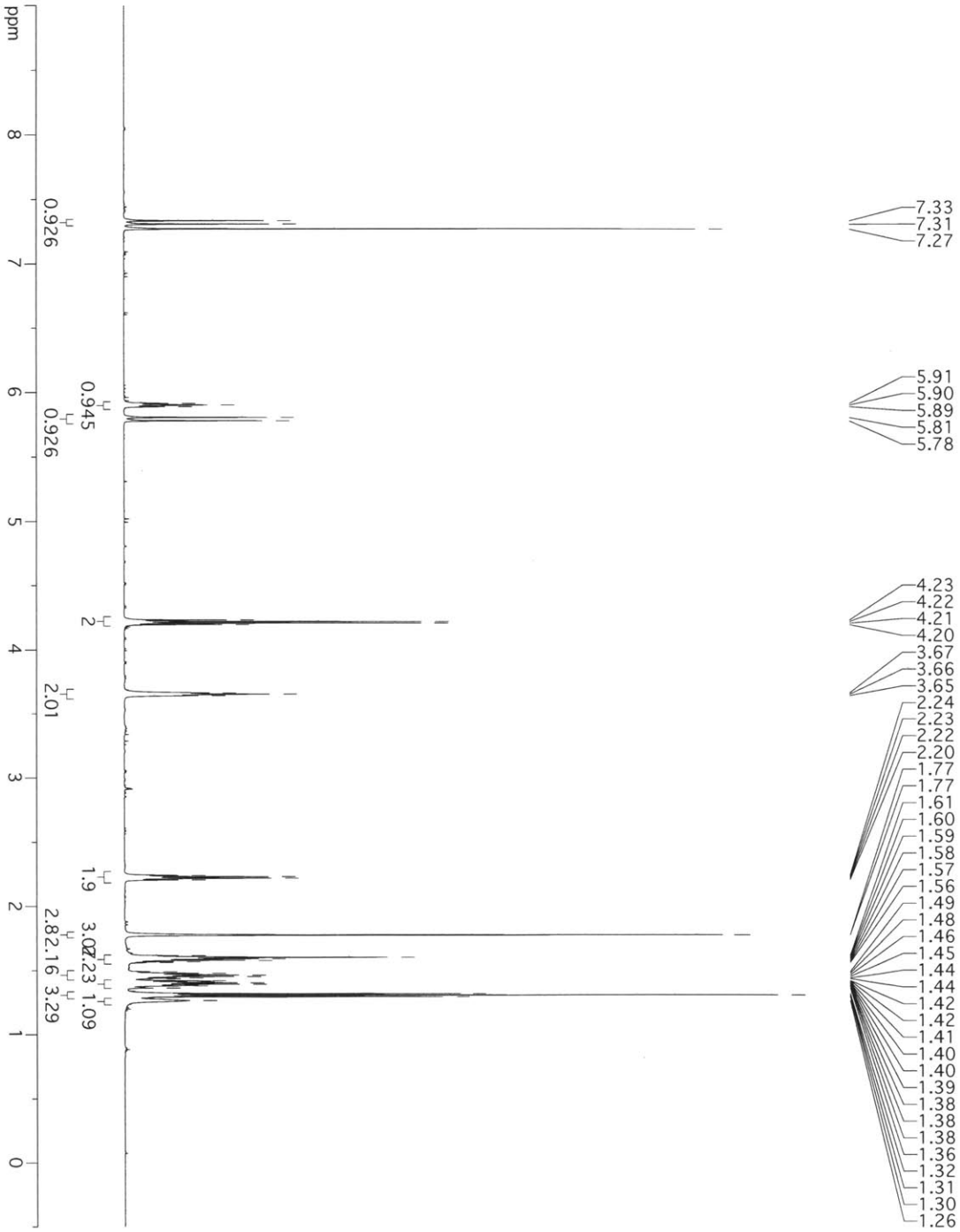
60.5
26.2
25.9
24.2
23.4
14.4


Me
HO
OEt
O

103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0.926
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1.9
3.02
7.23
1.09
2.82
2.16
3.29
7.33
7.31
7.27
5.91
5.90
5.89
5.81
5.78
4.23
4.22
4.21
4.20
3.67
3.66
3.65
2.24
2.23
2.22
2.20
1.77
1.77
1.61
1.60
1.59
1.58
1.57
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1.45
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1.38
1.36
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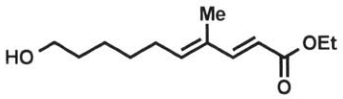
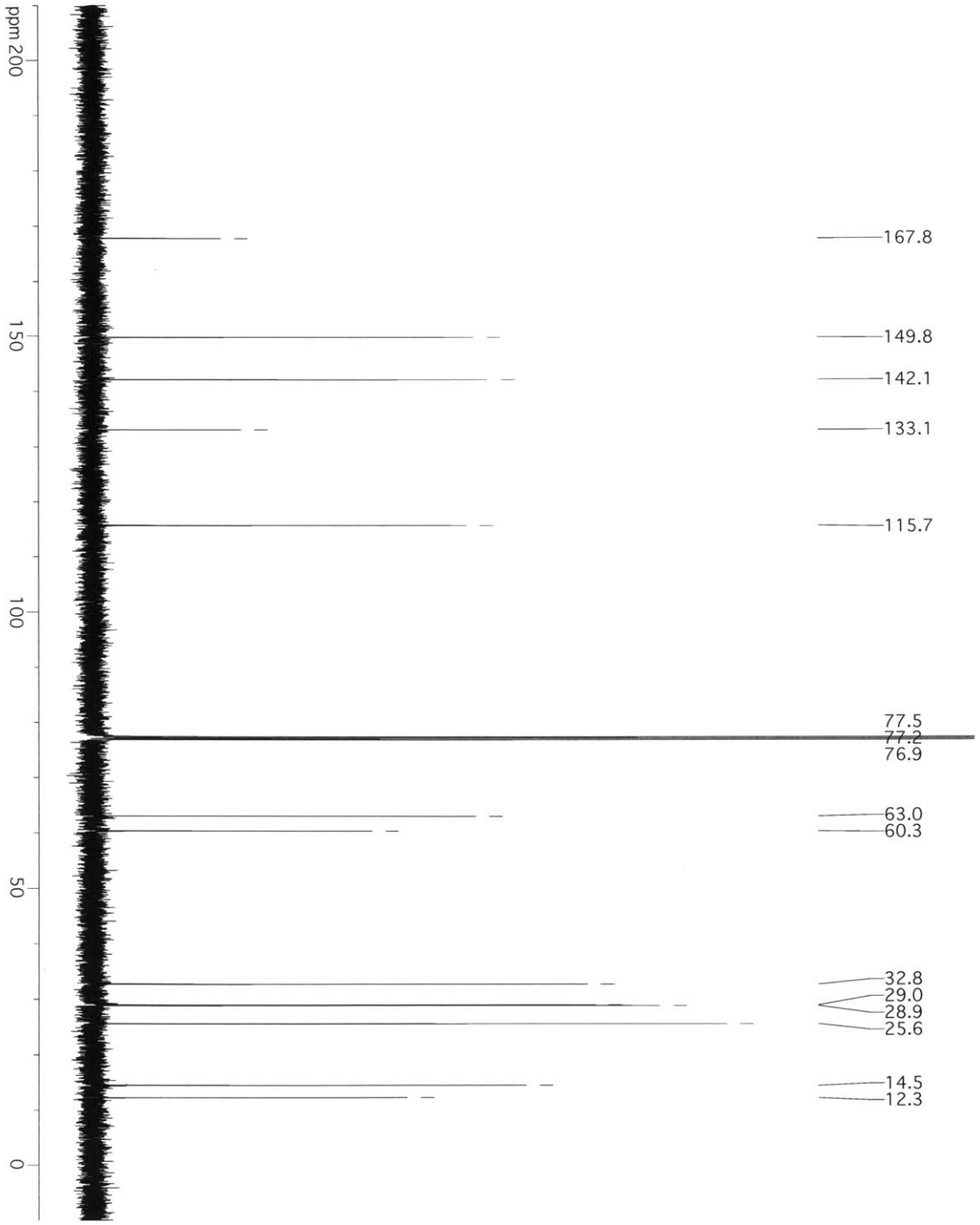
1.30
1.26


Me
HO
OEt
O

103


ppm
200
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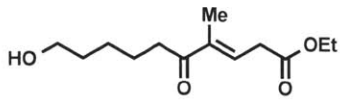
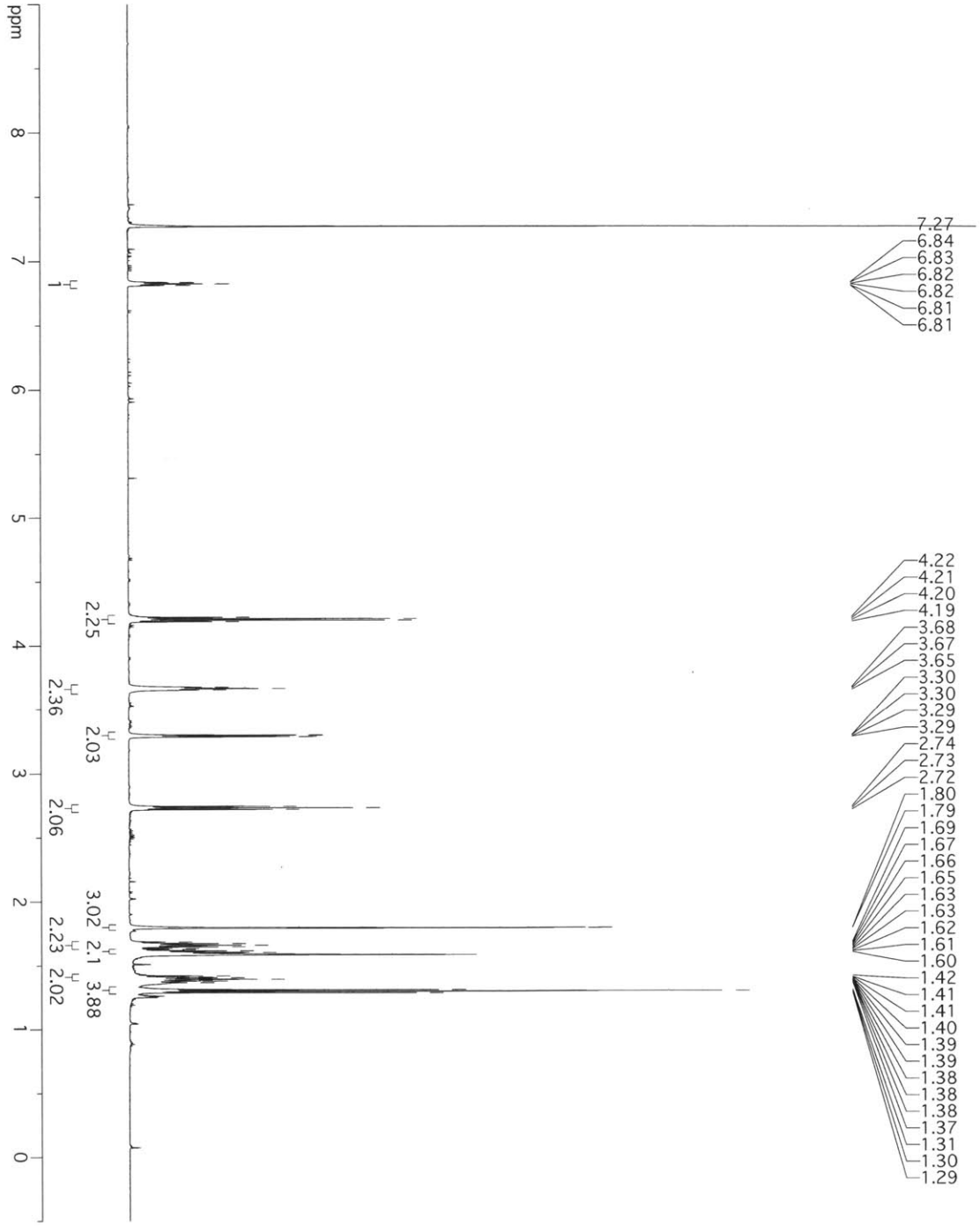
100
50
0
167.8
149.8
142.1
133.1
115.7
77.5
77.2
76.9
63.0
60.3
32.8
29.0
28.9
25.6
14.5
12.3


Me
HO
OEt
O
O

104


ppm
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2
1
0
1
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2.03
2.06
3.02
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3.88
2.23
2.02
7.27
6.84
6.83
6.82
6.82
6.81
6.81
4.22
4.21
4.20
4.19
3.68
3.67
3.65
3.30
3.30
3.29
3.29
2.74
2.73
2.72
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1.79
1.69
1.67
1.66
1.65
1.63
1.63
1.62
1.61
1.60
1.42
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1.41
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1.39
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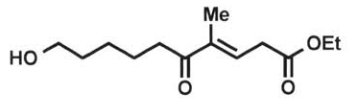
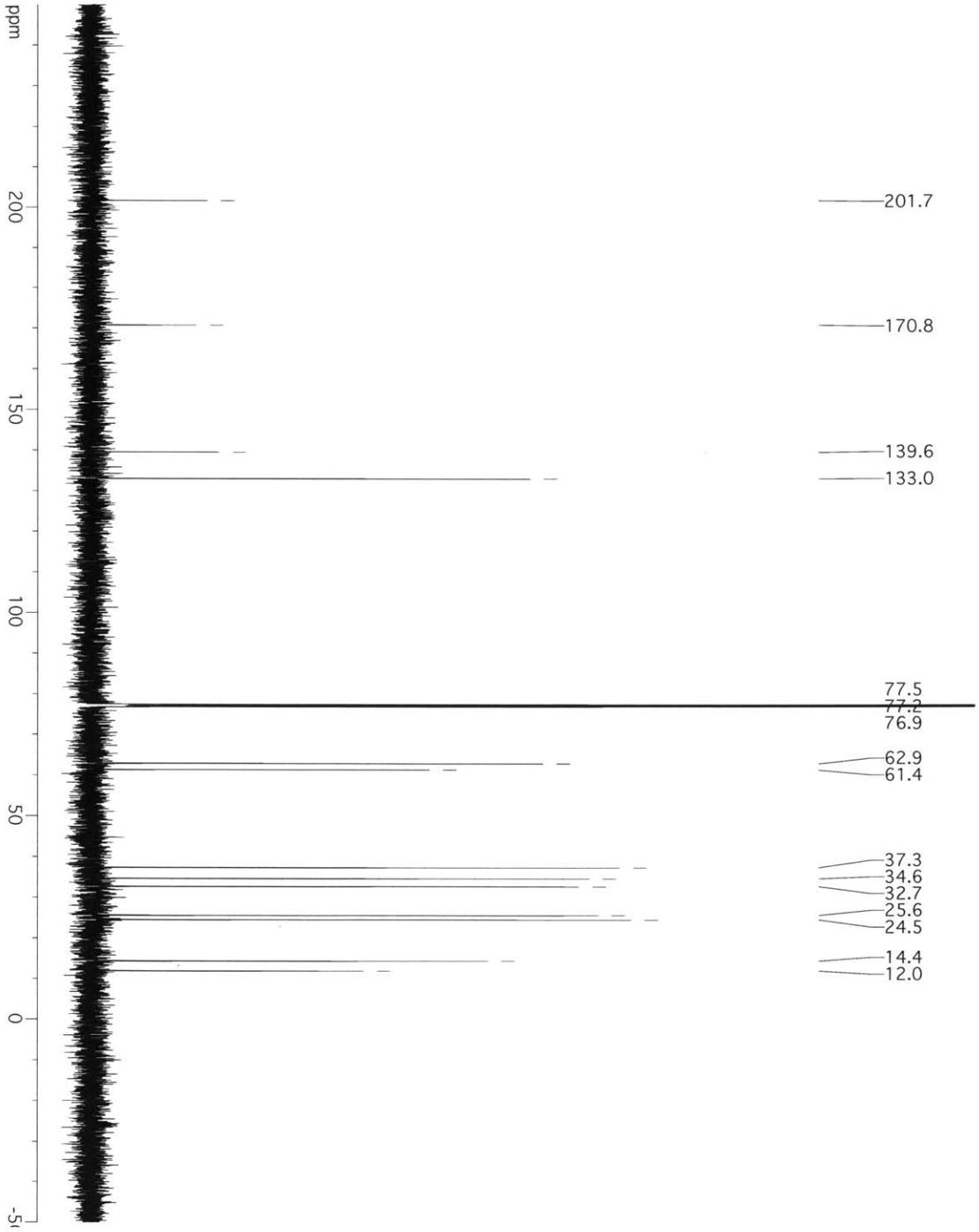
1.38
1.38
1.38
1.37
1.31
1.30
1.29


Me
HO
OEt
O
O

104


ppm
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50
0
-5
201.7
170.8
139.6
133.0
77.5
77.2
76.9
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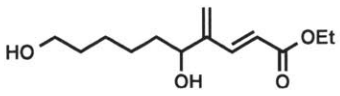
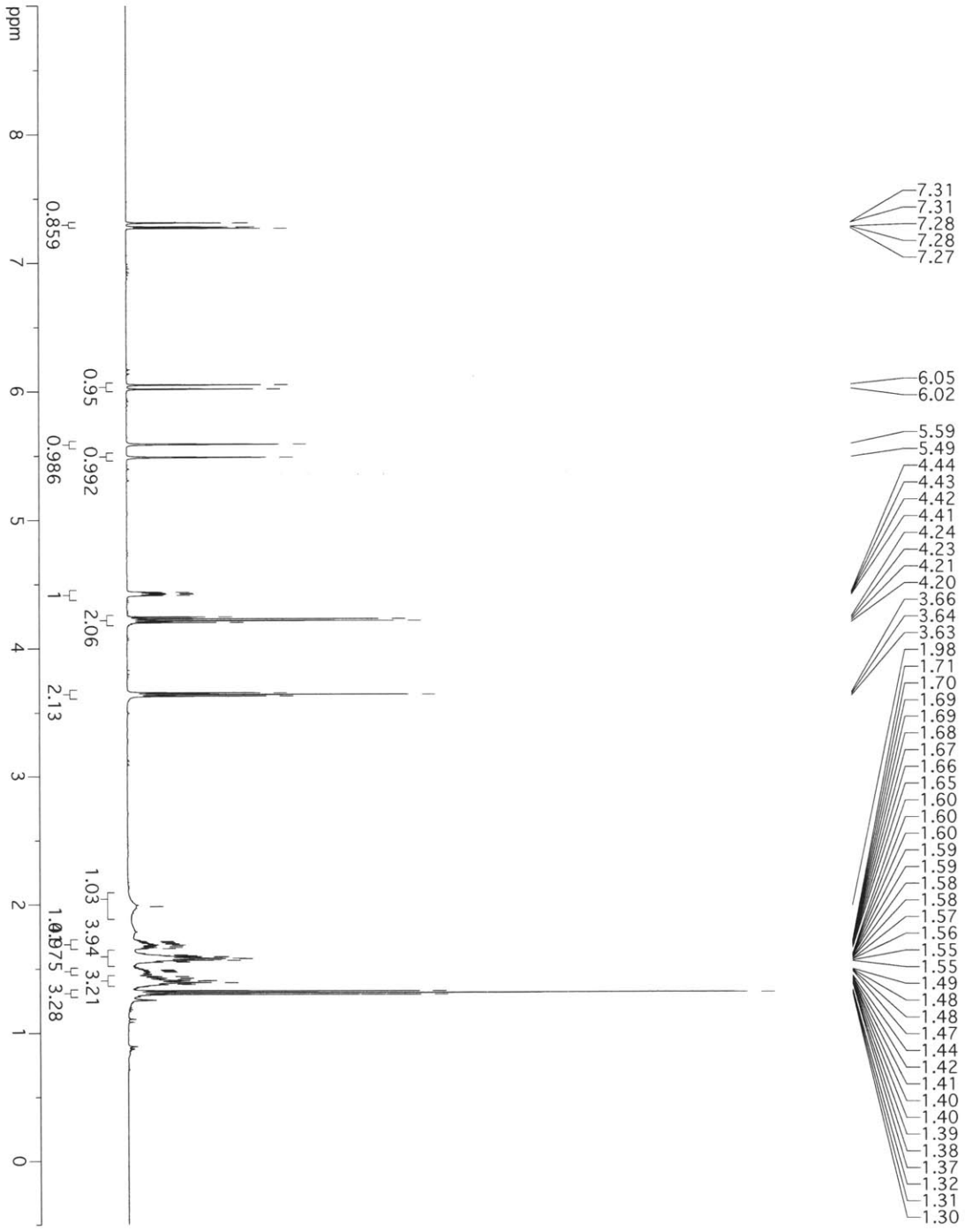
34.6
32.7
25.6
24.5
14.4
12.0


HO
OH
OEt
O

105


ppm
8
7
6
5
4
3
2
1
0
0.859
0.95
0.986
0.992
1
2.06
2.13
1.03
3.94
3.21
3.28
7.31
7.31
7.28
7.28
7.27
6.05
6.02
5.59
5.49
4.44
4.43
4.42
4.41
4.24
4.23
4.21
4.20
3.66
3.64
3.63
1.98
1.71
1.70
1.69
1.69
1.68
1.67
1.66
1.65
1.60
1.60
1.60
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1.58
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1.48
1.48
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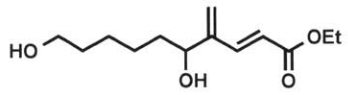
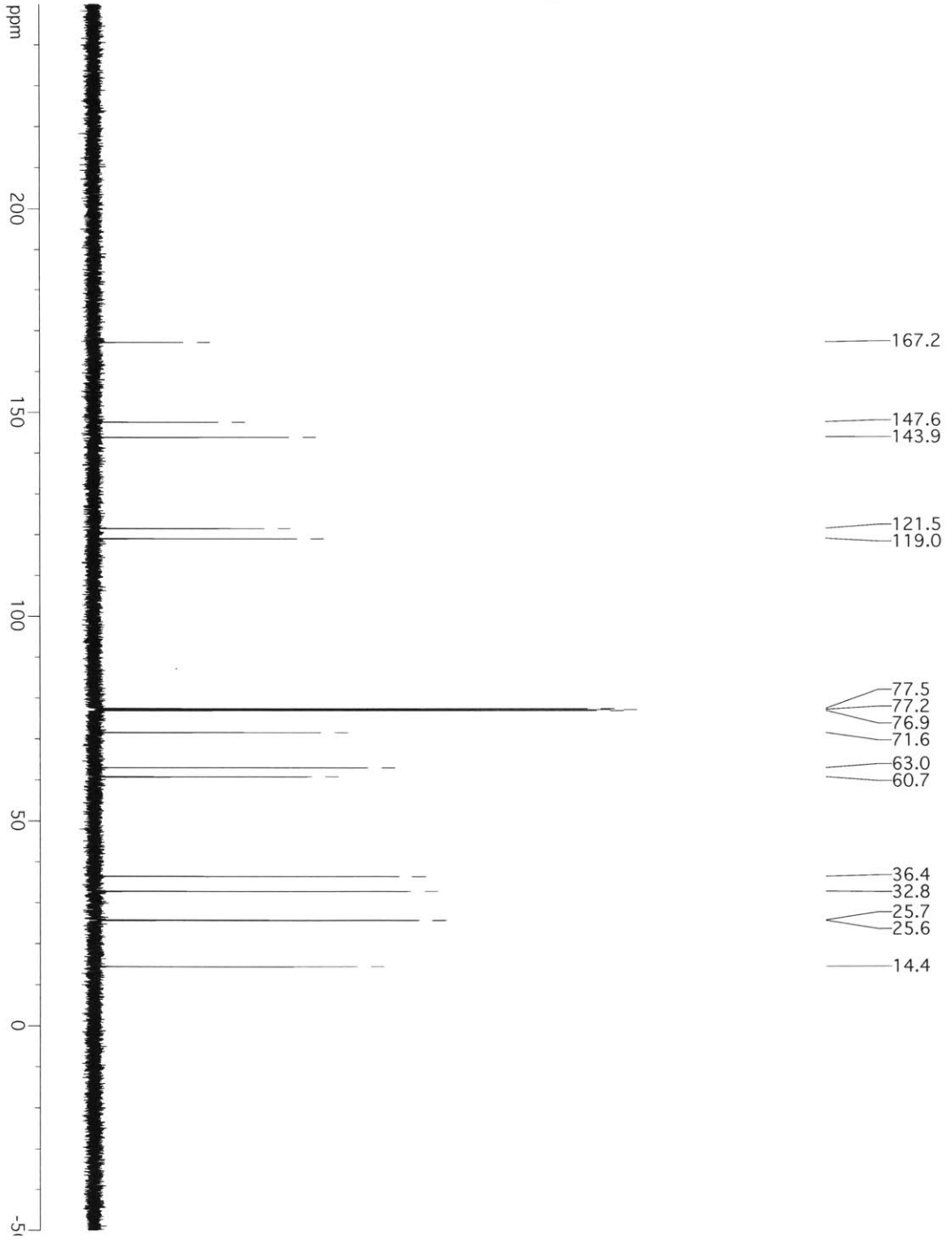
1.31
1.30


HO
OH
OEt
O

105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147.6
143.9
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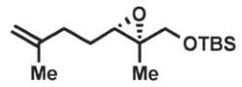
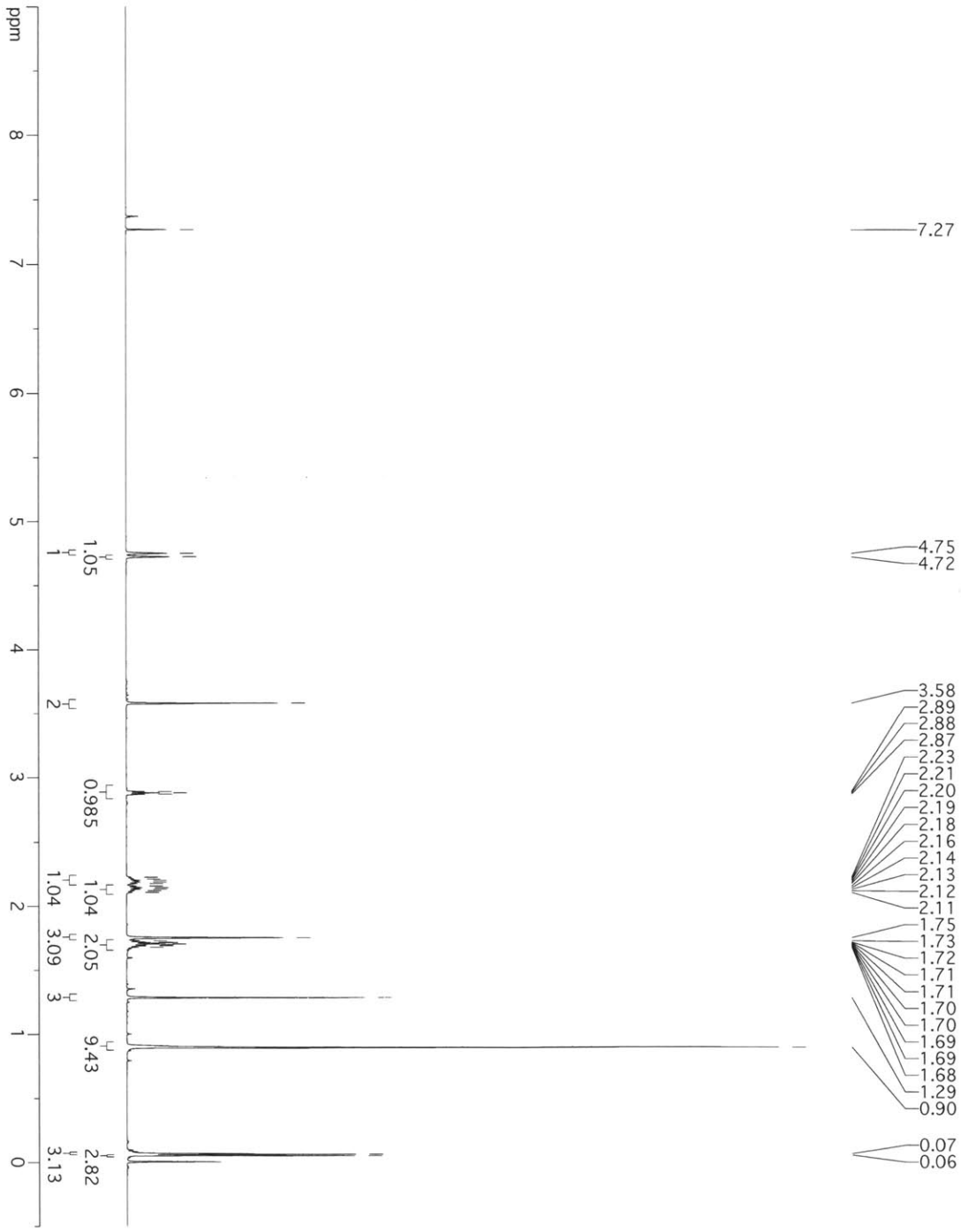
77.2
76.9
71.6
63.0
60.7
36.4
32.8
25.7
25.6
14.4


O
OTBS
Me
Me

48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6
5
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3
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1
0
1.05
0.985
1.04
1.04
2.05
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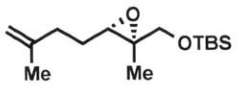
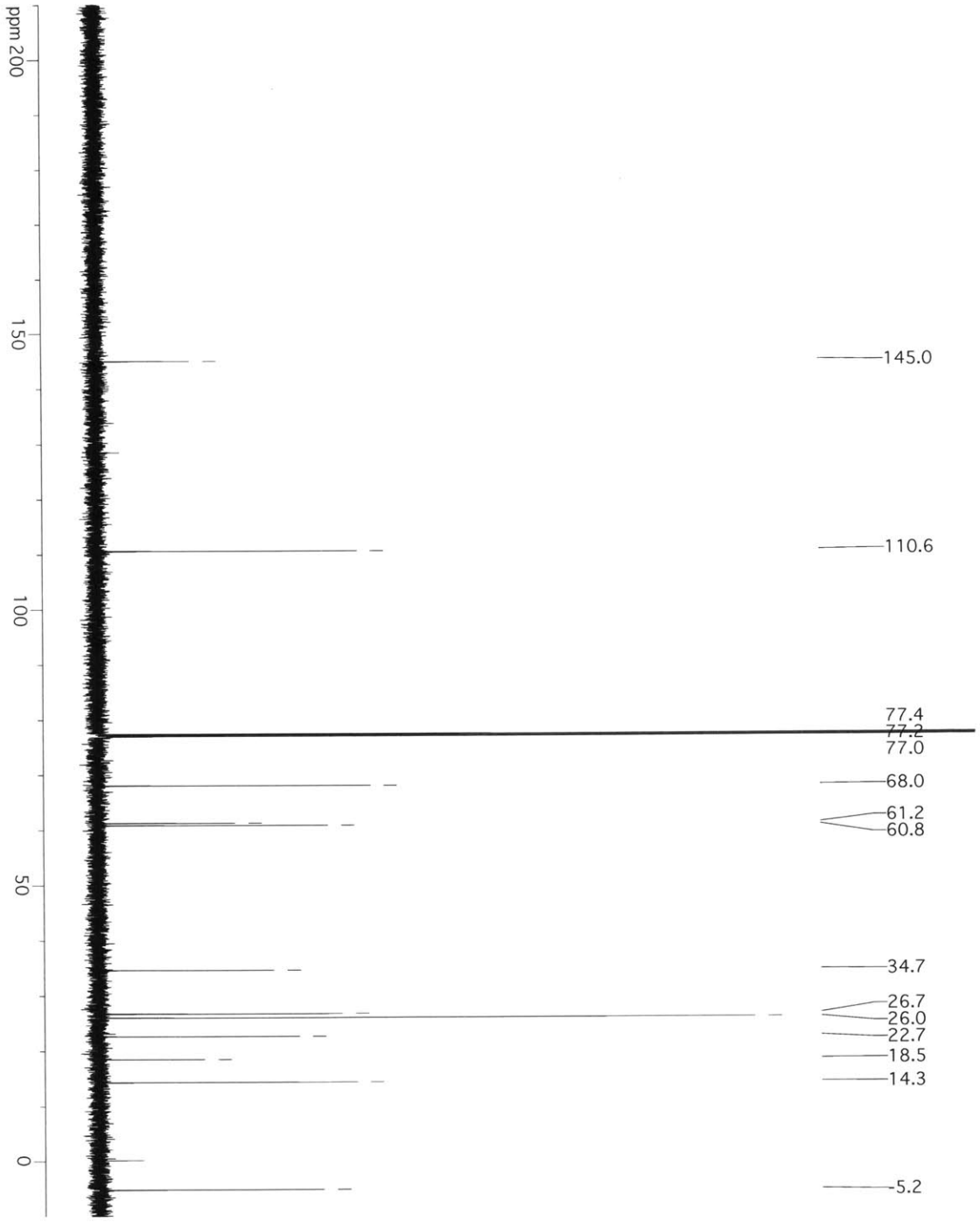
9.43
2.82
3.13
7.27
4.75
4.72
3.58
2.89
2.88
2.87
2.23
2.21
2.20
2.19
2.18
2.16
2.14
2.13
2.12
2.11
1.75
1.73
1.72
1.71
1.71
1.70
1.70
1.69
1.69
1.68
1.29
0.90
0.07
0.06


O
OTBS
Me
Me

48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61.2
60.8
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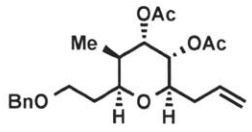
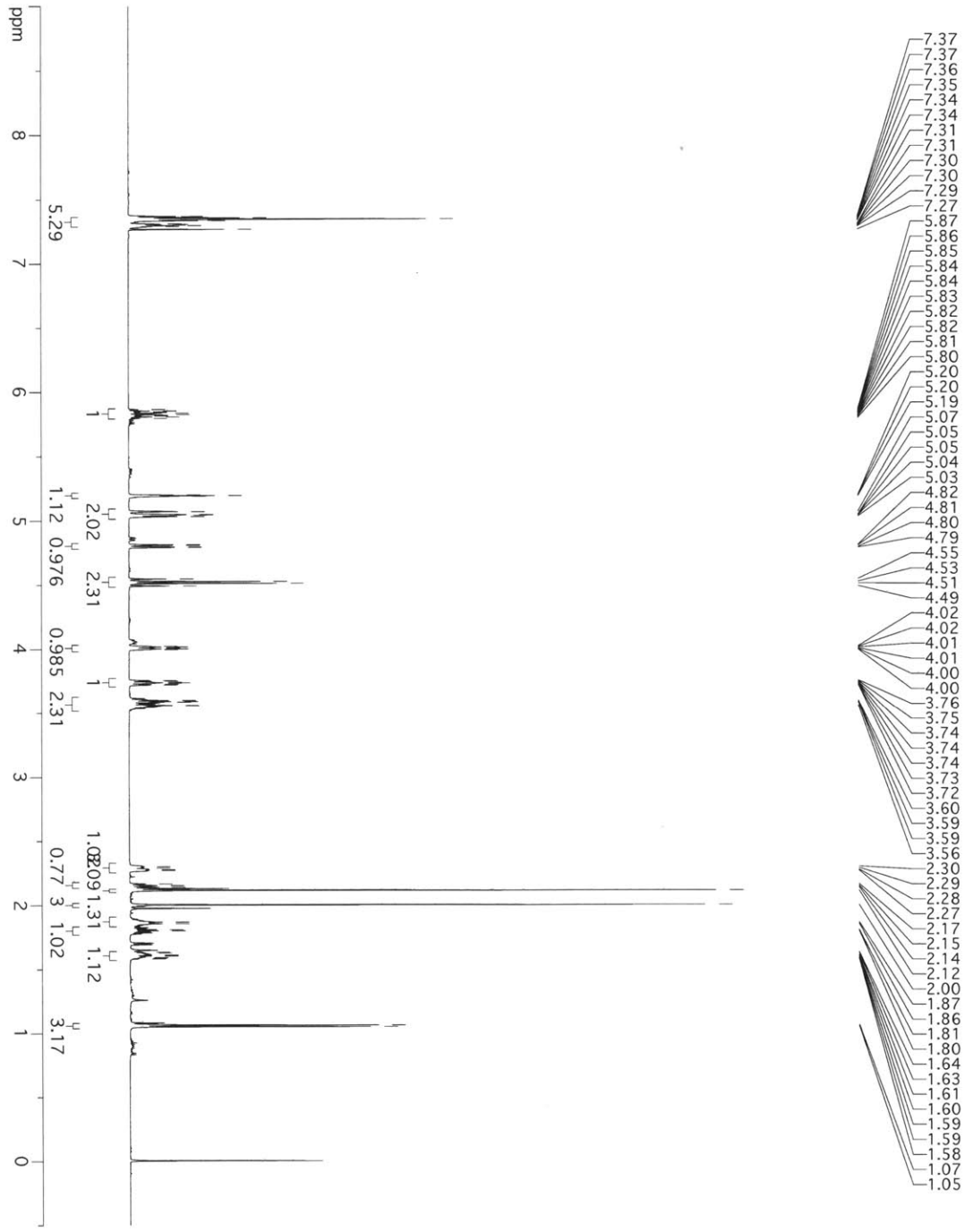
26.7
26.0
22.7
18.5
14.3
5.2


OAc
Me
OAc
BnO
H
O
H

46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5
4
3
2
1
0
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2.02
2.31
1.12
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0.985
2.31
1.02
1.31
1.12
0.77
3
1.02
3.17
7.37
7.37
7.36
7.35
7.34
7.34
7.31
7.31
7.30
7.30
7.29
7.27
5.87
5.86
5.85
5.84
5.84
5.83
5.82
5.82
5.81
5.80
5.20
5.20
5.19
5.07
5.05
5.05
5.04
5.03
4.82
4.81
4.80
4.79
4.55
4.53
4.51
4.49
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4.02
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3.76
3.75
3.74
3.74
3.74
3.73
3.72
3.60
3.59
3.59
3.56
2.30
2.29
2.28
2.27
2.17
2.15
2.14
2.12
2.00
1.87
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1.81
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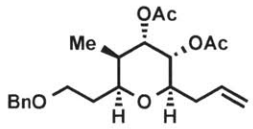
1.61
1.60
1.59
1.59
1.58
1.07
1.05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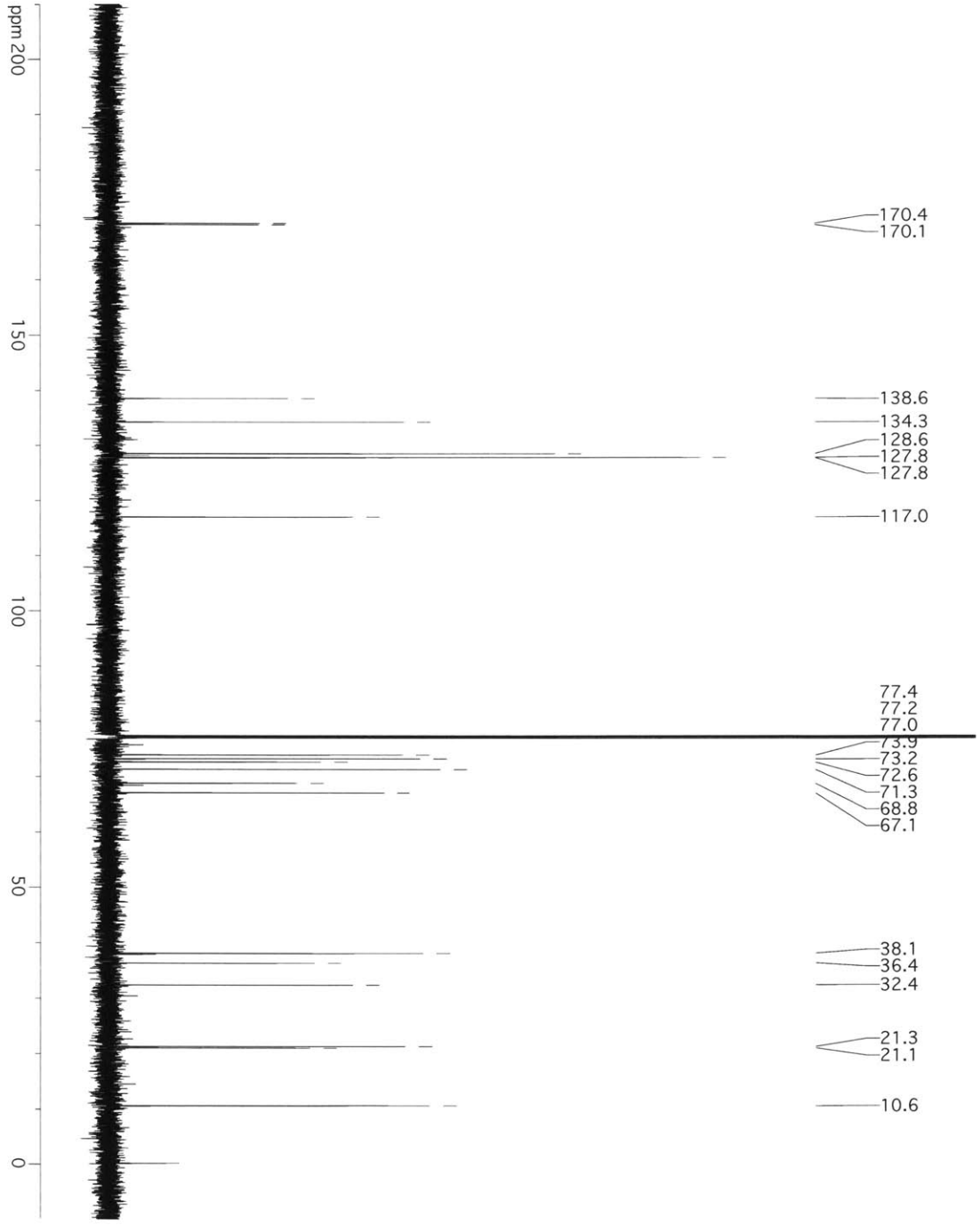
Me
OAc
BnO
O
H
H

46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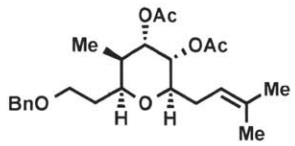
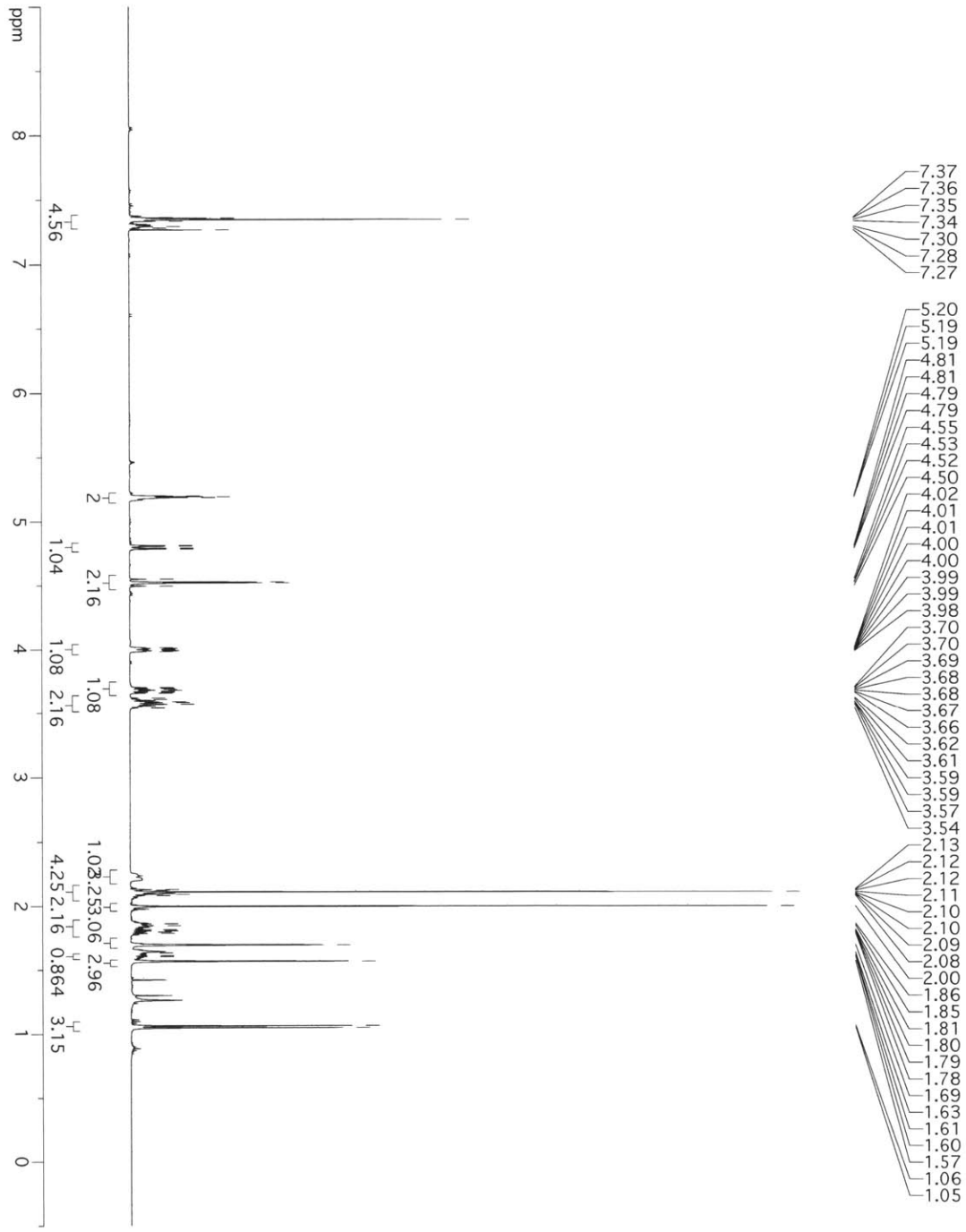
128.6
127.8
127.8
117.0
77.4
77.2
77.0
73.9
73.2
72.6
71.3
68.8
67.1
38.1
36.4
32.4
21.3
21.1
10.6


OAc
Me
OAc
BnO
H
O
H
Me
Me

107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5
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1
0
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2
1.04
2.16
1.08
1.08
2.16
1.02
3.25
3.06
2.96
4.25
2.16
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3.15
7.37
7.36
7.35
7.34
7.30
7.28
7.27
5.20
5.19
5.19
4.81
4.81
4.79
4.79
4.55
4.53
4.52
4.50
4.02
4.01
4.01
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3.68
3.68
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3.59
3.59
3.57
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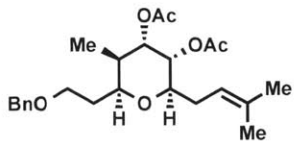
1.57
1.06
1.05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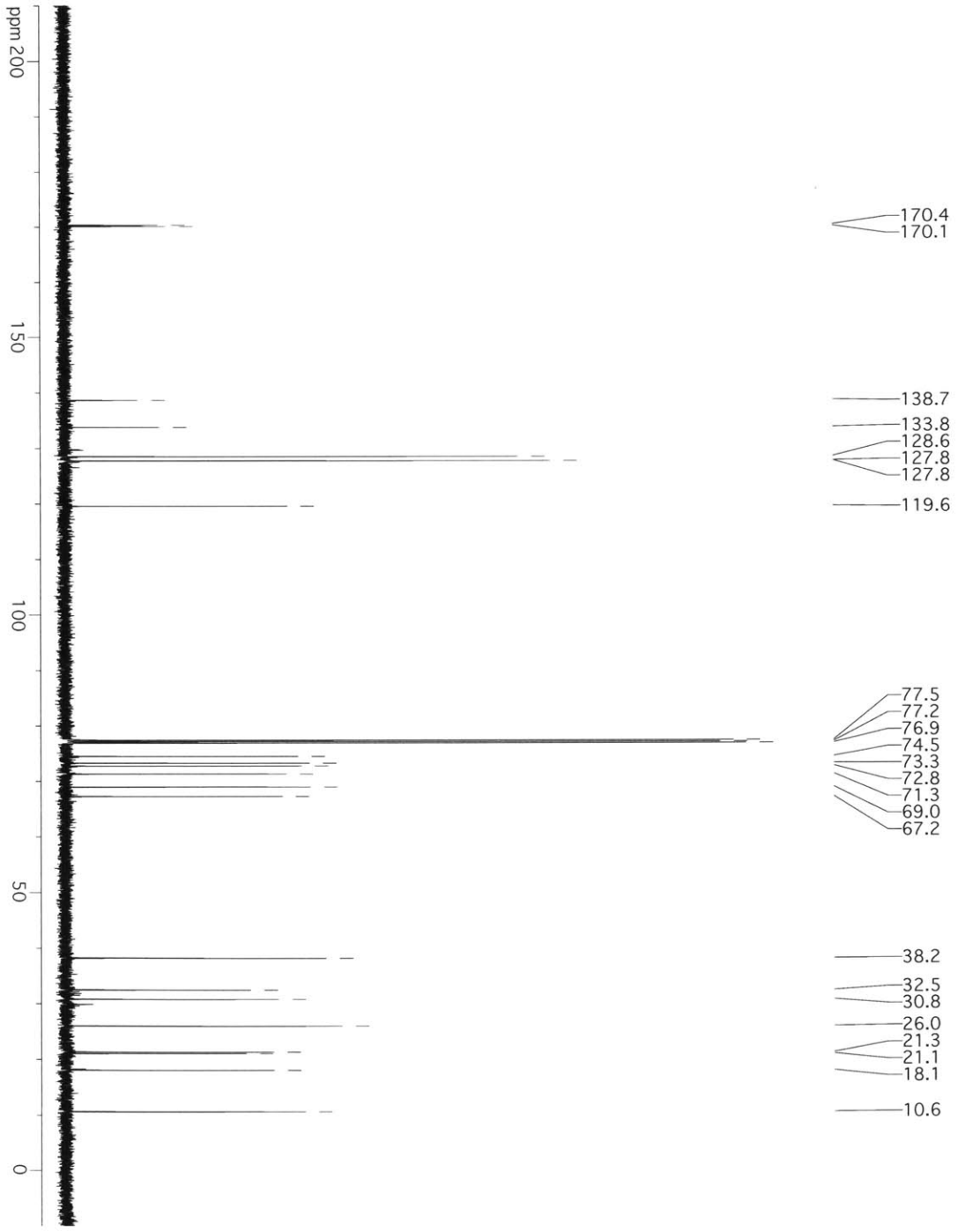
Me
OAc
BnO
O
H
H
Me
Me

107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170.1
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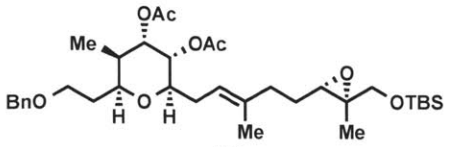
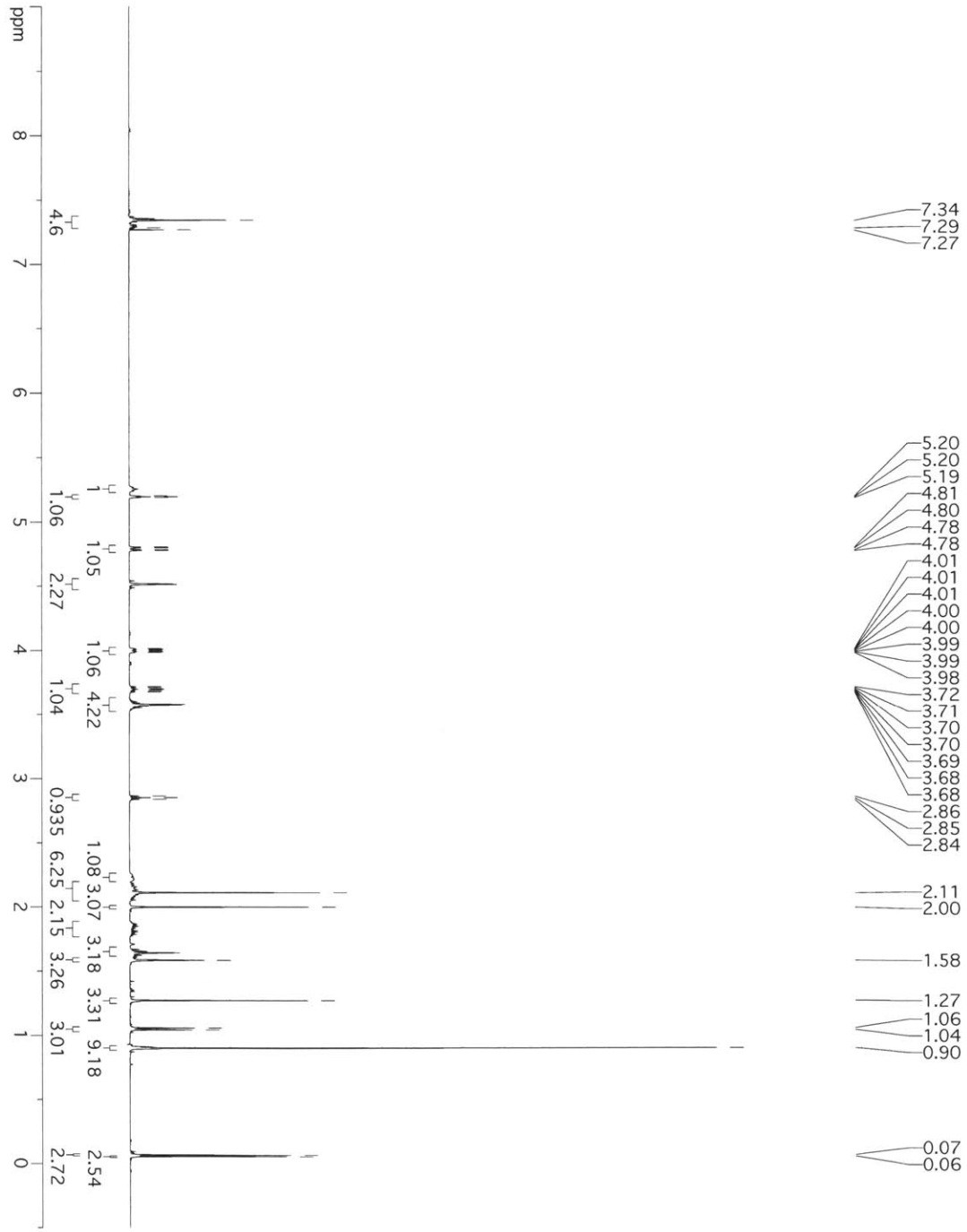
128.6
127.8
127.8
119.6
77.5
77.2
76.9
74.5
73.3
72.8
71.3
69.0
67.2
38.2
32.5
30.8
26.0
21.3
21.1
18.1
10.6


OAc
Me
OAc
BnO
H
O
H
O
OTBS
Me
Me

50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5
4
3
2
1
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4.6
1
1.06
1.05
2.27
1.06
4.22
1.04
0.935
6.25
1.08
3.07
2.15
3.18
3.26
3.31
3.01
9.18
2.54
2.72
7.34
7.29
7.27
5.20
5.20
5.19
4.81
4.80
4.78
4.78
4.01
4.01
4.01
4.00
4.00
3.99
3.99
3.98
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3.71
3.70
3.70
3.69
3.68
3.68
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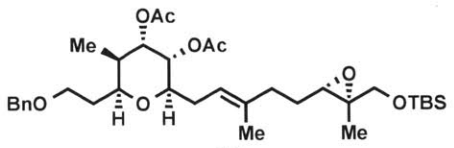
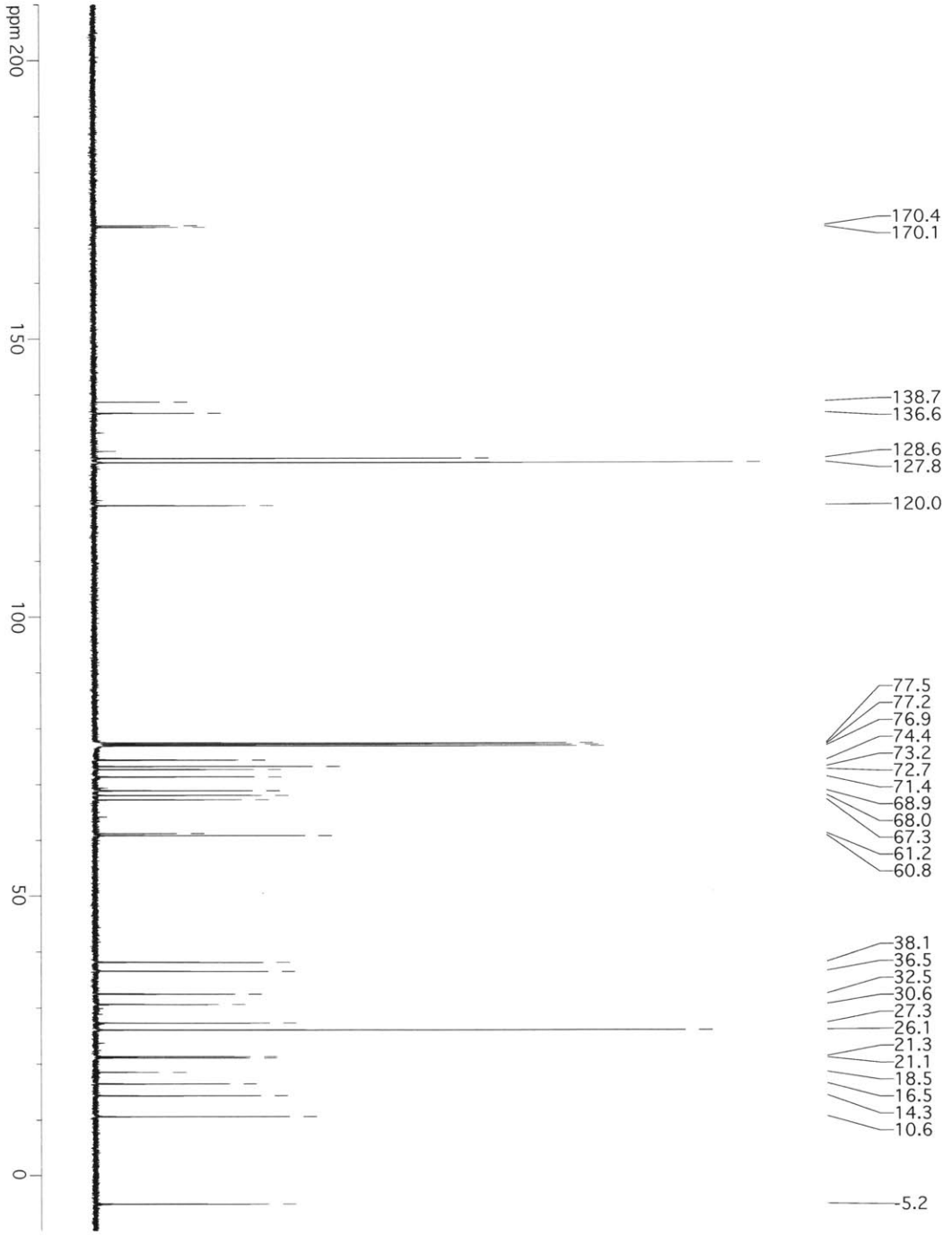
2.85
2.84
2.11
2.00
1.58
1.27
1.06
1.04
0.90
0.07
0.06


OAc
Me
OAc
BnO
O
H
H
O
Me
Me
OTBS

50


ppm
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170.1
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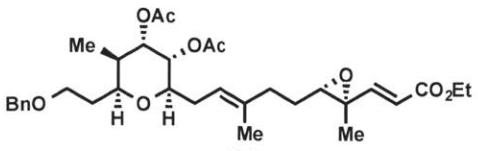
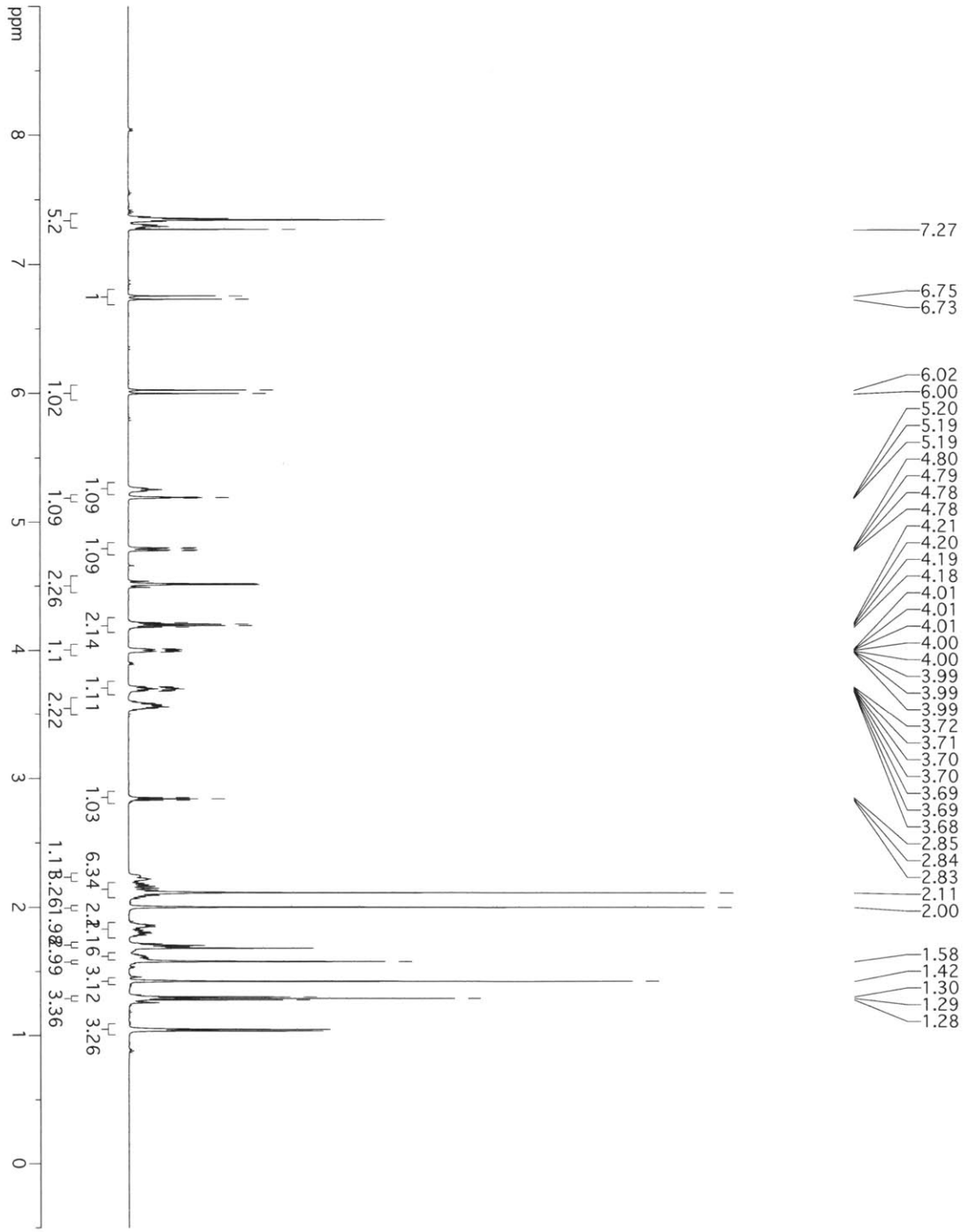
136.6
128.6
127.8
120.0
77.5
77.2
76.9
74.4
73.2
72.7
71.4
68.9
68.0
67.3
61.2
60.8
38.1
36.5
32.5
30.6
27.3
26.1
21.3
21.1
18.5
16.5
14.3
10.6
-5.2


OAc
Me
OAc
BnO
H
O
H
Me
Me
O
CO2Et

109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1.09
1.09
2.26
2.14
1.1
1.11
2.22
1.03
6.34
2.2
2.16
3.12
3.26
1.1
8.26
1.98
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3.36
7.27
6.75
6.73
6.02
6.00
5.20
5.19
5.19
4.80
4.79
4.78
4.78
4.21
4.20
4.19
4.18
4.01
4.01
4.01
4.00
4.00
3.99
3.99
3.99
3.72
3.71
3.70
3.70
3.69
3.69
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2.00
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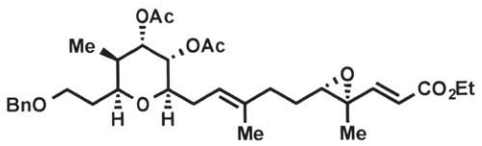
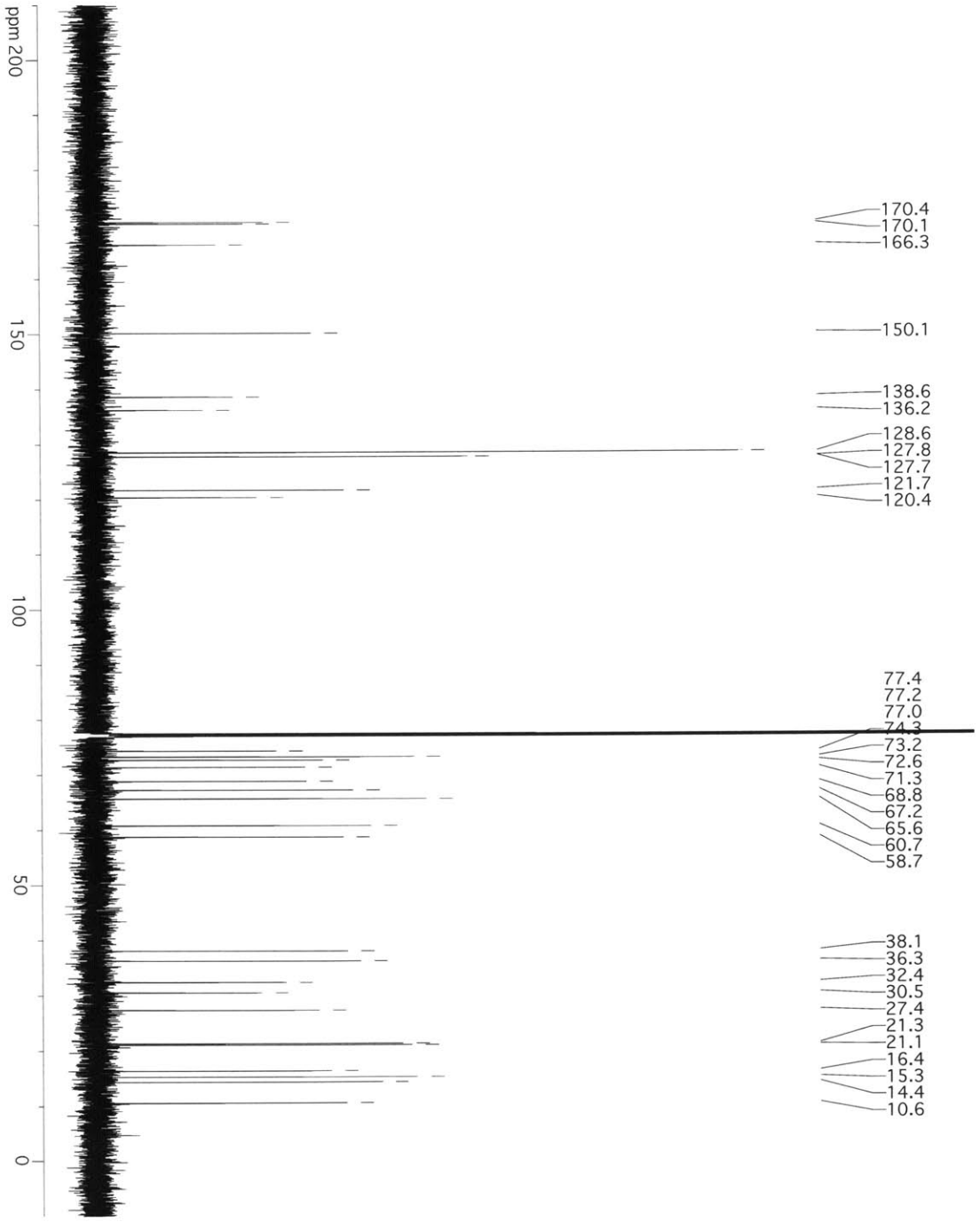
1.30
1.29
1.28


OAc
Me
OAc
BnO
O
H
O
H
Me
O
Me
CO2Et

109


ppm 200
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166.3
150.1
138.6
136.2
128.6
127.8
127.7
121.7
120.4
77.4
77.2
77.0
74.3
73.2
72.6
71.3
68.8
67.2
65.6
60.7
58.7
38.1
36.3
32.4
30.5
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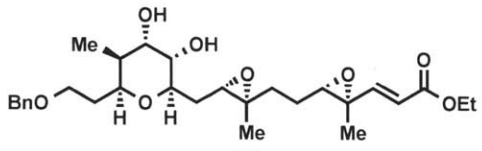
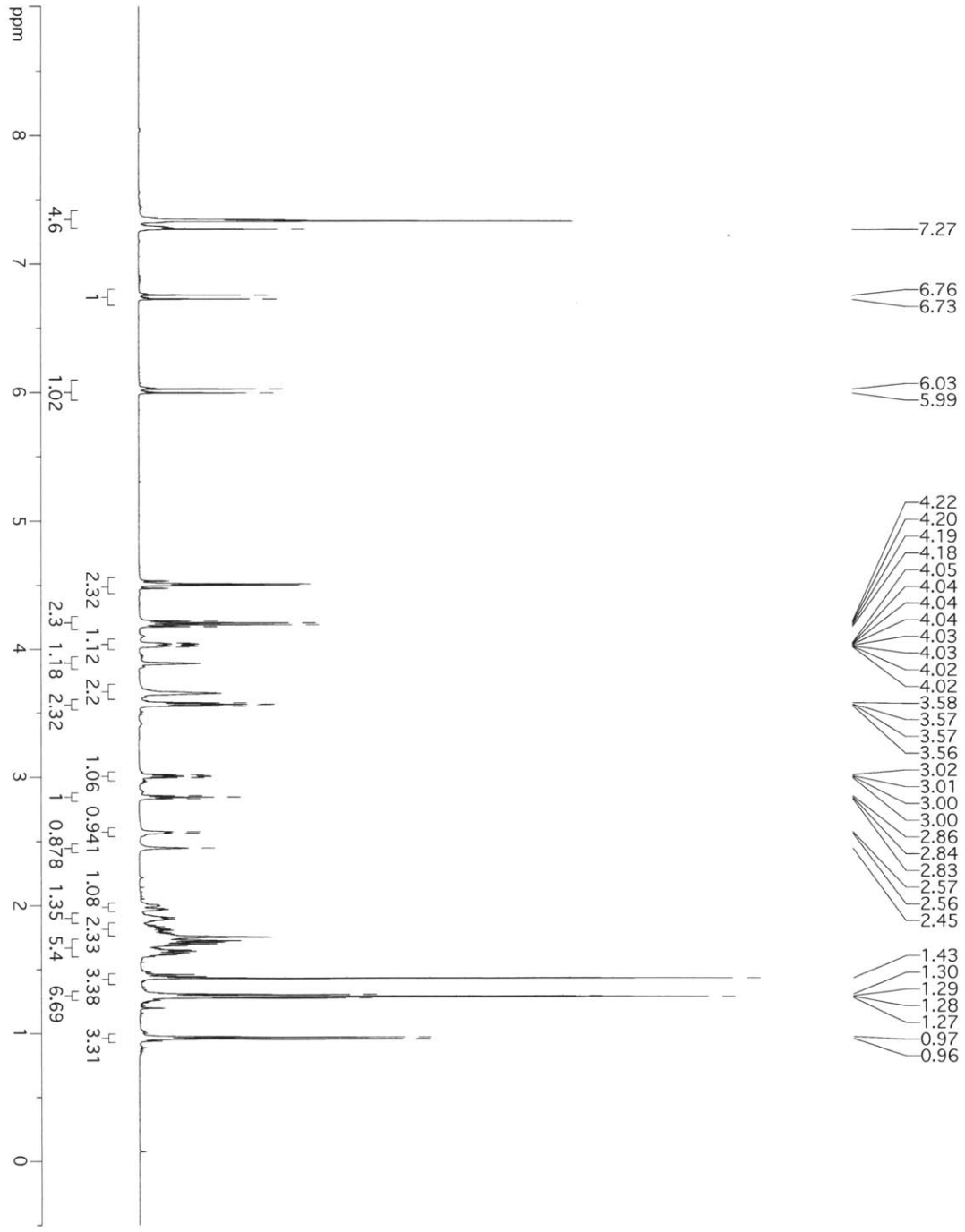
21.3
21.1
16.4
15.3
14.4
10.6


OH
Me
OH
BnO
H
O
H
O
O
O
Me
Me
OEt

95


ppm
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3
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1
0
4.6
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1.02
2.32
2.3
1.12
1.18
2.2
2.32
1.06
1
0.941
0.878
1.08
1.35
2.33
5.4
3.38
6.69
3.31
7.27
6.76
6.73
6.03
5.99
4.22
4.20
4.19
4.18
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4.04
4.04
4.04
4.03
4.03
4.02
4.02
3.58
3.57
3.57
3.56
3.02
3.01
3.00
3.00
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1.29
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1.27
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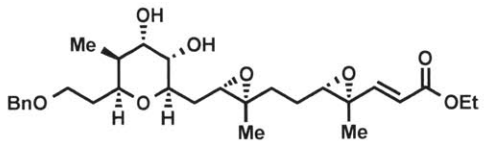
0.96


OH
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OH
BnO
O
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H
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Me
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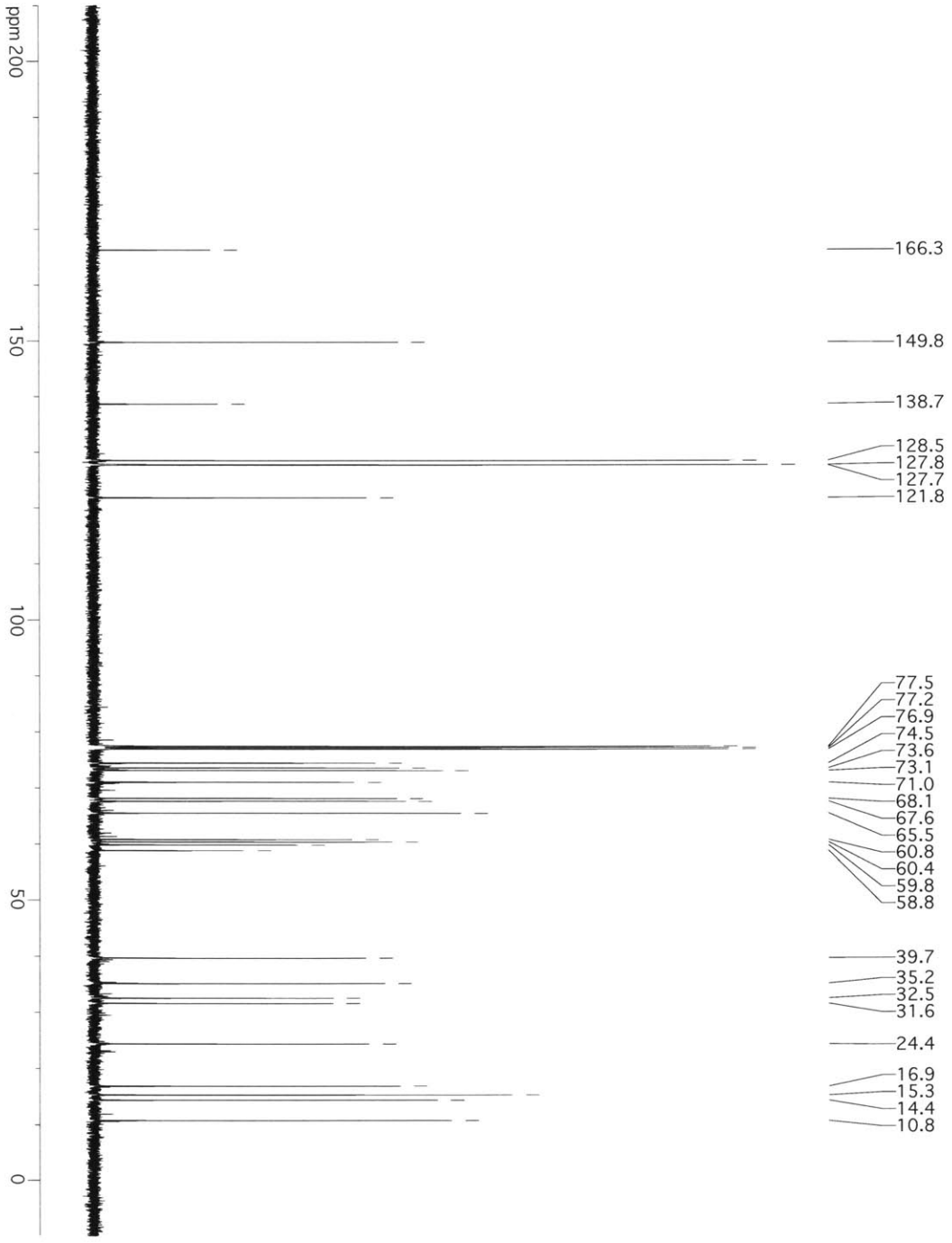
Me
O
OEt

95


ppm
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127.8
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77.2
76.9
74.5
73.6
73.1
71.0
68.1
67.6
65.5
60.8
60.4
59.8
58.8
39.7
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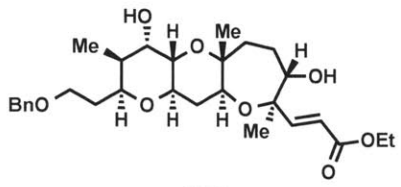
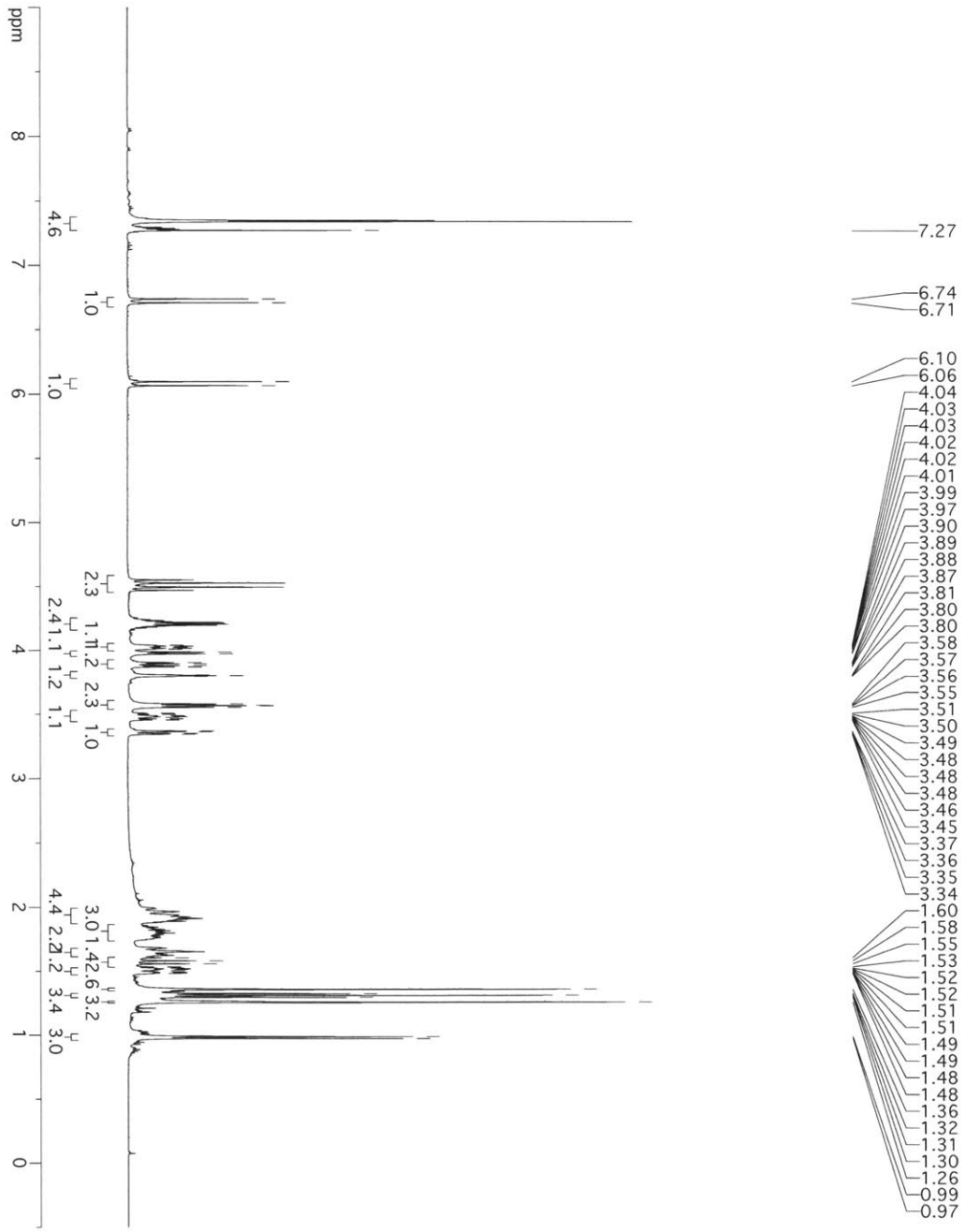
32.5
31.6
24.4
16.9
15.3
14.4
10.8


HO
H
Me
O
Me
H
OH
BnO
H
O
H
H
O
Me
OEt
O

106


ppm
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1.1
2.4
1.1
1.2
2.3
1.0
1.1
4.4
2.2
2.2
2.2
3.4
3.0
3.0
1.4
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4.03
4.02
4.02
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3.51
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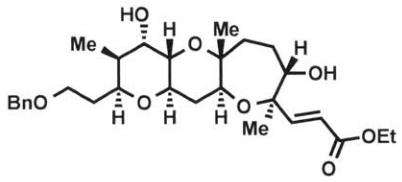
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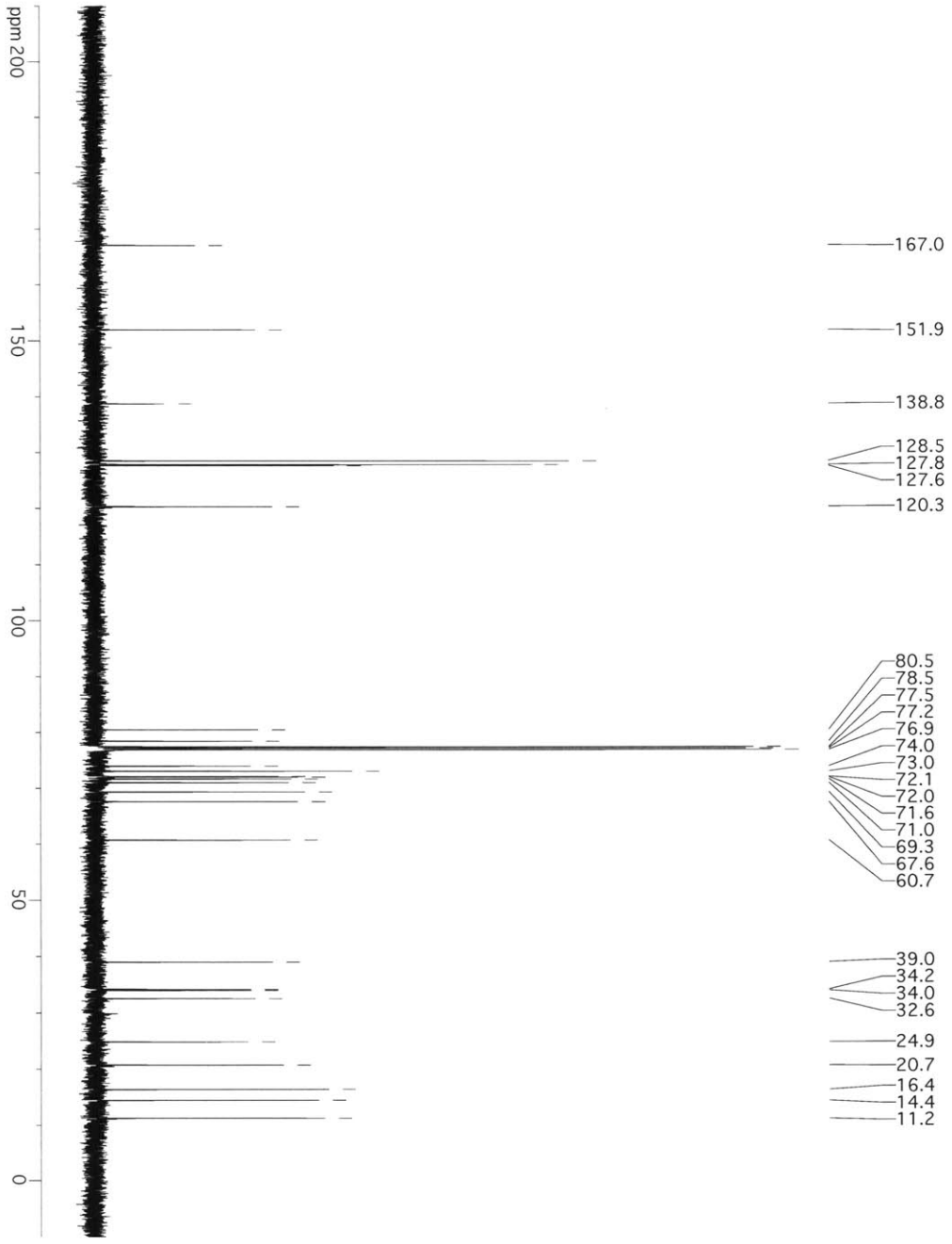
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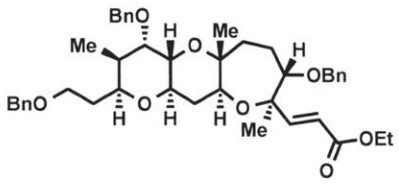
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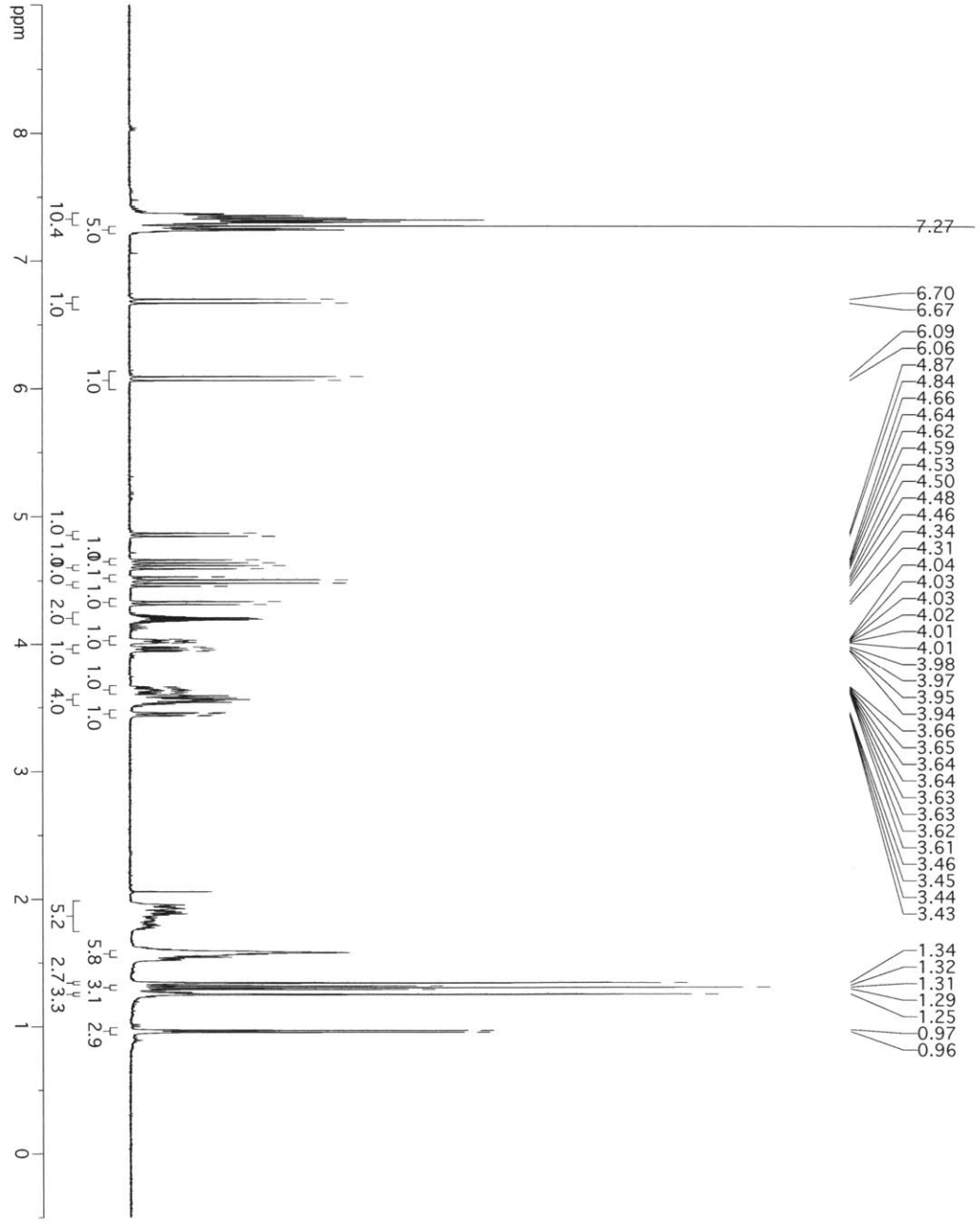
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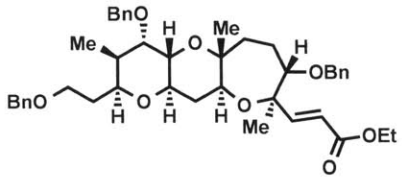
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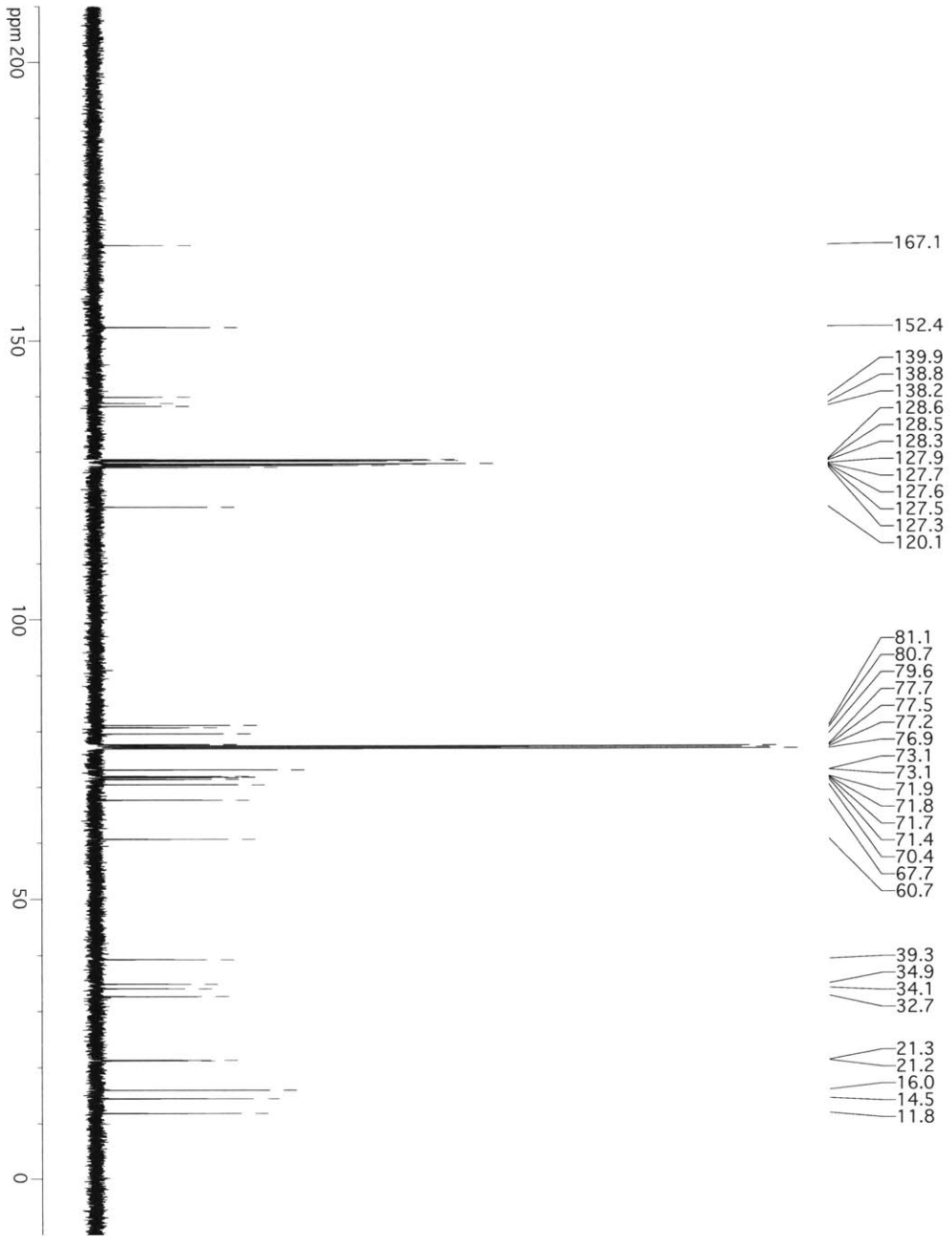
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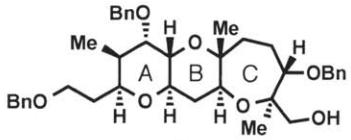
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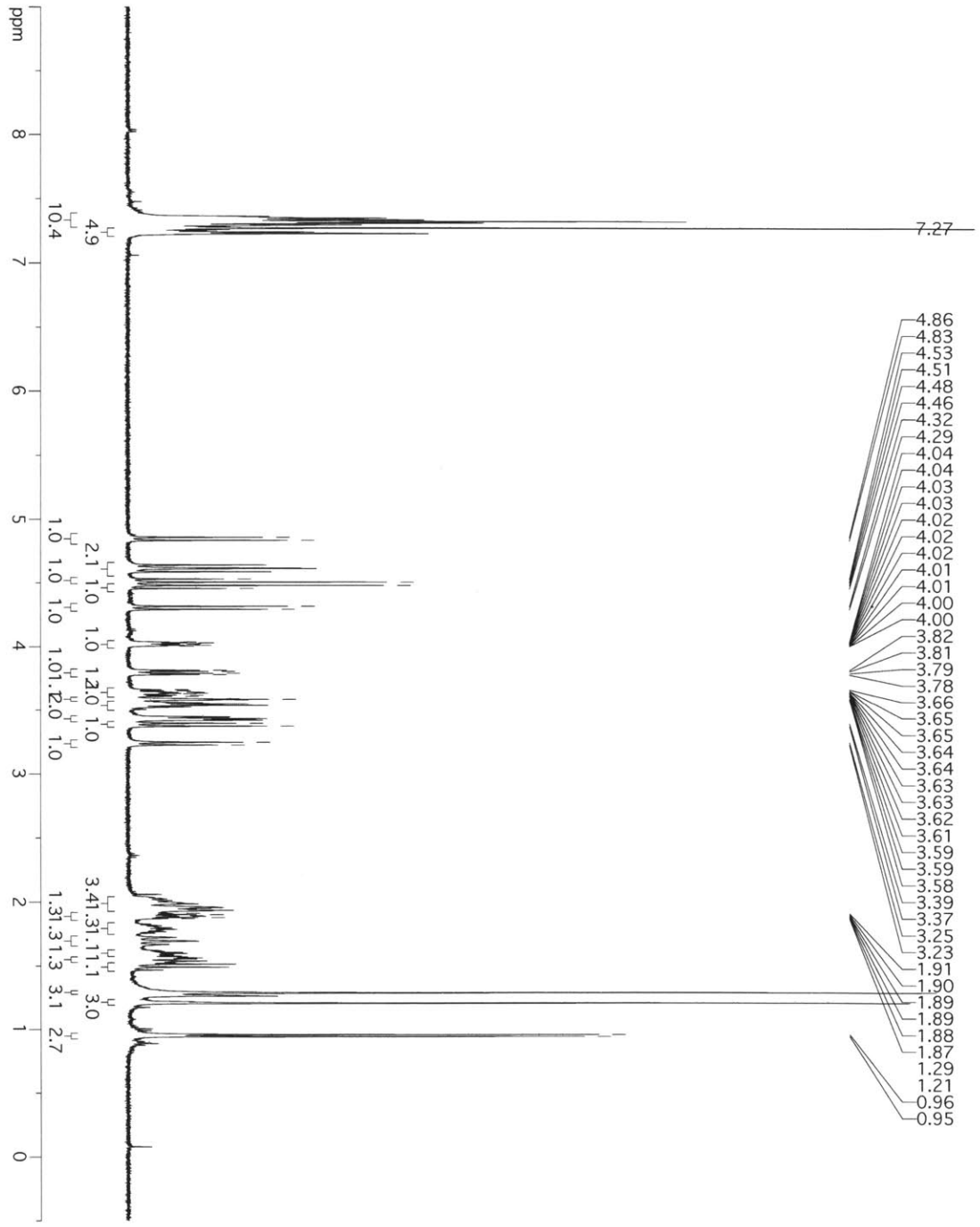
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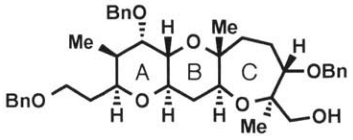
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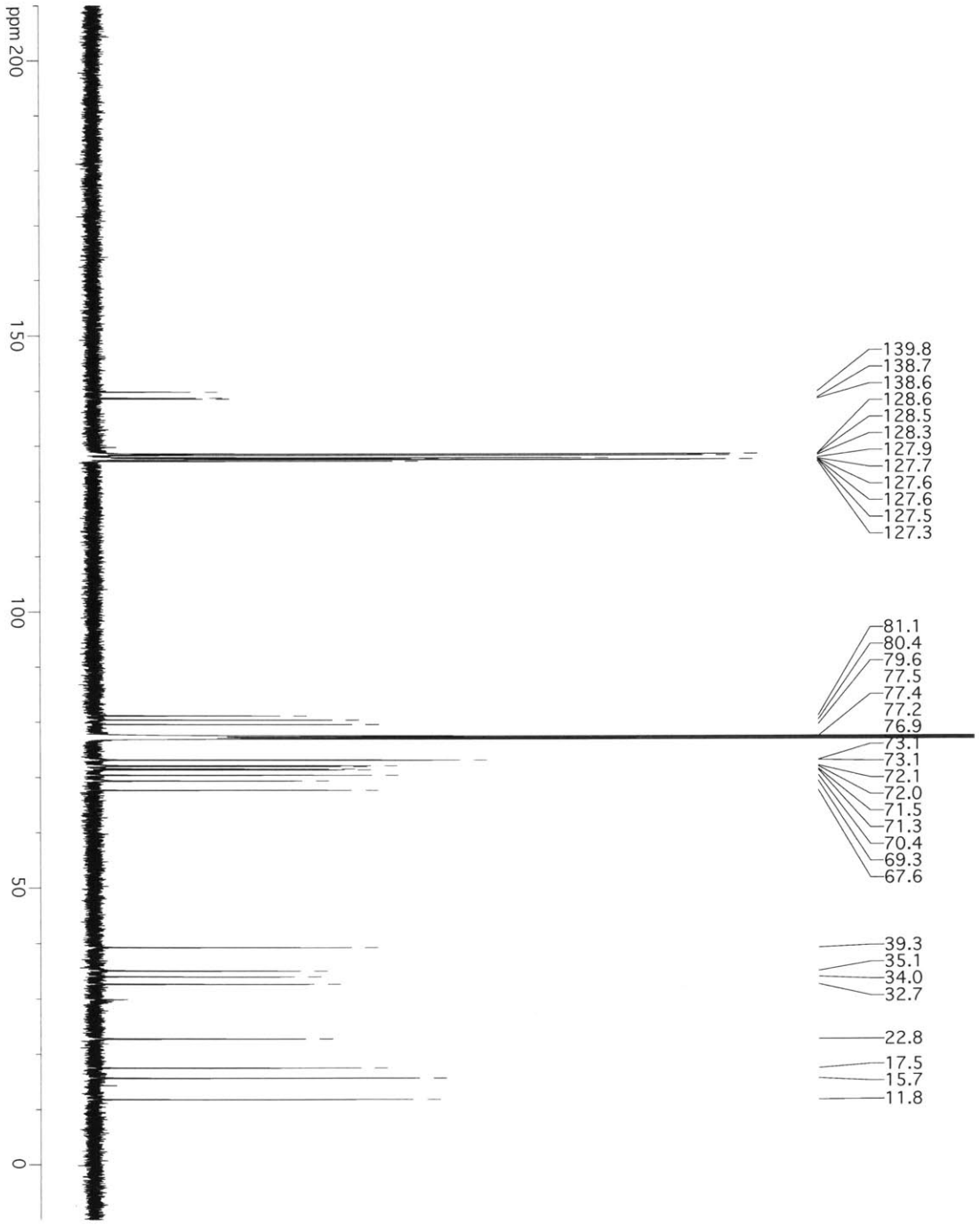
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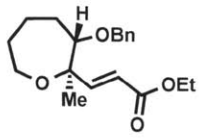
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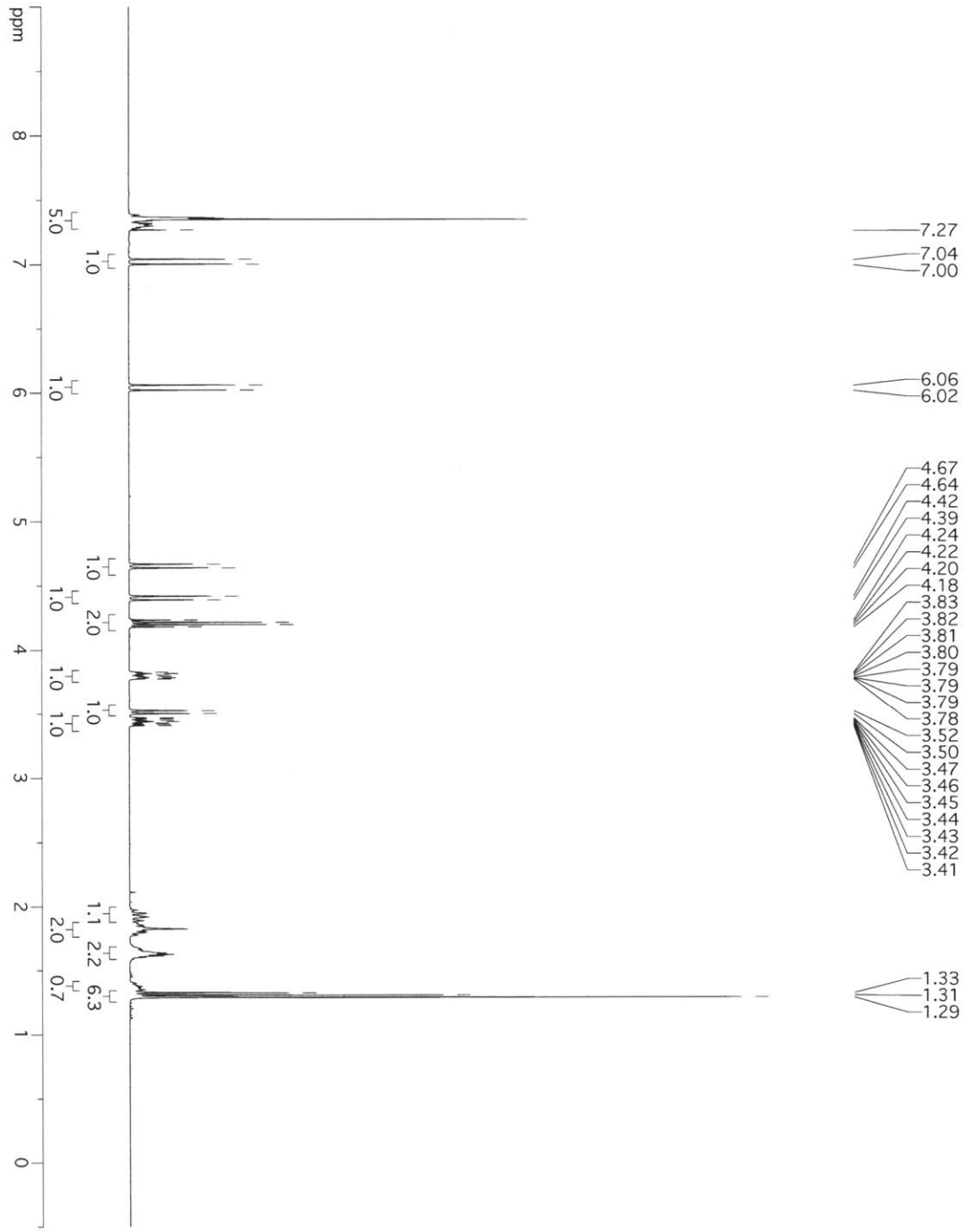
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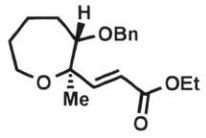
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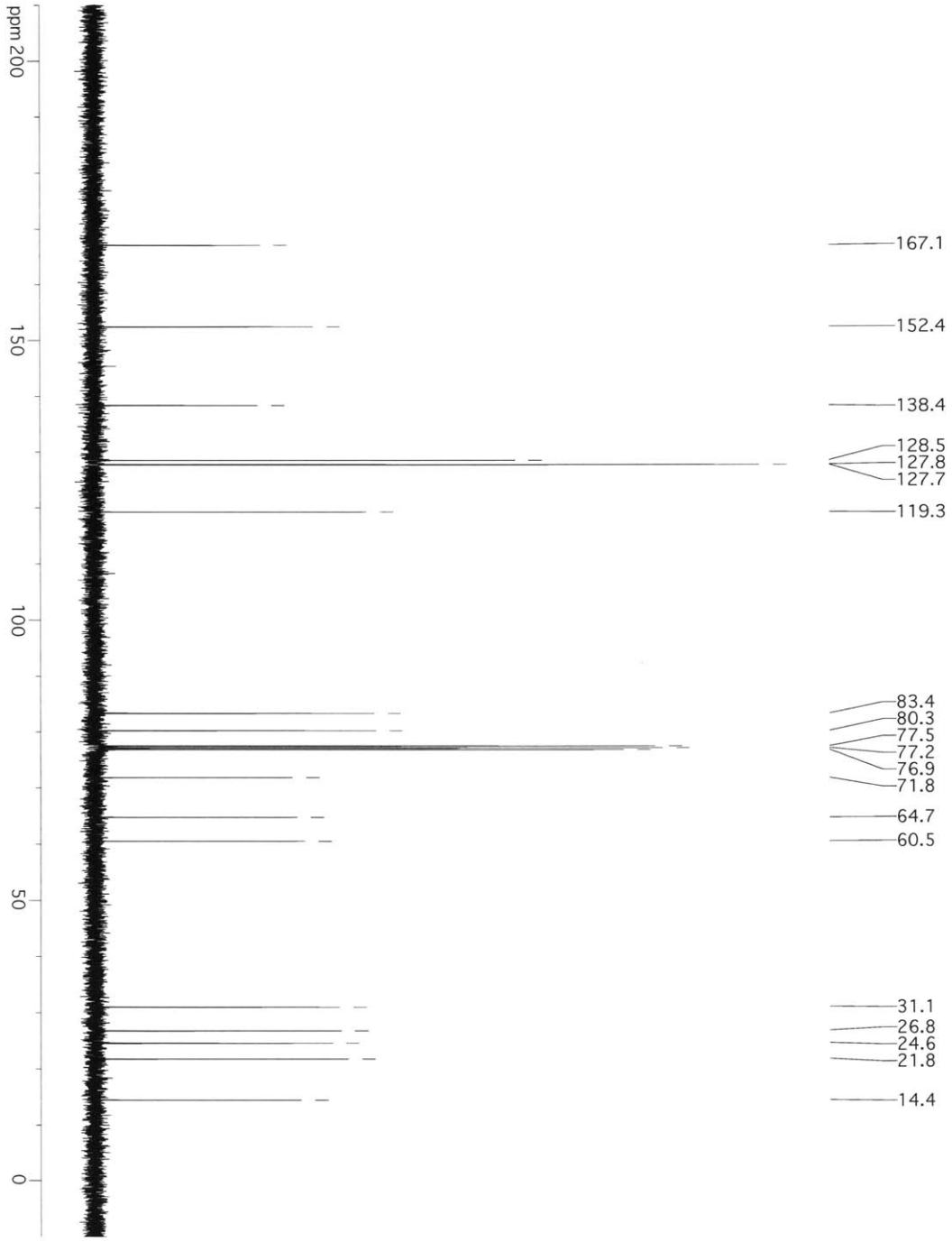
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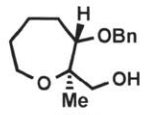
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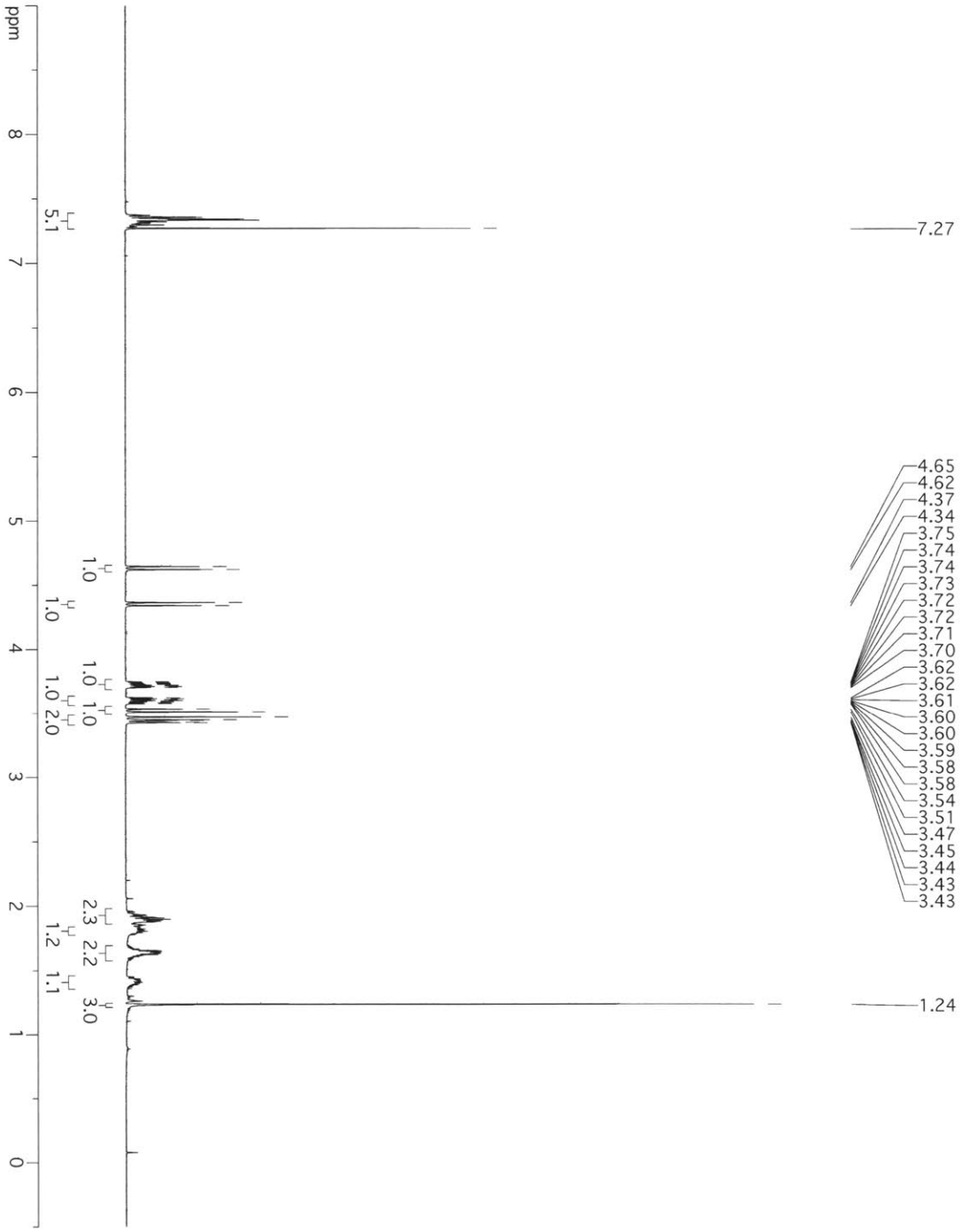
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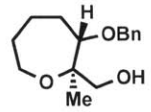
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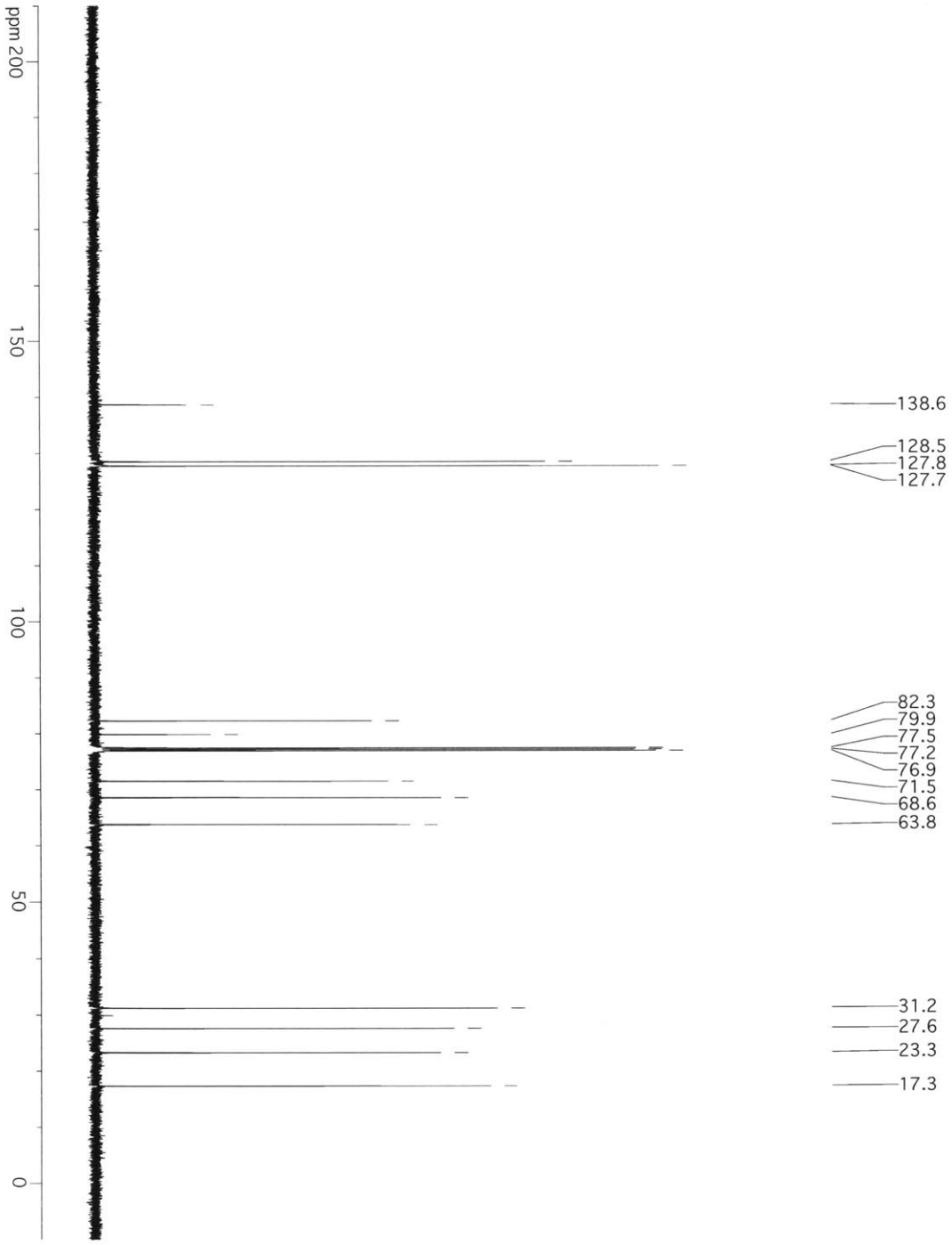
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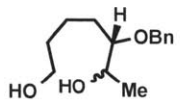
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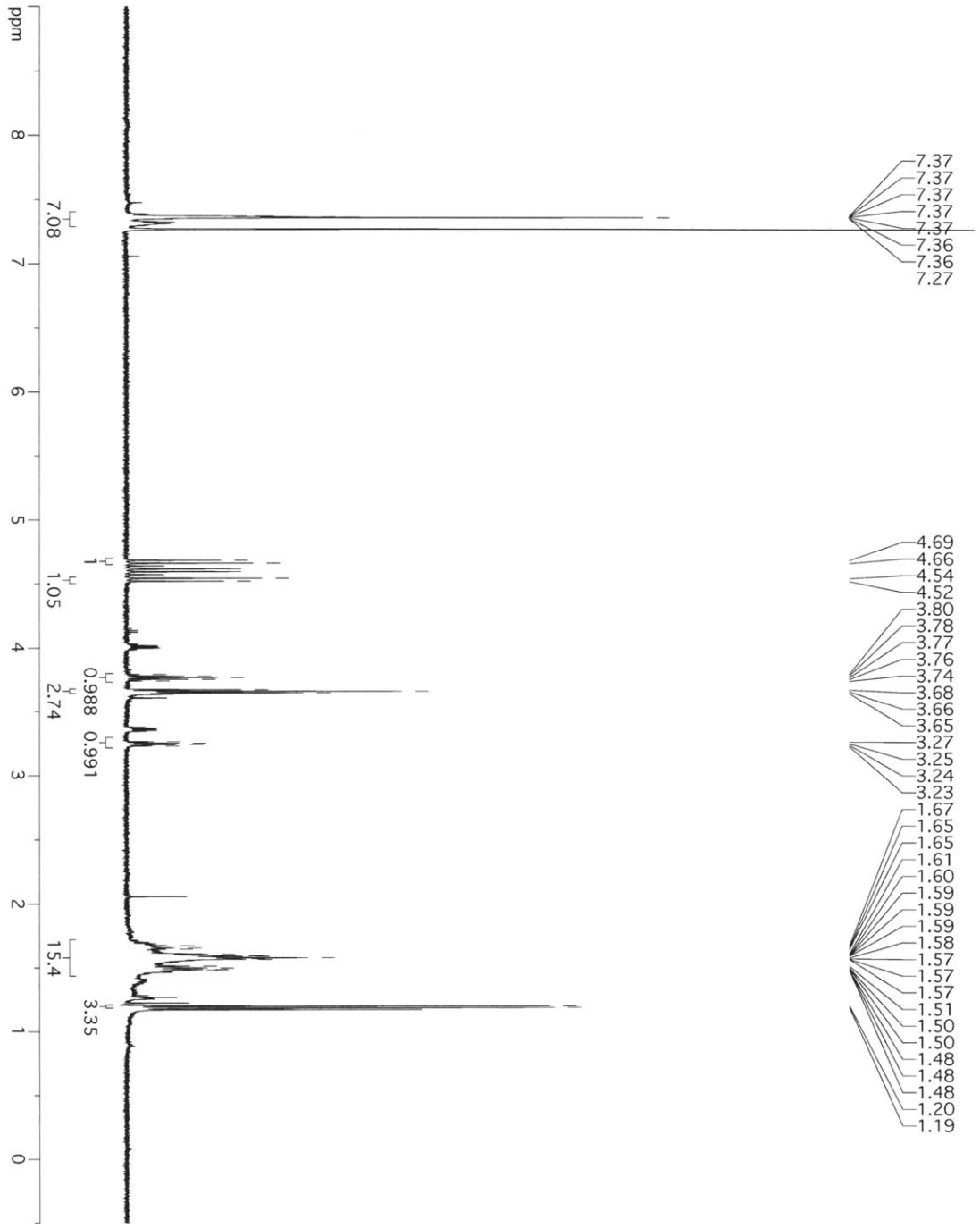
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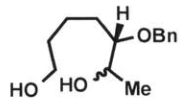
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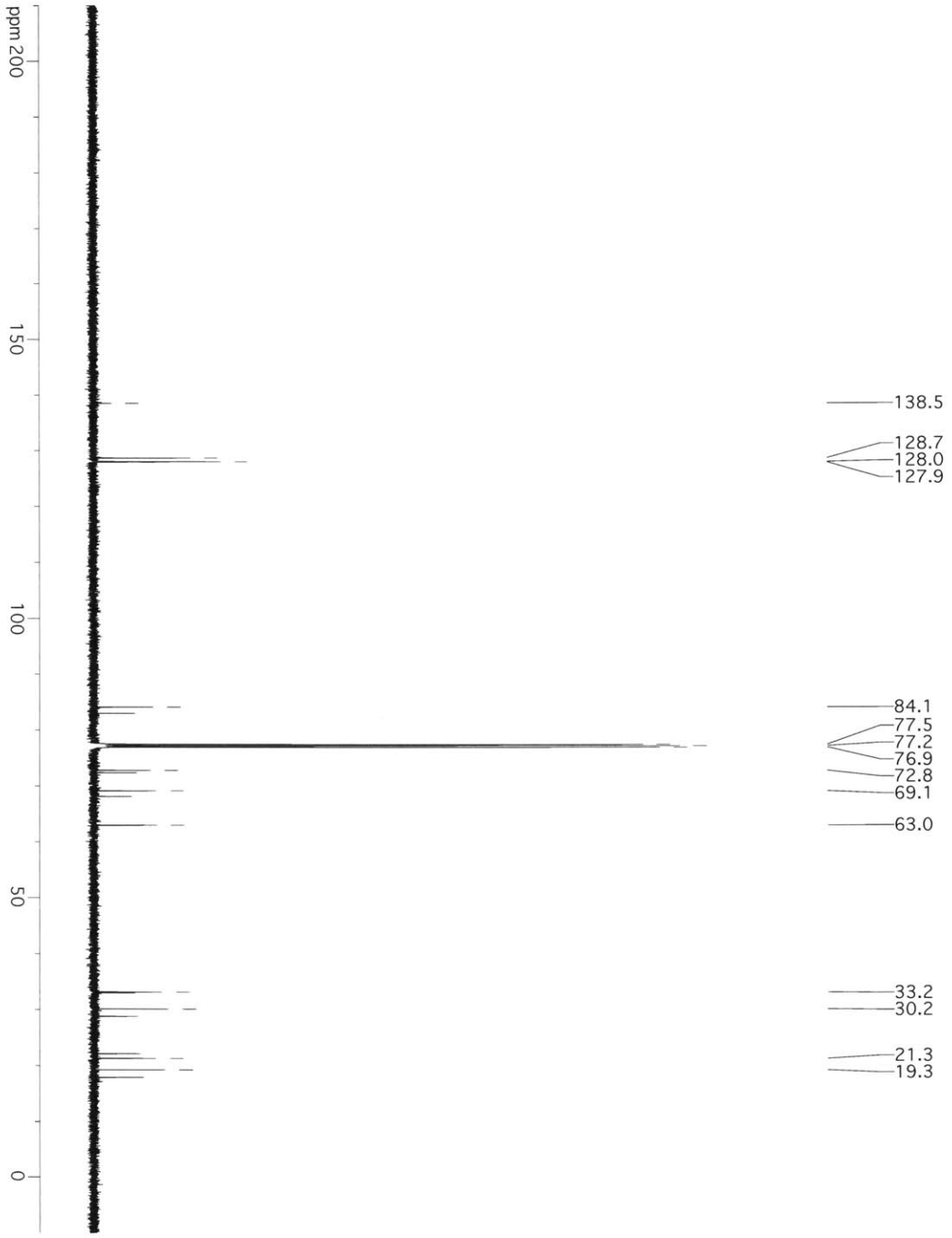
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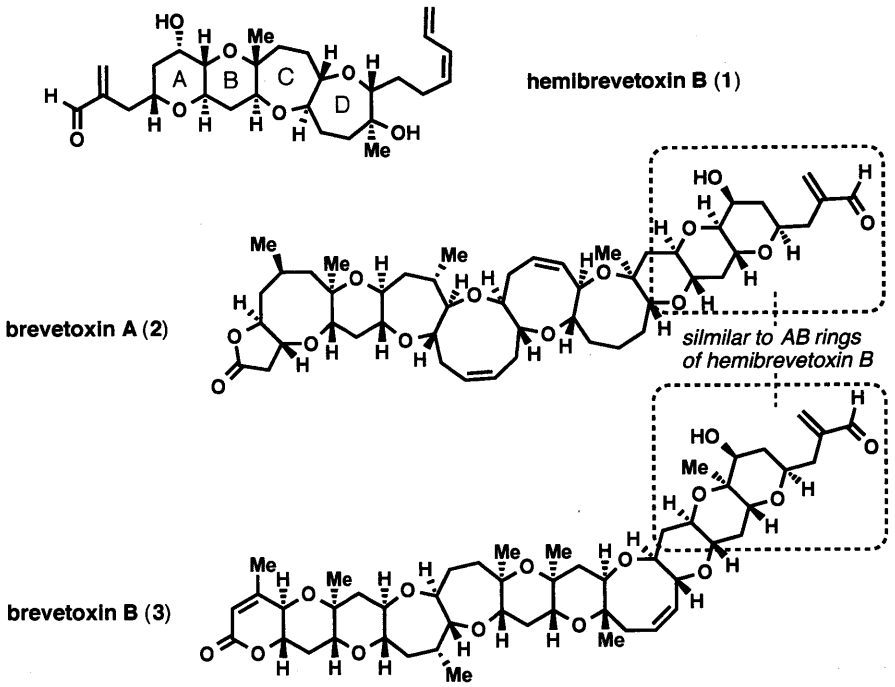
Chapter II

Rhodium-Catalyzed Epoxide-Opening Cascades: Synthetic Studies Toward Hemibrevetoxin B

A. Introduction to Hemibrevetoxin B

Having demonstrated the ability of $[Rh(CO)_2Cl]_2$ to promote site-selective initiation of cascades for the synthesis of the ABC and EF fragments of brevisin, we next wanted to explore the utility of Rh catalysis in a more challenging setting. We selected hemibrevetoxin B (**1**) as a suitable target, hoping to exploit the similarity of the ABC rings of **1** and brevisin. Isolated from cultures of *Karenia brevis*, hemibrevetoxin B shows cytotoxicity against mouse neuroblastoma cells (IC_{50} = 5 μM).[1] This natural product has attracted significant synthetic interest since the reported structural elucidation in 1989. While hemibrevetoxin B is smaller in comparison to closely related brevetoxins A (**2**) and B (**3**), it contains the key structural features found throughout the class, making it an ideal target to test new synthetic methodology (Figure 1). Additionally, the structural similarity of the AB rings of hemibrevetoxin B to fragments of **2** and **3** provide additional motivation for synthetic studies. Specifically, with four fused rings, 10 stereogenic centers, an axial methyl groups at the AB ring junction, and two fused oxepanes, hemibrevetoxin B provides an intricate challenge to synthetic chemists.

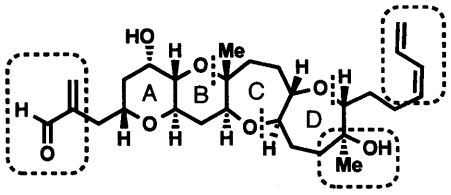
Figure 1. Structure of hemibrevetoxin B (**1**) and closely related brevetoxins A (**2**) and B (**3**)



[1] Prasad, A. V. K.; Shimizu, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6476.

Nicolaou and coworkers reported in 1992 the first total synthesis of hemibrevetoxin B, which was also the first total synthesis of any ladder polyether.[2] This landmark synthesis, achieved in 51 steps longest linear sequence (LLS) in 0.08% overall yield, utilized methodology developed towards a total synthesis of brevetoxin B.[3] The synthesis proceeded in a linear fashion, with stepwise formation of the A–D rings (Figure 2). The A ring was synthesized from D-mannose, followed by an epoxy alcohol cyclization to form the B ring. The C and D rings were formed sequentially by lactone formation, transformation to the thionolactone and cuprate addition. The D-ring methyl was installed via Grignard addition into a ketone, now typically used for this part of the molecule. Finally, the (*Z*)-diene was installed by a Wittig olefination, and the enal portion was synthesized via a in situ Swern oxidation and methylene transfer from Eschenmoser's salt. Attempts at shortening the LLS via a more convergent approach utilizing fragment coupling to form the CD rings provided the wrong stereochemistry at the CD ring junction.[4]

Figure 2. Summary of hemibrevetoxin B total synthesis by Nicolaou and coworkers



1
51 steps total
0.08% overall

Order of Ring Formation
A: from D-mannose
B: epoxy alcohol cyclization
C: lactone formation
D: lactone formation

D-ring methyl: Grignard addn to ketone, 3:2 dr
(*Z*)-diene installation: Wittig with $PhSe(CH_2)_3PPh_3I$/ox. elim.
Enal installation: one-pot Swern/Eschenmoser's salt

A number of additional formal and total syntheses have been published, many utilizing transformations from Nicolaou's groundbreaking effort. Instead of reviewing the large number of syntheses comprehensively, we will only highlight the key transformations used in the various syntheses toward the CD ring system.[5] Yamamoto and coworkers reported the second synthesis, with the C and D rings generated via the cyclization of γ-alkoxyallylstannanes onto aldehydes.[6] Nakata and coworkers first synthesized fused THPs and utilized a double ring expansion.[7] Mori

---

[2] Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X. Y. *J. Am. Chem. Soc.* **1992**, *114*, 7935.

[3] See the following for an account of efforts towards the total synthesis of brevetoxin B and hemibrevetoxin B: Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 588.

[4] Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X. Y.; Hwang, C. K. *J. Am. Chem. Soc.* **1993**, *115*, 3558.

[5] (a) Inoue, M. *Chem. Rev.* **2005**, *105*, 4379. (b) Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7182.

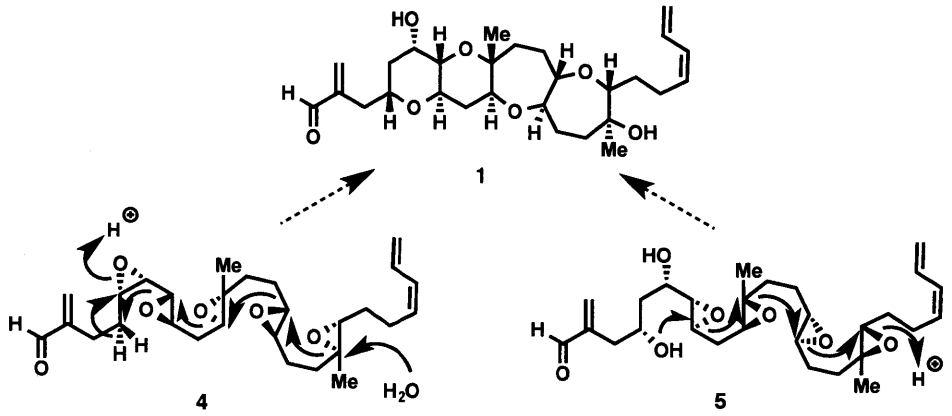
[6] Kadota, I.; Jungyoul, P.; Koumura, N.; Pollaud, G.; Matsukawa, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1995**, *36*, 5777.

[7] Morimoto, M.; Matsukura, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6365.

and coworkers synthesized the C and D rings sequentially through a two-step epoxy alcohol cyclization directed by a deactivating sulfone group to form a THP, followed by ring expansion.[8] Holton and coworkers synthesized the C ring as part of an epoxy alcohol cascade onto an in situ generated selenium ion, while the D ring was assembled via ring-closing metathesis.[9] Rainer and coworkers utilized a sequential cyclic enol ether formation via ring-closing metathesis, DMDO epoxidation, and in situ epoxide opening with an allyl Grignard reagent for the formation of each ring.[10] Rainer's synthesis also represents the shortest synthesis to date, in 29 steps LLS.

In line with our group's long-standing interest in the biosynthetic hypothesis for ladder polyethers, we looked to the epoxide-opening cascades proposed for hemibrevetoxin B for inspiration (Scheme 1). The first cascade, put forth by Shimizu in the isolation report, is very similar to the original brevetoxin B proposal.[1] Protonation of polyepoxide **4** would initiate the cascade by a 1,2-hydride shift, followed by trapping of the next epoxide by the newly generated carbocation. Subsequent all-*endo* epoxide trapping with a final methyl-directed quench by water would lead to **1**. Alternatively, switching the direction of the cascade leads to polyepoxide precursor **5** proposed by McDonald.[11] The initiation phase of this epoxide-opening cascade appears more straightforward, as it avoids hydride shifts; however, the need to override the *exo* directing effect of the proximal methyl group in the first ring closure also adds to the complexity of this cascade.

Scheme 1. Two proposals for the biosynthesis of hemibrevetoxin B

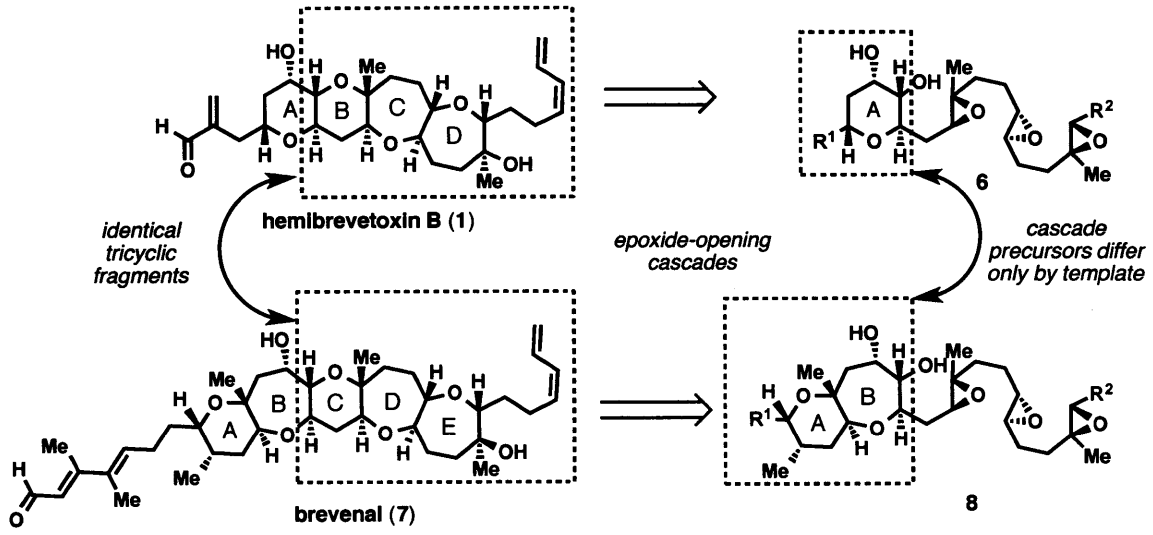


[8] Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Org. Chem.* **1998**, *63*, 6200.
[9] Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822.
[10] Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380.
[11] McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodríguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515.

B. Introduction and Previous Work on Triepoxide Cascade Toward Hemibrevetoxin B

Inspired by the proposed epoxide-opening cascades for hemibrevetoxin B, we were hoping to build upon our results from the synthesis of the ABC tricycle of brevisin. We were further encouraged to pursue the synthesis of hemibrevetoxin B as the same tricyclic fragment and side chain of hemibrevetoxin B (BCD rings) is also observed in brevenal (**7**, CDE rings), a potential lead for treating brevetoxin poisoning and cystic fibrosis (Scheme 2).[12] We anticipated that developing an epoxide-opening cascade for hemibrevetoxin B would allow us to leverage the similarities between **1** and **7** and readily translate the cascade to brevenal by modification of the template.[13] We chose to pursue hemibrevetoxin B first, given the known synthesis of templates similar to the A ring.[10]

Scheme 2. Similarities between hemibrevetoxin B and brevenal, with proposed epoxide-opening cascades



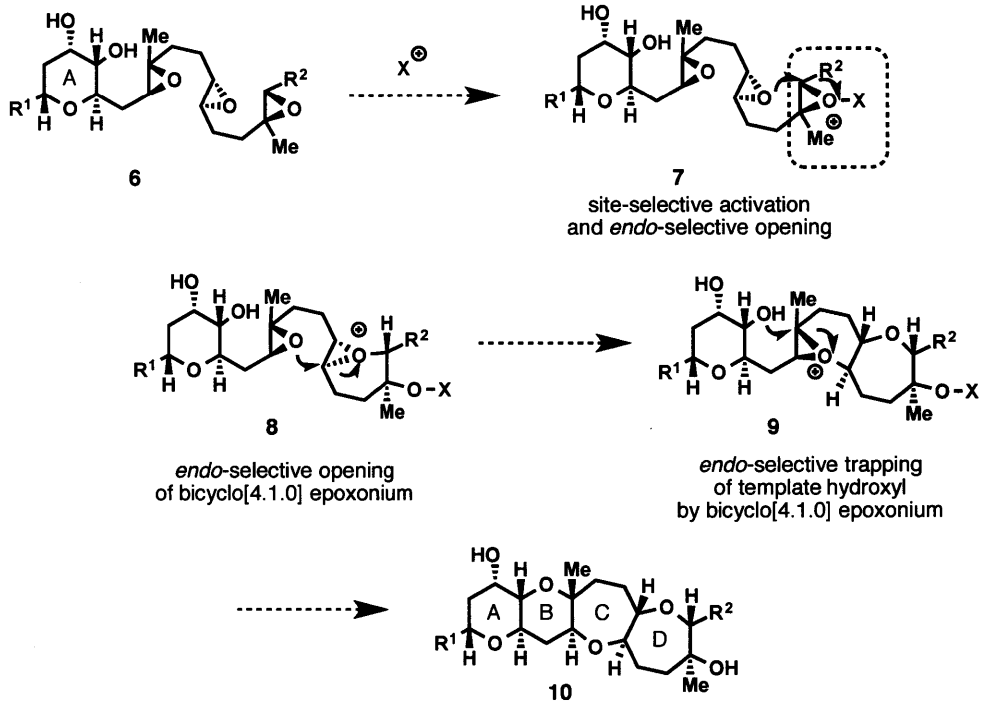
Our previous success in utilizing THP templates for biasing epoxy alcohol cyclizations to favor 6-*endo* closings, both in the water promoted reactions and in the site-selective, $[Rh(CO)_2Cl]_2$-catalyzed initiation of cascades for the synthesis of the ABC and EF ring systems of brevisin, led

[12] (a) Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, P. M.; Baden, D. G. *J. Nat. Prod.* **2005**, *68*, 2. (b) Abraham, W. M; Bourdelais, A. J.; Sabater, J. R.; Ahmed, A.; Lee, T. A.; Serebriakov, I.; Baden, D. G. *Am. J. Respir. Crit. Care Med.* **2005**, *171*, 26.

[13] While isolated oxepanes have been shown to be poor templates for water-promoted epoxy alcohol cyclizations toward THPs, the proposed template for the synthesis of brevenal would be a fused 6,7 system, likely reducing the conformational flexibility and restoring the proposed template effect. For a discussion of template rigidity and *endo* selectivity in water-promoted epoxy alcohol cyclizations, see: Byers, J. A.; Jamison, T. F. *Proc. Natl. Acad. Sci. U. S. A.* **2013**, *110*, 16724.

us to envision preforming the A ring for its potential use as a template in **6**. Mechanistically, we envisioned activation of the distal epoxide followed by *endo*-selective opening by the neighboring epoxide to generate a bicyclo[4.1.0] epoxonium (**7** to **8**, Scheme 3). We anticipated that this intermediate **8**, although lacking a methyl directing group, would react at least partially through the desired *endo* pathway based on the precedent from McDonald and Floreancig groups (**8** to **9**).[14] Finally, trapping of the second bicyclo[4.1.0] epoxonium intermediate **9** by the template alcohol would conclude the cascade (**9** to **10**), forming three rings including the challenging fused *trans*-bis-oxepane CD rings.

Scheme 3. Proposed cascade for the all-*endo* cascade toward the synthesis of hemibrevetoxin B



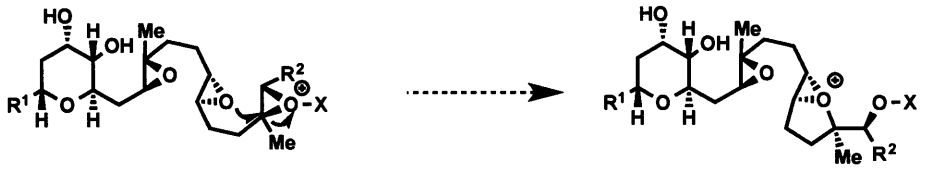
Preliminary investigations toward this end were initiated Dr. Kazuyoshi Obitsu, a former visiting scientist in our lab.[15] The first question that needed to be addressed was how to promote the desired *endo* regioselectivity in the first epoxide cyclization (**7** to **8**). The distal epoxide in the sequence contains a methyl group that could direct the next epoxide toward an *exo*-opening, forming an undesired bicyclo[3.1.0] epoxonium (**11** to **12**, Scheme 4). While limited examples of

[14] (a) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586. (b) Wan, S.; Gunaydin, H.; Houk, K. N.; Floreancig, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 7915.

[15] Dr. Kazuyoshi Obitsu developed the first generation synthesis of the cascade precursor, and investigated the cascade under various Lewis acid activators.

biasing cyclizations of similarly substituted epoxy alcohol toward the *endo* pathway are known,[16] no such reports exist for acid-promoted polyepoxide-opening cascades toward fused oxepanes. We hoped that a suitable directing group such as a vinyl substituent at the *endo* site of the distal epoxide (shown as R^2 in Schemes 2–4) would be able to successfully direct the first cyclization toward the desired *endo* product.

Scheme 4. Alternative *exo* epoxide closing for the first ring formation directed by methyl group

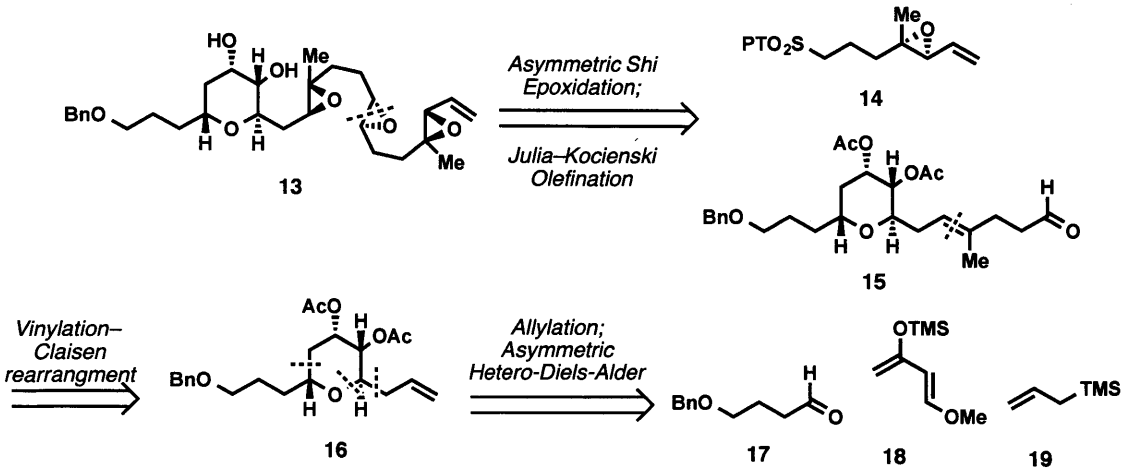


11 formation of bicyclo[3.1.0] epoxonium by *methyl-directed, exo trapping* of epoxide 12

An outline of our first generation synthesis of vinyl-substituted triepoxide **13** is shown in Scheme 5. The central two epoxides closest to the template ring were installed via asymmetric Shi epoxidation after fragment coupling of sulfone **14** and aldehyde **15** via Julia–Kocienski olefination. Aldehyde **15** was synthesized from alkene **16** through a sequence of oxidative alkene cleavage, Grignard addition and a one-pot Pd-catalyzed vinylation–Claisen rearrangement. Alkene **16** was formed from an asymmetric Ti/BINOL catalyzed hetero-Diels–Alder [4+2] cycloaddition of aldehyde **17** and Danishefsky's diene **18**, followed by elaboration of the ring system and acid-catalyzed allylation with **19**. The overall sequence to **13** was accomplished in 13 steps LLS and 21 steps overall.

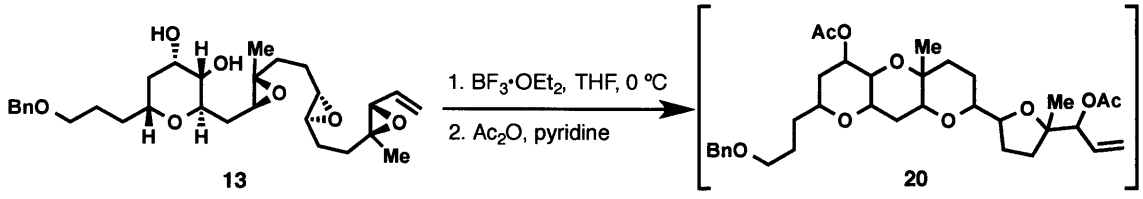
[16] (a) Nakata, T.; Nomura, S.; Matsukura, H. *Tetrahedron Lett.* **1996**, *37*, 213. (b) Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678.

Scheme 5. First generation synthesis of cascade precursor **13**



Subjecting epoxide **13** to a variety of conditions, e.g., BF_3•OEt_2 in THF or CH_2Cl_2, $La(OTf)_3$, or various aqueous conditions, failed to yield any desired product. All but BF_3•OEt_2 in THF gave complex mixtures likely resulting from epoxide hydrolysis (aqueous conditions), epoxide rearrangements, and undesired *exo*-pathways. The major product from BF_3•OEt_2 in THF could not be conclusively identified, but we proposed a likely structure **20** (Scheme 6) based on analysis of the vinyl cross peaks in the ^1H–^1H COSY spectrum of the acylated cascade product, which confirmed the *exo* opening of the vinyl epoxide.

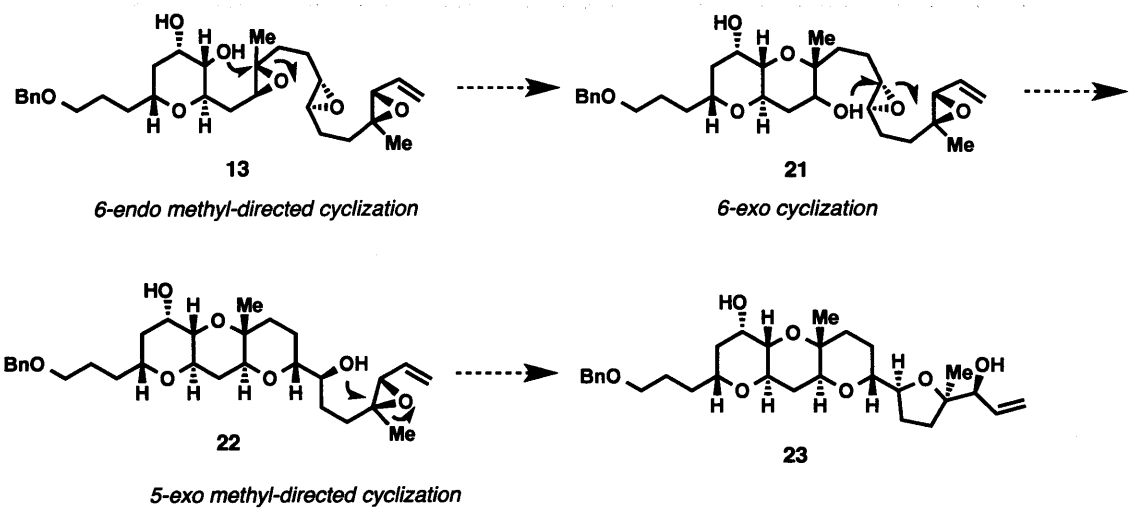
Scheme 6. Proposed product from cascade of polyepoxide **13**



We currently have two mechanistic proposals for the formation of **20**. The first involves an epoxonium-based, vinyl-to-template cascade, where the vinyl epoxide is opened by the next epoxide in an *exo* fashion (Scheme 4). The second pathway, shown in Scheme 7, invokes a template-to-vinyl cascade, where the nucleophilicity of the hydroxy group promotes rapid cyclization, outcompeting the desired bicyclo[4.1.0] epoxonium formation. The final cyclization from **22** to **23**, a 5-*exo*, methyl-directed cyclization, would be expected to predominate over the vinyl-directed, 6-*endo* cyclization. Most importantly, a template-to-vinyl cascade would be unable

to form the desired oxepane C-ring, as in **21** to **22**, a 6-*exo* cyclization would be significantly favored.

Scheme 7. Alternative mechanistic hypothesis for the formation of **20**



At this juncture, rather than investigating alternative π-stabilizing groups beyond vinyl,[17] which could also suffer from similar side product formation, we wanted to explore the ability of Rh catalysis to both override the *exo*-methyl directing effect for this epoxide substitution class, and to investigate Rh catalysis in a more challenging epoxide-opening cascade. Additionally, we hoped to eliminate alternative mechanisms, such as the template to vinyl pathway (Scheme 7), and further explore the potential for site-selective initiation to control the direction of epoxide-opening cascades (see Chapter 1 for further discussion).

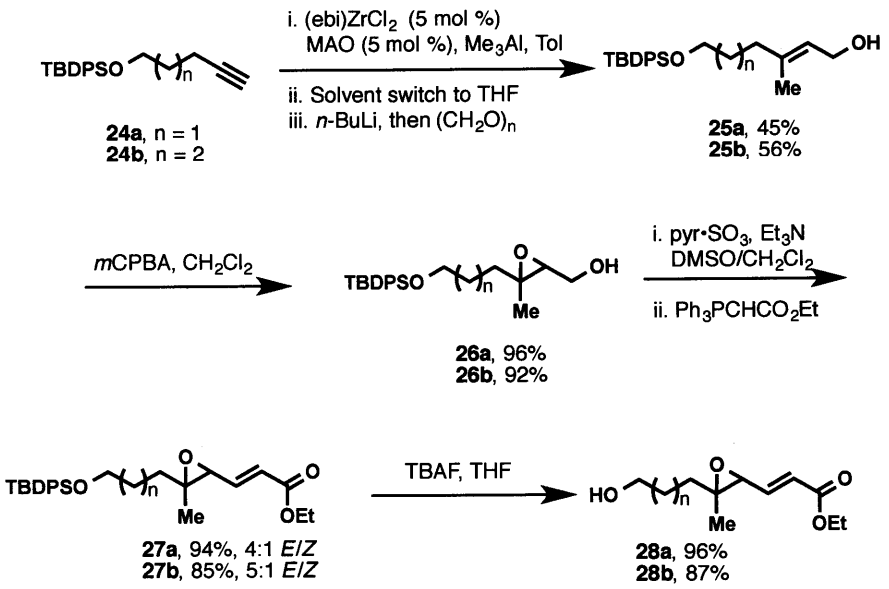
C. Model Studies of Proximal-Methyl Substituted Epoxy Alcohol Cyclizations Catalyzed by $[Rh(CO)_2Cl]_2$

Our previous success using model studies to explore the directing ability of $[Rh(CO)_2Cl]_2$ toward brevisin led us to pursue a similar approach for hemibrevetoxin B. We commenced by synthesizing a pair of epoxy alcohols (**28a**,**b**) to test the ability of the enoate/Rh combination to favor 6-*endo* and 7-*endo* cyclizations (Scheme 8). We synthesized the substrates for the model

[17] Model studies toward alternative π-stabilizing groups for 7-*endo* cyclizations of similar proximal-methyl substituted epoxy alcohols were studied in the Jamison lab by a former post-doctoral researcher Dr. Oleg Vechorkin (*unpublished results).* He found that (*Z*)-ethyl and *p*-NO_2-phenyl substituted alkenes had improved regioselectivity compared to vinyl, but some *cis*-oxepane formation was also observed.

studies in a similar manner as previously described, with the exception of the synthesis of the allylic alcohol **25**. We utilized a Zr-catalyzed carboalumination procedure with in situ aluminate formation and formaldehyde trapping to generate the desired (*E*)-trisubstituted allylic alcohols in >20:1 *E*/*Z* selectivity from alkyne **24**.[18] From allylic alcohol **25**, *m*CPBA epoxidation, alcohol oxidation, and in situ stabilized Wittig olefination, followed by desilylation provided the desired epoxy alcohols **28a** and **28b**.

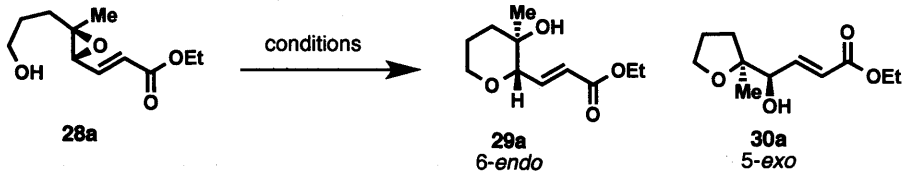
Scheme 8. Synthesis of epoxy alcohols **28** for model studies



We first used (±)-CSA in CH_2Cl_2 to explore the relative directing ability of the *exo*-methyl and *endo*-enoate epoxide substituents with the tethered nucleophile. With epoxy alcohol **28a**, we found a 1:>20 ratio for 6-*endo*/5-*exo*, demonstrating a significant barrier to overcome (Table 1, entry 1). This substrate proved to be very acid sensitive, readily cyclizing to the 5-*exo* product on unbuffered silica gel. Investigation of epoxy alcohol **28a** under $[Rh(CO)_2Cl]_2$ catalysis at room temperature provided a slight improvement in the regioselectivity, although the 5-*exo* product was still favored (entry 2). Inspired by the improvement in yields by heating the cascade toward the EF fragment of brevisin, we explored the effect of temperature on this reaction. To our delight, we found an increase in *endo* selectivity with increasing temperature, with 100 °C providing the best selectivity and yields at 9.8:1 *endo*/*exo* and 92% yield (entry 6).

[18] Lipshutz, B. H.; Butler, T.; Lower, A. *J. Am. Chem. Soc.* **2006**, *128*, 15396.

Table 1. Initial regioselectivity results for the cyclization of epoxy alcohol **28a**



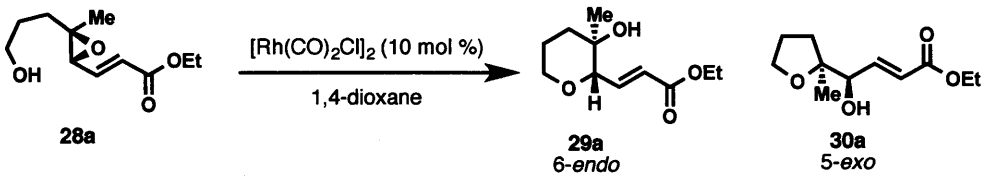
28a **29a** 6-*endo* **30a** 5-*exo*

entry	catalyst	solvent	temp[a]	**29a/30a** *endo/exo*	yield **29a** (%)[b]
1	(±)-CSA (10 mol %)	CH_2Cl_2	rt	1 : >20	–
2	$[Rh(CO)_2Cl]_2$ (10 mol %)	THF	rt	1 : 3.4	21
3	$[Rh(CO)_2Cl]_2$ (10 mol %)	THF	40 °C	1 : 1.6	36
4	$[Rh(CO)_2Cl]_2$ (10 mol %)	THF	60 °C	1.9 : 1	65
5	$[Rh(CO)_2Cl]_2$ (10 mol %)	THF	80 °C	3.3 : 1	78
6	$[Rh(CO)_2Cl]_2$ (10 mol %)	THF	100 °C	9.8 : 1	92

[a] Reactions run in sealed vials in oil bath. [b] Yields determined by ^1H NMR spectroscopy.

A screen of alternative solvents found 1,4-dioxane to also yield promising results (Table 2). Interestingly, we observed a similar increase in *endo* selectivity with increasing temperature for reactions in dioxane. While higher *endo* selectivity was observed at room temperature compared to THF (entry 1), we found a nearly identical maximum of 9.9:1 *endo/exo* selective at 80 °C (entry 4). A slight of drop in selectivity and yield was observed at 100 °C, which we attributed to decomposition of the catalyst in 1,4-dioxane.

Table 2. Effect of temperature on regioselectivity in 1,4-dioxane



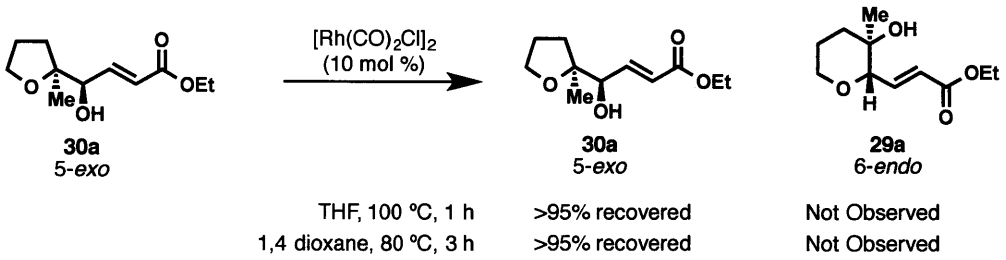
28a **29a** 6-*endo* **30a** 5-*exo*

entry	temp[a]	time	**29a/30a** *endo/exo*	yield **29a** (%)[b]
1	rt	18 h	1.6 : 1	42
2	40 °C	18 h	3.2 : 1	69
3	60 °C	18 h	6.5 : 1	91
4	80 °C	3 h	9.9 : 1	89
5	100 °C	1 h	7.1 : 1	85

[a] Reactions run in sealed vials in oil bath. [b] Yields determined by ^1H NMR spectroscopy

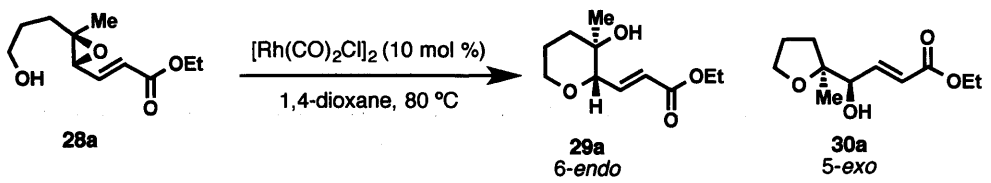
Attempting to run this reaction on larger scale (0.23 mmol instead of 0.02 mmol) in 1,4-dioxane at 80 °C, we observed a significant drop in regioselectivity (from 9.9:1 to 5:1 *endo/exo*) and yield of the desired 6-*endo* product **29a**. We investigated a few explanations for the change of reaction outcome. Previously the reaction was run for 3 h, but TLC monitoring during the scale-up found 30 min to be sufficient for full conversion of starting material. Given the time difference between the two reactions, we investigated whether the 5-*exo* product **30a** could be converted to the 6-*endo* product **29a** under the reaction conditions. Subjection of **30a** to $[Rh(CO)_2Cl]_2$ catalysis in either THF or 1,4-dioxane at elevated temperatures resulted in full recovery of starting THF **30a**, demonstrating that the reaction is irreversible (Scheme 9).

Scheme 9. Subjection of 5-*exo* product **30a** to reaction conditions to test for reversibility



We also considered the difference in the headspace between the screening and scale-up reactions, as these reactions are run in sealed vials. The ratio of headspace volume to solvent volume in the screening reaction was 25:1, while the scale up reaction only had a 3:1 headspace to reaction volume ratio, suggesting a key variable to investigate. We screened the reaction by varying the size of the vials to explore different headspace ratios from 1:1 up to 50:1, which allowed us to study the relationship between reactor headspace and regioselectivity. As shown in Table 3, we found that increasing the headspace correlated well with improved *endo* selectivity for this reaction, even to the extreme of 50:1. From these results we hypothesized the increase in headspace was allowing CO (after dissociating from Rh) to transfer out of solution, changing the active catalytic species to $Rh(CO)_{n-1}Cl$.

Table 3. Exploration of relationship between reaction headspace and regioselectivity



28a **29a** 6-*endo* **30a** 5-*exo*

entry	headspace vol/rxn vol	**29a/30a** *endo/exo*
1	1 : 1	3.0 : 1
2	3 : 1	3.8 : 1
3	8 : 1	9.6 : 1
4	25 : 1	10.2 : 1
5	50 : 1	11.2 : 1

Ratios determined by ^{1}H NMR spectroscopy.

We next attempted to investigate directly the relationship between the carbonyl/Rh ratio and regioselectivity, hoping to gain more insight by more directly modifying the catalyst structure. We conducted these experiments at 40 °C in dioxane (Table 4, entry 1), as these conditions yielded a moderate 3:1 *endo/exo* ratio and any change in regioselectivity would be easily observed. We first tested our hypothesis that excess CO in solution negatively impacts regioselectivity. Purging the headspace of the vial with $CO_{(g)}$ to form $Rh(CO)_3Cl$[19] resulted in the complete reversal of the regioselectivity toward the *exo* product, strongly supporting our hypothesis (entry 2).

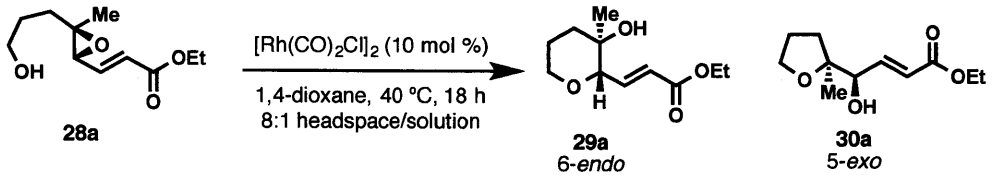
We postulated that the *endo*-selective catalyst resembled the structure of Rh(CO)(solv)Cl, with one CO undergoing exchange with a solvent molecule, likely a disfavored process given the strong affinity of CO for Rh(I). We attempted to assist this process by preheating the catalyst under a static vacuum followed by an Ar refill. Under this protocol, only a small increase in *endo* selectivity was observed, suggesting that 1,4-dioxane alone was not able to displace CO (entry 3). Alternatively, using a singly-carbonylated Rh(I) species, $[Rh(CO)(coe)Cl]_2$,[20] led to an improvement in regioselectivity to the highest observed in our headspace optimization studies at 10.5:1 *endo/exo* (entry 4). The conversion was lower, likely due to competitive binding between

[19] IR spectrum of the THF solution saturated with $CO_{(g)}$ was consistant with literature reports. See: Morris, D. E.; Burnham Tinker, H. *J. Organomet. Chem.* **1973**, *49*, C53.

[20] Premixing $[Rh(CO)_2Cl]_2$ with $[Rh(coe)_2Cl]_2$ in a 1:1 ratio has been shown to equilibrate to $[Rh(CO)(coe)Cl]_2$. Key signals from the IR spectrum matched the reported signals of interest. See the following report for more details: Varshavsky, Y. S.; Cherkasova, T. G.; Buzina, N. A.; Kormer, V. A. *J. Organomet. Chem.* **1974**, *77*, 107.

the coe and the substrate enoate. Importantly, $[Rh(coe)_2Cl]_2$ alone yielded poor regioselectivity and yield, lending additional evidence that a 1:1 carbonyl/Rh ratio is ideal (entry 5).

Table 4. Investigation of carbonylation state of catalyst on regioselectivity and yield



entry	change from standard conditions	conversion **28a** (%)[a]	**29a/30a** *endo/exo*	yield **29a** (%)[a]
1	none	>95	2.8 : 1	65
2	Flush rxn headspace with $CO_{(g)}$	87	1 : >20	>5
3	Preheat catalyst to 80 °C for 1 h, then flush with Ar	>95	3.2 : 1	63
4	1:1 $[Rh(CO)_2Cl]_2$/$[Rh(coe)_2Cl]_2$	54	10.5 : 1	21
5	$[Rh(coe)_2Cl]_2$	55	1 : 2.3	6
6	80 °C, open to air, 3 h	>95	13.5 : 1	81
7	0.25 mmol (10× scale), 80 °C, open to air, 3 h	>95	12.5 : 1	76[b]

[a] Yields determined by ^1H NMR spectroscopy. [b] Isolated yield.

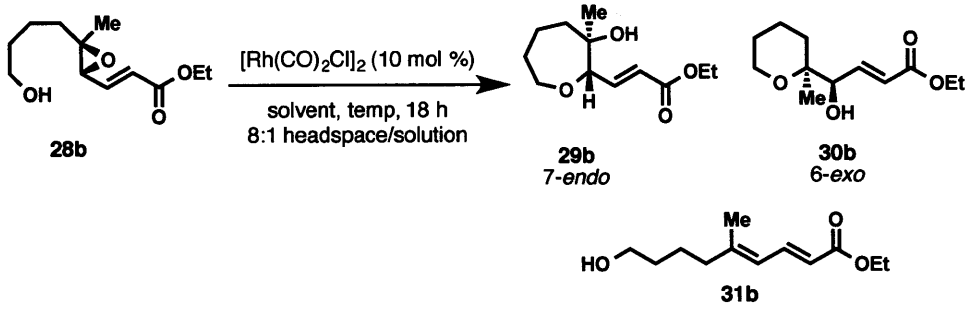
With the above results supporting to support our theory of the ideal CO/Rh ratio of 1:1 and the recognition that additional alkenes present in the reaction mixture result in lower reactivity and side-product formation, we sought to find optimal reaction conditions that didn't rely on a large reactor headspace. We found that running the reaction open to air at 80 °C provided the highest regioselectivity and yield (Table 4, entry 6). We hypothesized that quickly heating the solution of catalyst and **28a** more rapidly forms a species similar to Rh(CO)(enoate)Cl, which can catalyze the *endo* cyclization selectively.[21] We think that the small amount of *exo* product **30a** likely forms during an equilibration period, prior to loss of a CO to the atmosphere. Unlike the reaction run in sealed vials, the variant run open to the air was successfully performed at 0.25 mmol without significant erosion of yield or selectivity (entry 7).

We next explored the formation of oxepane **29b** from epoxy alcohol **28b**, hoping to capitalize on our previous discoveries concerning the carbonylation state of the catalyst. We

[21] Wender and Houk in their studies of $[Rh(CO)_2Cl]_2$ catalyzed [5+2] annulations with vinylcyclopropanes and alkynes suggest that coordination of the alkene and then loss of a CO is necessary prior to entering the catalytic cycle. See: Yu, Z.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 9154.

screened both THF and 1,4-dioxane, and were surprised to observe considerably lower conversion, selectivity, and yield (Table 5). Additionally, we isolated significant amounts of diene **31b**, a similar deoxygenated side product observed in small quantities in attempt to from oxocanes (see Chapter 1).[22] We reasoned the increased tether length and ring strain in the formation of oxepanes relative to THPs slowed the desired reaction enough to allow for side processes to prevail, especially at higher temperatures.

Table 5. Investigation of temperature and solvent effects on the cyclization of **28b**



entry	solvent	temp	conversion **28b** (%)[a]	**29b/30b** *endo/exo*	yield **29b** (%)[a]	yield **31b** (%)[a]
1	THF	rt	40	nd[b]	15	<5
2	THF	50 °C	55	3 : 1	24	15
3	THF	80 °C	>95	5 : 1	28	32
4	1,4-dioxane	rt	32	nd	8	7
5	1,4-dioxane	50 °C	58	nd	11	18
6	1,4-dioxane	80 °C	>95	nd	11	27

[a] Yields determined by ^{1}H NMR spectroscopy. [b] nd = not determined, as yield of **30b** was <5%.

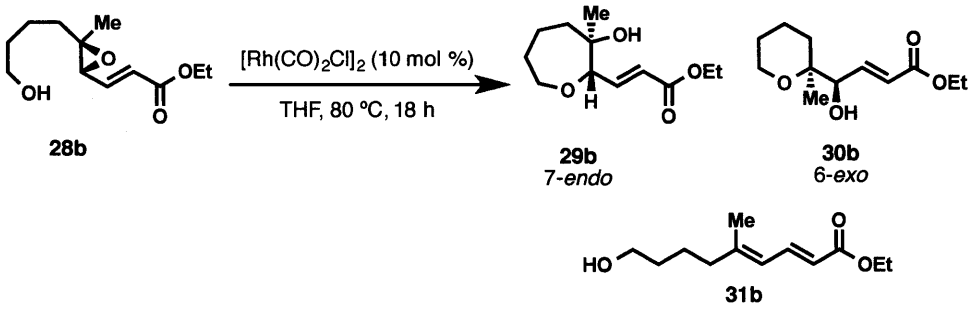
Also of note was the lower yields of oxepane **29b** in 1,4-dioxane compared to THF (entries 4–6 versus 1–3), as these results contrasted with the higher selectivity and yield for formation of THP **29a** in 1,4-dioxane versus THF (Table 1 versus Table 2). Given the lower polarity of 1,4-dioxane ($\varepsilon = 2$) versus THF ($\varepsilon = 8$), we think that the higher 6-*endo* selectivity in 1,4-dioxane with **28a** results from slowing of the 5-*exo* pathway relative to formation of the *endo* selective catalytic species via loss of CO, suggesting this pathway proceeds through a more polar intermediate.

[22] Also see the following report for examples of deoxygenation of arene oxides with $[Rh(CO)_2Cl]_2$: Ashworth, R. W.; Berchtold, G. A. *Tetrahedron Lett.* **1977**, *18*, 343.

However, it is possible the substantial decrease in rate for cyclization of **28b** could increase the lifetimes of the relevant catalytic intermediates, creating a greater importance for stabilizing such intermediates. We think THF is a superior solvent compared to 1,4-dioxane as it is best able to stabilize the various intermediates due to its greater polarity and coordinating ability, limiting catalyst decomposition and side processes.

Attempting to optimize the headspace/solvent ratio provided little improvement in yield and selectivity (Table 6). Performing the reaction in THF at 80 °C open to air provided a decrease in yield and conversion, in stark contrast to the previous work with epoxy alcohol **28a** (entry 3 versus Table 3). We observed the optimum headspace/solvent ratio to be 35:1 on small scale; producing a respectable 5.6:1 *endo*/*exo* ratio and 33% yield of oxepane **29b**. However, we were disappointed to observe incomplete conversion with lower yield and selectivity when attempting to increase the scale 10-fold. Rather than attempting to optimize further this system with $[Rh(CO)_2Cl]_2$, we set out to identify a new catalyst to overcome the low yield, selectivity and side product formation.

Table 6. Optimization of solvent/headspace ratio for selective formation of **29b**



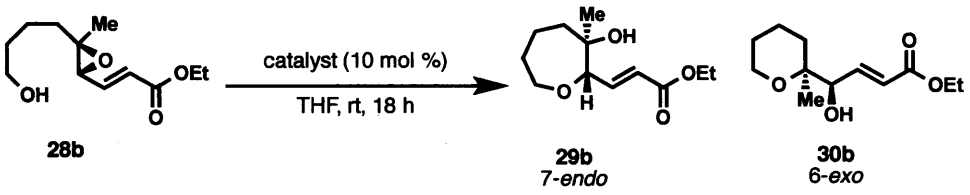
entry	headspace/solvent	conversion **28b** (%)[a]	**29b/30b** *endo*/*exo*	yield **29b** (%)[a]	yield **31b** (%)[a]
1	8 : 1	>95	5.0 : 1	28	32
2	35 : 1	>95	5.6 : 1	33	29
3	open to air	82	nd[b]	18	25
4[c]	35 : 1	85	4 : 1	22[d]	12[d]

[a] Yields determined by ^{1}H NMR spectroscopy. [b] nd = not determined, as yield of **30b** was <5%. [c] 10× scale (0.24 mmol), run in 200 mL Schlenk tube. [d] Isolated yield.

D. Cationic Rh(I) as *Endo*-Selective Catalysts for Epoxy Alcohol Cyclizations

To overcome the issues observed with $[Rh(CO)_2Cl]_2$ catalysis toward the formation of oxepane **29b**, we explored alternative Rh(I) species. We focused on CO-free species in hopes of limiting formation of diene **31b**, as well as potentially increasing the lifetime of the catalyst. We screened a variety of related Rh(I) Cl-containing catalysts, however no conversion was observed (Table 7, entries 1–3). Switching to more electron-deficient cationic $Rh(I)(diene)_2$, we observed the first Rh-based catalysts beyond $[Rh(CO)_2Cl]_2$ to produce measurable amounts of **29b** (entries 4–5). While both the bis-cod and bis-nbd species were *exo*-selective, we were intrigued by the improved yield and selectivity with nbd. We rationalized that the improvement in selectivity was correlated to increased backbonding from Rh to nbd relative to cod, with the more electron deficient Rh less able to directly activate the *exo* C–O bond of the epoxide. Further improvement in *endo* selectivity was achieved by reducing the diene/Rh ratio from 2:1 to 1:1, likely by opening additional sites at Rh for coordination of the enoate (entry 6).

Table 7. Exploration of alternative Rh(I) catalysts



28b | **29b** *7-endo* | **30b** 6-*exo*

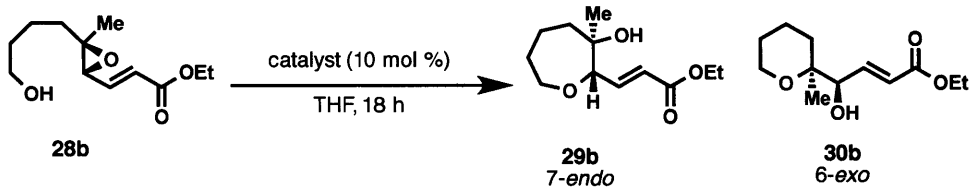
entry	catalyst	conversion **28b** (%)[a]	**29b/30b** *endo/exo*	yield **29b** (%)[a]
1	$Rh(PPh_3)_3Cl$	<5	nd[b]	–[c]
2	$Rh(CO)(PPh_3)_2Cl$	<5	nd[b]	–[c]
3	$[Rh(cod)Cl]_2$	<5	nd[b]	–[c]
4	$Rh(cod)_2BF_4$	81	1 : 7.5	10
5	$Rh(nbd)_2BF_4$	88	1 : 1.7	31
6	$[Rh(nbd)Cl]_2/AgBF_4$ (1:1)	89	2 : 1	53

[a] Yields determined by ^1H NMR spectroscopy. [b] nd = not determined, as yield of **30b** was <5%. [c] "–" represents product not observed by ^1H NMR spectroscopy.

Encouraged by the improvement in yield and lack of side product formation, we pursued a preformed variant of the active species formed in the anion exchange reaction, likely

$Rh(nbd)(THF)_nBF_4$.[23] Investigation of alternative solvents and anions showed variability in selectivity and conversion with the in situ catalyst formation process, which we attributed to incomplete Cl abstraction and/or excess Ag^+ salts.[24] To overcome these issues, we explored a series of bis-CH_3CN cationic Rh(I) catalysts, which are readily isolated from ligand exchange of a single diene from the $Rh(diene)_2X$ species in CH_3CN.[25] Surprisingly, we observed primarily *exo* opening with the preformed $Rh(nbd)(CH_3CN)_2SbF_6$ catalyst (Table 8, entry 1). Addition of the non-nucleophilic base DTBMP significantly limited the formation of the *exo* product, pointing to Brønsted acid catalysis as the source of the *exo* product **30b** (entry 2). Increasing the temperature improved conversion and yield, but failed to exceed 55% conversion (entry 3). Modifying either the counterion or diene component yielded improved conversion, however this was concurrent with a decline in *endo* selectivity (entries 4–5). We explored a variety of alternative solvents (CH_2Cl_2, toluene, 1,4-dioxane, 2-MeTHF, DMF, acetone, HFIP, and TFE), however, only THF provided conversions >10%.

Table 8. Exploration of preformed cationic Rh(I) catalysts



28b | **29b** *7-endo* | **30b** *6-exo*

entry	catalyst	temp	base (100 mol %)	conversion **28b** (%)[a]	**29b/30b** *endo/exo*	yield **29b** (%)[a]
1	$Rh(nbd)(CH_3CN)_2SbF_6$	rt	–	>95	1 : 11	7
2	$Rh(nbd)(CH_3CN)_2SbF_6$	rt	DTBMP	15	nd[b]	12
3	$Rh(nbd)(CH_3CN)_2SbF_6$	50 °C	DTBMP	55	4 : 1	40
4	$Rh(nbd)(CH_3CN)_2BF_4$	50 °C	DTBMP	100	1.3 : 1	45
5	$Rh(cod)(CH_3CN)_2BF_4$	50 °C	DTBMP	94	1 : 10	5

[a] Yields determined by ^1H NMR spectroscopy. [b] nd = not determined, as yield of **30b** was <5%.

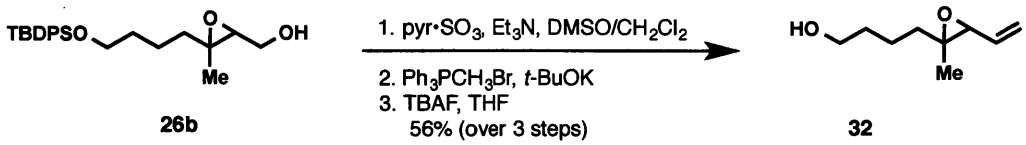
[23] Braun, W.; Calmuschi-Cula, B.; Salzer, A. *Acta Crystallogr. Sect. E Struct. Reports Online* **2007**, *63*, m517.

[24] $AgBF_4$ in THF at room temperature provided 20% of **30b** as the only product observed, suggesting excess Ag salts can promote the undesired *exo* pathway via Lewis acid catalysis.

[25] Green, M.; Kuc, T. A.; Taylor, S. H. *J. Chem. Soc. A* **1971**, 2334.

To improve further the *endo/exo* selectivity, we explored a more electron-rich vinyl substituent as an alternative π-stabilizing group, hoping to improve the binding with the electron-deficient catalyst. Vinyl epoxide **32** was readily synthesized from epoxide **26b** in three steps via alcohol oxidation, Wittig methylenation, and desilylation (Scheme 10).

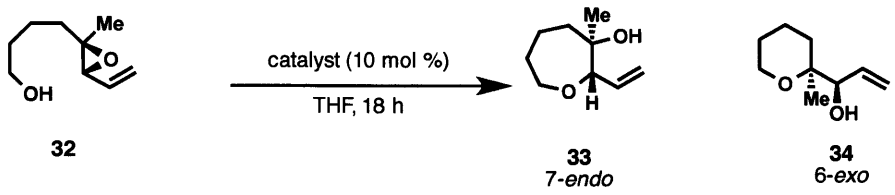
Scheme 10. Synthesis of vinyl epoxy alcohol for model studies



Subjection of vinyl epoxy alcohol **32** to Brønsted acid demonstrated a modest improvement in electronic biasing for the *endo* product by the vinyl substituent compared to the enoate, although the reaction was still *exo* selective (Table 9, entry 1).[26] Use of $[Rh(CO)_2Cl]_2$ only returned unreacted epoxide **32**, even at elevated temperatures (entry 2). Gratifyingly, the preformed $Rh(diene)(CH_3CN)_2X$ (X = SbF_6 or BF_4) catalysts provided higher yields and selectivities with the vinyl epoxide compared to the enoate epoxide, reaching 8:1 *endo/exo* selectivity and 60% yield of oxepane **33** (entries 3–5). While the cod-based catalyst was inferior for the enoate substrate, it provided a slight improvement over the nbd catalyst with the vinyl substituent. Attempting to lower the temperature proved unsuccessful, providing only partial conversion (entries 6–7). With our optimized conditions for the vinyl epoxide and cationic Rh(I) catalysts (entry 5), we returned our attention to the synthesis of the triepoxide cascade precursor for hemibrevetoxin B.

[26] Epoxy alcohol **32** was explored by Nakata and coworkers under PPTS catalysis, yielding similar results. See ref 16a.

Table 9. Cyclization studies of vinyl epoxy alcohol **32**



32 **33** *7-endo* **34** 6-*exo*

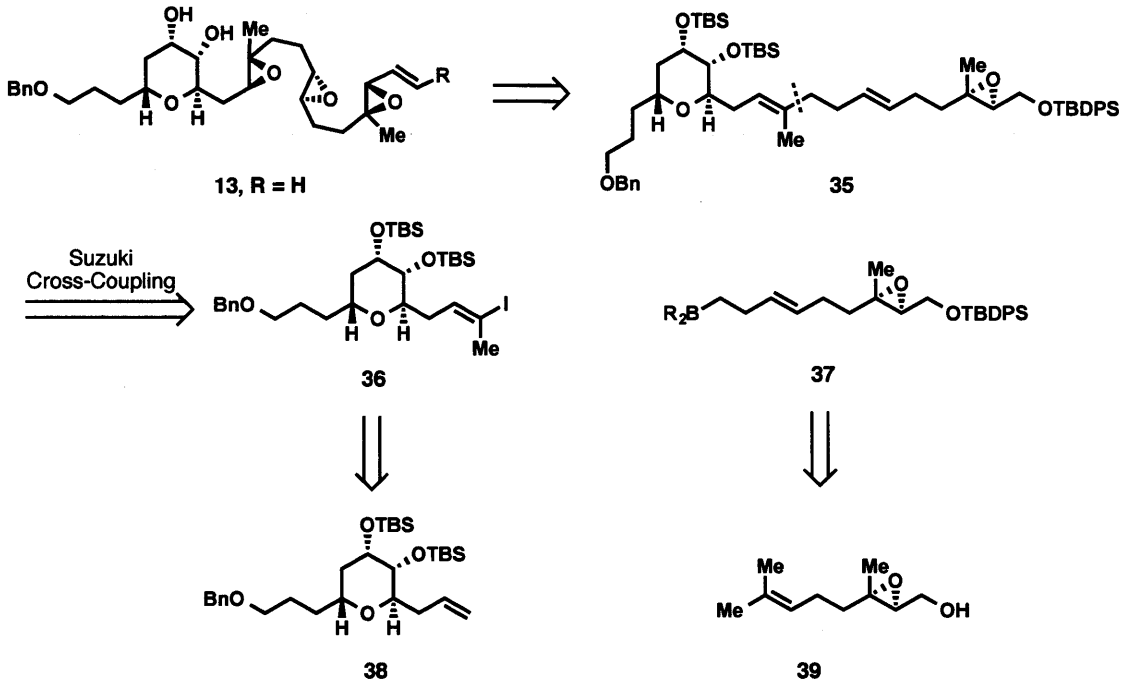
entry	catalyst	temp	base (100 mol %)	conversion **32** (%)[a]	**33/34** *endo/exo*	yield **33** (%)[a]
1[b]	(±)-CSA (50 mol %)	rt	–	>95	1 : 2.8	19
2	$[Rh(CO)_2Cl]_2$	rt *or* 50 °C	–	<5	–[c]	–[c]
3	$Rh(nbd)(CH_3CN)_2SbF_6$	50 °C	DTBMP	>95	6 : 1	53
4	$Rh(cod)(CH_3CN)_2BF_4$	50 °C	DTBMP	>95	1 : 1.5	28
5	$Rh(cod)(CH_3CN)_2SbF_6$	50 °C	DTBMP	88	8 : 1	60
6	$Rh(cod)(CH_3CN)_2SbF_6$	35 °C	DTBMP	54	7 : 1	33
7	$Rh(cod)(CH_3CN)_2SbF_6$	rt	DTBMP	27	nd[d]	14

[a] Yields determined by ^1H NMR spectroscopy. [b] Reaction performed with CH_2Cl_2 as solvent. [c] "–" represents product not observed by ^1H NMR. [d] nd = not determined, as yield of **34** was <5%.

E. Synthesis of Cascade Precursor for Hemibrevetoxin B

Returning to the synthesis of cascade precursor **13**, we saught to modify the previous synthetic route to enable late-stage diversification of the π-stabilizing group, as well as improve the convergence by moving the site of fragment coupling closer to the more elaborate preformed A ring template (**35**, Scheme 11). We planned to implement an sp^2–sp^3 Suzuki cross-coupling of alkenyl iodide **36** and alkyl borane **37**, based on precedent from Corey and coworkers. We planned on accessing alkenyl iodide **36** from THP **38**, which ultimately could be derived from a related sequence as used in the previous synthetic efforts (Scheme 5). We planned to utilize 2,3-epoxy geraniol to access alkyl borane **37**, via oxidative alkene cleavage and subsequent homologation.

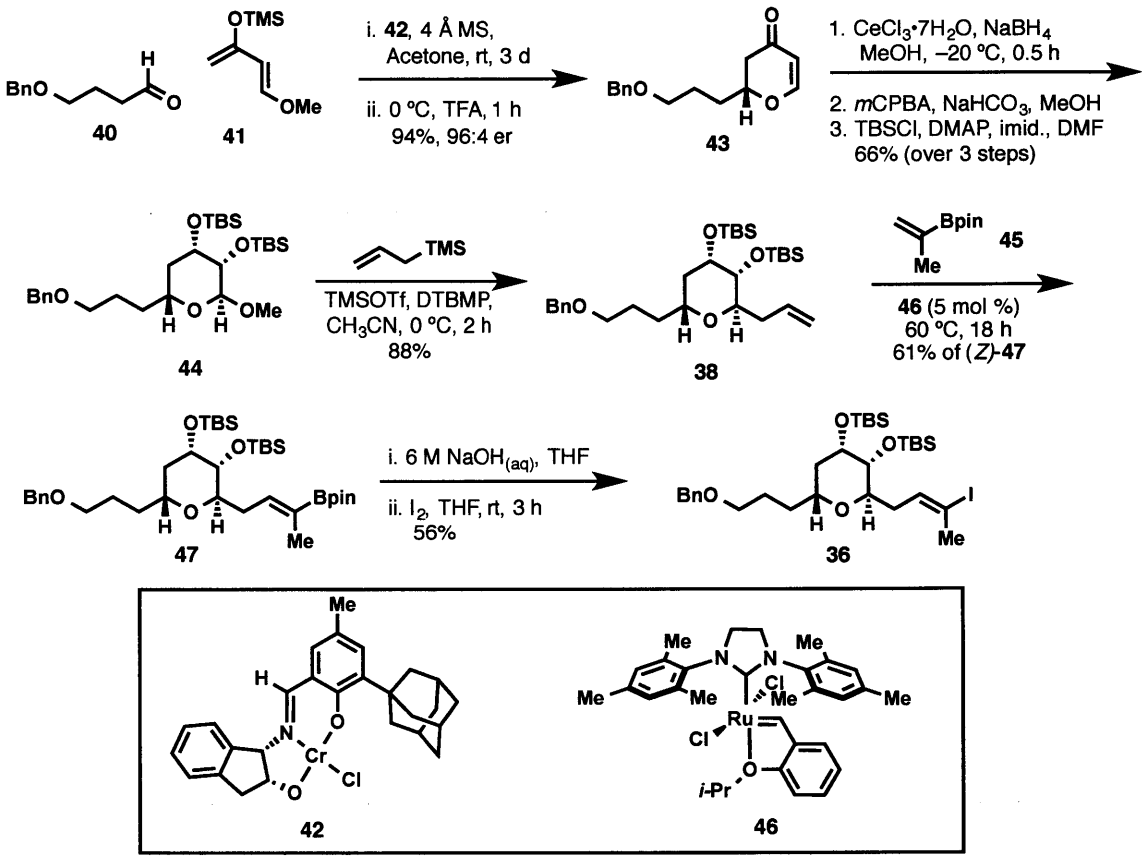
Scheme 11. Retrosynthetic analysis for the second-generation synthesis of **13**



Synthesis of the A-ring THP was initiated with a [4+2] asymmetric hetero-Diels–Alder cycloaddition of aldehyde **40** and diene **41**, catalyzed in good yield and enantioselectivity by Cr catalyst **42** (Scheme 12).[27] Elaboration of pyrone **43** proceeded by stereoselective Luche reduction, epoxidation, methanolysis, and silyl protection. Lewis acid mediated allylation of **44** installed the allyl functionality with high stereoselectivity and yield. Cross metathesis with isoprenyl boronic ester **45** provided **47**, which could readily be separated from the undesired *E* isomer.[28] Finally, stereoretentive iodo-deboronation yielded the desired (*E*)-alkenyl iodide in moderate yield.[29]

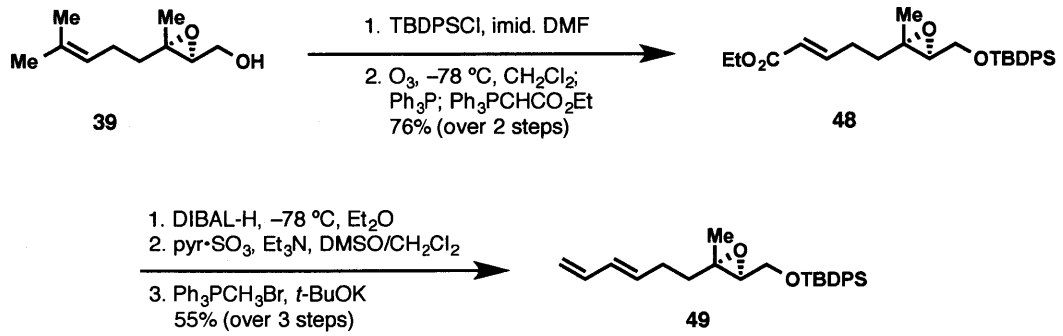
[27] Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2398.
[28] Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733.
[29] (a) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 5786. (b) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031.

Scheme 12. Synthesis of alkenyl iodide **36**



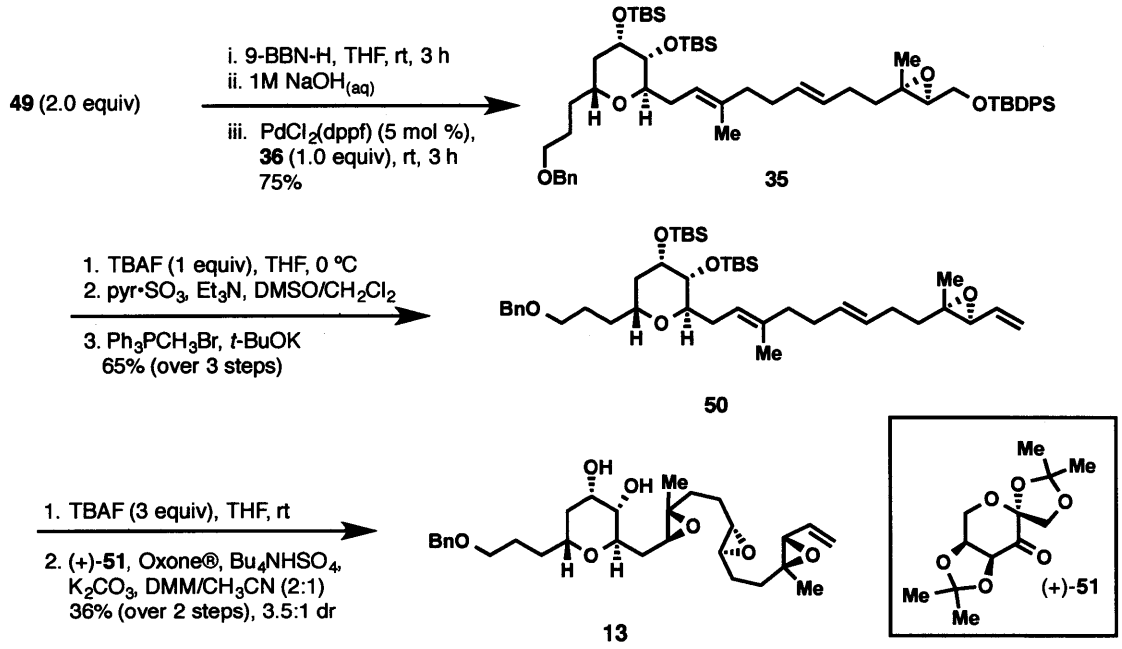
Synthesis of the cross coupling partner was accomplished starting from 2,3-epoxy-geraniol **39**, via TBDPS protection of the alcohol, ozonolysis of the alkene, and in situ stabilized Wittig olefination to provide enoate **48** (Scheme 13). Subsequent DIBAL-H reduction to the allylic alcohol, oxidation to the enal, and finally Wittig methylenation provided diene **49**.

Scheme 13. Synthesis of diene **49**



Fragment coupling via Suzuki cross coupling provided diene **35** in excellent yield and stereochemical purity, with good functional group tolerance for the preinstalled epoxide (Scheme 14). Selective desilylation of the 1° TBDPS ether in the presence of two 2° TBS ethers, followed by alcohol oxidation and methylenation provided triene **50**. Finally, exhaustive desilylation and asymmetric Shi epoxidation afforded the desired cascade precursor **13**. We attributed the low yield of the final two steps to incomplete epoxidation of the disubstituted alkene as well as modest amounts of epoxidation of the vinyl group.

Scheme 14. Fragment coupling and synthesis of triepoxide **13**



F. Exploration of Epoxide-Opening Cascade and Future Directions

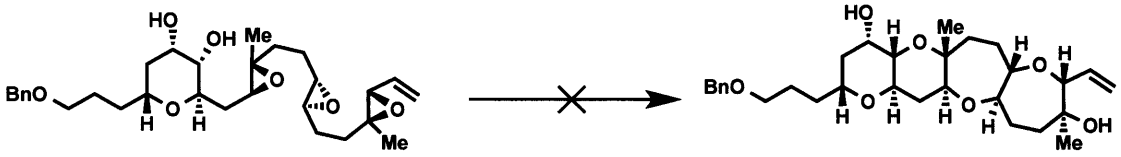
With triepoxide **13** in hand, we explored the proposed epoxide-opening cascade for the synthesis of hemibrevetoxin B. Application of the optimized conditions utilizing the cationic Rh(I) catalyst proved too reactive for the sensitive substrate, producing >10 products from analysis of the ^{1}H NMR spectrum of the crude reaction mixture (Table 10, entry 1). While we lacked an authentic sample of the desired tetracycle **52**, Yamamoto's route for the synthesis of hemibrevetoxin B proceeded through a nearly identical structure, differing only by the protecting group on the A-ring side chain (TIPS instead of Bn).[30] Comparison of the data provided for Yamamoto's intermediate to the ^{1}H NMR spectrum of the crude reaction mixture highly suggested that the complex mixture

[30] Kadota, I.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6597.

did not contain any of the desired product **52**. Attempts to lower the temperature or utilize the nbd catalyst did not significantly impact the reaction outcome (entries 2–3).

We hypothesized that the lower nucleophilicity of the disubstituted epoxide trapping nucleophile relative to the 1° alcohol used in the model studies could result in significant side reactivity. Additionally, THF could potentially outcompete intramolecular trapping by the neighboring epoxide, as these electrophilic epoxide-opening cascades are often performed in weakly or non-nucleophilic solvents like HFIP, CH_2Cl_2, or toluene. Since we observed significant signals corresponding to polymerized THF by ^1H NMR spectroscopy,[31] we attempted to run this reaction in cosolvent mixtures of either HFIP or TFE, however, no improvement was observed (entries 4–5).

Table 10. Investigation of epoxide–opening cascade of triepoxide **13**



13 52

entry	catalyst	temp	base (100 mol %)	solvent	result
1	$Rh(cod)(CH_3CN)_2SbF_6$	50 °C	DTBMP	THF	complex mixture
2	$Rh(cod)(CH_3CN)_2SbF_6$	rt	DTBMP	THF	complex mixture
3	$Rh(nbd)(CH_3CN)_2SbF_6$	rt	DTBMP	THF	complex mixture
4	$Rh(cod)(CH_3CN)_2SbF_6$	rt	DTBMP	3:1 HFIP/THF	complex mixture
5	$Rh(cod)(CH_3CN)_2SbF_6$	rt	DTBMP	3:1 TFE/THF	complex mixture

In addition to the solvent compatibility issues with the substrate, we also think that the cationic Rh(I) catalysts are too Lewis acidic for the sensitive triepoxide substrate. The proposed cascade shown in Scheme 3 requires site-selective initiation of the epoxide-opening cascade at the alkenyl epoxide in order to achieve the desired all-*endo* selectivity. Given the slow rate of cyclization observed in the model studies, an additional possibility is the early attack of the A-ring hydroxyl on the closest epoxide. While we lack direct evidence to support this theory, acid-catalyzed 6-*endo* cyclizations of this type are rapid, and could easily outcompete the desired

[31] Dreyfuss, M. P.; Dreyfuss, P. *J. Polym. Sci. Part A-1: Polym. Chem.* **1966**, *4*, 2179.

pathway. At this juncture, further work is needed to explore alternative π-stabilization groups and Rh catalysts that would allow for the desired reactivity under milder conditions.

Alternatively, we have proposed a modified synthesis of hemibrevetoxin B outlined in Scheme 15. Instead of utilizing a triepoxide cascade to form the BCD rings, we propose a $[Rh(CO)_2Cl]_2$-catalyzed diepoxide cascade to form the BC rings (**55** to **56**), similar to the ABC tricycle, and a subsequent cyclization of the D ring, utilizing $Rh(cod)(CH_3CN)_2SbF_6$ to catalyze the *endo*-selective closure of the vinyl epoxy alcohol (**60** to **52**). While modifying the alcohol nucleophile from 1° to 2° could potential slow down the rate of D-ring cyclization, this would likely be balanced by the increase in rate by removal of degrees of rotational freedom imposed by the ABC tricycle as compared to the model study substrates.

Starting from **47**, we envision a Pd-catalyzed sp^3–sp^2 Suzuki cross-coupling utilizing conditions developed by the Fu lab to synthesize epoxide **54**.[32,33] Subsequent Shi asymmetric epoxidation and desilylation should generate cascade precursor **55**. Given the similarities to the cascades for the synthesis of the EF and ABC fragments of brevisin, we think the cascade from **55** to **56** has a high likelihood of success. Synthesis of D-ring cyclization precursor **60** is proposed as a five-step sequence from ABC tricycle **56**. Following protection of the diol to a bis-silyl ether, cross metathesis with ethylene should provide alkene **57**. Hydroboration of alkene **57** and a subsequent in situ Pd-catalyzed Suzuki cross-coupling with alkenyl iodide **58** should rapidly generate the desired (*E*)-trisubstituted alkene **59**. Shi asymmetric epoxidation and desilylation should provide the D-ring cyclization precursor **60**. Cyclization of vinyl epoxy alcohol **60** under cationic Rh(I) catalysis would provide ABCD tetracycle **52**, representing the full core of hemibrevetoxin B. This modified sequence would only add two steps to the LLS toward **52** as compared to the previous triepoxide cascade approach.

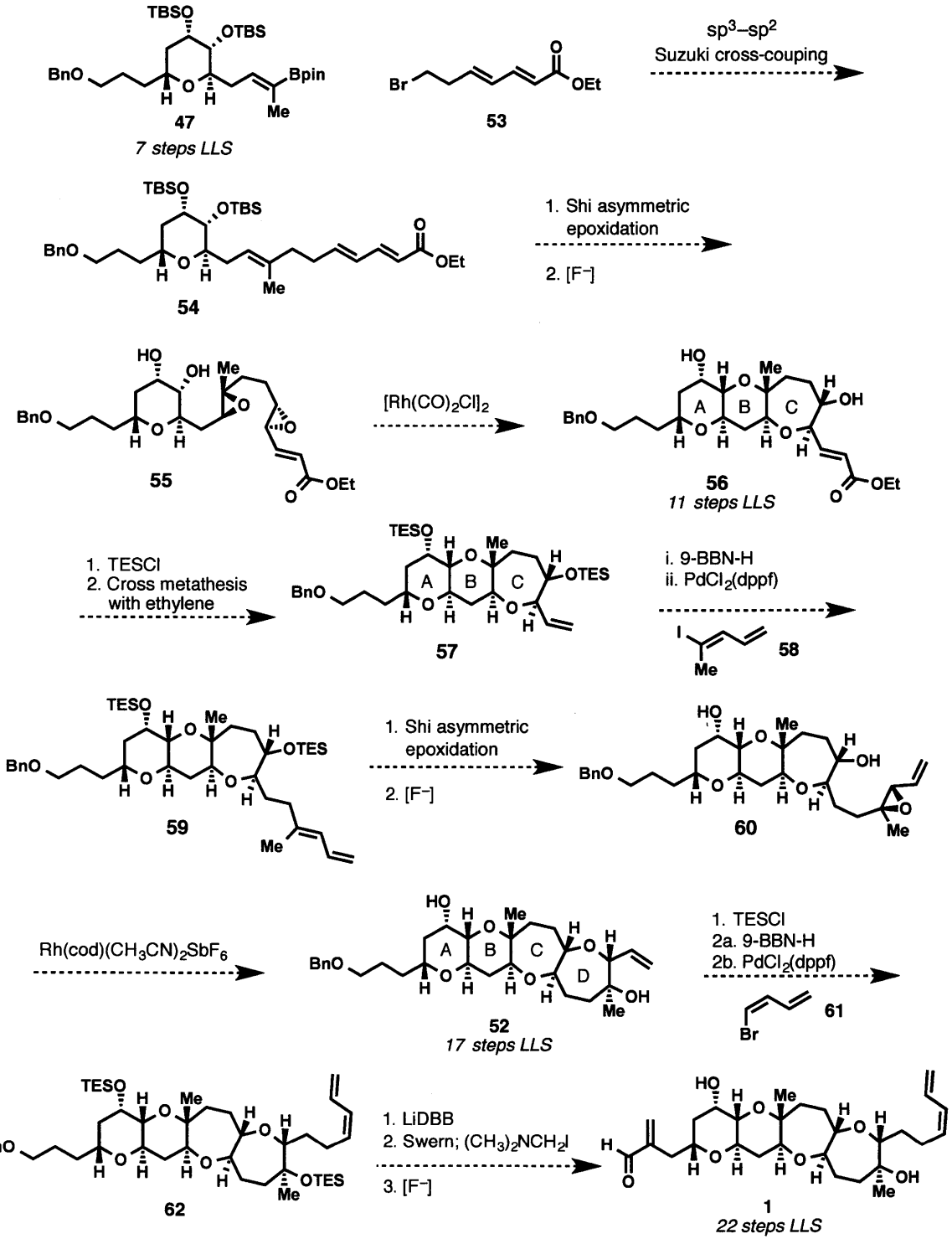
To complete our proposal for a total synthesis of hemibrevetoxin B, we propose utilizing a second hydroboration/Suzuki cross-coupling to rapidly form the (*Z*)-diene side chain (**52** to **62**). To install the enal functional group, we could utilize alcohol oxidation and in situ methylenation utilizing Eschenmoser's reagent, similarly to the synthesis of hemibrevetoxin B reported by Nicolaou and coworkers.[2] A final desilylation should complete the total synthesis of hemibrevetoxin B (**1**) in 22 steps LLS. Synthesis of the D ring via an epoxy alcohol cyclization would represent the first example of oxepane formation from an *endo*-selective proximal-methyl-

[32] Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662.

[33] A recently reported Fe-catalyzed cross coupling of alkenyl boronic pinacol esters and alkyl bromides may also be applied. See: Hashimoto, T.; Hatakeyama, T.; Nakamura, M. *J. Org. Chem.* **2012**, *77*, 1168.

substituted epoxide in the context of a ladder polyether synthesis, while also avoiding the late-stage methyl group installation utilized in other syntheses of **1**.

Scheme 15. Proposed synthesis of hemibrevetoxin B utilizing D ring cyclization



G. Conclusions

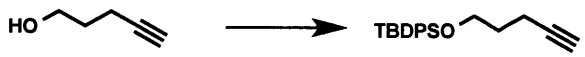
In summary, we have developed several combinations of Rh catalysts and π-stabilizing groups to override the typically high *exo* selectivity observed in cyclizations of proximal-methyl-substituted epoxy alcohols, allowing for the rapid synthesis of THPs and oxepanes. During the course of this study, we found that the optimum carbonyl/Rh ratio is 1:1 when using $[Rh(CO)_2Cl]_2$ as a catalyst to achieve high *endo* selectivity. Furthermore, we have found cationic Rh diene species to be highly efficient catalysts for these epoxy alcohol cyclizations as well. Towards the goal of a rapid synthesis of hemibrevetoxin B, we have developed a streamlined synthesis of triepoxide **13** that also allows for late-stage diversification of the π-stabilizing group for future studies.

H. General Experimental

All reactions were performed under an atmosphere of argon under anhydrous conditions, unless otherwise noted. Dichloromethane, tetrahydrofuran (THF), Et_2O, benzene, dioxane and triethylamine were purified via an SG Water USA solvent column system. Unless otherwise noted, all reagents were commercially obtained and used without further purification. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates, visualizing with a UV lamp (254 nm), $KMnO_4$, *p*-anisaldehyde, or CAM. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Silicycle silica gel (230–400 mesh) or Biotage® Isolera flash purification system on SNAP HP-SIL columns.

^1H NMR and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded at ambient temperature at 600 MHz and 150 MHz, respectively, using a Bruker AVANCE-600 spectrometer or 500 MHz and 125 MHz, respectively, using a Varian Inova-500 spectrometer. The ^1H NMR data are reported as follows: chemical shift in parts per million (ppm) from an internal standard of residual $CHCl_3$ in $CDCl_3$ (7.27 ppm) on the d scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz (Hz), and integration (H). Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.2 ppm).

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR or an Agilent Cary 630 FTIR Spectrometer. High-resolution mass spectra (HR-MS) were acquired on a Bruker Daltronics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer at the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured using a Jasco Model 1010 digital polarimeter at 589 nm and calculated using the formula: $[a]_D = a_{obs}/(l(c/1000))$, where c = (g of substrate/100 mL of solvent) and l = 1 dm.



24a

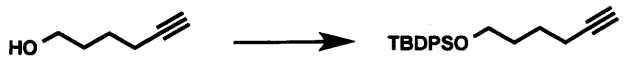
Alkyne 24a: To a solution of 4-pentyn-1-ol (4.21 g, 50.0 mmol) and imidazole (4.77 g, 70.0 mmol) in DMF (50 mL) cooled to 0 °C was added TBDPSCl (15.6 mL, 60.0 mmol). After 5 h, the reaction was quenched with the addition of H_2O (50 mL) and diluted with Et_2O (50 mL). The aqueous layer was separated and extracted twice with Et_2O (20 mL each). The combined organics were washed with H_2O (2 x 25 mL), sat. $NaCl_{(aq)}$ (25 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude alkyne **24a** as a pale yellow oil. The crude product was purified by flash chromatography (100% hexanes to 5% EtOAc in hexanes) to afford **24a** as a colorless oil (16.3 g, 48.5 mmol, 97%).

^1H NMR (500 MHz, $CDCl_3$): δ. 7.71-7.69 (m, 4H), 7.47-7.39 (m, 6H), 3.78 (t, J = 6.0 Hz, 2H), 2.38 (td, J = 7.2, 2.6 Hz, 2H), 1.94 (t, J = 2.7 Hz, 1H), 1.83-1.78 (m, 2H), 1.08 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.7, 134.0, 129.8, 127.8, 84.4, 68.5, 62.4, 31.6, 27.0, 19.4, 15.2.

IR (thin film): 3303, 3069, 2932, 2857, 1889, 1824, 1589, 1472, 1426, 189, 1361, 1259, 1189, 1104, 1007 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{21}H_{26}OSi$ $(M+H)^+$: 323.1826, found 323.1816.



24b

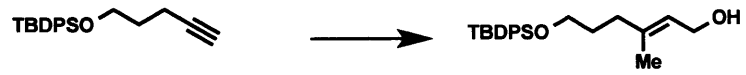
Alkyne 24b: To a solution of 5-pentyn-1-ol (3.93 g, 40.0 mmol) and imidazole (3.81 g, 56.0 mmol) in DMF (40 mL) cooled to 0 °C was added TBDPSCl (12.5 mL, 48.0 mmol). After 5 h, the reaction was quenched with the addition of H_2O (40 mL) and diluted with Et_2O (40 mL). The aqueous layer was separated and extracted twice with Et_2O (20 mL each). The combined organics were washed with H_2O (2 x 40 mL), sat. $NaCl_{(aq)}$ (40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford crude alkyne **24b** as a pale yellow oil. The crude product was purified by flash chromatography (100% hexanes to 5% EtOAc in hexanes) to afford **24b** as a colorless oil (12.8 g, 38 mmol, 95%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.45-7.38 (m, 6H), 3.69 (t, J = 5.9 Hz, 2H), 2.21 (td, J = 6.8, 2.6 Hz, 2H), 1.95 (t, J = 2.6 Hz, 1H), 1.72-1.62 (m, 4H), 1.06 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.7, 134.1, 129.7, 127.8, 84.7, 68.4, 63.5, 31.7, 27.0, 25.1, 19.4, 18.4.

IR (thin film): 3306, 3069, 2932, 2858, 1888, 1824, 1589, 1472, 1427, 1389, 1361, 1261, 1188, 1106, 1008 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{22}H_{28}OSi$ $(M+H)^+$: 337.1982, found 337.1969.



24a **25a**

Alcohol 25a:[34] To (±)-(ebi)$ZrCl_2$[35] (0.20 g, 0.48 mmol) was added $AlMe_3$ in toluene (7.2 mL, 2.0 M, 14.4 mmol), MAO in toluene (0.32 mL, 10 wt%, 0.48 mmol), and finally alkyne **24b** (3.10 g, 9.6 mmol). The reaction, which became very viscous, was stirred at room temperature. After 20 h, the reaction mixture was concentrated *in vacuo* (25 °C, 1 torr) and refilled with Ar. The viscous oil was diluted with THF (10 mL), and *n*-BuLi in hexanes (5.2 mL, 1.94 M, 10.1 mmol) was added dropwise over 2 min. After stirring at room temperature for 30 min, a suspension of paraformaldehyde (0.86 g, 28.8 mmol) in THF (20 mL) was added. After an additional 4 h, the reaction was diluted with hexanes (10 mL) and quenched with the dropwise addition of 1 M $HCl_{(aq)}$ (5 mL), and the combined mixture was poured into sat. Rochelle's salt in water (100 mL). After stirring vigorously for 10 min, the mixture was allowed to stand for 10 min, and the organic layer was separated from the gelatinous aqueous layer. To the aqueous layer was added hexanes (10 mL) and EtOAc (10 mL), and the combined mixture was vigorously stirred for 1 h, followed by separation of the organic layer. The combined organic layers were dried Na_2SO_4, filtered, and concentrated *in vacuo* to afford a yellow oil. The crude product was purified by flash chromatography (5–45% EtOAc in hexanes) to afford **25a** as a colorless oil (1.60 g, 4.3 mmol, 45%).

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[34] Procedure modified from the following report: Lipshutz, B. H.; Butler, T.; Lower, A. *J. Am. Chem. Soc.* **2006**, *128*, 15396.

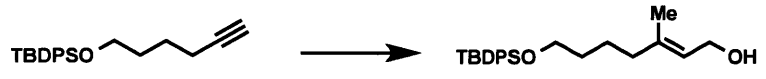
[35] Purchased from Strem Chemicals Inc.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70-7.68 (m, 4H), 7.46-7.38 (m, 6H), 5.40 (t, J = 6.9 Hz, 1H), 4.14 (d, J = 6.9 Hz, 2H), 3.67 (t, J = 6.4 Hz, 2H), 2.12 (t, J = 7.7 Hz, 2H), 1.73-1.67 (m, 2H), 1.66 (s, 3H), 1.23 (br, 1H), 1.07 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 139.7, 135.7, 134.2, 129.7, 127.8, 123.6, 63.6, 59.5, 35.9, 30.8, 27.0, 19.4, 16.4.

IR (thin film): 3326, 2068, 2931, 2856, 1888, 1825, 1668, 1589, 1472, 1427, 1388, 1304, 1253, 1188, 1106 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{23}H_{32}O_2Si$ $(M+NH_4)^+$: 386.2510, found 386.2501.



24b **25b**

Alcohol 25b:[36] To (±)-(ebi)$ZrCl_2$[37] (0.40 g, 0.96 mmol) was added $AlMe_3$ in toluene (14.4 mL, 2.0 M, 28.8 mmol), MAO in toluene (0.64 mL, 10 wt%, 0.96 mmol), and finally alkyne **24b** (6.46 g, 19.2 mmol). The reaction, which became very viscous, was stirred at room temperature. After 20 h, the reaction mixture was concentrated *in vacuo* (25 °C, 1 torr) and refilled with Ar. The viscous oil was diluted with THF (19 mL), and *n*-BuLi in hexanes (9.4 mL, 2.25 M, 21.1 mmol) was added dropwise over 2 min. After stirring at room temperature for 30 min, a suspension of paraformaldehyde (1.73 g, 57.6 mmol) in THF (40 mL) was added. After an additional 4 h, the reaction was diluted with hexanes (20 mL) and quenched with the dropwise addition of 1 M $HCl_{(aq)}$ (5 mL), and the combined mixture was poured into sat. Rochelle's salt in water (200 mL). After stirring vigorously for 10 min, the mixture was allowed to stand for 10 min, and the organic layer was separated from the gelatinous aqueous layer. To the aqueous layer was added hexanes (20 mL) and EtOAc (20 mL), and the combined mixture was vigorously stirred for 2.5 h, followed by separation of the organic layer. The combined organic layers were dried Na_2SO_4, filtered, and concentrated *in vacuo* to afford a yellow oil. The crude product was purified by flash chromatography (10–30% EtOAc in hexanes) to afford **25b** as a colorless oil (4.1 g, 10.7 mmol, 56%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.45-7.37 (m, 6H), 5.39 (tq, J = 7.0, 1.3 Hz, 1H), 4.15 (d, J = 6.9 Hz, 2H), 3.67 (t, J = 6.1 Hz, 2H), 2.01 (t, J = 7.1 Hz, 2H), 1.66 (d, J = 0.4 Hz, 3H), 1.57-1.49 (m, 5H), 1.06 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 139.7, 135.7, 134.1, 129.6, 127.7, 123.5, 63.8, 59.4, 39.3, 32.2, 27.0, 23.9, 19.3, 16.2.

IR (thin film): 3336, 3067, 2931, 2858, 1665, 1589, 1472, 1428, 1388, 1361, 1305, 1187, 1106 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{24}H_{34}O_2Si$ $(M+NH_4)^+$: 400.2666, found 400.2654.

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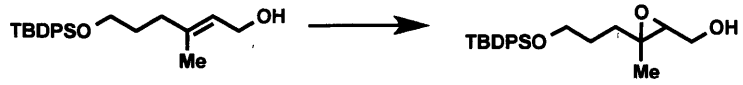
[36] Procedure modified from the following report: Lipshutz, B. H.; Butler, T.; Lower, A. *J. Am. Chem. Soc.* **2006**, *128*, 15396.

[37] Purchased from Strem Chemicals Inc.



25a **26a**

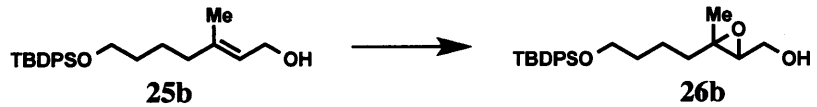
Epoxide 26a: To a solution of alcohol **25a** (1.28 g, 3.47 mmol) in CH_2Cl_2 (34 mL) at 0 °C was added *m*CPBA (≤ 77 wt %, 1.13 g, 5.0 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 2 h, and then quenched by addition of 10% $Na_2CO_{3(aq)}$ (50 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (25 mL each). The combined organic layer was washed with sat. $NaHSO_{3(aq)}$ (25 mL), and 10% $Na_2CO_{3(aq)}$ (25 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude alcohol **26a** as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 40% EtOAc in hexanes) to afford **26a** as a colorless oil (1.28 g, 3.33 mmol, 96%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68-7.65 (m, 4H), 7.45-7.38 (m, 6H), 3.80 (dd, J = 11.9, 3.9 Hz, 1H), 3.70-3.66 (m, 3H), 2.95 (dd, J = 6.6, 4.4 Hz, 1H), 1.73-1.58 (m, 5H), 1.28 (s, 3H), 1.06 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.7, 134.01, 134.00, 129.79, 129.79, 127.8, 63.6, 62.9, 61.6, 61.3, 35.0, 28.3, 27.0, 19.4, 17.0.

IR (thin film): 3410, 3054, 2931, 2857, 1590, 1472, 1427, 1386, 1361, 1255, 1188, 1105, 1087, 1026 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{23}H_{32}O_3Si$ $(M+Na)^+$: 407.2013, found 407.2029.



25b **26b**

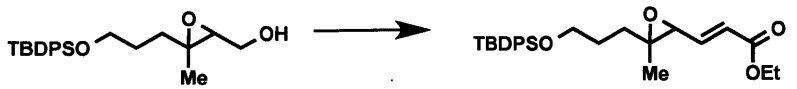
Epoxide 26b: To a solution of alcohol **25b** (3.50 g, 9.2 mmol) in CH_2Cl_2 (92 mL) at 0 °C was added *m*CPBA (≤ 77 wt %, 3.08 g, 13.7 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 2 h, and then quenched by addition of 10% $Na_2CO_{3(aq)}$ (90 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (50 mL each). The combined organic layer was washed with sat. $NaHSO_{3(aq)}$ (50 mL), and 10% $Na_2CO_{3(aq)}$ (50 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude alcohol **26b** as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 40% EtOAc in hexanes) to afford **26b** as a colorless oil (3.36 g, 8.43 mmol, 92%).

^{1}H NMR (MHz, $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.45-7.38 (m, 6H), 3.84 (d, J = 11.4 Hz, 1H), 3.71-3.66 (m, 3H), 2.95 (dd, J = 6.7, 4.2 Hz, 1H), 1.90 (br, 1H), 1.66-1.43 (m, 6H), 1.29 (s, 3H), 1.07 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.7, 134.1, 129.7, 127.8, 63.7, 63.0, 61.6, 61.5, 38.3, 32.5, 27.0, 21.6, 19.4, 16.8.

IR (thin film): 3405, 3069, 2931, 2858, 1472, 1428, 1386, 1187, 1105, 1027 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{24}H_{34}O_3Si$ $(M+Na)^+$: 421.2169, found 421.2186.



26a **27a**

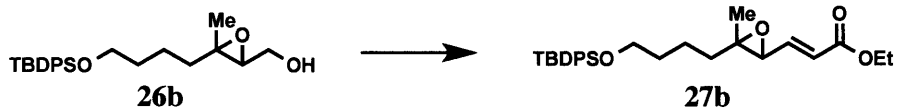
Epoxy Enoate 27a : To a solution of epoxy alcohol **26a** (1.24 g, 3.21 mmol) in CH_2Cl_2 (31 mL) was added DMSO (3.1 mL, 44 mmol) and Et_3N (2.2 mL, 16 mmol), cooled to 0 °C, and Pyr•SO_3 (0.99 g, 6.2 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (2.63 g, 7.56 mmol) was added as a solid at room temperature and stirred for 4 h. The reaction was quenched by addition of H_2O (20 mL) and diluted with CH_2Cl_2 (20 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (20 mL each). The combined organics were washed with H_2O (20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude enoate **27a** as a yellow oil. The crude product was purified by flash chromatography (5–10% EtOAc in hexanes) to afford **27a** as a colorless oil (1.36 g, 3.00 mmol, 94%, 4:1 *E*/*Z*). The product was purified further by MPLC (Biotage Ultra Column) with a gradient of solvents (6–12% EtOAc in hexanes) to afford **27a** as only the (*E*)-alkene (0.77 g, 1.70 mmol, 53%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68-7.66 (m, 4H), 7.46-7.38 (m, 6H), 6.82 (dd, *J* = 15.7, 6.5 Hz, 1H), 6.08 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.23 (qd, *J* = 7.1, 2.3 Hz, 2H), 3.68 (t, *J* = 5.7 Hz, 2H), 3.30 (dd, *J* = 6.5, 0.7 Hz, 1H), 1.79-1.62 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 3H), 1.06 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 143.0, 135.7, 133.95, 133.92, 129.82, 129.81, 127.84, 127.82, 125.0, 64.3, 63.5, 61.4, 60.7, 34.9, 28.3, 27.0, 19.4, 16.8, 14.4.

IR (thin film): 3069, 2932, 2858, 1718, 1653, 1589, 1472, 1428, 1387, 1366, 1301, 1259, 1175, 1105, 1038 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{27}H_{36}O_4Si$ $(M+NH_4)^+$: 470.2721, found 470.2737.



26b **27b**

Epoxy Enoate 27b : To a solution of epoxy alcohol **26b** (1.38 g, 3.46 mmol) in CH_2Cl_2 (34 mL) was added DMSO (3.5 mL, 49 mmol) and Et_3N (2.4 mL, 17 mmol), cooled to 0 °C, and Pyr•SO_3 (1.10 g, 6.9 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (2.41 g, 6.9 mmol) was added as a solid at room temperature and stirred for 5 h. The reaction was quenched by addition of H_2O (20 mL) and diluted with CH_2Cl_2 (20 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (20 mL each). The combined organics were washed with H_2O (20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford crude enoate **27b** as a yellow oil. The crude product was purified by flash chromatography (5–10% EtOAc in hexanes) to afford **27b** as a colorless oil (1.37 g, 2.93 mmol, 85%, 5:1 *E*/*Z*). The product was

purified further by MPLC (Biotage Ultra Column) with a gradient of solvents (5–10% EtOAc in hexanes) to afford **27b** as only the (*E*)-alkene (1.13 g, 2.42 mmol, 70%).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.68-7.67 (m, 4H), 7.45-7.38 (m, 6H), 6.85 (dd, *J* = 15.7, 6.4 Hz, 1H), 6.11 (d, *J* = 15.7 Hz, 1H), 4.26-4.20 (m, 2H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.29 (d, *J* = 6.5 Hz, 1H), 1.70-1.65 (m, 1H), 1.60-1.48 (m, 5H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.27 (s, 3H), 1.06 (s, 9H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 165.9, 143.1, 135.7, 134.1, 129.7, 127.8, 124.9, 64.5, 63.6, 61.5, 60.8, 38.2, 32.5, 27.0, 21.6, 19.4, 16.6, 14.4.

IR (thin film): 2934, 2858, 1716, 1654, 1472, 1428, 1387, 1366, 1301, 1258, 1175, 1105, 1041 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{38}O_4Si$ $(M+Na)^+$: 489.2432, found 489.2423.

27a **28a**

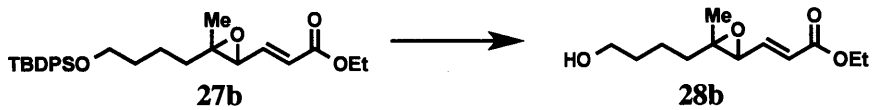
Epoxy Alcohol 28a: To a solution of enoate **27a** (0.77 g, 1.70 mmol) in THF (3.4 mL) at 0 °C was added TBAF (1.0 M in THF, 3.4 mL, 3.4 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 2 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et_3N in 50% EtOAc in hexanes, then 50% EtOAc in hexanes to 60% EtOAc in hexanes) to afford **28a** as a colorless oil (0.35 g, 1.63 mmol, 96%).

^{1}H NMR (MHz, $CDCl_3$): δ 6.81 (dd, *J* = 15.7, 6.4 Hz, 1H), 6.08 (dd, *J* = 15.7, 0.8 Hz, 1H), 4.18 (qd, *J* = 7.1, 1.4 Hz, 2H), 3.63 (t, *J* = 4.4 Hz, 2H), 3.34 (dd, *J* = 6.4, 0.6 Hz, 1H), 2.18 (br, 1H), 1.73-1.63 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.8, 142.6, 125.1, 64.2, 62.3, 61.6, 60.8, 34.7, 28.0, 16.6, 14.3.

IR (thin film): 3421, 2941, 2877, 1716, 1654, 1449, 1387, 1368, 1302, 1259, 1177, 1134, 1095, 1032 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{11}H_{18}O_4$ $(M+NH_4)^+$: 232.1543, found 232.1550.



27b **28b**

Epoxy Alcohol 28b: To a solution of enoate **27b** (0.76 g, 1.63 mmol) in THF (3.3 mL) at 0 °C was added TBAF (1.0 M in THF, 3.3 mL, 3.3 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 2 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et_3N in 50% EtOAc in

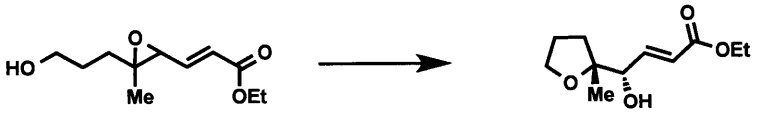
hexanes, then 50% EtOAc in hexanes to 70% EtOAc in hexanes) to afford **28b** as a colorless oil (0.32 g, 1.40 mmol, 87%).

^{1}H NMR (MHz, $CDCl_3$): δ 6.82 (dd, J = 15.7, 6.5 Hz, 1H), 6.09 (d, J = 15.7 Hz, 1H), 4.24-4.17 (m, 2H), 3.66 (t, J = 6.1 Hz, 2H), 3.32 (d, J = 6.5 Hz, 1H), 1.73-1.67 (m, 1H), 1.61-1.47 (m, 6H), 1.31-1.27 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.9, 142.9, 125.1, 64.4, 62.7, 61.4, 60.8, 38.2, 32.6, 21.6, 16.7, 14.4.

IR (thin film): 3425, 2939, 2867, 1718, 1653, 1459, 1368, 1304, 1260, 1176, 1096, 1038 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+Na)^+$: 251.1254, found 251.1240.



28a **30a**

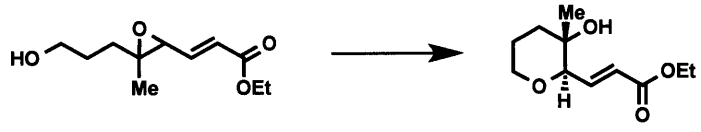
(±)-CSA promoted cyclization of epoxy alcohol 28a: To a 20 ml vial equipped with a magnetic stir bar was added epoxide **28a** (50 mg, 0.23 mmol) in CH_2Cl_2 (12 mL) and (±)-CSA (5 mg, 0.02 mmol) and stirred at room temperature. After consumption of the starting material (30 min, as determined by TLC analysis), the clear solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified mixture indicated a 1:>20 [*endo*(**29a**)/*exo*(**30a**)] ratio of products. The resultant clear film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford **30a** as a colorless oil (48 mg, 0.22 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (dd, J = 15.6, 4.6 Hz, 1H), 6.18 (dd, J = 15.6, 1.9 Hz, 1H), 4.25 (dd, J = 4.6, 1.9 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.95-3.85 (m, 2H), 2.57 (br, 1H), 2.02-1.87 (m, 3H), 1.50-1.44 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.21 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 145.4, 122.5, 85.1, 76.2, 68.7, 60.6, 31.4, 26.5, 23.8, 14.4.

IR (thin film): 3435, 2976, 2873, 1717, 1656, 1448, 1369, 1305, 1272, 1175, 1094, 1036 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{11}H_{18}O_4$ $(M+H)^+$: 215.1278, found 215.1291.



28a **29a**

[Rh(CO)$_2$Cl]$_2$ promoted cyclization of epoxy alcohol 28a: To a 100 ml round bottom flask equipped with a magnetic stir bar open to air was added epoxide **28a** (47.4 mg, 0.22 mmol) and a solution of $[Rh(CO)_2Cl]_2$ in 1,4-dioxane (8.5 mg, 22 μmol, in 4.4 mL 1,4-dioxane) and quickly heated to 80 °C in an oil bath. After consumption of the starting material (30 min, as determined

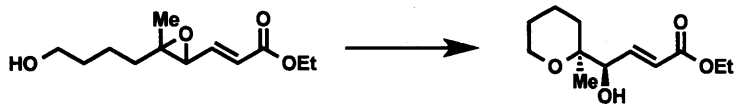
by TLC analysis), the reaction was removed from the oil bath and 150 mg of polymer-bound triphenylphosphine resin was added and stirred for 2 h. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. ^1H NMR spectroscopic analysis of the unpurified mixture indicated a 12.5:1 [*endo*(**29a**)/*exo*(**30a**)] ratio of products. The resultant pale yellow film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford **29a** as a colorless oil (35.5 mg, 0.20 mmol, 76%).

Characterization Data for 29a:
^1H NMR (500 MHz, $CDCl_3$): δ 7.07 (dd, J = 15.8, 4.2 Hz, 1H), 6.08 (dd, J = 15.8, 1.9 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.01 (ddt, J = 11.4, 3.1, 1.6 Hz, 1H), 3.80 (dd, J = 4.2, 1.9 Hz, 1H), 3.43 (td, J = 11.7, 2.5 Hz, 1H), 1.90-1.87 (m, 2H), 1.77-1.70 (m, 1H), 1.67-1.61 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.16 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 144.2, 122.4, 83.3, 70.3, 68.0, 60.5, 39.2, 24.7, 21.4, 14.4.

IR (thin film): 3448, 2976, 2939, 2856, 1700, 1658, 1449, 1368, 1304, 1262, 1174, 1116, 1069, 1050, 1033 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{11}H_{18}O_4$ $(M+H)^+$: 215.1278, found 215.1292.



28b **30b**

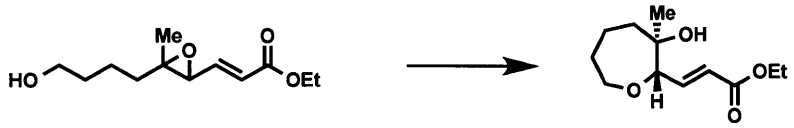
(±)-CSA promoted cyclization of epoxy alcohol 28b: To a 20 ml vial equipped with a magnetic stir bar was added epoxide **28b** (44.6 mg, 0.20 mmol) in CH_2Cl_2 (10 mL) and (±)-CSA (10 mg, 0.04 mmol) and stirred at room temperature. After consumption of the starting material (5 h, as determined by TLC analysis), the clear solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. ^1H NMR spectroscopic analysis of the unpurified mixture indicated a 1:>20 [*endo*(**29b**)/*exo*(**30b**)] ratio of products. The resultant clear film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford **30b** as a colorless oil (40.4 mg, 0.18 mmol, 90%).

^1H NMR (500 MHz, $CDCl_3$): δ 6.92 (dd, J = 15.6, 4.8 Hz, 1H), 6.16 (dd, J = 15.6, 1.9 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.11 (dd, J = 4.8, 1.8 Hz, 1H), 3.77-3.67 (m, 2H), 3.00 (br, 1H), 1.73-1.57 (m, 3H), 1.52-1.48 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.22 (s, 3H), 1.19 (dt, J = 12.9, 3.4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.6, 145.0, 122.7, 77.51, 75.6, 62.1, 60.5, 28.4, 26.0, 19.0, 18.1, 14.4.

IR (thin film): 3449, 2980, 2937, 2867, 1717, 1656, 1466, 1449, 1369, 1305, 1273, 1212, 1176, 1114, 1081, 1046 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+Na)^+$: 251.1254, found 251.1273.



28b **29b**

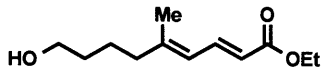
[Rh(CO)$_2$Cl]$_2$ promoted cyclization of epoxy alcohol 28b: To a 200 ml Schlenk tube equipped with a magnetic stir bar was added epoxide **28b** (53 mg, 0.23 mmol) and a solution of [Rh(CO)$_2$Cl]$_2$ in THF (8.9 mg, 23 μmol, in 4.6 mL THF), then the tube was sealed and quickly heated to 80 °C in an oil bath. After 18 h, the reaction was removed from the oil bath and 150 mg of polymer-bound triphenylphosphine resin was added and stirred for 1 h. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et_3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified mixture indicated a 4:1 [*endo*(**29b**)/*exo*(**30b**)] ratio of products. The resultant pale yellow film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford **29b** as a colorless oil (11 mg, 0.05 mmol, 21%) and **31b** as a colorless oil (1 mg, 5 μmol, 2%).

Characterization Data for 29b:
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (dd, J = 15.7, 3.9 Hz, 1H), 6.14 (d, J = 15.7 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.04 (dt, J = 11.8, 5.7 Hz, 1H), 3.95 (d, J = 1.7 Hz, 1H), 3.61-3.56 (m, 1H), 1.86-1.73 (m, 4H), 1.64-1.59 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.26 (br, 1H), 1.13 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 146.3, 121.8, 84.8, 75.5, 71.8, 60.5, 44.4, 31.1, 24.3, 20.8, 14.4.

IR (thin film): 3443, 2929, 2859, 1700, 1654, 1457, 1369, 1300, 1260, 1166, 1105, 1043 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{12}H_{20}O_4$ $(M+H)^+$: 229.1434, found 229.1441.



31b

Characterization Data for 31b:
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (dd, J = 15.2, 11.6 Hz, 1H), 6.00 (d, J = 11.6 Hz, 1H), 5.79 (d, J = 15.2 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.69-3.66 (m, 2H), 2.19-2.16 (m, 2H), 1.90 (d, J = 0.9 Hz, 3H), 1.58-1.56 (m, 5H), 1.30 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 149.7, 141.0, 123.6, 119.2, 62.9, 60.3, 40.1, 32.5, 24.0, 17.5, 14.5.

IR (thin film): 3404, 2926, 2855, 1706, 1634, 1368, 1306, 1272, 1214, 1157, 1137, 1033 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_{12}H_{20}O_3$ $(M+H)^+$: 213.1485, found 213.1496.

26b **32**

Vinyl Epoxide 32 : To a solution of epoxy alcohol **26b** (1.15 g, 2.89 mmol) in CH_2Cl_2 (29 mL) was added DMSO (2.9 mL, 40.8 mmol) and Et_3N (2.0 mL, 14.4 mmol), cooled to 0 °C, and Pyr•SO_3 (0.92 g, 5.8 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by addition of H_2O (20 mL) and diluted with CH_2Cl_2 (20 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (20 mL each). The combined organics were washed with sat. $NH_4Cl_{(aq)}$ (20 mL), H_2O (20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (5–20% EtOAc in hexanes) to afford a colorless oil that was used immediately in the next reaction.

To a solution of *t*BuOK (323 mg, 2.88 mmol) and Ph_3PCH_3Br (1.07 g, 3.00 mmol) in THF (12 mL) aged for 30 min at 50 °C then cooled to room temperature was added the previously obtained oil in THF (5 mL). After 1 h, the reaction was quenched by the addition of SiO_2 gel (8.0 g) and diluted with Et_2O (20 mL). The reaction mixture was concentrated *in vacuo* to afford a free flowing powder. This powder was purified by flash chromatography (5-15% EtOAc in hexanes) to yield a colorless oil.

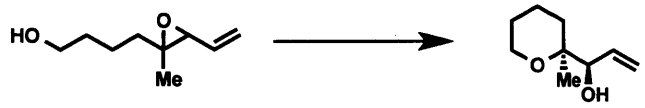
To a solution of the previously obtained oil in THF (3.0 mL) at 0 °C was added TBAF (1.0 M in THF, 3.0 mL, 3.0 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 1.5 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et_3N in 30% EtOAc in hexanes, then 30% EtOAc in hexanes to 60% EtOAc in hexanes) to afford **32** as a colorless oil (0.21 g, 1.36 mmol, 47%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 (ddd, J = 17.3, 10.4, 7.1 Hz, 1H), 5.44 (ddd, J = 17.2, 1.5, 0.9 Hz, 1H), 5.34 (ddd, J = 10.5, 1.5, 0.7 Hz, 1H), 3.65 (t, J = 6.4 Hz, 2H), 3.21 (d, J = 7.2 Hz, 1H), 1.69-1.63 (m, 1H), 1.59-1.47 (m, 5H), 1.26 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 133.6, 120.2, 63.6, 62.86, 62.83, 38.2, 32.7, 21.6, 16.7.

IR (thin film): 3419, 3088, 2936, 2865, 1640, 1458, 1385, 1242, 1162, 1066, 1046 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_9H_{16}O_2$ $(M+H)^+$: 157.1223, found 157.1224.



32 **34**

(±)-CSA promoted cyclization of epoxy alcohol 32: To a 20 ml vial equipped with a magnetic stir bar was added epoxide **32** (19 mg, 0.12 mmol) in CH_2Cl_2 (6 mL) and (±)-CSA (13 mg, 0.06 mmol) and stirred at room temperature. After consumption of the starting material (30 min, as determined by TLC analysis), the reaction was quenched with Et_3N (50 μL) and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified mixture indicated a 1:2.8 [*endo*(**33**)/*exo*(**34**)] ratio of products. The resultant clear film was purified by flash chromatography (10–50% Et_2O/pentanes) to afford **34** as a colorless oil (10.2 mg, 0.065 mmol, 54%) and **33** as a colorless oil (3.7 mg, 0.024 mmol, 19%).

Characterization Data for 34:
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 (ddd, J = 17.2, 10.6, 6.6 Hz, 1H), 5.37 (ddd, J = 17.2, 1.7, 1.5 Hz, 1H), 5.23 (ddd, J = 10.5, 1.8, 1.2 Hz, 1H), 3.92 (d, J = 6.4 Hz, 1H), 3.78-3.67 (m, 2H), 2.86 (s, 1H), 1.76 (td, J = 13.1, 4.4 Hz, 1H), 1.72-1.68 (m, 1H), 1.66-1.59 (m, 1H), 1.53-1.47 (m, 2H), 1.24 (dt, J = 13.1, 3.3 Hz, 1H), 1.18 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.6, 117.9, 79.6, 75.6, 62.2, 28.0, 26.2, 19.1, 18.0.

IR (thin film): 3471, 2936, 2864, 1473, 1374, 1349, 1259, 1211, 1084, 1049 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_9H_{16}O_2$ $(M+H)^+$: 157.1223, found 157.1241.

32 **33**

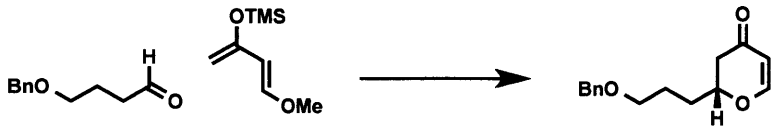
Rh(nbd)$(CH_3CN)_2SbF_6$ promoted cyclization of 32: To alcohol **32** (20 mg, 0.13 mmol) was added DTBMP (13 mg, 0.065) in THF (1.3 mL) and Rh(nbd)$(CH_3CN)_2SbF_6$ (6.6 mg, 0.013 mmol) in THF (1.3 mL). The reaction was heated to 50 °C in an oil bath. After 18 h, the reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified mixture indicated a 5:1 [*endo*(**33**)/*exo*(**34**)] ratio of products. The resultant clear film was purified by flash chromatography (10–50% Et_2O/pentanes) to afford **33** as a colorless oil (10.7 mg, 0.069 mmol, 54%).

Characterization Data for 33:
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 (ddd, J = 17.2, 10.7, 6.5 Hz, 1H), 5.33 (ddd, J = 17.3, 2.0, 1.4 Hz, 1H), 5.27 (ddd, J = 10.6, 2.0, 1.3 Hz, 1H), 3.99 (dt, J = 12.0, 5.9 Hz, 1H), 3.76 (d, J = 6.4 Hz, 1H), 3.64 (ddd, J = 12.1, 7.9, 5.7 Hz, 1H), 1.84-1.69 (m, 5H), 1.63-1.58 (m, 2H), 1.15 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.8, 117.5, 86.8, 74.9, 70.6, 43.4, 31.1, 24.0, 20.7

IR (thin film): 3417, 2933, 2864, 1456, 1374, 1274, 1104, 1054 cm^{-1}.

HR-MS (DART) *m/z* calcd for $C_9H_{16}O_2$ $(M+H)^+$: 157.1223, found 157.1231.



40 **41** **43**

Pyrone 43: To a suspension of aldehyde **40** (5.0 g, 28.1 mmol), 4 Å MS (5.0 g) and Cr cat. **42**[38] (0.41 g, 0.84 mmol) in acetone (6.2 mL, 84 mmol) aged for 30 min at room temperature then cooled to 0 °C was added diene **41** (7.3 mL, 33.7 mmol). The reaction was allowed to warm to

[38] From (1*S*,2*R*)-1-Amino-2-indanol following the reported procedure: Chavez, D. E.; Jacobsen, E. N. *Org. Synth.* **2005**, *82*, 34.

room temperature and stirred vigorously. After 3 d, the reaction mixture was cooled to 0 °C, diluted with CH_2Cl_2 (10 mL), and TFA (2.8 mL) was added. After stirring for 1 h, the reaction mixture was filtered through Celite and the Celite was flushed with CH_2Cl_2 (3 x 20 mL). The combined filtrate was quenched with sat. $NaHCO_{3(aq)}$ (20 mL), and the layers separated. The aqueous layer was reextracted with CH_2Cl_2 (2x10 mL). The combined organic layers were washed with sat. $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resultant red oil was purified by flash chromatography (20–50% EtOAc in hexanes) to afford **43** as a yellow oil (6.5 g, 26.4 mmol, 94%). Determination of the ee of **43** was accomplished by chiral analytical HPLC analysis (Chiracel OD–H; 10% *i*PrOH in hexanes, 1.00 mL/min; t_R(major) = 17.3 min, t_R(minor) = 24.2 min.

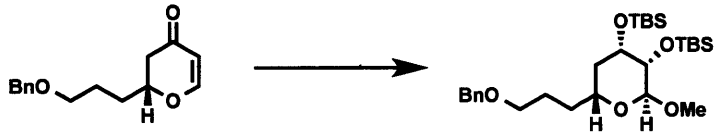
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.28 (m, 6H), 5.41 (d, J = 6.0, 1H), 4.52 (s, 2H), 4.42 (ddt, J = 13.1, 8.3, 4.3 Hz, 1H), 3.57-3.50 (m, 2H), 2.53 (dd, J = 16.7, 13.5 Hz, 1H), 2.44 (ddd, J = 16.7, 3.7, 1.0 Hz, 1H), 1.94-1.86 (m, 1H), 1.86-1.71 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 192.8, 163.4, 138.4, 128.5, 127.8, 107.1, 79.4, 73.1, 69.6, 42.0, 31.4, 25.3.

IR (thin film): 3059, 3032, 2934, 2857, 2798, 1672, 1592, 1496, 1454, 1405, 1362, 1270, 1229, 1203, 1095, 1033 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{13}H_{18}O_3$ $(M+Na)^+$: 269.1148, found 269.1156.

$[\alpha]^{23}_D = +103.6$ (c = 1.00, $CHCl_3$).[39]



43 **44**

THP 44: To a solution of pyrone **43** (4.48 g, 18.2 mmol) in MeOH (91 mL) open to air was added $CeCl_3$•$7H_2O$ (3.4 g, 9.1 mmol) at room temperature. After 30 min, the reaction mixture was cooled to –20 °C, and $NaBH_4$ (0.69 g, 18.2 mmol) was added as a solid in three portions over 10 min. After 30 min, the reaction was quenched by the addition of acetone (18 mL). The reaction was carefully concentrated *in vacuo*. The solid obtained was dissolved in Et_2O (100 mL) and H_2O (100 mL). After separating the layers, the aqueous layer was reextracted with Et_2O (2 x 50 mL), and the combined organic layers were washed H_2O (50 mL) and sat. $NaCl_{(aq)}$ (50 mL), dried Na_2SO_4, filtered, and concentrated *in vacuo* to afford a yellow oil.

To a solution of the previously obtained oil and $NaHCO_3$ (1.5 g, 18 mmol) in MeOH (91 mL) at 0 °C was added *m*CPBA (6.3 g, 36.4 mmol) as a solid, and then the reaction was allowed to warm to room temperature. After 1 h, the reaction was concentrated *in vacuo*, suspended between EtOAc (50 mL), H_2O (20 mL), and sat. $Na_2SO_{3(aq)}$ (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed sat. $K_2CO_{3(aq)}$ (20 mL), H_2O (20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4, filtered, and

[39] Lit. Reported $[\alpha]^{23}_D = +94.7$ (c = 0.530, $CHCl_3$) for 90% ee material; Gleason, M. M.; McDonald, F. E. *J. Org. Chem.* **1997**, *62*, 6432.

concentrated *in vacuo*. The yellow oil was purified by flash chromatography (70% EtOAc in hexanes to 100% EtOAc) to afford a pale yellow oil that was used immediately in the next reaction.

To a solution of the previously obtained pale yellow oil, imidazole (11.4 g, 168 mmol), and DMAP (0.37 g, 3.1 mmol) in DMF (76 mL) cooled to 0 °C was added TBSCl (11.5 g, 76 mmol), then allowed to warm to room temperature. After 20 h, the reaction was cooled to 0 °C, quenched with the addition of H_2O (80 mL), and vigorously mixed for 15 min. The reaction mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with H_2O (2 x 50 mL) and sat. $NaCl_{(aq)}$ (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resultant yellow oil was purified by flash chromatography (100% hexanes to 10% EtOAc in hexanes) to afford **44** as a pale yellow oil (6.30 g 12.0 mmol, 66%).

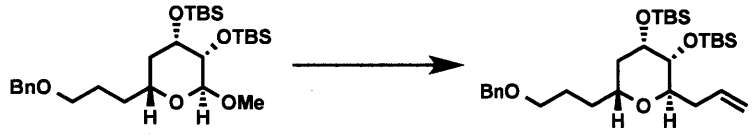
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.28 (m, 5H), 4.54-4.49 (m, 3H), 3.94 (ddd, J = 11.6, 4.3, 2.8 Hz, 1H), 3.65-3.59 (m, 2H), 3.54-3.46 (m, 2H), 3.30 (s, 3H), 1.86-1.78 (m, 2H), 1.71-1.53 (m, 3H), 1.40-1.37 (m, 1H), 0.90 (s, 9H), 0.90 (s, 9H), 0.08-0.06 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8, 128.5, 127.84, 127.69, 102.9, 73.1, 71.0, 70.6, 68.7, 68.0, 54.7, 35.0, 32.4, 26.28, 26.14, 26.04, 18.46, 18.39, -4.13, -4.26, -4.40, -4.57.

IR (thin film): 2953, 2929, 2900, 2857, 1472, 1388, 1361, 1313, 1253, 1160, 1128, 1102, 1067, 1007 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{28}H_{52}O_5Si_2$ $(M+Na)^+$: 547.3245, found 547.3227.

$[\alpha]^{23}_D = +18.3$ (c = 1.00, CH_2Cl_2).



44 **38**

Allyl THP 38: To a solution of **44** (7.50 g, 14.3 mmol), DTBMP (5.87 g, 28.6 mmol), and allyltrimethylsilane (4.5 mL, 28.6 mmol) in CH_3CN (143 mL) at 0 °C was added TMSOTf (2.6 mL, 14.3 mmol) dropwise over 2 min. The reaction was then allowed to warm to room temperature. After 2.5 h, the reaction was cooled to 0 °C and quenched by the addition of sat. $NaHCO_{3(aq)}$ (70 mL) and H_2O (30 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with sat. $NaCl_{(aq)}$ (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The oil obtained was purified by flash chromatography (3–6% EtOAc in hexanes) to afford **38** as a pale yellow oil (6.70 g 12.5 mmol, 88%).

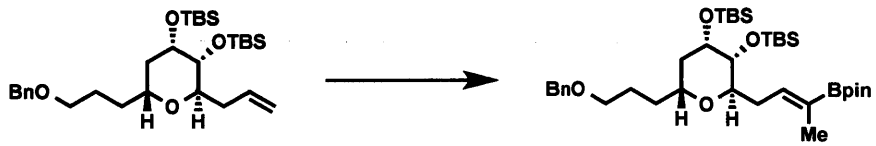
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.80 (ddt, J = 17.0, 10.1, 6.9 Hz, 1H), 5.10-5.06 (m, 2H), 4.53-4.48 (m, 2H), 3.90 (ddd, J = 10.3, 4.0, 2.7 Hz, 1H), 3.84 (ddd, J = 9.0, 6.2, 2.8 Hz, 1H), 3.60-3.56 (m, 2H), 3.52-3.48 (m, 2H), 2.37-2.31 (m, 1H), 2.29-2.21 (m, 1H), 1.83 (dt, J = 12.4, 10.2 Hz, 1H), 1.79-1.61 (m, 3H), 1.56-1.52 (m, 1H), 1.49 (dt, J = 12.7, 3.6 Hz, 1H), 0.91 (m, 18H), 0.07-0.05 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8, 135.2, 128.5, 127.84, 127.65, 116.9, 77.9, 73.0, 72.0, 70.5, 69.9, 68.6, 35.6, 34.9, 32.5, 26.30, 26.20, 26.11, 18.53, 18.37, -4.02, -4.20, -4.24, -4.44.

IR (thin film): 2951, 2929, 2889, 2857, 1464, 1369, 1252, 1100, 1059, 1004 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{30}H_{54}O_4Si_2$ $(M+H)^+$: 535.3633, found 535.3619.

$[\alpha]^{24}_D = +12.3$ (c = 1.01, $CHCl_3$).



38 **47**

Vinyl Boronic Ester 47: A mixture of **38** (0.54 g, 1.00 mmol), benzoquinone (11 mg, 0.10 mmol), Hoveyda–Grubbs 2nd generation catalyst (64 mg, 0.10 mmol) and isopropenylboronic acid pinacol ester[40] (0.94 mL, 5.00 mmol) was heated to 60 °C. After 36 h, the reaction was cooled to room temperature, diluted with CH_2Cl_2 (10 mL), and concentrated *in vacuo*. ^1H NMR spectroscopic analysis of the unpurified mixture indicated a 3:1 *Z*/*E* ratio of products. The resultant green oil was purified by flash chromatography (100% hexanes to 10% EtOAc in hexanes) to afford (*Z*)-**47** as a pale green oil (414 mg, 0.61 mmol, 61%) and (*E*)-**47** as a pale green oil (174 mg, 0.26 mmol, 26%).

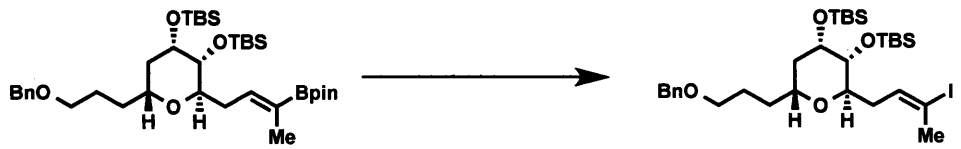
Characterization Data for (Z)-47:
^1H NMR (500 MHz, $CDCl_3$): δ 7.35-7.33 (m, 4H), 7.29-7.26 (m, 1H), 6.36 (td, J = 6.9, 1.6 Hz, 1H), 4.53-4.47 (m, 2H), 3.92-3.88 (m, 2H), 3.60-3.56 (m, 1H), 3.54 (t, J = 2.5 Hz, 1H), 3.52-3.44 (m, 2H), 2.37-2.34 (m, 2H), 1.82 (dt, J = 12.3, 10.1 Hz, 1H), 1.70 (s, 3H), 1.77-1.61 (m, 3H), 1.58-1.53 (m, 1H), 1.49 (dt, J = 12.5, 3.2 Hz, 1H), 1.25 (s, 12H), 0.90 (s, 18H), 0.06-0.04 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.3, 138.9, 128.5, 127.8, 127.6, 83.3, 77.8, 7 3.0, 72.2, 70.5, 70.1, 68.7, 35.6, 32.4, 29.5, 26.27, 26.12, 26.10, 24.9, 18.48, 18.35, 14.3, -4.08, -4.15, -4.24, -4.5.

IR (thin film): 2952, 2929, 2857, 1635, 1412, 1370, 1341, 1306, 1251, 1214, 1131, 1098, 1068, 1005 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{37}H_{67}BO_6Si_2$ $(M+H)^+$: 674.4678, found 674.4671.

$[\alpha]^{23}_D = +9.8$ (c = 0.99, $CHCl_3$).



47 **36**

Vinyl Iodide 36: To a solution of **47** (0.41 g, 0.61 mmol) in THF (4.1 mL) at room temperature was added 6 M $NaOH_{(aq)}$ (0.92 mL, 5.5 mmol). After stirring vigorously for 10 minutes, I_2 in THF (9.15 mL, 0.2 M, 1.83 mmol) was added dropwise by syringe pump over 1 h. After an additional 1 h of stirring, the reaction was diluted with Et_2O (25 mL) and quenched with sat. $Na_2S_2O_{3(aq)}$ (25

[40] Purchased from Sigma-Aldrich.

mL). After partitioning of the layers, the aqueous layer was extract with Et_2O (2 x 20 mL), and the combined organic layers were washed with H_2O (25 mL), sat. $NaCl_{(aq)}$ (25 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resultant yellow oil was purified by flash chromatography (100% hexanes to 8% EtOAc in hexanes) to afford **36** as a colorless oil (233 mg, 0.35 mmol, 56%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.34 (m, 4H), 7.31-7.26 (m, 1H), 6.21 (td, J = 7.3, 1.4 Hz, 1H), 4.52 (s, 2H), 3.87 (ddd, J = 9.2, 3.7, 2.8 Hz, 1H), 3.81 (ddd, J = 9.2, 5.5, 3.8 Hz, 1H), 3.59-3.54 (m, 1H), 3.53-3.45 (m, 3H), 2.37 (d, J = 1.4 Hz, 3H), 2.29-2.17 (m, 2H), 1.84-1.73 (m, 3H), 1.66-1.60 (m, 1H), 1.58-1.52 (m, 2H), 0.91 (m, 18H), 0.07-0.06 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9, 137.7, 128.5, 127.8, 127.6, 94.9, 75.9, 73.0, 72.4, 70.4, 68.9, 35.7, 32.1, 31.6, 27.9, 26.29, 26.24, 26.11, 18.44, 18.33, -3.94, -4.11, -4.24, -4.5.

IR (thin film): 2929, 2885, 2857, 1472, 1361, 1252, 1152, 1102, 1054, 1006 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{31}H_{55}IO_4Si_2$ $(M+H)^+$: 675.2756, found 675.2778.

$[\alpha]^{25}_D$ = +22.8 (*c* = 1.00, $CHCl_3$).

Enoate 48: To a solution of epoxide **39**[41] (0.32 g, 1.9 mmol) and imidazole (0.19 g, 2.8 mmol) in DMF (10 mL) cooled to 0 °C was added TBDPSCl (0.62 mL, 2.4 mmol). The reaction was allowed to warm up to room temperature. After 18 h, the reaction was quenched with H_2O (10 mL) and diluted with Et_2O (20 mL). After partitioning of the layers, the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic layers were washed with H_2O (2 x 20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resultant pale yellow oil was used in the next reaction without purification.

The previously obtained oil was diluted in CH_2Cl_2 (34 mL), cooled to –78 °C, and sparged with O_3 for 10 min. When the reaction changed to blue from colorless, the O_3 flow was stopped and replace with N_2 sparging for 5 minutes, followed by the addition of Ph_3P (0.6 g, 2.6 mmol) dissolved in CH_2Cl_2 (5 mL). The reaction was allowed to warm to room temperature over 1 h, then (carbethoxymethylene)triphenylphosphorane (1.19 g, 3.4 mmol) was added. After 30 min, the reaction was concentrated *in vacuo*, and the resultant yellow oil was purified by flash chromatography (5–15% EtOAc in hexanes) to afford **48** as a colorless oil (0.65 g, 1.44 mmol, 76%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72-7.68 (m, 4H), 7.47-7.39 (m, 6H), 6.96 (dt, J = 15.6, 6.8 Hz, 1H), 5.85 (dt, J = 15.6, 1.6 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.82 (dd, J = 11.5, 5.5 Hz, 1H), 3.75 (dd, J = 11.5, 5.3 Hz, 1H), 3.00 (t, J = 5.4 Hz, 1H), 2.31-2.26 (m, 2H), 1.75-1.62 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.14 (s, 3H), 1.08 (s, 9H).

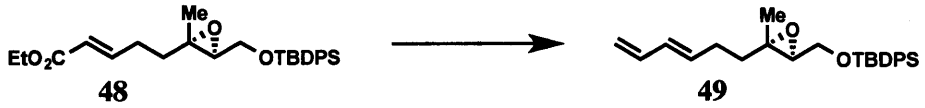
^{13}C NMR (125 MHz, $CDCl_3$): δ 166.6, 148.1, 135.74, 135.70, 133.6, 133.3, 130.0, 127.91, 127.90, 121.9, 62.85, 62.82, 60.4, 60.1, 36.7, 27.8, 26.9, 19.4, 16.9, 14.4.

[41] Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, 51, 1922.

IR (thin film): 3069, 2933, 2858, 1719, 1654, 1473, 1428, 1388, 1367, 1315, 1266, 1193, 1156, 1112, 1082, 1045 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{27}H_{36}O_4Si$ $(M+Na)^+$: 475.2274, found 475.2275.

$[\alpha]^{23}_D = -11.2$ (c = 1.01, $CHCl_3$).



48 49

Diene 49: To a solution of enoate **48** (0.80 g, 1.77 mmol) in Et_2O (18 mL) at –78 °C was added DIBAL–H (1.0 M in hexanes, 5.3 mL, 5.3 mmol) dropwise over three min. The reaction was stirred for 20 min, and then poured into an Erlenmeyer flask containing sat. aq. Rochelle's salt (30 mL), Et_2O (30 mL), and H_2O (30 mL) and stirred vigorously for 13 h at room temperature. The aqueous layer was separated and extracted with Et_2O (2x20 mL). The combined organics were washed with sat. $NaCl_{(aq)}$ (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 40% EtOAc in hexanes) to afford a colorless oil that was used directly in the next reaction.

To a solution of previously obtained oil in CH_2Cl_2 (16 mL) was added DMSO (1.6 mL, 22.5 mmol) and Et_3N (1.1 mL, 7.8 mmol), cooled to 0 °C, and Pyr•SO_3 (0.50 g, 3.12 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by addition of H_2O (20 mL) and diluted with CH_2Cl_2 (20 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (20 mL each). The combined organics were washed with sat. $NH_4Cl_{(aq)}$ (20 mL), H_2O (20 mL), sat. $NaCl_{(aq)}$ (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (5–25% EtOAc in hexanes) to afford a colorless oil that was used immediately in the next reaction.

To a solution of *t*BuOK (185 mg, 1.65 mmol) and Ph_3PCH_3Br (0.71 g, 2.0 mmol) in THF (13 mL) aged for 30 min at room temperature was added the previously obtained oil in THF (5 mL). After 1 h, the reaction was quenched by the addition of SiO_2 gel (5.0 g) and diluted with Et_2O (20 mL). The reaction mixture was concentrated *in vacuo* to afford a free flowing powder. This powder was purified by flash chromatography (5-15% EtOAc in hexanes) to afford **49** as a colorless oil (394 mg, 0.97 mmol, 55%).

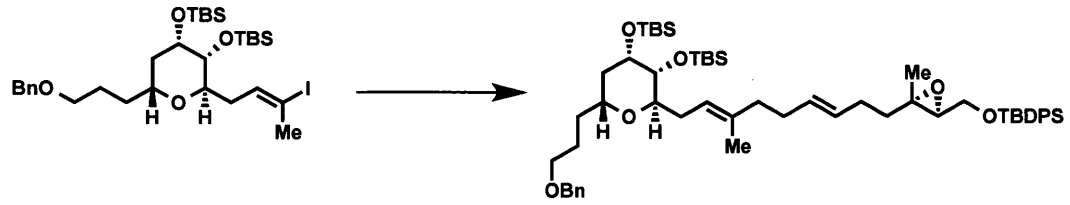
^1H NMR (500 MHz, $CDCl_3$): δ 7.71-7.67 (m, 4H), 7.47-7.39 (m, 6H), 6.30 (dt, J = 17.0, 10.3 Hz, 1H), 6.08 (dd, J = 15.2, 10.4 Hz, 1H), 5.70 (dt, J = 14.8, 7.3 Hz, 1H), 5.11 (d, J = 17.0 Hz, 1H), 4.99 (d, J = 10.1 Hz, 1H), 3.81 (dd, J = 11.5, 5.5 Hz, 1H), 3.74 (dd, J = 11.5, 5.3 Hz, 1H), 3.00 (t, J = 5.4 Hz, 1H), 2.24-2.15 (m, 2H), 1.72 (ddd, J = 13.7, 9.1, 6.4 Hz, 1H), 1.55 (ddd, J = 13.7, 9.6, 6.8 Hz, 1H), 1.14 (s, 3H), 1.08 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 137.2, 135.77, 135.73, 134.1, 133.6, 133.4, 131.6, 129.9, 127.91, 127.90, 115.5, 63.07, 62.96, 60.5, 38.1, 28.4, 27.0, 19.4, 16.9.

IR (thin film): 3073, 2998, 2931, 2858, 1652, 1590, 1472, 1428, 1385, 1361, 1308, 1246, 1189, 1112, 1075, 1003 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{26}H_{34}O_2Si$ $(M+Na)^+$: 429.2220, found 429.2210.

$[\alpha]^{23}_D = -11.5$ (c = 1.00, $CHCl_3$).



36 **35**

Diene 35: To a cooled (0 °C) solution of diene **49** (122 mg, 0.30 mmol) in THF (0.3 mL) was added 9-BBN-H in THF (0.90 mL, 0.5 M, 0.45 mmol). The reaction was allowed to warm to room temperature. After 2 h, degassed 1 M $NaOH_{(aq)}$ (0.83 mL, 0.83 mmol) was added and the mixture was stirred for an additional 30 min.

In a separate vessel, alkene **36** (100 mg, 0.15 mmol) and $PdCl_2$(dppf) (6.0 mg, 7.4 μmol) were premixed in THF (0.37 mL) then cooled to 0 °C. The mixture containing **49** was then transferred by cannula, and the reaction was stirred at 0 °C. After 3 h, the reaction mixture was diluted with Et_2O (5 mL) and H_2O (5 mL). The aqueous layer was separated and extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with H_2O (5 mL) and sat. $NaCl_{(aq)}$ (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant orange oil was purified by flash chromatography (1–10% EtOAc in hexanes) to afford **35** as a colorless oil (105 mg, 0.11 mmol, 75%).

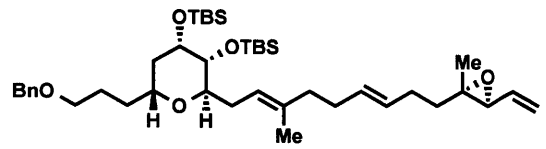
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71-7.69 (m, 4H), 7.46-7.39 (m, 7H), 7.36-7.33 (m, 4H), 7.29-7.26 (m, 1H), 5.47-5.38 (m, 2H), 5.17 (t, J = 6.7 Hz, 1H), 4.54-4.48 (m, 2H), 3.92 (dt, J = 10.0, 3.1 Hz, 1H), 3.82-3.73 (m, 3H), 3.60-3.57 (m, 2H), 3.53-3.45 (m, 2H), 3.00 (t, J = 5.4 Hz, 1H), 2.29-2.20 (m, 2H), 2.10-2.06 (m, 6H), 1.84 (q, J = 11.3 Hz, 1H), 1.78-1.74 (m, 1H), 1.71-1.64 (m, 3H), 1.62 (s, 3H), 1.58-1.46 (m, 3H), 1.13 (s, 3H), 1.08 (s, 9H), 0.92 (s, 19H), 0.08-0.06 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8, 136.8, 135.74, 135.69, 133.6, 133.4, 130.6, 129.9, 129.4, 128.5, 127.88, 127.78, 127.61, 120.6, 78.8, 73.0, 71.8, 70.5, 69.9, 68.7, 63.05, 63.01, 60.6, 39.9, 38.6, 35.6, 32.5, 31.4, 28.9, 28.4, 26.9, 26.26, 26.12, 26.10, 19.4, 18.47, 18.35, 16.9, 16.6, -4.09, -4.16, -4.26, -4.43.

IR (thin film): 2929, 2885, 2856, 1482, 1386, 1361, 1252, 1104, 1074, 1006 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{57}H_{90}O_6Si_3$ $(M+NH_4)^+$: 972.6383, found 972.6371.

$[\alpha]^{24}_D = -0.3$ (c = 2.07, $CHCl_3$).



50

Triene 50: To a solution of triene **35** (57 mg, 0.060 mmol) in THF (0.60 mL) at 0 °C was added TBAF in THF (60 μL, 1.0 M, 0.05 mmol). After 1.5 h, the reaction was diluted with H_2O (3 mL) and Et_2O (3 mL). The aqueous layer was separated and extracted with Et_2O (2 x 3 mL). The combined organic layers were washed with sat. $NaCl_{(aq)}$, dried over Na_2SO_4, filtered, and

concentrated *in vacuo*. The afforded colorless oil was purified by flash chromatography (10–40% EtOAc in hexanes) to afford a colorless oil that was used directly in the next reaction.

To a solution of previously obtained oil in CH_2Cl_2 (0.6 mL) was added DMSO (0.12 mL, 1.7 mmol) and Et_3N (0.10 mL, 0.71 mmol), cooled to 0 °C, and Pyr•SO_3 (38 mg, 0.24 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by addition of H_2O (3 mL) and diluted with CH_2Cl_2 (3 mL). The aqueous layer was separated and extracted twice with CH_2Cl_2 (3 mL each). The combined organics were washed with sat. $NH_4Cl_{(aq)}$ (2 mL), H_2O (2 mL), sat. $NaCl_{(aq)}$ (2 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (5–30% EtOAc in hexanes) to afford a colorless oil that was used immediately in the next reaction.

To a solution of *t*BuOK (8 mg, 0.07 mmol) and Ph_3PCH_3Br (29 mg, 0.08 mmol) in THF (0.6 mL) aged for 30 min at room temperature was added the previously obtained oil in THF (1 mL). After 10 min, the reaction was quenched by the addition of SiO_2 gel (50 mg) and diluted with Et_2O (5 mL). The reaction mixture was concentrated *in vacuo* to afford a free flowing powder. This powder was purified by flash chromatography (5-25% EtOAc in hexanes) to afford **50** as a colorless oil (28 mg, 0.039 mmol, 65%).

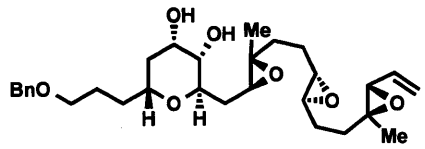
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.27 (m, 5H), 5.74 (ddd, *J* = 17.3, 10.4, 7.1 Hz, 1H), 5.46-5.37 (m, 3H), 5.34 (ddd, *J* = 10.5, 1.5, 0.7 Hz, 1H), 5.16 (t, *J* = 6.6 Hz, 1H), 4.53-4.48 (m, 2H), 3.90 (ddd, *J* = 10.4, 3.9, 2.8 Hz, 1H), 3.77 (td, *J* = 7.6, 2.5 Hz, 1H), 3.59-3.55 (m, 2H), 3.52-3.44 (m, 2H), 3.20 (d, *J* = 7.2 Hz, 1H), 2.29-2.17 (m, 2H), 2.11-2.03 (m, 6H), 1.86-1.79 (m, 1H), 1.75-1.63 (m, 4H), 1.61 (s, 3H), 1.55-1.52 (m, 2H), 1.47 (d, *J* = 12.5 Hz, 1H), 1.26 (s, 3H), 0.90 (m, 18H), 0.07-0.04 (m, 12H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8, 136.8, 133.7, 130.8, 129.4, 128.5, 127.81, 127.63, 120.6, 120.1, 78.8, 73.0, 71.9, 70.6, 70.0, 68.7, 63.8, 62.7, 39.9, 38.6, 35.6, 32.5, 31.5, 28.9, 28.4, 26.28, 26.15, 26.11, 18.49, 18.37, 16.8, 16.6, -4.08, -4.15, -4.24, -4.42.

IR (thin film): 2929, 2855, 1462, 1385, 1251, 1098, 1051, 1005 cm^{-1}.

HR-MS (ESI) *m/z* calcd for $C_{42}H_{72}O_5Si_2$ $(M+Na)^+$: 735.4810, found 735.4824.

$[\alpha]^{25}_D$ = +9.5 (*c* = 1.31, $CHCl_3$).



13

Triepoxide 13: To a solution of triene **50** (20 mg, 0.028 mmol) in THF (2.0 mL) at 0 °C was added TBAF in THF (200 μL, 1.0 M, 0.20 mmol). After 3 h, the reaction was diluted with H_2O (5 mL) and Et_2O (5 mL). The aqueous layer was separated and extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with sat. $NaCl_{(aq)}$, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The afforded yellow oil was purified by flash chromatography (30–80% EtOAc in hexanes) to afford a colorless oil that was used directly in the next reaction.

To a solution of the previously obtained oil and chiral ketone (+)-**51**[42] (37 mg, 0.14 mmol) in DMM/MeCN (2:1, 3.3 mL) was added a solution of 0.05 M $Na_2B_4O_7$•$10H_2O$ in 4 x 10^{-4}

[42] Jamison, T. F.; Ikeuchi, Y. Epoxidation Catalysts. U.S. Patent 8,680,303 B2, Mar. 25, 2014

Na_2EDTA (2.2 mL) and nBu_4HSO_4 (10 mg, 0.03 mmol), and the mixture was cooled to 0 °C. To this vigorously stirred reaction mixture was added, simultaneously over 1 h via syringe pump, a 0.212 M solution of Oxone® in 4 x 10^{-4} Na_2EDTA (1.6 mL) and a 0.89 M solution of K_2CO_3 in H_2O (1.6 mL). Upon completion of syringe pump addition, the reaction mixture was diluted with Et_2O/H_2O (1:1, 5 mL) and warmed to room temperature. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were washed with sat. $NaCl_{(aq)}$ (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The afforded colorless oil was purified by flash chromatography (70% EtOAc in hexanes to 100% EtOAc) to provide a **13** as a colorless oil (5.1 mg, 9.9 μmol, 3.5:1 dr, 36% over two steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.32 (m, 4H), 7.30-7.26 (m, 1H), 5.73 (ddd, J = 17.3, 10.4, 7.0 Hz, 1H), 5.45 (d, J = 17.1 Hz, 1H), 5.35 (d, J = 10.5 Hz, 1H), 4.53-4.47 (m, 2H), 4.06 (dt, J = 8.8, 4.4 Hz, 1H), 3.93 (dt, J = 8.6, 4.3 Hz, 1H), 3.66 (dt, J = 8.3, 4.3 Hz, 1H), 3.63 (t, J = 3.3 Hz, 1H), 3.53-3.45 (m, 2H), 3.22 (d, J = 7.2 Hz, 1H), 2.88 (t, J = 5.9 Hz, 1H), 2.71-2.68 (m, 2H), 1.93 (ddd, J = 14.9, 8.9, 6.2 Hz, 1H), 1.83 (dt, J = 13.3, 4.0 Hz, 1H), 1.78-1.56 (m, 14H), 1.27-1.26 (m, 6H).

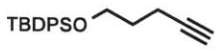
^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7, 133.3, 128.5, 127.78, 127.65, 120.5, 74.0, 73.0, 70.34, 70.25, 69.5, 66.5, 63.4, 62.2, 60.2, 59.9, 58.39, 58.31, 35.2, 34.6, 34.4, 32.0, 29.1, 27.71, 27.56, 26.2, 16.94, 16.80.

IR (thin film): 3423, 2924, 2857, 1454, 1386, 1246, 1208, 1094, 1074 cm^{-1}.

HR-MS (ESI) m/z calcd for $C_{30}H_{44}O_7$ $(M+Na)^+$: 539.2979, found 539.2975.

$[\alpha]^{25}_D$ = +1.5 (c = 0.99, $CHCl_3$).

I. ^{1}H and ^{13}C NMR Spectra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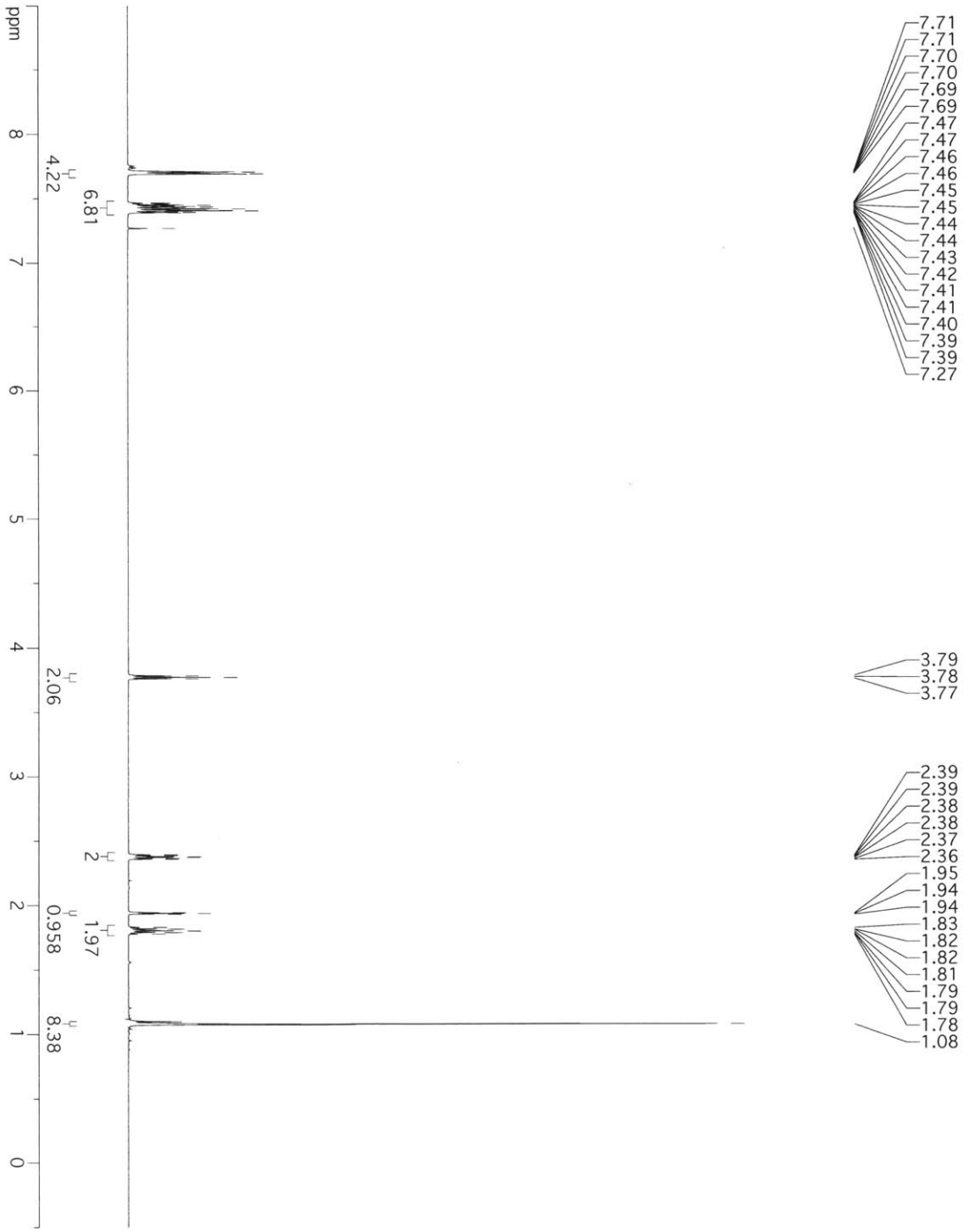
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2.38
2.38
2.37
2.36
1.95
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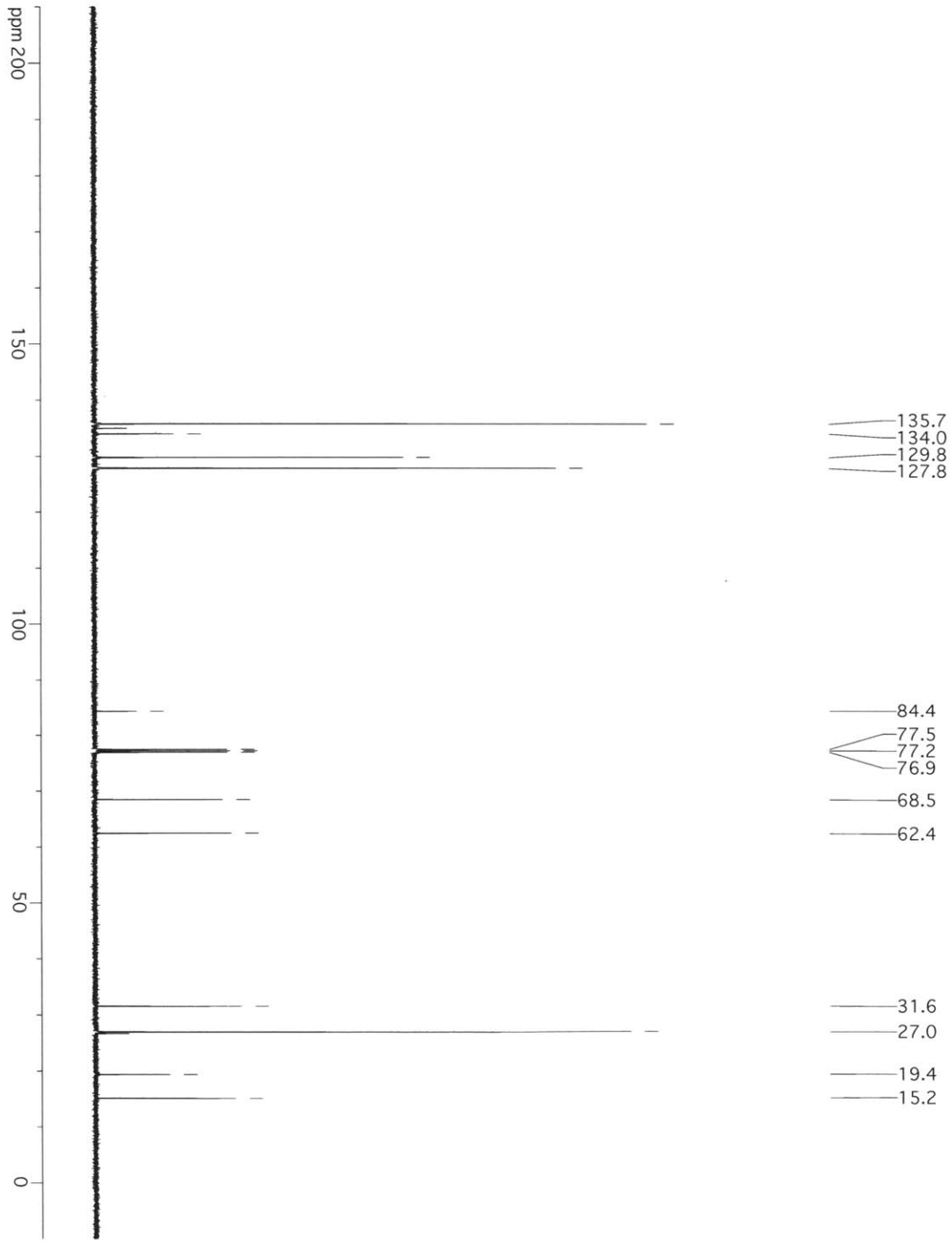
1.78
1.08


TBDPSO

24a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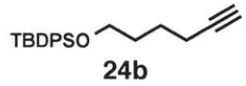
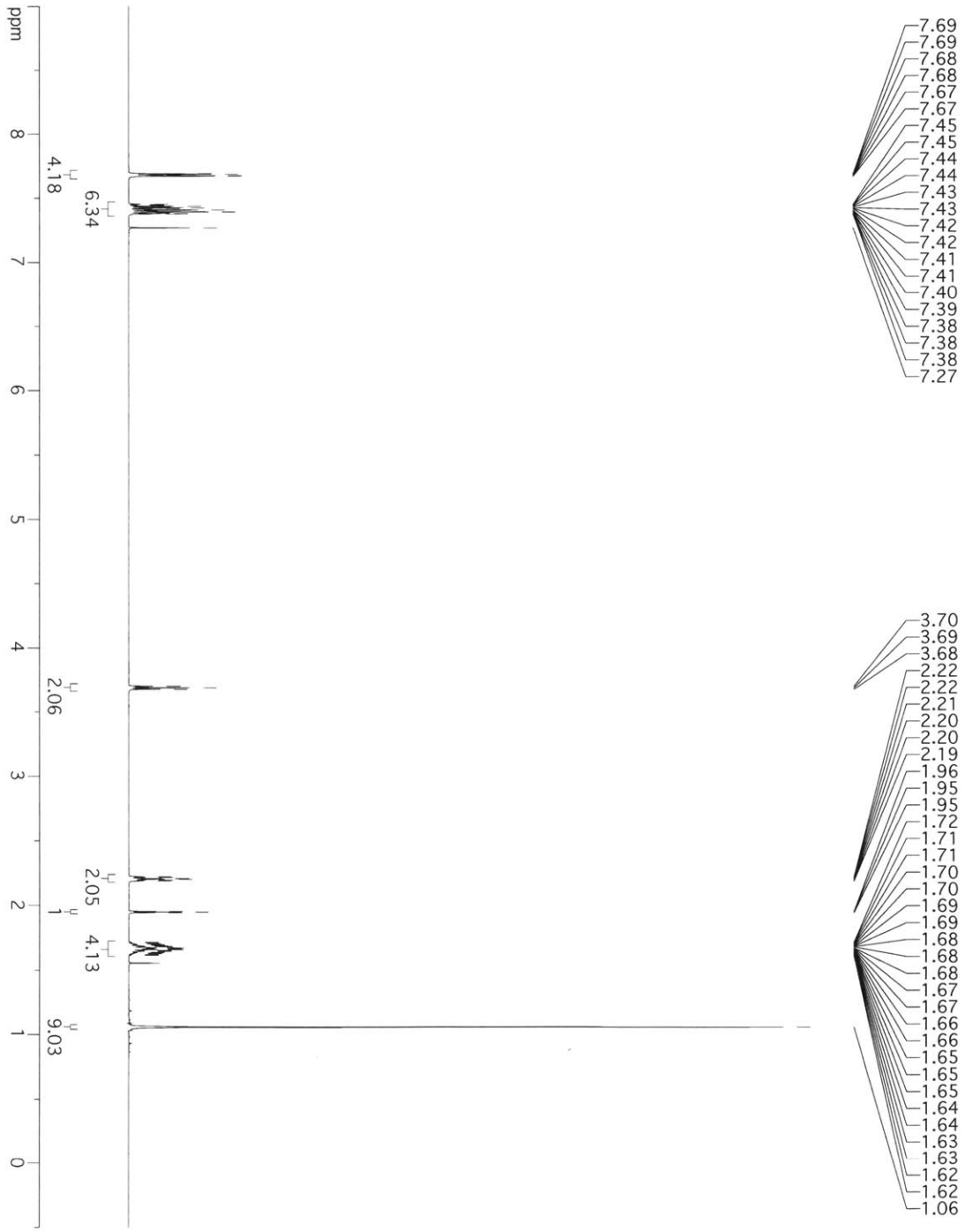
15.2


TBDPSO

24b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2.05
4.13
1
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7.69
7.69
7.68
7.68
7.67
7.67
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7.45
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7.44
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7.39
7.38
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7.38
7.27
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3.69
3.68
2.22
2.22
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2.20
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1.95
1.95
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1.71
1.70
1.70
1.69
1.69
1.68
1.68
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1.67
1.67
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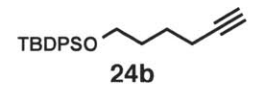
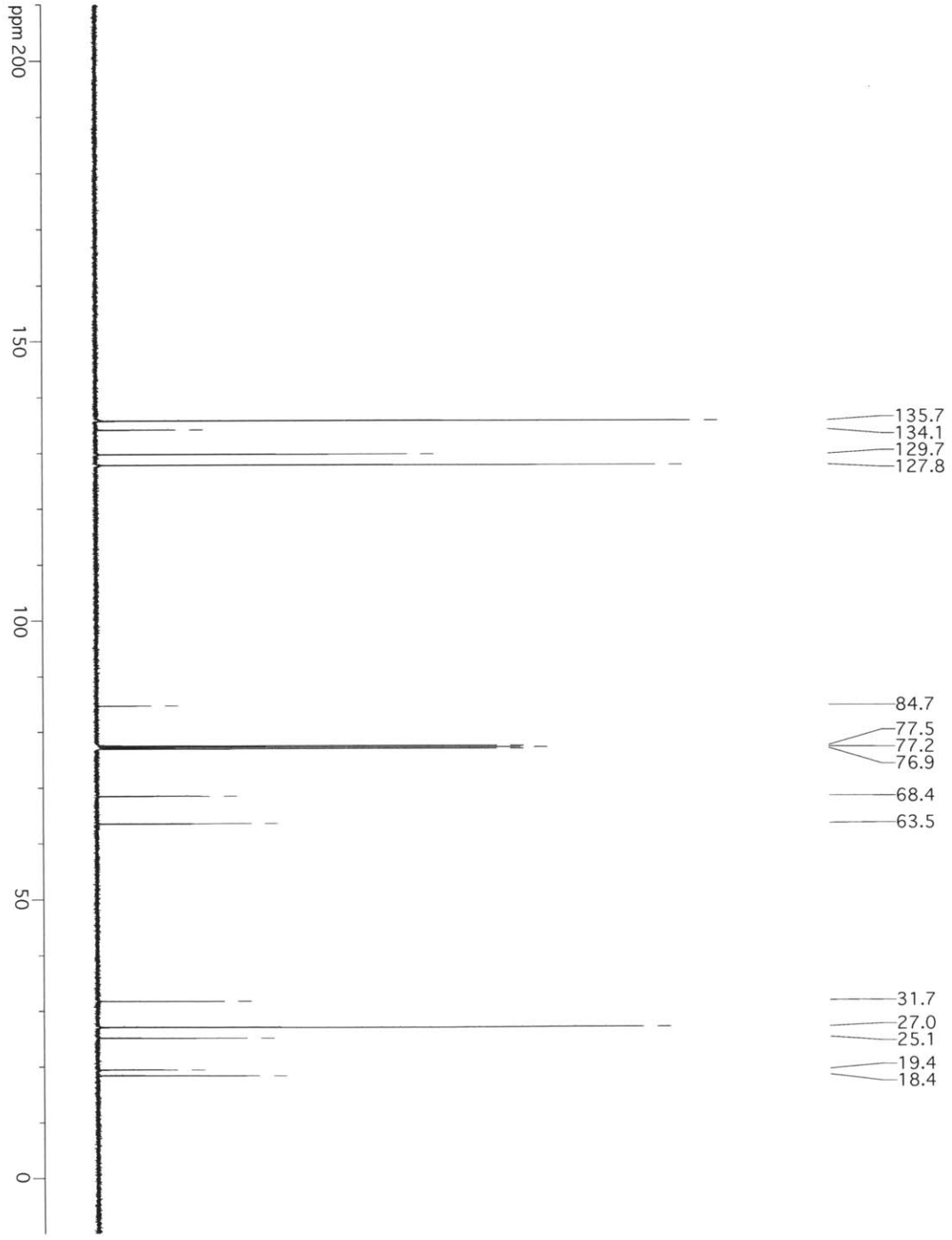
1.06


TBDPSO

24b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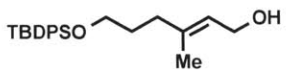
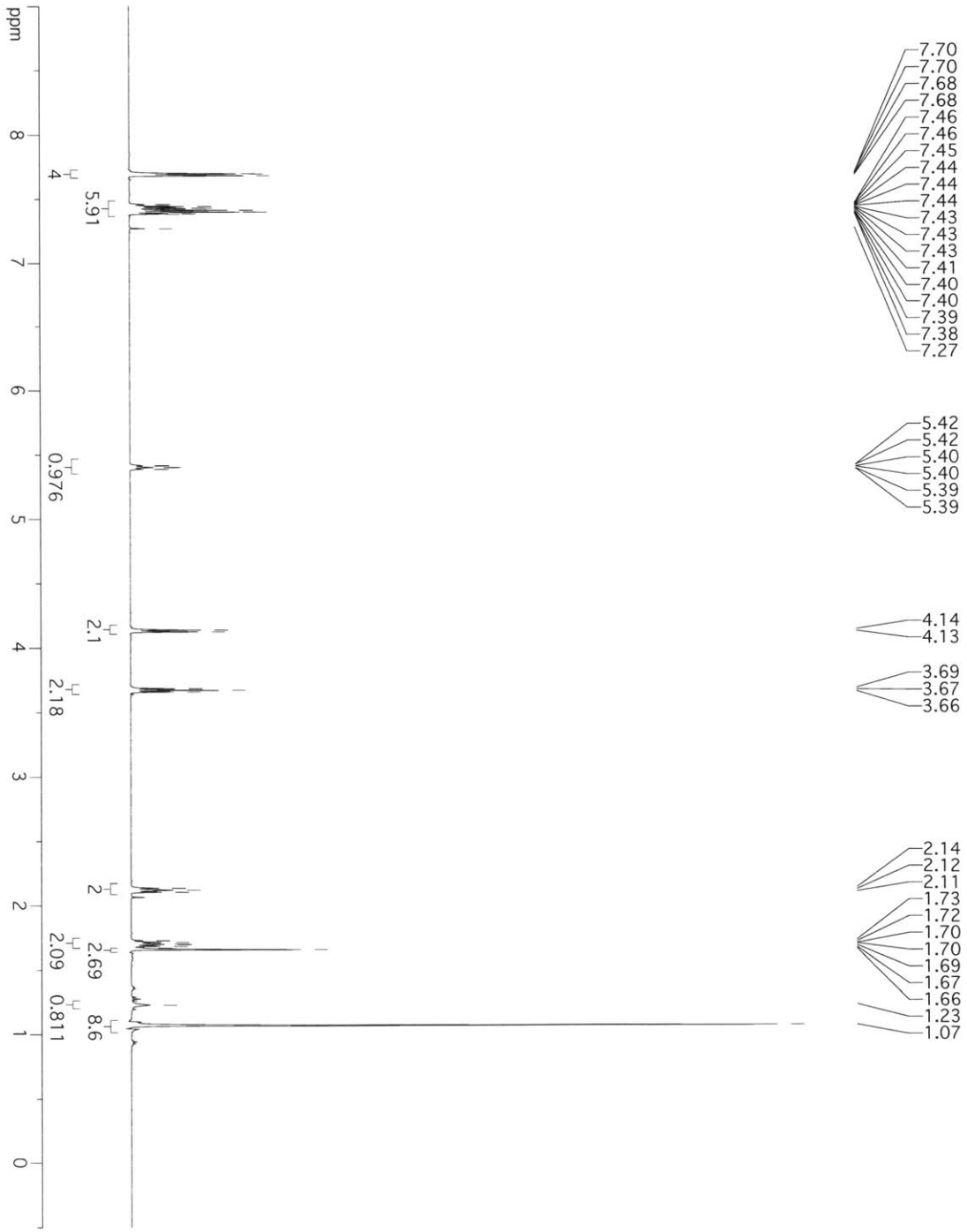
18.4


TBDPSO
OH
Me

25a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2
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2.09
0.811
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7.70
7.68
7.68
7.46
7.46
7.45
7.44
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7.44
7.43
7.43
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4.14
4.13
3.69
3.67
3.66
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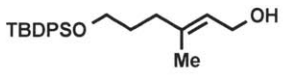
1.07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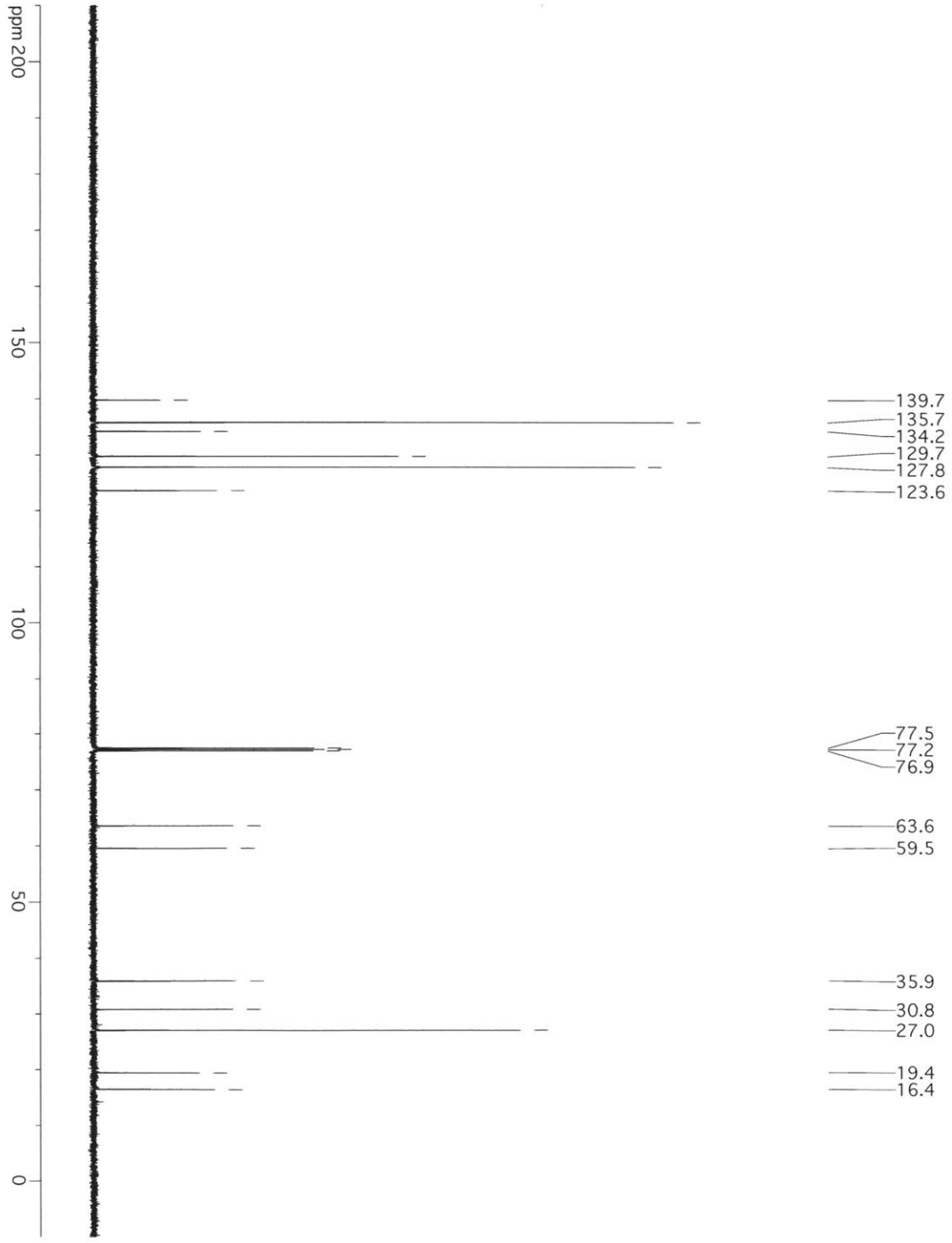
OH
Me

25a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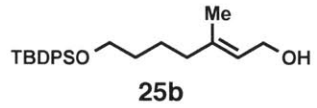
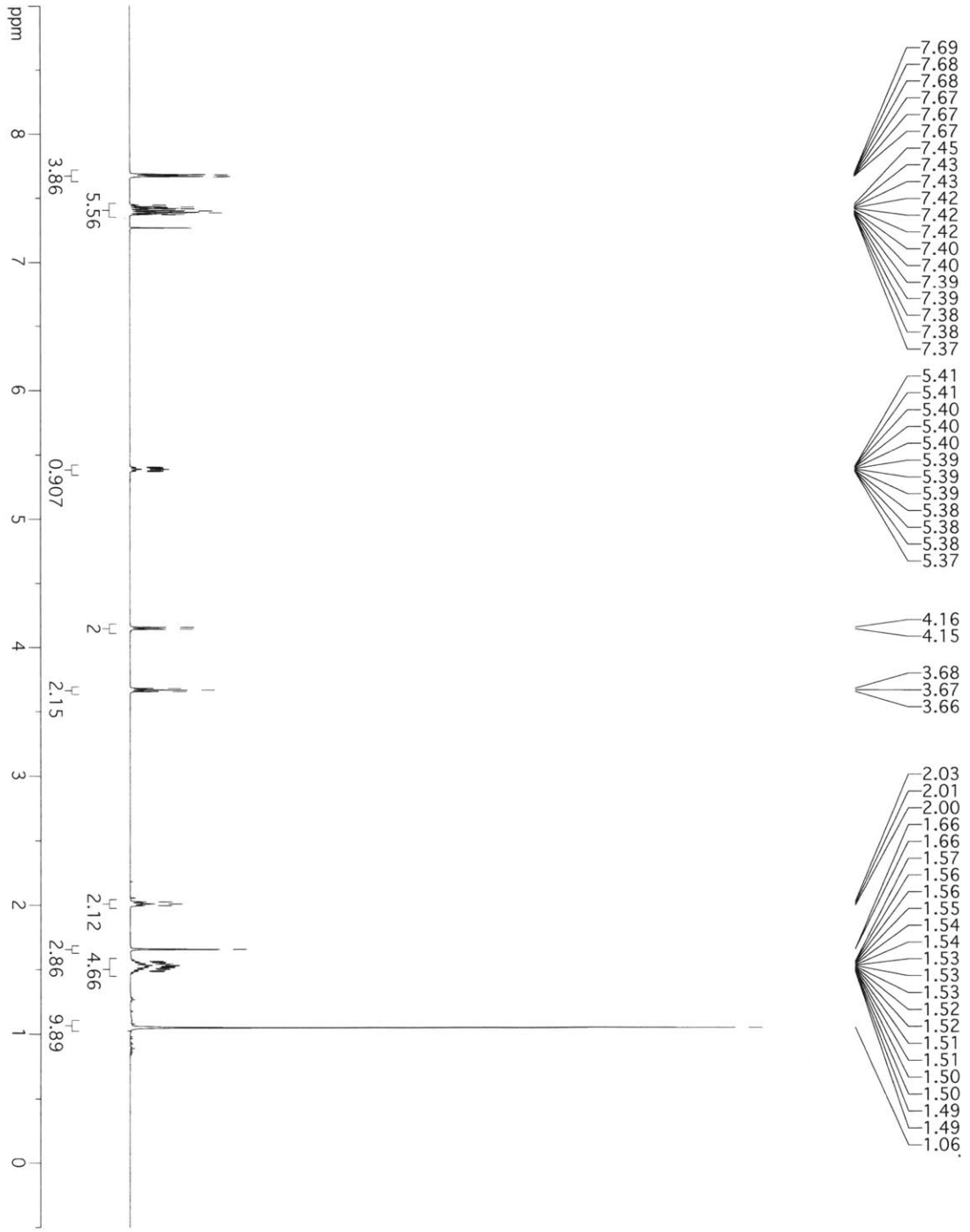
59.5
35.9
30.8
27.0
19.4
16.4


Me
TBDPSO
OH

25b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2
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7.68
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7.67
7.67
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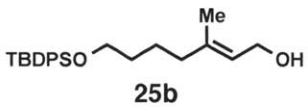
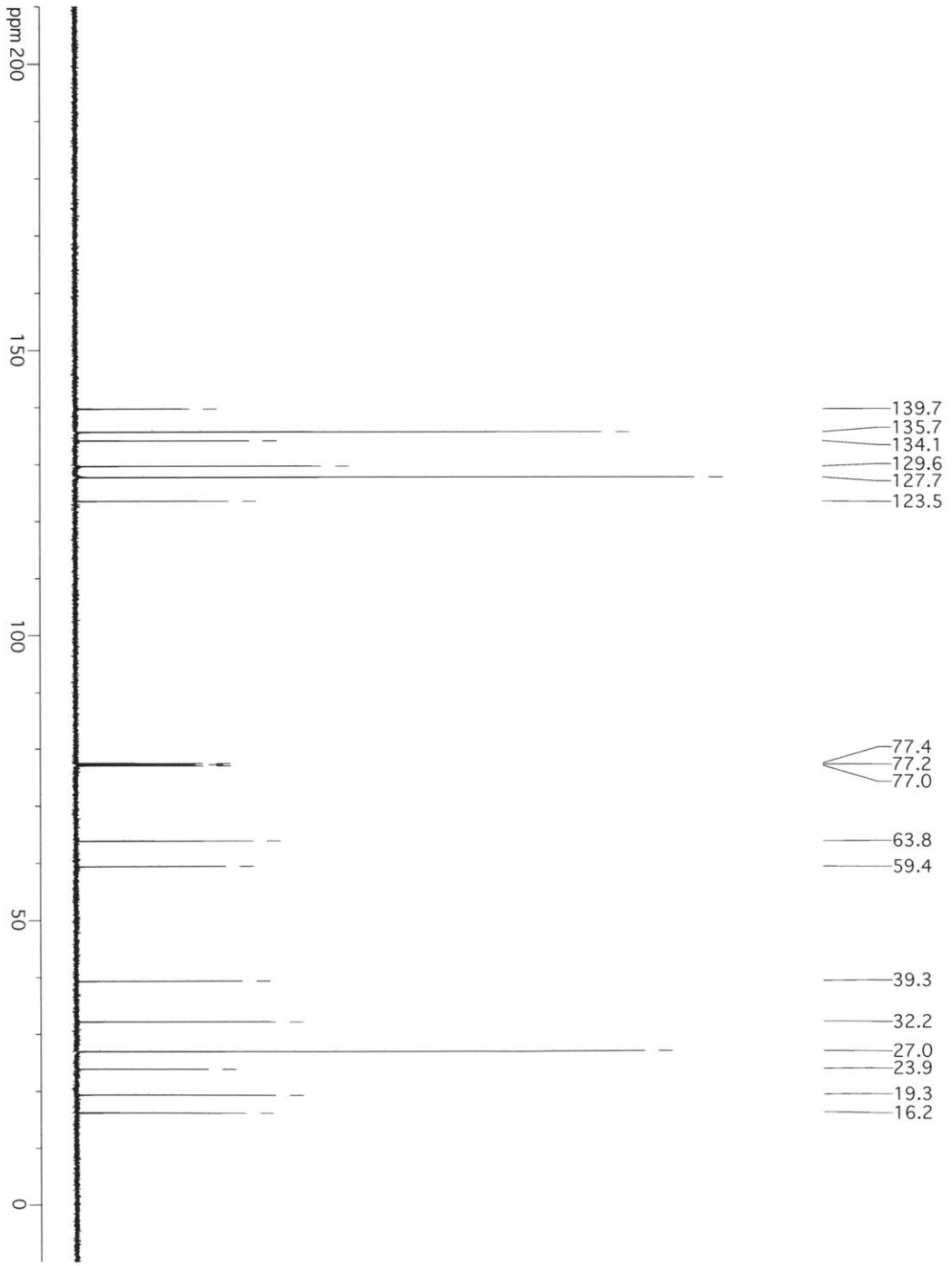
1.49
1.06


Me
TBDPSO
OH

25b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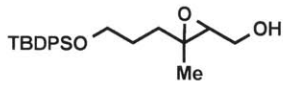
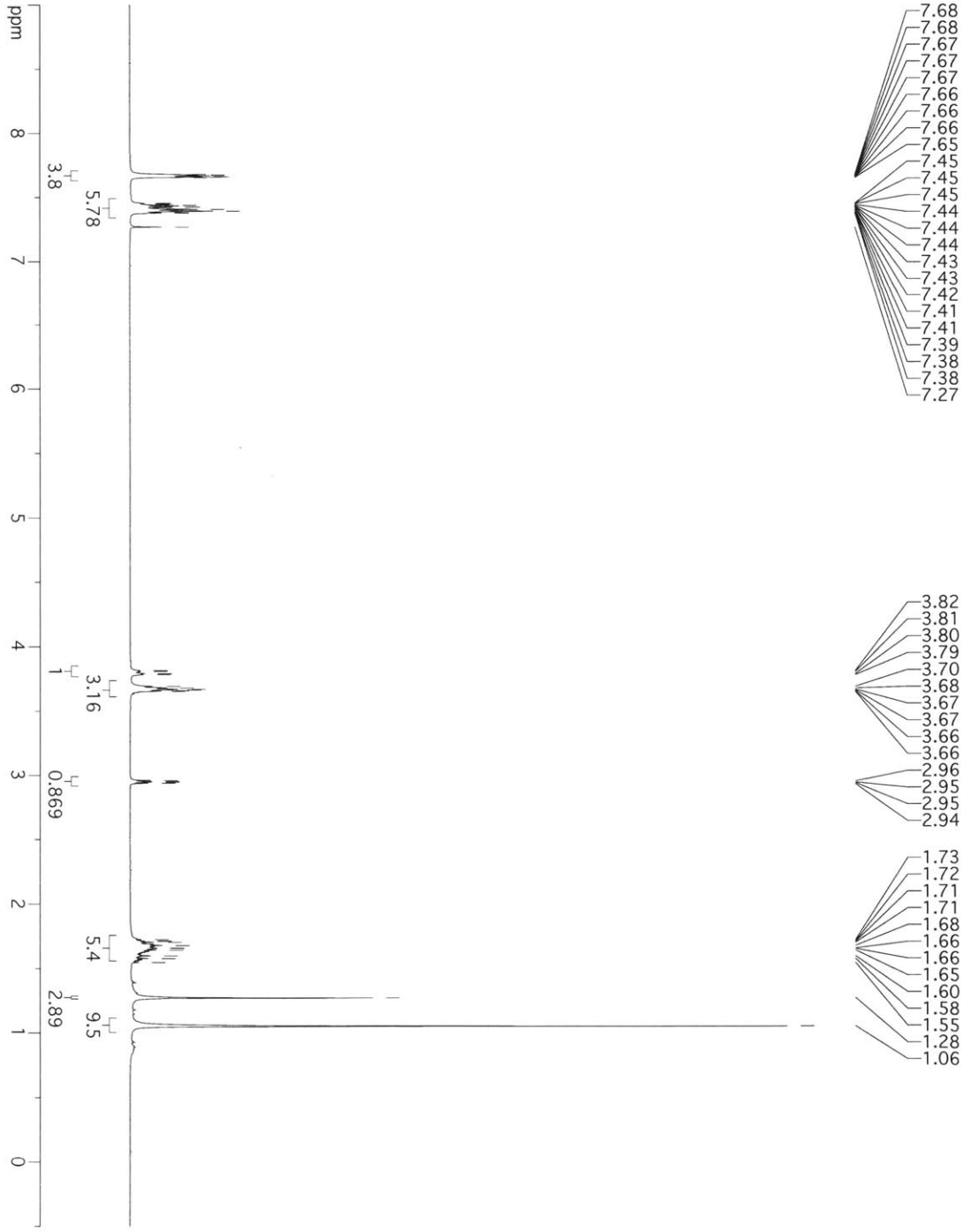
39.3
32.2
27.0
23.9
19.3
16.2


TBDPSO
O
OH
Me

26a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7.68
7.67
7.67
7.67
7.66
7.66
7.66
7.65
7.45
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7.41
7.41
7.39
7.38
7.38
7.27
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3.81
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3.79
3.70
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3.67
3.67
3.66
3.66
2.96
2.95
2.95
2.94
1.73
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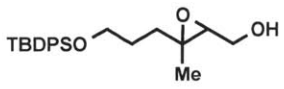
1.06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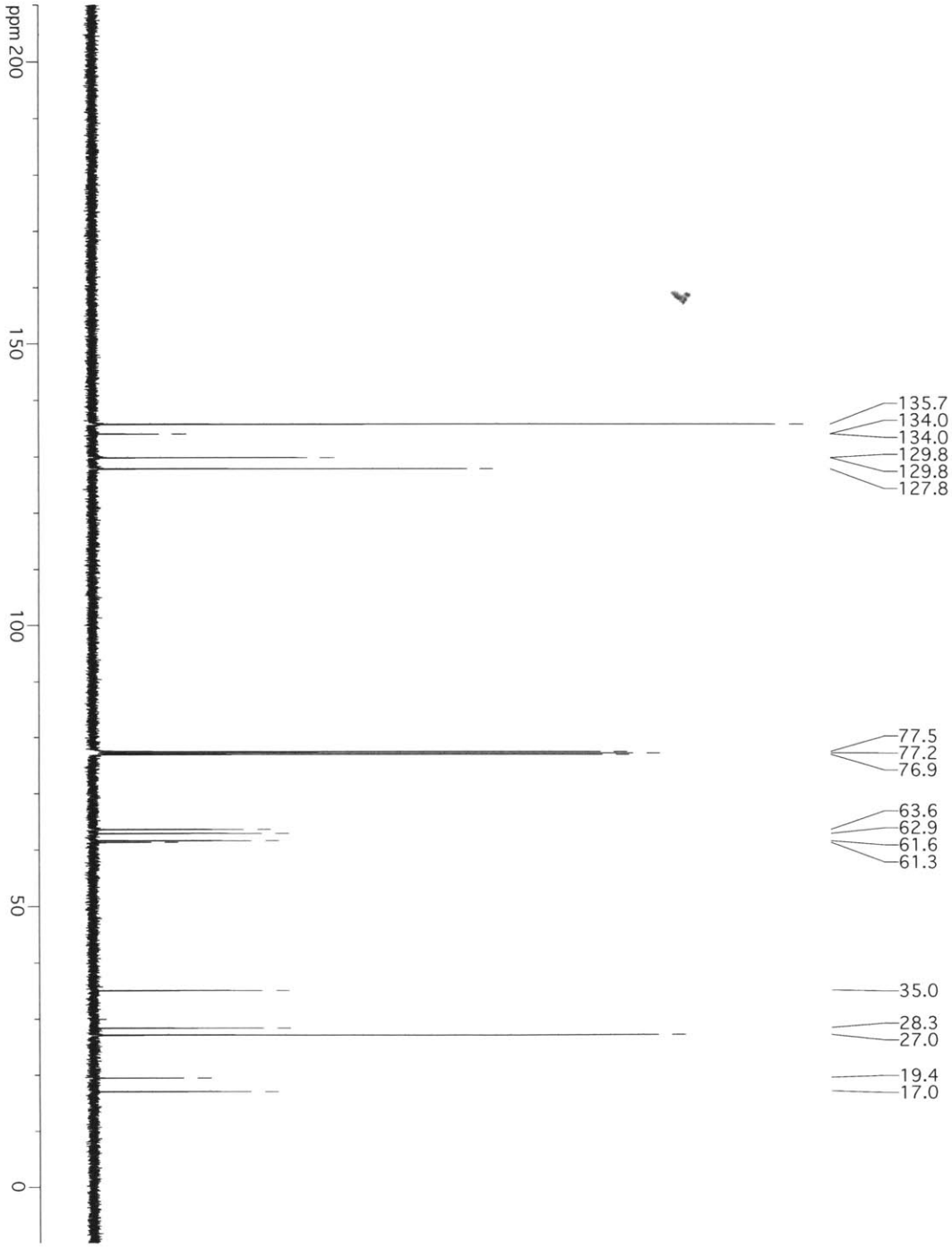
OH
Me

26a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62.9
61.6
61.3
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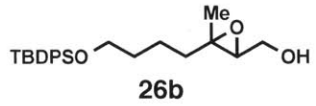
17.0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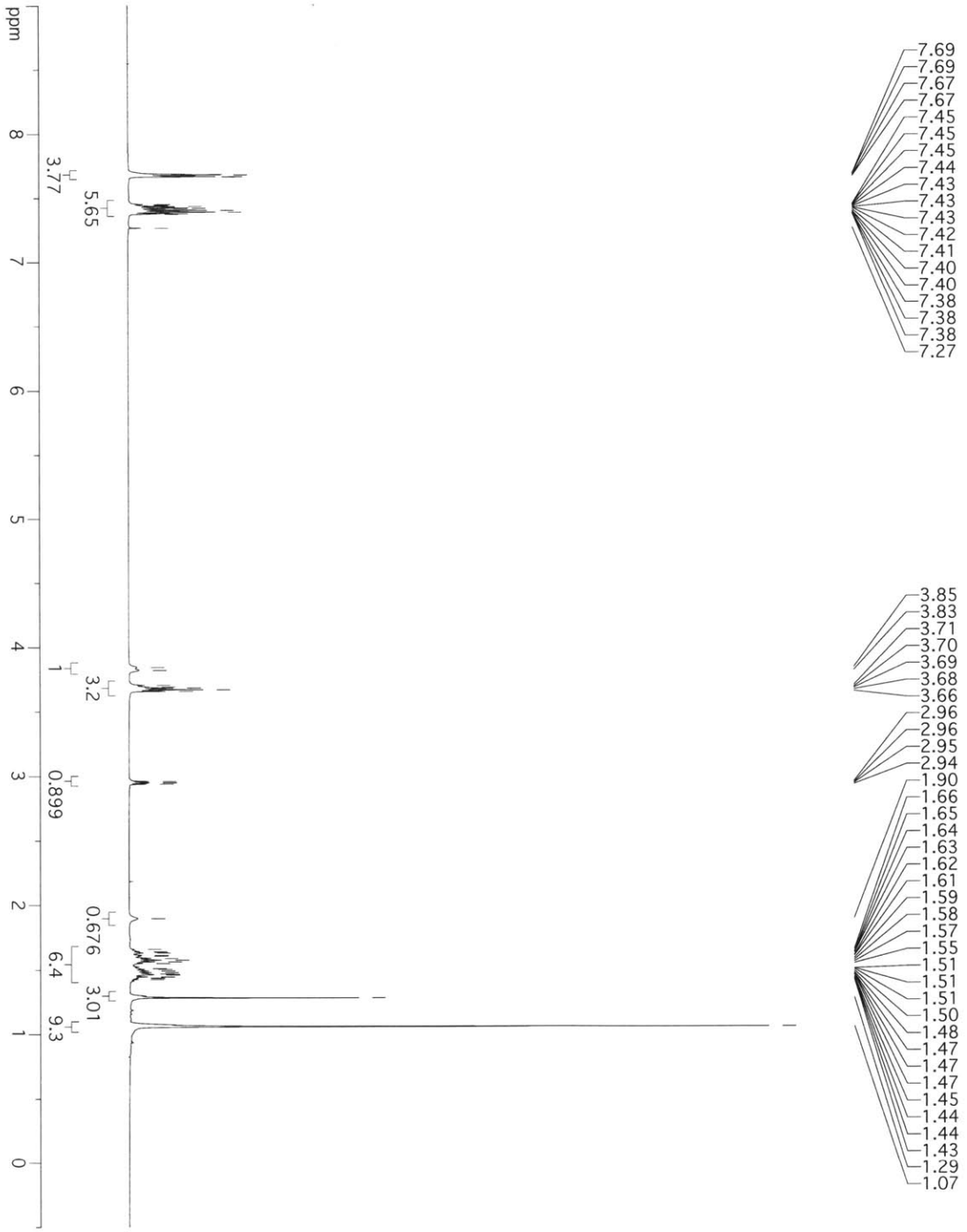
TBDPSO
OH

26b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3.66
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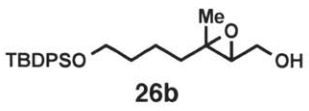
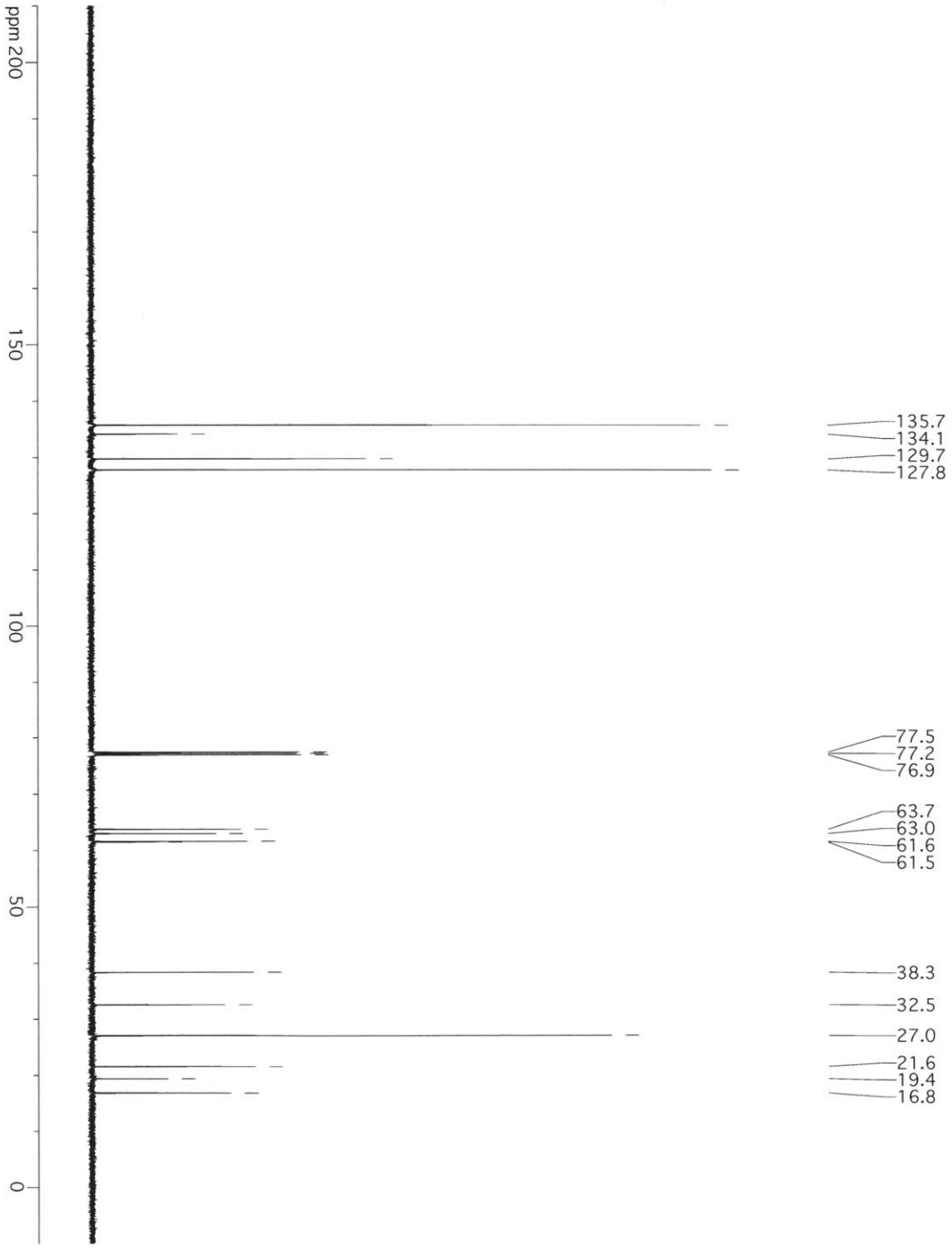

Me
O
TBDPSO
OH

26b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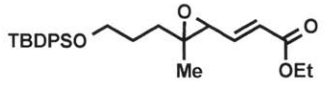
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OEt
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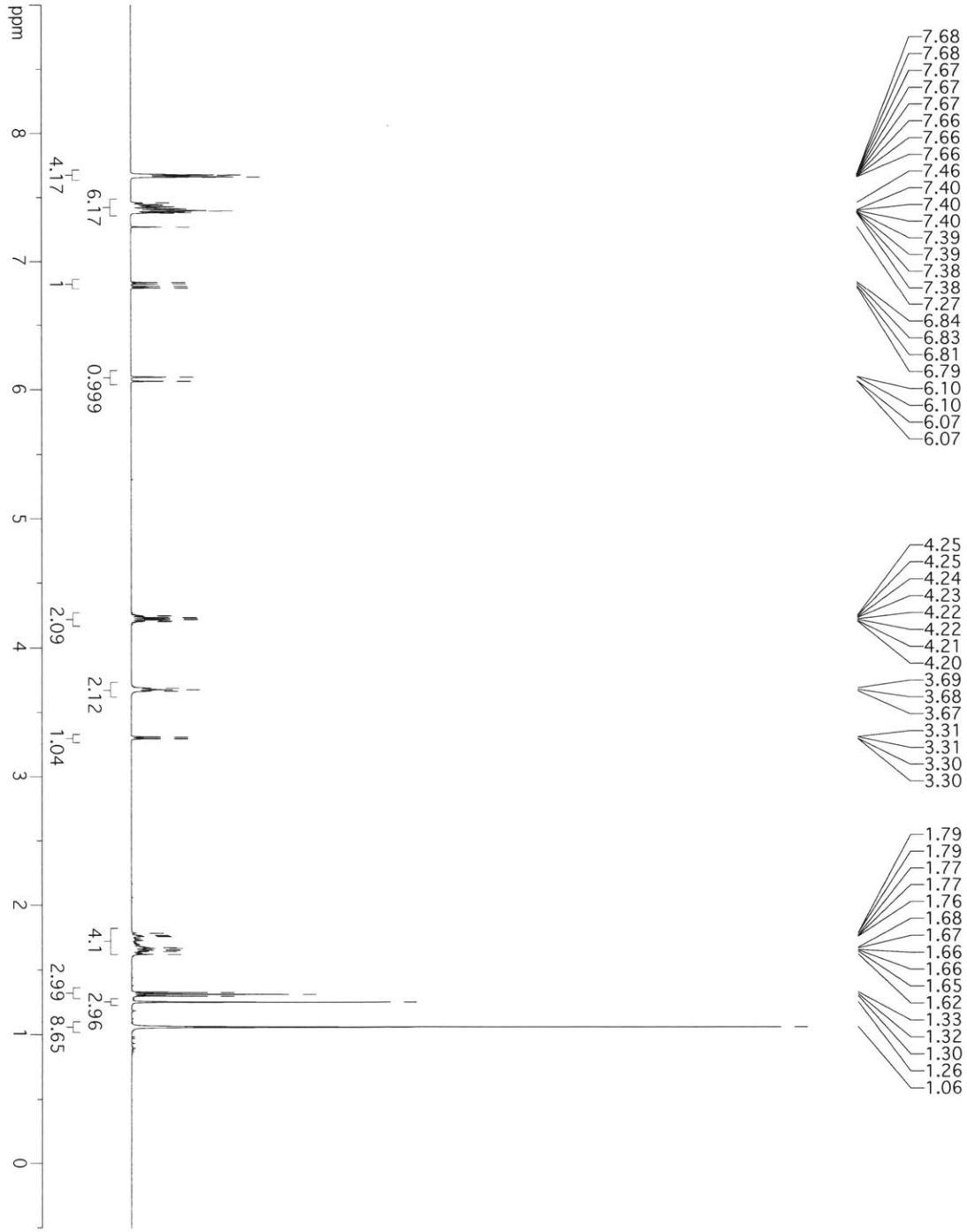
27a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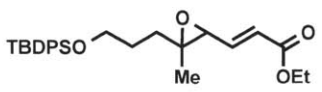
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OEt
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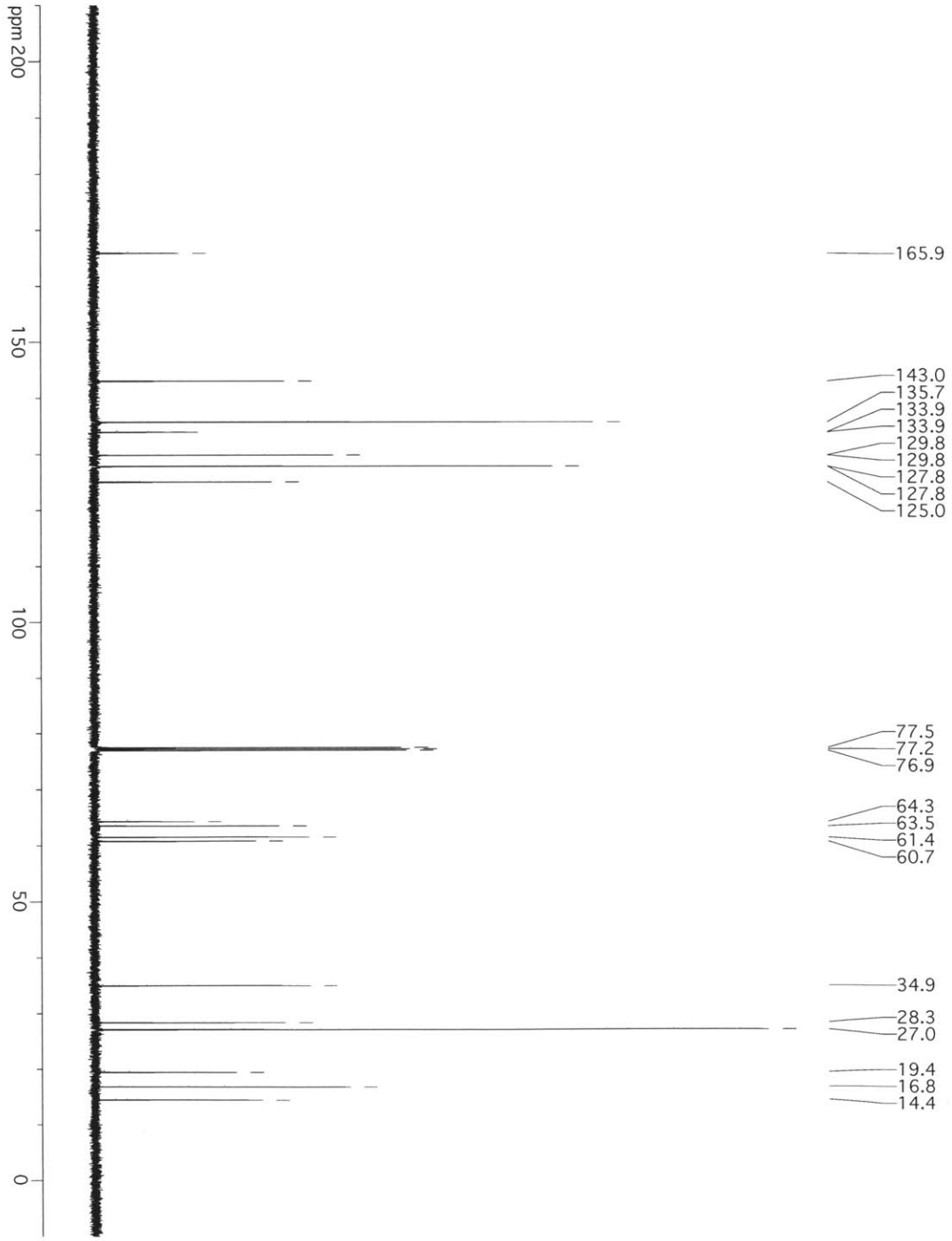
27a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127.8
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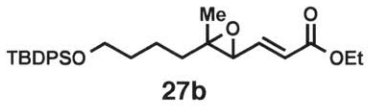
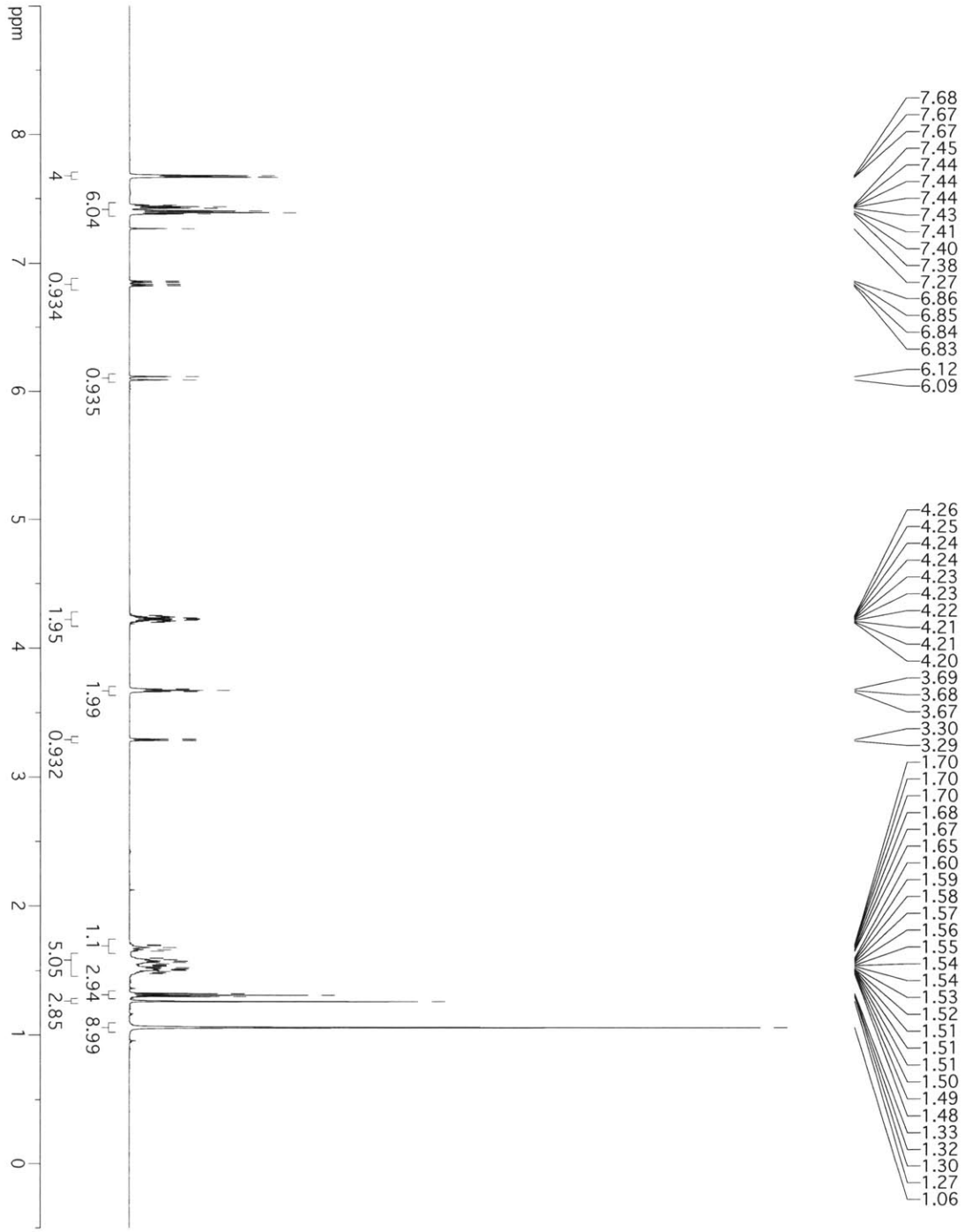
14.4


Me
O
O
TBDPSO
OEt

27b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5.05
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7.43
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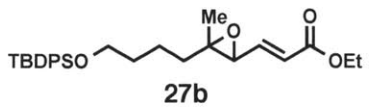
Me
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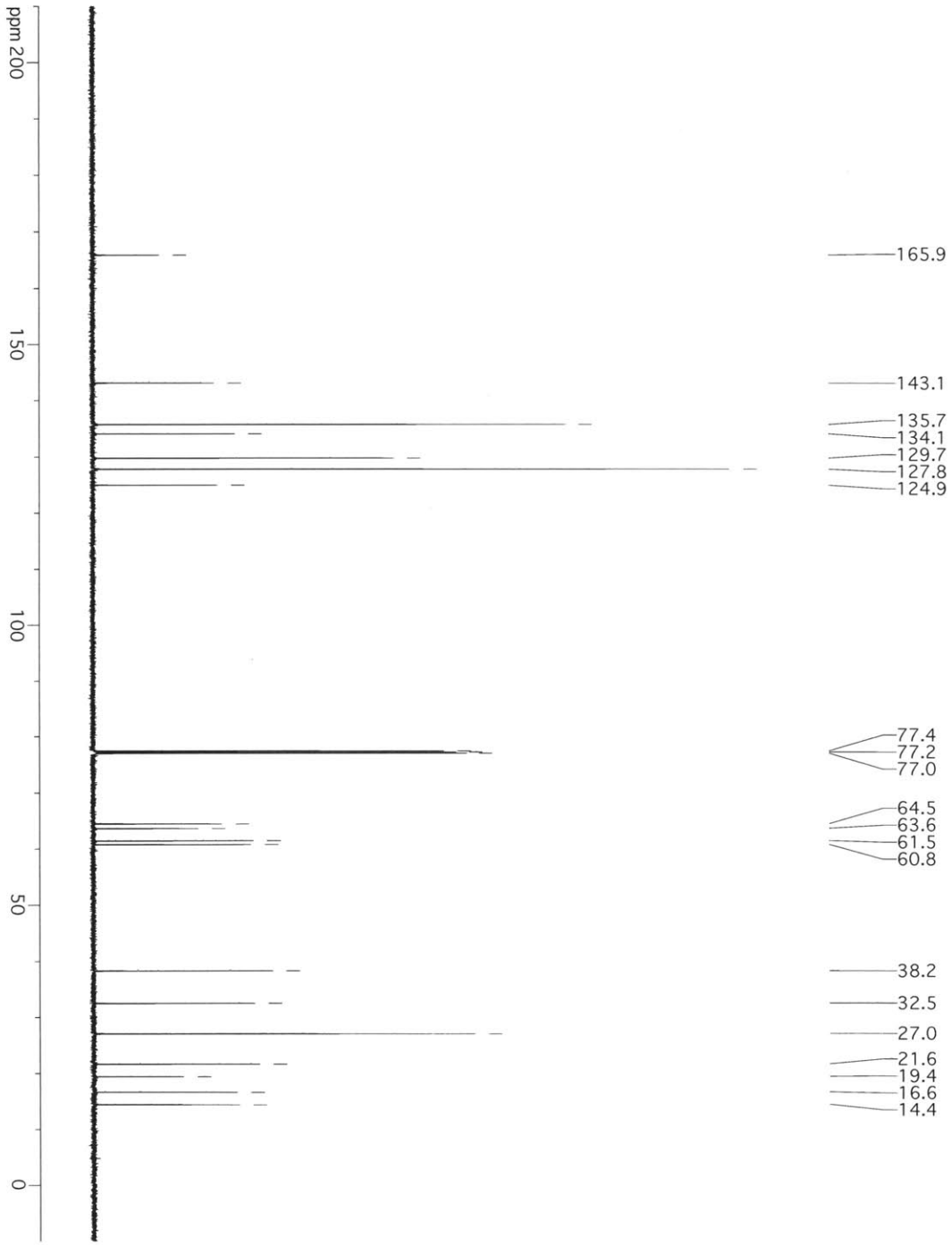
O
TBDPSO
OEt

27b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127.8
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77.2
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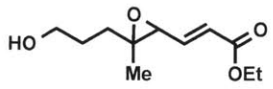
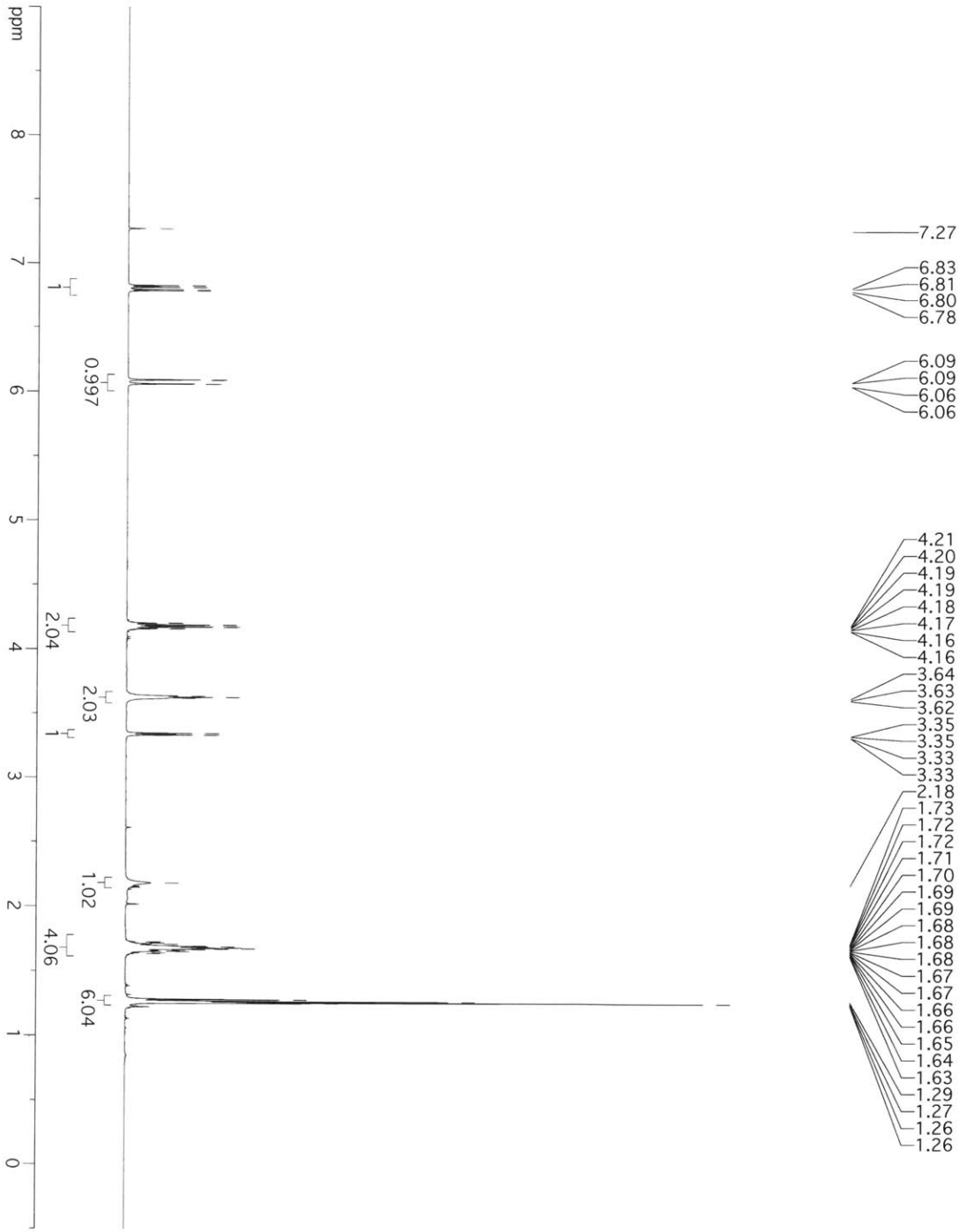
16.6
14.4


HO
O
O
Me
OEt

28a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1
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6.04
7.27
6.83
6.81
6.80
6.78
6.09
6.09
6.06
6.06
4.21
4.20
4.19
4.19
4.18
4.17
4.16
4.16
3.64
3.63
3.62
3.35
3.35
3.33
3.33
2.18
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1.72
1.72
1.71
1.70
1.69
1.69
1.68
1.68
1.68
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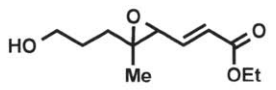
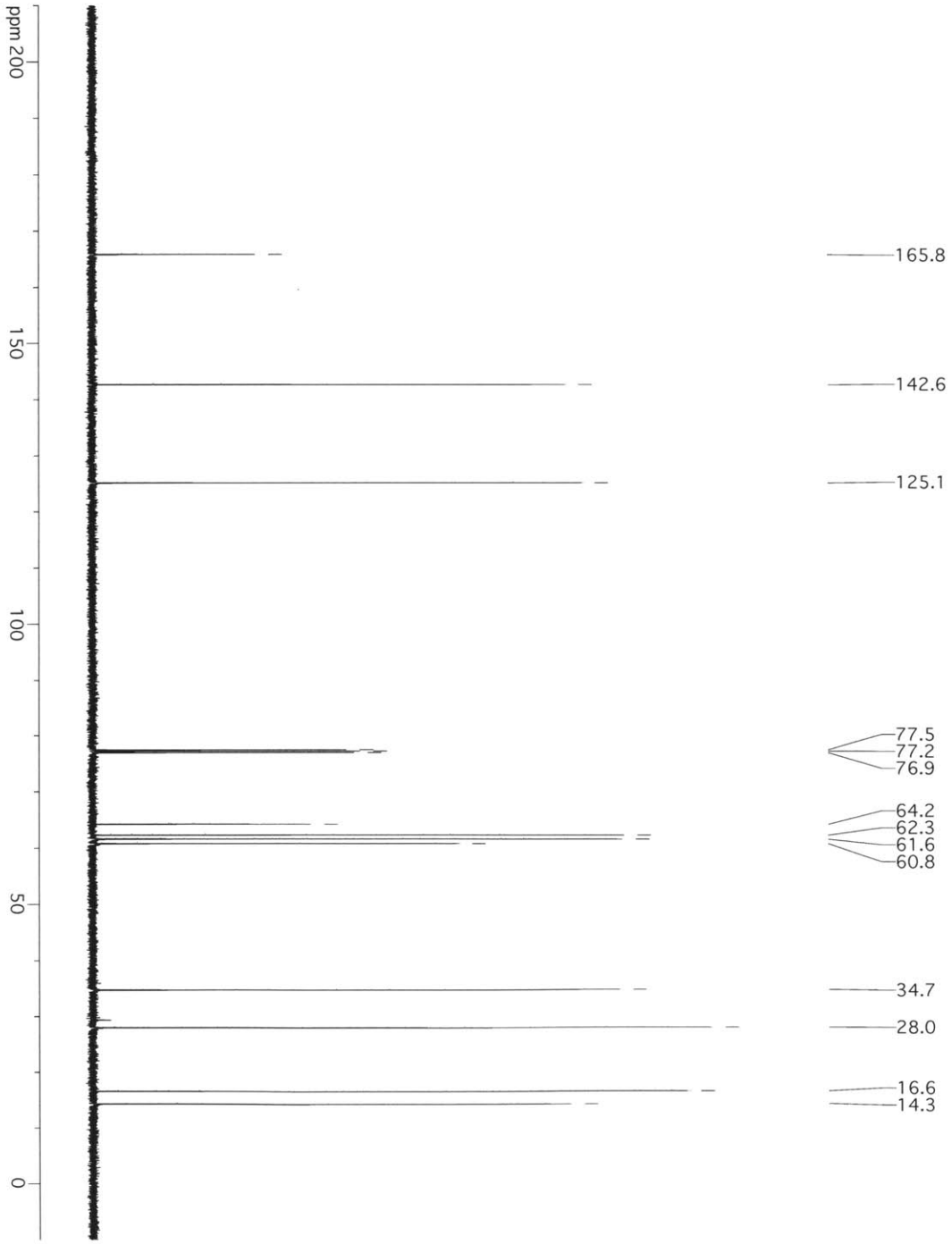
1.66
1.65
1.64
1.63
1.29
1.27
1.26
1.26


HO
O
Me
OEt
O

28a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142.6
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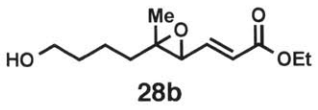
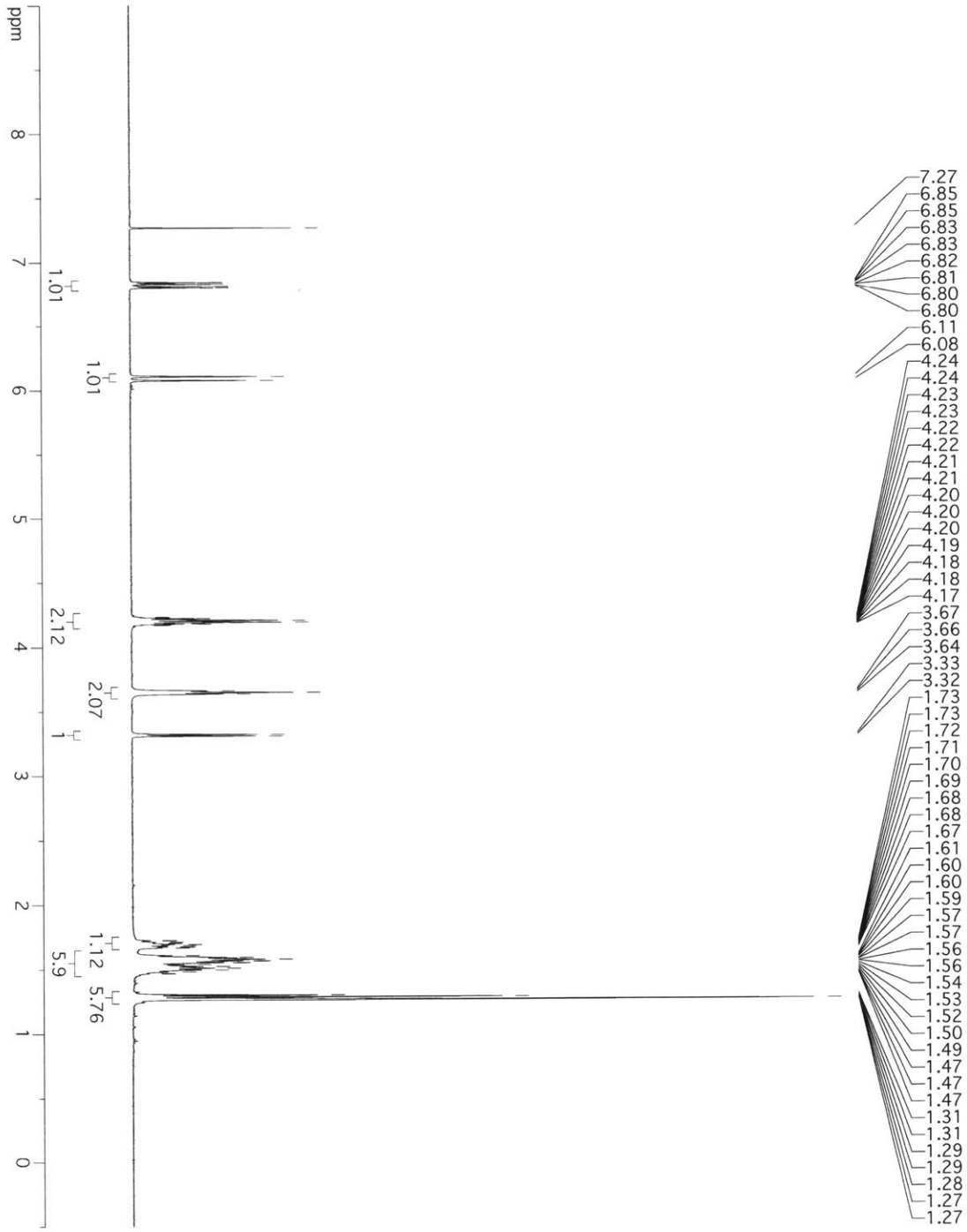
62.3
61.6
60.8
34.7
28.0
16.6
14.3


Me
O
O
HO
OEt

28b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3
2
1
0
1.01
1.01
2.12
2.07
1
1.12
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7.27
6.85
6.85
6.83
6.83
6.82
6.81
6.80
6.80
6.11
6.08
4.24
4.24
4.23
4.23
4.22
4.22
4.21
4.21
4.20
4.20
4.20
4.19
4.18
4.18
4.17
3.67
3.66
3.64
3.33
3.32
1.73
1.73
1.72
1.71
1.70
1.69
1.68
1.68
1.67
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1.60
1.60
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1.53
1.52
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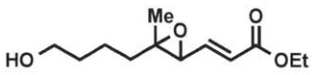
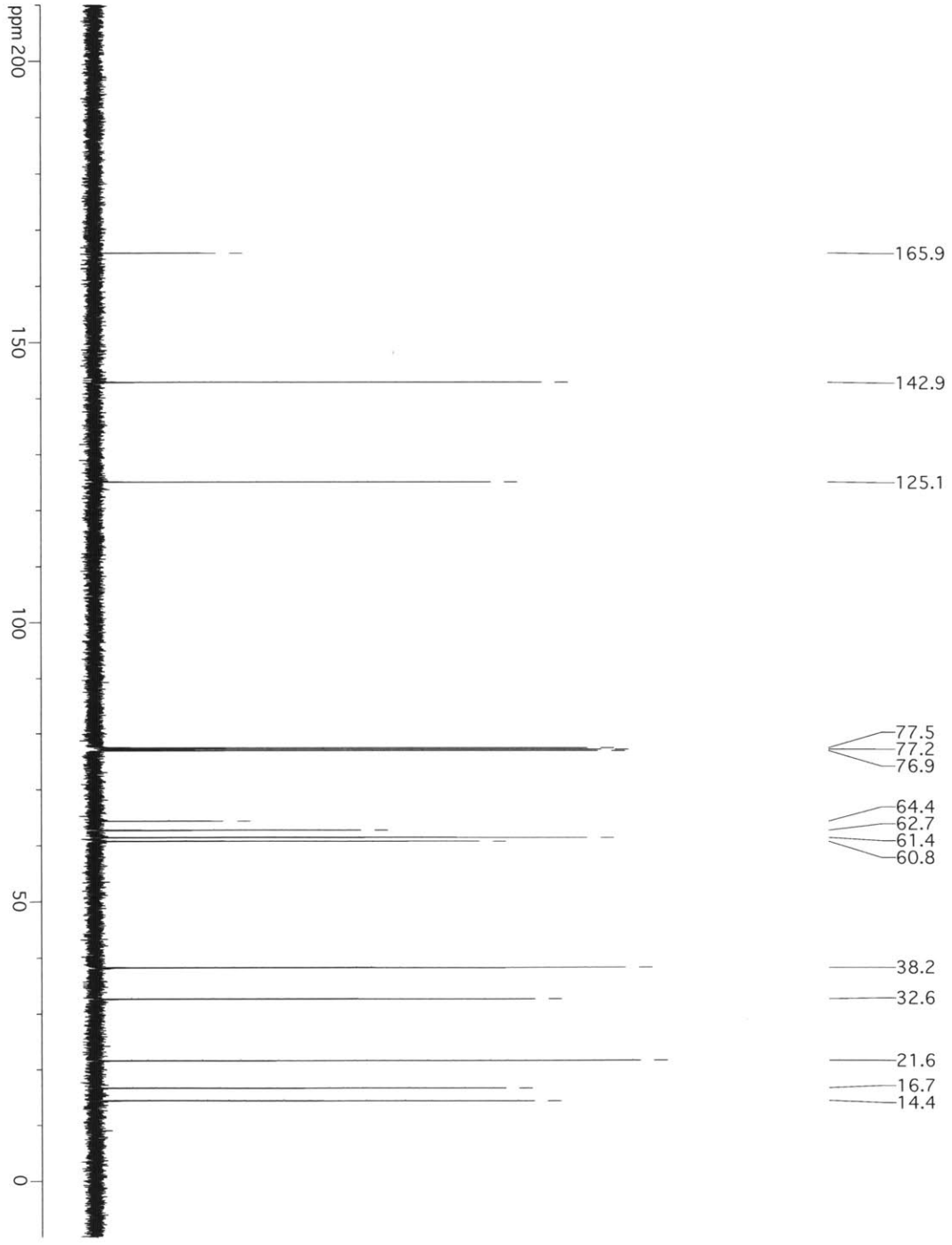
1.27
1.27


Me
O
O
HO
OEt

28b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100
50
0
165.9
142.9
125.1
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77.2
76.9
64.4
62.7
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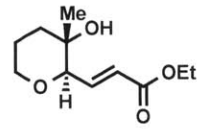
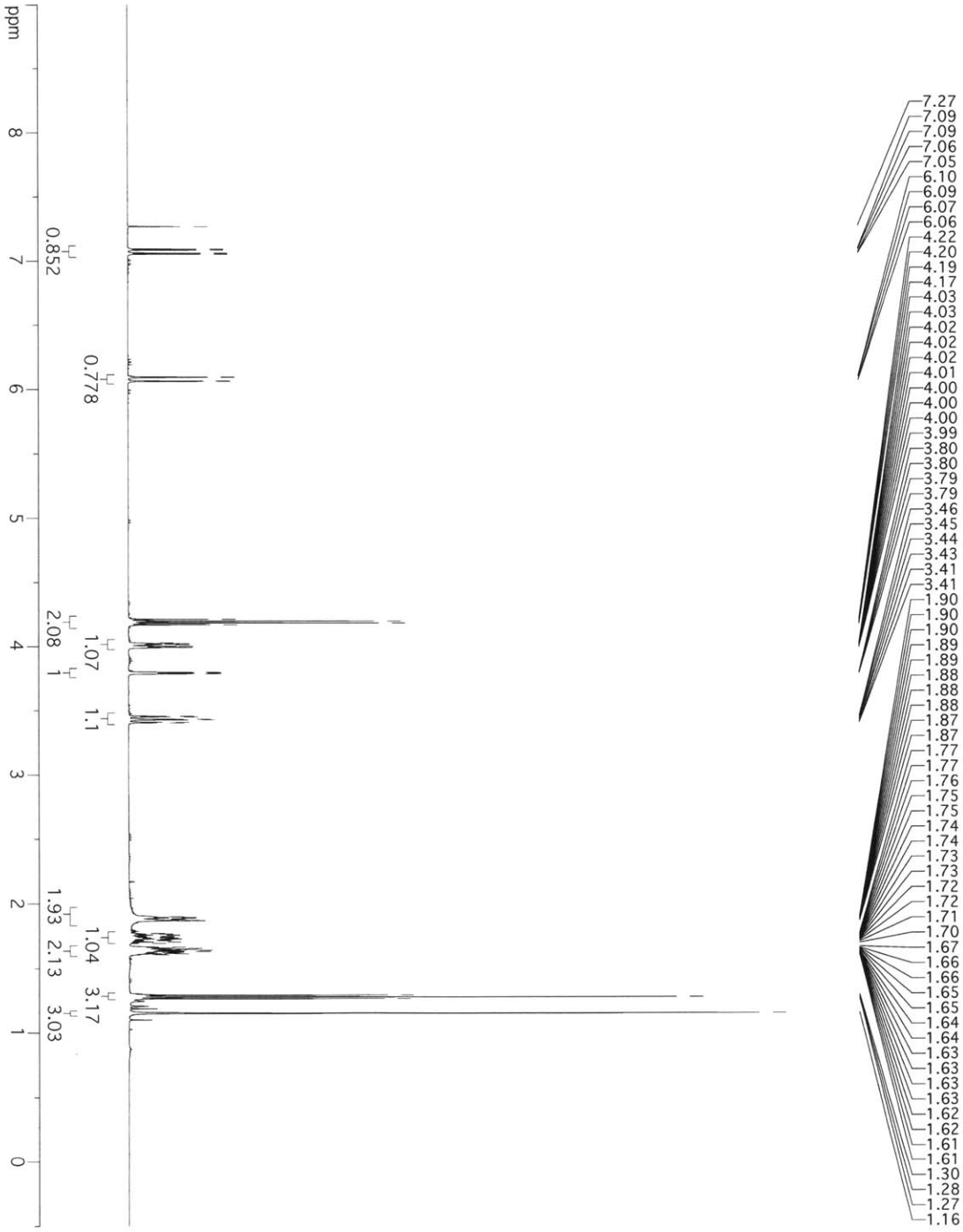
60.8
38.2
32.6
21.6
16.7
14.4


Me
OH
O
H
OEt
O

29a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5
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7
8
0.852
0.778
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1
1.07
1.1
1.93
2.13
1.04
3.17
3.03
7.27
7.09
7.09
7.06
7.05
6.10
6.09
6.07
6.06
4.22
4.20
4.19
4.17
4.03
4.03
4.02
4.02
4.02
4.01
4.00
4.00
4.00
3.99
3.80
3.80
3.79
3.79
3.46
3.45
3.44
3.43
3.41
3.41
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1.90
1.90
1.89
1.89
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1.88
1.88
1.87
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1.66
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1.65
1.64
1.64
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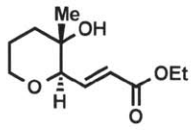
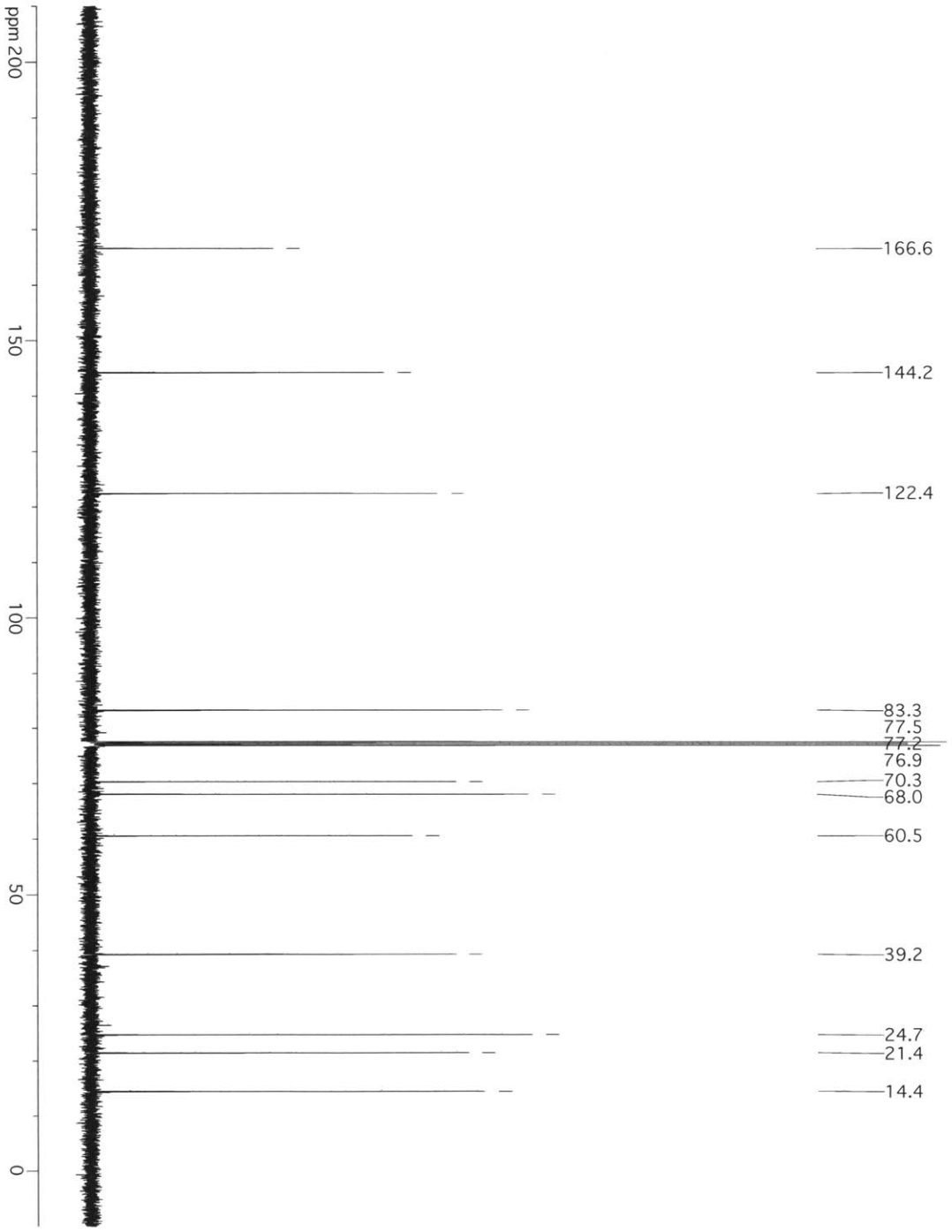
1.61
1.61
1.30
1.28
1.27
1.16


Me
OH
O
H
OEt
O

29a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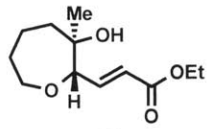
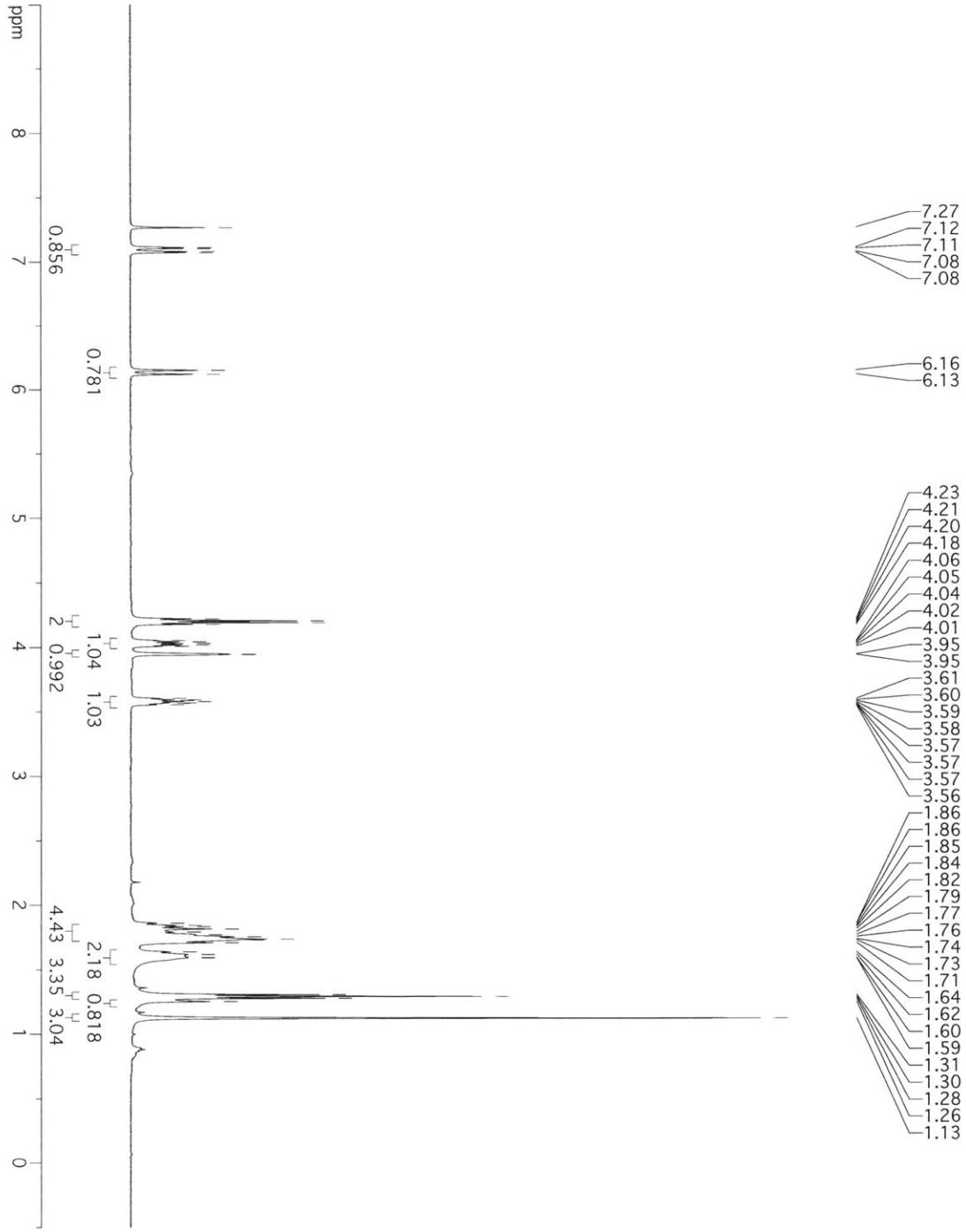
100
50
0
166.6
144.2
122.4
83.3
77.5
77.2
76.9
70.3
68.0
60.5
39.2
24.7
21.4
14.4


Me
OH
OEt
O
H
O

29b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2
0.992
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3.35
2.18
0.818
3.04
7.27
7.12
7.11
7.08
7.08
6.16
6.13
4.23
4.21
4.20
4.18
4.06
4.05
4.04
4.02
4.01
3.95
3.95
3.61
3.60
3.59
3.58
3.57
3.57
3.57
3.56
1.86
1.86
1.85
1.84
1.82
1.79
1.77
1.76
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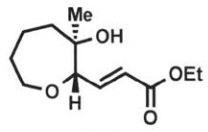
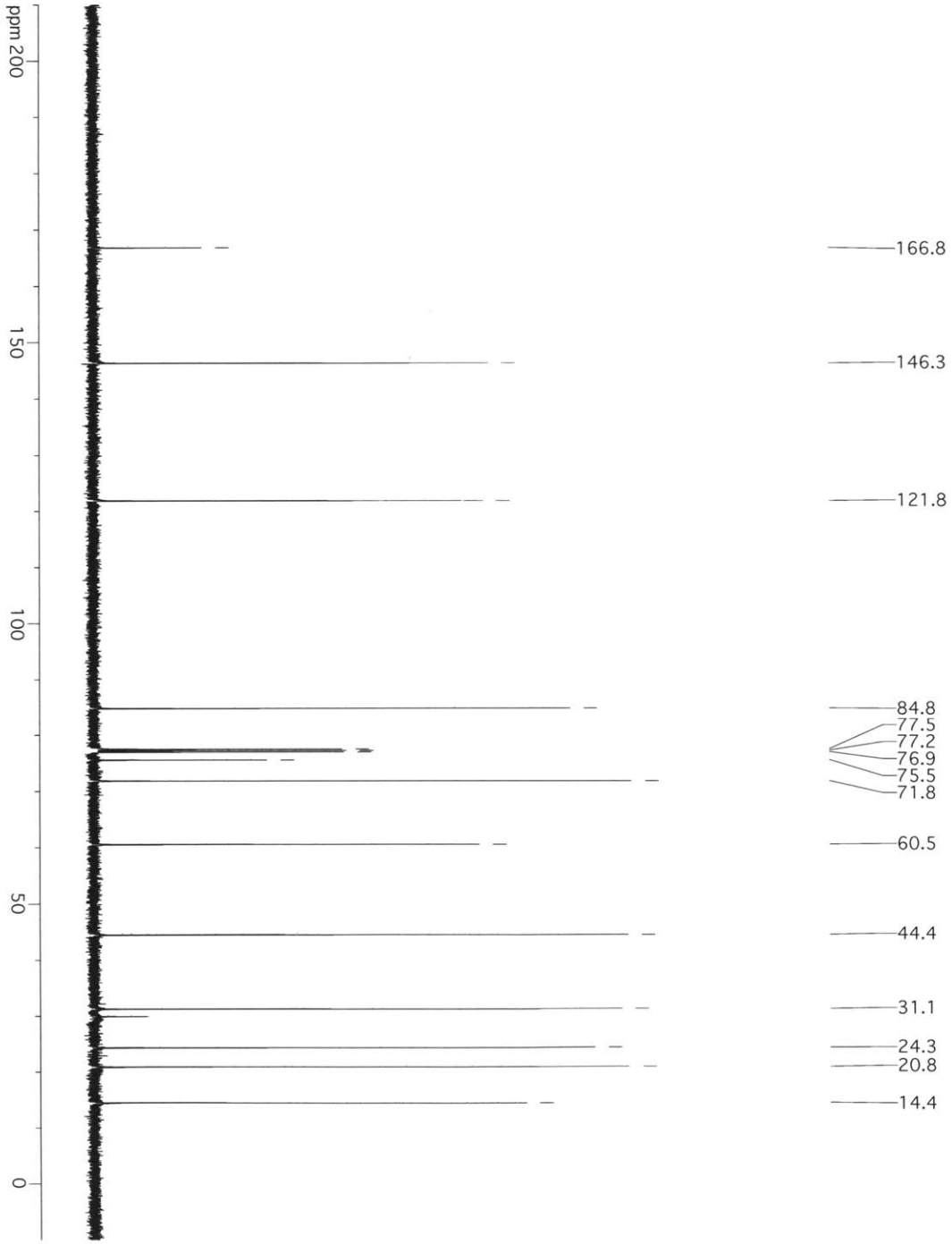
1.59
1.31
1.30
1.28
1.26
1.13


Me
OH
OEt
O
H
O

29b


ppm
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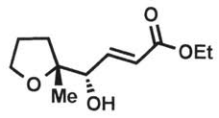
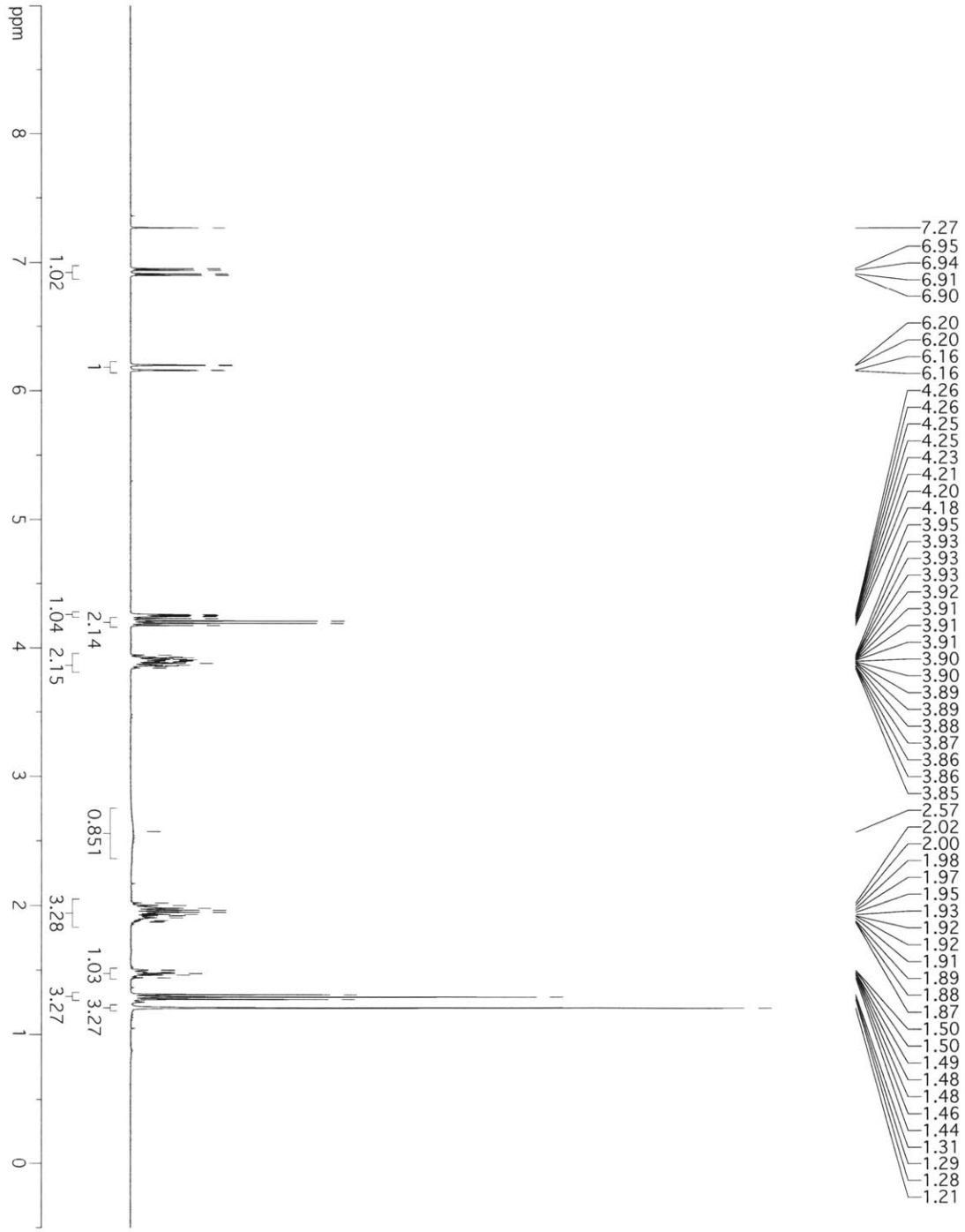
150
100
50
0
166.8
146.3
121.8
84.8
77.5
77.2
76.9
75.5
71.8
60.5
44.4
31.1
24.3
20.8
14.4


O
OEt
O
Me
OH

30a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6
5
4
3
2
1
0
1.02
1
1.04
2.14
2.15
0.851
3.28
1.03
3.27
3.27
7.27
6.95
6.94
6.91
6.90
6.20
6.20
6.16
6.16
4.26
4.26
4.25
4.25
4.23
4.21
4.20
4.18
3.95
3.93
3.93
3.93
3.92
3.91
3.91
3.91
3.90
3.90
3.89
3.89
3.88
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3.86
3.86
3.85
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1.89
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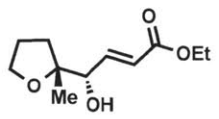
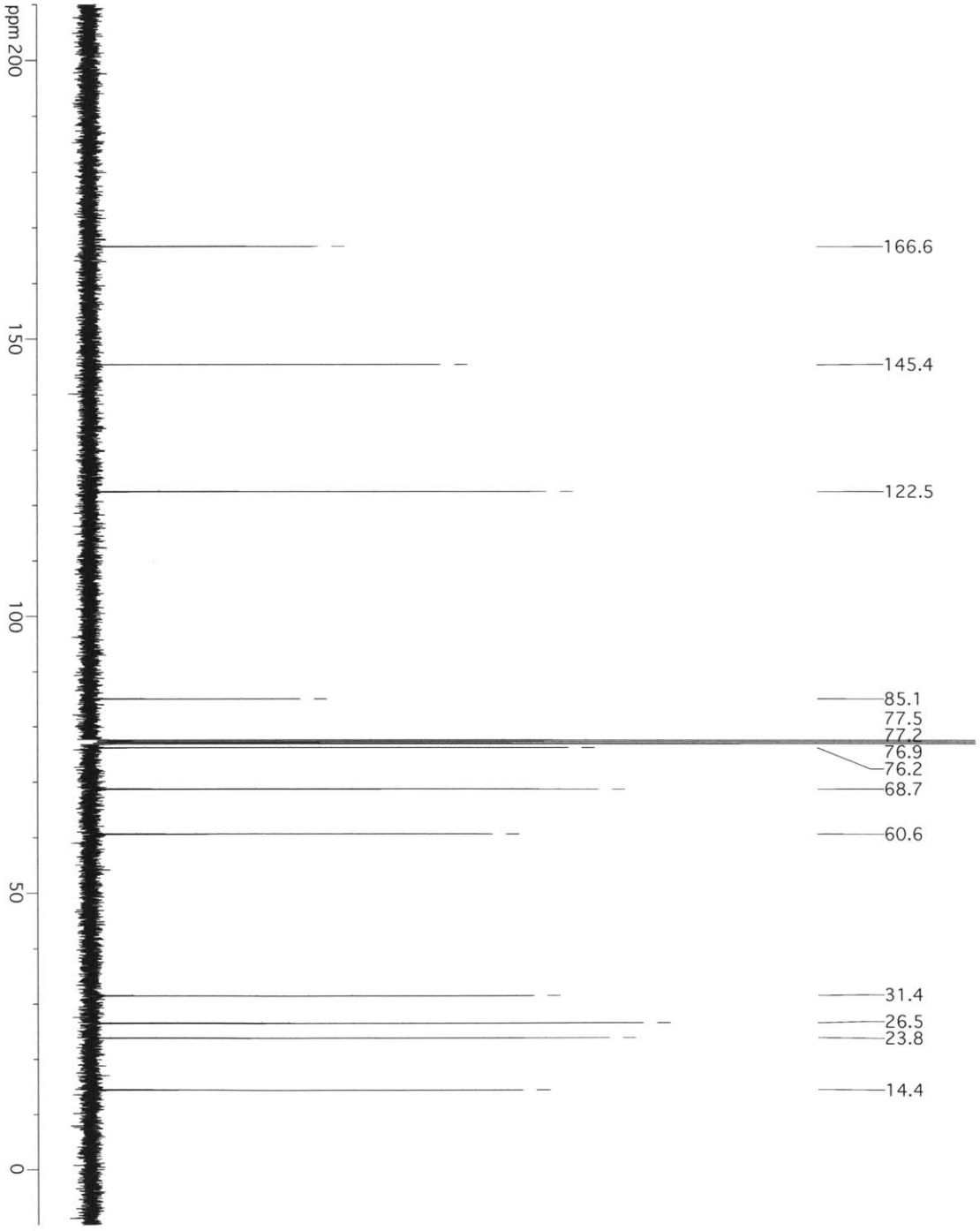
1.46
1.44
1.31
1.29
1.28
1.21


O
OEt
O
Me
OH

30a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100
50
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145.4
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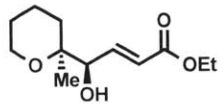
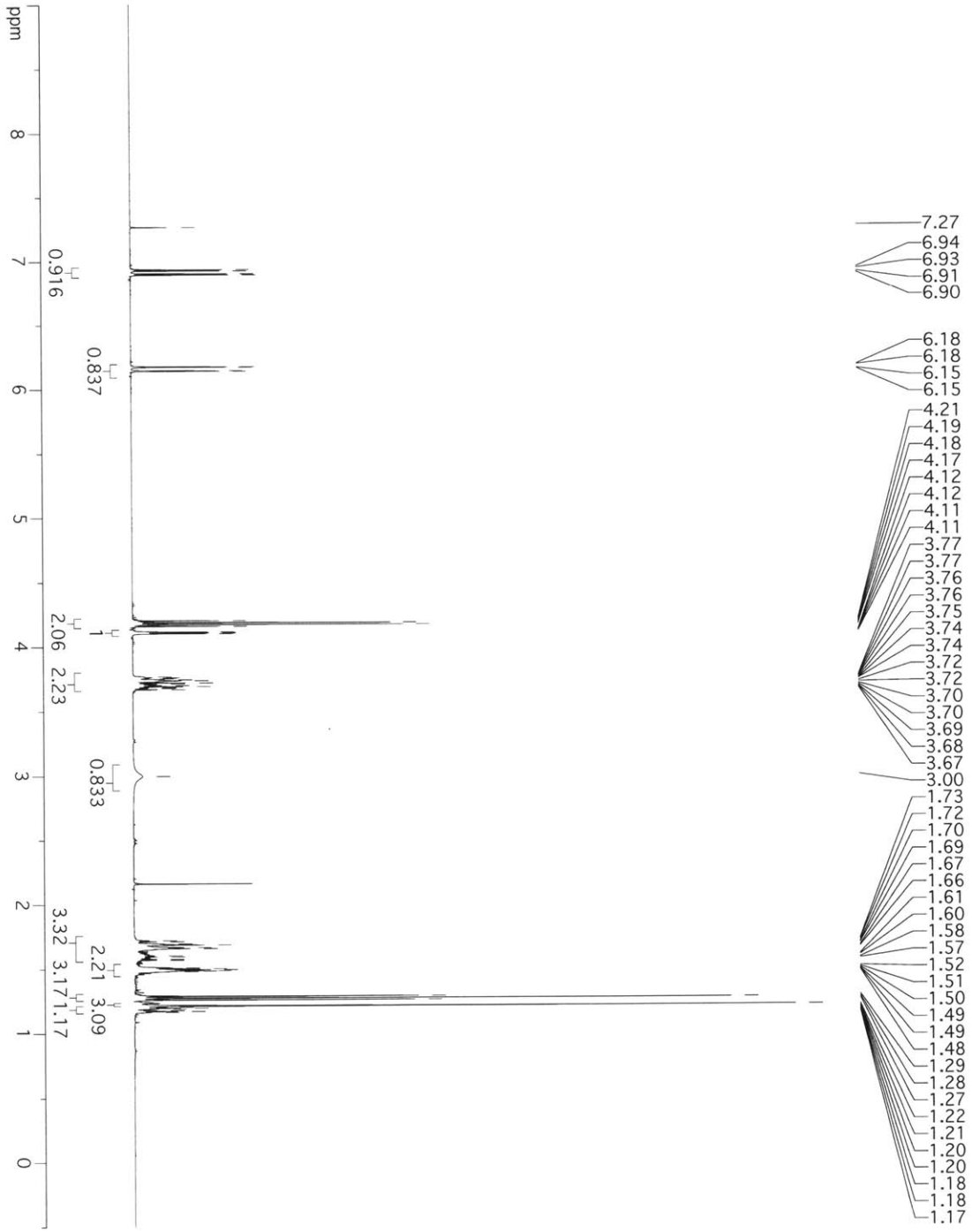
85.1
77.5
77.2
76.9
76.2
68.7
60.6
31.4
26.5
23.8
14.4


O
OEt
O
Me
OH

30b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6
5
4
3
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0.837
2.06
1
2.23
0.833
3.32
3.17
2.21
3.09
1.17
7.27
6.94
6.93
6.91
6.90
6.18
6.18
6.15
6.15
4.21
4.19
4.18
4.17
4.12
4.12
4.11
4.11
3.77
3.77
3.76
3.76
3.75
3.74
3.74
3.72
3.72
3.70
3.70
3.69
3.68
3.67
3.00
1.73
1.72
1.70
1.69
1.67
1.66
1.61
1.60
1.58
1.57
1.52
1.51
1.50
1.49
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1.20
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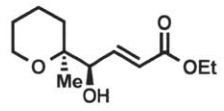
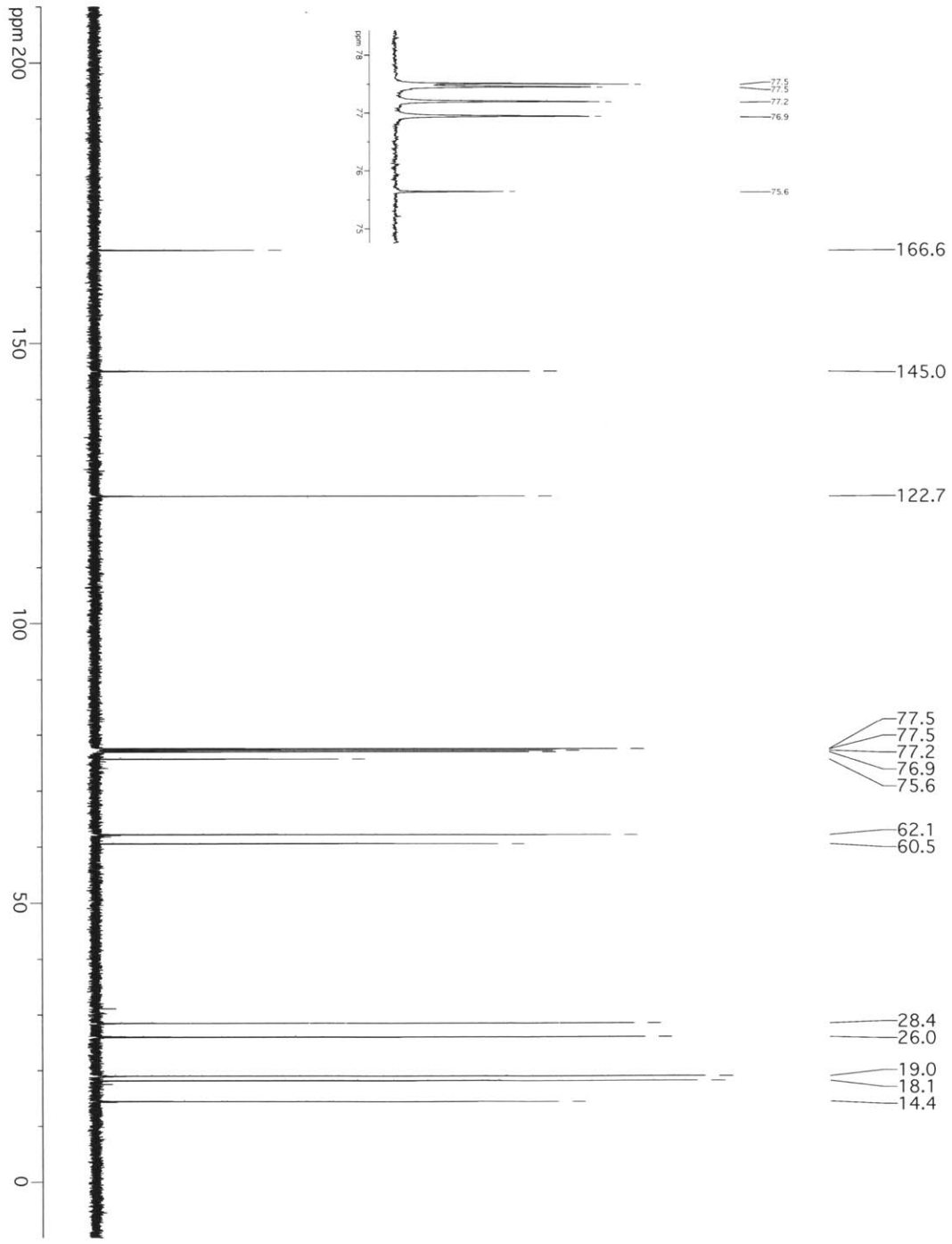
1.18
1.17


O
OEt
Me
OH

30b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122.7
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77.5
77.2
76.9
75.6
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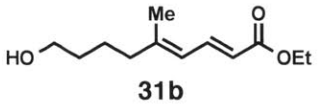
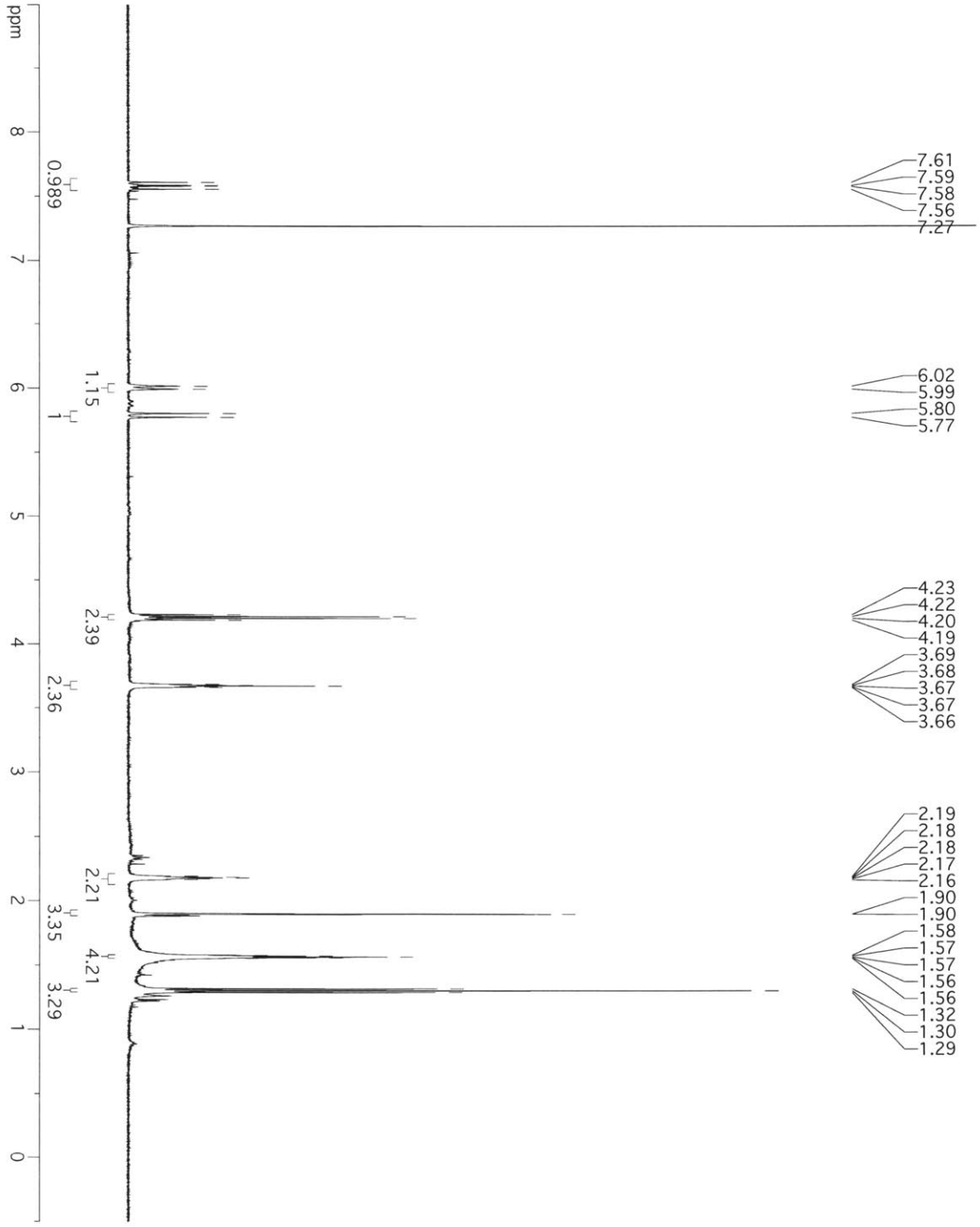
60.5
28.4
26.0
19.0
18.1
14.4


Me
O
HO
OEt

31b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1
2.39
2.36
2.21
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3.29
7.61
7.59
7.58
7.56
7.27
6.02
5.99
5.80
5.77
4.23
4.22
4.20
4.19
3.69
3.68
3.67
3.67
3.66
2.19
2.18
2.18
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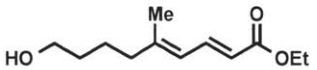
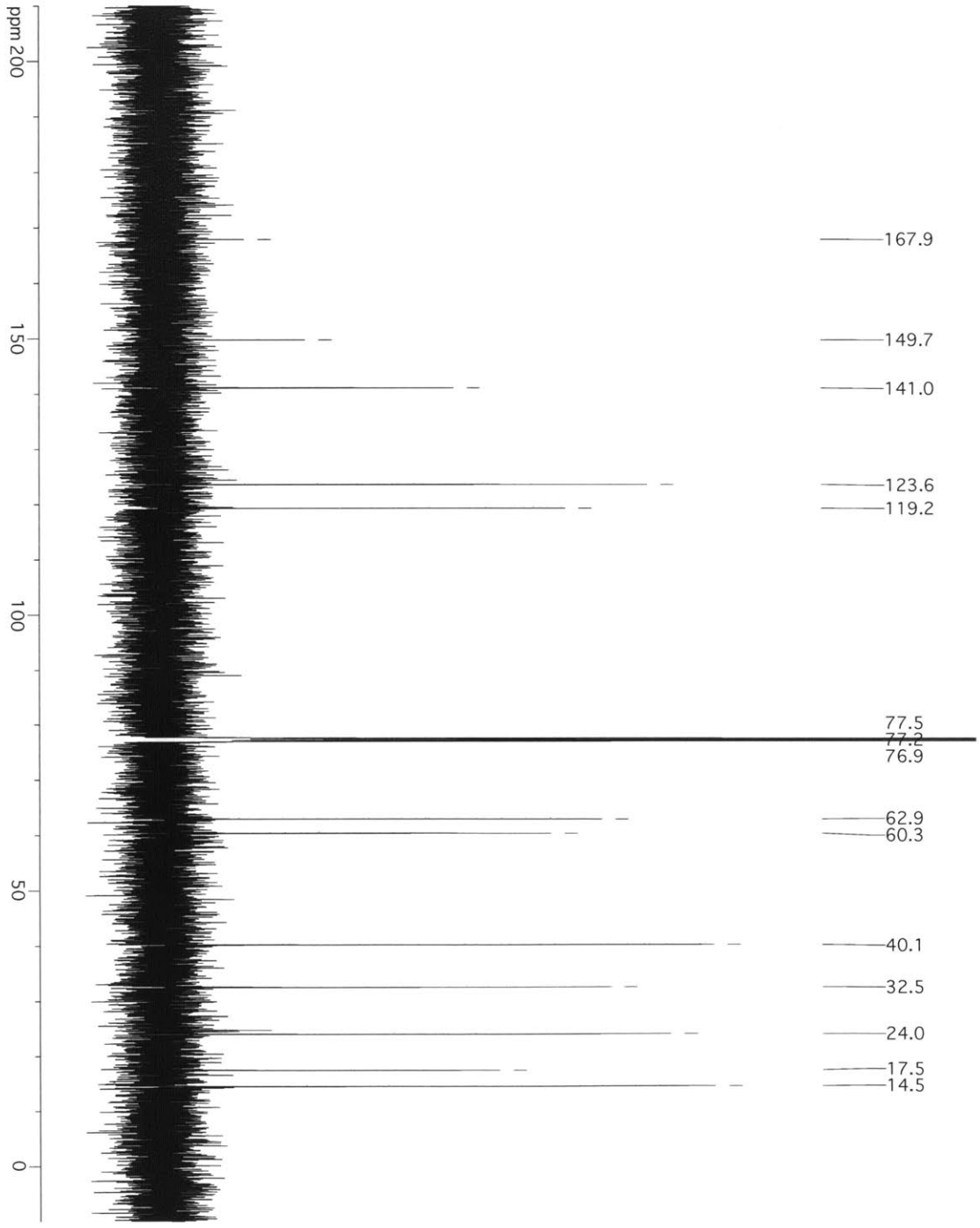
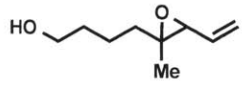
1.57
1.56
1.56
1.32
1.30
1.29

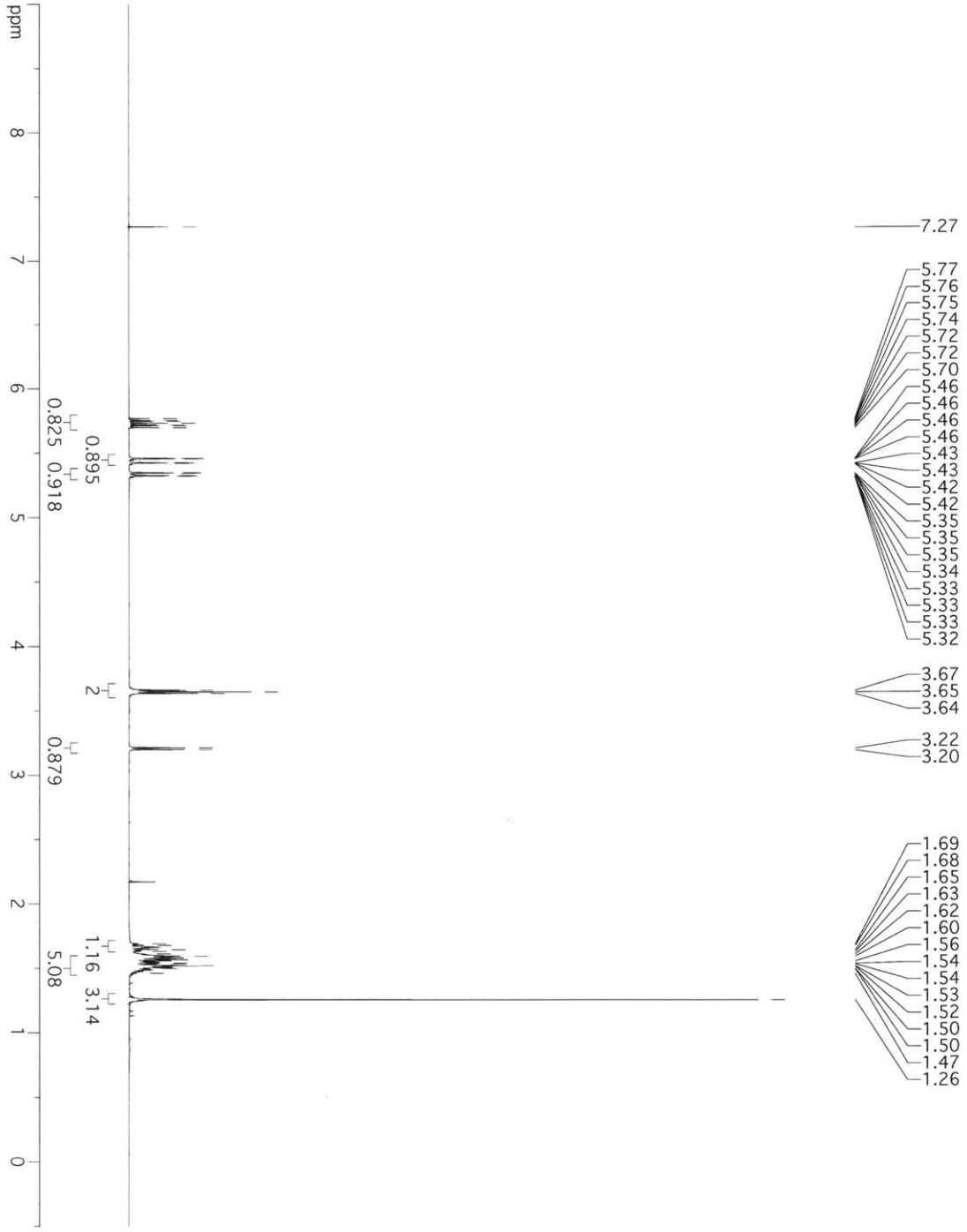

Me
O
HO
OEt

31b


ppm 200
150
100
50
0
167.9
149.7
141.0
123.6
119.2
77.5
77.2
76.9
62.9
60.3
40.1
32.5
24.0
17.5
14.5


HO
O
Me

32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5
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0.895
2
0.879
1.16
3.14
5.08
7.27
5.77
5.76
5.75
5.74
5.72
5.72
5.70
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5.46
5.46
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5.33
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5.33
5.32
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3.65
3.64
3.22
3.20
1.69
1.68
1.65
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1.52
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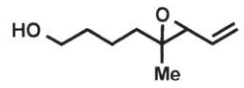
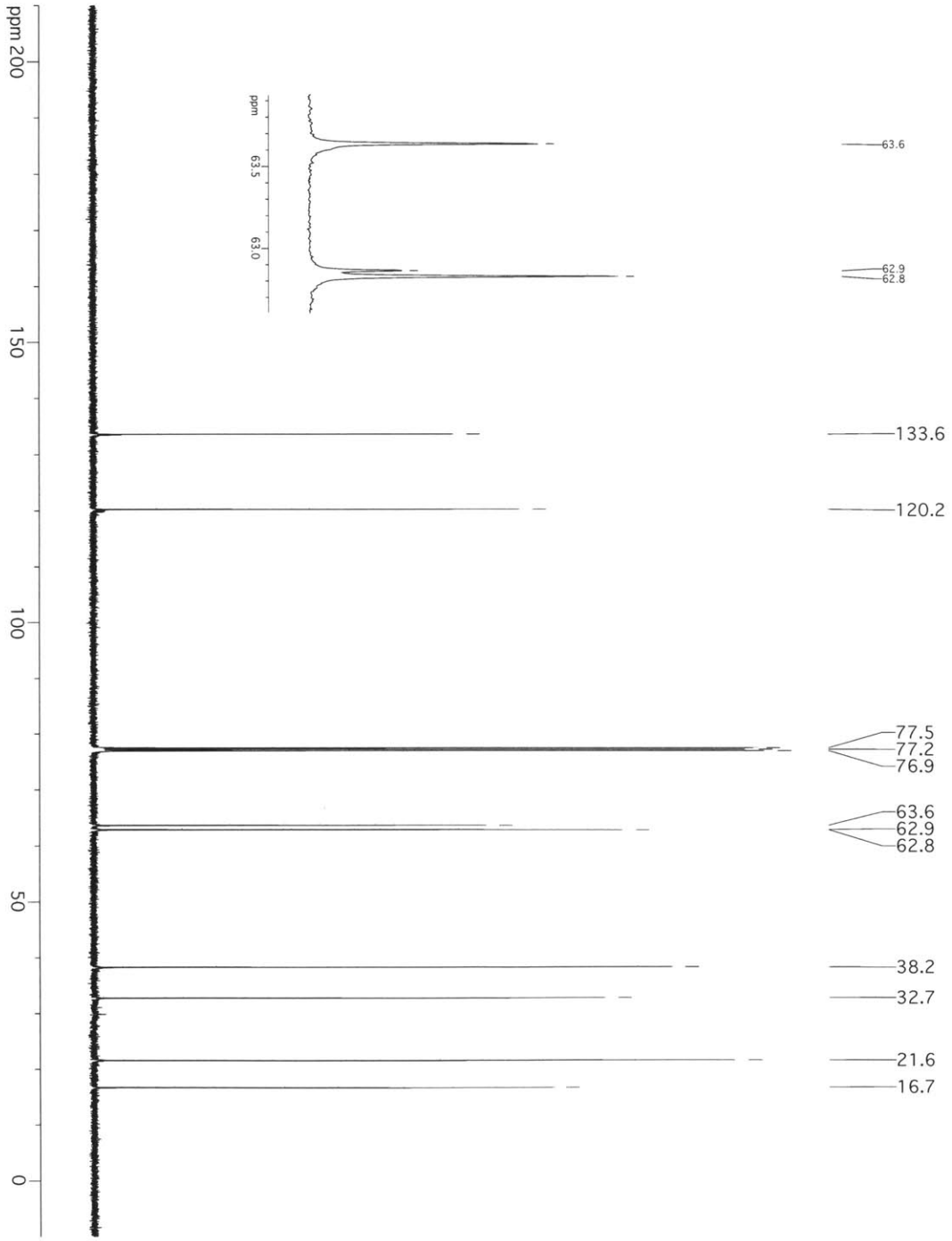
1.47
1.26


HO
O
Me

32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50
0
ppm
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63.0
63.6
62.9
62.8
133.6
120.2
77.5
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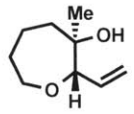
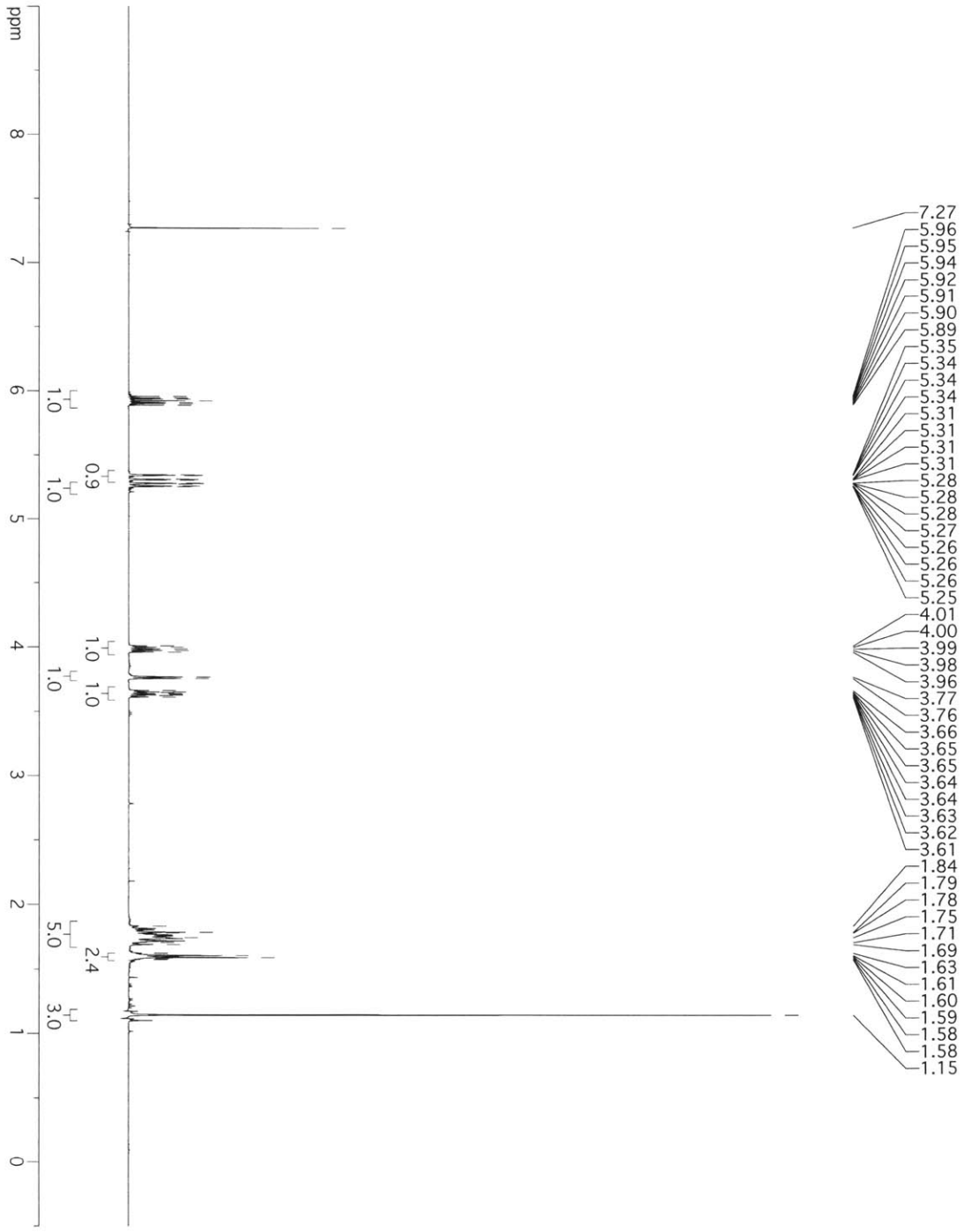
62.9
62.8
38.2
32.7
21.6
16.7


Me
OH
O
H

33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2.4
3.0
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5.94
5.92
5.91
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5.89
5.35
5.34
5.34
5.34
5.31
5.31
5.31
5.31
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5.28
5.28
5.27
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5.26
5.26
5.25
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4.00
3.99
3.98
3.96
3.77
3.76
3.66
3.65
3.65
3.64
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3.63
3.62
3.61
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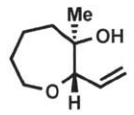
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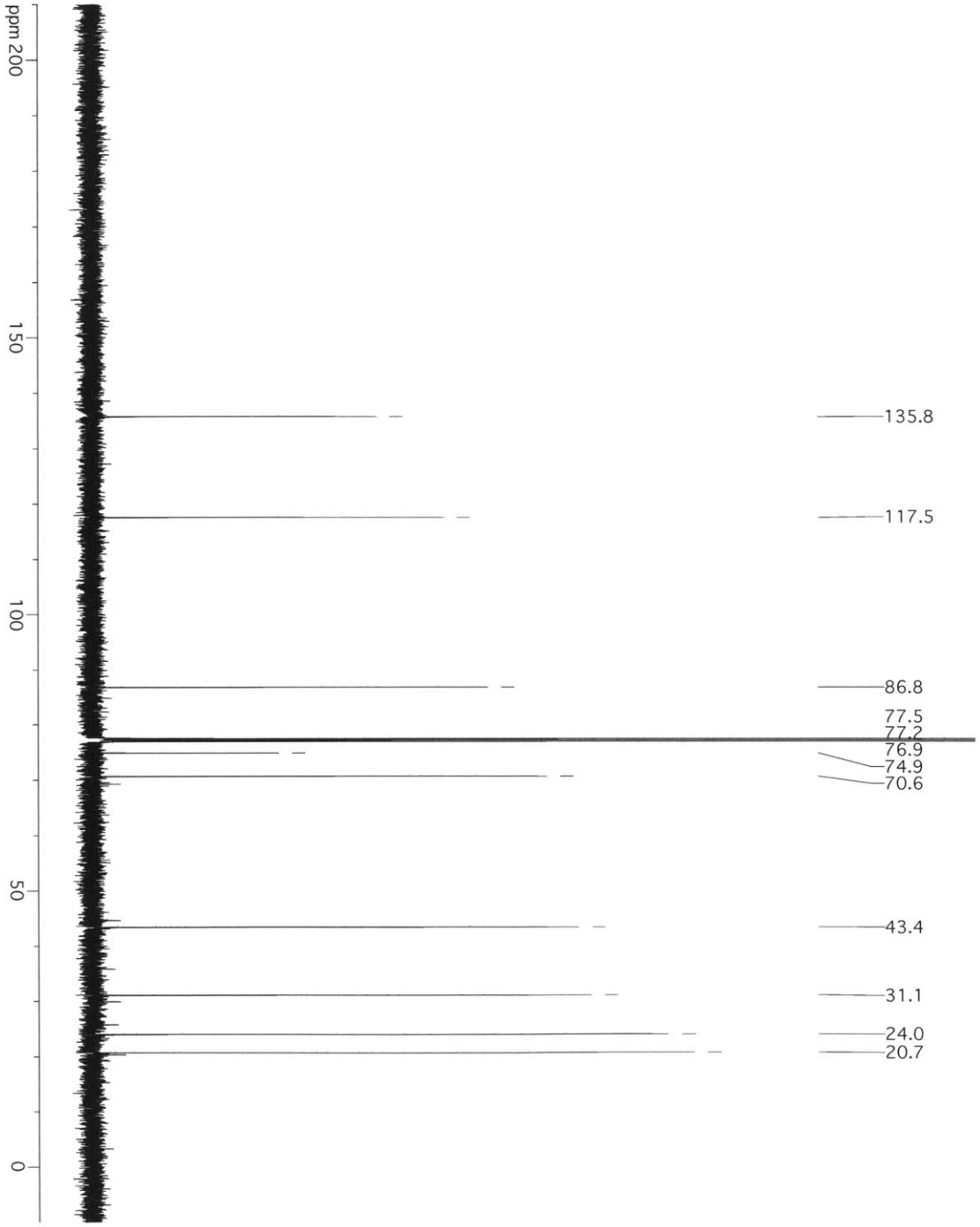
H

33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24.0
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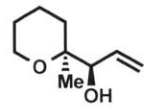
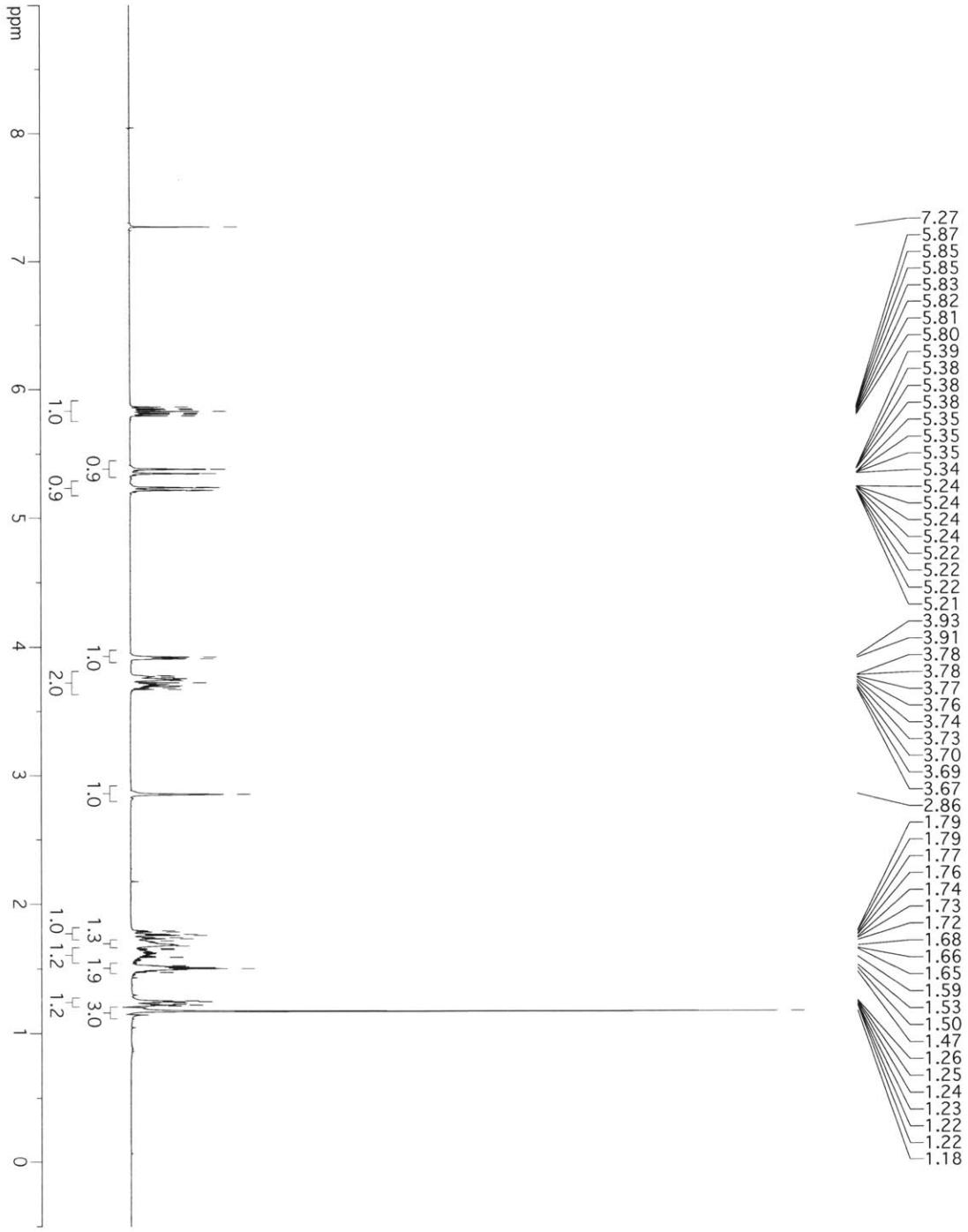

O
Me
OH

34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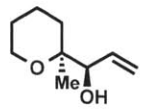
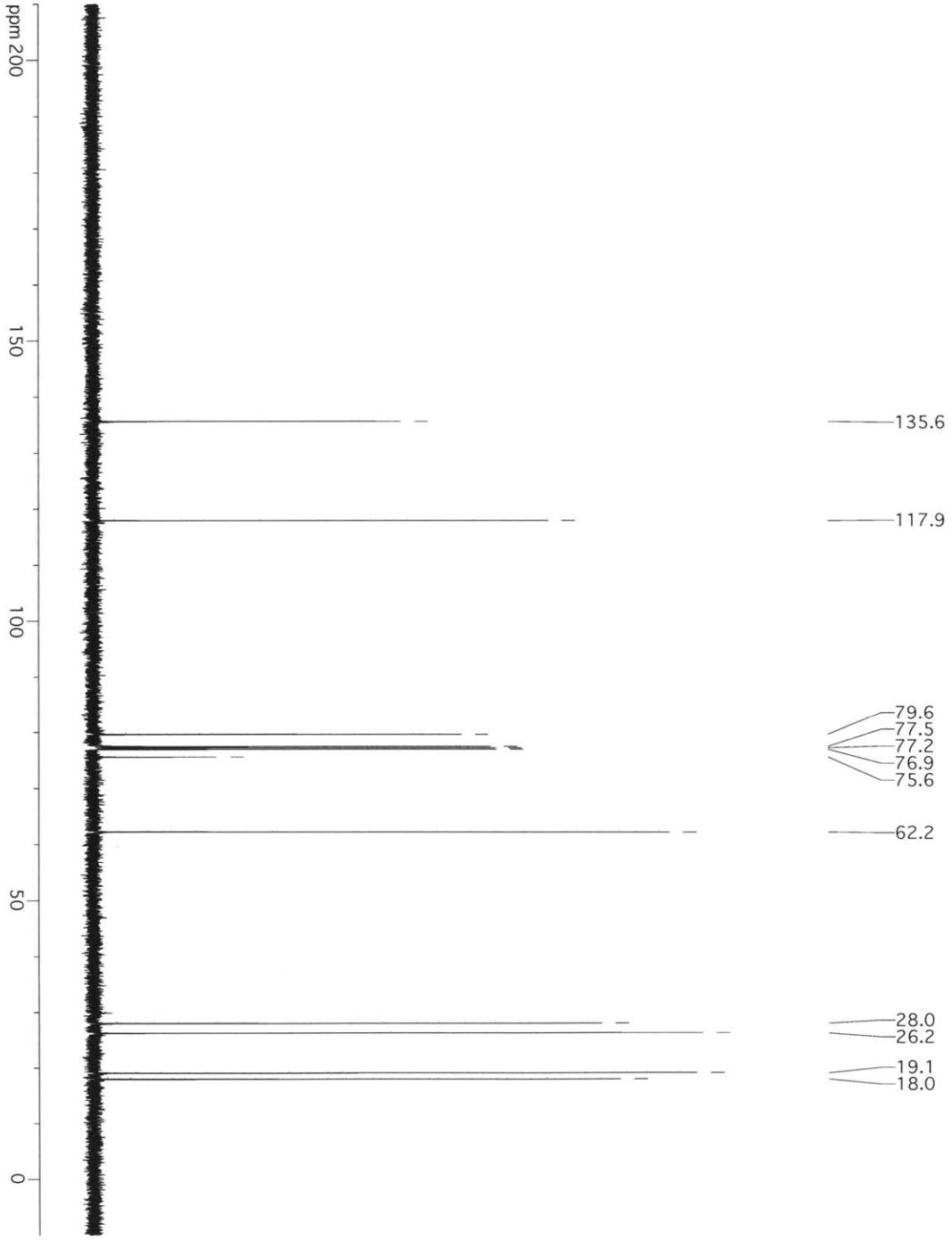

O
Me
OH

34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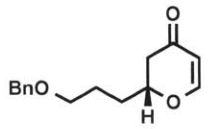
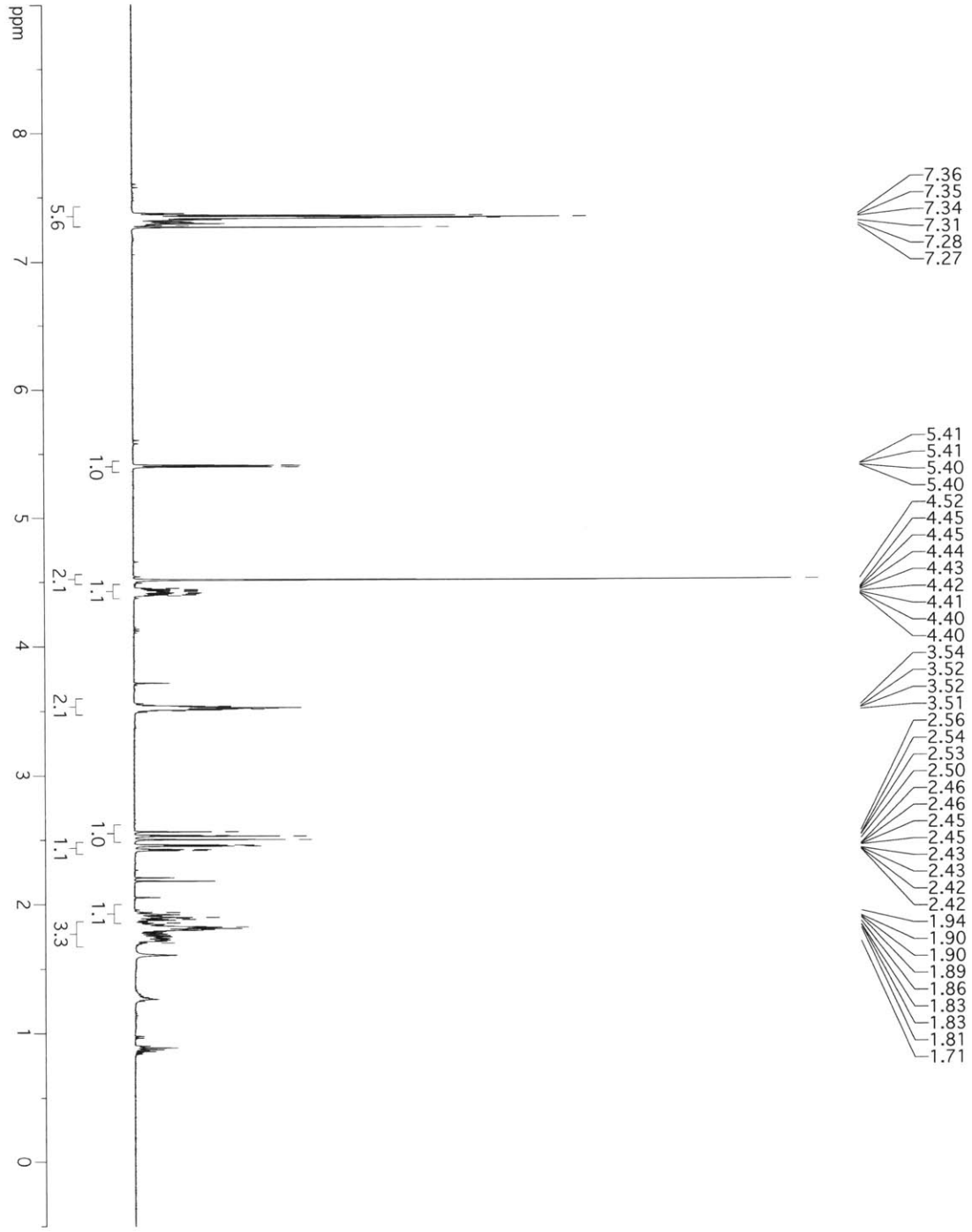
18.0


O
BnO
O
H

43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2.46
2.45
2.45
2.43
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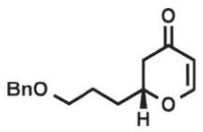
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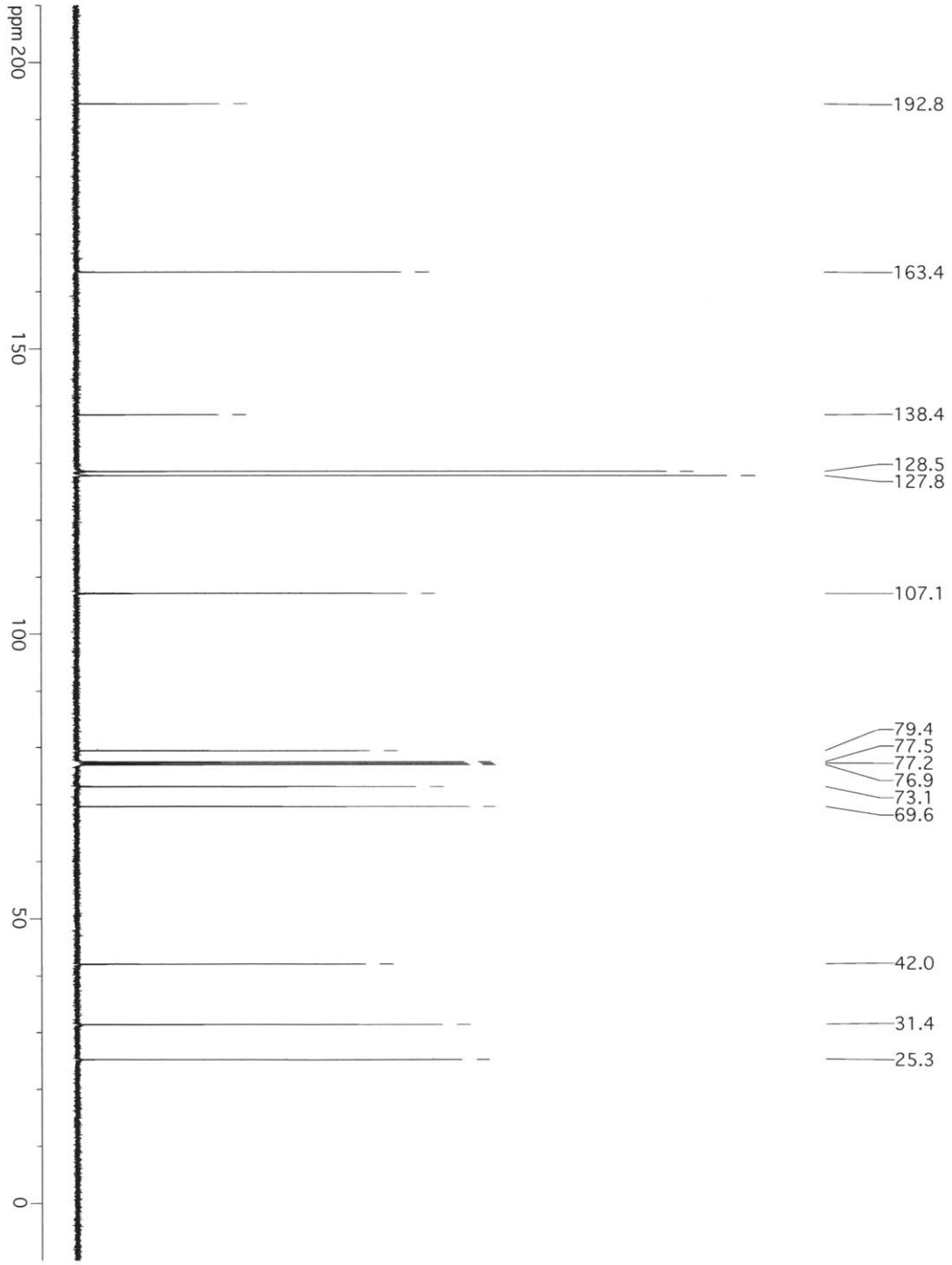
H
O

43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73.1
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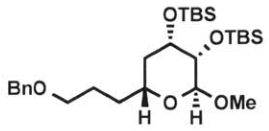
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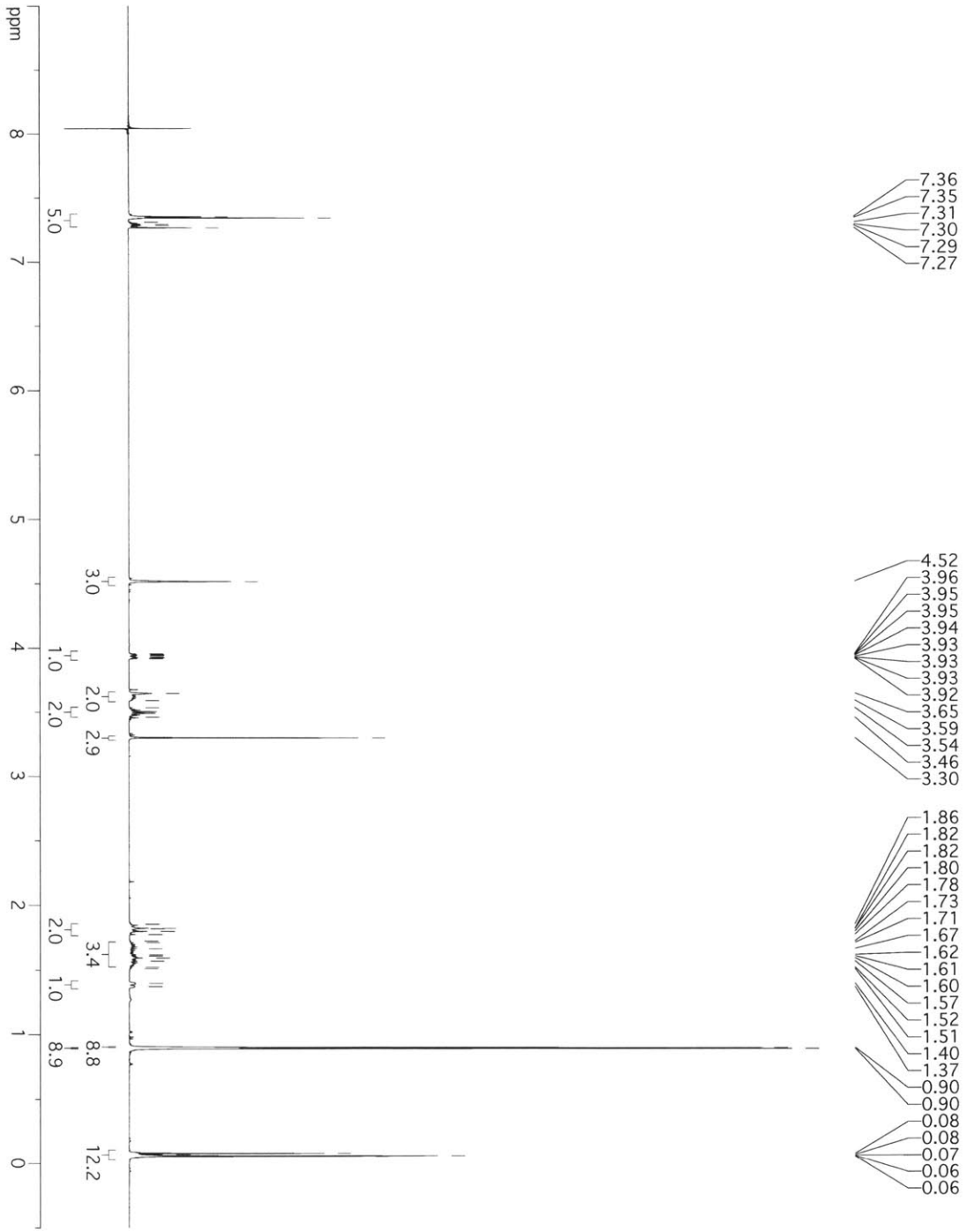
OMe
H
H

44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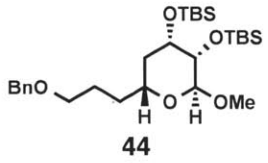
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H
H
OMe

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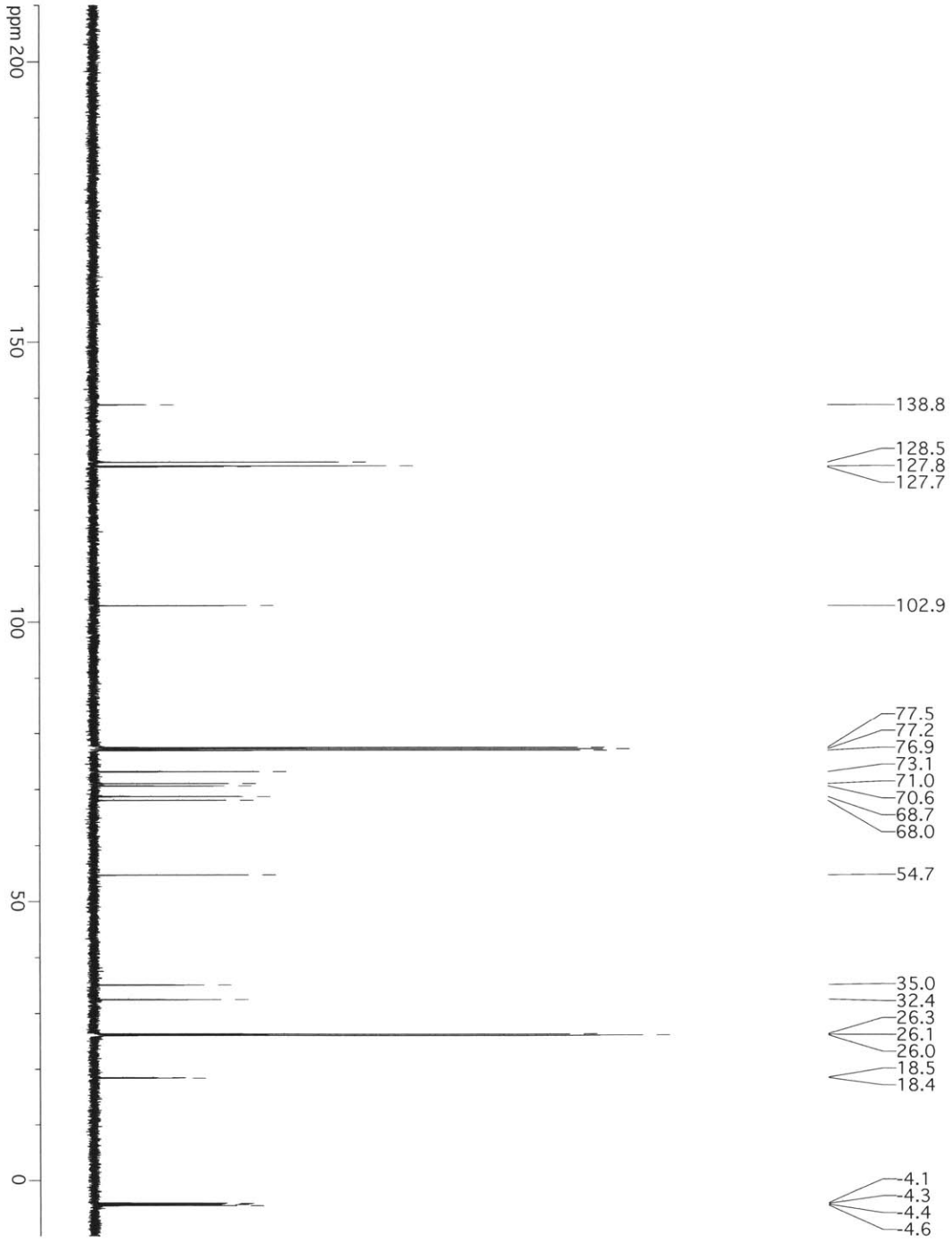
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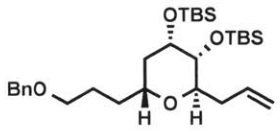
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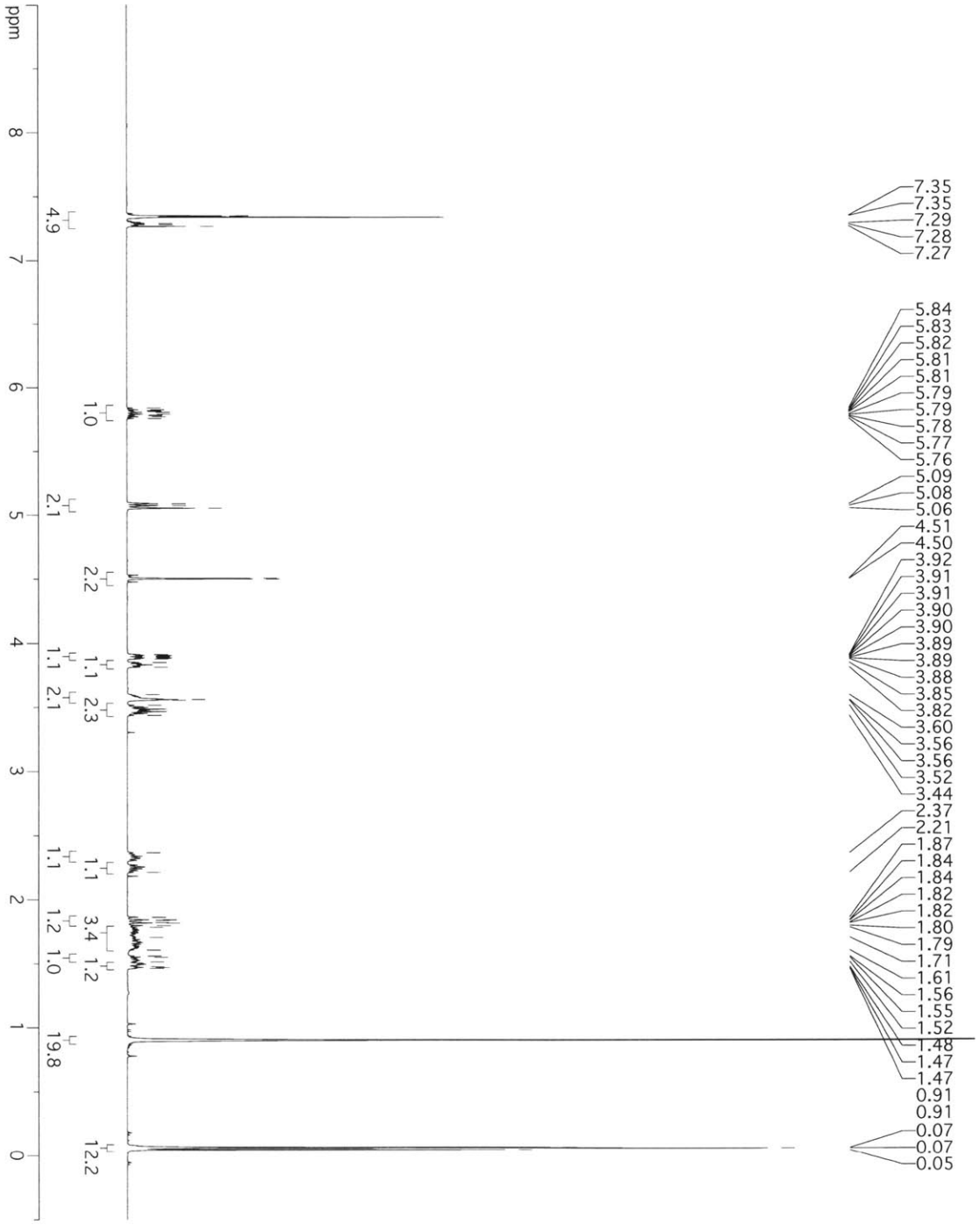
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1.1
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1.2
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1.0
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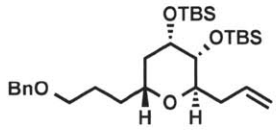
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O
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H

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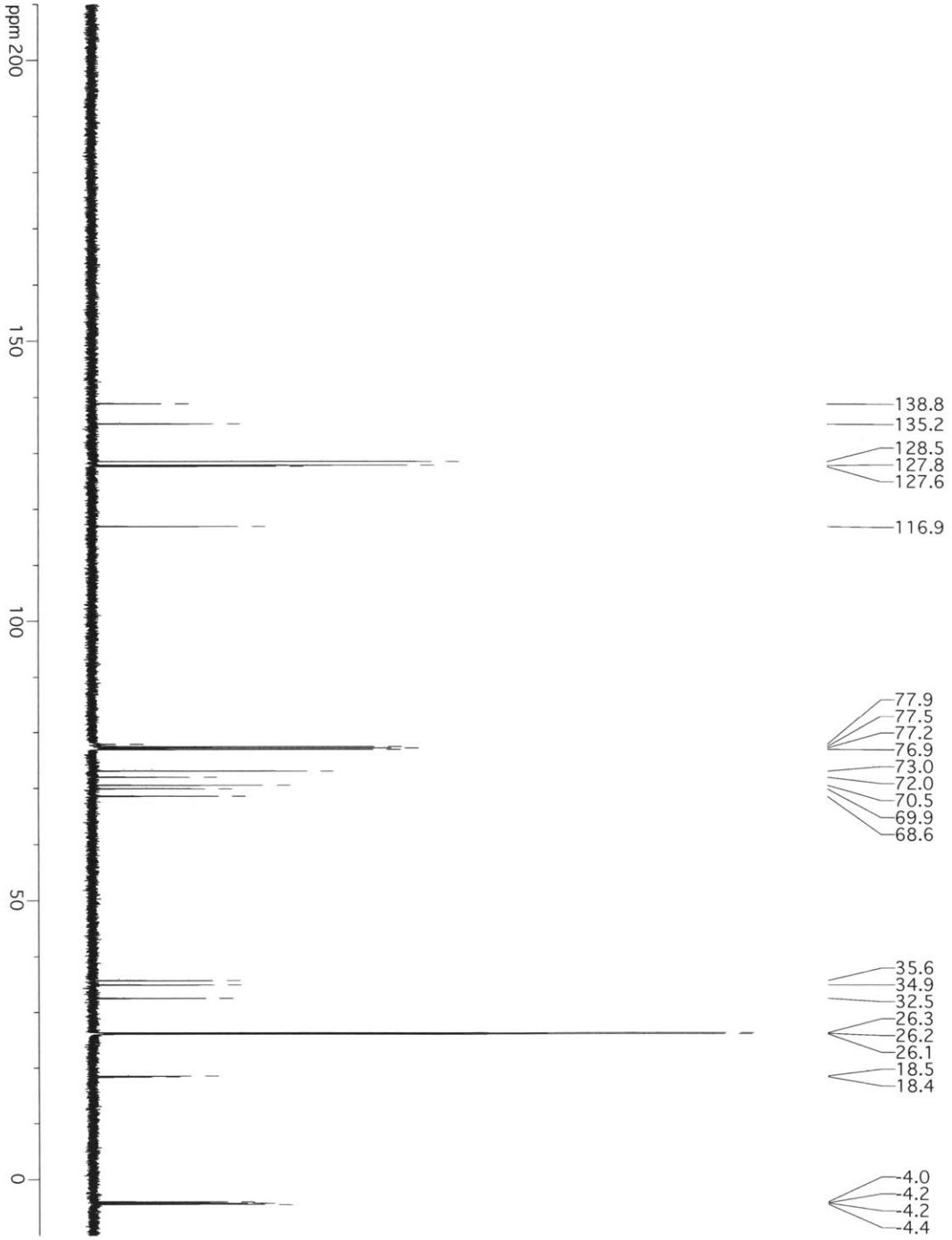
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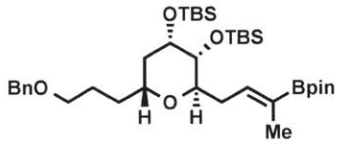
-4.4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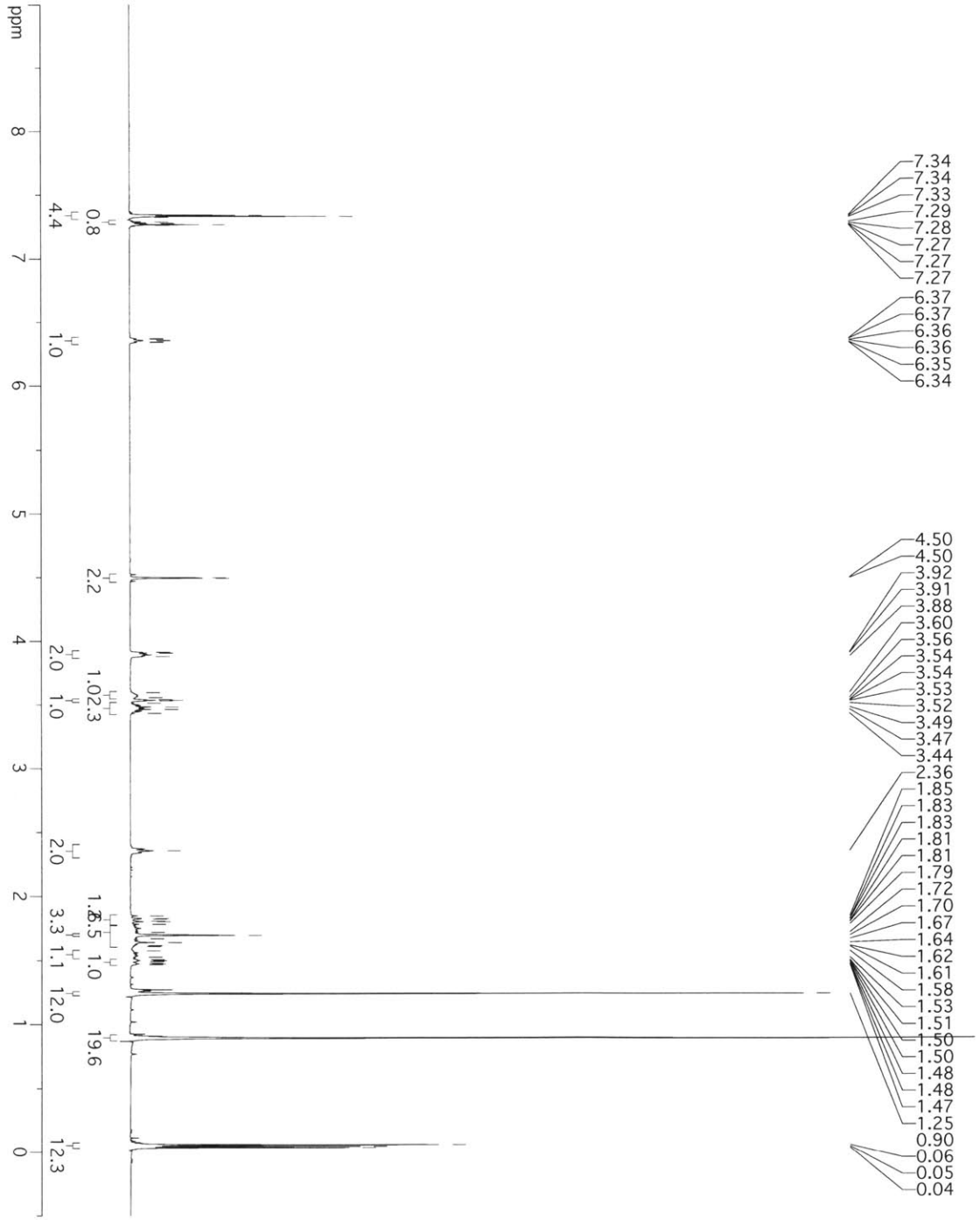
H
H
Bpin
Me

47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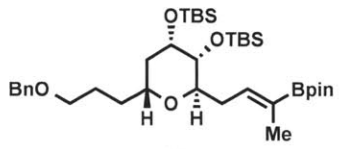
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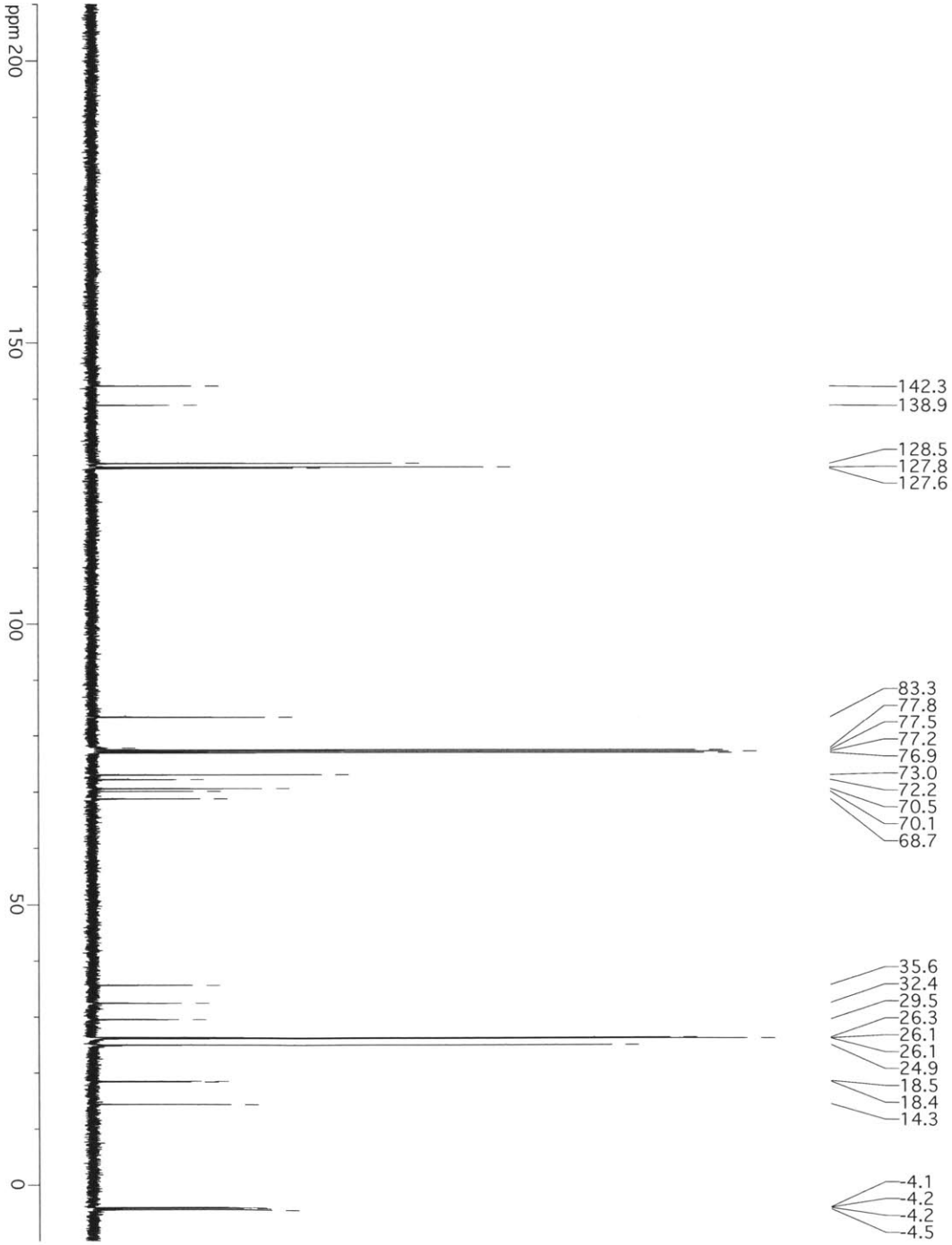
Me

47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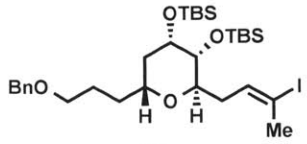
4.5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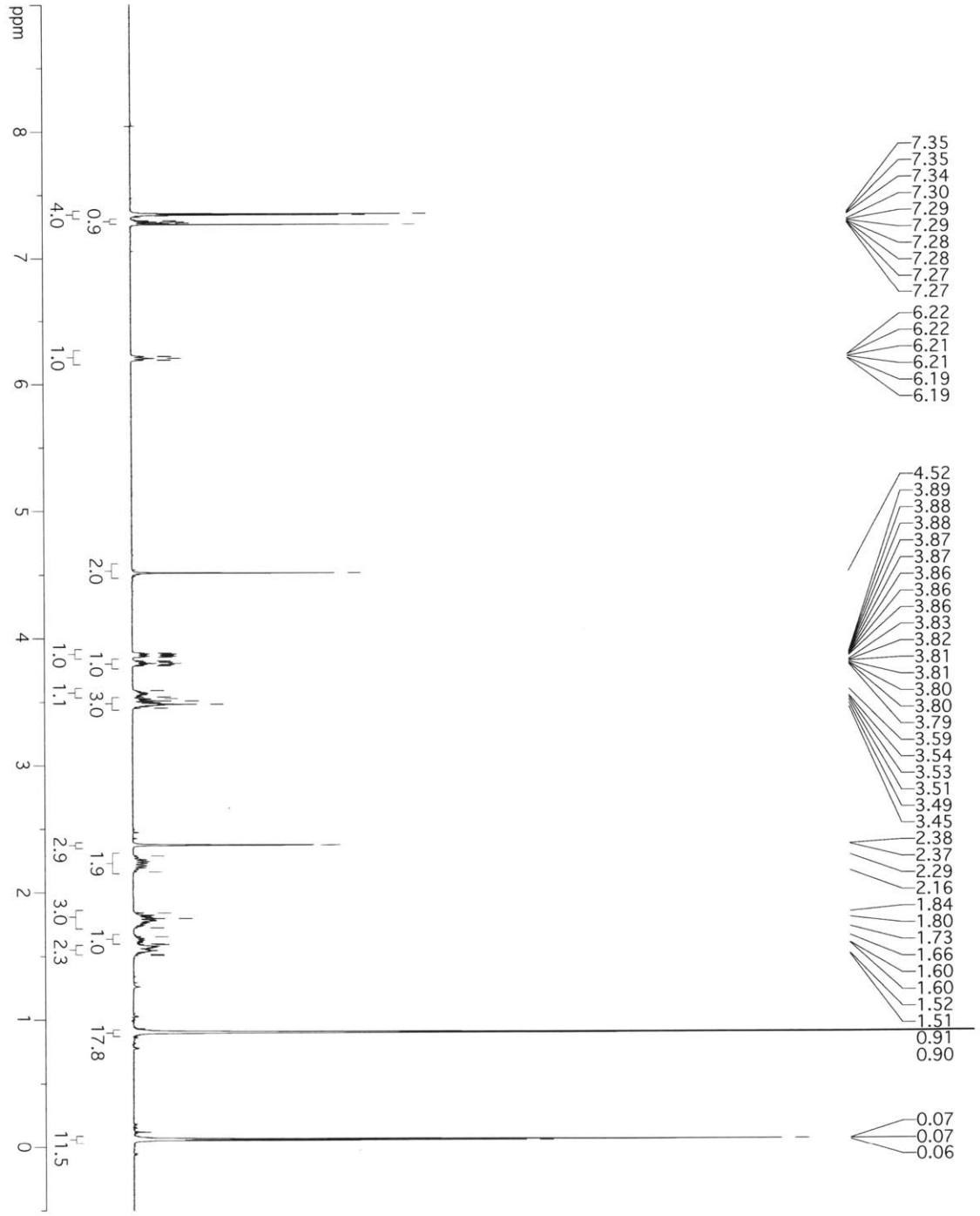
H
I
Me

36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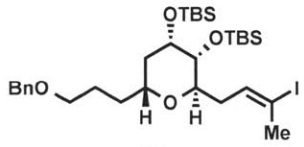
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Me

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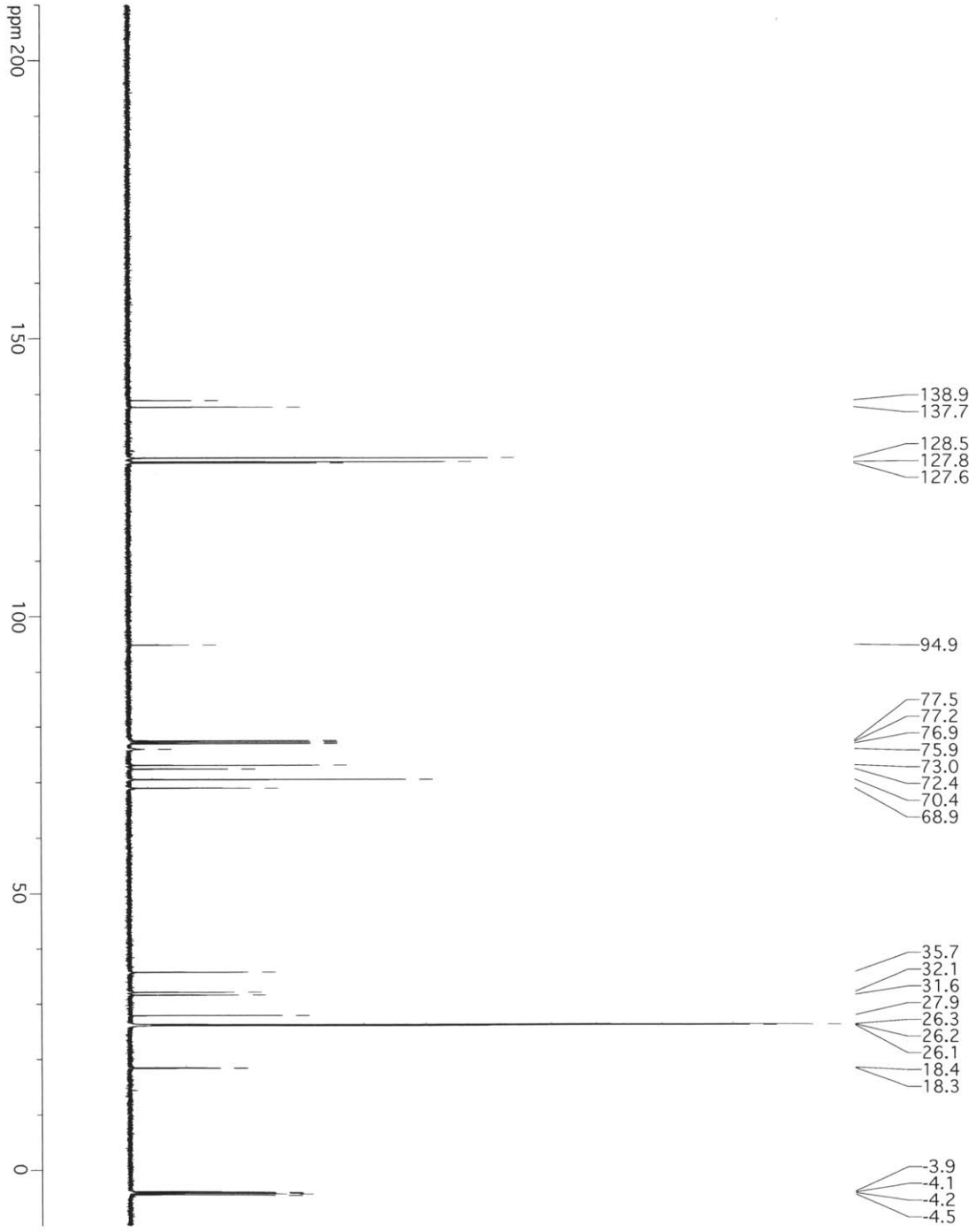
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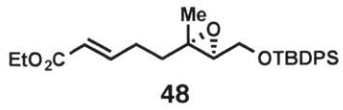
-4.5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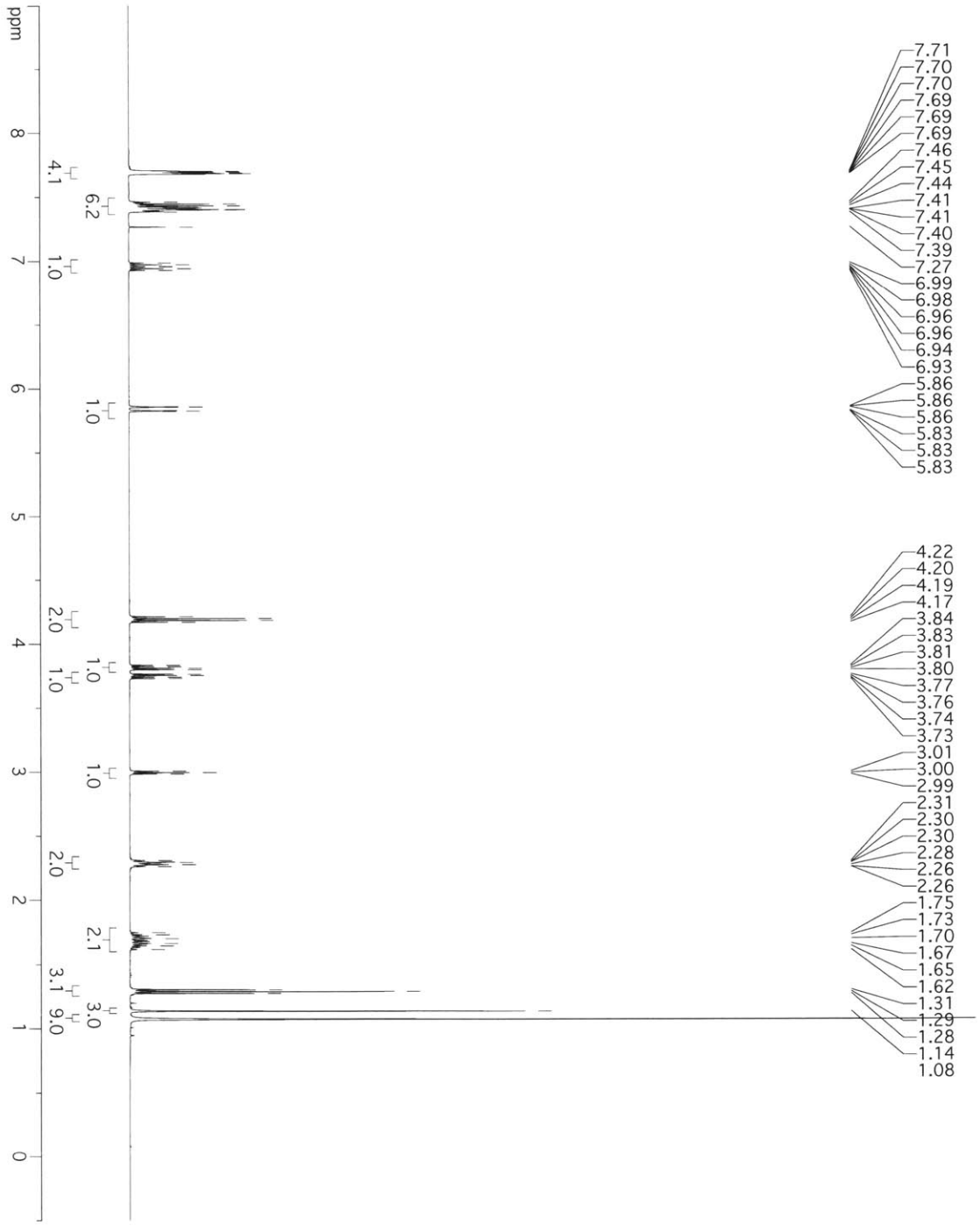
EtO2C
OTBDPS

48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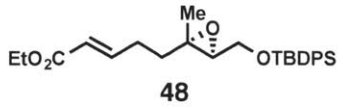
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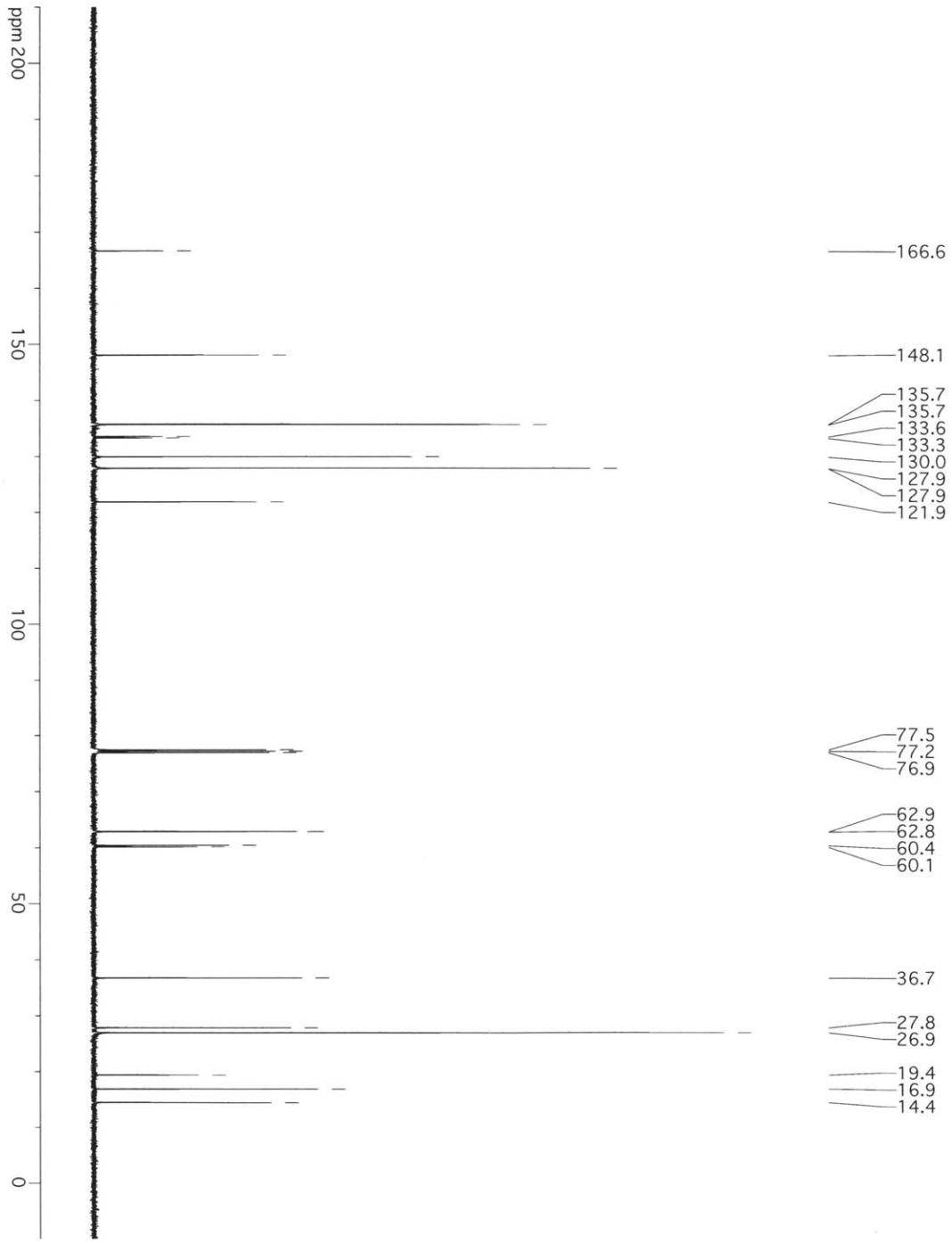
48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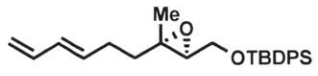
Me
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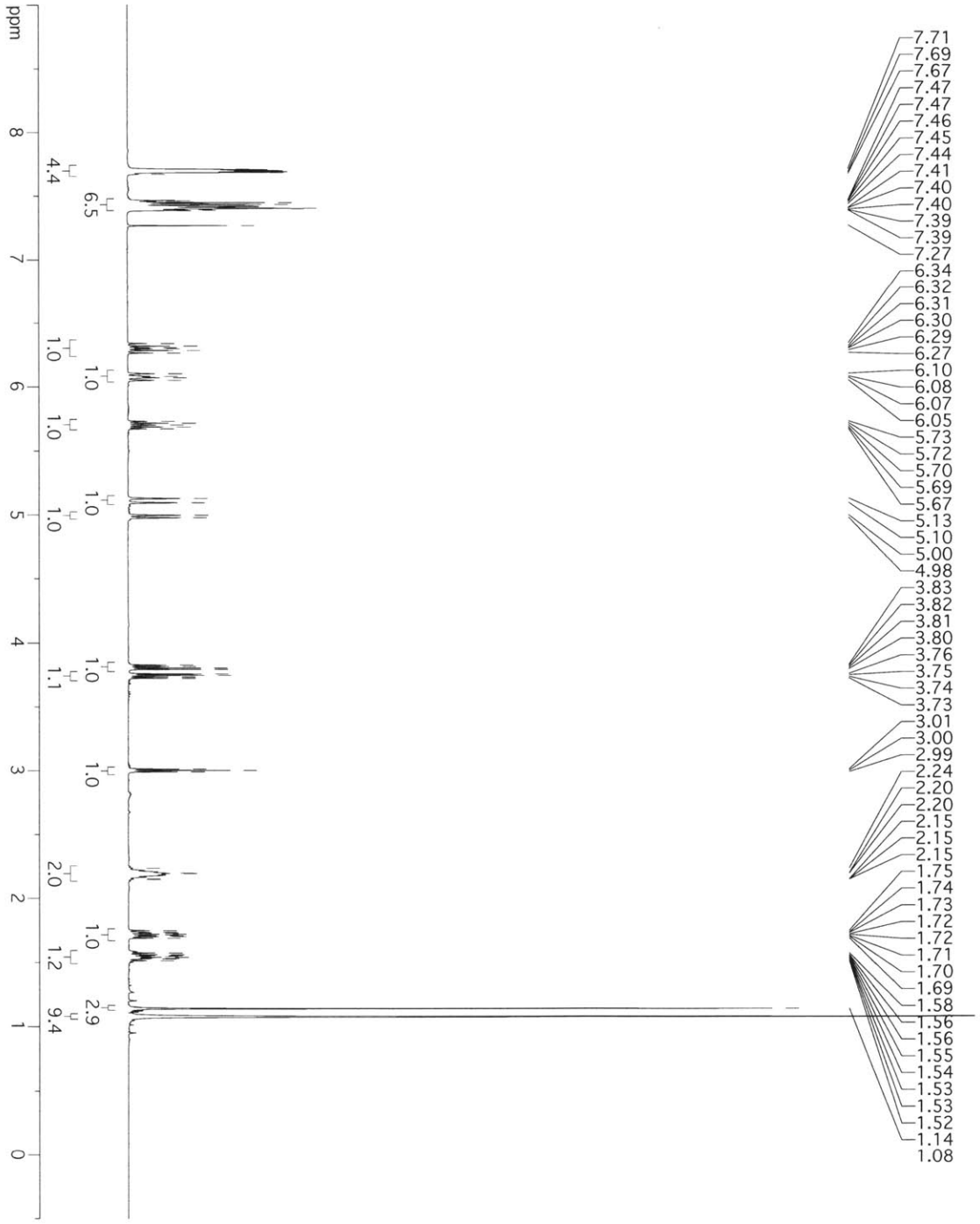
49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2.0
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3.00
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2.20
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2.15
2.15
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1.74
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1.71
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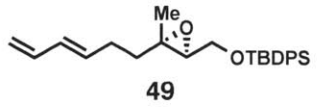
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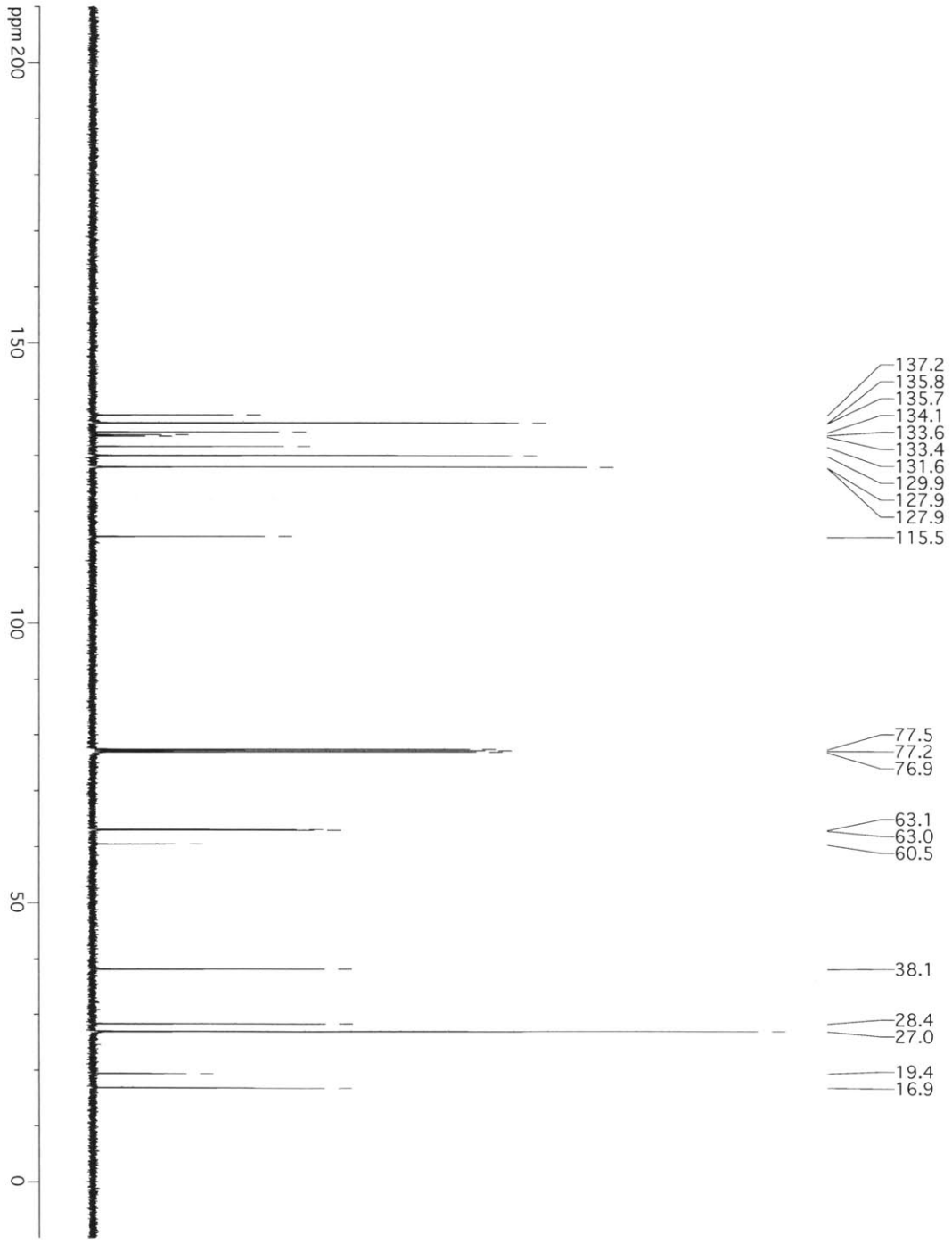
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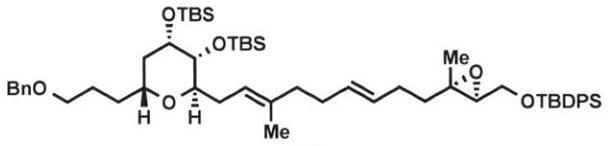
16.9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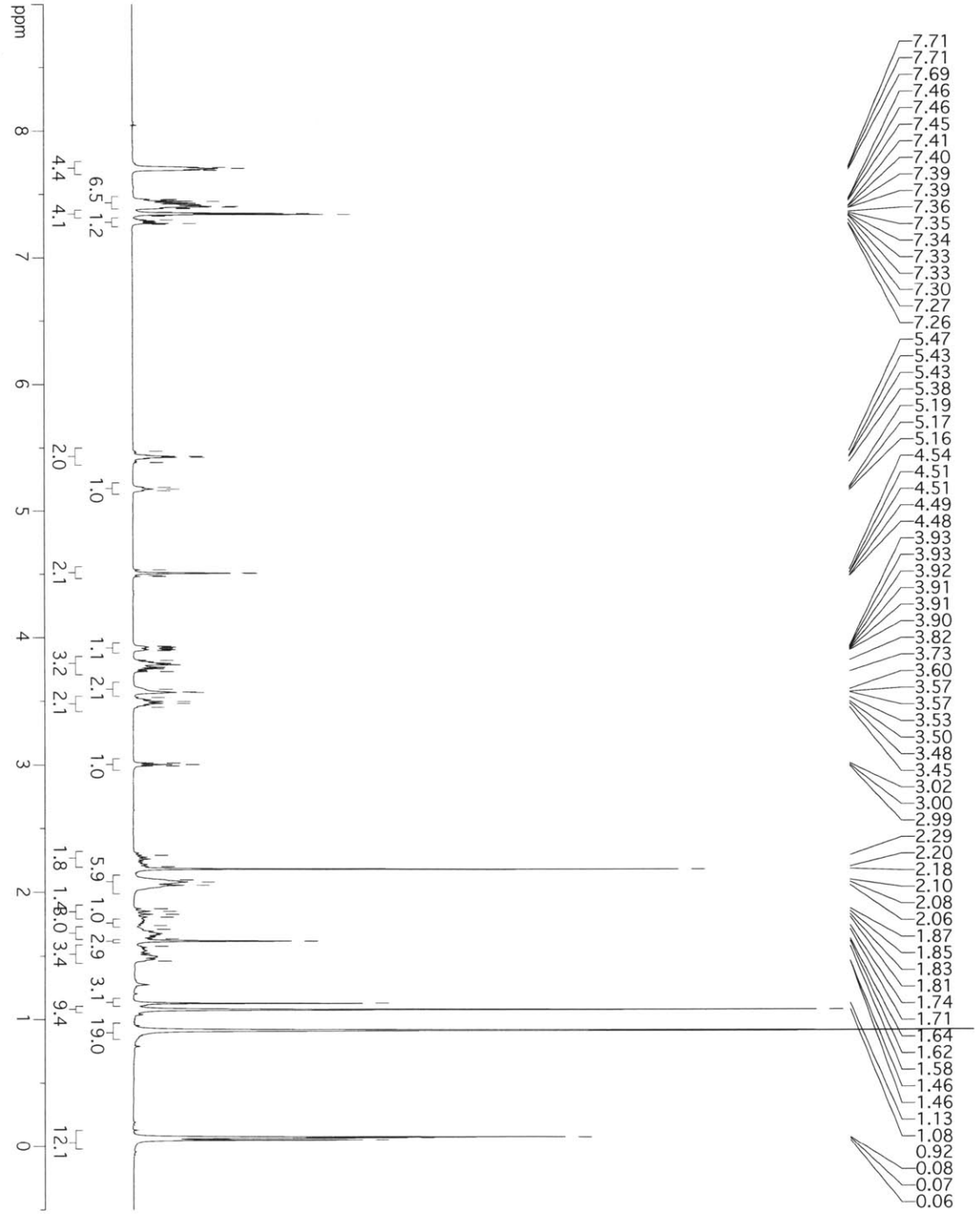
Me
Me
O
OTBDPS

35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3.57
3.53
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3.48
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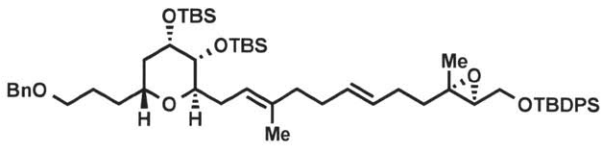
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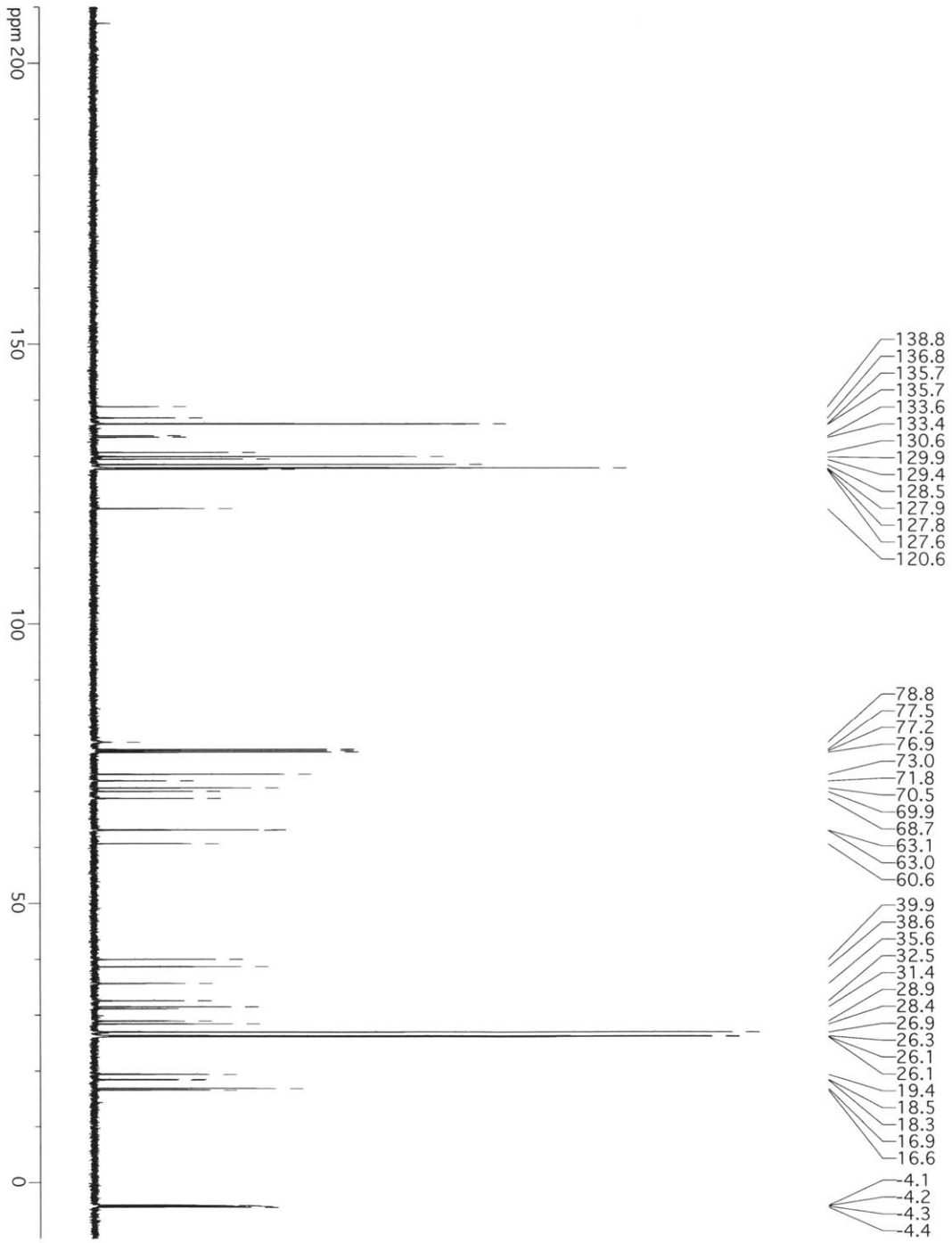
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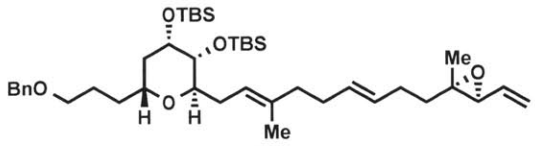
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Me
O

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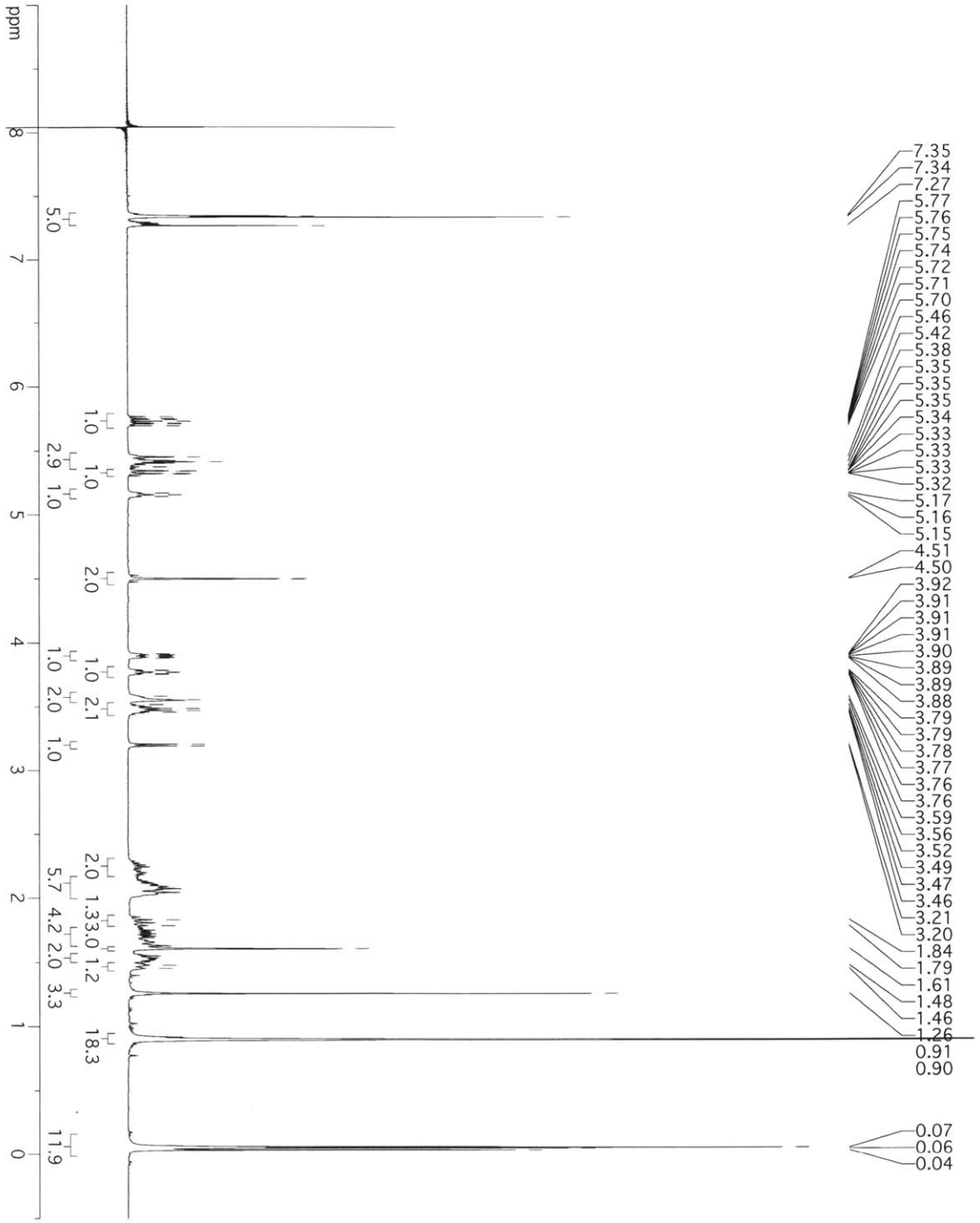
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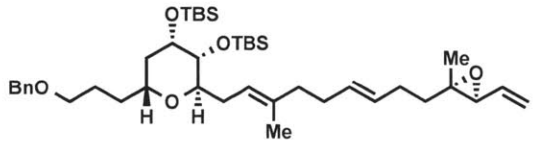
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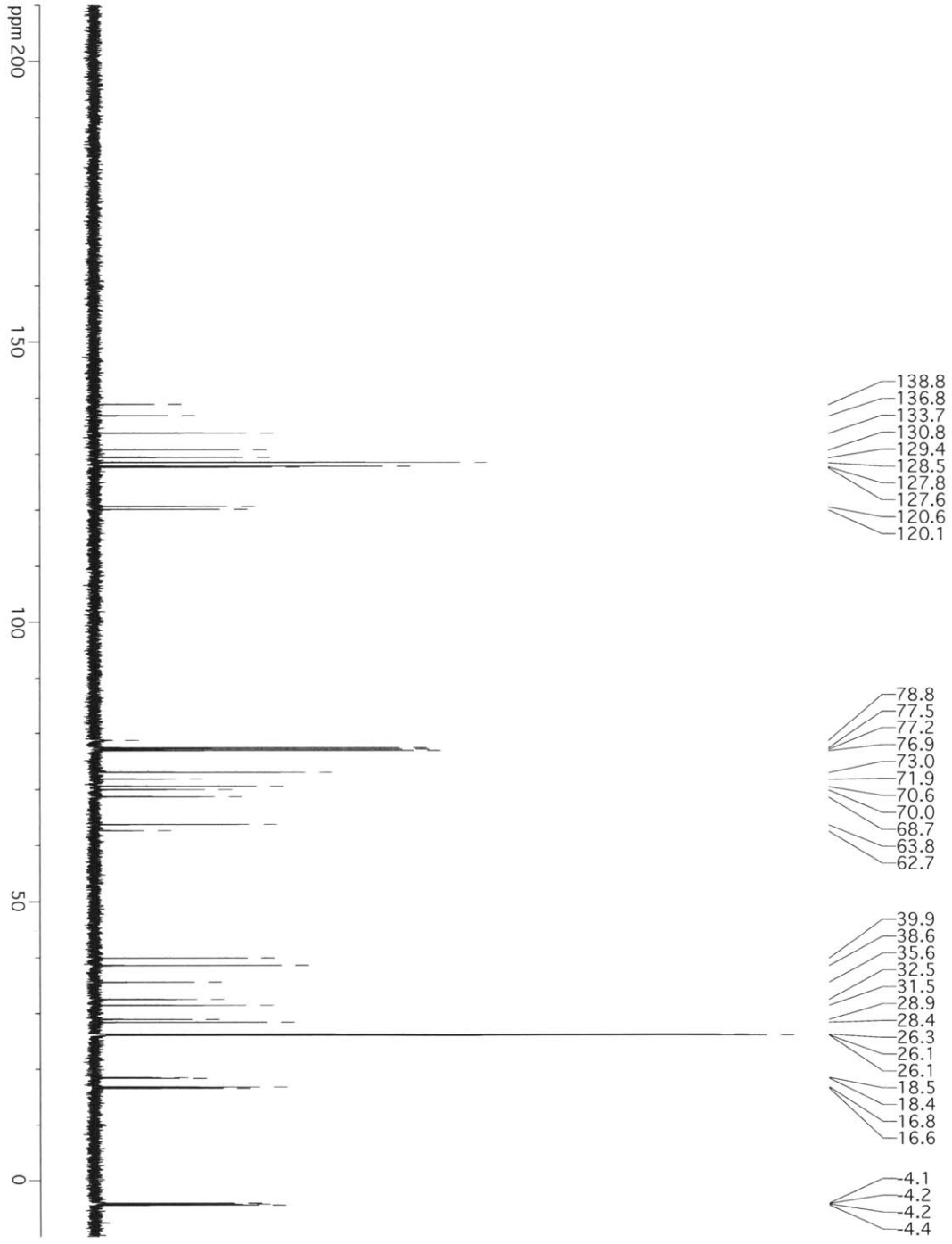
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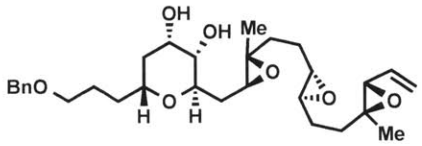
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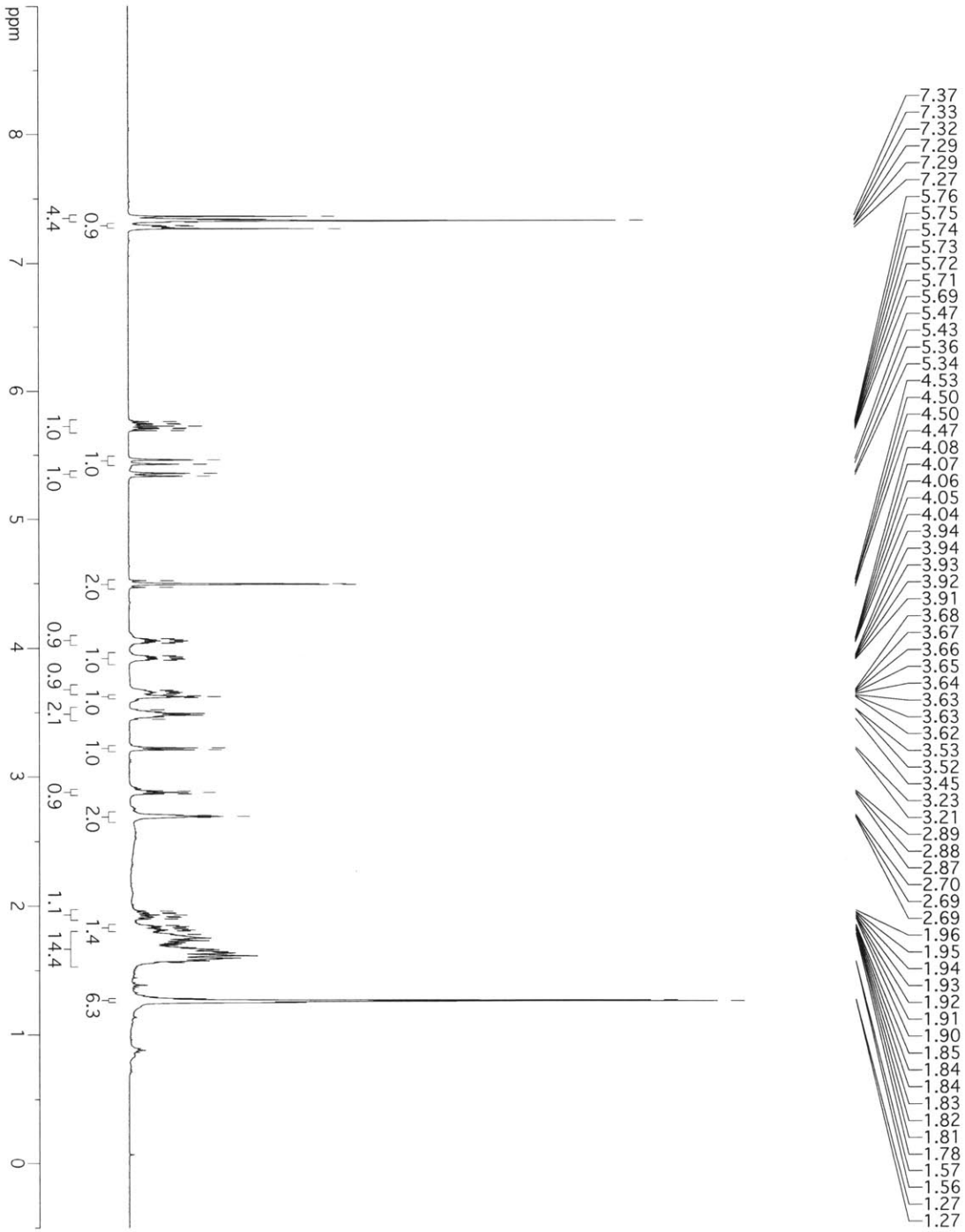
13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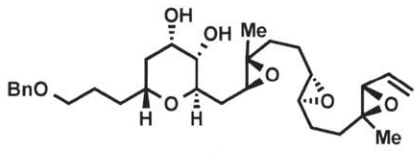
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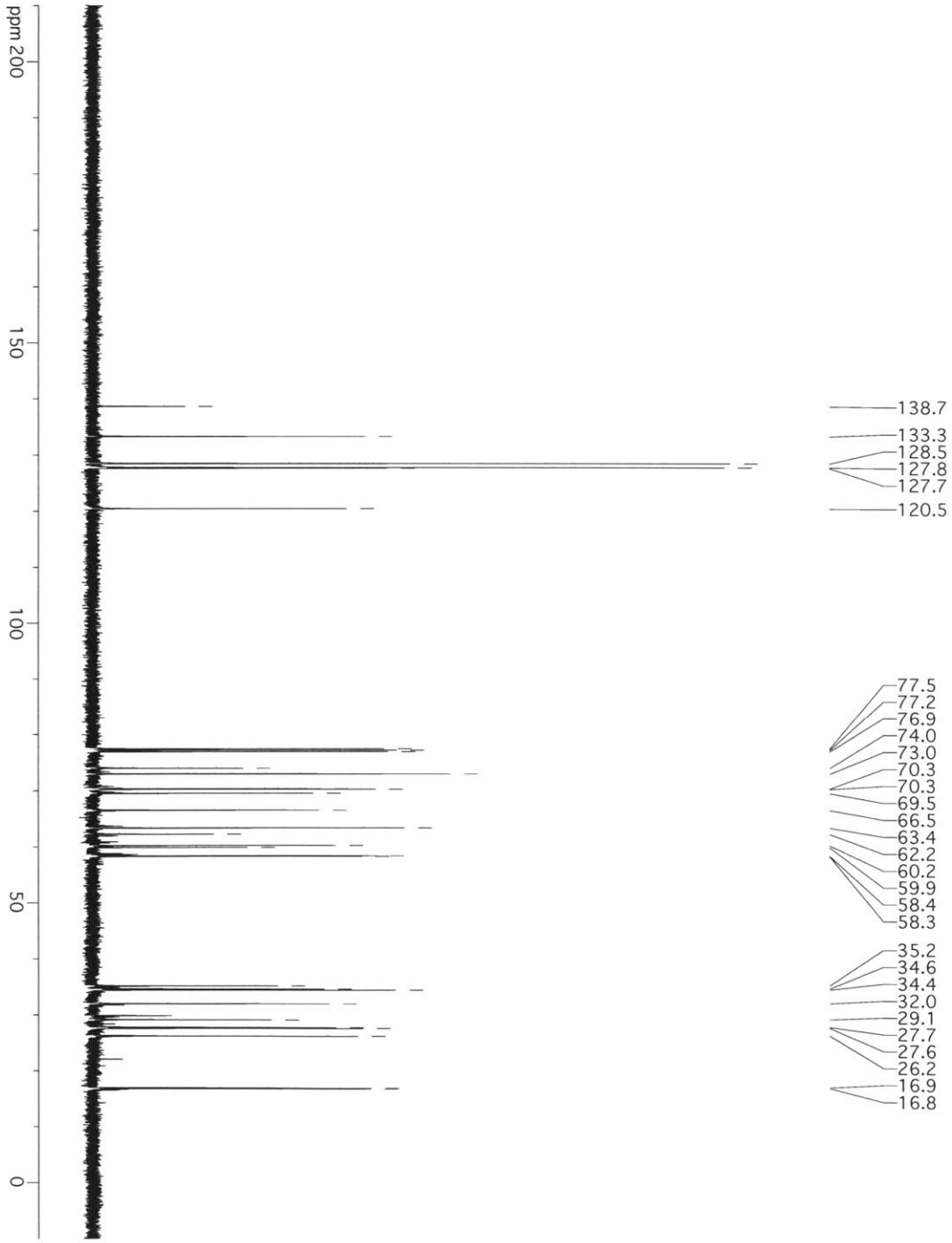
13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26.2
16.9
16.8

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EMAIL: kwa@mit.edu • CELL: (617) 895-7135 • LAB: (617) 253-7233

EDUCATION AND RESEARCH EXPERIENCE

2008-Present **Massachusetts Institute of Technology, Cambridge, MA**
Candidate for Ph.D. 2014 in Organic Chemistry, Advisor: Timothy F. Jamison.
National Science Foundation Graduate Research Fellow
Robert T. Haslam Presidential Graduate Fellow
- Synthesis of oxepanes and formal synthesis of marine ladder polyether brevisin via rhodium-catalyzed epoxy-alcohol cyclizations and cascades

2003-2007 **Brown University, Providence, RI**
B.Sc. in Chemistry with Honors, *magna cum laude*, Advisor: Matthew B. Zimmt
- Synthesis and investigation of enantioenriched diols towards patterned monolayer formation

PUBLICATIONS

Tong, W.; Wei, Y.; Armbrust, K. W.; Zimmt, M. "Dipolar Side Chain Control of Monolayer Morphology: Symmetrically Substituted 1,5-(Mono- and diether) Anthracenes at the Solution–HOPG Interface." *Langmuir* **2009**, *25*, 2913–2923.

Wei, Y.; Tong, W.; Wise, C.; Wei, Y.; Armbrust, K. W.; Zimmt, M. B. "Dipolar Control of Monolayer Morphology: Spontaneous SAM Pattering." *J. Am. Chem. Soc.* **2006**, *128*, 13362-13363.

PRESENTATIONS

Armbrust, K. W. "Rhodium-Catalyzed Endo-Selective Epoxide-Opening Cyclizations and Cascades: Toward Oxepanes and Marine Ladder Polyether Natural Products." Research Presentation, *2nd Boston Symposium on Organic & Bioorganic Chemistry*, Boston, MA, October 16th, 2013.

AWARDS AND HONORS

2009	Award for Outstanding Teaching by a Graduate Student
2007	ACS Outstanding Senior Prize, Brown University
2006	Pfizer Summer Undergraduate Research Fellowship

TEACHING AND MENTORSHIP EXPERIENCE

2013	Organic Chemistry Teaching Assistant, MIT
2011-2013	MIT Chemistry Outreach: Chemistry Demonstrations in Massachusetts High Schools
2012	MIT Graduate Student Teaching Certificate Program
2010-2012	Graduate Synthetic Organic Chemistry Teaching Assistant, MIT
2008-2009	Introductory Organic Chemistry Teaching Assistant, MIT
2007	Summer Organic Chemistry Lab Teaching Assistant, Brown University